Official Journal of the
Malaysian Medical Association

MJM Case Reports Journal

Volume: 2

Issue No: 3

December 2023

ISSN 2948-3859

MJM Case Reports

Official Journal of the Malaysian Medical Association

Volume 2 Number 3 December 2023

EDITORIAL BOARD

PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 2948-3859

The MJM Case Reports Journal is published three times a year.

All articles which are published represent the opinion of the authors and are not necessarily those of the Malaysian Medical Association unless otherwise expressed.

Advertisement Rates:
Enquiries to be directed to the Secretariat.

Secretariat Address:
Malaysian Medical Association
4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
Website: www.mma.org.my

Medical Journal of Malaysia Case Reports

MJM Case Reports

INSTRUCTION TO AUTHORS

Requirements
All submission must be in English. All authors are encouraged to follow the MJM format and ICMJE and COPE guidelines. The case reports (maximum five patients/cases) must follow these requirements:

- Case reports, excluding abstract and references, should not exceed 2,000 words
- A maximum of two (2) tables; three (3) photographs; and up to ten (10) references.
- It shall adhere to the stipulated *MJM Case Reports* format
- There should be no more than seven (7) authors. All authors must have made an individual contribution to the writing of the article and not just involved in the patient's care.
- Patient's details are anonymised as much as possible and appropriate consent/permission obtained
- The case has never been published or has currently been submitted elsewhere for publication

Manuscript text should be submitted as Microsoft Word documents. Tables and flow-charts should be submitted as Microsoft Word documents. Images should be submitted as separate JPEG files (minimum resolution of 300 dpi).

Submissions must conform to the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. The Editorial Board reserves the right to reject manuscripts that do not conform to this and policies of *MJM Case Reports*. Neither the Editorial Board nor the Publishers accept responsibility for the views and statements of authors expressed in their contributions.

Authors are advised to adhere closely to the Instructions to Authors. Manuscripts not meeting all the requirements will not be considered for publication and be returned to the authors for correction. Manuscripts should be submitted online through *MJM Case Reports Editorial Manager*.

All submissions must be accompanied by a completed Author Declaration Form, Copyright Transfer Form and Conflict of Interest Form duly signed by all authors. (Forms can be download here).

Article Processing Charge
The *MJM Case Reports* Article Processing Charge (APC) is a non-refundable administrative fee. The current rate takes into account the administrative process required for each submission, and this is a new journal. Hence, the fee will be reviewed from time to time. Payment of the APC does not guarantee acceptance of the manuscript. Submitted manuscripts will only be sent for reviews once the APC has been successful completed.

MMA Member - RM 400.00
Non-Member/ Overseas - RM 500.00

Preparing your manuscript

Manuscripts should be divided into individual section headings and contain the following information. It should not exceed 2000 words (excluding title page, abstract and references).

Title page:
The title page should clearly state the title of the case report without the use of any abbreviations, include full name(s) of the author(s), degrees (limited to one degree or diploma), and affiliations. All the authors' affiliations shall be provided after the authors' names. Indicate the affiliations with a superscript number at the end of the author's degrees and at the start of the name of the affiliation. If the author is affiliated to more than one (1) institution, a comma should be used to separate the number for the said affiliation.

Do provide preferred abbreviated author names for indexing purpose, e.g.L Rampal (for Lekhraj Rampal), BS Liew (for Liew Boon Seng), B Abdullah (for Baharudin Abdullah), Hoe VC (for Victor Hoe Chee Wai).

Please indicate the corresponding author and provide the affiliation, full postal address and email.

Summary:
The abstract should provide a background to the case, summarise its key points, highlight its novelty, learning outcome and implication for clinical practice. It should not be longer than 250 words.

Keywords:
Keywords allows appropriate indexing of the published article to aid future searching. Three to five keywords related to the case report should be provided.

Introduction:
The introduction provides a background and overview of the problem that will be highlighted in the case report. It also aims to summarise the relevant literature pertaining to the topic. It ends with an introduction to the patient/clinical condition that will be discussed in the following section.

Case presentation:
This section provides details of the case. The following is a suggested order of the case presentation.

- Case history – demographic details and medical history
- Physical examination results
- Results of relevant tests or investigations
- Treatment plan
- Outcome of the treatment plan

Discussion:
This section expands on the background written in the introduction. It will focus on the importance of the case and its novelty. Relevant literature should be cited to put this case in the context of the wider published papers.

Conclusion:
The case report ends with a summary of the key points and how it adds to our understanding of specific disease or condition.

Acknowledgements:
This section acknowledges the contribution of others who assisted in the production of the case report manuscript but do not fulfil authorship criteria.

Declarations:
A statement confirming ethical approval and patient (or carer/guardian) consent for publication must be provided. Any funding information should be provided here. Any competing interests by the authors with the manuscript must be declared in this section.

Abbreviations:
If abbreviations are used in the manuscript, they should be defined in the text at first use in the abstract and main text sections, unless they are standard unit of measurements. No abbreviations should be used in the title in the Title Page. Abbreviations should be kept to a minimum.

Formatting of text:
Numbers one to ten in the text are written out in words unless they are used as a unit of measurement, except in figures and tables. Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph. Do not use the automated formatting of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Submit the manuscript in plain text only and removed all 'field codes' before submission.

Do not include line numbers. Include only page numbers.

References:
MJM Case Reports, follows the Vancouver numbered referencing style. Citations to someone else's work in the text, should be indicated by the use of a number. In citing more than one article in the same sentence, you will need to include the citation number for each article. A hyphen should be used to link numbers which are inclusive, and a comma used where numbers are not consecutive. The following is an example where works 1,3,4,and 5 have been cited in the same place in the text.

- Several effective drugs are available at fairly low cost for treating patients with hypertension and reducing the risk of its sequelae.[1,3-5]

The list of all of the references that are cited in the article should be presented in a list labelled as 'References'. This reference list appears at the end of the paper. Authors are responsible for the accuracy of cited references and these should be verified by the author(s) against the original documents before the manuscript is submitted. It is important that the author should never place in the list of references a document that he or she has not seen. The journals' names should be abbreviated according to the style used in the Index Medicus. All authors when six or less should be listed; when seven or more list only the first six and add et al.

If you are citing the author's name in your text, you must insert the citation number as well.

- Jewell BL [8] underlined that as focus in the SARS-CoV-2 pandemic shifts to the emergence of new variants of concern (VOC), characterising the differences between new variants and non-VOC lineages will become increasingly important for surveillance and maintaining the effectiveness of both public health and vaccination programme.

If you are citing more than one author's name in your text and you want to cite author names in your text, use 'et al.' after the first author.

- Example: Rampal et al. [9] highlighted that the. disregard of the manuscript guidelines and instruction to authors of the journal you submit, is one of the common reasons for 'Rejection' of the article.

Example of references:
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

Tables:
All tables and figures should have a concise title explaining its content and should not occupy more than one printed page. They should be numbered consecutively with Arabic numerals (e.g. Table 1)., and placed after the sections of the manuscript which they reflect, particularly the results which they describe on separate pages. Cite tables in the text in consecutive order. Indicate table footnotes with lower-case letters in superscript font. Place the information for the footnote beneath the body of the table.

Photographs:
Clinical Photographs should conceal the subject's identity. Images should be submitted as separate JPEG files (minimum resolution of 300 dpi). Proof of permission and/or consent from the patient or legal guardian must be submitted with the manuscript. A statement on this must be included as a footnote to the relevant photograph.

Colour reproduction:
Illustrations and diagrams are normally reproduced in black and white only. Colour reproductions can be included if so required and upon request by the authors. However, a nominal charge must be paid by the authors for this additional service; the charges to be determined as and when on a per article basis.

Editorial policy
The journal follows ICMJE and COPE guidelines with regards to concerning its editorial policies on publication ethics, scientific misconduct, consent and peer review criteria. Authors are encouraged to follow the CARE guidelines (for CAse REports).

CONTENTS Page

Case Reports

- A transient bradycardic presyncope in a man with dengue fever: an unusual manifestation of dengue myocarditis 157
  Lee Yee Lim, Meriel Nicole Pu Sze Wong, Thee Ken Goh, Avan Sian Song Tong, Kuan Yee Lim
- The role of motivational interviewing in addressing depression and poor motivation in an individual with traumatic brain injury: a case report 160
  Natasha Subhas, Azizul Awaluddin, Nathisha Thrichelvam, Jagmohni Kaur Sidhu
- Severe presentation of Plasmodium vivax malaria in Melaka, Malaysia 164
  Shazelin Alipitchay, Nor Zaila binti Zaidan, Norain Mansor, Adibah Ibrahim
- Clinical presentation and outcome of progressive multifocal leukoencephalopathy in a person living with HIV - review of three cases in North-Western Malaysia 168
  Lim Zi Xiong, Jerome Gan Jheng Rhong, Saw Li Sean
- Sterotactic surgery for multiple brain lesions: a paradigm shift 172
  Hardip Singh Gendeh, Ramesh Kumar, Fuad Ismail, Marfuah Nik Eexamuddeen, Shahizon Azura Mohamed Mukari, Siti Khadijah Hamsan
- Interesting presentation of Systemic lupus erythematosus in a postpartum lady 175
  Teo Kye Vonn, Ng Kwang How, Lim Chun Liang
- A Cluster of In-patient Scabies in 5 Unrelated Immunosuppressed Females: A Coincidence or Not? 180
  Ingrid Ting Pao Lin, Teo Hock Gin, Teo Yan, Kiing Jiu Wen, Tang Min Moon
- Rare Cause of Failed Intubation: Lingual Tonsillar Hypertrophy: Case Report 186
  Abdul Majid Ghazal, Surrej Darshain Singh Sran, Ti Phing Phang,Nurul Izzah Azmi
- A markedly high pancreatic cyst fluid of carcinoembryonic antigen and amylase in a postnatal woman 189
  Wan Norlina Wan Azman, Wan Mohd Saifuhisam Wan Zain, Zulkarnain Mustapha, Wan Faiziah Wan Abdul Rahman, Ikhwan Sani Mohamad
- A parturient with COVID-19 pneumonia, complicated with posterior reversible encephalopathy syndrome in puerperium 193
  Tan Kok Tong, Leong Chee Loon, Shanthi Viswanathan, Norzaini Rose Mohd Zain, Muniswaran Ganeshan
- A rare ocular manifestation of Chikungunya – retinal vasculitis and cystoid macular oedema: a case report 197
  Ying Jie Liow, Ee Ling Ang, Kamalden Tengku Ain
- Percutaneous drainage of a bleeding pancreatic duplication cyst: a case report 200
  Zaim HO, Nabillah MJ, Nor Hafizah AH
- A case of lupus hepatitis 204
  Mohamed Amin Bin Kader, Yun Fei Liang, Zulaikha Binti Che
- A case report of Plummer–Vinson Syndrome in a young adult with poor eating habits 207
  Siti Nur Hakimah Hashim, Woo Wing Hang, Kok Wei Hao, Lee Chong Chearn, Khairul Najmi Muhammad Nawawi
- Extended surgery with en block resection of the right external iliac vessels for lymph node metastasis of colon carcinoma, a case report 210
  Ehab Said, Kishen Raj Chandra Sakaran, Putera Mas Pian, Sellymiah Adzman

CONTENTS Page

- Feasibility and outcome of sequential scoliosis surgeries in twins with adolescent idiopathic scoliosis (AIS): a report of two pairs of twins 215
  Yee Wern Evonne Tan, Chun Hong Ngan, Saturveithan Chandirasegaran, Weng Hong Chung, Chee Kidd Chiu, Chris Yin Wei Chan, Mun Keong Kwan
- Endobronchial hamartoma: an unusual cause of focal bronchiectasis 218
  Ing Shan Kai, Lee Yih Hoong, Kelly Wong Kee Yung, Teresa Chua Fuh Guang, Chao Khai Fatt, Kho Sze Shyang
- Case series of seizure control post exicison of cavernoma 221
  Yugaraj Thangavelu, KS Kung, YY Neoh, M Syahiran, M Premananda, M Azhari
- Monoarticular gouty arthropathy of the acromioclavicular joint: a rare manifestation 224
  Chong Jung Syn, Lim Zhuang Li, Emad Faris Adnan, Fatin 'Amira Mohamed Anwar
- Caecal bascule: a rare cause of intestinal obstruction 228
  Boon Khang Soh, Guo Hou Loo, Syed Abdul Wahhab Eusoffee Wan Ali, Sze Li Siow
- Application of mesenchymal stem cells in a multi-modal approach in the treatment of stroke 232
  Danaraj Navaratnam, Danaraj Navaratnam, Danaraj Navaratnam, Angelina Tiah
- A severe case of systemic lupus erythematosus-associated diffuse alveolar haemorrhage post-COVID-19 infection 236
  Whei Chuern Yeoh, Ai Lee Lim
- Non-diabetic hypoglycaemia secondary to non-islet cell tumour. A diagnosis that cannot be missed!: a case report 240
  Najihah Abd Razak, Mohammad Che Man, Shahidah Che Alhadi
- A Case of pleural solitary fibrous tumour with paraneoplastic hypoglycaemia - Doege-Potter syndrome 243
  Chong Kong Yong, Benedict Dharmaraj, Diong Nguk Chai, Narasimman Sathiamurthy, Noraini Mohd Dusa
- Delayed diagnosis of an advanced abdominal pregnancy with optimal maternal and neonatal utcome: a case report 247
  Dharshini Nadaraja, Buvanes Chelliah, Aruku Naidu, Marvinash Rao
- COVID-19 and Phlegmasia cerulea dolens: a case report and review of the literature 251
  Yap Wai Leong, Norfarahin Hasim, Mimi Azliha Abu Bakar, Mohd Hashairi Fauzi, Tuan Hairulnizam Tuan Kamauzaman, Kamarul Aryffin Baharuddin
- Hoarseness of voice: a case report on three different underlying causes 257
  Leelavathi Muthupalaniappen, Magaletchumi Chelladorai
- When the unusual strikes: an uncommon occurrence of pyogenic liver abscess induced by *Parvimonas micra* 260
  Priyadarsini Appalaramoo, Anim Md Shah
- Variation of hearing function in children with Apert Syndrome: A case report of three patients 263
  Semiramis Zizlavsky, Indira Sari, Fikry Hamdan Yasin, Ghaisani Fadiana, Mohamad Yanuar Amal, Ayu Astria Sriyana
- The Great Masquerader: A successful pulmonary vein isolation with cryoablation for paroxysmal atrial fibrillation manifesting with recurrent syncopal episodes 267
  Mohd Ridzuan Mohd Said, Murshidah Ainun Mukhtar, Mohd Al-Baqlish Mohd Firdaus, Kantha Rao Narasamuloo, Saravanan Krishinan

Acknowledgement 271

A transient bradycardic presyncope in a man with dengue fever: an unusual manifestation of dengue myocarditis

Lee Yee Lim, MRCP[1], Meriel Nicole Pu Sze Wong, MBBS[2], Thee Ken Goh, MD[2], Avan Sian Song Tong, MD[1], Kuan Yee Lim, Dr Int Med[3]

[1]Department of Internal Medicine, Queen Elizabeth Hospital II, Kota Kinabalu, Sabah, [2]Department of Internal Medicine, Queen Elizabeth Hospital, Kota Kinabalu, Sabah, [3]Department of Medicine, Hospital Canselor Tuanku Muhriz, Jalan Yaacob Latif, Bandar Tun Razak, Kuala Lumpur

SUMMARY

Myocarditis is an inflammatory condition of the myocardium leading to various degrees of myocardial dysfunction. It has a wide range of clinical manifestations, from subtle asymptomatic tachyarrhythmia or bradyarrhythmia to life-threatening heart failure with cardiogenic shock. The aetiologies of myocarditis include infections, connective tissue or autoimmune disorders, and idiopathic, of which viral infections such as dengue fever and influenza are the leading causes of myocarditis. Due to the lack of specific clinical manifestations of myocarditis, high clinical suspicion with the aid of laboratory investigations such as cardiac enzymes and imaging with echocardiogram are crucial to ensure a timely diagnosis and appropriate management. Nevertheless, the management of myocarditis is usually supportive. We report a case of dengue fever complicated with viral myocarditis and cardiogenic shock, which recovered well with supportive management.

INTRODUCTION

Dengue fever is a vector-borne acute viral infection, spread primarily by the *Aedes aegypti* and *A. albopictus* mosquitoes. The global incidence of dengue infections is rising, affecting mainly the tropical and subtropical regions, including countries like Malaysia. The geographical variation of dengue incidence can be explained by the meteorological factors such as high rainfall and temperature and low wind speed to encourage the growth of vectors in tropical and subtropical regions.[1] Thus, the main approach to reducing the incidence of dengue infections is to reduce the population and growth of vectors.

Dengue fever has a broad spectrum of clinical manifestations, ranging from a mild febrile illness to severe dengue shock syndrome with failure of multiple organs. Mild dengue fever can be treated as an outpatient with supportive management. However, severe dengue infections require close monitoring in the intensive care unit (ICU) and have high mortality rates. Organs affected in severe dengue infections include kidneys, liver and heart. Dengue myocarditis is not uncommon and similarly has a wide spectrum of clinical manifestations, ranging from a subtle asymptomatic cardiac arrhythmia to life-threatening heart failure with cardiogenic shock.[2]

CASE PRESENTATION

A 20-year-old man presented with a day of fever and lethargy associated with four episodes of vomiting and two episodes of loose stools. The vomitus contained food particles and clear fluids without blood or bilious content, and the stools were brownish without blood or mucus. Otherwise, he had no abdominal pain and no history of travelling and sick contact. He had no known medical illness and no previous hospitalisation.

He was orientated with full Glasgow Coma Scale upon presentation. His physical examination revealed a febrile man in systemic shock with a body temperature, blood pressure and heart rate of 38.9°C, 89/40 mmHg and 119 beats per minute, respectively. His systemic examinations were otherwise unremarkable with good peripheral perfusion. His initial blood investigations confirmed the diagnosis of a severe dengue fever with a positive dengue virus non-structural protein 1, haemoconcentration with an elevated haematocrit of 50.2% and acute kidney injury with a serum creatinine level of 129 µmol/L, and estimated glomerular filtration rate of 70.2 ml/min/1.73m^2. Other laboratory investigations particularly the venous blood gas, serum lactate, white cells and platelets counts and liver function test were normal.

He was given intravenous fluid resuscitation with boluses of normal saline at a rate of 20 ml/kg/h up to a cumulative 5 L fluid; however, he remained hypotensive and required vasopressor with intravenous infusion of noradrenaline at a rate of 0.1 µg/kg/minute to maintain a blood pressure of 142/80 mmHg. However, he developed acute pulmonary oedema after the resuscitation, with a respiratory rate of 38 breaths per minute and an oxygen saturation of 64% under room air. His physical examination revealed end-inspiratory fine crackles at bilateral lower zones of lungs, with pulmonary oedema and upper lobe diversion in his chest radiograph (Figure 1). He was immediately given intravenous frusemide of 40 mg and oxygen supplementation with a non-rebreathing mask and was admitted to ICU.

He was given supportive management and non-invasive ventilatory support with continuous positive airway pressure in the ICU. His clinical conditions improved after a day in the ICU with a stable haemodynamic and oxygenation without vasopressor and ventilatory support, and he became afebrile.

This article was accepted: 20 August 2023
Corresponding Author: Kuan Yee Lim
Email: limkuanyee@gmail.com

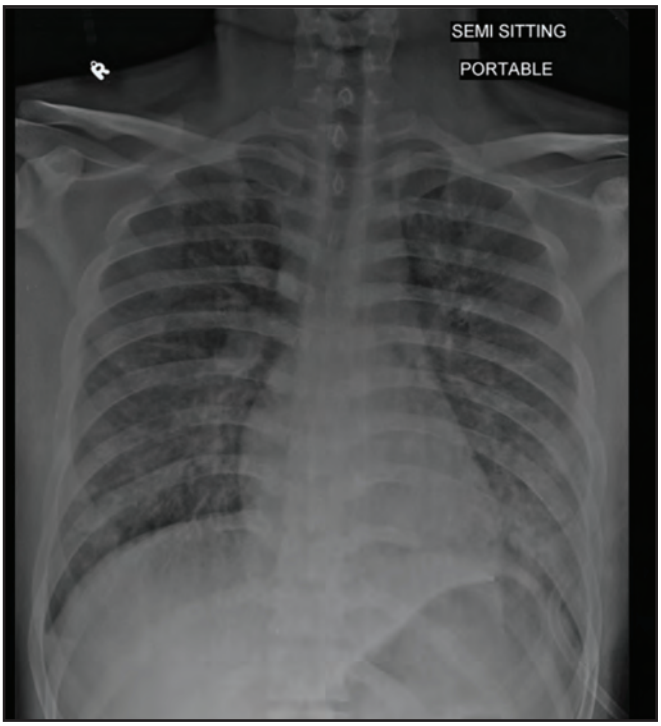

Fig. 1: Chest radiograph showed pulmonary oedema and upper lobe diversion.

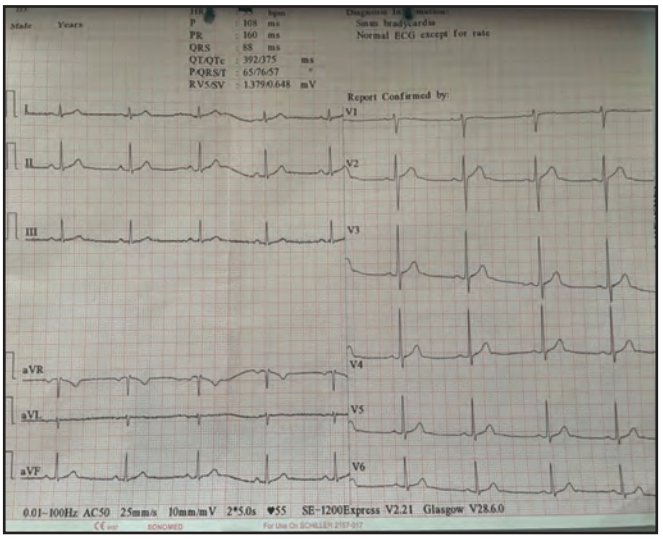

Fig. 2: Electrocardiogram showed sinus bradycardia.

However, he developed a transient episode of presyncope with dizziness and diaphoresis the following day, which coincided with hypotension and bradycardia with a blood pressure of 67/47 mmHg and a heart rate of 50 beats per minute. The incident happened when he was lying on the bed, with a sudden onset of dizziness and diaphoresis, which lasted for 10 minutes. His blood pressure and heart rate prior to the event were 140/80 mmHg and 88 beats per minute, respectively. His electrocardiogram during the event showed sinus bradycardia (Figure 2). His repeated blood investigations revealed raised cardiac enzymes with troponin I of 86 ng/ml, aspartate transaminase of 55 U/L, and lactate dehydrogenase of 523 U/L. An echocardiogram after the event showed a mild left ventricular systolic dysfunction with an ejection fraction of 45%, hypokinesia at basal to mid-inferoseptal of left ventricle, and a dilated right ventricle. He was discharged well after a seven-day hospital stay with a normal follow-up echocardiogram after a month.

DISCUSSION

The clinical manifestations of myocarditis are non-specific with great heterogeneity, thus requiring individualised diagnostic approach and management. Recent onset heart failure, cardiac arrhythmias, and chest pain are three main patterns of presentation of myocarditis, which may represent any structural heart and coronary artery diseases. The findings of most investigations, such as cardiac enzymes, electrocardiogram, and echocardiography, are not specific to differentiate myocarditis from other heart diseases. A cardiac magnetic resonance imaging offers a good accuracy in diagnosing myocarditis while endomyocardial biopsy with histopathologic analysis is the only way to confirm a diagnosis of myocarditis. Nevertheless, endomyocardial biopsy is an invasive procedure, thus only recommended to be done in severe cases with severe left ventricular dysfunction and life-threatening arrhythmias.[3] Therefore, any unexplainable haemodynamic changes should raise the suspicion of myocarditis.

The exact pathophysiology of myocardial injury in dengue fever is not fully understood yet, and it is postulated to be a result of direct dengue virus invasion or cytokine-mediated immunological response.[2] Cardiac involvement in dengue fever is usually underdiagnosed as any haemodynamic instabilities such as hypotension, tachycardia, and pulmonary oedema are commonly presumed to be attributed to dehydration and capillary leakage in dengue fever.[4] Our current case demonstrated a misdiagnosed dengue myocarditis during presentation with cardiogenic shock unresponsive to fluid resuscitation, only able to raise the suspicion of myocarditis after a transient bradycardic presyncope. Early recognition of myocardial involvement in this case could have prevented overzealous fluid resuscitation, leading to pulmonary oedema.

Bradyarrhythmia, mainly sinus bradycardia, is the most common cardiac conduction abnormality seen in dengue infections. It is usually benign and self-limiting, as demonstrated in our case. Other cardiac conduction disturbances that might require intervention with anti-arrhythmic medications and cardiac pacing include various degrees of atrioventricular block, supraventricular and ventricular tachyarrhythmias, and non-specific electrocardiographic changes. The mainstay therapeutic approach in a suspected or confirmed case of myocarditis is supportive management to ensure haemodynamic stability and optimal fluid status.[2-4] Steroidal therapy has no strong evidence in myocarditis and is only recommended in severe cases for certain types of myocarditis confirmed by endomyocardial biopsy.[3]

CONCLUSION

Myocarditis has no specific clinical manifestation. The diagnosis of myocarditis greatly depends on the clinical acumen of the attending doctor. Although the treatment of myocarditis is mainly supportive, early recognition of myocarditis is crucial to ensure an appropriate fluid regime and vasopressor support to restore the haemodynamic stability and to avoid complications such as pulmonary oedema.

DECLARATION

There is no competing interests by the authors with the manuscript. There is no funding. A written consent was taken from the patient for publication.

REFERENCES

1. Singh S, Herng LC, Sulaiman LH, Wong SF, Jelip J, Mokhtar N, et al. The effects of meteorological factors on dengue cases in Malaysia. Int J Environm Res Public Health 2022; 19(11): 6449.
2. Lee K, Lee WH, Liu JW, Yang KD. Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. Int J Infect Dis 2010; 14(10): e919-22.
3. Sinagra G, Anzini M, Pereira NL, Bussani R, Finocchiaro G, Bartunek J, et al. Myocarditis in clinical practice. InMayo Clinic Proceed. 2016; 91(9): 1256-66.
4. Parchani A, Krishnan VS G, Kumar VS. Electrocardiographic changes in dengue fever: a review of literature. Int J Gen Med. 2021: 5607-14.

CASE REPORT

The role of motivational interviewing in addressing depression and poor motivation in an individual with traumatic brain injury: a case report

Natasha Subhas, MMedPsych[1], Azizul Awaluddin, MMedPsych[1], Nathisha Thrichelvam, MMedPsych[2], Jagmohni Kaur Sidhu, FRACGP[3]

[1]Department of Psychiatry and Mental Health, Hospital Putrajaya, Ministry of Health Malaysia, Jalan 9, Presint 7, Wilayah Persekutuan Putrajaya, Malaysia, [2]Department of Psychiatry and Mental Health, Hospital Selayang, Ministry of Health Malaysia, B1, Batu Caves, Selangor, Malaysia, [3]Department of Family Medicine and Clinical Skills, International Medical University, Jln Jalil Perkasa 19, Bukit Jalil, Kuala Lumpur, Malaysia

SUMMARY

Traumatic brain injury (TBI) is an evolving disease that leads to neurobehavioural disability that causes poor psychosocial outcomes. The commonest sequelae in TBI include major depressive disorder and motivational deficits, especially in rehabilitation engagement and social reintegration. Here, we discuss a 34-year-old man who had TBI and developed depression and poor motivation as sequelae. This case report highlights the use of Motivational interviewing (MI), a person-centered counselling method, to strengthen and enhance his motivation to take his medications and go for the rehabilitation program. Following MI, the patient improved, adhered to medication for depression and decided to go for rehabilitation programme, proving the intervention successful.

INTRODUCTION

In 1848, John Harlow famously described personality changes in Phineas Gage, who survived an iron rod through his skull, damaging the frontal lobe.[1] Following the incident, this premorbid socially well-adapted responsible man became profane, negligent and irresponsible. This altered state of mind was termed 'traumatic insanities' by Adolf Meyer– behavior disturbances from head injuries which included psychosis, mood disturbances, alterations in consciousness and neurological symptoms.[1]

Acquired brain injury (ABI) is a brain injury that occurs after birth and is not related to a degenerative or congenital disease.[2] Traumatic brain injury (TBI) is defined as brain damage from an external mechanical force and is an ABI.[1,2] It is frequently underreported and amongst the top three admissions to the intensive care units.[3] Road traffic accidents affecting males aged 15–24 years make up 80% of the trauma cases in Malaysia.[4] TBI is an evolving disease that leads to neurobehavioural disability (NBD).[3,5] NBD describes neuropsychological disabilities (i.e. executive and attentional dysfunction, lack of insight/awareness, inadequate impulse control) and behavioural or mood disturbances (i.e. labile mood, depressed mood, personality changes) which lead to poor psychosocial outcomes.[5] Major depressive disorder (MDD) is the commonest psychiatric sequelae in TBI.[1] The management of MDD in these cohort of patients involves a multi-pronged approach requiring judicious use of pharmacotherapy, taking into consideration the potential anticholinergic side-effects of certain antidepressants that may further exacerbate cognitive impairment. In addition, psychotherapy, which is another modality of treatment, needs to be tailored accordingly to the cognitive limitations that may arise in these patients. TBI victims also suffer from motivational deficits, which may hinder rehabilitation engagement as well as social reintegration.[5]

This case report highlights the use of motivational interviewing (MI) in a 34-year-old man diagnosed with TBI and MDD who did not adhere to his medications and declined to enter a rehabilitation program. The Consultation Liaison psychiatry team used MI to help him get insight about the benefits of rehabilitation. He showed good improvement a month later.

CASE PRESENTATION

In February 2022, MF, 34-year-old man, with no past medical history was involved in a major motor vehicle accident and developed TBI. He suffered from multiple intracranial haemorrhages over the right occipital and thalamus, right frontal extradural haemorrhage and subarachnoid haemorrhage, pneumothorax and fractures over right T1 and T2 transverse spinal processes, right posterior rib and clavicle and closed fracture of his right fibula. His Glasgow Coma Scale (GCS) was 10/15 (E4 V2 M4) upon initial assessment, and he was intubated for 10 days in view of moderate head injury. He was referred to the rehabilitation physician after extubation and subsequent recovery.

On examination, he had 4/5 power over his bilateral lower limbs. Cognitive tests showed that he scored 5/26 in Montreal Cognitive Assessment (MOCA), and he was Level V (Confused-inappropriate) in the Ranchos Los Amigo Scale. His Patient Health Questionnaire (PHQ-9) test was 13, and he expressed frustration about his condition and guilt that his youngest brother died in the same accident. Although he recovered from his injuries, he was limited in his mobility, and he felt his thinking was slow.

This article was accepted: 17 August 2023
Corresponding Author: Jagmohni Kaur Sidhu
Email: jagmohni_sidhu@imu.edu.my

Table I: Chronology of Events

February 2022	August 2022	28 September 2022	07 December 2022	18 January 2023
MF was involved in a major motor vehicle accident, and developed TBI. His Glasgow Coma Scale (GCS) was 10/15 (E4 V2 M4) upon initial assessment and he was intubated for 10 days in view of moderate head injury. He suffered from multiple intracranial hemorrhages as well as multiple fractures. He was referred to the rehabilitation physician after extubation and subsequent recovery. Cognitive tests showed : 5/26 in Montreal Cognitive Assessment (MOCA) : Level V (Confused-inappropriate) in the Ranchos Los Amigo Scale : Patient Health Questionnaire (PHQ-9) test was 13/27	There was an improvement in his MOCA scores to 17/30 PHQ-9 scores had increased to 16/27, indicative of worsening depressive symptoms. MF with diagnosed with Major Depressive Disorder secondary to TBI. He was commenced on an antidepressant (Tablet Sertraline 50 mg at night)	MF felt demotivated, hopeless and worthless with negative self-esteem. He was switched to tablet mirtazapine 15 mg ON due to acute dyskinesia over his right hand. He was in the precontemplation stage of change and due to poor motivation, low mood and anhedonia, he refused to enter a rehabilitation program. He was assessed using motivational interviewing using open-ended questions focusing on his ambivalence.	Affirmations and reflective questioning were used to validate and support MF focusing on his strengths and efforts. He subsequently began to consider he options of rehabilitation, moving him from the pre-contemplative stage of change to contemplative stage.	MF moved from contemplation to action stage. He had a well-defined goal and was keen to enroll in the return to work (RTW) programme. His PHQ-9 scores had shown a reduction to 3/27 as well.

Table II: Motivational Interviewing Strategies utilised with MF

MI strategies	Example - verbatim excerpts of session quotes	Reason for questioning
Using Open-ended questions in order to explore his motivations and goals while eliciting statements that develop discrepancies.	'Would it be ok with you if we discuss about your issues now' 'I understand you have some concerns about illness and your medications, could you tell me about them' 'MF, I can see this is difficult for you, I would like to understand why do you not want to go to the rehabilitation program'	With this type of questioning, we are encouraging the patient to do most of the talking. The psychiatrist/family medicine practitioner will also learn more about why MF feels demotivated, his values and goals, and also what he cares about. There is active listening and empathy.
Using Affirmations in the form of compliments, appreciation and understanding to enhance rapport and highlight the positive changes.	'MF, thank you for telling me what is troubling you. I appreciate that you were open to me about feeling sad and demotivated.' "MF, I know it wasn't easy for you to tell me that you were not taking your medications. If you remember, in our last appointment, your mood improved a lot while being on medication. You were very good being compliant to your medications at that time. Why don't we retry taking the medications again and see what is the outcome?'	Affirmations support and validate MF's journey to change. The psychiatrist has a better rapport through this strategy. By highlighting his previous compliance to medications, MF's strengths and efforts are highlighted and affirmed.
Utilising Reflections by rephrasing statements used to foster motivation and build trust.	'MF, I know that telling me all this is difficult. Being diagnosed with TBI must be hard for you. On top of that, you are grieving on the loss of your brother. It is easy to stay in the house, not take your medications and stay in your room from morning to night. However, if you realize, you are feeling very demotivated and sad. You are still young and capable, there is still hope for you and everyone (family members and doctors) are trying to help you get on your feet.'	The psychiatrist rephrases MF's statement in order to capture its implicit meaning and emotion. Reflection is a way to tell the patient that the psychiatrist is listening to him and is helping him understand what are his motivations. It can be used to reinforce desire to improve and get better.
Summarising in an empathetic way in order to point out discrepancies between his current situation and future goals.	'MF, so far you mentioned to me that you have been feeling down and helpless about your situation. Am I correctly understanding the situation you are facing?' 'From what I understand, your Rehab physician says you have good potential and is willing to accommodate to all your requests, which will lead to a better future. You do not have to depend on your relatives. What are you worries about starting the program? Maybe after this discussion you can go home and think about entering the program?' 'You are still feeling sad and demotivated. Why don't you start retaking Mirtazapine since your mood improved the last time?' 'Why don't we discuss the pros and cons of not taking the medications' 'Give yourself sometime to think about our conversation. Its ok not to be 100% sure about this'	Through this strategy, the psychiatrist helps the patient to see the positives in doing the rehabilitation program and taking his medications. MF shows his ambivalence about the program and medication instead of reluctance, which is an acceptable state of mind that empowers change. This helps him realize that he has a better future if he joins the program.

His subsequent appointment in August 2022, noted an improvement in his MOCA scores to 17/30. However his PHQ-9 scores had increased to 16/27, indicative of worsening depressive symptoms. The Consultation-Liaison psychiatrist diagnosed MF with Major Depressive Disorder secondary to TBI. He predominantly suffered from low mood, anhedonia, hopelessness, worthlessness, sleep disturbances and guilt regarding his brother's death. He felt useless because he was having memory gaps. He became more withdrawn and kept to himself. The Rehabilitation physician started him on an antidepressant (tablet sertraline 50 mg at night); however, due to acute dyskinesia over his right hand, his medication was switched to tablet Mirtazapine 15 mg at night. He experienced mild improvements in his mood and his sleep.

In the next review, he was not adherent to his medications for one month. MF felt demotivated, hopeless and worthless, with negative self-esteem. He was in the precontemplation stage of change due to poor motivation, low mood and anhedonia. He refused to enter a rehabilitation program. Table I depicts an overview of MF's case.

MI, a person-centered counselling method, was used to strengthen and enhance MF's motivation to take his medications and go for the rehabilitation program.6 The administration of MI using the transtheoretical model (Prochaska & DiClemente, 1982) is used as a framework in order to evoke his motivations, strengths and resources and leverage those for change by seeing and developing change talk. This was done to facilitate collaborative care as well as realistic goal-setting in order to reach the desired outcome of rehabilitation and gainful employment. MF demonstrated a reluctance to participate and engage in rehabilitation exercises initially, and MI was utilised to enhance MF's intrinsic motivation to change by working on his ambivalence and increasing self-efficacy. The sessions were conducted by a Consultation-Liaison fellow, with a Masters in Psychiatry and were conducted during hour-long sessions, over three visits. The MI strategies are described in Table II.

At the end of the interview, MF went from precontemplation to contemplation stage, wherein he initially was unwilling to engage with the rehabilitation team and did not seem to recognise there was a problem with that. In the contemplative stage, upon evoking change talk, he became more confident and was willing to change, and during his next review with the Rehabilitation team a month later, MF was in the action stage. He had a clear goal setting. He was keen to undergo the return to work (RTW) program and had applied back to the Rehabilitation Center. He was compliant with his antidepressant, and his PHQ-9 scores showed a reduction from 16/27 to 3/27, indicative of an improvement in his depressive symptoms. Prochaska and DiClemente's transtheoretical model of change using MI was used as the framework to move MF through the stages.[6] He was initially in a pre-contemplative stage, which was predominantly defined by a lack of engagement as well as motivation and proceeded through the stages of contemplating the options and strategies needed to get to his end goal of rehabilitation and subsequently taking the action of enrolling in a RTW programme. Although these motivations were intrinsic and subjective, the changes were observable in his actions by the treating team.

DISCUSSION

Neurobehavioural disabilities in TBI patients are thought to be due to low levels of neurotransmitters, neural circuits damage and diffuse axonal injuries involving the prefrontal cortex, hippocampus, amygdala, thalamus and basal ganglia.[1,5] When it comes to motivation, each neurotransmitter plays a role. Dopamine helps in reward-based decision-making processes, norepinephrine helps in generating adequate levels of motivation and serotonin deals with rewards and punishment.[5]

The aim of rehabilitation in TBI is to improve their disability and cognitive function, reintegrate into society, and have a fairly good quality of life without much dependence on caregivers or family.[2] MF's injuries involved the right frontal and occipital area. The frontal lobes have the highest concentration of adrenergic and serotonergic fibers, therefore, Mirtazapine, an antidepressant with norepinephrine and serotonergic properties, was used as a mode of treatment.[7]

MI was used to enhance his confidence and engage his commitment to neurorehabilitation for a meaningful life post-injury.[8] It is important to target the early stages of recovery as patients with TBI tend to show a lack of engagement in neurorehabilitation activities.[9] In order to engage with the patient, a non-confrontation, collaborative and self-efficacious intervention would prove beneficial.[9] During MI, reflective listening and acceptance are used to resolve patient's ambivalence about change.[9] By enhancing MF's confidence and determination, he believes that change is possible and is therefore willing to go forward. One month after the MI, MF showed noticeable improvements and was working towards his goals of engaging in the return to work (RTW) programme with the aim of securing sustained employment.

MI techniques have been shown to promote an increased sense of self-awareness and engagement in rehabilitation following acquired brain injury and a conceptual framework to guide rehabilitation goals has been discussed in literature.[9] This case demonstrates the clinical improvement noted in MF and to note the improvement in his goals as he moves through the stages of change utilising the principles of motivation interviewing.'

MI proved beneficial because of several factors. This was a collaborative effort between the psychiatrist and the patient. By using the strategies, motivation for change was enhanced by drawing on his own aspirations, goals and values. The psychiatrist affirmed the patient's autonomy, encouraging him to think about the benefits of taking the medications and going into the program.

CONCLUSION

In conclusion, the common sequelae for patients with TBI is depression, which can lead to poor insight, worthlessness and hopelessness. These patients suffer from psychological and cognitive issues, which has the potential to impair their motivation as well as decision-making abilities. MI, a non-confrontation, collaboration and self-efficacious intervention, may be useful in helping the patient participate in rehabilitation activities.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health, Malaysia, for his permission to publish this article. The authors are grateful and thankful to the patient for giving us permission to publish this article.

CONSENT

Written informed consent was obtained from the patient for publication of this case report.

COMPETING Interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Schwarzbold M, Diaz A, Martins ET, Rufino A, Amante LN, Thais ME, et al. Psychiatric disorders and traumatic brain injury. Neuropsychiatr Dis Treat. 2008; 4(4): 797-816.
2. Yeh TC, Chien WC, Chung CH, Liang CS, Chang HA, Kao YC, et al. Psychiatric disorders after traumatic brain injury: a nationwide population-based cohort study and the effects of rehabilitation therapies. Arch Phys Med Rehabil. 2020; 101(5): 822-31.
3. Arulsamy A, Shaikh MF. Current status of traumatic brain injury research in Malaysia: a systematic review. Neurosci Res Notes. 2020; 3(4): 1-21. Available from: https://neuroscirn.org/ojs/index.php/nrnotes/article/view/52
4. Jamaluddin SF, Wahab MA, Mohamed FL, Saiboon IM. National trauma database January to December 2007–second report. Ministry of Health Malaysia. 2009. [Retrieved from http://www.acrm.org.my/ntrd/report/20091001_NTrDReportfinal.pdf]
5. Palmisano S, Fasotti L, Bertens D. Neurobehavioral initiation and motivation problems after acquired brain injury. Front Neurol. 2020; 11: 23.
6. Hall K, Gibbie T, Lubman DI. Motivational interviewing techniques - facilitating behaviour change in the general practice setting. Aust Fam Physician. 2012; 41(9): 660-7.
7. Talsky A, Pacione LR, Shaw T, Wasserman L, Lenny A, Verma A, Hurwitz G, Waxman R, Morgan A, Bhalerao S. Pharmacological interventions for traumatic brain injury. BC Med J. 2011; 53(1): 26-31.
8. Holloway M. Motivational interviewing and acquired brain injury. Social Care Neurodisabil. 2012; 3(3): 122-30.
9. Medley AR, Powell T. Motivational interviewing to promote self-awareness and engagement in rehabilitation following acquired brain injury: a conceptual review. Neuropsychol rehabil. 2010; 20(4): 481-508.

CASE REPORT

Severe presentation of Plasmodium vivax malaria in Melaka, Malaysia

Shazelin Alipitchay, MPH[1], Nor Zaila binti Zaidan, M.Med[2], Norain Mansor, DrPH[1], Adibah Ibrahim, DrPH[3]

[1]Vector Borne Disease Control Unit, Malacca State Health Department, Melaka, [2]Medical Department, Malacca Hospital, Melaka, [3]Disease Control Unit, Malacca Tengah Health District Office, Melaka

SUMMARY

A 26-year-old immigrant woman presented with fever, chills, rigor and headache. The blood smears showed *Plasmodium vivax (P. vivax)* malaria. Patient had persistent abdominal pain with sudden drop in haemoglobin level despite achieving clearance of parasitaemia after started on anti-malarial agents. Further radiological investigation revealed that she developed splenic infarcts. Even though *P. vivax* malaria is known to be the non-aggressive type of human malaria, severe infection and complications can still occur. Appropriate imaging modality in correlation with clinical sign and symptoms is crucial to detect splenic infarct that might turn into a fatal splenic rupture.

INTRODUCTION

Plasmodium vivax (P. vivax) has been recognised as the aetiology for severe malaria manifestations.[1,2] Vivax malaria can present in severe form despite low level of peripheral blood parasitaemia.

Melaka, a state in Malaysia, has had zero records of indigenous human malaria for the past 10 years. A total of 24 cases of malaria were reported from 2012 to 2021. Out of which 67% of the cases were human malaria. All human malaria cases were imported, with the most common being *P. vivax*. A total of 17% of the cases were severe malaria, all attributable to *Plasmodium Falciparum (P. falciparum)*.[3] This study described a patient with presentation of severe vivax malaria during an admission to the hospital in 2022.

CASE PRESENTATION

A 26-year-old Indonesian woman has been residing in Melaka, Malaysia since 2018 with a working permit in an electrical equipment manufacturing company. She lived in a hostel near an industrial area in Melaka. The hostel was 5 km away from her workplace where she worked as a production operator in the company. She had a history of traveling back to her hometown at Desa Nagur, Medan, Indonesia for almost a month after the re-opening of the international borders post-COVID-19 pandemic in June 2022. In Indonesia, she stayed only with her family and visited the nearest family member and friends within her hometown. At the end of June 2022, she made her way back to Malaysia and she continued her daily routine which is working in the factory every day from 7 am to 6 pm, Monday through Friday.

Five days after her return, she had a fever with chills and rigor with occasional headaches. On day 2 of illness, she was brought by her employer to a private clinic complaining of headache and vomiting, subsequently diagnosed as 'viral fever' and treated symptomatically. On day 4 of illness, she was brought to another private clinic for persistent symptoms of fever and vomiting, where she was advised to seek further treatment at a secondary centre which was unfortunately ignored.

Two days later, on day 6 of illness, she presented to our institution with fever, vomiting five times a day and abdominal discomfort. The initial diagnosis given at the emergency department (ED) was dengue fever with compensated shock, and she was directly admitted to intensive care unit (ICU) for further treatment. Significant history regarding one of her family members in Medan being diagnosed with malaria was obtained once she was in ICU.

On examination at ED, she was alert and conscious but was extremely lethargic. She was also hypotensive with systolic blood pressure (BP) of 80 mmHg and diastolic BP of 40 mmHg, tachycardic with a pulse rate of 130 beats per minute (bpm) and febrile with a temperature of 38°C. Her pulse oximetry oxygen level was 97%. Auscultation of the lungs was clear with equal air entry. Cardiac heart sounds were normal. Abdomen was tender and there was guarding over left hypochondriac region. No organomegaly was elicited. She had no rash or lymphadenopathy.

She was admitted to ICU and managed as severe dengue with decompensated shock. Without inotropic support, her BP was borderline (94/58 mmHg), she was tachycardic (106 bpm) and saturating at 97% on 3 L/m oxygen via nasal prong. Blood investigations were as shown in Table I. Her diagnosis was revised to severe malaria upon receiving the positive result of her blood film for malaria parasite (BFMP). BFMP was sent earlier given the history of her recent visit to Medan in Indonesia. She was immediately started on intravenous (IV) artesunate 150 mg, then at 12 hours and 24 hours followed by 150 mg daily. Oral doxycycline 100 mg twice daily was also prescribed in combination with the IV artesunate, and she was planned for oral primaquine 30 mg once daily for 14 days for the eradication of liver hypnozoites.

However, the next day she continued to complain of severe abdominal pain. At this point, doxycycline was withheld as it was aggravating her vomiting and primaquine was started. Despite worsening abdominal symptoms, the serial blood smears showed that the sexual parasites had cleared by day 3 of IV artesunate therapy.

This article was accepted: 02 September 2023
Corresponding Author: Norain Mansor
Email: norainmansor88@gmail.com

Table I: Summary of laboratory findings during admission

Laboratory parameters	Day of illness										
	Day 6	Day 7	Day 8	Day 9	Day 10	Day 10	Day 11	Day 14	Day 15	Day 16	Day 18
Hb	10.7	10.8	10.0	9.9	10.0	10.3	9.5	8.7	9.6	9.8	10.2
TWC	7.1	6.3	5.0	6.4	5.5	6.0	6.9	14.2	15.6	12.8	9.0
Platelet	23	49	27	75	58	136	207	533	689	575	539
Urea	2.9	2.1	1.8	3.0	2.8						4.9
Sodium	132	137	138	130	137						137
Potassium	3.4	3.1	3.7	4.2	4.3						4.3
Creatinine	68	44	41	59	44						58
TP	70	53	57	58	63			81			84
TSB	35.1	22.3	13.8	17.2	10.6			23.5			13.8
Albumin	39	27	28	29	31			40			42
Globulin	31	26	29	29	32			40			42
ALT	85	59	65	54	56			45			27
ALP	107	79	75	68	73			97			111
AST	66	46	45	45	53			39			23
CK	47	30	25								
LDH	369	310	283					694		652	508
CRP	85	-	200.8	102.1							
Amylase	28	28									
Ca/Ca Corr		1.67	1.9/2.14	1.87	2.01/2.19						
PO4		0.54	0.77	0.43	1.03						
Mg		0.57	0.97	0.57	0.79						
PH	7.49										
HCO3	25.9										
PCO2	28										
Lactate	1.8										
Base excess	2.8										
RTK Dengue	Negative NS1, IgM, IgG										
BFMP		P. vivax:8040/520 parasite/uL blood	P. vivax:7680/400 parasite/uL blood	P. vivax:80/0 parasite/uL blood	P. vivax:80/0 parasite/uL blood	0 parasite/uL blood	0 parasite/uL blood	0 parasite/uL blood	0 parasite/uL blood		

Hb: Haemoglobin; TWC: Total white cell count; TP: Total protein; TSB: Total rerum bilirubin; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate transferase;CK: Creatinine kinase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; Ca/Ca corr: Calcium/calcium corrected; PO4: Phosphate; Mg: Magnesium; HCO3: Bicarbonate; PCO2:Partial pressure of carbon dioxide; BFMP: Blood film for malaria parasite

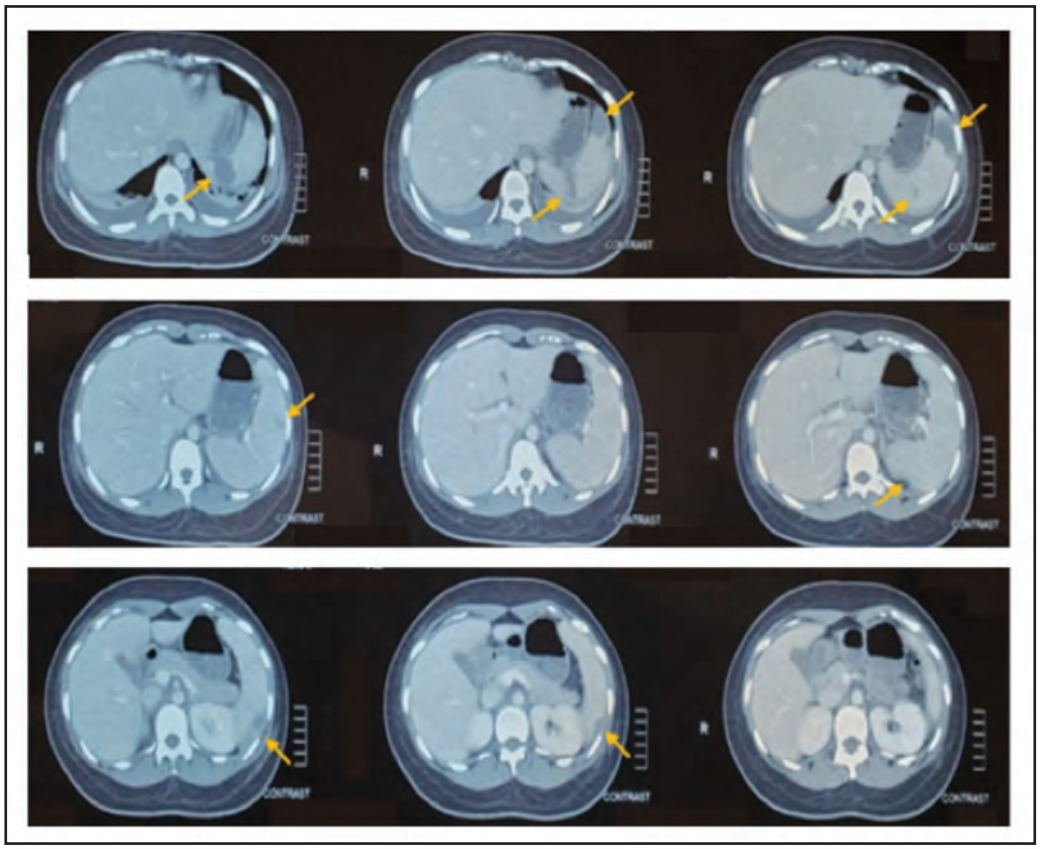

Fig. 1: CT Abdomen and pelvis showing multiple wedge-shaped non-enhancing hypodense lesions in the spleen with the largest lesion in the upper pole measuring 2.2 cm × 4.0 cm × 2.9 cm, representing splenic infarct (yellow arrows pointing to the infarcts within the spleen).

In view of increasing abdominal pain, an urgent ultrasound (USG) abdomen was carried out which showed free fluid in the pelvis. On the next day, the pain intensified. It was localised at the left hypochondriac region with radiation to the tips of the scapula and aggravated by breathing. Thus, an urgent CT of the abdomen was done revealing multiple splenic infarcts with the largest lesion in the upper pole measuring 2.2 cm × 4.0 cm × 2.9 cm (Figure 1).

She was managed with analgesic and close monitoring. She required one-pint packed cell transfusion due to symptomatic anaemia when her haemoglobin (Hb) dropped from 10.3 g/dl to 8.7 g/dl. Her haemoglobin level was stable subsequently. Over the next few days, she responded well to the treatment, and her symptoms resolved. IV artesunate was switched to tablet Riamet. On day 18 of illness, after three consecutive negative smears, she was then discharged with oral primaquine to complete the 14 days eradication therapy course as outpatient.

The patient has completed her treatment with artesunate and primaquine. She was scheduled for monthly BFMP for one year. Repeated BFMP done during follow-up and was negative for 6 months consecutively. She complied with the follow-up schedule and did not complain of any adverse event or reoccurrence of symptoms.

DISCUSSION

This case is classified as an imported human malaria case. *P. vivax* and *P. falciparum* represent the two most frequent forms of human malaria. In terms of severity, *P. falciparum* has received more attention than *P. vivax*. It is a well-known phenomenon that *P. falciparum* causes cytoadherence to endothelial receptors mediated by the surface proteins, thus facilitating the sequestration of parasitised red blood cells in the microvasculature.[4] However, it is increasingly appreciated that *P. vivax* is also capable to cause severe manifestations of malaria as well as mortality.

In this case, a young patient presented with prostration and shock during admission. Based on WHO, these two findings are part of manifestation of severe malaria.[5] A systematic review on clinical impact on vivax malaria revealed that young children and pregnant mothers are particularly vulnerable to severe form of vivax malaria infection. The review mentioned that the common manifestation of severe vivax malaria reported were cerebral malaria, respiratory distress, acute renal injury and severe anaemia. Severe anaemia was associated with patients with recurrent parasitaemia.[1] Another review revealed that thrombocytopenia was the most commonly reported severity sign, followed by circulatory collapse or shock and severe anaemia. While the least prevalent severity sign was respiratory dysfunction.[6] Findings on splenic infarct and splenic rupture were not mentioned and investigated in both reviews.

A clinical study of vivax malaria in South Korea on splenic infarction revealed that 12 out of 92 vivax malaria patients presented with splenic infarction. Six had localised pain in the upper left abdomen whereas the remaining six patients did not present with abdominal pain at the time of investigation. Splenic rupture was noted in one of the patients. All patients recovered spontaneously after treatment and observation without any surgery or intervention. Univariate analysis showed that anaemia and prolonged fever were risk factors for splenic infarction.[7]

In our patient, there was a history of 7 days of fever with persistent complain of localised abdominal pain. Interestingly from the Korean study, six of the 12 patients had no abdominal pain (asymptomatic). The diagnosis of splenic infarction may be difficult without imaging because it can be asymptomatic. The study also did not describe the size of the focal infarct. Size of the focal infarct lesion may be relevant to the symptom of the localized pain. Additionally, the accessibility of CT scan in South Korea under a well-established national health insurance system is a helpful tool to detect infarction and monitoring of patients.

Therefore, the complaint of left upper quadrant abdominal pain before or during the antimalarial treatment should trigger a possibility of splenic hematoma or splenic infarct and need to be managed accordingly to prevent further complications which may require surgical intervention. Such patients should be monitored to look for the persistence of abdominal pain or even deterioration of clinical signs.

Splenic infarct is a rare presentation of malaria which can occur despite appropriate antimalarial treatment with no known predictive signs and may lead to haemorrhagic shock from subcapsular hematoma that ruptures into the peritoneal cavity.[8] Splenic rupture is a fatal complication. However, the association between splenic infarction and rupture remains unclear. Infarcts can occur in both falciparum and vivax malaria, however, a systematic review by Hwang et al noted its prominence in vivax malaria.

The pathophysiology of splenic response is still unknown. Literature indicates a few possibilities. The first is hypercoagulopathy due to decrease levels of antithrombin III, protein C, protein S as well as increase levels of von Willebrand factor and plasminogen activator inhibitor.[9,10] Another possibility is vascular congestion and occlusion due to cytoadhesion of infected red blood cells with splenic cellular hyperplasia and hypoxemia due to anaemia.[8]

Accessibility to imaging is a helpful diagnostic tool in detecting infarction by showing hypodense multifocal areas within the spleen. Diagnosis of splenic infarct can be made via USG or CT, though CT has emerged as the preferred imaging modality. The use of imaging, a non-invasive in vivo human study, alongside clinical observations can provide a full dynamic view of the role of the spleen in normal and pathological conditions caused by malaria.

CONCLUSION

Occurrence of imported malaria cases in Malaysia is a continuing threat. *Plasmodium vivax* malaria infection can cause severe manifestation despite low level of parasitaemia. Clinical awareness on this possibility should be raised. Occurrence of splenic infarct and splenic rupture need to be managed accordingly to prevent fatality which align with the global vision of zero malaria deaths.

A prevalence study of severe vivax malaria in Malaysia describing details on clinical features and complications with occurrence of splenic infarct and splenic rupture is appropriate to understand this less known malaria infection compared to malaria falciparum.

ACKNOWLEDGEMENT

The authors also would like to thank the Director General of Health Malaysia for his permission to publish this article.

DECLARATION

The authors declared no conflict of interest.

INFORMED CONSENT

Written informed consent was obtained from the patient for publication of this case report.

REFERENCES

1. Kotepui M, Kotepui KU, Milanez GD, Masangkay FR. Prevalence and risk factors related to poor outcome of patients with severe Plasmodium vivax infection: a systematic review, meta-analysis, and analysis of case reports. BMC Infectious Diseases 2020; 20(1): 1-4.
2. Naing C, Whittaker MA, Nyunt Wai V, Mak JW. Is Plasmodium vivax malaria a severe malaria: a systematic review and meta-analysis. PLoS Negl Trop Dis 2014; 8(8): e3071.
3. Melaka State Health Department. Annual Malaria Report 2012-2022. Melaka State Health Department, 2022.
4. Ochola LB, Siddondo BR, Ocholla H, Nkya S, Kimani EN, Williams TN, Makale JO, Liljander A, Urban BC, Bull PC, Szestak T. Specific receptor usage in Plasmodium falciparum cytoadherence is associated with disease outcome. PloS one. 2011; 6(3): e14741.
5. World Health Organization: a practical handbook - management of severe malaria. 2012. Geneva: World Health Organization, 3.
6. Phyo AP. Clinical impact of vivax malaria: a collection review. PLOS Medicine 2022; 18. doi.org/10.1371/journal.pmed.1003890
7. Im JH, Chung MH. Splenic infarction in Plasmodium vivax infection in South Korea. Am J Trop Med Hyg 2019; 101(4): 803–5. doi:10.4269/ajtmh.19-0101
8. Hwang JH, Lee CS. Malaria-induced splenic infarction. Am J Trop Med Hyg 2014; 91(6): 1094.
9. Deroost, K, Pham, TT, Opdenakker, G Van den Steen, PE. The immunological balance between host and parasite in malaria. FEMS Microbiol Rev 40(2); 208-57.
10. Madkhali M et al. Elevated levels of procoagulant microvesicles and tissue-factor bearing microvesicles in malaria patients. Int J Gen Med 2023; 16: 1205–15.

CASE REPORT

Clinical presentation and outcome of progressive multifocal leukoencephalopathy in a person living with HIV - review of three cases in North-Western Malaysia

Lim Zi Xiong, MRCP, Jerome Gan Jheng Rhong, MRCP, Saw Li Sean, MRCP

Department of Medicine, Hospital Pulau Pinang, Malaysia

SUMMARY

We reviewed the clinical presentations and outcomes of three cases of progressive multifocal leukoencephalopathy (PML) in a person living with HIV in our setting and compare with general literature review. The clinical presentations can vary among individuals but most invariably will have certain neurological symptoms. The diagnosis of PML in all the three patients are done through clinical and radiological approach. The outcomes are generally poor. The mainstay of PML in HIV patients is to start antiretroviral therapy (ART), despite the poor outcome of PML in the patients. The purpose of The highly active antiretroviral therapy (HAART) is to prevent any other opportunistic infections from occurring in HIV patients. Background and objectives: To review and compare the clinical presentations and outcomes of Progressive Multifocal Leukoencephalopathy (PML) in a Person living with HIV (PLHIV) at Penang General Hospital (PGH), Pulau Pinang.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a form of demyelinating disease of the central nervous system (CNS), caused by infection of human polyomavirus 2 (JC virus).. It occurs almost exclusively in immunosuppressed individuals. There has been a dramatic evolution in how PML is diagnosed over the years with clinical, laboratory, radiological and tissue biopsy procedures. Its incidence has reduced dramatically with the invention of ART; however, the outcomes remain poor. The purpose of this study is to review the clinical presentations and outcomes of PML patients in Penang General Hospital, which has longed serves as a reference hospital in the northern part of Malaysia. In these case studies, we are using clinical and radiological method to explain the clinical finding and the outcomes of PML in three different HIV patients.

CASE PRESENTATION

Case 1

A 45-year-old Indian man, presented with weight loss and neurological symptoms (unsteady gait, slurring of speech and weakness over the left arms) in July 2022 for 6 months. He was initially treated as hemiplegic stroke. Bur due to extreme weight loss, he was tested for HIV test. He was diagnosed with HIV during admission (CD4: 18 cells/mm^3, VL: 131417 copies/ml during presentation). After discharge, he had been semi dependent with residual weakness in the left side of his body. Initial plan was to start him on HAART in July 2022; however, it was delayed as patient admitted again for COVID pneumonia in August 2022 and septic shock with pneumonia in September 2022. In October 2022, he was admitted again due to worsening lethargy and inability to ambulate for 2 weeks. During admission in October 2022, he had spastic tetraplegia with bilateral CN VII nerve palsy. He is now wheelchair bound and ADL dependent.

Case 2

A 63-year-old Chinese man with hypertension, presented with fever, weight loss, loss of appetite and respiratory symptoms (breathlessness, reduced effort tolerance) in September 2021. He underwent CECT TAP and it showed an infected lung nodule. HIV test was positive (CD 4: 36 cells/mm^3, VL 798982 copies/ml), lumbar puncture was performed as he developed high intracranial pressure. His CSF C & S and blood C & S showed cryptococcal neoformans. He was given intensive antifungal flucytosine and fluconazole. As he had persistent diarrhoea, a colonoscopy was done, and it showed extensive ileocolonic ulcers. The biopsy results showed cytomegalovirus colitis. He was subsequently treated with IV ganciclovir for 2 weeks. After discharge, he immediately started on ART. He had multiple admissions from September 2021 till September 2022 for frequent chest infections and anaemia. He had a few episodes of fittings in between September and October 2022. He was diagnosed with PML after CT and MRI brain. Despite started on HAART, he never improved from PML. He is now bed bound and ADL dependent.

Case 3

A 54-year-old Chinese woman, presented with fever, headache and neurological symptoms in February 2018. Her initial neurological symptoms include altered behaviour, unilateral body weakness and facial asymmetry. Her HIV test turned out positive (CD 4: 158.3 cells/mm^3, VL: 181 copies/ml). With her significant clinical symptoms, she was initially treated as meningitis and cerebral toxoplasmosis. The meningitis and cerebral toxoplasmosis treatment were stopped as there were no signs of clinical improvement despite a week of antibiotics. Her CSF investigations were all negative (culture/HSV/CMV/TB). She was diagnosed with PML after an MRI was done. She was initiated on ART therapy subsequently. She remains bed bound to date and ADL dependent despite given ART.

This article was accepted: 02 September 2023
Corresponding Author: Ingrid Ting Pao Lin
Email: ingrid_tpl15@hotmail.com

Table I:

Characteristic	Case 1	Case 2	Case 3
Age	46	63	54
Underlying comorbidities	No known medical illness	Hypertension	No known medical illness
cART	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON	Tenofovir + Emtricitabine 1 tab ON Efavirenz 600 mg ON
CD4 count	18 cells/mm³ (on 15/07/22)	36 cells/ mm³ (on 03/10/21)	158 cells/ mm³ (26/2/18)
Clinical manifestation			
- Headache	No	No	Yes
- Fever	No	No	Yes
- Neck stiffness	No	No	No
- Impaired consciousness	No	Yes	Yes
- Focal neurological deficit	Yes	Yes	Yes
Serum toxoplasmosis	IgM/IgG non-reactive	IgM/IgG non-reactiv	IgM NR/IgG Reactive
CSF parameters			
- Opening pressure	-	-	-
- Cell count	Nil	Nil	Nil
- Glucose	3.7 mmol/L	2.6 mmol/L	2.92mmol/L
- Protein	0.67 g/L	0.38 g/L	0.49g/L
- Culture & Sensitivity	No Growth	No Growth	No Growth
- India Ink	Negative	Negative	Negative
Neuroimaging	Multiple T2W/FLAIR hyperintensities in bilateral subcortical and deep white matter at bilateral frontal, bilateral parietal lobe, bilateral external capsule, bilateral internal capsule, bilateral putamen, bilateral globus pallidus and midbrain	T2W/FLAIR high signal intensity in both cerebellar hemisphere (right > left), right side of midbrain, pons and left cerebellum	Low T1 and high T2 and FLAIR signal lesions in the white matter of the right temporal lobe and left medial temporal lobe and lateral dorsal aspect of the right midbrain. No focal enhancing lesion or meningeal enhancement
Outcome, GOS	3	3	3

Table II:

Antiviral therapy **1. JCV cell entry inhibitor**		**Immune response modulator** **1. Cytokines**		**Immunisation** **1. Passive immunisation**	
Chlorpromazine Citalopram	Block serotonin receptors	IFN α	Stimulate innate, adaptive immune response	Recombinant anti JCV VP 1 monoclonal antibodies	To neutralise JCV
IL- 2 Mirtazapine	Stimulate T cell lymphocyte growth		JCV specific cytotoxic T lymphocytes	Lysis, clearance of JCV JCV infected cells	
IL- 7 Risperidone	Stimulate lymphoid lineage development				
1. DNA replication inhibitors		**1. Inflammation inhibitors**		**1. Active immunisation**	
Cidofovir	Inhibit viral DNA polymerase	Maraviroc	Blocks CCR 5 mediated tissue inflammation	IL 7 + JCV VP 1 vaccine	JCV capsid protein with recombinant IL 7 to boost JCV T cell response
Cytarabine Ganciclovir Leflunomide	Inhibit DNA, RNA polymerase, nucleotide reductase	Inhibit viral DNA polymerase Inhibit mitochondrial enzyme	Glucocorticoid	General immune system suppression	

The above Table I compares the background history, clinical presentation, and radiological findings of our three PML patients. The outcome of all the three patients is poor with a disability requires daily care. Glasgow Outcome Scale (GOS) is an objective description or scale to measure the outcome of patient with brain injury.

DISCUSSION

PML is a demyelinating disease of the CNS, particularly the white matter. It is caused by reactivation of JC virus.[1] JC virus exposure is usually asymptomatic and occurs in childhood or adolescence. The JC virus only infects humans, where it resides in latent form in various tissues, including the brain.[2] A JC virus spreads through interpersonal contact or by fomites in the environment to the oropharynx, where it replicates and produces variants.[3] Nearly 85% of the cases of PML associated with HIV infection have CD4 counts below 200 cells/mm^3. It can occur at the initial presentation of HIV or during immune recovery following ART initiation. JC virus incidence has been reported to be low in India and Africa (possibly due to diagnostic limitations and differences between isolates). The most common symptoms of PML are motor weakness (hemiparesis/hemiplegia), impaired vision (homonymous hemianopia) and changes in mental status (personality changes, memory loss, emotional lability, and dementia).[4] Rarer forms can present with movement disorders instead of focal neurological deficits. The diagnosis of PML can be done, either based on a brain biopsy or by clinical and imaging features. Brain biopsy is the most accurate method to diagnose PML, however it is invasive and comes with complications of post biopsy haemorrhage.[5] There is a chance of a false negative result if the sample obtained are necrotic brain tissues.[6] The histopathology of PML tissue biopsy usually exhibits triad of demyelination, enlarged oligodendrocyte nuclei and bizarre astrocytes.[7] PML can also be diagnosed through clinical and radiological findings combined with JCV DNA virus via PCR (from CSF). JVV PCR is one of the sensitive tests that can be utilised. It is highly specific (92-99%) and sensitive (74-93%).[8] PCR results may be falsely negative if the viral counts are low in the CSF.[9] We have able to diagnose the patients in these three cases through the approach of clinical manifestation and radiological presentation. We have limited capabilities to be able to run JCV DNA PCR in our setting due to high cost of the test. MRI brain with multisequence protocol allows us to differentiate PML by a distinctive demyelination pattern (hyperintense on T2 weighted MRI and hypointense on T1 weighted MRIs). There is a direct correlation between PML and HIV.[10] HAART is currently the mainstay of PML treatment and has been shown to reduce PML mortality in HIV patients.[11] The prognosis depends on the initial CD4 count and compliance to HAART.[12] HAART can improve PML outcomes in person living with HIV (PLHIV), but it can also unmask inflammatory PML during immune reconstitution (IRIS), which is associated with worsen clinical and radiological outcomes. The exact mechanism of IRIS is not fully understood, and more research is needed to improve the treatment of IRIS in these high-risk patients. The common treatment of IRIS involves a usage of high dose of corticosteroids that can help in suppress the exaggerated immune mechanism after the introduction of HAART. These PML IRIS patients generally have poor outcomes despite being treated with ART and high dose corticosteroid.[13] There are a few studies focus on finding the effective anti JCV treatment and PML prophylaxis. To date, there are no absolute and definite treatment to PML. These treatments are made up of antiviral agent, immune response modulator and immunisation. The antiviral agent is designed to prevent the JCV entry and to prevent further DNA replication. Immune modulators function to restore the protective defence mechanism and to inhibit exaggerated response in PML-IRIS. Immunisation strategies is a form of passive immunisation meant to introduce the monoclonal antibodies generated from human donors. The treatments are not widely recognised as there is a limitation of study size. The treatments are also very dose dependent as it needs higher doses to reach the blood–brain barrier.

The above Table II further explains the different agents and mechanisms that are studied before but not widely used due to limitation of sample populations.

CONCLUSION

The outcome of the above three cases is poor, in keeping with most literature reviews regarding the outcome of person living with HIV (PLHIV) with progressive multifocal leukoencephalopathy (PML). All of them were bed bound and ADL independent (with GOS 3) despite started on antiretroviral therapy (ART). It is possibly and likely due to the late presentation and late diagnosis of illness. It is always challenging when come to diagnose brain infection in a HIV patient especially PML infection. There are other CNS opportunistic infections that healthcare providers need to think of before concluding for what possible brain infection a patient might have. These case studies are to raise awareness among healthcare providers regarding the clinical presentation, outcome and treatment options in a HIV patient living with PML. ART remains the upmost important treatment in the light of PML and HIV infection. As PML infection ends with a poor outcome, many research and studies are done and performed widely to find the cure for PML. In the hope of near future, many useful and definite therapy will surface to help those HIV living with PML patient especially with these antiviral agent, immunomodulator and passive immunisation.

REFERENCES

1. Berger, JR, Aksamit, AJ, Clifford, DB, Davis, L, Koralnik, IJ, Sejvar, JJ et al. PML diagnostic criteria. Neurol 80(15): 1430-8.
2. Paz, SP, Branco, L, Pereira, MA, Spessotto, C, Fragoso, YD. Systematic review of the published data on the worldwide prevalence of John Cunningham virus in patients with multiple sclerosis and neuromyelitis optica. Epidemiol Health 2018; 40: e2018001.
3. Cortese, I, Reich, DS, Nath, A. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease. Nat Rev Neurol 2020; 17(1): 37-51.
4. Berger, JR. The clinical features of PML. Cleve Clin J Med 2011; 78(11 suppl 2): S8-S12.
5. Schuette, AJ, Taub, JS, Hadjipanayis, CG, Olson, JJ. Open biopsy in patients with acute progressive neurologic decline and absence of mass lesion. Neurol 2010; 75(5): 419-24.
6. Wang, M, Zhang, Z, Shi, J, Liu, H, Zhang, B, Yan, J. Progressive multifocal leukoencephalopathy in an HIV patient was diagnosed by 3 times lumbar punctures and 2 times brain biopsies. J NeuroVirol 2020; 26(6): 952-6.

7. Chalkley, JJ, Berger, JR. Progressive Multifocal Leukoencephalopathy in multiple sclerosis. Curr Neurol Neurosci Rep 2013; 13(12).
8. Lee, S, Ko, H, Kim, S, Lee, Y, Son, B. Progressive multifocal leukoencephalopathy diagnosed by brain biopsy, not by the DNA test for JC virus. Asian J Neurosurg 2019; 14(1): 240-44.
9. Landry, ML, Eid, T, Bannykh, S, Major, E. False negative PCR despite high levels of JC virus DNA in spinal fluid: Implications for diagnostic testing. J Clin Virol 2008; 43(2): 247-49.
10. Pavlovic, D, Patera, AC, Nyberg, F, Gerber, M, Liu, M. Progressive multifocal leukoencephalopathy: Current treatment options and future perspectives. Ther. Adv. Neurol. Disord 2015; 8(6); 255-73.
11. Cinque, P, Koralnik, IJ, Gerevini, S, Miro, JM, Price, RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. Lancet Infect Dis 2009; 9(10): 625-36.
12. Khanna, N, Elzi, L, Mueller, N, Garzoni, C, Cavassini, M, Fux, C et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV cohort study. Clin Infec Dis 2009; 48(10): 1459-66.
13. Eskut, N, Inci, I, Ozdemir, H, Gedizlioglu, M, Tosun, S. This time in a reverse order: Seizure, progressive multifocal leukoencephalopathy, and then AIDS was diagnosed. Neurol India 2021; 69(3): 768.

CASE REPORT

Sterotactic surgery for multiple brain lesions: a paradigm shift

Hardip Singh Gendeh[1,2], Ramesh Kumar, FRCS[3,4], Fuad Ismail, FRC[5], Marfuah Nik Eexamuddeen, MCO[5], Shahizon Azura Mohamed Mukari, MMed Rad[6], Siti Khadijah Hamsan, MMed Physics[4]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala, Lumpur, Malaysia, [2]Allergic Unit, Hospital Canselor Tuanku Muhriz, Bandar Tun Razak, Kuala, Lumpur, Malaysia, [3]Neurosurgical Unit, Department of Surgery, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala, Lumpur, Malaysia [4]Gamma Knife Centre, UKM Specialist Centre, Kuala, Lumpur, Malaysia, [5]Department of Oncology, Hospital Canselor Tuanku Muhriz, Bandar Tun Razak, Kuala, Lumpur, Malaysia, [6]Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala, Lumpur, Malaysia

SUMMARY

Brain metastasis are common and may be multiple. This often results in a dilemma in treatment. Prior to this, the understanding of the role of stereotactic radiosurgery such as Gamma Knife is limited to three or less brain metastasis. A paradigm shift has occurred in Malaysia whereby stereotactic radiosurgery is now being used for the treatment of multiple brain tumours exceeding ten lesions. A seventy-year-old gentleman with small cell lung carcinoma and more than thirty brain metastases underwent Gamma Knife treatment for his brain lesions post chemotherapy. There was resolution of cerebral lesions with small residual at the left cerebellum. He had no adverse side effects. Therefore, stereotactic radiosurgery is now being used for multiple brain metastatic lesions as it provides improved palliation, less neurocognitive deterioration with improved quality of life. This discovery places whole brain radiotherapy for the treatment of metastatic brain lesions as a treatment of the past.

INTRODUCTION

Brain metastasis is common for lung, breast and gastrointestinal tumors. Up to 40% of patients with cancer will experience brain metastasis.[1] This becomes a dilemma as metastatic lesions are often multiple, surgically inaccessible, decrease length of survival and ultimately results in poorer prognosis. The cerebrum is most commonly affected (85%) followed by cerebellum (10-15%) and brainstem (up to 3 %). Gamma Knife (GK) was first used to treat a recurrent solitary brain metastasis of a cerebral hypernephroma in 1989.[1]

The initial understanding of the role of stereotactic radiotherapy such as Gamma Knife (GK) is to provide a concentrated and targeted stereotactic beam to a small single lesion within the brain which is inaccessible by surgery, or if surgery will cause more morbidity to the patient. However, this poses a dilemma for patients with multiple brain lesions or metastasis whereby the primary site has been dealt with. Prior to this many have thrown in the towel after chemotherapy or when other modalities of systemic therapy have failed, leaving the patient on the palliative pathway. GK stereotactic radiosurgery has been prescribed in 3-4 small brain metastasis. What about multiple brain metastasis exceeding four lesions? Therefore, the aims of this manuscript are to discuss the feasibility of GK radiosurgery for multiple brain metastasis of 10 or more lesions; its advantages and disadvantages and to debunk the current myth of GK in treating a sole metastatic brain disease.

CASE PRESENTATION

A seventy-year-old chronic smoker was diagnosed with metastatic small cell lung carcinoma. At presentation, he had extensive disease involving the lung, mediastinal lymphadenopathy, liver and brain metastases. Prior to his illness, he had no medical illness. He spent majority of his life in United Kingdom where he studied and worked as an analyst. He lived alone and led an independent but active life. He developed imbalance three months prior with worsening gait one week prior to his presentation. Besides, he had expressive dysphasia which was progressive over a three month period.

Magnetic Resonance Imaging (MRI) showed multiple brain metastasis of more than 30 lesions (Figure 1) with a total brain volume of 9.261cm^3. He was given options of whole brain RT or GK, but opted for GK stereotactic radiosurgery (Elekta AB, Stockholm) treatment in October 2020. The lesions were treated with a range of 22-30Gy at 50% isodose, single fraction over three days. The brain metastasis protocol via a double contrast MRI was adopted. He was observed overnight in hospital.

Two weeks after GK, he commenced on etoposide/platinum chemotherapy. He had remarkable response clinically and radiologically each cycle. On clinical re-assessment at two weeks post GK, his imbalance and expressive dysphasia had resolved whereby he resumed a normal gait and could express himself well. CT reassessment after 4 cycles of chemotherapy on December 2020 revealed reduction in the thoracic lesions, mediastinal and supraclavicular adenopathy. Unfortunately, there were new liver metastases. He declined second line chemotherapy treatment.

He developed twitching of the facial muscles some three months later in January 2021. There was however no other new neurological deficit. The MRI of the brain at twelve

This article was accepted: 12 September 2023
Corresponding Author: Assoc Prof Dr Ramesh Kumar
Email: rameshkumar71@hotmail.com

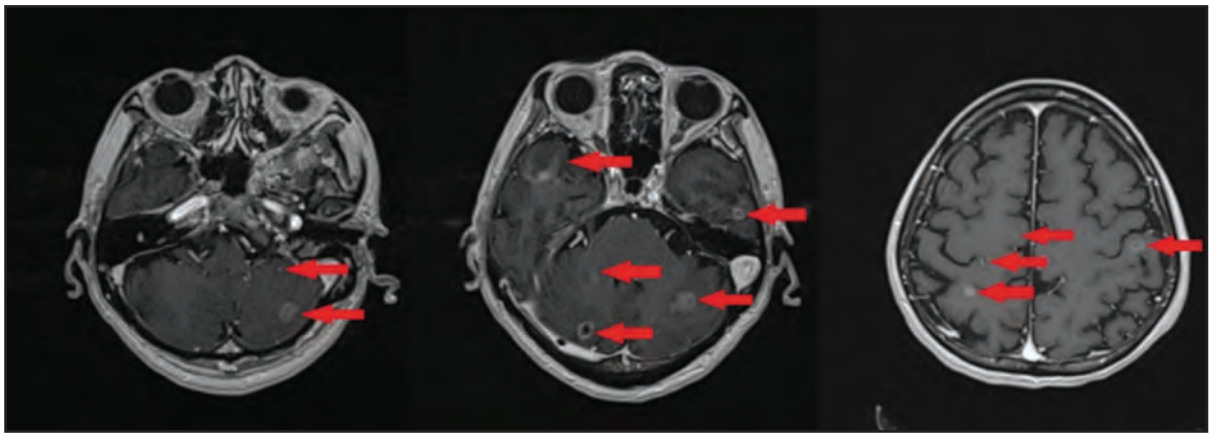

Fig. 1: Axial cuts of MRI showing multiple brain metastasis (red arrows)

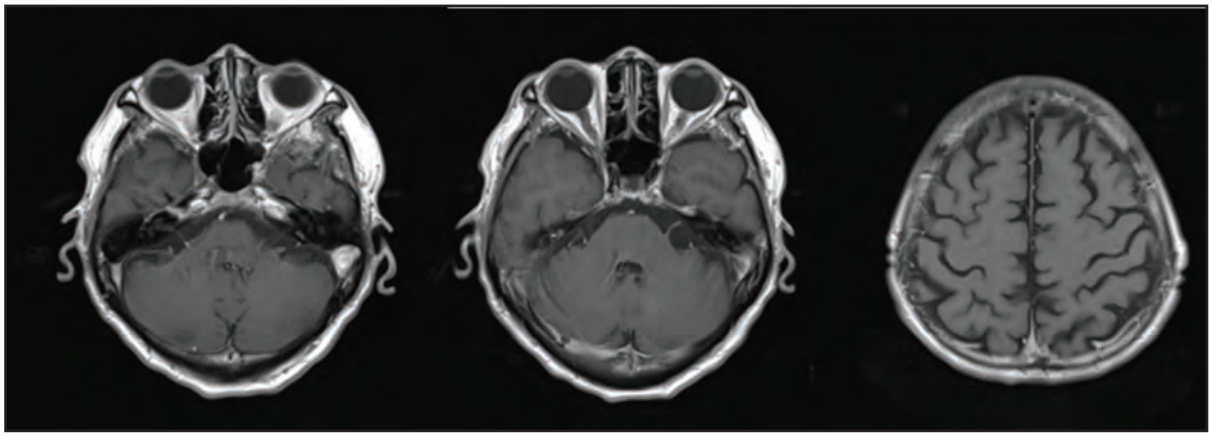

Fig. 2: Previous lesions in Figure 1 were no longer visible post tretment with GK.

weeks post treatment in January 2021 showed resolution of supratentorial grey white matter lesions with minimal residual lesions in the left cerebellum (Figure 2).

He deteriorated from his liver secondary and passed away in April 2021. Despite the disease progression, he managed to maintain his independence and cognition which were his priorities upon deciding treatment

DISCUSSION

This case presents a patient with metastatic small cell lung cancer with multiple lesions to the brain. Although the treatment of multiple brain lesions treated with GK was experimented since the early millennium, this was the first use of GK for the treatment of multiple brain lesions at the Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia since the recent launch of its GK center. As technology improves, many have experimented with pushing the boundaries, resulting in a paradigm shift with greater role for stereotactic radiosurgery. Known assumptions of GK are single fraction radiation for multiple tumors is inadequate for optimal treatment; brain metastasis is radio resistant; stereotactic radiosurgery is limited to cases with 3 or less brain metastases and brain metastases are to be treated with whole brain radiotherapy (WBRT).

Prior to GK, the treatment of the case above will be WBRT with systemic steroids. Median survival rates with WBRT are 1 -2 months. Some have advocated the use of radio sensitizers to increase the sensitivity and uptake of radiotherapy to the brain. However, results were not promising with little or no benefit to tumor size and survival.[2] Andrews et al. 2004 looked into WBRT with and without stereotactic radiosurgery for patients with three or less brain metastatic lesions. Patients with WBRT and stereotactic radiosurgery showed an improvement of medial survival of 5.5 compared to 4.9 months for the WBRT group alone.[3] GK can be used as a salvage treatment for failure of WBRT.

Chang et al. 2009 performed a randomized control trial comparing only stereotactic radiosurgery and stereotactic radiosurgery with WBRT. The stereotactic radiosurgery group with WBRT had brain lesion recurrence within 1 year (73% vs 27%) post treatment but showed higher risk of significant learning and memory decline by 4 months of treatment.[4] In another study of 1194 patients with 5-10 multiple brain metastasis, stereotactic radiosurgery had shown to be not inferior to stereotactic radiosurgery and WBRT with brain metastasis.[5] A Cochrane review by Tsao et al. 2012 recommended the consideration of stereotactic radiosurgery exclusively for brain metastasis in selected patients. Therefore, previously held believe that WBRT radio resistant brain metastases respond to GK with the number metastasis

being limited to less than 10 is now irrelevant with no difference in overall survival.

Questions have been raised about dosage and toxicity of GK stereotactic radiosurgery due to concerns with cumulative radiation when treating multiple brain lesions. Radiation doses are often calculated based on cumulative tumor volumes. Heterogeneous distribution allows for cumulative doses delivered to the whole brain to be small. This decreases its potential toxicity. Whole brain exposure of 8Gy is acceptable and considered non-toxic.[6] Thus, the total GK radiation over multiple sessions and not number of brain metastasis is key in predicting side effects.

Furthermore, there are considerations for repeating GK stereotactic surgery with an interval when multiple lesions are involved as the radiobiological effect of GK is 2.5x than that of fractionated radiotherapy. A total dose of 30-40Gy is delivered by radiotherapy which is equivalent to 12-16Gy in GK stereotactic surgery.[6] Therefore, this shows that dose homogeneity is not essential whereby GK allows gradients aimed to protect surrounding tissue with a low dose distribution for brain metastasis and the ability of dose sculpturing.

Is there a role of stereotactic radiosurgery in post operated brain metastasis? A phase 3 trial by Mahajan et al 2017 compared 68 patients observed post brain resection of up to three brain metastases measuring 4cm or less with 64 patients receiving stereotactic radiosurgery. The observation group had a 43% 12 months' freedom from local recurrence compared to 72% in the stereotactic radiosurgery group.[7] This was the hallmark study that promoted the use of GK in maintaining local control in post resection of brain metastasis.

A review of 3498 patients by Higuchi et al 2018 showed brain radio-necrosis to be less than 3% with GK stereotactic surgery [8]. Stereotactic radiosurgery provides similar survival rates for patients with more than 10 brain metastatic tumors.[8] In the patient above, although there were residual tumors within the left cerebellum, the use of stereotactic GK allowed for good performance status with minimal or no neurological deficit with the exception of an occasional twitching of the left facial muscle, which is an acceptable side effect. This allowed the patient a better remaining quality of life. Most patients will often succumb to the progression of their primary disease, as so did with our patient above. However, the prognostic factors for overall survival and intracranial disease free with single fraction GK is dependent on the initial number of brain metastasis and adjuvant systemic disease administered.[11]

Brain metastasis exceeding 8 to 10mls in size are often best treated surgically.[9] However, patients with brain metastasis who are unable to undergo general anesthesia may be favorable to multiple fractions of GK stereotactic radiosurgery, involving 2 to 3 stages.[10] The adverse side effects of GK are local oedema which are often transient and due to inaccurate planning and high dosage. This has a bimodal distribution whereby it may occur six to eight or twelve months post treatment. Meanwhile factors associated with less side effects are a total volume of the largest brain metastasis being less than 5mls, brain radiation being between 12 to 30Gy; hypo fractionation and no previous WBRT.[9,12] Boundaries have been extended for solitary single metastatic tumour volumes up to 33.5 have shown to respond favorably with less adverse events. Future work explores the role of systemic chemotherapy and immunotherapy with stereotactic radiosurgery for cases involving distant brain control in metastasis to decrease the re-occurrence of new brain lesions.[9]

CONCLUSION

The current use of GK stereotactic radiosurgery can be used for multiple brain metastasis exceeding ten or more lesions with less side effects compared to WBRT. It may offer palliation with better quality of life in patients with advanced primary disease and multiple brain metastases.

ACKNOWLEDGEMENTS

The authors would like to thank the Gamma Knife unit for their assistance in this manuscript.

DECLARATION

Patient consent was obtained prior. This manuscript has not received any funding. All authors have no competing interest to declare.

REFERENCES

1. Lindquist C. Gamma knife surgery for recurrent solitary metastasis of a cerebral hypernephroma: case report. Neurosurgery. 1989; 25(5): 802-4
2. Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N, Xu W, Sahgal A. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev. 2012; 2012(4): CD003869. Published 2012 Apr 18.
3. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004 22; 363(9422): 1665-72
4. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009; 10(11): 1037-44.
5. Yamamoto M, Serizawa T, Higuchi Y, Sato Y, Kawagishi J, Yamanaka K, Shuto T, Akabane A, Jokura H, Yomo S, Nagano O, Aoyama H. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 Study Update): irradiation-related complications and long-term maintenance of Mini-Mental State Examination scores. Int J Radiat Oncol Biol Phys. 2017; 99(1): 31-40
6. Yamamoto M, Ide M, Nishio SI, Urakawa Y. Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment?. International Journal of Radiation Oncology, Biology,Physics. 2002; 53(5): 1279-83.

7. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, Settle S, Prabhu SS, Lang FF, Levine N, McGovern S, Sulman E, McCutcheon IE, Azeem S, Cahill D, Tatsui C, Heimberger AB, Ferguson S, Ghia A, Demonte F, Raza S, Guha-Thakurta N, Yang J, Sawaya R, Hess KR, Rao G. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017; 18(8): 1040-8.
8. Higuchi Y, Yamamoto M, Serizawa T, Aiyama H, Sato Y, Barfod BE. Modern management for brain metastasis patients using stereotactic radiosurgery: literature review and the authors' gamma knife treatment experiences. Cancer Manag Res. 2018; 5; 10: 1889-99.
9. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. Cancer Treat Rev. 2014; 40(1): 48-59.
10. Aiyama H, Yamamoto M, Kawabe T, Watanabe S, Koiso T, Sato Y, Higuchi Y, Ishikawa E, Yamamoto T, Matsumura A, Kasuya H, Barfod BE. Complications after stereotactic radiosurgery for brain metastases: Incidences, correlating factors, treatments and outcomes. Radiother Oncol. 2018; 129(2): 364-369.
11. Noyama T, Katano A, Shinya Y, Kawashima M, Shin M, Saito N, Yamashita H. Prognostic Factors for Patients With Brain Metastases Treated With Single-fraction Gamma Knife Radiosurgery. Anticancer Res. 2021; 41(6): 3179-3185.
12. Mishra, A., Koffler, D., Calugaru, E. et al. Let's make size not matter: tumor control and toxicity outcomes of hypofractionated Gamma Knife radiosurgery for large brain metastases. J Neurooncol (2023). https://doi.org/10.1007/s11060-023-04365-9

CASE REPORT

Interesting presentation of Systemic lupus erythematosus in a postpartum lady

Teo Kye Vonn, MD[1], Ng Kwang How, MRCP[2], Lim Chun Liang, MRCP[3]

[1]Department of Medicine, Hospital Cyberjaya, Malaysia, [2]Department of Cardiology, Hospital Sultanah Aminah, Malaysia, [3]Department of Medicine, Hospital Segamat, Malaysia

SUMMARY

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease and is commonly affecting women of childbearing age. It can present for the first-time during pregnancy, causing diagnostic and treatment challenges and resulting in poor maternal and foetal outcomes. Cardiac tamponade as the manifestation in SLE is rare. We reported a case of cardiac tamponade as the presentation of SLE in a post-partum patient, where both the patient and the new-born had a good outcome and discussed its management.

INTRODUCTION

SLE is a systemic autoimmune disease that affects multiple organs and hence causing various clinical presentations. Cardiac involvement such as pericardial effusion is well recognized in SLE. However, it is usually small and hemodynamically insignificant.[1] The incidence of cardiac tamponade in SLE is usually less than 1%.[2] The risk factors of cardiac tamponade in SLE are female, presence of anaemia, renal disease, pleuritis, higher ESR or lower C4 levels.[1] Urgent pericardiocentesis, high doses of glucocorticoids and hydroxychloroquine are usually the mainstay of treatment. We presented a rare case of cardiac tamponade as the presentation of SLE in a post-partum patient, and described its predisposing factors, management and its successful outcome.

CASE PRESENTATION

Mrs A, a 27-year-old para 2 female presented to us with heart failure symptoms for one month after delivery. Antenatally, she was under another hospital follow up for persistent proteinuria, which was detected at 36 weeks of gestation. 24 hours urine protein was 1.24g/dL. She was normotensive throughout the pregnancy. However, toward the end of her pregnancy she started to have mild pedal oedema, otherwise no other symptom. Clinically she had no features of connective tissue disease. She delivered a baby boy via normal vaginal delivery in that particular hospital uneventfully. She developed failure symptoms after delivery and it was progressively worsening. Upon arrival she was tachypnoea and tachycardia. Her blood pressure was 98/67 mmHg, heart rate was 138 beat/minute and respiratory rate was 28 breath/minute. Cardiovascular examinations showed jugular venous pressure (JVP) elevated with muffled heart sound. Her condition worsened rapidly and was intubated for impending respiratory distress. Electrocardiography (ECG) revealed sinus tachycardia with decreased voltage (Figure 1). Her chest X-ray showed cardiomegaly. Bedside echocardiogram showed large circumferential pericardial effusion with evidence of cardiac tamponade (Figure 2). Left ventricular (LV) systolic function was severely impaired with the ejection fraction of 25-30%. She was initially diagnosed as cardiac tamponade secondary to acute heart failure with peripartum cardiomyopathy. An urgent pericardiocentesis was performed under echocardiographic guidance after consulted cardiology team of the referral centre. 1.5 litre of yellowish pericardial fluid was drained. Haemodynamic monitoring was immediately improved after pericardiocentesis. She was admitted to intensive care unit for close monitoring and further care.

Laboratory investigations revealed anaemia (Hb 8.1g/dL) with normal white cell and platelet counts. Iron studies confirmed iron deficiency anaemia. Pro BNP was elevated to 792pg. Further investigations were performed to determine the underlying cause. Immunological workup showed a strongly positive antinuclear antibodies (ANA) with the titre of 1:1280, homogenous and speckled pattern, positive anti-double stranded DNA (DsDNA) and low C3 complement. 24 hours urinary protein was 2g/day. Otherwise, troponin I, thyroid function test, sputum tuberculosis tests and renal ultrasound were normal (Table I). With the positive ANA, clinical and immunological findings, she was diagnosed as SLE after rheumatology consultation. She was started with intravenous (IV) methylprednisolone and hydroxychloroquine. Renal biopsy was performed subsequently by nephrology team and the result showed class III lupus nephritis. Cyclophosphamide was added. She was given IV Cyclophosphamide 0.75g/BSA for total of 6 cycles. She responded well to the treatment given. Currently she is on maintenance therapy with oral Azathioprine. Both the mother and the baby were subsequently discharged well. The baby does not have any lupus rash or bradycardia. She was seen in clinic during follow up, clinically she was well. Repeated echocardiography showed an improvement of LV ejection fraction to 48% with minimal pericardial effusion without recurrence (Figure 3).

DISCUSSION

Our patient presented with cardiac tamponade, which is a medical emergency that requires urgent intervention. The clinical features include chest discomfort, dizziness, shortness of breath, tachycardia and tachypnoea. Beck's triad with

This article was accepted: 17 September 2023
Corresponding Author: Teo Kye Vonn
Email: kyvonn91@gmail.com

Table I

INVESTIGATIONS	RESULTS
C3	0.19 g/L (0.9 - 1.8)
C4	0.11 g/L (0.1 - 0.4)
ANA	Positive, 1:1280, homogenous & speckled
ENA	Ro52, Ro60, SSB positive
DsDNA	Positive 517IU/ml
Lupus anticoagulant	Not detected
Anti-cardiolipin antibody	Normal
Anti-beta 2 glycoprotein 1	Normal
Pericardial fluid FEME	Yellowish
pH: 8	
No cell count	
No organism	
Pericardial fluid biochemistry	Glucose: 7.36
Protein: 41.9g/L (serum 69)	
LDH: 219U/L (serum 530)	
Pericardial fluid culture	No growth
Pericardial fluid cytology	Atypical cells seen. Likely reactive mesothelial cells
Pericardial fluid MTB C&S	No MTB isolated

muffled hearts sounds, hypotension and jugular venous distension might be demonstrated in physical examinations. The diagnosis is usually supported by the specific ECG changes and chest X-ray. The classical yet uncommon ECG change is electrical alternans, and the more common change is sinus tachycardia or decreased voltage. The diagnosis is usually confirmed by echocardiography, which can determine the size of pericardial effusion, look for collapsed ventricles and assess the diastolic function.

Cardiac tamponade occurs when accumulation of pericardial fluid is causing increased intrapericardial pressure to the critical point where ventricular filling is restricted and subsequently reduced cardiac output and haemodynamic instability. Pericardial effusion can be caused by increased production of pericardial fluid or by accumulation of pericardial fluid due to increase in systemic venous pressure resulting in reduced reabsorption, which is commonly seen in heart failure or pulmonary hypertension.[3] The development of cardiac tamponade also depends on the rate of pericardial fluid accumulation. In the case of rapid accumulation, such as trauma, small amounts of pericardial fluid may lead to cardiac tamponade.[3] If the pericardial fluid increases slowly the pericardial sac can expand to accommodate more fluid before the development of cardiac tamponade. The common causes of cardiac tamponade are pericarditis, tuberculosis, malignancy and trauma. Other uncommon causes include pneumopericardium, bacterial infection, aortic dissection, uraemia, post-myocardial infarction, radiation induced and collagen vascular diseases, as seen in our patient.[3] It is important not to miss SLE as the underlying cause of cardiac tamponade as SLE can affects both the mother and the foetus. Pregnant mother is at risk of developing pre-eclampsia, gestational diabetes, and lupus nephritis.[4] Foetal is at risk of congenital heart block, miscarriage, intrauterine growth restriction, intrauterine foetal death or preterm labour.[5]

SLE is a multi-systemic chronic autoimmune disease and commonly affects women in child bearing age. It is commonly diagnosed from 15-44 years old with females to males in 12:1 ratio.[6] Studies showed that in pregnant patient there is a 2-3-fold increase in SLE activity.[7] The common presentations of SLE include constitutional symptoms, occurred in 50-90% of patients, musculoskeletal up to 90% of patients and cutaneous involvement seen in 50% of patient.[7] Most cases of SLE involve cutaneous or musculoskeletal lesion, however, it was not seen in our patient. Other organs involvements are renal, pulmonary involvement and cardiac manifestation. The most common cardiac manifestation in SLE patients is pericarditis, with or without pericardial effusion, occur in up to 25% of patients.[7] Other cardiac manifestations include myocarditis and coronary artery disease. It is commonly associated with high ANA levels. Other positive lupus serologies include Anti-DsDNA, anti-Smith and Anti-Histone Antibodies [6]. it is also important to check Ro/SSA and La/SSB as they are associated with congenital heart block. However, there are no complication during our patient's pregnancy and baby is born without notable rash and has normal heart rate.

In a retrospective study of 409 SLE patients conducted in India, 104 patients (25%) was diagnosed with pericarditis and 24 patients (5.9%) diagnosed with cardiac tamponade. Out of the 24 patients with cardiac tamponade, 12 (2.9%) had cardiac tamponade as the presenting feature.[8] In another series of 395 SLE patients, it shows that 75 patients (19%) had pericarditis. 10 of them (2.5%) developed tamponade and 4 patients (1%) presented as the initial presentation.[1] Therefore, it is rare for cardiac tamponade to occur in SLE, either throughout the disease course and or as the initial presentation.

The treatment of SLE involves aiming for disease remission, preventing flares and reducing their severity. Steroids should be initiated especially in severe cases such as cardiac tamponade or lupus nephritis. Hydroxychloroquine is a safe medicine in pregnancy. It is also effective in preventing disease flare, pre-eclampsia and neonatal heart block.[9] Aspirin is a useful and safe medicine in pregnancy and

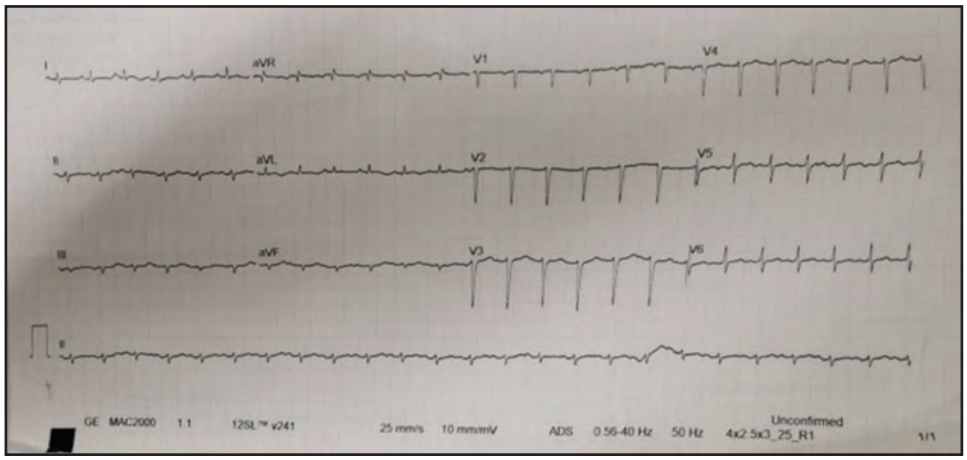

Fig. 1: ECG

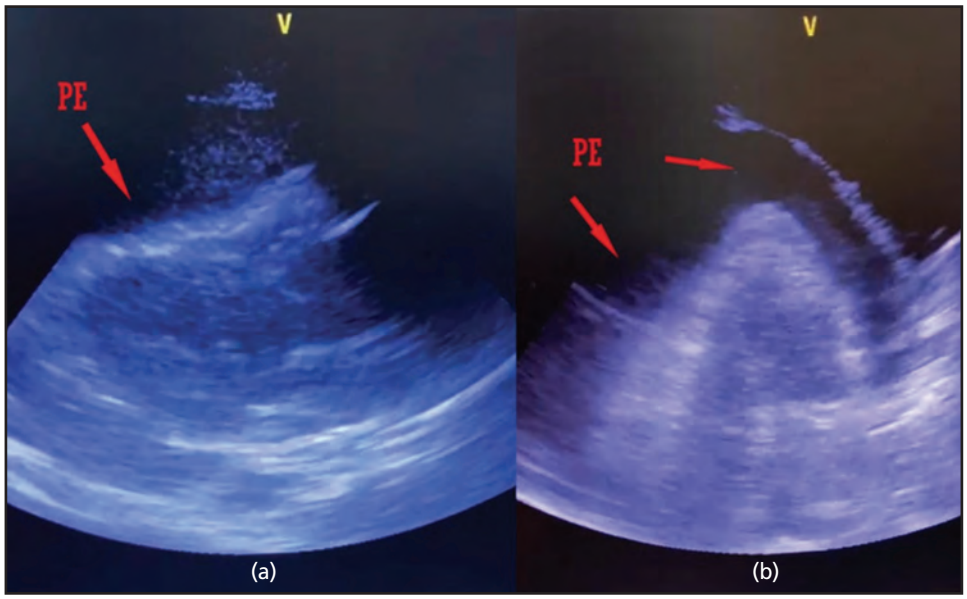

Fig. 2: a) Subcostal view: arrow showed large pericardial effusion compressing right atrium and right ventricle. b) Apical 4 chambers view: arrows showed global pericardial effusion.

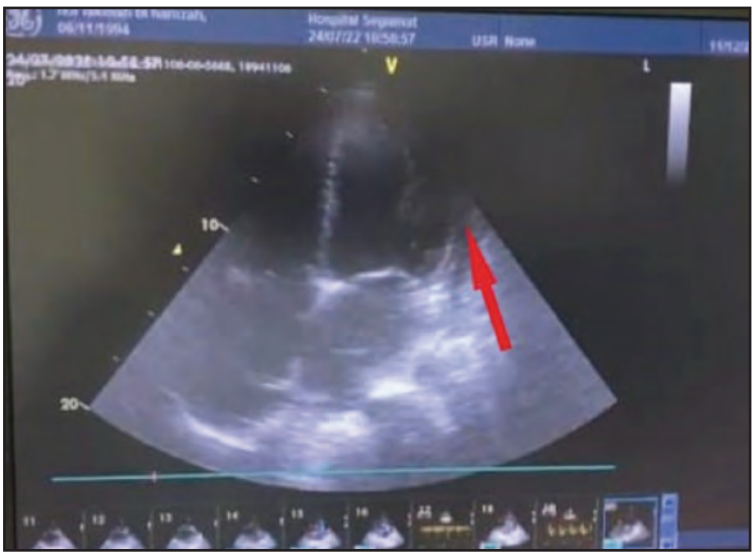

Fig. 3: Arrow showed minimal pericardial effusion

should be started at 12 weeks' gestation.[9] Immunosuppressants such as mycophenolate and cyclophosphamide are contraindicated in pregnancy.

CONCLUSION

Cardiac tamponade is a life-threatening medical emergency that could be fatal. This case highlights the interesting atypical presentation of SLE in a post-partum lady and the diagnostic and treatment challenges especially in a district hospital. Our intention of reporting this case is to emphasize the importance of early detection, high index of suspicion, timely intervention and collaborative multi-disciplinary team approach to ensure the optimal outcomes for the patient and the new-born.

TAKE HOME MASSAGE

SLE is diagnosed by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria, which consists of different organs. Patients may present with variety of features and manifestation, and may be overlooked and lead to delay in making the diagnosis. Hence, in patients present with symptoms involving more than one organ, they should be follow up closely and a suspicion for SLE should be high.

REFERENCES

1. Kahl LE. The spectrum of pericardial tamponade in systemic lupus erythematosus. Report of ten patients. Arthritis Rheum. 1992 Nov;35(11):1343-9. doi: 10.1002/art.1780351115. PMID: 1445451.
2. Chourabi C, Mahfoudhi H, Sayhi S, Dhahri R, Taamallah K, Chenik S, Haggui A, Hajlaoui N, Lahidheb D, Faida A, Abdelhafidh NB, Louzir B, Fehri W. Cardiac tamponade: an uncommon presenting feature of systemic lupus erythematosus (a case-based review). Pan Afr Med J. 2020 Aug 28;36:368. doi: 10.11604/pamj.2020.36.368.25044. PMID: 33235645; PMCID: PMC7666689.
3. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015 Nov 7;36(42):2921-2964. doi: 10.1093/eurheartj/ehv318. Epub 2015 Aug 29. PMID: 26320112; PMCID: PMC7539677.
4. Lateef A, Petri M. Systemic Lupus Erythematosus and Pregnancy. Rheum Dis Clin North Am. 2017 May;43(2):215-226. doi: 10.1016/j.rdc.2016.12.009. Epub 2017 Mar 14. PMID: 28390564.
5. Petri M. Pregnancy and Systemic Lupus Erythematosus. Best Pract Res Clin Obstet Gynaecol. 2020 Apr;64:24-30. doi: 10.1016/j.bpobgyn.2019.09.002. Epub 2019 Oct 8. PMID: 31677989.
6. Liu LW, To D (2018) An Atypical Presentation of Systemic Lupus Erythematosus. Med Rep Case Stud 3: 158. doi: 10.4172/2572-5130.1000158
7. Malaweera A, Huang LL. A 31 Year Old Lady with Post-Partum Systemic Lupus Erythematosus. Ann Clin Case Rep. 2019; 4: 1662.
8. Goswami RP, Sircar G, Ghosh A, Ghosh P. Cardiac tamponade in systemic lupus erythematosus. QJM. 2018 Feb 1;111(2):83-87. doi: 10.1093/qjmed/hcx195. PMID: 29048543.
9. Marder W. Update on pregnancy complications in systemic lupus erythematosus. Curr Opin Rheumatol. 2019 Nov;31(6):650-658. doi: 10.1097/BOR.0000000000000651. PMID: 31464707z

CASE REPORT

A Cluster of In-patient Scabies in 5 Unrelated Immunosuppressed Females: A Coincidence or Not?

Ingrid Ting Pao Lin, MMed, Teo Hock Gin, MRCP, Teo Yan, MRCP, Kiing Jiu Wen, AdvMDerm, Tang Min Moon, AdvMDerm

Dermatology Department, Sarawak General Hospital, Kuching, Sarawak, Malaysia

SUMMARY

Introduction: Scabies is identified as one of the neglected tropical diseases. It is extremely contagious with the potential to cause an outbreak if early, accurate diagnosis and effective medical management are not put in place. We present the unusual presentations of scabies in immunocompromised patients and their management. Case Presentation: We reported five cases of scabies including crusted scabies diagnosed in Sarawak General Hospital between March and April 2022. All patients had a rheumatological condition and required admission due to different reasons. Management and outcome: Each patient was managed separately and treated with permethrin 5%. All of them recovered. The investigation, management, and prevention of scabies outbreaks in healthcare facilities involving multiple disciplines were performed. Three cases acquired the scabies infection from the community with the remaining two having an indeterminate source of infection. Epidemiology link in 2 patients could not be excluded. We screened 87 healthcare workers involved in patients' care. None of them had or developed scabies. Conclusion: After thorough investigation, the clusters of scabies occurring is likely a coincidence. Precise diagnosis and effective medical management are required, encompassing both patients and healthcare workers to prevent an outbreak.

INTRODUCTION

Scabies is an infestation with *Sarcoptes scabiei var hominis*. It is identified as one of the neglected tropical diseases.[1] It is extremely contagious and can cause an outbreak in an institution. The incubation period is three to six weeks for primary infestation but can be as short as one to three days in cases of re-infestation.[2] Scabies outbreaks are difficult to control and significantly impact public health in developed countries. It incurs significant economic losses relating to staffing and treatment.[3] Thus, it is important to have early and accurate diagnosis together with effective medical management of affected patients and healthcare settings, specific principles and strategies for disease management are required to prevent the spread of disease in the communities. This report aims to describe five cases of unusual presentation of scabies that occurred over a period of two months in four females with systemic lupus erythematosus (SLE) and another female with rheumatoid arthritis (RA) patients on immunosuppressive agents and how we managed a suspected scabies outbreak.

CASE PRESENTATION

Five cases of scabies including a crusted scabies in this report occurred in the span of two months in Sarawak General Hospital. The clinical characteristics of the patients were summarized in Table I.

Case description

The first patient, a 28-year-old, lady a bird's nest processor, presented to the hospital for SLE with mucocutaneous flare on 15th March 2022. She complained of an itchy rash over the upper and lower limbs for four days. Her husband had similar symptoms. The patient had SLE diagnosed a year ago and she was taking daily prednisolone. Physical examination revealed discrete erythematous papules over the web spaces of the hands and feet. This was her fourth admission to the ward within 3 months for recalcitrant active SLE. Oral methotrexate was added to her existing systemic corticosteroids. Topical permethrin 5% was administered once a week for two doses.

Two weeks later, on 1st April 2022, a 35-year-old, housewife, presented to the hospital with acute SLE complicated with pericardial effusion. She had thick grey-yellow crusts on the skin throughout the body which had been occurring for 5 months. The initial lesions were intensely pruritic discrete red papules at the abdomen, slowly spreading to the chest and scalp. She did not have children. Family members under the same roof did not have similar symptoms. The patient had her SLE diagnosed 4 months prior. She was on high-dose systemic corticosteroid and oral azathioprine 50mg daily. Physical examination revealed moderately thick greyish-white-yellow crusts with surrounding erythema (Figure 1a&b). Scrapping of the crusted plaques at ear pinna examined under a microscope at 10x magnification revealed numerous mites, eggs, and faeces (Figure 1c). Topical therapies of permethrin 5% were administered. The patient was managed in an isolation room while in the ward. Her SLE was treated with pulse intravenous methylprednisolone for 3 days followed by mycophenolate mofetil 500 mg daily in addition to oral prednisolone 30 mg daily. Her symptoms improved gradually, and topical permethrin was continued daily for a total of four weeks and then continued once a week for another four weeks. Extended permethrin was given until clearance of the crust. She had post-scabies eczema which symptoms controlled with a topical corticosteroid (Figure 1 d & e). She was discharged home following 14 days of in-patient care.

This article was accepted: 17 September 2023
Corresponding Author: Ingrid Ting Pao Lin
Email: ingrid_tpl15@hotmail.com

Table I: Summary of clinical characteristics of 5 females with rheumatological conditions who infested with scabies

Case	Age in years	Comorbid	Onset of scabies symptoms	Date of admission	Date presented to Dermatology	Source of infestation	Duration of immune-suppression	Type of Scabies	Treatment	Duration of recovery	Outcome
1	28	SLE	March 2022	15th March 2022	15th March 2022	Family	13 months	Classical	Permethrin 5% on the night once a week for 2 doses (Standard regimen)	2 weeks	Complete remission
2	35	SLE	Dec 2021	1st April 2022	1st April 2022	indeterminate	4 months	Crusted	Permethrin 5% on the night every day for 4 weeks then once a week for another 4 weeks	8 weeks	Post scabies eczema
3	25	SLE	March 2022	28th February 2022	18th April 2022	Ward	4 months (cyclophosphamide Feb 2022)	Classical	Permethrin 5% on the night every week for 6 weeks	6 weeks	Post scabies eczema
4	68	RA	April 2022	20th April 2022	18th April 2022	Family	12 months	Classical	Permethrin 5% on the night once a week for 2 doses (Standard regimen)	2 weeks	Complete remission
5	46	SLE	March 2022	15 February 2022	21st April 2022	Family	4 months (cyclophosphamide Jan 2022)	Classical	Permethrin 5% on the night once a week for 2 doses (Standard regimen)	2 weeks	Complete remission

SLE- systemic lupus erythematosus; RA – rheumatoid arthritis

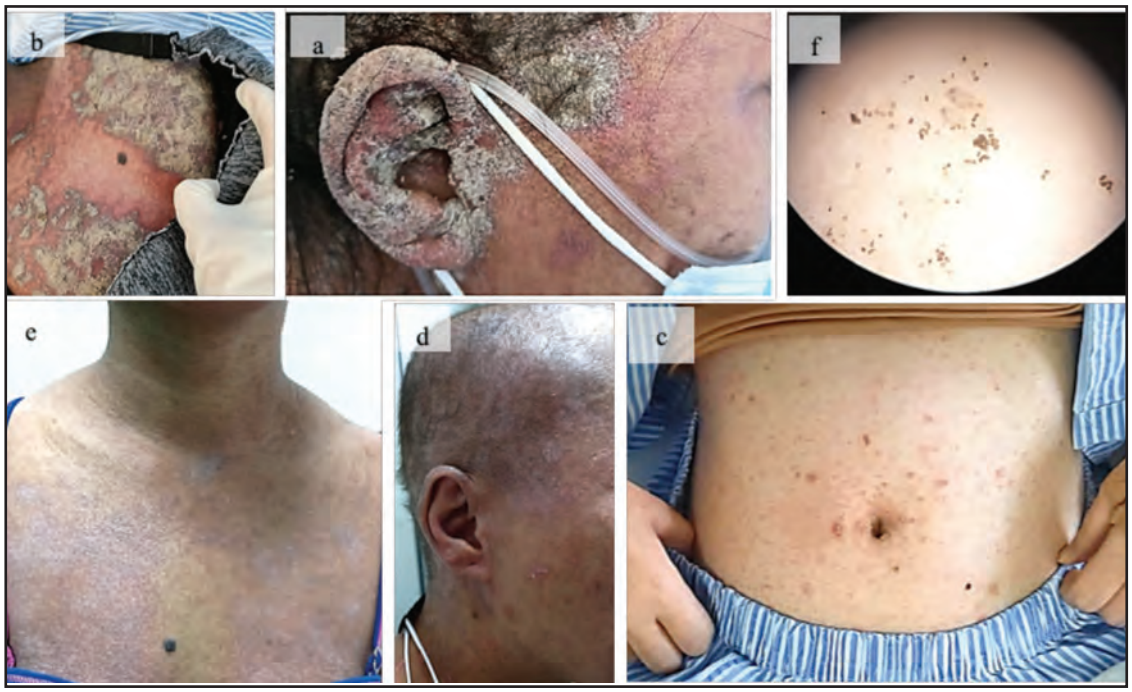

Fig. 2: (a & b) Thick greyish-white-yellow crusts with surrounding erythema over the chest and scalp in patient 2; (c) Microscopic examination 10x magnification revealed numerous mites, eggs, and feces in skin with scrapped samples from ear pinna of patient 2; (d&e) thick plaques resolved with residual erythematous patches following 4 weeks of treatment in patient 2; (f) multiple papules over the umbilicus in patient 3.

Our third patient, a 25-year-old, lady, a research assistant, with underlying SLE diagnosed 18 months ago, presented to the hospital two weeks on 19th April 2022 while our second patient was managed in the isolation ward. She had a recent history of admission to the medical ward in late March 2022, with concomitant hospitalization of our second patient for SLE flare with gut lupus. She was given intravenous cyclophosphamide during her 4-day hospitalization in March 2022. There was no direct contact between the two patients in the ward. She presented with generalized itchiness immediately after being discharged from the ward early April 2023 for two weeks before being readmitted for scabies. Her younger brother who stayed under the same roof interestingly did not have similar symptoms. Physical examination revealed multiple discrete erythematous pruritic papules with excoriations involving the interdigital web spaces of hands and feet and umbilicus (Figure 1f). Topical permethrin 5% were administered. It was applied from neck to toe once a week for two weeks. She was discharged from the ward after 2 days with no adjustment of her immunosuppressant. However, her scabies symptoms did not improve, and her younger brother who stayed together had not been treated due to miscommunication, thus retreatment with permethrin 5% was given another 2 weeks together with the younger brother. Unfortunately, inadequate response was observed after 2 weeks with the appearance of new papules. Treatment was extended for another two weeks, and the method of application was re-emphasized. Complete resolution was observed at two months of treatment.

Our fourth case was a 68-year-old, housewife who presented to the Dermatology clinic on 18th April 2022 with generalized nocturnal itchiness for 5 days. She had rheumatoid arthritis for a few years on prednisolone and sulfasalazine with good control. She had no recent admission to the ward except for regular follow-ups at the Rheumatology clinic. Her husband did not have similar symptoms. She did not have school-going children. Physical examination revealed multiple pustules over the armpit, fingers, scalp, and web spaces. Topical therapies of permethrin 5% were administered as an outpatient however, she was admitted a few days later as the scabies was complicated with right-hand cellulitis. Intravenous ampicillin with sulbactam was initiated. Her cellulitis responded to the antibiotic, and she was discharged home 4 days later with another 3 days of oral combination of ampicillin and sulbactam.

Our fifth case was a 46-year-old, housewife who presented to Dermatology Clinic with generalized pruritus for a month involving the bilateral hand, trunk, and lower limb, especially at night. Her husband also had similar symptoms for a week. Her son, an engineer, who stayed together, however did not have similar symptoms. She had SLE on prednisolone and immunosuppressant mycophenolate mofetil. She was hospitalized thrice within 4 months where in January she was given pulse intravenous cyclophosphamide. She had anemia with fluid overload and neutropenic sepsis which resulted in 2 hospital admissions in February 2022. Physical examinations revealed discrete papules over the hands' hand, trunk, and web spaces. Topical therapies of permethrin 5% were administered as an outpatient.

All the household members of the five patients were also treated with permethrin one dose on same-day patient-initiated treatment.

The measures to control disease transmission, including educating patients and families on the disease and cleaning contaminated clothing, home appliances, and other fomites were endorsed.

Outbreak prevention management

An outbreak was suspected due to the presentation of five patients with chronic rheumatological conditions who regularly attended the Rheumatology clinic. Three of them had frequent admission to the same medical ward in a month. The infection prevention and control team and Hospital Occupational Health and safety unit were notified. Investigations were done at the hospital level by both teams together with the Dermatology team.

Measures that were carried out in all 3 medical wards where the patients were admitted included a daily change of all in-patient bed linen. Bed linen laundry was handled as foul or infected. Briefly, the laundries were placed into an alginate bag and then into a secure outer bag. It will then be heat treated before washing with detergent and antiseptic. Contact precautions were practiced by all health care workers (HCWs) attending the patients until scabies treatment for the patient was completed and the rash had dried, and the crusts dropped off. The contact precaution includes wearing plastic aprons and disposable gloves when carrying out treatment or attending to patients' personal hygiene needs. Environmental cleaning using multipurpose disinfectant and quaternary ammonium compound disinfectant was done in all involved units.

A total of 88 staff including 62 nurses, 21 doctors, and 5 ward attendants from the Rheumatology clinic, Dermatology clinic, and 3 medical wards were screened over 2 days. Among them, only 24 had a history of contact with those scabies cases and had proper contact precautions when attending to patients' needs. During the interview, all of them had no symptoms or signs of scabies infection. All staff was offered prophylactic permethrin treatment. All staff was counseled regarding symptoms and signs of scabies. Scabies training includes explaining about scabies, its sign and symptoms, the incubation period, their treatment, and prevention. Leaflets were provided to each staff. After 6 months period, there was no scabies reported among the staff.

DISCUSSION

Human scabies is characterized by intense pruritus with nocturnal exacerbation and contagiousness.[4] The presence of scabietic nodules and skin burrows is pathognomonic. Scabies is suspected with the clinical history, skin morphology, and distribution and confirmed with the presence of mites, eggs, or faeces under light microscopic examination of the scrapped lesion. However, in patients who are immunocompromised, and on prolonged corticosteroids, nodular scabies can present with an atypical clinical pattern which is the crusted or Norwegian scabies.[5] This can be observed in our five cases where all of them had prolonged systemic corticosteroid therapy for their underlying conditions which were systemic lupus erythematosus (SLE) and rheumatoid arthritis. One of them presented with crusted scabies in which thick yellow crusts were the main phenotype instead of classical discrete papules. It could be mistaken as other skin condition and lead to delay in diagnosis. Chronic use of corticosteroids is one of the most important factors for a delayed diagnosis of scabies in hospitalized patients.[6]

Crusted scabies is characterized by crusting of the skin with hyperkeratosis, which is caused by the hyperproliferation of mites as a result of the altered host response to the infestation. The hyperkeratotic plaques can carry up to 4000 mites per gram of skin compared to about 20 mites on the entire skin of individuals with ordinary scabies.[7] Various medical conditions such as cutaneous, neurologic, and immunologic diseases are risk factors for the development of crusted scabies.[8] Some congenital and acquired immunocompromised conditions which include human immunodeficiency virus (HIV), hematologic malignancy, neurologic illnesses, and SLE are also predisposed to crusted scabies.[8] Therefore, this hyper-infestation can cause an institutional outbreak if no prevention control is being put in place.

The immune system plays an important role in the clinical manifestation of the disease. In SLE, the immune system can be defective in so many ways. The leukocytes show functional abnormalities, such as defective phagocytosis, and decreased leukocyte chemotaxis. Cellular immunity is depressed too as is a selective humoral response to certain external antigens. It will be the trigger to make scabies in SLE more severe and florid than usual. The number of CD4+ was generally lower in patients with SLE compared to healthy individuals. Hence, the symptoms of pruritus are also lower in crusted scabies in SLE patients.[9] CD8+ were much more dominant than CD4+ in SLE patient. It is further hypothesized that these CD8+ T lymphocytes might be the cause of keratinocytes apoptosis leading to epidermal hyperproliferation in crusted scabies.[10]

Scabies may be introduced into the healthcare facility through an unrecognized infected new patient, visitors, or through healthcare workers who had scabies contact at home or community.[11] General contact through daily procedures such as helping to bathe a patient/resident, and any other extensive hands-on contact provides an opportunity for mite transmission. Mites also can be transmitted via contaminated clothing or bed linen. Fomites play a minor role in situations where the infestation in the source case is classical scabies. The inanimate environment of patients/residents with atypical scabies, however, is heavily contaminated with mature and immature mites.

After thorough investigation, our cases 1, 4, and 5 likely acquired scabies from the community due to the presence of similar symptoms among family members. There was no history of prior contact in the hospital. However, epidemiological link between case 2 and 3 could not be excluded as both had been managed in the same ward. Although there was no evidence of direct skin-to-skin contact among both, indirect contact with contaminated material could have been occurred. They were both admitted to the ward during COVID-19 pandemic when all healthcare workers practiced COVID-19 standard precaution with personal protective equipment. These may have prevented our staff from acquiring scabies.

The risk of an institutional outbreak is high with crusted scabies. From a study by Lay et al., a review of 20 hospital outbreaks of scabies, 16 out of 19 index cases were crusted scabies.[6] Another review analyzing 19 outbreaks showing all but one of the index cases had crusted scabies.[12] A scabies outbreak was suspected in our medical wards due to the presence of more than two confirmed cases of scabies including crusted scabies over the span of a month. This fulfilled the scabies outbreak definition per the UK Health Security Agency (UKSHA) where the outbreak is defined as the presence of two (2) or more epidemiologically linked cases of scabies within eight weeks.[13] Scabies transmission from HCW can be suspected if there are two or more HCWs who worked in the same area of the facility, and who do not have any contact source outside the facility within the last six weeks. The severity of scabies transmission in a facility depends on the mite load, the level of care of the source case, as well as the duration of the exposure period.[11]

Outbreak management should include planning for personal protective equipment (PPE) and pharmacy supplies.[11] Thus, measures need to be taken up early to prevent outbreaks in healthcare facilities. The action was taken to notify the Infection control and prevention team and Occupational Health and Safety team so that investigations can be carried out to look for a possible source. Concomitantly, environment cleaning and education of ward staff regarding contact precautions and management of soiled linen were performed. Our team made swift action evaluating all HCWs in all affected units to identify and remove any HCWs with signs and symptoms of scabies. HCWs were also educated on how to make a quick evaluation and monitoring of patients who are in close contact. These were by recommendation by Scabies Prevention and Control Guidelines for Healthcare settings revised in July 2019.[11]

A person who had direct "hands-on" contact, handling contaminated clothing or bed linen, or slept in the same bed as the patient/resident during the exposure period is defined as a close contact. However, for crusted scabies, close contact includes persons who had substantial contact with an atypical scabies patient's/resident's environment, including HCWs who worked both regularly and temporarily in the same area as the patient/resident during the exposure period. If the patient/resident was placed in more than one area before control measures were initiated, each area is considered affected.[11]

We used permethrin 5% lotion for cases 1, 4, and 5. This is in accordance with the Malaysian Guideline for Management of Scabies in Adults and Children. For crusted scabies, the treatment includes a combination of oral ivermectin and permethrin. The European guideline for the management of scabies (2017) recommends a combination of topical permethrin 5% cream or benzoate lotion 25% (applied daily for 7 days, then twice weekly until the patient is cured) and oral ivermectin (200 micrograms/kg/dose, with food) as three (days 1, 2, and 8), five (days 1, 2, 8, 9, and 15), or seven doses (days 1, 2, 8, 9, 15, 22, and 29), depending on the severity of infection.[14] Ivermectin is not available in our institution, thus we decided to give permethrin 5% daily and liquid paraffin to soften the crust, extended up to 4 weeks due to persistent thick plaque on weekly review. Subsequently frequency of application was reduced to once weekly till complete clearance.

As for case 3, the patient has been given permethrin 5% lotion for a total of 6 courses instead of the standard 2 courses for classical scabies because, after completion of 2 weeks of treatment, the patient had worsening pruritus where repeated skin scrapping showed the presence of mites' eggs which compel us to repeat the treatment for her for a longer period of 4 weeks. Subsequently, the patient had resolved symptoms. Treatment failure should be considered if symptoms persist after 6 weeks of treatment completion and most cases of treatment failure are likely due to poor compliance to treatment, inadequate treatment, or re-infestation from untreated contacts.[3] To ensure treatment success, the correct application of topical permethrin is of cardinal importance. Treatment should be applied to the whole body (except the head and neck), including web spaces of fingers and toes, the genitalia, and under the nails. However, in elderly and immunocompromised people the application should be extended to the scalp, neck, face, and ears. Treatment should be reapplied to the hands if they wash them during the treatment period. All members of the affected household should be treated at the same time. The application should be washed off after 12 hours for permethrin and clothes and bed linen machine washed at temperatures above 50°C.[15]

CONCLUSION

In conclusion, we described five unrelated females with SLE and RA who had scabies within 2 months, two of whom may be epidemiologically linked. The rest were likely coincidental. Scabies outbreaks could happen in a hospital setting. Precise diagnosis, prompt action with effective remedial measures is required to prevent or to control scabies outbreak in hospital.

LEARNING POINTS

- In patients who are on long-term immunosuppressants and immunocompromised, we will need to have high index of suspicion for scabies as the patients can have atypical presentations. They also require close monitoring to ensure clearance.
- Vigilant monitoring of contacts and surveillance of scabies outbreak in institutions is important to prevent institutional outbreak.

DECLARATIONS

None to declare.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This article does contain studies with the human participant and was registered via the National Medical Research Register, Ministry of Health Malaysia with ID NMRR ID-22-01692-YQW

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants

CONFLICT OF INTEREST

The authors declare no competing interests

FUNDING

The authors declare no financial disclosure

AUTHOR'S CONTRIBUTION

IPLT was responsible for the study design, data collection, manuscript writing, HGT, YT, and JWK, and participated in data collection. MMT was involved in the discussion, manuscript editing, and language proofreading. All authors read and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the Medical Records Unit, Sarawak General Hospital. However, restrictions apply to the availability of these data, which were used under special written permission and consent of patients for the current case report and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Medical Records Unit, Sarawak General Hospital, and Ministry of Health, Malaysia.

ACKNOWLEDGMENT

The author would like to thank the Director-General of Health Malaysia for the permission to publish this paper. We acknowledge Rheumatology team in collaboration in patients' managements and all the staff of Department of Dermatology Sarawak General Hospital in the data collection.

REFERENCES

1. Engelman D, Marks M, Steer AC, Beshah A, Biswas G, Chosidow O, et al. A framework for scabies control. PLoS neglected tropical diseases. 2021; 15(9): e0009661.
2. Chosidow O. Scabies. New England Journal of Medicine. 2006; 354(16): 1718-27.
3. Chandler DJ, Fuller LC. A review of scabies: an infestation more than skin deep. Dermatology. 2019;235(2):79-90.
4. Chouela E, Abeldaño A, Pellerano G, Hernández MI. Diagnosis and treatment of scabies: a practical guide. American journal of clinical dermatology. 2002; 3: 9-18.
5. Park JH, Kim CW, Kim SS. The diagnostic accuracy of dermoscopy for scabies. Annals of dermatology. 2012; 24(2): 194-9.
6. Lay C-J, Wang C-L, Chuang H-Y, Chen Y-L, Chen H-L, Tsai S-J, et al. Risk factors for delayed diagnosis of scabies in hospitalized patients from long-term care facilities. Journal of clinical medicine research. 2011: 72-7.
7. Yee BE, Carlos CA, Hata T. Crusted scabies of the scalp in a patient with systemic lupus erythematosus. Dermatology Online Journal. 2014; 20(10).
8. Maghrabi MM, Lum S, Joba AT, Meier MJ, Holmbeck RJ, Kennedy K. Norwegian crusted scabies: an unusual case presentation. The Journal of Foot and Ankle Surgery. 2014; 53(1): 62-6.
9. La Cava A. T-regulatory cells in systemic lupus erythematosus. Lupus. 2008; 17(5): 421-5.
10. Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. Journal of immunology research. 2014; 2014.
11. Scabies Prevention and Control Guidelines for Healthcare settings. July 2019.
12. Vorou R, Remoudaki H, Maltezou H. Nosocomial scabies. Journal of Hospital Infection. 2007; 65(1): 9-14.
13. Guidance UKHSA guidance on the management of scabies cases and outbreaks in long-term care facilities and other closed settings. 2023.
14. Salavastru C, Chosidow O, Boffa M, Janier M, Tiplica G. European guideline for the management of scabies. Journal of the European Academy of Dermatology and Venereology. 2017; 31(8): 1248-53.
15. Johnston G, Sladden M. Scabies: diagnosis and treatment. Bmj. 2005; 331(7517): 619-22.

CASE REPORT

Rare Cause of Failed Intubation: Lingual Tonsillar Hypertrophy: Case Report

Abdul Majid Ghazali, MMED Anaesthesiology (IIUM), Surrej Darshain Singh Sran, MBBS (AIMST), Ti Phing Phang, MBBS(UNIMAS), Nurul Izzah Azmi, MD (UI)

Department of Anaesthesia and Intensive Care, International Islamic University Malaysia

SUMMARY

We report a case of unanticipated difficult intubation due to lingual tonsillar hypertrophy. This is a case of a 45-year-old lady with hypertension undergoing Scarf Osteotomy and Wedge osteotomy right first metatarsal bone and soft tissue McBride procedure due to Bilateral hallux valgus stage 4 under general anaesthesia. Preoperative airway assessment did not suggest a potentially tricky airway case. After an uneventful induction, 3 attempts to intubate via direct laryngoscopy and video laryngoscopy were undertaken; however, they failed due to poor view. Attempts to ventilate with a supraglottic airway device failed also, and the decision was made to reverse the patient and postpone surgery after investigating the reason for the difficult airway. After Ear, Nose, and Throat (ENT) assessment, it was ascertained that this patient's difficult intubation was due to lingual tonsil hypertrophy. Lingual tonsil hypertrophy is frequently asymptomatic and can be an anaesthetic emergency if undiagnosed before anaesthesia. Lingual tonsil hypertrophy causes difficulty in ventilation and intubation. Fibreoptic intubation will be the preferred airway management option for general anaesthesia patients with known lingual tonsil hypertrophy.

INTRODUCTION

The lingual tonsil is a standard component of Waldeyer's ring, consisting of lymphoid tissue at the tongue's base.[4] There have been few reported cases of lingual tonsil hypertrophy as a cause of unexpected difficult intubation.[2] Lingual tonsil hypertrophy is known to be frequently asymptomatic; however, it is associated with patients with obstructive sleep apnoea.[2] Routine preoperative clinical assessments may often miss this diagnosis as a cause of a difficult airway. In most lingual tonsil hypertrophy cases, the physical examination did not suggest a predicted difficult airway.[2] Unexpected lingual tonsil hypertrophy can be a cause of difficult intubation as well as difficult ventilation. Ventilation via a supraglottic airway device may also be challenging[7]. Symptoms may vary from asymptomatic to odynophagia, and dysphonia, causing obstructive sleep apnea and upper airway obstruction.

A cadaveric study of 497 corpses determined there was a discovery of enlarged lingual tonsils in 3.2% of patients[1].

CASE PRESENTATION

A 45-year-old lady was scheduled for Scarf Osteotomy and Wedge osteotomy right first metatarsal bone and soft tissue McBride procedure due to Bilateral hallux valgus stage 4. Her background medical condition was hypertension with a history of allergy to Non-steroidal anti-inflammatory drugs(NSAIDs). Upon assessment in the anaesthesia clinic, she was completely asymptomatic and free from any recent upper respiratory tract infections. Initial airway assessments were unremarkable, except her Mallampati score was grade III. Otherwise, externally there was no mass at the face and neck; her BMI was 25; her inter-incisor gap: was 6cm; her sternomental distance: was 18cm, her thyromental distance: was 8cm, Upper lip bite test: class 1; her Range of motion neck: >35 degrees and Neck circumference: 35cm.

The patient was to receive a general anaesthetic. She was induced with 100mcg of fentanyl, 150mg of propofol, and 40mg of rocuronium. Mask ventilation was tested before administration of muscle relaxant, and it was documented in an excellent tidal volume of 300-500mls per breath. The first intubation attempt was abandoned as it was Cormack Lehane (CL) view 3 using direct laryngoscope size 3. The second intubation attempt was unsuccessful despite using a video laryngoscope Macintosh size 3, able to visualise but unable to advance endotracheal(ETT) size 7.5. The third attempt used a smaller ETT size of 6.5; with the guidance of bougie, however, there was still the difficulty of advancing ETT further, so we abandoned it. Then we decided to insert a supraglottic airway; however, there was difficulty in generating good tidal volume, and the patient developed laryngospasm. Laryngospasm was treated by deepening anaesthesia with propofol bolus 50mg and increasing inhaled sevoflurane concentration of 6%. The decision was made to wake the patient as the surgery was not urgent. The patient needed 16mg/kg of sugammadex as it was a profound neuromuscular blockade, and she was extubated safely. Throughout the procedure, the was no desaturation, and she was haemodynamically stable. The patient was discharged to the ward well and was subsequently referred to the ENT team for assessment.

Upon assessment by the ENT team, from oral examination, it was discovered that the patient has Friedman tongue position grade 4 (only able to see hard palate) while other structures appeared normal. Flexible nasopharyngoscopy showed bulky sublingual tonsils, which led us to the cause of the difficult intubation.

This article was accepted: 29 September 2023
Corresponding Author: Abdul Majid Ghazali
Email: drabdulmajid@iium.edu.my

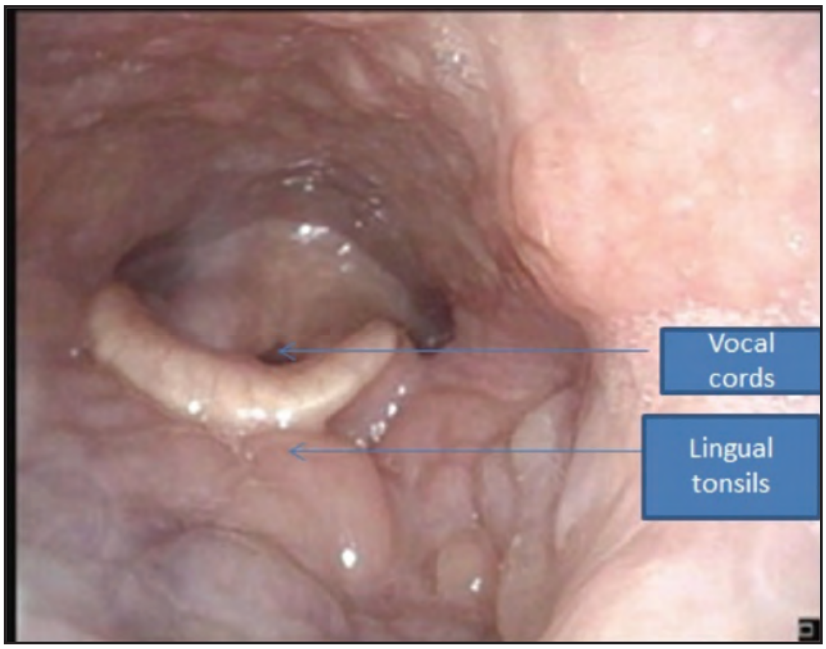

Fig. 1: Picture from flexible nasopharyngoscopy showing bulging of lingual tonsils hypertrophy, compressing the vocal cord

Other findings of the scope were normal. The patient was discharged home well and underwent her surgery under regional anaesthesia 6 weeks later.

DISCUSSION

To the best of our knowledge, this is the first case report of lingual tonsil hypertrophy causing unexpected difficult intubation in Malaysia. This is a very rare case whereby in the united states, the prevalence was 2-3% based on a postmortem study of 497 patients.[1] LTH is often asymptomatic (2). A patient with lingual tonsil hypertrophy may present with a sore throat, dysphagia, globus sensation, snoring, the feeling of having a lump in the throat, alteration of voice, chronic cough, snoring, obstructive sleep apnea, and two-thirds of patients with lingual tonsil hypertrophy have had a palatine tonsillectomy or adenoidectomy.[2,3]

LTH is often diagnosed incidentally, for example, in difficult intubation.[2] The risk factors for lingual hypertrophy include chronic infections, allergies, obesity, previous history of tonsillectomy in childhood, peri-menopausal females, heavy smokers, and gastro-oesophagal reflux disease.[5]

Routine preoperative airway examination includes Mallampati test, thyromental distance, mouth opening, head extension and subluxation of the mandible.[11] The epiglottis and supra epiglottic areas are not assessed routinely in preoperative airway assessment, which may lead to a poor positive predictive value in diagnosing LTH.[2] Lingual tonsils are located at the base of the tongue between the circumvallate papilla anteriorly and the epiglottis posteriorly and consist of lymphoid tissue. Factors that contribute to difficult intubation in lingual tonsils hypertrophy are the presence of lingual tonsil hypertrophy at the base of the tongue in the pre-epiglottic space, which will prevent proper placement of the laryngoscope blade and the obstruction of the airway lumen by the lingual tonsil which interfere with the direct laryngoscopy and indirect epiglottis elevation difficult.[4]

Our patient had no signs, symptoms or features suggesting any possibility of difficult intubation or lingual tonsil hypertrophy. We followed difficult airway society (DAS) guidelines, where after a trial of 3 intubations, we abandoned the intubation and proceeded to insert third generation supraglottic airway.[7] However, tidal volume was not achieved. LTH may cause supraglottic airway misplacement, reduce ventilation effectiveness, and generate good tidal volumes.[10] Furthermore, lingual tonsils have no capsule; multiple intubation attempts may cause bleeding and oedema.[3,6] This may precipitate laryngospasm and lead to a "cannot-intubate-cannot-ventilate" situation.

Follow up for LTH are mostly conservative; tonsillectomy is only done when a patient is symptomatic, as mentioned above.[9]

Patients with known LTH should undergo awake fibreoptic intubation.[3,6] In case of unexpected findings of LTH intraoperatively, further intubation attempts should be discontinued. Instead, patients should be awakened and awake fibreoptic intubation should be performed to avoid further airway trauma.[6] We suggest that patients with LTH should be seen by an ENT surgeon prior to future anaesthetics to assess the progression of LTH.

CONCLUSION

It is sporadic to find cases of lingual tonsil hypertrophy, which may cause significant morbidity and mortality. Based on our experience and literature before this, we espouse that

anaesthesiologists should be aware of this diagnosis and consider it when encountering difficult airways. For future anaesthetics with patients with diagnosed LTH, awake fibreoptic intubation would be the best choice for airway management after careful discussion with an ENT surgeon. In the case of emergency cases, the practitioner is recommended to opt for fibreoptic intubation or establishing a surgical airway if the situation arises.

REFERENCES

1. Breimeier D, Wilke N et al. The Lingual Tonsillar Hyperplasia in relation to Unanticipated Difficult Intubation: Is There Any Relationship Between Lingual Tonsillar Hyperplasia and Tonsillectomy? The American Journal of Forensic Medicine and Pathology. 2005; 26(2): 131-5.
2. Ovassapian A, Glassenberg R, Randel GI et al. The unexpected difficult airway and lingual tonsil hyperplasia: a case series and a review of the literature. Anesthesiology 2002; 97(1): 124-32.
3. Davies S, Ananthanarayan C, Castro C. Asymptomatic lingual tonsillar hypertrophy and difficult airway management: a report of three cases. Can J Anesth 2001; 48: 1020-4.
4. Crosby E . Chapter 37, Airway management of a patient with an unanticipated difficult laryngoscopy (lingual tonsillar hypertrophy). Hung O, & Murphy M.F.(Eds.), Management of the Difficult and Failed Airway, 2e. McGraw Hill. (2012)
5. Kumar S, Verma N, Agarwal A, Lingual tonsillar hypertrophy: Cause of unanticipated difficult intubation. J Anaesthesiol Clin Pharmacol. 2014 Oct; 30(4): 590-1.
6. Asbjørnsen H, Kuwelker M, Søfteland E, A case of unexpected difficult airway due to lingual tonsil hypertrophy. Acta Anaesthesiologica Scandinavica, 2008; 52(2): 310-2.
7. C. Frerk et al, Difficult Airway Society intubation guidelines working group, Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults, BJA: British Journal of Anaesthesia, Volume 115, Issue 6, December 2015, Pages 827-48
8. Golding-Wood DG, Whittet HB. The lingual tonsil. A neglected symptomatic structure? J Laryngol Otol. 1989 Oct; 103(10): 922-5.
9. JESBERG N. Chronic, hypertrophic, lingual tonsillitis. AMA Arch Otolaryngol. 1956 Jul; 64(1): 3-13
10. Fundingsland BW, Benumof JL: Difficulty using a laryngeal mask airway in a patient with lingual tonsil hyperplasia (letter). A nesthesiology 1996; 84: 1265-6.
11. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P: Predicting difficult intubation. Br J Anaesth 1988; 61: 211-6

A markedly high pancreatic cyst fluid of carcinoembryonic antigen and amylase in a postnatal woman

Wan Norlina Wan Azman, MPath[1,4], Wan Mohd Saifuhisam Wan Zain, MPath[1,4], Zulkarnain Mustapha, MSc[1,4], Wan Faiziah Wan Abdul Rahman, MPath[2,4], Ikhwan Sani Mohamad, MSurg[3,4]

[1]Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kota Bharu, Kelantan, Malaysia, [2]Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kota Bharu, Kelantan, Malaysia, [3]Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kota Bharu, Kelantan, Malaysia, [4]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, 16150 Kota Bharu, Kelantan, Malaysia

SUMMARY

Many pancreatic cystic lesions (PCL) are accidentally found during abdominal imaging for unrelated procedures. This was a case report of a 32-year-old woman who had an uncomplicated spontaneous vaginal delivery presented with an abdominal mass 1 month postnatally. Her computed tomography (CT) abdomen showed a retroperitoneal cystic lesion with differential diagnoses include mucinous cystadenoma of the pancreas, pancreatic pseudocyst and cystic lymphangioma. The pancreatic cyst fluid levels for carcinoembryonic antigen (CEA) and amylase were markedly high, 4216 ng/ml and 3232 U/L, respectively. The patient subsequently underwent distal pancreatectomy with splenectomy. The histopathological examination (HPE) revealed a mucinous cystadenoma of the distal pancreas with no evidence of malignancy. A large spectrum of imaging and clinical characteristics render challenges in assessing PCL. Pancreatic cystic fluid CEA and amylase levels help in distinguishing mucinous cystic neoplasms (MCN), a malignant potential type of PCL from other non-mucinous, non-malignant type of PCL. Higher concentrations of CEA and amylase in pancreatic cyst fluid are suggestive of MCN. Nevertheless, the test results should be correlated with imaging studies and HPE.

INTRODUCTION

Pancreatic cystic lesions (PCL) are sometimes accidentally detected due to the extensive use of imaging investigations. The mucinous cystic neoplasms (MCN) are PCL with malignant potential and may necessitate surgical intervention.[1] MCN predominantly affects females, which suggests that sex hormones may be a factor for its development.[1] The diagnosis might be obscured by pregnancy's subtle symptoms and physical changes. The rapid postpartum growth of a benign MCN may be associated with hormonal levels during pregnancy, considering the ovarian-type stroma and the presence of hormonal (oestrogen and progesterone) receptors in this neoplasm.[2] Pre-operative biochemical investigations for example pancreatic cyst fluid carcinoembryonic antigen (CEA) and amylase analysis can act as supportive modalities in the differential diagnosis of PCL.[3]

CASE PRESENTATION

A 32-year-old Malay woman with no known medical illness presented with a 1-month history of an abdominal mass post uncomplicated spontaneous vaginal delivery. The mass was located at the left hypochondriac region and progressively increased in size. It was associated with chest discomfort and fatigue. She denied history of fever, trauma, nausea, vomiting and any abdominal pain. There was no past medical history of pancreatitis and no history of malignancy in the family. The general examination was unremarkable. Abdominal examination showed a mass at the left hypochondriac region, measured approximately 15 × 20 cm extending to the left lumbar region. It was mobile, non-tender, not pulsatile, not moving with respiration and not fixed to underlying muscle or skin.

She was subsequently referred to the hepatopancreaticobiliary (HPB) team in Hospital Universiti Sains Malaysia (Hospital USM) for further investigations. Computed tomography (CT) abdomen pelvis was performed and reported as a substantial well-defined non-enhancing retroperitoneal cystic lesion measuring 12.5 × 20.0 × 16.0 cm. The differential diagnoses were mucinous cystadenoma of the pancreas, pancreatic pseudocyst and cystic lymphangioma. Pre-operative blood investigations showed a full blood count of hypochromic microcytic most likely secondary to iron deficiency due to disease progression and postpartum period. The coagulation profile, electrolytes, liver and renal function tests, serum lactate dehydrogenase (LDH) and plasma glucose were within the reference range (Table I). The normal serum LDH indicates there was no significant tissue damage and the lesion could be benign. However, serum LDH is not a specific marker for malignancy. The patient is also non-diabetic as indicated by the normal plasma glucose. The serum amylase and CEA levels were normal, however, the pre-operative pancreatic cyst fluid CEA and amylase were markedly high at 4216 ng/ml, and 3232 U/L, respectively. Post-operative, the pancreatic cyst fluid CEA and amylase levels were markedly reduced by 84.5%, and 97.4%, respectively (Table II). Peritoneal fluid for cytology showed no malignant cells seen. Given the possible malignant cyst, the patient was scheduled for distal pancreatectomy with splenectomy. The splenic artery and

This article was accepted: 16 October 2023
Corresponding Author: Wan Mohd Saifuhisam Wan Zain
Email: wansaifu1985@usm.my

Table I: Pre-operative blood investigations

Blood tests	Result	Unit	Reference range
Complete full blood count			
WBC	$4.30x10^9$	/L	3.4-10.1
RBC	$5.16x10^{12}$	/L	3.52-5.16
Hb	11.6	g/dL	11.6-15.1
Hct	35.5	%	31.8-42.4
MCV	68.8	fL	77.5-94.5
MCH	22.5	pg	24.8-31.2
MCHC	32.7	g/dL	29.4-34.4
Plt	179 x109	/L	158-410
Coagulation profile			
PT	13.90	s	12.6-15.7
INR	1.00		0.06-1.14
APTT	44.90	s	30-45.8
Liver function tests profile			
Total Protein	68.0	g/L	65-83
Albumin	40.0	g/L	38-44
Globulin	28.0	g/L	
AG ratio	1.43		
AST	14.0	U/L	5-34
ALP	42.6	U/L	42-98
ALT	9.0	U/L	<34
Total bilirubin	13.0	umol/L	3.4-17.1
Renal function tests profile			
Urea	3.3	mmol/L	1.7-8.3
Sodium	140	mmol/L	135-145
Potassium	3.7	mmol/L	3.5-5.0
Chloride	106	mmol/L	98-107
Creatinine	59	umol/L	70-130
Serum LDH	330	U/L	<480
Plasma glucose	4.1	mmol/L	3.5-7.7

WBC white blood cell, RBC red blood cell, Hb haemoglobin, Hct haematocrit, Plt platelet, MCV mean corpuscular volume, MCH mean corpuscular haemoglobin, MCHC mean corpuscular haemoglobin concentration, CEA carcinoembryonic antigen, PT prothrombin time, APTT activated partial thromboplastin time, INR international normalized ratio, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, ALP alkaline phosphatase, AG Albumin-Globulin.

Table II: Serum and pancreatic fluid cyst for amylase and carcinoembryonic antigen (CEA)

Date/parameters	April 2020	Pre-operation	Day 3 post-operation	Day 4 post-operation	Reference range
serum amylase (U/L)	43	50.1	89	46	28-100
pancreatic fluid cyst amylase (U/L)	3232	2830	83	38	-
serum CEA (ng/ml)	0.2	< 0.2	-	-	<5.2
pancreatic fluid cyst CEA (ng/ml)	4216	-	654.1	-	-

vein were ligated at the root to ensure no tumour dissemination, and the pancreas was transected at the neck and removed en bloc with the spleen (Figure 1). The surgical specimens were sent for HPE and reported as a cyst within the pancreas, lined by a single layer mucinous epithelium consistent with mucinous cystadenoma without evidence of malignancy (Figure 2). The patient was discharged well post-operatively and was scheduled for a follow-up to assess her symptom and repeat imaging study.

DISCUSSION

This case illustrated the increased pre-operative CEA and amylase levels in pancreatic cyst fluid compared to the serum levels. It has been hypothesised that utilising the pancreatic cysts fluid analysis as a supplementary marker is essential for managing PCL. Differentiating MCN from other types of PCL is important as MCN may necessitate surgical intervention.[1] A high level of cyst fluid CEA suggests a mucin-producing tumour or MCN3 and may differentiate MCN with other types of PCL.

The pancreatic cyst fluid in this case was collected by ultrasound guided abdominal fluid tapping using fine-needle aspiration. CEA was analysed on Roche Cobas e411 analyser whilst amylase on Abbott Architect analyser. Dilution of the sample was required and was done according to the manufacturer's recommendation. The levels post-dilution were within the analysers measuring ranges. The assays are however, not intended to be used for the pancreatic cyst fluid measurement and ideally, method validation should be performed for more accurate measurement. It is, however, laborious, time-consuming and expensive to the laboratory, especially if the test is not routinely requested.

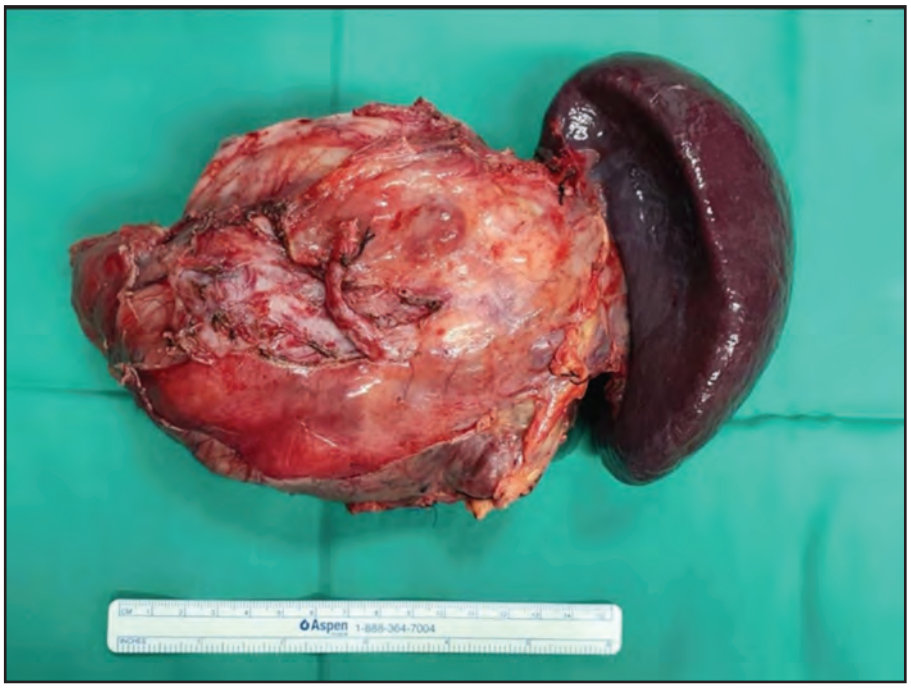

Fig. 1: Pancreatic tissue with cyst formation.

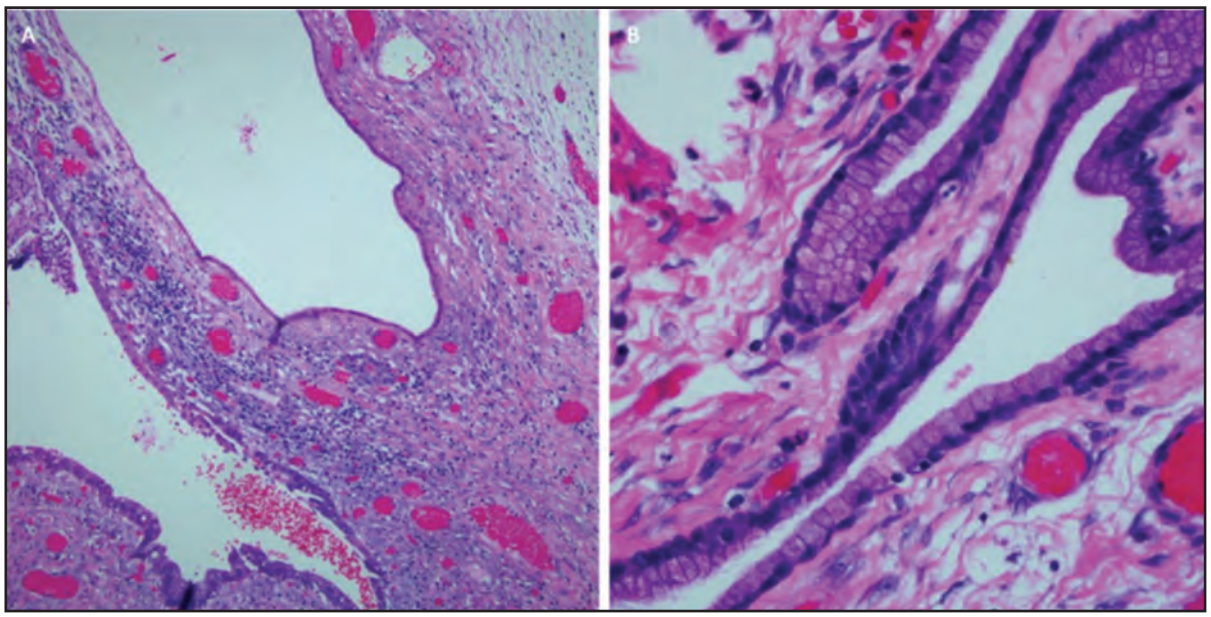

Fig. 2: Pancreatic tissue with cyst formation.

There were various cut-off levels for cyst fluid CEA used in pancreatic cyst disease. A cystic fluid CEA of 192 ng/mL distinguished mucinous and non-mucinous cystic lesions with a diagnostic accuracy of 79%.4 Another study showed different results with CEA levels ranging from 30 ng/mL to 480 ng/mL for optimum mucinous cyst detection.[5] The cut-offs differ from one study to another because of differences in sample size and analyser used. In this patient, the pancreatic cyst fluid CEA level was markedly elevated above all the cut-offs mentioned thus, highly suggestive of MCN. The cyst fluid in this patient also demonstrated a higher level of amylase, which suggested a pseudocyst rather than other pancreatic cysts. A pooled review studies showed that a cyst fluid amylase level of < 250 IU/L exhibited a 98% specificity for eliminating pseudocysts.5 Nonetheless, high levels of cyst fluid amylase also are often seen in MCN.[5]

CONCLUSIONS

Pancreatic cystic fluid carcinoembryonic antigen (CEA) and amylase levels help in distinguishing mucinous cystic neoplasms (MCN), a malignant potential type of pancreatic cystic lesions (PCLs) from other non-mucinous, non-malignant type of PCL. Higher concentrations of CEA and

amylase in pancreatic cyst fluid are suggestive of MCN. Nevertheless, the test results should be correlated with imaging studies and histopathological examination.

ACKNOWLEDGEMENTS

We would like to thank the patient for her verbal consent and cooperation in completing this case report.

REFERENCES

1. Din NU, Zubair M, Abdul-Ghafar J, Ahmad Z. Pancreatic mucinous cystic neoplasms: a clinicopathological study of 11 cases and detailed review of literature. Surg Exp Pathol 2020; 3(1): 6. doi:10.1186/s42047-020-0059-2.
2. Kitagawa H, Okabayashi T, Nishimori I, Kobayashi M, Sugimoto T, Akimori T, et al. Rapid growth of mucinous cystic adenoma of the pancreas following pregnancy. Int J Gastrointest Cancer 2006; 37(1): 45–8. doi:10.1385/IJGC:37:1:45.
3. Raman A, Lennon AM. Cyst fluid biomarkers-diagnosis and prediction of malignancy for cystic lesions of the pancreas. Visc Med 2018; 34(3): 178–81. doi:10.1159/00490137.
4. Zhang W, Linghu E, Chai N, Li H. New criteria to differentiate between mucinous cystic neoplasm and serous cystic neoplasm in pancreas by endoscopic ultrasound: A preliminarily confirmed outcome of 41 patients. Endosc ultrasound. 2017; 6(2): 116. doi: 10.4103/eus.eus_8_17.
5. Rockacy M, Khalid A. Update on pancreatic cyst fluid analysis. Ann Gastroenterol Q Publ Hell Soc Gastroenterol 2013; 26(2): 122.

A parturient with COVID-19 pneumonia, complicated with posterior reversible encephalopathy syndrome in puerperium

Tan Kok Tong, MMED[1], Leong Chee Loon, MMED[1], Shanthi Viswanathan, MRCP[2], Norzaini Rose Mohd Zain, MMED[3], Muniswaran Ganeshan, MOBGYN/MRCOG[4]

[1]Department of Internal Medicine, Kuala Lumpur General Hospital, Malaysia, [2]Department of Neurology, Kuala Lumpur General Hospital, Malaysia, [3]Department of Radiology, Kuala Lumpur General Hospital, Malaysia, [4]Department of Obstetrics and Gynaecology, Kuala Lumpur General Hospital, Malaysia

SUMMARY

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may give rise to vascular complications and endothelial dysfunction, leading to the posterior reversible encephalopathy syndrome (PRES). Of note, steroids and immunomodulatory agents are known to precipitate PRES. Here we report a case of a 25-year-old postpartum woman with PRES, presumably caused by laboratory-confirmed COVID-19 during the recovery phase. At the gestational age of 34 weeks, she was initially hospitalised for mild COVID-19 infection. However, she developed COVID-19-related hyperinflammation on day five of the illness and was treated with remdesivir (antiviral agent), high-dose steroids, and tocilizumab (TCZ, an interleukin-6 inhibitor). In anticipation of ongoing respiratory compromise, she underwent an elective caesarean section, with a healthy 2.6 kg baby girl born. Her condition was stabilised post-operatively, but by day ten of the illness, she developed severe headaches, confusion, and seizures that were aborted pharmacologically. Throughout the hospitalisation, she was normotensive. The findings of brain magnetic resonance imaging (MRI) were consistent with the diagnosis of PRES. Her condition steadily improved with symptomatic treatment, consisting of adequate hydration, close monitoring, and antiepileptic agents. On day fourteen of the illness, she achieved a complete recovery. In this case, we highlight that PRES is a potential neurological complication of COVID-19 infection in the context of pregnancy without pre-eclampsia or eclampsia and should be considered as one of the differential diagnoses in the presence of abrupt neurologic manifestations. Additionally, the use of steroids and immunomodulatory agents in treating the COVID-19 infection should be judicious.

INTRODUCTION

Since the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a novel culprit of pneumonia in 2019, approximately five hundred million people across the globe have been diagnosed with COVID-19, with more than seven million deaths at present.[1] As of July 11, 2022 in the United States, 222372 pregnant women had COVID-19, with 304 (0.14%) deaths being reported.[2] Recent studies have shown that pregnant women are at higher risk of developing severe COVID-19 pneumonia, especially those with obesity, pre-existing medical conditions, and obstetric complications.[2] Though the clinical course of COVID-19 among pregnant women is often insidious, this cohort deserves timely treatment for COVID-19, including steroids, antiviral agents, and immunomodulatory agents.

Neurological manifestations are not uncommon among pregnant women with COVID-19. The spectrum of symptoms can range from fatigue, myalgia, headaches to seizures, delirium and stroke-like manifestations. Interestingly, any type of neurologic complaint can be a warning sign of severe COVID-19 infection and debilitating neurological complications. The neurological complications are, for instance, stroke, encephalopathy and Guillain-Barré syndrome (GBS), which can potentially have an adverse impact on maternal and neonatal outcomes. Additionally, antenatal changes in physiology and immunomodulation can trigger an exacerbation of COVID-19 disease, as well as the neuroinvasive propensity of the SARS-CoV-2 virus.[3]

A scoping review conducted by João et al. summarised 18 case reports of COVID-19 pneumonia in pregnancy that were published from inception until November 25, 2021.[4] Of 18 cases with COVID-19-related neurological involvement in pregnancy, only four (22.2%) had PRES with hypertension. Of note, PRES is seemingly a rare but severe complication of COVID-19 in pregnancy. In this article, we described a puerperal case with COVID-19 and PRES without hypertension, pre-eclampsia, or eclampsia, that was diagnosed on clinical, laboratory, and radiological grounds.

CASE PRESENTATION

A 25-year-old primigravida at 34-week gestation, presented to our centre with fevers for one day. The antenatal period was uneventful, and she had received two doses of the COVID-19 vaccine to date. The blood pressure (BP) readings during antenatal care were normotensive. She was in close contact with her husband, who had COVID-19. As the COVID-19 saliva test was positive and the home quarantine was unfeasible, she was hospitalised for a mild COVID-19 illness. On arrival, she was not in respiratory distress, with an

This article was accepted: 23 October 2023
Corresponding Author: Kok Tong Tan
Email: kttanid@outlook.com

unremarkable respiratory examination and stable hemodynamic parameters. Notably, she was normotensive. The nasopharyngeal swab of rtPCR for SARS-CoV-2 performed in the ward was positive for COVID-19 infection, with the RdRp CT value of 15 and E gene of 15.36. The baseline laboratory investigations were normal (Table I).

On day four of the illness, she became dyspnoeic, requiring high-flow oxygen therapy. Further laboratory evaluation is described in Table I. At that juncture, a 3-day course of intravenous remdesivir (a loading dose of 200 mg/day, followed by 100 mg/day) was administered for viral pneumonitis. On day 5 of illness, her condition declined further with pulmonary involvement (Figure IA and 1B) and an uptrend in inflammatory parameters (Table I). Due to the development of COVID-19-related hyperinflammation, she was treated with a 10-day course of intravenous methylprednisolone, 2 mg/kg/day for the first 3 days, followed by 1 mg/kg/day for another 3 days, then oral prednisolone with an equivalent dose of dexamethasone, 6 mg/day for the remaining 4 days. Additionally, a dose of intravenous TCZ, 8 mg/kg was administered. In anticipation of further clinical deterioration, she underwent an elective caesarean section under general anaesthesia on day 6 of the illness, and a live baby girl weighing 2.6 kg was delivered with a good Apgar score. No intraoperative complications were encountered. Postoperatively, she was extubated and transferred to the general ward. At the hospital, her condition had stabilised, and the oxygen requirement was gradually weaned off by day eight of the illness.

On day 10 of the illness, as well as the fifth postoperative day, she developed thunderclap headaches and vomiting, followed by multiple episodes of seizures on the same day. Seizures were later aborted by phenytoin. Apart from having a fluctuating Glasgow Coma Scale (GCS) ranging from 13 to 14 (eye opening scaled by three points, verbal response scored four to five, and motor response scaled by six), she was found hemodynamically stable and normotensive with the BP ranging 100-120/70-80. Throughout the entire hospitalisation, there was no fluctuation or uptrend in blood pressure readings. Apart from having an abnormal GCS score, other neurological findings were grossly normal, with absent meningism. She did not exhibit any visual disturbances. The laboratory assessment immediately performed at that point did not specifically pinpoint any organ impairment or electrolyte imbalances. The autoimmune screen was negative. The inflammatory biomarkers described in Table I, were normal. The brain MRI with gadolinium contrast (Figure IC-F) depicts T1-weighted hypointense and T2-weighted/(fluid-attenuated inversion recovery) FLAIR/apparent diffusion coefficient (ADC) hyperintense lesions in bilateral fronto-parieto-occipital areas, in favour of vasogenic oedema in PRES. Additionally, diffused-weighted imaging (DWI) does not demonstrate the feature of restricted diffusion, and there is no intracranial haemorrhage on the brain MRI. The electroencephalogram (EEG) did not detect any epileptiform discharges. A lumbar puncture was not performed as her husband had not consented.

She was managed conservatively and successfully evolved, with a complete GCS recovery by day 14 of her illness before she was discharged home with her newborn. One year later, she remained well and did not report any significant complications caused by previous insults. The antiepileptic agent was successfully ceased. No head MRI was repeated in the interim.

DISCUSSION

We report the case of a pregnant woman with COVID-19 who developed PRES. First described by Hinchey et al. in 1996,[5] PRES was often described in the presence of malignant hypertension, along with other special conditions including renal disease, auto-immune diseases, pre-eclampsia or eclampsia. The incidence of PRES is increasing among non-pregnant individuals with severe COVID-19 infection. Most reported cases required mechanical ventilation and immunomodulatory therapy.[6,7] The diagnosis of PRES in our case was confirmed clinically and radiologically. Thus far, none of these patients were found to have strong evidence of the SARS-CoV2 genome in the cerebrospinal fluid.

Historically, it was believed that PRES was characterised by dysregulation of cerebral circulatory flow caused by malignant hypertension, severe infection, inflammation or vasotoxicity. Of note, eclampsia preceded by chronic hypertension and pre-eclampsia is a common aetiology for developing PRES. It can be implicitly explained by a rapid alteration in blood pressure that has disrupted cerebral perfusion, leading to an eventual breakdown of the blood brain barrier and causing cerebral oedema. Interestingly, dysregulation of placental ACE2 caused by COVID-19 infection can significantly lead to preeclampsia or eclampsia, which later explains the development of PRES.[8] As opposed to the previous idea, our case did not exhibit signs of preeclampsia or eclampsia, and the patient remained normotensive throughout the pregnancy. To date, data are limited to correlating the relationship between the normal physiological changes in pregnancy and COVID-19-related PRES. Further scrutiny is required.

On the other hand, recent studies suggested that the disturbance of cerebral microcirculation and vascular endothelial glycocalyx caused by the direct binding of SARS-CoV-2 with ACE2 receptors on capillary endothelium was the leading cause of PRES in normotensive individuals affected by COVID-19 infection.[7,9] In addition, an immune dysregulation caused by the SARS-CoV-2 virus may potentially facilitate the production of cytokines, notably IL-6 and TNF-α, thereby giving rise to a detrimental effect on endothelial layers in the CNS, increasing the permeability of the blood brain barrier and causing the formation of vasogenic oedema.[6,7] Another potential leading theory of the pathogenesis of PRES suggests that SARS-CoV-2 virions directly gain entry into the CNS and bind with ACE2 receptors on neurons and glial cells, conspicuously culminating in direct neurological damage and hence cytotoxic oedema of brain tissues.[7]

Owing to the anti-inflammatory effects, steroids and TCZ are strongly advised as one of the mainstay treatments for COVID-19-related cytokine release syndrome. Following

evidence-based reviews of the benefits of low-dose dexamethasone in treating COVID-19-related hyperinflammation, TCZ was later advocated by the COVID-19 treatment guidelines panels.[10] Notwithstanding, data on the efficacy and safety net of high-dose steroids used in COVID-19 treatment, for instance, pulse steroid therapy, is limited, and its use may exhibit detrimental effects on clinical outcomes.[11] In fact, the administration of TCZ and high-dose steroids may potentially contribute to PRES. Although its mechanism has not been well studied, the possible harmful effects of TCZ and high-dose steroids on the neurological system are essentially based on previous case reports.[6,12-14]

Interestingly, Sofía Lallana et al. reported eight cases of PRES associated with COVID-19, and half of those patients were given TCZ.6 The inhibitory effect of TCZ on IL-6 receptor blockade resulted in an abrupt accumulation of IL-6 levels in cerebral microvascular endothelial cells, leading to direct injury to endothelial walls.[12] Similarly, there is a time-related association between PRES and steroid exposure, as demonstrated in previous studies.[13,14] In our case, the brief duration of steroid administration raises the possibility that the development of PRES is presumably caused by high-dose steroids, even though our patient did not have hypertension or reversible cerebral vasoconstriction syndrome (RCVS). Though the mechanism by which steroids cause PRES is unknown, a plausible explanation for steroid-induced PRES includes hypertension caused by the effect of mineralocorticoids or RCVS.[13] Given the possibility of neurological complications from TCZ and high-dose steroids, their use should be cautious.

In the acute or subacute setting, the spectrum of PRES-related clinical characteristics is heterogeneous, ranging from headaches or visual disturbances to encephalopathy, for instance, seizures, focal neurological deficits and altered sensorium. Among the adult population with COVID-19 and PRES, not involving pregnant women, hypertensive crisis and altered mental status were the most common presentations, and the rates of invasive mechanical ventilation and intensive care unit (ICU) admission were high, up to 80%.15 Interestingly, João et al. reported nine COVID-19 cases in pregnancy with hypertensive presentation and CNS involvement, of which four had PRES with acute cognitive impairment and seizures.[4] These manifestations are strongly associated with well-recognised risk factors, including blood pressure fluctuation, renal impairment, malignancy, immunosuppressive or cytotoxic agents, autoimmune disorders, pre-eclampsia and eclampsia.

Besides clinical signs and symptoms, radiological findings are mandatory to help diagnose PRES. Classically, the brain imaging demonstrates symmetrical vasogenic oedema involving bilateral parietal and occipital lobes, characterised by hypodense lesions on CT and hyperintense areas on T2-weighted and FLAIR MRI. Interestingly, sites of atypical PRES may include the frontal lobes, brainstem, cerebellum and basal ganglia. Provided with MRI imaging availability, MRI should be considered to exclude other differential diagnoses, for instance, stroke, hypoxic encephalopathy, viral encephalitis/meningitis, vasculitis, demyelination disorders, venous thrombosis and metabolic diseases. Additionally, Rubaya Yeahia et al. reported that most patients (15/30, 50%) exhibited haemorrhagic foci on brain MRI imaging.[15]

Notably, PRES is often self-limiting if the precipitating cause is treated or removed, and the target BP remains within a normal range. Indeed, optimal blood pressure control and stabilisation of COVID-19-associated hyperinflammation are of paramount importance for treating PRES. Additionally, a prompt cessation of offending drugs, for instance, cytotoxic and immunomodulatory agents should be executed. The outcome of COVID-19-related PRES is overall favourable, provided with appropriate medical management. Even though it is rare, a small portion of patients with COVID-19-associated PRES may experience continuous disease progression, leading to cerebral haemorrhage, necrotising cystic cavitations, and even death.[15] Noteworthy to mention is that the obstetric and neonatal outcomes vary among the non-COVID-19 pregnant cases with PRES, determined by prompt treatment of the underlying diseases. To date, the national maternity dataset on COVID-19 complicated with PRES is not widely available.

CONCLUSION

PRES is recognised as one of the neurological complications of severe COVID-19 among pregnant women. Notwithstanding the fact that the association of COVID-19 infection with PRES is known, there are cases in normotensive puerperal individuals without pre-eclampsia or eclampsia, and the outcomes are less commonly described. Coupled with the impairment of vasoreactivity and potential adverse effects of tocilizumab (TCZ), these risk factors may place pregnant women with COVID-19 at a higher risk of PRES. Given that neurological manifestation is one of the key features of COVID-19 infection, clinicians should consider PRES as a potential cause of encephalopathy in pregnancy. Physicians should judiciously utilise steroids and TCZ in treating the COVID-19 infection. Little information is known about the association between pregnancy-related PRES and COVID-19. Future studies on further exploration of their relationship should be considered.

REFERENCES

1. COVID-19 statistics [Internet]. World Health Organisation 2023 [cited Oct 2023]. Available from: https://covid19.who.int/.
2. COVID-19 in pregnancy [Internet]. Centers for Disease Control and Prevention 2023 [cited Oct, 2023]. Available from: https://covid.cdc.gov/.
3. Figueiredo R, Falcão V, Pinto MJ, Ramalho C. Peripheral facial paralysis as presenting symptom of COVID-19 in a pregnant woman. BMJ Case Rep 2020; 13(8): e237146.
4. Magalhães JE, Sampaio-Rocha-Filho PA. Pregnancy and neurologic complications of COVID-19: A scoping review. Acta Neurol Scand 2022; 146 (1): 6-23.
5. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A Reversible Posterior Leukoencephalopathy Syndrome. N Engl J Med 1996; 334 (8): 494-500.
6. Lallana S, Chen A, Requena M, Rubiera M, Sanchez A, Siegler JE, et al. Posterior reversible encephalopathy syndrome (PRES) associated with COVID-19. J Clin Neurosci 2021; 88: 108-12.

7. Iftikhar S, Rehman AU, Ameer MZ, Nawaz A, Ur Rehman MA, Farooq H, et al. The association of posterior reversible encephalopathy syndrome with COVID-19: A systematic review. Ann Med Surg (Lond) 2021; 72: 103080.
8. Sayad B, Mohseni Afshar Z, Mansouri F, Salimi M, Miladi R, Rahimi S, et al. Pregnancy, preeclampsia, and COVID-19: susceptibility and mechanisms: a review study. Int J Fertil Steril 2022; 16 (2): 64-9.
9. Rovas A, Osiaevi I, Buscher K, Sackarnd J, Tepasse P-R, Fobker M, et al. Microvascular dysfunction in COVID-19: the MYSTIC study. Angiogenesis 2021; 24 (1): 145-7.
10. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. National Institutes of Health 2022. [cited July 2022). Available from: https://www.covid19treatmentguidelines.nih.gov/.
11. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395 (10223): 473-5.
12. Butryn M, Mewes S, Feist E, Beuing O, Müller C, Neumann J. Tocilizumab-associated posterior reversible encephalopathy syndrome in giant-cell arteritis – case report. BMC Neurology 2021; 21 (1): 228.
13. Parikh NS, Schweitzer AD, Young RJ, Giambrone AE, Lyo J, Karimi S, et al. Corticosteroid therapy and severity of vasogenic edema in posterior reversible encephalopathy syndrome. J Neurol Sci 2017; 380: 11-15.
14. Morrow SA, Rana R, Lee D, Paul T, Mahon JL. Posterior reversible encephalopathy syndrome due to high dose corticosteroids for an ms relapse. Case Reports in Neurological Medicine 2015; 2015: 325657.
15. Yeahia R, Schefflein J, Chiarolanzio P, Rozenstein, A, Gomes, W, Ali S et al. Brain MRI findings in COVID-19 patients with PRES: a systematic review. Clin Imaging 2022; 81: 107-13.

A rare ocular manifestation of Chikungunya – retinal vasculitis and cystoid macular oedema: a case report

Ying Jie Liow, MBBS[1,2], Ee Ling Ang, MSOphthal (UM)[1], Kamalden Tengku Ain, M.Ophth (Mal)[2]

[1]Department of Ophthalmology, Hospital Pulau Pinang, Penang, Malaysia, [2]UM Eye Research Centre (UMERC), Department of Ophthalmology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

SUMMARY

Chikungunya, a mosquito-borne disease caused by the arbovirus chikungunya virus, is endemic in Malaysia. It is known for causing sudden fever and severe arthralgia. The most typical eye symptom associated with this disease is anterior uveitis. Additional ocular symptoms that may occur include conjunctival injection, episcleritis, scleritis, uveitis accompanied by glaucoma, isolated chorioretinitis, neuroretinitis and oculomotor nerve palsies. However, we describe a case in which a patient did not exhibit any signs of anterior chamber activity or those mentioned above. Instead, the patient had retinal vasculitis and cystoid macular oedema (CMO) after a quiescent interval following systemic infection. This highlights that viral uveitis can have a myriad of presentations. No dedicated antiviral treatment exists for chikungunya infection and randomised controlled trials have not been conducted to assess the specific treatment of ocular inflammatory conditions related to chikungunya.

INTRODUCTION

Chikungunya is a mosquito-borne viral disease that has been reported in Malaysia. It is caused by the Chikungunya virus – an arbovirus, primarily transmitted to humans through the bite of infected Aedes mosquitoes, particularly Aedes aegypti and Aedes albopictus.[1] During the initial phase of the illness (within 3 weeks after infection), patients experience a variety of non-specific symptoms including high fever (greater than 39°C), headache, fatigue, rash, muscle aches and joint pain. Among these, the most common and often incapacitating symptom is the intense swelling and discomfort in the joints.[1] The post-acute stage (extending from the third week to as long as three months after infection) is marked by the disappearance of the symptoms experienced during the acute phase, except for the persistent polyarthritis, which is frequently characterised by joint stiffness, pain and swelling.[1] Ocular manifestations do occur and have become more prevalent recently.[2] In Malaysia, chikungunya infection was first recorded in Port Klang in Year 1998-1999. Subsequently, outbreaks and re-emergence of Chikungunya infection occurred periodically in 2006-2009 throughout the states in Peninsular Malaysia.[3] Since year 2004, chikungunya has spread rapidly and has been identified in more than 60 countries throughout Asia, Africa, Europe and the Americas.[4] We report a rare case of retinal vasculitis and cystoid macular oedema (CMO) that happened at the post-acute stage i.e. after a quiescent interval following systemic infection.

CASE PRESENTATION

A 61-year-old Malay woman with no known medical illness presented with progressive bilateral painless blurring of vision for 3 weeks. It is associated with metamorphopsia. There was no associated eye redness or eye discharge during this episode. No visual field defect was reported. Systemic and ocular history are unremarkable other than a recent hospital admission for Chikungunya infection 6 weeks prior to her presentation, which was confirmed via real time PCR. During the hospital stay, her clinical course was stable with no haemodynamic compromise and no organ failure. She reported 3 days of bilateral eye mild redness and tearing which resolved spontaneously without any treatment during her hospital stay.

Her presenting vision was 6/18 OD and 6/24 OS. No relative afferent pupillary defect was detected. Slit lamp examination of the anterior segment was unremarkable. No anterior chamber activity and no anterior vitreous cells were detected. There was early nuclear sclerosis in both the eyes and normal intraocular pressure for both the eyes: 15 mmHg OD and 16 mmHg OS.

Posterior segment examination in both the eyes revealed perivascular sheathing, intraretinal haemorrhages, dull foveal light reflex and cystoid macula oedema (Figure 1). There was no optic disc swelling or vitritis, no retinitis or choroiditis seen. Macula oedema in both the eyes were further confirmed by SD-OCT findings (Figure 2).

A full blood panel including full blood count, renal profile, serum calcium and albumin levels, erythrocyte sedimentation rate, C-reactive protein were within normal range. Infectious work-up e.g., syphilis, HIV, hepatitis B were negative. Toxoplasma IgM was negative while IgG serology was positive. Mantoux test was negative, measured induration was 6 mm. Chest X-ray did not reveal any lung parenchymal or hilar abnormalities. Urinalysis was normal except for few white cells seen.

Fundus fluorescein angiography (FFA) was done. Arteriovenous transit time was normal at 12 seconds. No findings of hot disc. There was focal vascular leakage in the infero-temporal macula denoting vasculitis (Figure 2).

A provisional diagnosis of retinal vasculitis and cystoid macular oedema secondary to Chikungunya infection was made after ruling out other possible causes. Treatment option of anti-vascular endothelial growth factor or trial of topical

This article was accepted: 24 October 2023
Corresponding Author: Ying Jie Liow
Email: liowyingjie@yahoo.com

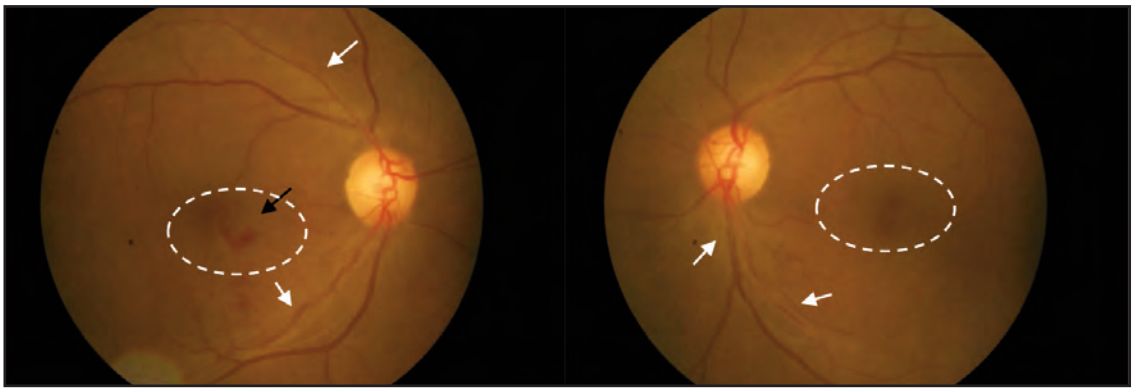

Fig. 1: Fundus photo showing perivascular sheathing (white arrowheads) predominantly in the inferotemporal vascular arcades, intraretinal haemorrhages (black arrowhead) in the macula and macula oedema (circled area).

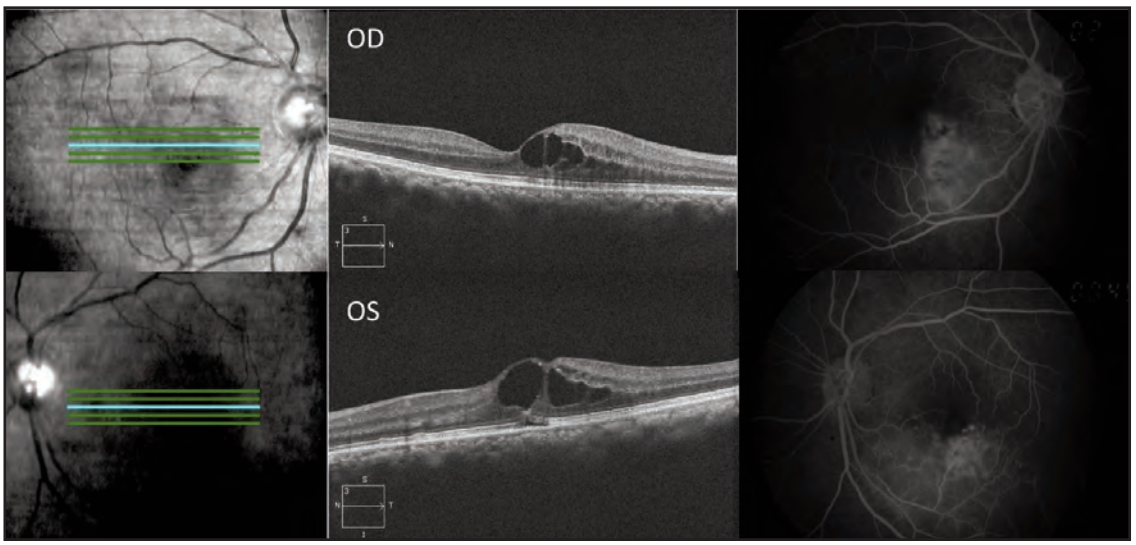

Fig. 2: HD 5-line Raster of the right and left eye showing cystoid macular oedema, worse in the left eye. Corresponding FFA image at late venous phase showing vascular leakage denoting vasculitis in the infero-temporal quadrant extending to the macula.

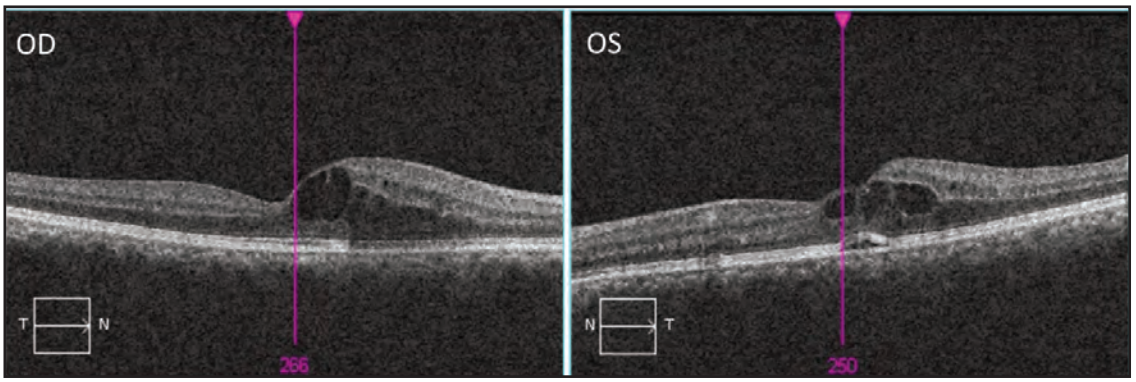

Fig. 3: OCT imaging of the macula 2 months after topical NSAIDs treatment was initiated. Her presenting vision of 6/18 OD and 6/24 OS improved to best corrected visual acuity of 6/12 OU.

NSAIDs were discussed with the patient and she opted for a more conservative approach with trial of topical NSAIDs. Intravitreal steroid therapy was not offered to her as she was still phakic with minimal cataract. After 2 months of treatment with topical NSAIDS, there was a modest reduction in central retinal thickness and improved vision following treatment. She achieved best corrected visual acuity of 6/12 OU was achieved. Subjectively she also reported less metamorphopsia.

Following that the patient was scheduled to be seen in another month but has since defaulted treatment and is lost to follow-up.

DISCUSSION

Chikungunya is a systemic infection that has many associated systemic manifestations.[5] In addition to inducing joint discomfort, the virus can also impact various other organs and systems, including the nervous system, cardiovascular system, skin and kidneys.[5] The exact mechanism of ocular involvement following Chikungunya infection has not yet been studied in detail. Ocular manifestations of Chikungunya can happen concurrent with systemic symptoms or can appear after a quiescent interval. A case series by Mittlal et.al found around two thirds of patients developed ocular symptoms concurrently with systemic illness, while the remaining presented within 6 weeks following resolution of initial illness.[5] The delayed onset of symptoms are postulated to be due to antigenic mimicry, delayed hypersensitivity reaction, or stimulation of a pathogenic lymphocyte reaction.[5] In clinical setting, it is a challenge to clarify the exact interval between the beginning of systemic symptoms and the establishment of eye symptoms. However, awareness about ocular manifestations of Chikungunya should be raised. In this case, we had to explore the patient's medical history in detail before the history of recent hospital admission was reported as it was thought by the patient to be irrelevant to the presenting symptoms.

In this particular case, Toxoplasma IgM was negative while IgG was positive. We do not think that it is toxoplasmosis as our patient lacks the vitritis that is usually present in toxoplasmosis and there are no chorioretinal scars seen. Other retinal vasculopathies like retinal vein occlusion is also less likely as the patient lacks any risk factors and the retinal haemorrhages occurring in this patient is at the macula instead of along the vascular arcades.

The ocular manifestations of Chikungunya are vast. The most common is anterior uveitis, followed by optic neuropathy.6 In a retrospective, observational case series conducted by Lalitha et al., anterior uveitis represented almost one third of cases in in the 37 cases of ocular complications related to Chikungunya infection.[6] Other reported ocular manifestations that can occur infrequently are conjunctival hyperaemia, episcleritis, scleritis, uveitis with glaucoma, monofocal chorioretinitis, neuroretinitis and oculomotor palsies. Conjunctival petechiae, intermediate uveitis, multifocal chorioretinitis, retinal vasculitis and maculopathy are thought to be rare complications.[6]

There is no specific antiviral therapy for Chikungunya infection and treatment is merely symptomatic. For treatment of its ocular complications, there is no difference from treatment of same manifestation due to other aetiologies. As of date, there are no randomised controlled trials for specific treatment of ocular inflammatory diseases associated with Chikungunya.

Our patient had modest improvement in visual acuity and decrease in central retinal thickness following initiation of treatment with topical NSAIDs drops. However, it is unclear whether the disease is by itself self-limiting or whether treatment is truly beneficial. Prognosis varies, ranging from full resolution to permanent vision loss despite intervention.[5]

CONCLUSIONS

Retinal vasculitis with cystoid macular oedema (CMO) is a rare ocular manifestation, but significantly affects vision resulting in morbidity. In recent years, due to the ease of international travel, Chikungunya infection is increasingly reported in both endemic and non-endemic regions, therefore awareness about vast ocular manifestations of Chikungunya should be raised. Other than ophthalmologists, it is also favourable if primary care doctors are made aware of the possible ocular complications that can occur so an early referral to a specialist can be instituted.

DISCLOSURE

No potential competing interest to declare. Informed consent was obtained from the patient in line with COPE standards.

REFERENCES

1. Malaquias C, Fernanda, Fonseca S, Virgílio Frota Rossato, Carlos D, De J, et al. Ocular manifestations of chikungunya infection: a systematic review. Pathogens 2022; 11(4): 412–2.
2. Mahendradas P, Avadhani K, Shetty R. Chikungunya and the eye: a review. J Ophthalmic Inflamm Infec 2013; 3(1): 35.
3. Wolbachia Malaysia [Internet]. Medical Entomology Unit, Institute for Medical Research Malaysia 2023 [cited Oct 23]. Available from: https://www.imr.gov.my/wolbachia/2017/01/16/malaysian-dengue-and-zika-scenario/
4. Chikungunya fact sheet [Internet]. 2023. [cited Oct 23]. Available from: https://www.who.int/news-room/fact-sheets/detail/chikungunya#cms
5. Mittal A, Mittal S, Bharathi JM, Ramakrishnan R, Sathe PS. Uveitis during outbreak of chikungunya fever. Ophthalmol 2007; 114(9): 1798-1798.e3.
6. Lalitha P, Rathinam S, Banushree K, Maheshkumar S, Vijayakumar R, Sathe P. Ocular involvement associated with an epidemic outbreak of chikungunya virus infection. Am J Ophthalmol 2007; 144(4): 552–6.

CASE REPORT

Percutaneous drainage of a bleeding pancreatic duplication cyst: a case report

Zaim HO, Dr. Surg (Paeds)[1], Nabillah MJ, Dr. Rad[2], Nor Hafizah AH, MMed. Rad[2]

[1]Department of Surgery, Hospital Melaka, Melaka, Kementerian Kesihatan Malaysia, Malaysia, [2]Department of Radiology, Hospital Melaka, Melaka, Kementerian Kesihatan Malaysia, Malaysia

SUMMARY

Pancreatic duplication cyst is rare in children. Diagnosis may be difficult as it usually presents with abdominal pain and other varying non-specific symptoms. Cross-sectional imaging such as computed tomography (CT) scan is usually needed to diagnose the condition and provide more information for surgical planning. Definitive treatment remains excision of the cyst. We report a case of pancreatic tail duplication cyst in a 2-year-old girl who presented with abdominal pain and anaemia due to a bleeding and perforated cyst diagnosed by ultrasound and CT scan. The patient was managed initially with percutaneous drain insertion followed by spleen-preserving distal pancreatectomy and excision of the cyst. The diagnosis of pancreatic duplication cyst was confirmed on histopathology. The child remained well after one year of follow-up.

INTRODUCTION

Pancreatic duplication cysts are the rarest among duplication cysts.[1] Diagnosis is difficult and presentations vary, most often presenting as abdominal pain.[2-6] Excision of the cyst with or without excision of parts of the pancreas is the management of choice.[2-4] We report a pancreatic duplication cyst presenting with abdominal pain and anaemia that was initially managed with percutaneous drainage before definitive surgery.

CASE PRESENTATION

A 2-year-old girl presented with fever, abdominal pain, non-bilious vomiting and diarrhoea for 1 week. She had a similar episode of pain at 1-year-old with abdominal fullness in the left abdomen but did not seek further treatment or investigation for the symptoms. She otherwise did not have any other significant medical history or history of trauma. The child was pale, but active on examination with a pulse rate of 134/min, blood pressure 118/58 mmHg, and temperature of 38°C. There was a tender left abdominal mass. Full blood count revealed haemoglobin of 6.3 g/dL, total white blood count of 9.7 × 10^9/L, platelet 440 × 10^9/L. Renal profile and liver function tests were normal. Serum amylase was 77 units/L. A provisional diagnosis of intussusception was made.

Abdominal ultrasound revealed a large left paracolic collection measuring 5 × 5 × 10 cm (Figure 1A). No evidence of intussusception was seen. The initial diagnosis of intraabdominal abscess was made. The child was transfused with 240 mL of packed cells followed by ultrasound-guided percutaneous drain insertion that drained up to 500mL of stale blood. Fluids sent for cultures and acid-fast bacilli were negative, while fluid for amylase was 138 units/L.

The child was treated with intravenous cefotaxime and metronidazole for 7 days. Her pain and fever resolved, and she regained her appetite. However, she continued to drain about 200 mL per day, at first hemoserous, then serous after 6 days. The colour of the drain output turned to light green with blackish sediments after 7 days. The persistent and unusual drain output prompted further investigations.

Repeated ultrasound revealed a gut signature sign of the cystic lesion which is relatively specific for duplication cyst (Figure 1B). Contrast-enhanced computed tomography (CT) abdomen performed showed rim-enhancing collection in the left retroperitoneal region. A bifid pancreatic tail was seen with a subjacent cystic mass measuring 1.6 × 2.6 × 2.1 cm and a claw sign at the ventral tail of the pancreas (Figure 2). The wall of the cystic lesion has a corrugated appearance resembling a gastric wall. A separate collection was seen anterior to the left Gerrota's fascia measuring 3.0 × 1.7 × 2.8 cm with the tip of the percutaneous catheter in situ. A tiny defect in the cystic wall that communicated with the collection suggested perforation (Figure 3). The distal pancreatic duct was dilated but did not demonstrate any connection to the cystic lesion. There was no radiological evidence of pancreatitis.

A laparotomy was performed with the operative findings of a distal pancreatic cyst measuring 6 × 7 cm. Spleen preserving distal pancreatectomy and excision of the cyst was performed. The histopathology report described the cyst as composed of full-thickness gastric tissues with an abnormal dilated pancreatic duct structure. The surrounding pancreas showed changes of chronic pancreatitis with areas of mucosal ulcerations along the pancreatic duct.

Post-operatively the child recovered uneventfully. She was followed up in the clinic 1 year after the surgery without further complications.

DISCUSSION

The incidence of alimentary tract duplications that may occur from the mouth to the anus is 1:4500, with duplication of the pancreas the rarest among them.[1] Pancreatic

This article was accepted: 28 October 2023
Corresponding Author: Zaim Hazin bin Onn
Email: zaimhazinonn@moh.gov.my

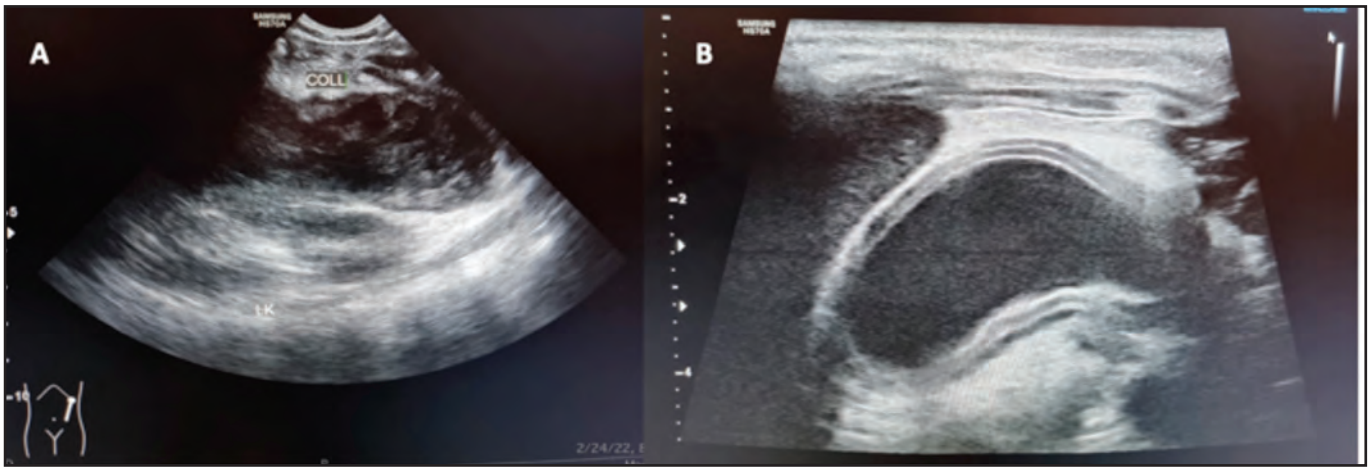

Fig. 1: Initial ultrasound showed heterogenous hypoechoic collection in the left retroperitoneal region (A). Targeted relook ultrasound showed a cystic lesion with the gut signature sign, with echogenic mucosa and hypoechoic muscularis propria, relatively specific for duplication cyst (B).

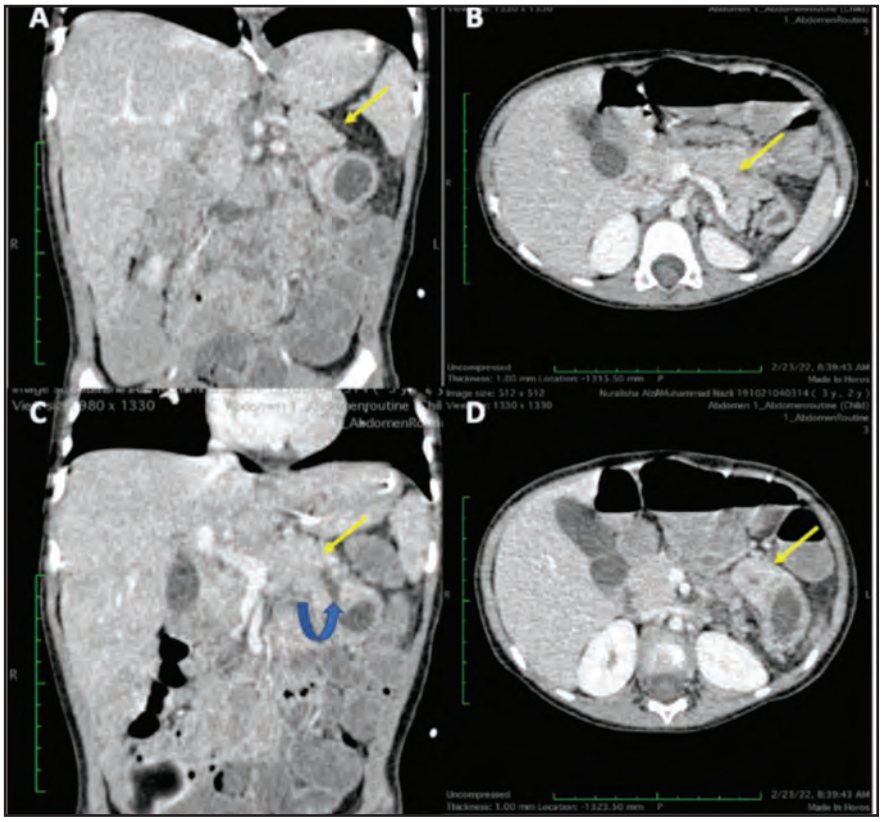

Fig. 2: Contrast-enhanced CT abdomen on coronal reconstruction and axial view showing a bifid pancreatic tail with dorsal tail (A, B) and ventral tail (C, D). Note that the thick-walled cystic lesion is subjacent to the ventral tail of the pancreas, with a dilated distal pancreatic duct as denoted by curved arrow (C). Note that the thick wall cystic lesion has a claw sign with an adjacent ventral tail of the pancreas (D).

duplication cyst with gastric-type mucosa lining is rarer still.[5,6] In the literature, the nomenclature of duplication cysts may be defined based on anatomical origin or histological features.[4,7] In our report, we prefer to classify duplication cysts based on the anatomical origin to avoid confusion. The majority (50%) of the cysts originate from the head of the pancreas, while origin from the body and the tail represent about a quarter each.[4]

Several reports described pancreatic duplications associated with bifid pancreas similar to our case.[2,3,7,8] The cyst may or may not communicate with the main or accessory pancreatic buds.[3,7] These various associations and communication with the pancreatic ducts suggest embryological malformation.[3,7,8]

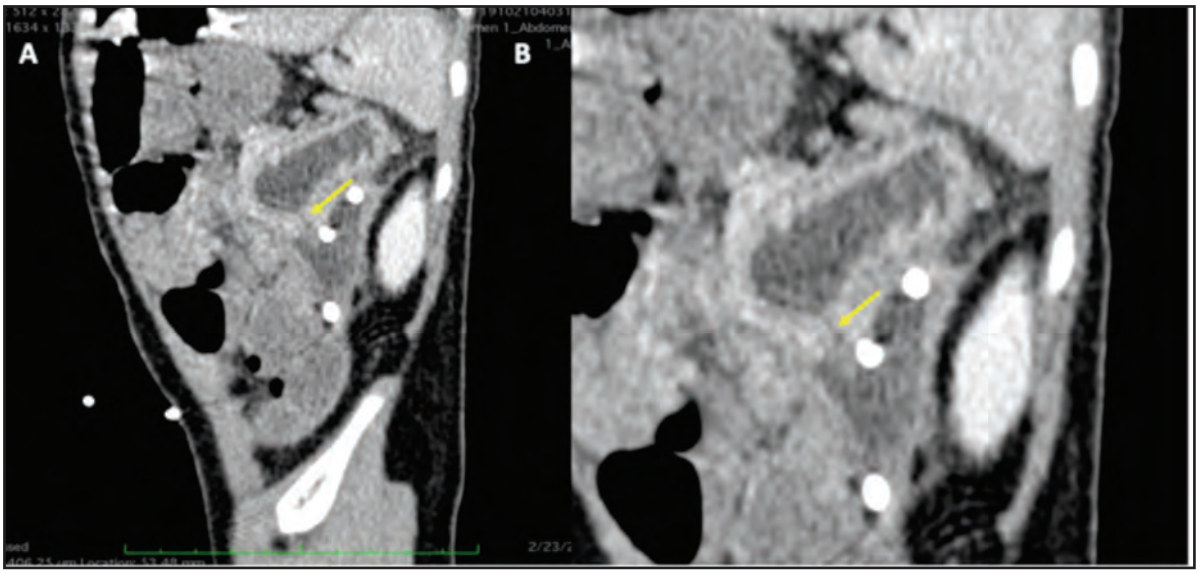

Fig. 3: Contrast-enhanced CT abdomen on sagittal reconstruction showed a focal wall defect at the inferior aspect of the cystic lesion which communicates with the left retroperitoneal collection (A, B). Note the corrugated appearance of the wall of the cystic lesion resembling the gastric wall (B).

There are a few postulations regarding the formation of duplication cysts including partial twinning, split notochord theory, diverticula and canalization defects, and environmental factors.[1] In pancreatic duplication cysts, the most popular theory to its formation is due to a traction diverticula formation along the neuroenteric band between the stomach and the pancreas due to impaired separation of the notochord and endodermal layers.[7,8] This theory may also explain the common association of gastric duplication or pancreatic duplication containing gastric-type mucosa with the formation of a bifid pancreas as the malformation may develop on either end.[8]

The majority of pancreatic duplication cysts present with abdominal pain (67–72%).[2-4] The pain may be due to inflammation and ulceration of the cyst, pancreatitis or perforation leading to peritonitis.[2-4] Repeated infections, obstruction of the pancreatic duct from viscous mucus secretions, or biliary sludge may exacerbate the pancreatitis and ulceration of the cyst.[3] This may be associated with vomiting and the presence of an abdominal mass.[4] Anorexia and weight loss have been reported mimicking presentations of pancreaticoblastoma.5 Rarely the cyst may bleed resulting in anaemia and ulceration into a bowel manifesting as a gastrointestinal (GI) bleed due to hydrochloric acid secretion from gastric mucosa lining the cyst which most likely occurred in our patient.[6,8]

Serum amylase and lipase levels are usually raised but may be normal.[2] Ultrasonography is the first-line imaging for diagnosis and the appearance of the 'gut signature sign' is specific for duplication cysts.[9] However, this feature may not be seen due to the chronic inflammation and perforation of the cyst that has disrupted the cyst wall and was only seen later after drainage of the collection in our patient. Hence CT scan or MRI would be required to identify the location, extent, anatomic relations, and characteristics of the lesion to differentiate it from other cystic pancreatic lesions such as pancreatic neoplasms and pancreatic pseudocyst.[10] MRCP, ERCP, endoscopic ultrasound, and intra-operative pancreaticography are useful adjuncts to further delineate the relationship of the cyst with pancreatic ductal anatomy although all these procedures require general anaesthesia if performed in small children. Ultimately operative findings and histology are required for the final diagnosis.[3,10]

Excision of the cyst is curative.[4] The type of surgical management depends on the location of the pancreatic cyst. For lesions located at the tail of the pancreas, spleen-preserving distal pancreatectomy and cyst excision are recommended to prevent recurrence of the cyst and pancreatitis as well as to prevent potential malignant transformation.[3] Excision of the cyst without damaging the surrounding pancreatic tissue is possible although some patients with lesions at the head of the pancreas may require pancreaticoduodenectomy or Roux-en-Y cystojejunostomy.[4] The overall outcome of pancreatic duplication cyst is good with very low complications.[4]

Although surgical excision is the definitive treatment for the lesion, initial drainage of the cyst should be considered in selected patients. Placement of a drain offers initial symptomatic relief, aid in the diagnosis, and treat infective collections that may potentially progress to sepsis while planning for surgical management of the patient. The presence of stale blood and later greenish fluids that may likely be pancreatic fluids or bile in this case prompted a reassessment of the patient with further imaging that led to the final diagnosis of pancreatic duplication cyst. Percutaneous drain insertion should only be considered if there is an adequate window for puncture and drainage of the collection without injuring vital surrounding structures. Endoscopic transgastric cystogastrostomy has been reported for initial symptomatic relief for pancreatic duplication but this technique is more invasive and would require general anesthesia.[7] Percutaneously inserted drain is less invasive

and can be performed with sedation. This was performed for our patient without any complications and with marked improvement in symptoms before spleen-preserving distal pancreatectomy and cyst excision were performed.

CONCLUSION

Pancreatic duplication cyst is a rare anomaly that usually presents with abdominal pain but rarely with anaemia due to bleeding and perforated cyst. Diagnosis is difficult, a computed tomography (CT) scan is usually needed for diagnosis and surgical planning. In selected patients, an initial percutaneous drain insertion to evacuate the collection from the perforation or the cyst is feasible to provide early symptomatic relief and allow time for further work-up and surgical planning. Treatment of the lesion remains excision of the cyst, preferably with the surrounding pancreatic parenchyma to prevent recurrence and risk of malignant change.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for permission to publish this article. The authors also acknowledge and thank Dr. Zakaria Zahari for performing the surgery for this patient. We would also like to thank the Radiology Department of Hospital Melaka for the diagnostic imaging required and the insertion of a percutaneous drain for the patient. Special thanks also to Puan Delarina for assisting with the submission of this report.

CONFLICT OF INTERESTS

There was no conflict of interest to be declared.

ETHICS BOARD APPROVAL

For the publishing of this article, approval was sought and exempted by the Medical Research and Ethics Committee MREC on 27 March 2023.

CONSENT

Permission was obtained from the parents for this case report.

REFERENCES

1. Russell KW, Holcomb III GW. Alimentary tract duplication. In: Holcomb III GW, Murphy JP, St. Peter SD, Gatti JM, Editors. Holcomb and Ashcraft's Pediatric Surgery. 7th Edition. Edinburgh, Elsevier; 2020 629-40.
2. Banerjee R, Singh G, Aggarwal SK. A rare presentation of Y-duplication of the pancreatic tail with enteric duplication cyst as intussusception in a child : a case report. Int J Surg Case Rep 2021; 78: 96–8. Available from: https://www.sciencedirect.com/science/article/pii/S2210261220311603?via%3Dihub doi: https://doi.org/10.1016/j.ijscr.2020.11.131
3. Fujishiro J, Kaneko M, Urita Y, Hoshino N, Jinbo T, Sakamoto N, et al. Enteric duplication cyst of the pancreas with duplicated pancreatic duct. J Pediatr Surg 2011; 46(8): e13–6. Available from: https://www.jpedsurg.org/article/S0022-3468(11)00387-3/fulltext doi: http://dx.doi.org/10.1016/j.jpedsurg.2011.04.056
4. Hunter CJ, Connelly ME, Ghaffari N, Anselmo D, Gonzalez I, Shin C. Enteric duplication cysts of the pancreas : a report of two cases and review of the literature. Pediatr Surg Int 2008; 24: 227–33. Available from: https://link.springer.com/article/10.1007/s00383-007-2084-6 doi: 10.1007/s00383-007-2084-6
5. Lee CL, Che Daud ZC, Ismail R. Intrapancreatic gastric duplication cyst - a rare cause of chronic abdominal pain in childhood. J Clin Ultrasound 2014; 42(1): 42–4. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcu.22029 doi: https://doi.org/10.1002/jcu.22029
6. Rao KL, Sunil I, Pimpalwar A,Vaiphei K, Chowdhary S. Intrapancreatic gastric duplication cyst presenting as lower gastrointestinal bleeding. J Pediatr Surg Case Rep 2003; 38(2): 243-4. Available from: https://www.jpedsurg.org/article/S0022-3468(02)63061-1/pdf doi: http://doi.org/10.1053/jpsu.2003.50053
7. Rousek M, Kachlik D, Nikov A, Pintova J, Ryska M. Gastric duplication cyst communicating to accessory pancreatic lobe: a case report and review of the literature. World J Clin Cases 2018; 6(16): 1182-8. Available from: https://www.wjgnet.com/2307-8960/full/v6/i16/1182.htm doi: 10.12998/wjcc.v6.i16.1182
8. Spence RK, Schnaufer L, Mahboubi S. Coexistant gastric duplication and accessory pancreas: clinical manifestations, embryogenesis, and treatment. J Pediatr Surg 1986; 21(1): 68–70. Available from: https://www.jpedsurg.org/article/S0022-3468(86)80659-5/pdf doi: http://doi.org/10.1016/S0022-3468(86)80659-5
9. Fonseca EKUN, Sameshima YT. Gut signature sign in enteric duplication cysts. Abdom Radiol (NY) 2018; 43(12): 3513-4. doi: 10.1007/s00261-018-1620-2.
10. Johnson PR V, Spitz L. Cysts and tumours of the pancreas. Semin Pediatr Surg 2000; 9(4): 209–15. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1055858600070031X?via%3Dihub doi: http://dx.doi.org/10.1053/spsu.2000.18845

CASE REPORT

A case of lupus hepatitis

Mohamed Amin Bin Kader, MMed[1], Yun Fei Liang, MRCP[1], Zulaikha Binti Che, MPath[2]

[1]Department of Internal Medicine, Hospital Sultanah Nora Ismail, Batu Pahat, Malaysia, [2]Department of Pathology, Hospital Pakar Sultanah Fatimah, Muar, Malaysia

SUMMARY

Systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) are autoimmune diseases with a multisystem involvement. Hepatic manifestations do occur in these patients. There are various aetiologies for an abnormal liver function tests in this group of patients. Among the differentials include primary SLE-related liver disease called lupus hepatitis. We report a case of a young female who presented with cutaneous and hepatic manifestations of an SLE and scleroderma overlap disease. After ruling out other aetiologies, the patient was then diagnosed as lupus hepatitis. The patient responded well to steroids and is currently on regular follow-ups.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which can affect the skin, joints and kidneys.[1] Liver involvement has been shown to be common in SLE despite not being included in classification criteria.[2] There are various aetiologies for an abnormal liver function in this group of patients. Common causes are drug reaction, viral hepatitis and fatty liver disease.[3] After excluding other causes of abnormal liver function test, the patient was then diagnosed as lupus hepatitis. Lupus hepatitis a non-specific reactive liver disease characterised by asymptomatic elevated alanine transaminases level.[1] The prevalence of it in SLE patients has been reported to be around 3–23%.[3] We report a case of lupus hepatitis in a young female who presented with cutaneous and hepatic manifestation of an SLE and scleroderma overlap disease.

CASE PRESENTATION

A 26-year-old female was admitted with generalised maculo-papular rash involving the face, trunk and limbs (Figure 1). The rashes started 3 days prior to admission and were described as itchy and painless. It was associated with fever and polyarthralgia for 2 weeks. There was no oral ulcer or vasculitic skin lesion seen. She denies a history of allergies, illicit drug or traditional medication consumption. The patient also had incidental acute hepatitis whereby her alanine aminotransferase (ALT) test was almost > 10x ULN. An ultrasound of the abdomen revealed she had hepatosplenomegaly with no biliary duct obstruction. Her antinuclear antibody was positive with titre 1:320, speckled pattern. Her anti-dsDNA level and extranuclear antibody (ENA) were negative. She had a low C4 complement at the level of 0.11 g/L with normal complement C3 level, high anti-Cardiolipin Ig G level at 36.8U/ml and other workout for antiphospholipid syndrome were all negative. Hepatitis B, hepatitis C screening and AIH/PBC (autoimmune hepatitis, primary biliary cholangitis) workout were negative. Therapeutic drug monitoring for paracetamol was sent randomly and reported a level of 0.6mcg/ml, which was not significant. She was then counselled for a liver and skin biopsy. She strongly refused a liver biopsy. A skin biopsy was then done over the left back, revealing lymphohistiocytic cells infiltrates at the perivascular and periadnexal area, correlating to the diagnosis of acute cutaneous lupus. At the same time, dense thickened collagen bundle was seen in the dermal area, which is suggestive of scleroderma (Figure 2). She fulfilled 2019 EULAR/ACR classification criteria for SLE. She was diagnosed with lupus hepatitis and acute cutaneous lupus with underlying SLE scleroderma overlap syndrome after correlating with her skin biopsy result. A tapering dose of oral prednisolone together with topical hydrocortisone 1% cream was initiated, and she responded well to it. Her skin rashes had fairly subsided, and her liver function test has almost normalised. Her serial liver function is shown below (Table I).

DISCUSSION

SLE and systemic sclerosis (SSc) can have a multisystem involvement involving the skin, kidneys and the central nervous system. Liver involvement is not part of its criteria but can affect at least 60% of its patients. The most common causes of involvement in these patients would include drug-induced hepatitis, viral hepatitis such as hepatitis B or hepatitis C and autoimmune hepatitis which is characterised by elevated serum immunoglobulin levels and presence of autoantibodies. In this patient, however, the results were all negative. Hence, the patient was diagnosed as lupus hepatitis in the setting of an SLE and SSc overlap disease. Bessone et al.[4] described lupus hepatitis as entity with asymptomatic elevated transaminitis in the setting of an active SLE flare.[4] Recent studies into hepatic manifestations in SLE patients have found that the presence of ribosomal P autoantibodies to be involved. 70% of SLE patients with lupus hepatitis are known to have this autoantibody.[5] It is an antilymphocyte antibody that specifically reacts with activated T cells.[5] The most common hepatic manifestation with SSc would include primary biliary cholangitis (PBC). PBC is characterised by the presence of a positive antimitochondrial antibody or presence of a florid duct lesion based on liver biopsy. However, this patient refused for liver biopsy during the current admission. As the patient was initially thought to

This article was accepted: 02 November 2023
Corresponding Author: Yun Fei Liang
Email: Yunfei9539liang@hotmail.com

Table I: Serial liver function test of the patient showed resolving transaminitis after started on steroid

	Day 1	Day 4 Started steroid	Day 5 1 week on steroid	Day 10 2 weeks on steroid
TB	13.5	41.3	14.1	12.9
ALT	981	1026	362	82
AST	529	387	61	23
LDH	1489	1281	266	/
HB	14.4	14.3	13.1	13.8
TWC	13.63	11.25	13.7	16.80
EOS Abs	0.13	0.13	0.04	0.01
EOS %	1.0	1.2	0.3	0.1
PLT	259	170	346	416

TB: total bilirubin umol/L, ALT: alanine aminotransferase U/L, AST: aspartate aminotransferase U/L, LDH: lactate dehydrogenase U/L, HB: haemoglobin 10^9/L, TWC: total white count 10^9/L, EOS Abs: eosinophil absolute count 10^9/L, EOS: eosinophil percentage %, PLT: platelet 10^9/L.

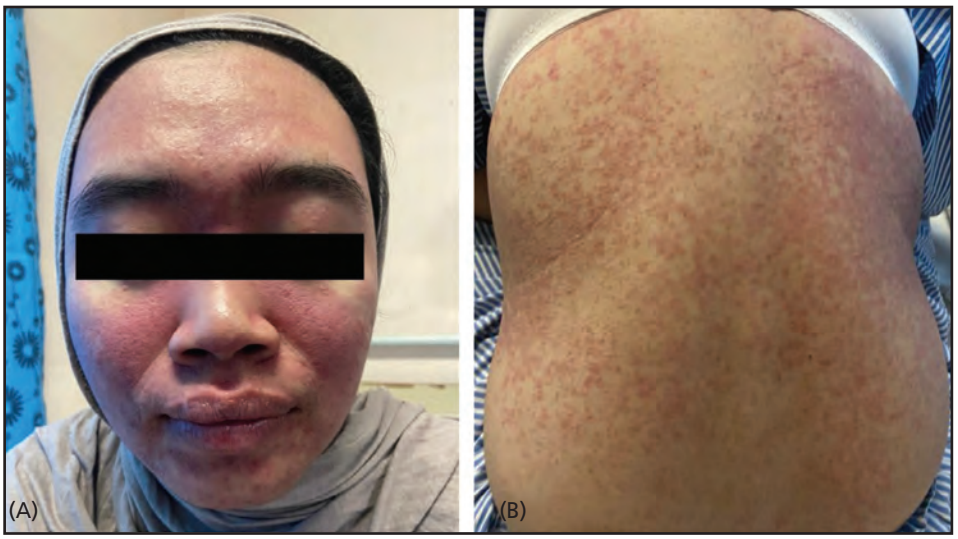

Fig. 1: (A) Facial erythema (B) Back of trunk with maculo-papular rashes.

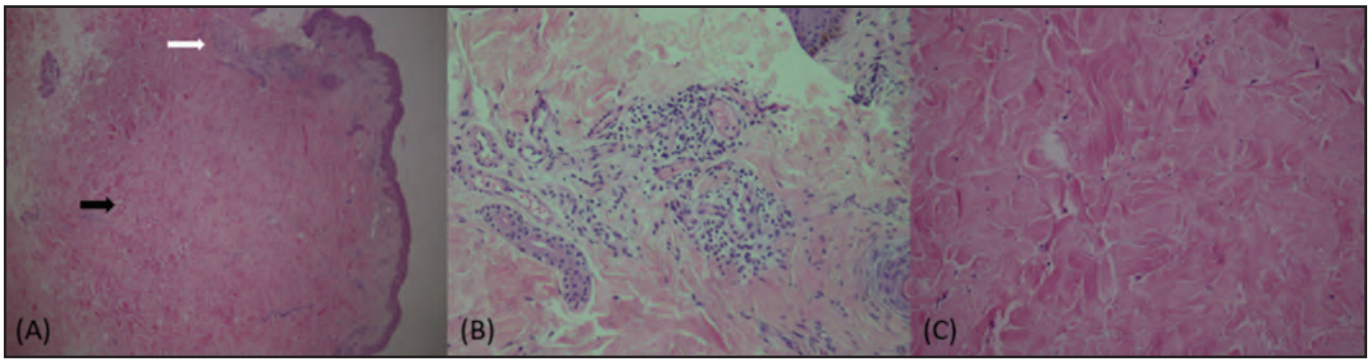

Fig. 2: Skin biopsy (A) White arrow: Mild lymphohistiocytic cells infiltrate at perivascular and periadnexal area. Black arrow: Dense thickened collagen bundle in the dermal area with a displacement of adnexal structures, 10×. (B) lymphohistiocytic cells infiltrate at perivascular and periadnexal area, 40×. (C) Dense thickened collagen bundle, 40×.

have a lupus flare, she was initiated with a tapering course of corticosteroids. She began improving for both her skin lesion and liver function. She is currently on the low prednisolone dose, 5 mg daily and her quality of life has improved tremendously. She does not exhibit other manifestations of SSc at the time being such as Raynaud's phenomenon or 'CREST' syndrome (Syndrome of calcinosis, Raynaud phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia).

CONCLUSION

Lupus hepatitis, though uncommon, has to be considered in any patients with SLE and SSC overlap syndrome presenting with a deranged liver function. Liver biopsy would be beneficial to clinch the diagnosis. However, in this case, the patient refused. Prompt investigations to exclude other causes and early treatment initiation would be beneficial.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

ACKNOWLEDGEMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

PATIENT CONSENT

Patient reviewed the photos and agreed for the publications of her history and photos.

REFERENCES

1. González-Regueiro JA, et al. Hepatic manifestations in systemic lupus erythematosus. Lupus 2020; 29(8): 813–24.
2. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Liver involvement in patients with systemic autoimmune diseases. Maedica (Bucur). 2013; 8(4): 394–7.
3. Imran S, Thabah M, Azharudeen M, et al. Liver abnormalities in systemic lupus erythematosus: a prospective observational study. 2021; Cureus 13(6): e15691.
4. Bessone F. Challenge of liver disease in systemic lupus erythematosus: clues for diagnosis and hints for pathogenesis. World J Hepatol 2014; 6(6): 394.
5. Patel S, Demory Beckler M, Kesselman MM. Lupus and the liver: a case study. Cureus 11(8): e5477.

A case report of Plummer–Vinson Syndrome in a young adult with poor eating habits

Siti Nur Hakimah Hashim, MMed, Woo Wing Hang, MMed, Kok Wei Hao, MMed, Lee Chong Chearn, MMed, Khairul Najmi Muhammad Nawawi, FRCP

Gastroenterology Unit, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

SUMMARY

Iron deficiency anaemia (IDA) is a very common disease, especially in poor and developing countries. It has a high prevalence in children and young adults. In young patients with no other confounding factors other than nutritional deficiency, the treatment is straightforward with either an oral or intravenous iron supplementation. Nonetheless, IDA in older patients requires attention to red-flag symptoms such as dysphagia, loss of appetite, early satiety and loss of weight. Further investigations including an oesophagogastroduodenoscopy (OGDS) are required to identify any sinister causes in such cases. We report an IDA case of a young woman who presented with dysphagia, in which further investigations with OGDS and a barium swallow test revealed a diagnosis of Plummer–Vinson syndrome.

INTRODUCTION

Oesophageal web is a thin, semi-circular membranous structure in cervical oesophagus consisting of mucosa and scanty fibrous tissue. It is a rare cause of dysphagia. Plummer–Vinson syndrome (PVS) is characterised by the triad of oesophageal web, dysphagia and IDA. PVS is a predominantly disease of middle age females and rarely happen in young adult or childhood.[1] The overall incidence of PVS has declined over the years due to improved nutritional status.[2] However, profound transition in lifestyle and eating habits among young adult has placed them in nutritionally vulnerable population that fail to achieve dietary requirements, predisposing them to develop PVS. We have reported a case of PVS in a young woman who presented with dysphagia and history of bad eating habits.

CASE PRESENTATION

A previously fit 18-year-old Malay lady presented to a gastroenterology clinic with a complaint of dysphagia for a two-month duration. She described the dysphagia as difficulty to swallow solid food which was slightly relieved with a small amount of fluid. Otherwise, there was no significant loss of weight, loss of appetite, gastroesophageal reflux symptoms or change in bowel habit. She also denied any haematochezia or melaena and autoimmune disease symptoms. She had an uneventful birth history with normal vaginal delivery without developmental delay. There was no family history of malignancy.

Her clinical examination revealed a pale underweight woman of body mass index 18 kg/m^2 with angular cheilitis. Other systemic physical examinations were otherwise unremarkable. There was IDA from her blood investigations with a hypochromic microcytic anaemia with haemoglobin level of 7.7 g/dL, mean cell volume (MCV) of 54 fL, and mean cell haemoglobin (MCH) of 15.6 pg, and low iron, ferritin and transferrin saturation levels of 2.2 µmol/L, 7.9 µg/L and 2.7% respectively. Other blood tests including renal profile, liver function test and thyroid function test were unremarkable.

An OGDS demonstrated a web-like narrowing of upper oesophagus immediately post-cricoid at 17 cm from incisor (Figure 1). A normal calibre gastroscope was not able to advance beyond the stricture. Therefore, a slim calibre gastroscope with a diameter of 5.5 mm was subsequently used to pass through the oesophageal web, which spontaneously tore the web and dilated the stricture. No biopsy was done due to the mild bleeding of the tear. The remaining parts of the oesophagus were unremarkable without white exudates, concentric rings, or longitudinal furrows to suggest an eosinophilic oesophagitis. Stomach mucosa was normal, while the second and third part of duodenum did not show any endoscopic features of celiac disease, such as mucosal or villous atrophy or scalloping of the mucosa. Subsequently, a barium swallow test revealed a suspicious filling defect in the oesophagus (Figure 2). She was eventually diagnosed with Plummer–Vinson syndrome taking into consideration overall clinical findings. On further questioning of the patient's dietary habit, she admitted having poor eating habits since childhood. She usually skipped breakfast with only one heavy meal per day, which consists mainly of carbohydrates. Besides, she preferred to eat snacks and sweet beverages which contained high sugar with low fibre, protein and micro- or macronutrients. She denied any incidence of body shaming or fear of gaining weight. She had no issues at school or with peers.

She was given iron infusion with 1 g of ferric carboxymaltose followed by oral iron supplementation for 6 weeks. Oral proton pump inhibitors were also given to help in mucosal healing. A follow-up OGDS 6 weeks later revealed a wider oesophageal lumen at the previous oesophageal web, passable by a normal calibre gastroscope with gentle manoeuvre (Figure 3). Her symptoms resolved completely 6 weeks after OGDS and iron supplement. Her repeated blood parameters after 6 weeks showed haemoglobin of 11.8 g/dL with MCV of 72 fL and MCH of 26.6 pg, and iron, ferritin and

This article was accepted: 03 November 2023
Corresponding Author: Khairul Najmi Muhammad Nawawi
Email: khairulnajmi84@gmail.com

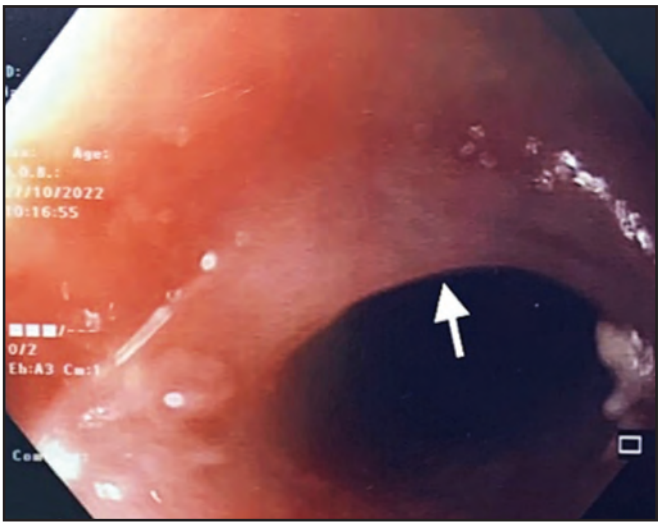

Fig. 1: White arrow showing the circular thin membrane (web) at upper oesophagus.

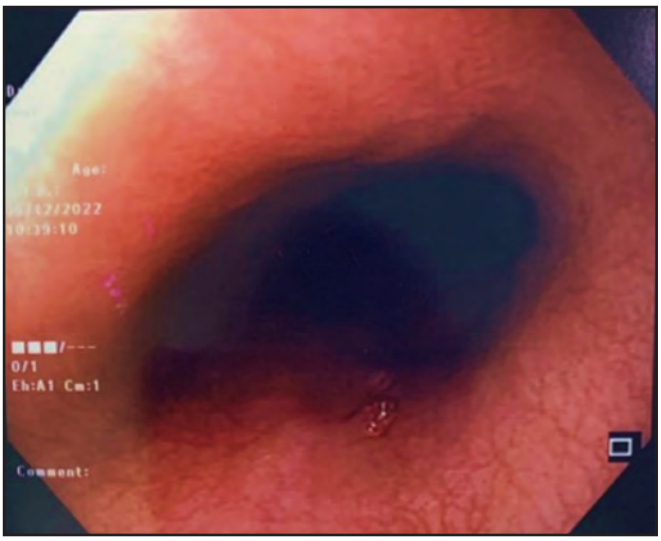

Fig. 3: Follow-up oesophagogastroduodenoscopy 6 weeks later showed resolution of oesophageal web and wider oesophageal lumen.

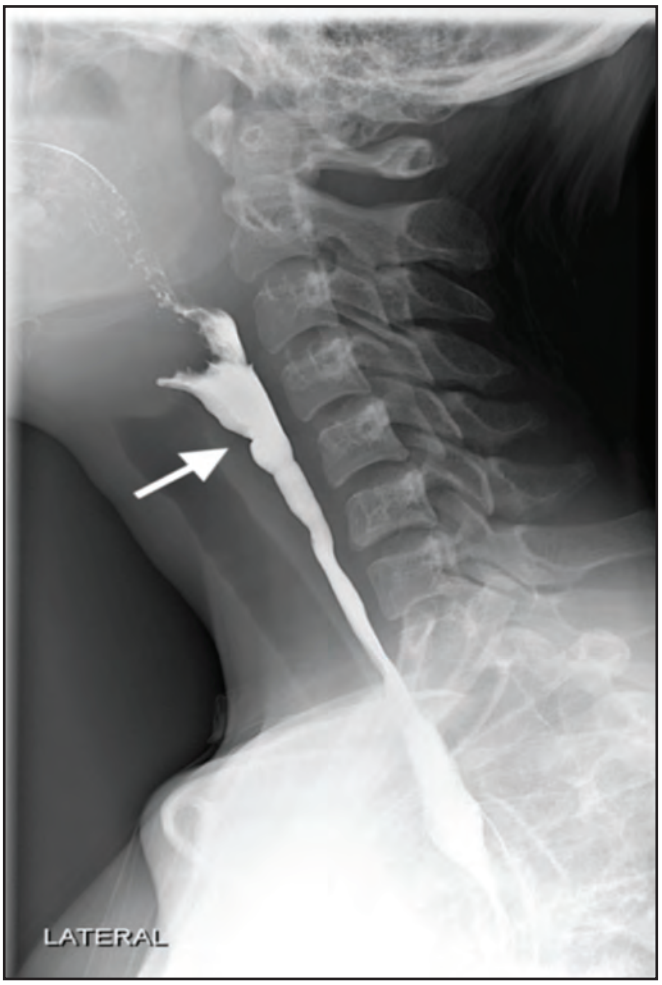

Fig. 2: White arrow showing suspicious filling defect in oesophagus.

transferrin saturation levels of 12.9 µmol/L, 114 µg/L and 24.5% respectively. She remained asymptomatic during a follow-up 4 months later with normalisation of her blood parameters with haemoglobin, iron, ferritin and transferrin saturation levels of 12.5 g/dL, 21.2 µmol/L, 31.8 µg/L and 34% respectively.

DISCUSSION

Plummer–Vinson syndrome is also known as the Paterson Brown–Kelly syndrome, which is a syndrome of a classical triad of dysphagia, oesophageal web and hypochromic microcytic anaemia. It was first reported by Henry Stanley Plummer in 1912 and is commonly found in middle-aged women. Nowadays, the syndrome is very rare due to improvements in nutritional status in developed countries. There is no recent data on the incidence and prevalence of this syndrome due to its rarity.[3] PVS often presents with symptoms of painless dysphagia, which is intermittent or progressive over years. It is usually confined to solid food and is occasionally associated with weight loss. Patients with PVS may manifest the signs and symptoms of anaemia, such as lethargy, palpitation, glossitis, angular cheilitis and koilonychias.

The exact aetiology of PVS is still unknown; numerous potential causes were proposed, including iron deficiency, autoimmune-related disorders, thyroid disease and malnutrition. IDA is postulated to be the aetiology as the symptoms usually improve with iron supplementation. This can be explained by the myasthenic changes in the alimentary tract muscles due to rapid depletion of iron-dependent oxidative enzymes in IDA, leading to mucosal degeneration, muscle atrophy and oesophageal web formation.[4] Inadequate iron intake is the predominant cause of IDA in developing countries. In our case, poor eating habits and a dietary deficiency of iron were the culprits in developing PVS.

Oesophageal webs can be detected by barium swallow radiography and endoscopy. The webs appear smooth, thin,

eccentric, and commonly located at the anterior wall of the oesophagus. OGDS has the advantage of direct visualisation of the webs, taking tissue biopsy and permitting treatment in the same setting. However, the webs may be missed by OGDS as its location is very close to the upper oesophageal sphincter.[5]

The management of Plummer–Vinson syndrome is generally straightforward. Iron supplementation is the standard first-line therapy which can effectively alleviate the symptoms. Intravenous iron therapy is more efficacious and can rapidly increase iron and ferritin levels compared to oral iron supplements.[6] An observational study by Das et al.[7] comparing the efficacy of oral and intravenous iron in raising the haemoglobin and ferritin levels after 28 days of treatment showed a statistically significant result ($p < 0.001$) in the intravenous iron group. Other than giving iron supplements, a healthy diet is important as these patients usually have concomitant vitamins and electrolytes deficiencies. However, in those patients with dysphagia who do not improve with iron supplementation, a mechanical dilation of the oesophageal web is needed. A single or serial dilatation might be needed to relieve the oesophageal stricture by using endoscopic bougies or balloon dilatation.[8] A study by Huynh et al.[9] showed that a single session of balloon dilation is able to dilate the web with low risk of perforation and recurrence. Although the treatment is simple and symptoms can completely resolve after the correction of IDA, most patients need a scheduled follow-up as this syndrome is considered a precancerous state with a risk of squamous cell carcinoma of hypopharynx and upper oesophagus. About 10% of patients with Plummer–Vinson syndrome have a high risk of developing squamous cell carcinoma thus a surveillance endoscopy three-yearly is recommended.[10] In addition, for patients who have lack of symptoms and biochemical resolution despite medical and endoscopic interventions, relevant investigations to look for autoimmune and rheumatological disorders need to be performed, especially if the clinical suspicion index is high.

CONCLUSION

High index of suspicion for Plummer–Vinson syndrome in patients with dysphagia and IDA is crucial to prompt diagnosis and initiate treatment in order to prevent the development of complications such as oesophageal stricture and malignancy.

REFERENCES

1. Atmatzidis K, Papaziogas B, Pavlidis T, Mirelis CH, Papaziogas T. 2003. Plummer-Vinson syndrome. Dis Esophagus 16: 154-57.
2. Patil M, Malipatel R, Devarbhavi H. 2021. Plummer–Vinson syndrome: a decade's experience of 132 cases from a single center. J Gastroenterol Hepatol 36(1): 181-85.
3. Verma S, Mukherjee S. 2019. Plummer Vinson syndrome. Europe PMC.
4. Karthikeyan P, Aswath N, Kumaresan R. 2017. Plummer–Vinson syndrome: a rare syndrome in male with review of the literature. Case Rep Dentist v.2017: 1-5.
5. Goel A, Bakshi SS, Soni N, Chhavi N. 2017. Iron deficiency anemia and Plummer–Vinson syndrome: current insights. J Blood Med v.2017(8): 175-84.
6. Bhandal N, Russell R. 2006. Intravenous versus oral iron therapy for postpartum anaemia. BJOG 113(11): 1248-52.
7. Das SN, Devi A, Mohanta BB, Choudhury A, Swain A, Thatoi PK. 2020. Oral versus intravenous iron therapy in iron deficiency anemia: an observational study. J Fam Med Primary Care 9(7): 3619.
8. Novacek G. 2006. Plummer-vinson syndrome. Orphanet J Rare Dis 1(1): 1-4.
9. Huynh PT, de Lange EE, Shaffer Jr HA. 1995. Symptomatic webs of the upper esophagus: treatment with fluoroscopically guided balloon dilation. Radiology 196(3): 789-92.
10. Messmann H. 2001. Squamous cell cancer of the oesophagus. Best Practice Res Clin Gastroenterol 15(2): 249-65.

CASE REPORT

Extended surgery with en block resection of the right external iliac vessels for lymph node metastasis of colon carcinoma, a case report

Ehab Said, MBBCh[1,2,3], Kishen Raj Chandra Sakaran, MBBS[4], Putera Mas Pian, MD[4,6], Sellymiah Adzman, MBBS[5]

[1]Surgical Department, Kuala Lumpur Hospital, [2]Surgical Department, University Malaya Medical Centre, [3]MRCS Edinburgh, [4]Surgical Department, Hospital University Kebangsaan Malaysia, [5]Pathology Department, Kuala Lumpur Hospital, [6]Fellow of Vascular Surgery Fellowship Ministry of Health Malaysia

SUMMARY

We report herein the case of a 26-year-old woman who underwent surgery for recurrent adenocarcinoma of the caecum. Recurrent metastatic lymph nodes had invaded the right external iliac vessels. Neither distant metastases nor peritoneal dissemination were recorded. Extended surgery with en bloc resection of the right external iliac vessels, right kidney, right ureter, uterus, bilateral ovaries and bilateral fallopian tubes and femorofemoral bypass were performed. Postoperatively, the patient recovered well and was discharged 3 weeks after surgery. The procedure may well significantly prolong survival time and improve quality of life of patients with identical or very similar conditions.

INTRODUCTION

In the majority of cases, patients with recurrent colorectal adenocarcinoma are not made to undergo re-resection and neither do they respond well to chemotherapy. It has however been established that patients with resectable recurrent tumours usually have longer-term survival than those with unresectable tumours.[1,2] This report describes the case of a patient in whom extended lymphadenectomy for recurrent adenocarcinoma was successfully performed with en bloc resection of the right external iliac artery and vein.

CASE PRESENTATION

A 26-year-old female patient was found to have a tumour in the right lower quadrant of the abdomen by a computed tomography (CT) scan. She had previously undergone a right hemicolectomy having been diagnosed with poorly differentiated adenocarcinoma of the caecum. Pathological findings demonstrated that cancer cells had invaded through the muscularis propria into pericolorectal tissues with vascular invasion and metastasis to one regional lymph node. Adjuvant chemotherapy with oral capecitabine and oxaliplatin was prescribed post surgery; however the patient had low tolerance towards the chemotherapy regime. The treatment was subsequently terminated at the end of the fifth cycle. A CT scan surveillance done five months later showed soft tissue lesion, 2.8 X 3.2 X 4.7 cm in size with adjacent clumping of small bowel loops at the side of a previously enlarged necrotic node anterior to the right psoas muscle. It was suspected to be a local recurrence with extensive portal vein and superior mesenteric vein thrombosis (Figure 1). A much delayed Positron Emission Tomography (PET) scan later confirmed the hypothesis was a correct one. The tumour had by then enlarged to 5.3 X 6.4 X 5.4 cm in size and had infiltrated into the adjacent small bowel loops, right common iliac vessels, right adnexa and right distal ureter causing right obstructive uropathy (Figure 2). Several repeated examinations later concluded that no other distant metastases or malignancies of the remnant colorectum were present.

A multi-disciplinary team comprising of colorectal surgeon, vascular surgeon, orthopaedic surgeon, gynaecologist, urologist, pathologist and radiologist recommended excision of the tumour to which the patient consented. The procedure was made according to the standard operation and guidelines in Ministry of Health of Malaysia; (General Surgical Services Operational Policy 2018, Safe Surgery Guidelines 2018, General Hospital Operational Policy and Clinical Practice Guidelines for the Management of Colorectal Carcinoma).

A laparotomy was performed after a lapse of six months based on the diagnosis of local recurrence of metastatic lymphadenopathy. A tan-greyish tumour with areas of necrosis and ulceration was found to have invaded the right external and internal iliac vessels. The fundus of uterus, right ovary, right fallopian tube and right ureter were also observed to have been infiltrated. However, no peritoneal dissemination or other lymphadenopathies were observed. The tumour was resected together with segments of incorporated small bowels, right external iliac vessels, right kidney, right ureter, bilateral ovaries, bilateral fallopian tubes and uterus. A femorofemoral bypass with a polytetrafluoroethylene graft was also carried out.

Grossly, the right external iliac vessels, the right ureter, right ovary and right fallopian tube were completely embedded in the tumour which was probably composed of conglomerated lymph nodes. Microscopically, the tumour was confirmed to be metastasis of poorly differentiated adenocarcinoma to the lymph nodes. Its histology was essentially identical to that of the caecal adenocarcinoma resected previously (Figures 3 - 5). The re-sectioned margins were free of tumour cells. No malignancy was identified in the right kidney, right ureter, uterus, right ovary and fallopian tube.

Postoperatively, the patient recovered well and was

This article was accepted: 03 November 2023
Corresponding Author: Ehab Said
Email: ehab.said.talib@gmail.com;saidtlb@yahoo.com

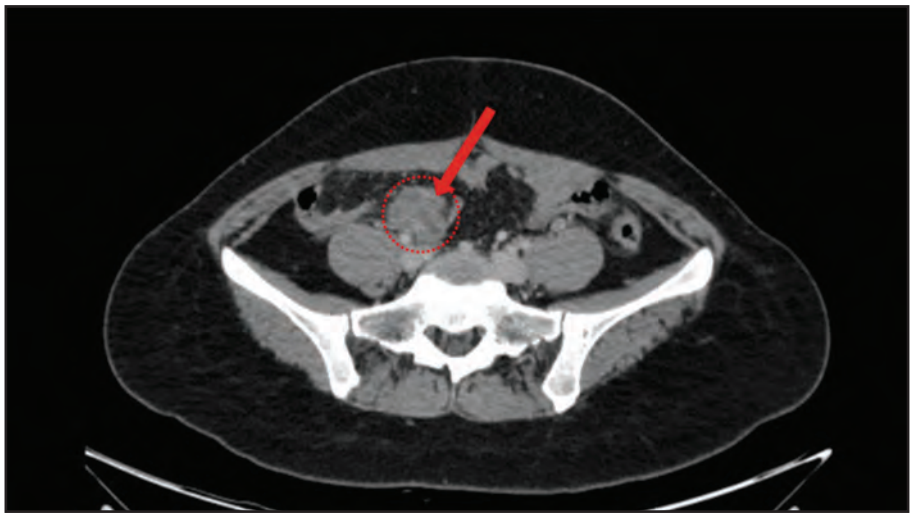

Fig. 1: Pre-operative contrast enhanced computerized tomography of the thorax and abdomen showing local recurrence. (Four months post surgery).

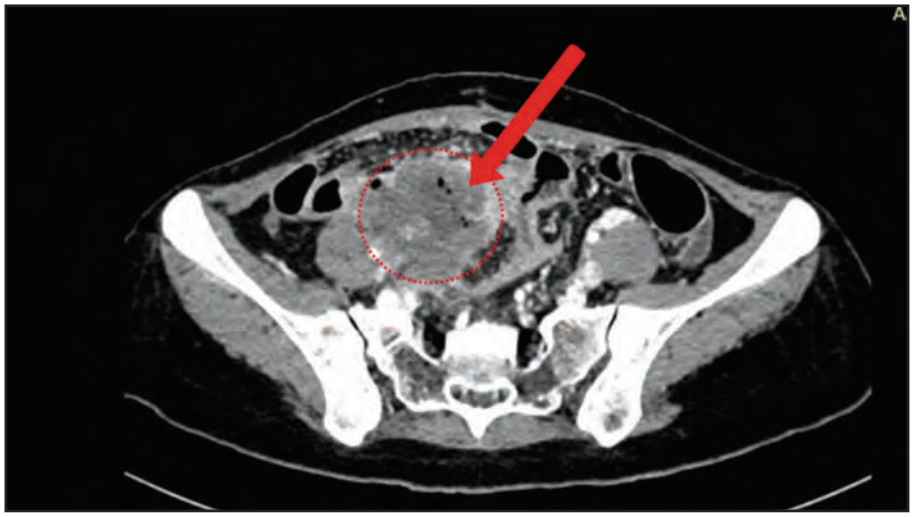

Fig. 2: Preoperative contrast enhanced computerized tomography of the thorax and abdomen showing tumour infiltration into adjacent small bowel loops, right common iliac vessels, right adnexa and right distal ureter (30 weeks post surgery).

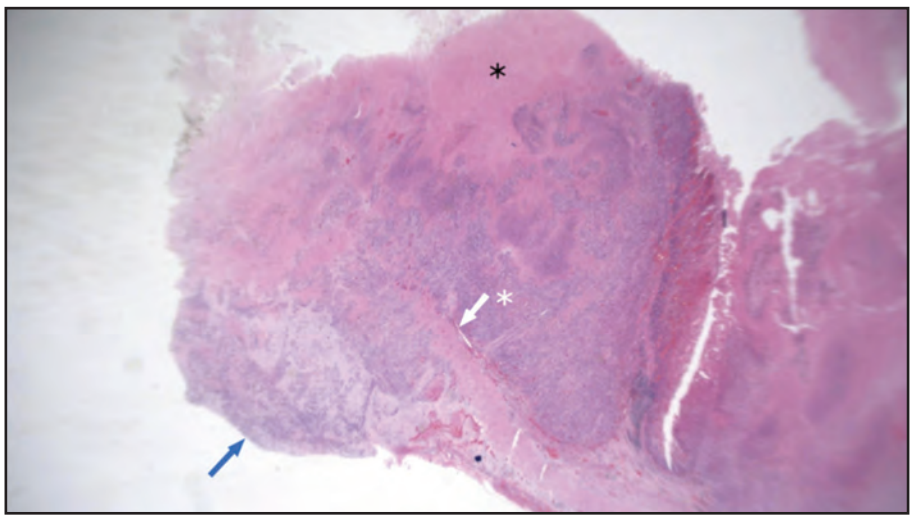

Fig. 3: The tumour has ulcerated and necrotic mucosal surface (black asterisk *). The viable tumour (white asterisk *) has infiltrated the muscularis propria layer (white arrow) and serosa (blue arrow) [H&E,x20].

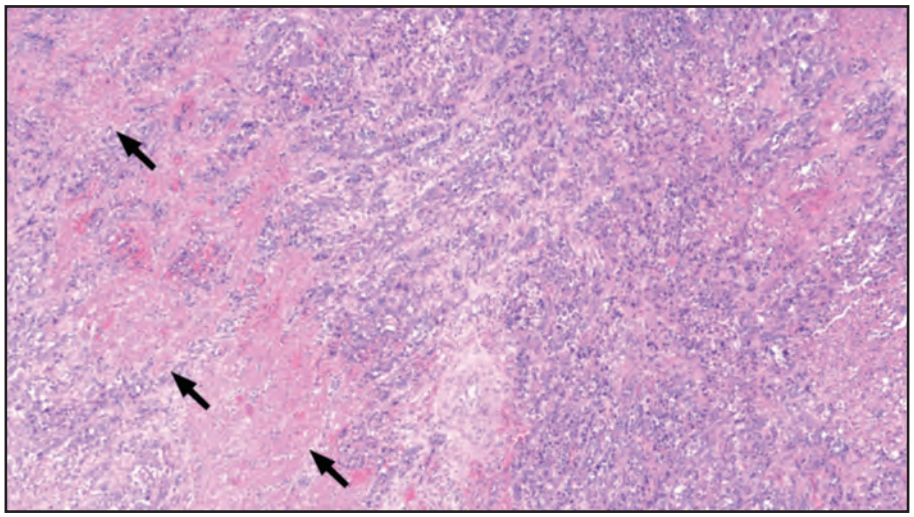

Fig. 4: Higher power showing the tumour cells infiltrating the muscularis propria layer (black arrows). The tumour cells mainly arranged in cords with no obvious tubular or glandular formation [H&E, x40].

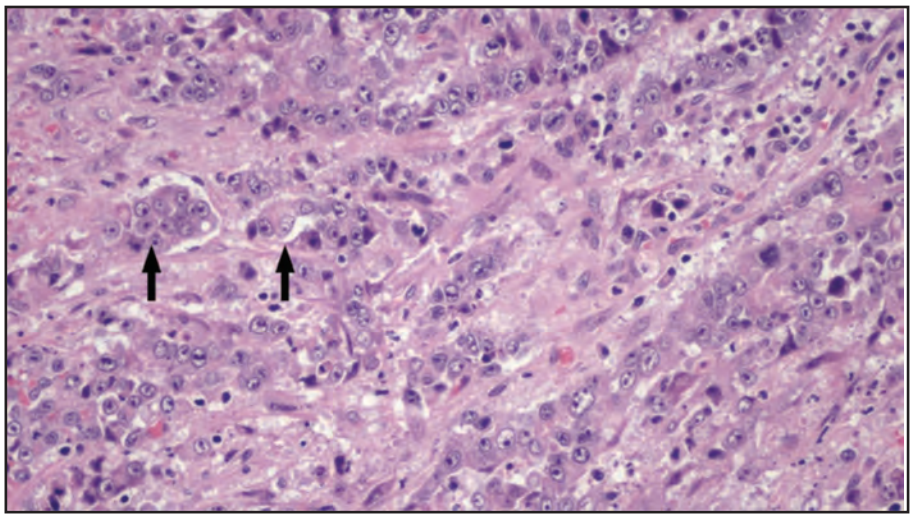

Fig. 5: The tumour cells have pleomorphic vesicular nuclei, prominent nucleoli and moderate amount of cytoplasm. There is also intratumoural lymphocytic infiltration. Some vague glandular formation is appreciated (black arrows) [H&E, x200].

discharged three weeks later. She was given five courses of weekly chemotherapy, as 5-fluorouracil 500mg/m^2 and leucovorin 30mg/m^2. Peritoneal dissemination was subsequently identified by computed tomography (CT) after her operation, and she died 4 months later

DISCUSSION

Poorly differentiated adenocarcinomas of the colon and rectum seem to be more aggressive and are accompanied by less favorable prognosis than lesions classified as well-differentiated adenocarcinomas as observed by D'Eredita et al.[3] It has been suggested that poorly differentiated adenocarcinomas may have an increased incidence of local extension, resulting in lower rates of curative and overall resection. More significantly, poorly differentiated adenocarcinomas might also have an increased incidence of both local recurrence and distant metastases that lead to decreased overall survival, particularly when the tumour is located in the rectum or rectosigmoid area.

Local recurrence is more frequently observed in patients with poorly differentiated adenocarcinoma than in those with well-differentiated adenocarcinomas. Post resection local recurrence of colorectal tumors may occur via operative implantation of viable cells or as a result of growth of residual tumour cells as suggested by Welch et al.[4] Aggressive surgical excision is therefore required, with wide margins and complete dissection of the tumour extending into adjacent structures with systemic lymphadenectomy. Recent improvements in radiation technology and chemotherapeutic agents now allow better targeted treatments according to the observed pattern of recurrence. However, radiation therapy and chemotherapy alone have only a palliative effect, concluded Lopes et al.[5]

Femorofemoral crossover bypass is a surgical arterial revascularization modality which is commonly performed for unilateral aortoiliac occlusive disease. It is primarily applied to patients with intermittent claudication or chronic threatening limb ischemia in whom underlying anatomic constraints rule out endovascular means of restoring in-line flow and those who do not qualify for anatomic reconstruction due to the comorbid conditions that preclude a more invasive open surgical approach. Contraindications for femorofemoral crossover bypass surgery includes compromised inflow aortoiliac arterial segment, advanced obesity which can lead to unfavourable graft geometry, and excessive medical risks for all types of surgical procedures, stated Ascher et al.[6] During early postoperative period, close hemodynamic monitoring is obligatory to optimize the outcomes. Standard anti-aggregant and/or anti-coagulant therapy should be initiated in early postoperative period. Another important issue is the care of surgical wounds, because existence of prosthetic graft increases the risk of infections caused by resistant microorganisms, thus surgical wounds should be examined meticulously in terms of early signs of infection, which should be treated immediately when observed. Prophylactic antibiotics should be administered before the future surgical procedures which can lead to bacteremia, like orodental interventions. Patients should be followed closely in terms of the development of potential complications. Reported primary patency rates vary between 71% and 94% at 1 year, 49% and 89% at 5 years, and 48% and 84%at 10 years, while secondary patency rates are between 79% and 98% at 1 year, 68% and 93% at 5 years, and 63% and 83% at 10 years as recorded by Johnson et al.[7] The most observed complications following femorofemoral crossover bypass operation are hematoma, bleeding which required early reoperation, wound healing problems, superficial wound infections, graft infections, graft thrombosis and occlusion, and false aneurysm formation. Pai et al.[8] observed that major amputation rates reported in the literature varies between 1.4% and 3.5%. The most preferred grafts for femorofemoral crossover bypass operations are synthetic grafts such as polytetrafluoroethylene and Dacron grafts. Autogenous grafts such as great saphenous vein are rarely used as femorofemoral crossover bypass graft. There are conflicting results regarding the use of great saphenous vein as femorofemoral crossover bypass graft in the literature. Mingoli et al.[9] reported that 5- and 8- year patency rates of great saphenous vein graft were significantly lower than synthetic grafts. However, Pai et al.[8] stated that great saphenous vein as a femorofemoral crossover bypass graft was as effective and durable as a synthetic graft. Nonetheless, it is known that great saphenous vein should not be used as graft material in the existence of deep vein thrombosis. Comparative studies related to graft choice in the literature have been most commonly focused on the comparison of Dacron and polytetrafluoroethylene (PTFE) grafts. These studies have demonstrated that Dacron and polytetrafluoroethylene (PTFE) grafts affect the short-term and long-term patency similarly, and there is no significant difference between both synthetic graft materials according to Johnson et al.[7]

After searching the database of Medline and Web of Sciences, only one case of extended curative surgery for metastatic lymph nodes of the colon with en bloc resection of the common iliac vessels have been reported in the English language medical literature. Ueda et al.[10] reported a case in 2001 in a 63-year-old woman who was found to have had a local recurrence of metastatic lymphadenopathy. She had previously undergone a right hemicolectomy under the diagnosis of mucinous carcinoma of the cecum. The patient underwent surgery and the tumor was resected together with the right common iliac artery, common iliac vein, ureter, invaded mesenterium, and regional paraaortic lymph nodes, and a femorofemoral bypass with a polytetrafluoroethylene graft was carried out. Microscopically, the tumor was confirmed to be metastasis of mucinous carcinoma to the lymph nodes, the histology of which was the same as that of the caecal carcinoma resected at the previous operation. Postoperatively, a graft thrombosis developed which was successfully treated by prompt Fogarty catheter thrombectomy. The patient had adjuvant chemotherapy after the operation and died of disease 18 months later from peritoneal dissemination. If tumour cells have invaded the regional vessels, lymphadenectomy alone cannot remove all the malignant tissue, because cancer cells remain on the surface of regional vessels. While en bloc resection together with the invaded vessels can be curative, extended surgery, especially with resection of major blood vessels, is associated with higher rates of morbidity and mortality than palliative surgery. Moreover, in most countries, distant lymph node metastasis indicates systemic disease, so aggressive surgery is generally not performed. On the other hand, in Japan, systematic lymphadenectomy is thought to be the most effective procedure for prolonging the survival of patients with colorectal cancer as reported by Yoshida et al.[11] Although patients with distant lymph node metastasis have a poor prognosis, they may still undergo systematic lymphadenectomy in Japan, observed Masaki et al.[12] We believe that systematic lymphadenectomy is ineffective for paraaortic lymph node metastasis but that it is effective for regional lymph node metastasis. In our patient, no recurrent tumor was identified by radiological examinations although she died of peritoneal dissemination 4 months after her second operation.

Admittedly, our case and that reported by Ueda et al.10, differ significantly in age. However, we have not found literature that reported pathological difference between malignancies associated with age.

We suggest that extended lymphadenectomy with en bloc resection of invaded blood vessels for metastasis of colon carcinoma can prolong survival and enhance the quality of life as compared to palliative surgery alone. Therefore, it is important to carry out careful follow-up examinations for early detection of recurring tumours.

ACKNOWLEDGMENTS

We the authors of this report hereby would like to thank and acknowledge the contributions of everyone who worked on the case as a matter of duty as well as encouraging the writing of this report:

Doctors Mohd Razali Bin Ibrahim, Mohana Raj, Putera Mas Pian, Mohd Ammar Bin Ahmad, Sellymiah Adzman, Abdullah Hanif Bin Rosdi and Sarawana of Hospital Kuala

Lumpur as well as Dr Muhammad Syafiq Bin Idris of University of Malaya Medical Centre.

We also with to express our gratitude to all staff: nurses, medical assistants, technicians, support staff serving the departments of surgery, radiology, pathology, nuclear medicine at HKL without whose contribution, this report could hardly have been possible.

REFERENCES

1. Schiessel R, Wunderlich M, Herbst F (1986) Local recurrence of colorectal cancer: effect of early detection and aggressive surgery. Br J Surg 73: 342–4.
2. Goldberg RM, Fleming TR, Tangen CM, Moertel CG, Macdonald JS, Haller DG, Laurie JA (1998) Surgery for recurrent colon cancer: strategies for identifying resectable recurrence and success rates after resection. Ann Intern Med 129: 27-35
3. D'Eredita G, Serio G, Neri V, Polizzi RA, Barberio G, Losacco T. A survival regression analysis of prognostic factors in colorectal cancer. Aust N Z J Surg. 1996 Jul; 66(7): 445-51.
4. Welch JP, Donaldson GA (1979) The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 189: 496–502
5. Lopes A, Rossi BM, Ferreira FO (1997) Internal hemipelvectomy in the treatment of recurrent carcinoma of the colon. Dis Colon Rectum 40: 1504-7.
6. Ascher E, Veith FJ. Extra-anatomic bypasses. In: Ascher E, Hollier LH, Strandness DE, Towne JB, eds. Haimovici's Vascular Surgery. 5th ed. Malden, MA: Blackwell Publishing, Inc.; 2004: 625-36, Chapter 51
7. Johnson WC, Lee KK. Comparative evaluation of externally supported Dacron and polytetrafluoroethylene prosthetic bypasses for femorofemoral and axillofemoral arterial reconstructions. Veterans Affairs Cooperative Study #141. J Vasc Surg. 1999 Dec; 30(6): 1077-83.
8. Pai M, Handa A, Hands L, Collin J. Femoro-femoral arterial bypass is an effective and durable treatment for symptomatic unilateral iliac artery occlusion. Ann R Coll Surg Engl. 2003 Mar; 85(2): 88-90.
9. Mingoli A, Sapienza P, Feldhaus RJ, Di Marzo L, Burchi C, Cavallaro A. Femorofemoral bypass grafts: Factors influencing long-term patency rate and outcome. Surgery. 2001 Apr; 129(4): 451-8.
10. Ueda K, Nagayama H, Narita K, Kusano M, Aiba M, Yamada M, Takaba T, Shirasawa K. Extended surgery with en bloc resection of the right common iliac vessels for lymph node metastasis of mucinous colon carcinoma: report of a case. Surg Today. 2001; 31(3): 238-41.
11. Yoshida K, Suzuki M, Watanabe K, Takayanagi Y, Tenma Y, Yasuhara S, Takasaki K (1995) Study on lymph node dissection of colon cancer (in Japanese with English abstract). Nippon Daichyo Koumonbyo Kaishi (J Jpn Soc Coloproctol) 48: 477– 48
12. Masaki T, Muto T, Yasutomi M (1997) Clinicopathological characteristics of sigmoid colon and rectal cancers with central node involvement. Multi-institutional questionnaire study (in Japanese with English abstract). Nippon Daichyo Koumon byo Kaishi (J Jpn Soc Coloproctol) 50: 318-30

Feasibility and outcome of sequential scoliosis surgeries in twins with adolescent idiopathic scoliosis (AIS): a report of two pairs of twins

Yee Wern Evonne Tan, MBBS, Chun Hong Ngan, MBBS, Saturveithan Chandirasegaran, MS Orth, Weng Hong Chung, MS Orth, Chee Kidd Chiu, MS Orth, Chris Yin Wei Chan, MS Orth, Mun Keong Kwan, MS Orth

Department of Orthopaedic Surgery (NOCERAL), Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

INTRODUCTION

Genetic predisposition in idiopathic scoliosis (IS) has been reported in the English literature.[1] It is not uncommon to have twins diagnosed with IS as higher concordance level of IS in monozygotic twins has been reported in the literature.[2,3]

Scoliosis corrective surgery is a major operation, with an overall complication rate of 5.7% which often results in increased parental anxiety.[4] Preoperative counselling is pivotal in deciding on same-day sequential surgeries versus separate-day surgeries for twin patients. We would like to share our experience and report the outcome of two pairs of adolescent idiopathic scoliosis (AIS) twins operated sequentially on the same day and the psychosocial impact on their parents.

CASE PRESENTATION

Case 1: First Pair of Twins

The first pair of twins had Lenke 1AN curves. The main thoracic (MT) Cobb angle of Twin 1 was 45°. She underwent posterior spinal fusion (PSF) T4-L1. The operative duration was 107 minutes, with blood loss of 600 ml and blood salvage of 376 ml.

Twin 2 had a MT Cobb angle of 51°. She underwent PSF T4-L1 on the same day after her twin sister's surgery with an operative duration of 85 minutes, estimated blood loss of 550 ml and blood salvage of 120 ml. She was discharged well together with her twin sister.

Both twins were discharged on postoperative day 3. Figure 1 shows the preoperative radiographs, postoperative radiographs, latest follow-up radiographs, preoperative clinical photographs and latest follow-up clinical photographs.

Case 2: Second Pair of Twins

Twin 1 presented with a Lenke 5CN curve with lumbar Cobb angle of 57°. She underwent PSF T10-L4. The operative duration was 97 minutes, with blood loss of 511 ml and blood salvage of 228 ml.

Twin 2 similarly had Lenke 5CN curve with lumbar Cobb angle of 55°. She underwent PSF T10-L4 on the same day as her twin. The operative duration was 126 minutes, with blood loss of 664 ml and blood salvage of 283 ml. She was discharged well together with her twin at day 3 post-operation.

Figure 2 shows their preoperative radiographs, postoperative radiographs, latest follow-up radiographs, preoperative clinical photographs and immediate postoperative clinical photographs.

Both mothers shared their experience through phone call interview. Table I depicts further information of the detailed interview with them.

The aim of surgery in AIS is deformity correction and to prevent the worsening of the curve.[5] Kwan et al.[6] reported the overall complication rate and mortality rate for AIS surgery were 1.5% and 0.014%, respectively, with a five-fold decrement in overall complication rates from 2004–2007 to 2013–2016. Even though the complication risk had decreased in the past decade, studies reported that 42–47% of parents of children undergoing surgeries are under a significant level of stress and anxiety.[7,8] Parental anxiety can directly affect children's anxiety level.[9] Anxiety can have a negative impact on the child's recovery, leading to increased postoperative pain, analgesic usage, sleep disorders and delayed recovery milestones.[9,10]

Due to the genetic predisposition[2,3], it is not uncommon to have twins diagnosed with AIS. Parents commonly have difficulties deciding between same-day sequential scoliosis surgeries and separate-day scoliosis surgeries for the twins. During preoperative counselling, surgeons should discuss the advantages and disadvantages of both approaches, which will help in the shared decision-making.

In this case report, the average operation duration was 106 minutes, and the average estimated blood loss was 581 ml. Both parents would still opt for same-day sequential scoliosis surgeries instead of separate-day scoliosis surgeries if they faced the same scenario again. They preferred to go through the stress and anxiety in one single day. Even though their surgeries funding was insurance-funded, they believed that same-day surgeries saved time, energy, and cost as the preoperative preparations, hospital admissions, discharges, postoperative care and follow-ups were done together. Both parents felt that their children were less afraid due to the

This article was accepted: 07 November 2023
Corresponding Author: Mun Keong Kwan
Email: munkeong42@hotmail.com

Table I: Intraoperative parameters and detailed description of the interview

Intraoperative parameters and detailed description of the interview	First pair of twins		Second pair of twins		Average or Comments
	Twin 1	Twin 2	Twin 1	Twin 2	
Operative Duration (minutes)	107	85	97	136	106
Estimated blood loss (ml)	600	550	511	664	581
Mean blood salvage (ml)	376	120	228	283	251
Would you choose same-day sequential scoliosis surgeries or separate-day scoliosis surgeries if facing same scenario again?	Same-day sequential scoliosis surgeries		Same-day sequential scoliosis surgeries		Same-day sequential scoliosis surgeries
Parental VAS-Anxiety score during the twins' surgeries	5		1		3
Do you think same-day sequential surgeries have higher, same or lower levels of stress and anxiety, compared to separate-day surgeries?	Same		Lower		Lower or same
Do you prefer to go through the stress and anxiety on one day in same-day sequential scoliosis surgeries or twice as during separate-day scoliosis surgeries?	One day		One day		One day
Travel time from hometown (hours)	3.75		2		2.88
Transportation cost (USD)	43		216		130
Accommodation cost (USD)	0		32		16
Do you think same-day sequential surgeries save time, energy, and costs compared to separate-day surgeries?	Yes		Yes		Yes
In your opinion, are the twins more, same or less afraid of the surgeries in same-day sequential surgeries, compared to separate-day surgeries?	Less		Less		Less
In your opinion, do the twins have better, same or worse motivation, emotional support and companionship in same-day sequential scoliosis surgeries, compared to separate-day surgeries?	Better		Better		Better

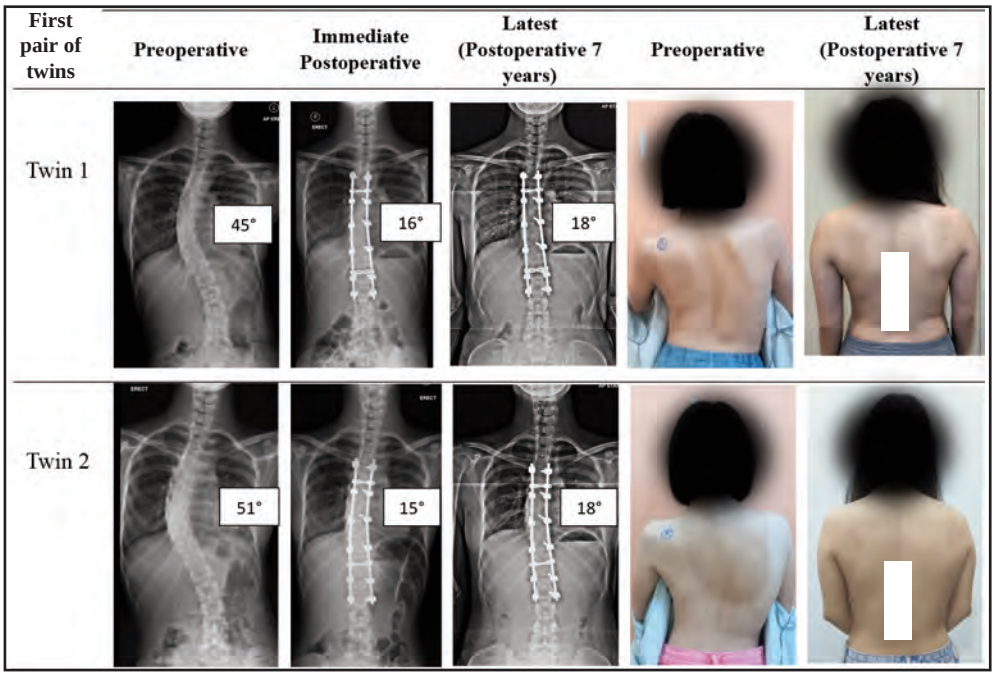

Fig. 1: Preoperative radiographs, immediate postoperative radiographs, latest follow-up radiographs, preoperative clinical photographs and latest postoperative clinical photographs of the first pair of twins.

Written consents were taken from the patients for the publication of their radiographs and clinical photographs.

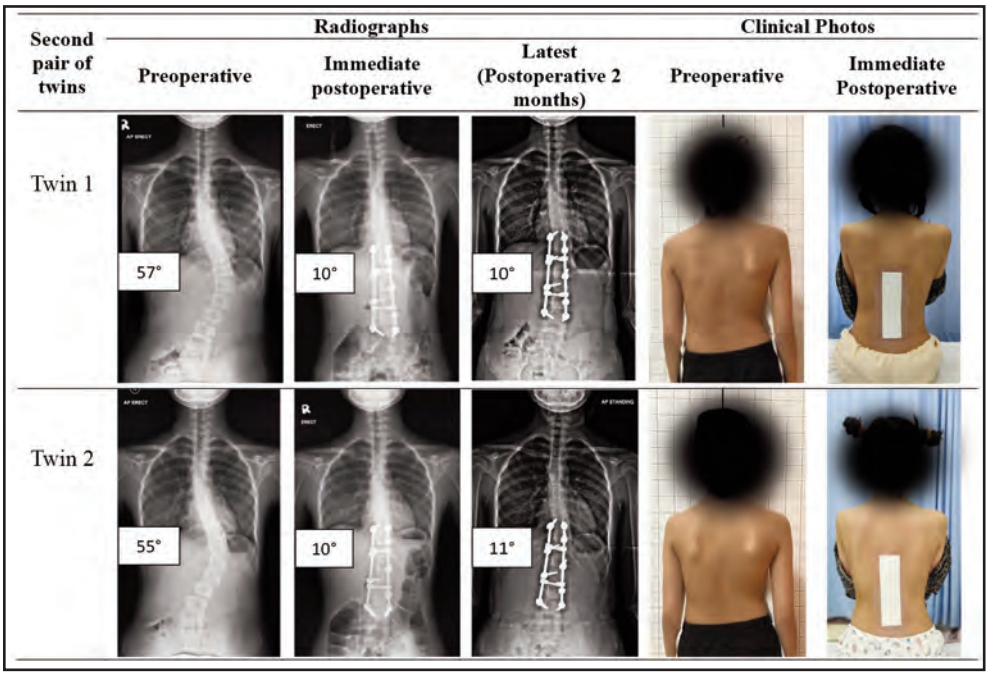

Fig. 2: Preoperative radiographs, immediate postoperative radiographs, latest follow-up radiographs, preoperative clinical photographs and immediate postoperative clinical photographs of the second pair of twins.

emotional support and companionship of the other twin. However, we acknowledged that some parents may have the opinion that the risks of occurrence of events or complications may change with performing surgeries on the same day or on different days.

All the surgeries were performed by the same team which comprises of two spine surgeons who operated together via dual attending surgeon strategy. While surgeons' fatigue is always being debated, this dual surgeon approach inevitably promotes tacit understanding between both surgeons during the surgery. It is also proven that dual attending surgeon strategy improves perioperative outcomes while decreasing complications in scoliosis surgeries.[11,12]

However, we did not have twins who had chosen separate-day surgeries. Therefore, we could not share the advantages and disadvantages of this approach. In addition, the curves in both pairs of twins were not severe (single curve and less than 60°). This might also explain why performing sequential day surgery was feasible for both cases.

CONCLUSION

We found that sequential same-day scoliosis surgeries in twins were feasible and safe. Parents of twins perceived that this approach could be advantageous from the psychosocial and financial perspectives. This report could be a reference for twin patients that could aid their decision-making.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for the permission to publish this article.

REFERENCES

1. Riseborough EJ, Wynne-Davies R. A genetic survey of idiopathic scoliosis in Boston, Massachusetts. J Bone Joint Surg Am 1973; 55(5): 974-82.
2. Grauers A, Rahman I, Gerdhem P. Heritability of scoliosis. Eur Spine J 2012; 21(6): 1069-74.
3. Inoue M, Minami S, Kitahara H, Otsuka Y, Nakata Y, Takaso M, et al. Idiopathic scoliosis in twins studied by DNA fingerprinting: the incidence and type of scoliosis. J Bone Joint Surg Br 1998; 80(2): 212-7.
4. Coe JD, Arlet V, Donaldson W, Berven S, Hanson DS, Mudiyam R, et al. Complications in spinal fusion for adolescent idiopathic scoliosis in the new millennium. A report of the Scoliosis Research Society Morbidity and Mortality Committee. Spine (Phila Pa 1976) 2006; 31(3): 345-9.
5. Weinstein SL, Ponseti IV. Curve progression in idiopathic scoliosis. J Bone Joint Surg Am 1983; 65(4): 447-55.
6. Kwan KYH, Koh HY, Blanke KM, Cheung KMC. Complications following surgery for adolescent idiopathic scoliosis over a 13-year period. Bone Joint J 2020; 102-b(4): 519-23.
7. Thompson N, Irwin MG, Gunawardene WMS, Chan L. Pre-operative parental anxiety. Anaesthesia 1996; 51(11): 1008-12.
8. Shirley PJ, Thompson N, Kenward M, Johnston G. Parental anxiety before elective surgery in children A British perspective. Anaesthesia 1998; 53(10): 956-9.
9. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children. Predictors and outcomes. Arch Pediatr Adolesc Med 1996; 150(12): 1238-45.
10. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. Pediatrics 2006; 118(2): 651-8.
11. Chan CYW, Kwan MK. Perioperative outcome in posterior spinal fusion for adolescent idiopathic scoliosis: A prospective study comparing single versus two attending surgeons strategy. Spine (Phila Pa 1976) 2016; 41: E694-E9.
12. Hayes JW, Feeley I, Davey M, Borain K, Green C. Comparison of a dual-surgeon versus single-surgeon approach for scoliosis surgery: a systematic review and meta-analysis. Eur Spine J 2021; 30: 740-8.

CASE REPORT

Endobronchial hamartoma: an unusual cause of focal bronchiectasis

Ing Shan Kai, MD[1], Lee Yih Hoong, MB BCh BAO[1], Kelly Wong Kee Yung, FRCR[2], Teresa Chua Fuh Guang, MPath[3], Chao Khai Fatt, MRCP[1], Kho Sze Shyang, MRCP[4]

[1]Department of Medicine, Sibu General Hospital, Ministry of Health Malaysia, Sibu, Sarawak, Malaysia, [2]Department of Radiology, Sibu General Hospital, Ministry of Health Malaysia, Sibu, Sarawak, Malaysia, [3]Department of Pathology, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia, [4]Division of Respiratory Medicine, Department of Medicine, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia

SUMMARY

Bronchiectasis, a chronic and debilitating disease, is becoming increasingly prevalent worldwide and causing a growing burden on healthcare systems. This condition can be categorised as diffuse or focal, depending on the underlying cause. Accurate and early diagnosis is essential for effective management and prognosis. Endobronchial hamartomas are a potential cause of recurrent post-obstructive pneumonia with focal bronchiectasis. In this report, we present a case of an elderly gentleman with recurrent pneumonia and right middle lobe bronchiectasis despite receiving courses of antimicrobial therapy. CT thorax showed an oval-shaped endoluminal lesion with popcorn calcifications and fat within the right middle lobe bronchus associated with right middle lobe bronchiectasis. Subsequent flexible bronchoscopy revealed a round, smooth, yellowish intraluminal lesion obstructing the airway of the right middle lobe. We are able to recanalise the airway by removing the endobronchial lesion completely, and the HPE was consistent with endobronchial hamartoma. However, the distal airway was already bronchiectatic. This case emphasises the importance of having a strong clinical suspicion for intraluminal obstruction when focal bronchiectasis is encountered. Bronchoscopy plays a crucial role in obtaining tissue diagnosis and is essential for its therapeutic benefits.

INTRODUCTION

Bronchiectasis is a progressive respiratory disease characterised by permanent bronchial dilatation, cough, sputum production and recurrent respiratory infections.[1] A careful history, review of radiological features and laboratory testing are essential to identify the underlying aetiology. Focal bronchiectasis should raise suspicion of endobronchial obstruction due to recurrent post-obstructive pneumonia, while bilateral diffuse bronchiectasis may suggest systemic illness (i.e. immunodeficiency or previous childhood infection).[2] Identifying the underlying cause of bronchiectasis is critical for treatment and prognostication. Endobronchial obstruction can be caused by malignant or benign diseases including hamartomas.[3] Pulmonary hamartomas within the lung parenchymal are often asymptomatic and were frequently an incidental finding on imaging. In contrast, endobronchial hamartomas commonly present with symptoms of airway obstruction and frequently require bronchoscopy to differentiate malignancy from other benign causes.[4] We present a case of endobronchial hamartomas as the cause of focal right middle lobe bronchiectasis due to recurrent post-obstructive pneumonia.

CASE PRESENTATION

A 66-year-old Iban gentleman who is an ex-chronic smoker with underlying hypertension and chronic obstructive pulmonary airway disease presented with chronic productive cough and recurrent chest infection. Physical examination revealed a healthy man with normal vital parameters. Coarse crepitations were auscultated over the lower half of the right hemithorax, and there was no clubbing or cervical lymphadenopathy.

Initial plain chest radiograph revealed right middle lobe consolidation and bronchiectasis. His sputum smear for acid-fast bacilli and mycobacterium culture were negative. However, despite multiple courses of oral antibiotics, there was no associated radiological resolution. Hence, contrast-enhanced computed tomography (CT) thorax (Figure 1a–c) was arranged which demonstrated an oval-shaped hypoattenuating endoluminal lesion with popcorn calcifications and fat within the right middle lobe bronchus associated with right middle lobe bronchiectasis. Three-dimensional airway reconstruction revealed an endobronchial lesion arising from the posterior wall of the right middle lobe bronchus (Figure 2a, b). Flexible bronchoscopy under conscious sedation then confirmed a round and yellowish intraluminal lesion with smooth surface obstructing the lumen of right middle lobe bronchus (Figure 2c, d); using flexible forceps, the growth was removed en bloc, exposing an erythematous and oedematous right middle lobe sub-segmental bronchus with purulent secretion distally. Minimal post-biopsy bleeding was secured with argon plasma coagulation. Bronchial washing was then performed at the right middle lobe bronchus.

Histopathological examination of the debulked endobronchial lesion revealed bland spindle cells in myxoid stroma with some fibroadipose tissue, smooth muscle, cartilage and bone with overall features suggestive of endobronchial hamartoma. Patient was continued to be followed up regularly and was enrolled in pulmonary rehabilitation with assistance in airway clearance. Patient is

This article was accepted: 15 November 2023
Corresponding Author: Shan Kai Ing
Email: shankai1992@gmail.com

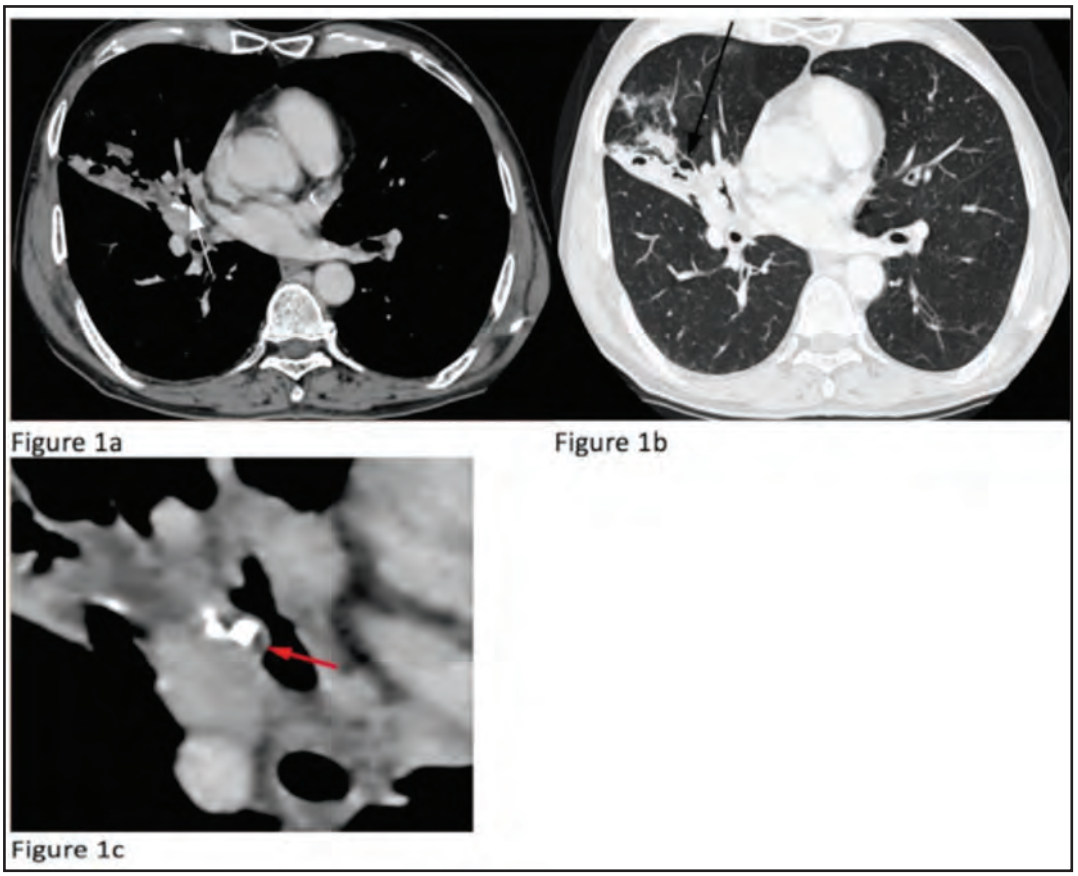

Fig. 1: Contrast-enhanced CT Thorax in mediastinal window (Figure 1a) and lung window (Figure 1b) axial views show an oval-shaped hypoattenuating endoluminal lesion with popcorn calcifications (white arrow in Figure 1a) as well as macroscopic fat with an attenuation value of -40HU (red arrow in close-up image in Figure 1c) within the right middle lobe bronchus. It is associated with bronchiectatic airways of the right middle lobe (black arrow in Figure 1b).

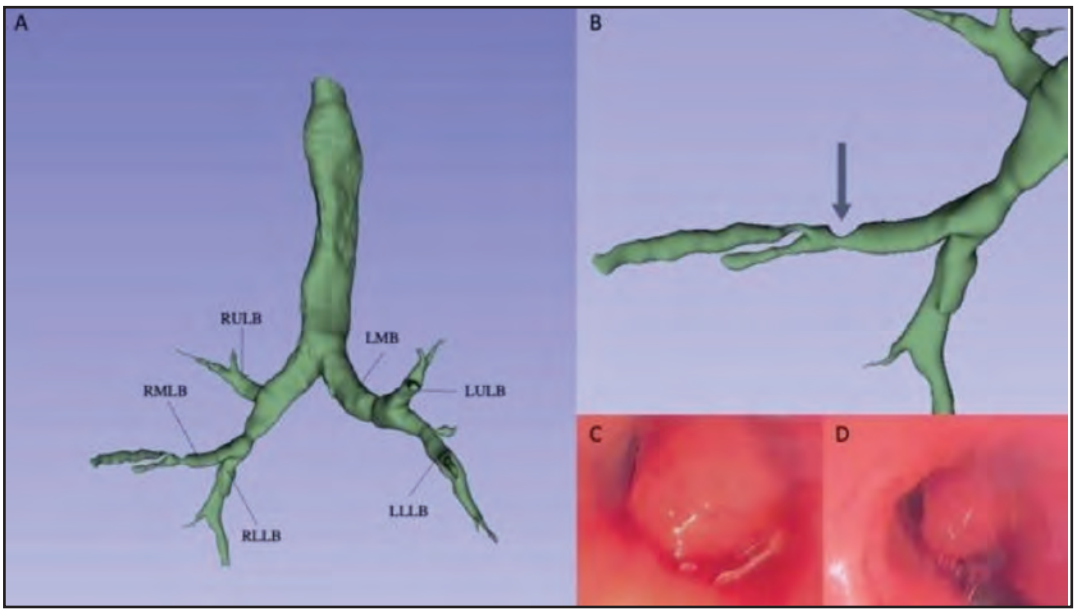

Fig. 2: Three-dimensional airway reconstruction (A) revealed a stenotic right middle lobe bronchus with bronchiectatic dilatation of distal airways (B) which was confirmed by flexible bronchoscopy with an intraluminal mass (C) and was removed en bloc (D) via flexible forceps.

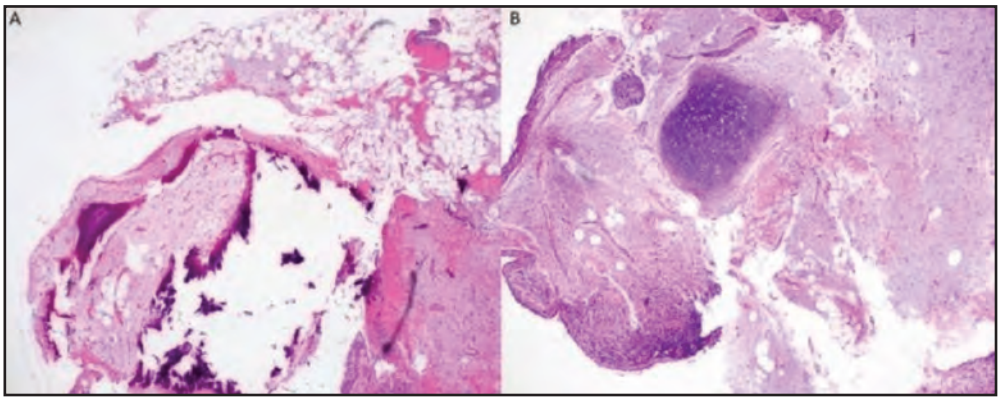

Fig. 3: Histopathological examination of the removed tumour demonstrated bland spindle cells in myxoid stroma with some fibroadipose tissue, smooth muscle, bone (A), and cartilage (B) with overall features suggestive of endobronchial hamartoma. (×40 magnification, haematoxylin and eosin stain).

doing well now with no further recurrent admission for pneumonia. His vaccination status is also up to date as an important preventive healthcare measure for patient with bronchiectasis.

DISCUSSION

Endobronchial hamartomas are rare benign lesions with an incidence of 0.025–0.032% typically affect males in their fifth and sixth decade of life with a higher prevalence in smokers.[5] The presentation varies from asymptomatic to bronchial obstruction, which can cause atelectasis, chronic cough, and recurrent chest infections. Radiologically, they can be difficult to distinguish from malignant lesions, but generally present as well-circumscribed nodules or masses, with typical *"popcorn"* calcifications present in 20–30% and fat seen in up to 60% of lesions.[6] Tissue biopsy via bronchoscopy thus remains the gold standard for diagnosis and exclusion of other causes of endobronchial obstruction. Furthermore, it also offers therapeutic options by enabling airway recanalization through tumour debulking.[7]

Early detection and treatment of bronchiectasis can potentially reverse and stabilise the condition. It is important to determine the underlying cause as a variety of factors can contribute to bronchiectasis including systemic illnesses and severe childhood infections. In regions with a high prevalence of pulmonary tuberculosis, post-tuberculous bronchiectasis remains a common cause of bronchiectasis. These aetiologies frequently presented with typical distribution, i.e., bi-basal symmetrical distribution for systemic diseases and bi-apical involvement for tuberculosis.[8] Hence, when bronchiectasis was focal in distribution which was limited only to a segment or lobe, clinician should consider more localised diseases such as sequestrated lung, congenital bronchial atresia, extrinsic compression and endobronchial obstruction. In this case, we present a patient with recurrent post-obstructive pneumonia resulting in focal right middle lobe bronchiectasis due to endobronchial obstruction from an endobronchial hamartoma. Unfortunately, the distal segment from the endobronchial lesion was already bronchiectatic due to recurrent post-obstructive pneumonia.

CONCLUSION

Although endobronchial hamartomas are benign lesions, it is crucial to make an early and accurate diagnosis as an endobronchial lesion can cause non-resolving obstructive pneumonia and eventually irreversible focal bronchiectasis. Early diagnosis can prevent progression to bronchiectasis and other complications such as corpulmonale and respiratory failure. Therefore, clinicians should have a high index of suspicion for endobronchial lesions in patients with recurrent post-obstructive pneumonia, and prompt investigation with tissue biopsy, ideally via bronchoscopy, is recommended to facilitate early diagnosis and management.

ACKNOWLEDGEMENT

The authors would like to thank the Director General of Health Malaysia for the permission to publish this article.

REFERENCES

1. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-cfbronchiectasis. Thorax 2010; 65(Suppl 1): i1-i58.
2. Chan ED, Wooten WI, Hsieh EWY, et al. Diagnostic evaluation of bronchiectasis. Respir Med 2019; 1: 100006.
3. Sehgal IS, Dhooria S, Ram B, et al. Foreign body inhalation in the adult population: Experience of 25,998 bronchoscopies and systematic review of the literature. Respir Care 2015; 60(10): 1438-48.
4. Ahmed S, Arshad A, Mador MJ. Endobronchial hamartoma; a rare structural cause of chronic cough. Respir Med Case Rep 2017; 22: 224-7.
5. Sarioglu N, Susur A, Goksel T, et al. An unexpected cause of hemoptysis: endobronchial lipomatous hamartoma. Med Archiv 2014; 68(1): 65.
6. Klein JS, Braff S. Imaging evaluation of the solitary pulmonary nodule. Clin Chest Med 2008; 29(1): 15-38.
7. Sim JK, Choi JH, Oh JY, et al. Two cases of diagnosis and removal of endobronchial hamartoma by cryotherapy via flexible bronchoscopy. Tubercul Respir Dis 2014; 76(3): 141.
8. Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. Int J Infect Dis 2015; 32: 87-93.

Case series of seizure control post exicison of cavernoma

Yugaraj Thangavelu, MBBS, KS Kung, MBBS, YY Neoh, MSurg, M Syahiran, MSurg, M Premananda, MSurg, M Azhari, MSurg

Department of Neurosurgery Hospital Raja Permaisuri Bainun Ipoh, Perak, Malaysia

SUMMARY

This case series looks into a series of cases involving cavernomas, from 2018- 2021, that underwent surgical intervention within our facility. The cases showed diversity in their locations, with non-eloquent sites consisting of 75%, while the eloquent domain occupied the remaining 25%. Patients presented with seizures in 75% of cases, and weakness in the remaining 25%. Microsurgical resection was offered to our patients. Post excision of cavernoma in these patients' robust seizure control was achieved. Postoperatively, a reduction in anti-epileptic medications was achieved for patients. Some patients became free from seizures. In this series of compelling cases, microsurgery was found to be effective in achieving seizure control.

INTRODUCTION

Cavernomas are vascular abnormalities of the brain. They commonly occur either sporadically or hereditarily. Patients can present in an array of ways, such as seizures, haemorrhages, hydrocephalus, or incidentally. The ideal imaging technique to diagnose this condition is magnetic resonance imaging (MRI) of the brain. The management of this condition relies on the site of the lesion and the symptoms. Treatment options include microsurgical resection, stereotactic radiosurgery, and conservative approaches. We have included all four cases of cavernomas that were operated on at our facility from 2018 to 2021.

CASE PRESENTATION

Case 1: Left Frontal Cavernoma

A 14-year-old Malay girl with no known medical illnesses presented with a generalised tonic–clonic seizure that lasted for 5 minutes. The seizure was preceded by episodes of vomiting. Upon examination, her Glasgow Coma Scale (GCS) was full, and she exhibited no neurological deficits. A plain brain computed tomography (CT) scan was performed, revealing a hyperdense lesion in the left frontal region. Subsequently, a computed tomography angiography of the brain was conducted, revealing an ill-defined hyperdense lesion with subtle enhancements in the left frontal region. An MRI later indicated a hyperintense lesion in the left frontal region, suggestive of a cavernoma with a recent haemorrhage.

Surgery was offered as the lesion was superficial, aimed at improving seizure control and due to the increased risk of recurrent bleeding associated with the presence of recent haemorrhage. On September 6, 2020, a left craniotomy was performed, and the cavernoma was excised. The histopathology report confirmed the diagnosis. Post-operatively, the patient's GCS was full, and she exhibited no neurological deficits. A repeated MRI conducted 3 months later showed no residual lesion. Since the operation, the patient has been seizure-free, despite not being on any anti-epileptic medication.

Case 2: Left Temporal Cavernoma

A 12-year-old girl with no known medical illnesses presented to us with a generalized tonic–clonic seizure that lasted for 30 seconds. Apart from this, her GCS was full, and she exhibited no neurological deficits. A CT scan of the brain revealed a hyperdense lesion in the left temporal region. An MRI was conducted, showing a multiloculated focal lesion with blooming artefacts in the left temporal region. When offered, both the patient and her family were keen on surgery to optimise seizure control compared to medical therapy. On September 22, 2020, a left craniotomy was performed, and the cavernoma was excised. Intraoperatively, a mulberry-like lesion with its hemosiderin deposition was excised. Histopathological analysis confirmed the diagnosis as a cavernoma.

Post-operatively, the patient's GCS was normal, and there were no neurological deficits. The patient has remained seizure-free since her operation, and her dosage of anti-epileptic medication was successfully reduced

Case 3: Right Frontal Cavernoma

A 25-year-old woman presented to us with a history of recurrent seizure episodes since 2012. An MRI conducted in 2013 suggested the presence of a cavernoma in the right frontal lobe. At that time, the patient was counselled for surgery, but she preferred medical therapy. In February 2018, the patient returned with a status epilepticus episode. During examination, her GCS score was E3V1M5, and her pupils were bilaterally reactive with a size of 3/3. The patient was intubated and administered phenytoin. Afterward, she was successfully extubated and returned to her pre-seizure condition. Due to continued poor seizure control despite being on anti-epileptic medication, the patient was once again advised for surgery. On July 17, 2018, a right craniotomy was performed, and the cavernoma was excised. Intraoperatively, the lesion appeared yellowish-grey and vascular, located in the right frontal region.

Following the surgery, the patient was extubated and her GCS was normal upon discharge, with no neurological deficits. Post-operative MRI of the brain revealed no residual

This article was accepted: 19 November 2023
Corresponding Author: Yugaraj Thangavelu
Email: yugarajthangavelu@gmail.com

cavernoma. Currently, the patient remains seizure-free since the operation, despite not being on anti-epileptic drugs.

Case 4: Left Thalamic Bleed

This is a case of a 7–year old boy who presented to us with worsening right sided body weakness and myoclonic seizure of right upper and lower limb. On examination, the child was alert and conscious. However, his right upper and lower limb had a power of 4/5 and the child was having left facial nerve palsy. A plain CT brain was done in which a left thalamic bleed was seen. An MRI brain was then done, in which a left thalamic cavernoma with intracranial bleed at the site was appreciated. Surgery was offered in this child despite the lesion being in a eloquent area as the presence of bleed makes recurrent bleeds of high risk. This child then underwent excision of cavernoma. Lesion resected was sent for histopathology examination, in which it was confirmed to be cavernoma. Post-operative an MRI was repeated for this patient and showed no residual cavernoma. Despite having focal seizure post operative and anti-epileptic medication had to be increased, the patient was subsequently fit–free and his medication dosage was subsequently reduced during follow–up. However, weakness over the right upper and lower limbs was still present.

DISCUSSION

Cavernoma or cerebral cavernous malformation is a vascular abnormality of the brain comprising of abnormal, hyalinized capillaries surrounded by hemosiderin deposit and a gliotic margin.[1] It comprises 10–15% of central nervous system (CNS) vascular malformation and develops in 0.4–0.8% of the population. It is found to be located supratentorial in 46–86%, in the brain stem in 20–35% and basal ganglia in 5–10%.[2] It is said to occur sporadic and hereditary, with multiple lesions being more common with hereditary. However, 12–20% of those that occur sporadic can have multiple lesions.[2] Those which occur hereditarily are said to be inherited in an autosomal dominant manner. Genes which are involved KRIT1(CCM1), malcavernin(CCM2) and PDC10(CCM3).[2]

The presentation of patient's suffering with this condition is usually seizure in 50%, haemorrhage in 25%, neurological deficit without haemorrhage, hydrocephalus or as an incidental finding in 20–50%.[3] Risk of recurrence after the first unprovoked seizure is 94%. Patient has a lower threshold to develop seizure if the cavernoma site is supratentorial, has cortical involvement and mesiotemporal involvement. Risk of haemorrhage in an incidentally discovered cavernoma is 0.08%. It is of higher risk of bleeding if it has bleed previously or if it is brain stem in origin.[2]

The pathophysiology of cavernoma-related epilepsy has not been fully understood. However, certain structural alterations have been studied, which could be the triggering factor. A rim of astroglial reaction, a common finding in cavernomas, could be an epileptogenic factor. Despite the theory of hamosiderin deposits being the triggering factor, many believe that it merely suggests damage has occurred in this area rather than being epileptogenic in nature. Lastly, the leakage of blood components, notably albumin, has been shown to be pro-epileptogenic.[11]

In our series, generalized seizures were seen in 75% of cases, and focal seizures in 25%. Due to a small study group and the absence of proper electroencephalogram data in all our patients, the collected data were not consistent with other research, such as that by Mohamed et al, in which focal seizures were seen in the majority of cases followed by focal seizures with secondary generalisation.[11]

The diagnostic imaging of choice is MRI and more superior if with either gradient echo T2WI or susceptible weighted with high sensitivity to susceptibility artefact from blood breakdown products within and around the cavernoma.[1] Gross appearance of this lesion is said to resemble a mulberry. Microscopically, the smooth muscle layer is absent with endothelial layer showing gapping of tight junctions and sparse or poorly characterised subendothelial smooth muscle cells.

Option of treatment offered for cavernoma is medical therapy, surgery and stereotactic radiosurgery (SRS). Medical therapy is usually chosen when cavernoma are less accessible via surgery, multiple and in non-refractory seizure. No added benefit is seen in surgery over medical therapy in non-refractory seizure.1 Fernández et al noted in their study that surgical intervention for patients with non-refractory epilepsy associated with cavernous malformations did not lead to a significant reduction in the risk of future seizures when contrasted with conservative management. During their investigation, they closely monitored 17 patients who received conservative medical management for a duration of 5 years. Remarkably, 12 of these patients (70.6%) maintained seizure freedom throughout this period.[8] However, there is inadequate randomised control trial conducted to justify the optimal treatment as most of the studies conducted were based on case reviews and did not observe patients for long term. Hence, in view of surgical treatment preventing further neurological deficit and acute haemorrhage, it was found to be more superior in the long-term prognosis of patient. Surgery is usually indicated for accessible lesion with focal deficit, symptomatic haemorrhage or seizure control. For less accessible lesions, surgery is indicated if there is repeated bleed with progressive neurological deterioration. Patients who present with seizure in cavernoma will benefit from complete resection of cavernoma as they are likely to be seizure-free. 75% of patients with supratentorial cavernoma become seizure-free post-resection of cavernoma according to research conducted by Englot et al.[10] Factors which increase successful seizure control in patients post resection of cavernoma are gross total resection, resection within 1 year since presentation, size of cavernoma <1.5cm and having a single cavernoma. Stereotactic radiosurgery is controversial as it is able to reduce risk of recurrent haemorrhage after 2 years latency period from SRS from 32.5 to 10.8%.[1] Lunsford et al demonstrated a reduction in the risk of haemorrhage, decreasing from 32.5% within the initial 2 years to 10.8%, and further declining to just 1% after 2 years.[9] However, was related to an increase in radiation induced morbidity. SRS can be considered in inoperable cavernoma.[1]

CONCLUSION

Cavernoma is a common CNS vascular malformation. The most common presentation of patient with cavernoma is

seizure. Cavernoma are more commonly found supratentorial. MRI brain is highly sensitive in diagnosing cavernoma. The choice of treatment is based on the site of cavernoma and symptoms. The choice of treatment that can be offered is medical therapy and excision of cavernoma. Based on this study excision of cavernoma is related to better control of seizure as patients who underwent complete resection of cavernoma in our centre showed better seizure control.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patients' consent forms. In the form, the patients have given their consents for their images and other clinical information to be reported in this journal. The patients understand that their name and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

REFERENCES

1. Mouchtouris N, Chalouhi N, Chitale A, Starke RM, Tjoumakaris SI, Rosenwasser RH, Jabbour PM. Management of Cerebral Cavernous Malformations: From Diagnosis to Treatment. Scientif World J. 2015; 2015: 808314.
2. Stapleton CJ, Barker FG 2nd. Cranial Cavernous Malformation. AHAJournals. 2018; 49(4): 1029-35.
3. Greenberg MS. Handbook of Neurosurgery. 9th ed. Thieme; 2020. 1310-6.
4. Spiegler S, Rath M, Paperlein C, Felbor U. Cerebral Cavernous Malformations: An Update on Prevalence, Molecular Genetic Analyses, and Genetic Counselling. Mol Syndromol. 2018; 9: 60-9.
5. Bradac O. Cavernoma of the CNS. Springer Nature Switzerland AG; 2020.
6. Rigamonti D, Drayer BP, Johnson PC, Hadley MN, Zabramski J, Spetzler RF. The MRI appearance of cavernous malformations (angiomas). J Neurosurg. 1987; 67(4): 518-24.
7. Shoubash L, Nowak S, Greisert S, Al Menabbawy A, Rathmann E, von Podewils F, Fleck S, Schroeder HHW. Cavernoma-Related Epilepsy: Postoperative Epilepsy Outcome and Analysis of the Predictive Factors, Case Series. World Neurosurg. 2023;172: e499–e507. ISSN 1878-8750.
8. Fernández S, Miró J, Falip M, Coello A, Plans G, Castañer S, Acebes JJ. Surgical versus conservative treatment in patients with cerebral cavernomas and non-refractory epilepsy. Seizure. 2012 Dec; 21(10): 785-8.
9. Lunsford LD, Khan AA, Niranjan A, Kano H, Flickinger JC, Kondziolka D. Stereotactic radiosurgery for symptomatic solitary cerebral cavernous malformations considered high risk for resection. J Neurosurg. 2010; 113(1): 23-9.
10. Englot DJ, Han SJ, Lawton MT, Chang EF. Predictors of seizure freedom in the surgical treatment of supratentorial cavernous malformations. J Neurosurg. 2011 Dec; 115(6): 1169-74.
11. Khallaf M, Abdelrahman M. Supratentorial cavernoma and epilepsy: Experience with 23 cases and literature review. Surg Neurol Int. 2019; 10: 117.

CASE REPORT

Monoarticular gouty arthropathy of the acromioclavicular joint: a rare manifestation

Chong Jung Syn, MBBS[1,2], Lim Zhuang Li, MBBS[3], Emad Faris Adnan, MBBCh[4], Fatin 'Amira Mohamed Anwar, MBBS[5]

[1]Department of Orthopaedics, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia, [2]Department of Orthopaedics, International Islamic University of Malaysia, Kuantan, Malaysia, [3]Department of Orthopaedics, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia, [4]Department of Orthopaedics, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia, [5]Department of Pathology Hospital Tengku Ampuan Afzan, Kuantan, Malaysia

SUMMARY

Gouty arthritis is a common cause of inflammatory arthropathy affecting joints of the extremities. However, involvement of the acromioclavicular joint is almost unheard of and only a handful were reported in the literature. If not approached prudently, inaccurate diagnosis could lead to suboptimal management. A thorough history taking correlating a positive past episode of gout, ultrasound findings and joint aspiration contribute to the diagnosis of gouty arthritis involving atypical joint. Like gout of any joint, medical treatment is the cornerstone of management, while surgical drainage is reserved for specified cases only.

INTRODUCTION

Gout is a disease due to the accumulation of monosodium urate crystal that predominantly affects synovial joints, although it does have an extraarticular predilection such as subcutaneous tophi and urolithiasis. Known risk factors include genetic, obesity, high alcohol consumption, high purine diet, diuretic usages and comorbidities such as hypertension and chronic kidney disease. As the burden of non-communicable diseases such as hypertension and obesity are on the rise, in addition to the purine-rich dietary practices, gout has become a common inflammatory arthritis we frequently see in our day-to-day clinic.

Rarely does gout involve the acromioclavicular joint.[1] Like gout of any other joints, there are a variety of other diagnoses that can masquerade as an acromioclavicular gouty arthritis. Since they share common signs of joint inflammation, diagnosis of gouty arthritis relies on a detailed history taking. Small joint aspiration may be challenging but detection of monosodium urate crystal on microscopy is confirmative. Ultrasonography examination is useful to elicit characteristic features of gout, though it requires both a skilful operator and a capable device.[2]

In all cases of arthritis, it is always pertinent to rule out septic arthritis as the delay in its treatment may result in devastating consequences. Urgent drainage and joint washout are indicated for septic arthritis, but surgical treatment for gout tends to be associated with poor wound healing hence only recommended in indicated cases such as infection or ulceration.[3] Here, we describe our encounter and management of an enigmatic case of a monoarticular acromioclavicular joint pain that was initially suspicious of septic arthritis and eventually confirmed to be a tophaceous gouty arthritis.

CASE PRESENTATION

A 68-year-old man presented with a painful swelling over his left shoulder of 1 month duration. The pain occurred insidiously, throbbing in nature and aggravated primarily upon shoulder motion. He denied any preceding trauma, fever or any other articular involvement. He visited a health clinic a fortnight before and was treated for an immature abscess. He completed a 2-week course of oral cloxacillin with some symptom abatement, albeit temporarily. He has underlying hypertension, hyperlipidemia, ischemic heart disease and stent placement on aspirin and life-long warfarin. He also gives positive history suggestive of gouty arthritis involving the great toes, which he self-manages with over-the-counter analgesics only. His last gouty attack was 3 years ago.

On clinical examination, there was a small, localized, firm swelling over the left acromioclavicular region (Figure 1(a)) with no overlying erythema, punctum or discharge. It was mildly tender, not warm, and non-fluctuant. His shoulder motion was quite preserved. There were no gouty tophi involving other joints. Plain radiograph examination of the left shoulder appeared unremarkable (Figure 1(b)). We initially treated him as an exacerbation of left acromioclavicular joint osteoarthritis. His concurrent antibiotics were discontinued, and he was given a review in 2 months with some analgesia.

However, he presented again after 2 days with worsening localized symptoms of pain and swelling. Examination showed increased swelling, tenderness and now, erythema. Biochemical investigation revealed normal white counts of 10.9×10^9/L, elevated erythrocyte sedimentation rate of 87 mm/hour and C-reactive protein of 66.2 mg/L. Bedside sports ultrasound using a *Philips Lumify L12-4* linear transducer demonstrated a large, well-circumscribed swelling overlying the anterior and superior aspect of the left ACJ, suggesting a possible effusion with mixed echogenic substance enclosed within the distended lesion with the absence of increased

This article was accepted: 20 November 2023
Corresponding Author: Chong Jung Syn
Email: chong.js@live.iium.edu.my

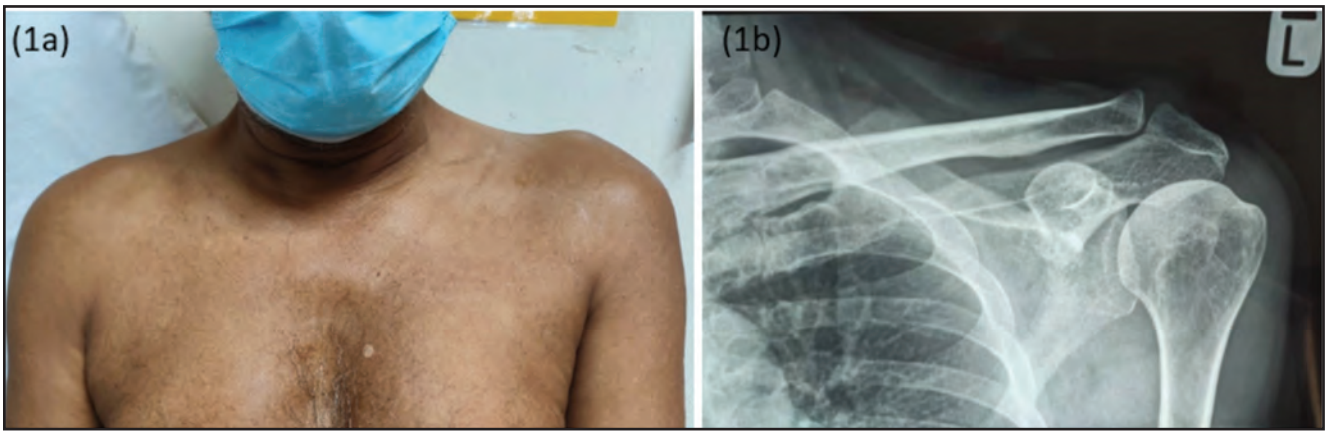

Fig. 1: (A) A localised swelling over the left ACJ with no overlying erythema.* (B) Plain radiograph of the left shoulder with no discernible intra- or peri-articular abnormality. There was a mild increase in soft tissue shadow over the ACJ.
*Patient's consent is obtained prior to publication of this article.

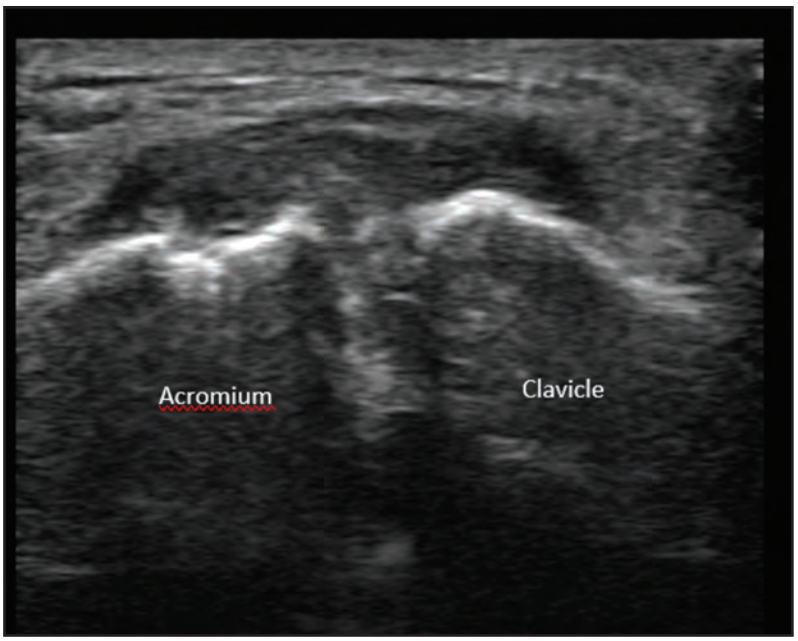

Fig. 2: Bedside sports ultrasound demonstrated a large, well circumscribed swelling overlying the superior and anterior aspect of the acromioclavicular joint suggesting a possible effusion with mixed echogenic substance enclosed within the distended lesion. There was also presence of juxta-articular sclerotic margins.

vascular flow. There was the presence of suspicious juxta-articular sclerotic margins overlying the joint (Figure 2). Our working diagnosis was possible septic arthritis involving the left acromioclavicular joint, and the patient was counselled for a joint drainage and washout procedure.

Intra-operatively, there appeared to be a subcutaneous oedema but no localized collection. There were tophaceous materials deposited onto the otherwise intact joint capsule (Figure 3a). Arthrotomy was not done. The wound was irrigated with normal saline and left open fearing the presence of infection. He was immediately commenced on colchicine 1mg thrice daily post-operatively. A review of his uric acid which was only available the following day showed a borderline high result (426 umol/L, normal range: 208–428umol/L) which further supported our clinical suspicion of an acute gouty arthritis.

The patient was discharged well the following day. Intra-operative tissue cultures were negative for any organism, and at day 7 post-operation, he underwent secondary suturing for wound closure. After 1 month post-operatively, the wound appeared well-healed. His left shoulder range of motion was full, and patient had returned to his daily activities. However, the patient's serum uric acid level only showed minor decrement. A review of the histopathological results showed fragments of crushed fibrotic tissue containing occasional irregular nodules of amorphous eosinophilic material, with areas of mixed inflammatory cell infiltrates and aggregates of histiocytes and urate crystals, which were suggestive of tophaceous gout. The patient was later given a 3-monthly appointment and urate-lowering therapy was continued.

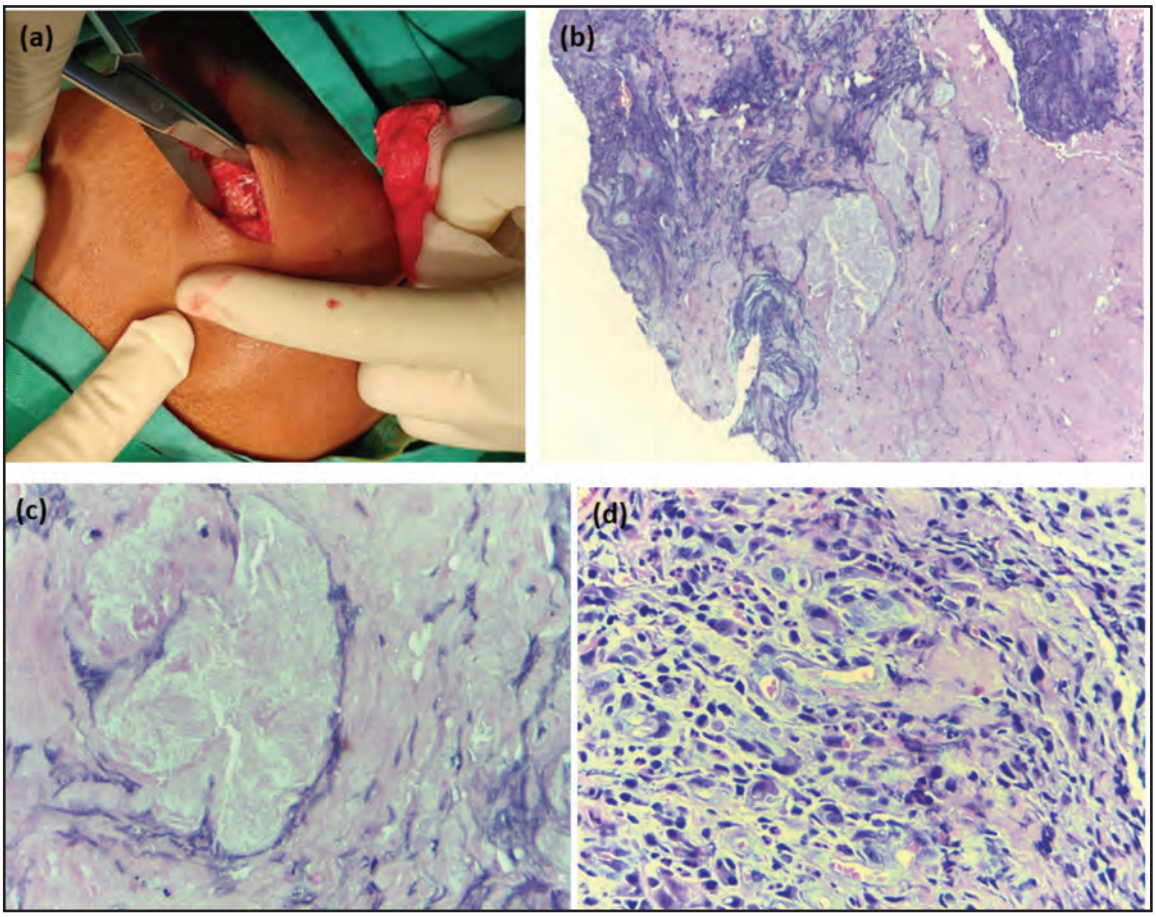

Fig. 3: (A) Intraoperative picture showing tophaceous deposition on the acromioclavicular joint capsule.
(B) Crushed fibrotic tissue containing irregular nodules of amorphous material (H&E ×4)
(C) Aggregates of urate crystals (long and needle-shaped), dissolved after the processing (H&E ×10)
(D) Mixed inflammatory reaction consisting of foreign body giant cells, histiocytes, neutrophils and lymphocytes. (H&E ×10)

DISCUSSION

Gouty arthritis is a crystal-induced arthropathy most commonly affecting the first metatarsophalangeal joint. Nevertheless, it also affects other small and large joints of the appendicular skeleton. The diagnosis of gouty arthritis can sometimes be perplexing in view of potential overlapping characteristics with other differential diagnoses such as pseudogout, septic arthritis, osteoarthritic exacerbation or autoimmune arthritis. In contrast to the other differentials, patients with gout may manifest, for example with a previous history of similar joint pain after certain trigger, sinus with tophaceous discharge or subcutaneous tophi.

Gouty arthritis of the acromioclavicular joint is clinically a rare entity. Coincidentally, all reported cases happened to occur in patients with underlying gout. Certain cases have been associated with other secondary causes such as immunosuppression, lead toxicity, drug (gemfibrozil) use.[1,4,5] Other reported cases include Santis et al who reported a patient with a painless acromioclavicular cyst secondary to gout, and Maxwell et al who reported a case of gouty polyarthropathy with involvement of acromioclavicular joint.[6,7] In contrast, our case presented with a painful monoarticular acromioclavicular gouty arthritis. Historically, warfarin was postulated to increase serum uric acid production and gout manifestation, however, was debunked by another study that shows no significant increase in uric acid concentration in patients on warfarin therapy.[8,9] We postulated that his prophylactic low-dose aspirin for ischemic heart disease might have been the precipitating cause of this atypical gouty flare. Anecdotally, low-dose aspirin use is known to decrease urinary uric acid excretion and has been associated with gout attacks.[10]

This clinical case was perplexing in view of the subacute presentation and atypical joint involvement. Our patient's gout was thought to be in remission since he was flare-free for the past 3 years. These factors initially did not favour the present diagnosis. The narrative of improving symptoms with antibiotic usage and worsening swelling after antibiotic cessation somehow favoured septic arthritis as our principle working diagnosis and therefore, joint aspiration was not suggested initially.

Retrospectively, consideration to perform an intralesional aspiration with a large bore needle prior may have an added diagnostic value and to avoid morbidities associated with an open excision.[6,7] However, aspiration of such a small joint is

often challenging due to narrow joint space and low synovial fluid volume. In addition, synovial Gram stain from arthrocentesis has a low sensitivity with 45%–71% false-negative rates. Presence of negatively birefringent monosodium urate crystals is specific to gout, but nevertheless, septic arthritis can rarely coexist with gout in about 1.5% of cases.[11] A positive synovial fluid culture would be the gold standard for septic arthritis, but it will take at least a few days to detect bacterial growth. Therefore, in cases with high suspicion of infection, an inconclusive synovial fluid analysis should not delay operative intervention for diagnostic and therapeutic purposes.

Ultrasonography examination did confirm a pathological joint but did not objectively aid the decision-making. Perhaps, utilizing a higher resolution ultrasonography device instead of a hand-held screening device may lead to better diagnostic appreciation of pathognomonic features of gout such as the presence of a 'double-contour sign' or 'snowstorm appearance'. A systematic review reported that ultrasound for diagnosis of gout showed high specificity ranging from 0.65 to 1.00.[2] Thus, when in doubt, ultrasonography assessment by a musculoskeletal radiologist would be beneficial in suspected cases of gout.

Gouty arthritis commonly demonstrates a raised serum uric acid; however, in about half of cases, it may remain normal even within periods of acute flare. Serum leucocytes count, erythrocytes sedimentation rate and C-reactive protein are overall not specific for diagnosis but more relevant to monitor clinical progress and resolution.[12]

Lifestyle modification and medications are the mainstay of treatment of gouty arthritis. Intralesional steroid injection together with colchicine or NSAID may supplant the need for surgery.[12] Maxwell et al reported a similar case in 2009 in which they successfully treated the patient with colchicine, oral prednisolone, local intraarticular steroid injection and was able to avoid surgical drainage.[7] Surgical drainage is often associated with poor wound healing and skin necrosis and therefore applied only to indicated cases of tophaceous gout.[3]

Gout is a systemic disease with a wide range of atypical presentations. It could affect the joints of both the appendicular and axial skeleton.13 Other than atypical joint localization, gout can also have out of the norm presentation such as erythema nodosum, flexor tenosynovitis, giant cell tumour, tumour-like lumps, acute locked knee, finger flexion deformity and carpal tunnel syndrome.[14-17] The causes of such atypical presentations are unclear, possible correlations being genetic, serum uric acid concentration, presence of other systemic illnesses, and usage of drugs interfering with uric acid metabolism.

CONCLUSION

In patients presenting with an atraumatic acromioclavicular joint pain and underlying gout, gouty arthritis should be considered even in normo-uricemia state. Eliciting a detailed past medical history needs to be emphasized. Findings of characteristic features of gouty arthritis on ultrasonography by an experienced operator are helpful. In suspicious cases, diagnostic aspiration may be attempted under ultrasound guidance. Most patients with gouty flare recover well with optimal medical therapy. Surgical drainage remains an option only when infection is suggestive, or when diagnosis remains inconclusive even after a thorough workup. Finally, the link between low-dose aspirin intake and acromioclavicular gouty arthritis is still unclear and requires more understanding by research.

REFERENCES

1. Musgrave DS, Ziran BH. Monoarticular acromioclavicular joint gout: a case report. Am J Orthop (Belle Mead NJ). 2000; 29(7): 544-47.
2. Zhang Q, Gao F, Sun W, et al. The diagnostic performance of musculoskeletal ultrasound in gout: A systematic review and meta-analysis. PLoS One 2018; 13(7): e0199672
3. Fang ZH, Waizy H. Current concepts in the treatment of gouty arthritis. Orthop Surg 2013; 5(1): 6-12.
4. Podgorski, M R et al. "Case report 445. Bilateral acromioclavicular gouty arthritis with pseudo-tumor of the outer end of the right clavicle: saturnine gout." Skeletal Radiol 1987; 16: 589-91.
5. Miller-Blair D, White R, Greenspan A. Acute gout involving the acromioclavicular joint following treatment with gemfibrozil. J Rheumatol 1992; 19(1): 166-8.
6. De Santis D, Palazzi C, D'Amico E, Di Mascio DE, Pace-Palitti V, Petricca A. Acromioclavicular cyst and 'porcupine shoulder' in gout. Rheumatology (Oxford) 2001; 40(11): 1320-1.
7. Maxwell JR, Wernham EM, Winfield J. Cystic swelling of the acromioclavicular joint: an unusual complication of gout. Rheumatology (Oxford) 2009; 48(10): 1217.
8. Menon RK, Mikhailidis DP, Bell JL, Kernoff PB, Dandona P. Warfarin administration increases uric acid concentrations in plasma. Clin Chem 1986; 32(8): 1557-9.
9. Walker FB 4th, Becker DM, Kowal-Neeley B, Krongaard LS. Lack of effect of warfarin on uric acid concentration. Clin Chem 1988; 34(5): 952-4.
10. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi H. Low-dose aspirin use and recurrent gout attacks. Ann Rheum Dis 2014; 73(2): 385-90.
11. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. Acad Emerg Med 2011; 18(8): 781-96.
12. Suresh E. Diagnosis and management of gout: a rational approach. Postgrad Med J. 2005; 81(959): 572-9.
13. Ting Zhang, Fan Yang, Jie Li, Zhenglun Pan. Gout of the axial joint—a patient level systemic review. Semin Arthritis Rheum 2019; 48: 649-57.
14. Abdel-Khalek A, Tariq A, White JA, Cheema AR, Dhillon S, Tiesenga F. Atypical presentation of gout: a case report. Cureus 2023; 15(3): e36707.
15. Wang S, Doughty R. Atypical first presentation of gout as flexor tenosynovitis. Proceedings of UCLA Health 2020; 24.
16. Bagdia A, Hegde P, Janu A, Khirwal K, Puri A, Gulia A. Unusual presentation of gout as giant cell tumor of bone: a case report. J Orthop Case Rep 2020; 10(4): 17-9.
17. Sakti M, Usman MA, Lee J, Benjamin M, Maulidiah Q. Atypical musculoskeletal manifestations of gout in hyperuricemia patients. Open Access Rheumatol 2019; 11: 47-52.

CASE REPORT

Caecal bascule: a rare cause of intestinal obstruction

Boon Khang Soh, MBBS[1], Guo Hou Loo, Dr of Surgery[1], Syed Abdul Wahhab Eusoffee Wan Ali, Dr of Surgery[1], Sze Li Siow, FRCS[1,2,3]

[1]Department of Surgery, Sarawak General Hospital, Sarawak, Malaysia, [2]Department of Surgery, Taylor's University School of Medicine, Subang Jaya, Selangor Darul Ehsan, Malaysia, [3]Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia

SUMMARY

Caecal bascule is a rare clinical entity, in which a mobile caecum folds anteriorly on the ascending colon without any mesenteric torsion. It accounts for 1–2% of all colonic intestinal obstructions and can progress to a closed-loop obstruction in the presence of a competent ileo-caecal valve. We report a case of a middle-aged man with a history of craniotomy and tumour debulking for pineal parenchymal tumor who was admitted to neurosurgical ward for management of breakthrough seizure and was later found to have a 3-month history of intermittent abdominal pain and distension. The finding of a grossly distended air-filled large bowel on supine abdominal radiograph suggestive of caecal volvulus prompted further imaging with computed tomography scan of the abdomen and pelvis to rule out bowel ischaemia. This was shown to be features of caecal bascule. In addition, the appendix was prominent with a measurement of 0.9 cm in its outer diameter. The patient underwent laparotomy, appendectomy and caecopexy to the lateral abdominal wall and had since recovered well. The case aims to highlight the importance of holistic approach in managing patients with advanced cancer who may have multiple coexisting diseases requiring concurrent treatment. The early diagnosis had led to appropriate management with good patient outcomes and improved quality of life.

INTRODUCTION

Caecal bascule is an uncommon subtype of caecal volvulus, in which a mobile caecum folds anteriorly on the ascending colon without any torsion.[1] There are three subtypes of caecal volvulus, a rare medical condition with an average incidence of 2.8–7.1 per million people per year, described in the literature, and caecal bascule is the rarest subtype. Caecal bascule was first described by Treves in 1884,[2] but it was only in 1938 that the first detailed clinical and radiological description was described by Weinstein.[3] It accounts for 5–17% of all cases of colonic volvulus and can progress to a closed-loop obstruction, particularly in the presence of a competent ileocaecal valve, leading to bowel ischemia, necrosis or perforation.[4,6] The clinical presentation of caecal bascule is usually less acute than the two other subtypes of caecal volvulus as there is no axial rotation of bowel with mesenteric vascular compromise. The main complaints are generally of recurrent intermittent abdominal pain or symptoms related to intestinal obstruction. The diagnosis is often made with computed tomography (CT) scan or at laparotomy.[6] Surgical intervention is the most common primary treatment modality, ranging from caecopexy to right hemicolectomy, with non-resectional surgery considered in the absence of bowel ischaemia.[4] Our case highlights the importance of holistic approach in the evaluation of an individual with advanced malignancy presenting with a rare clinical entity that could have been missed as the chief complaint of breakthrough seizure was a non-related complaint. Accurate clinical assessment had led to early diagnosis and surgical treatment, with good outcomes.

CASE PRESENTATION

A man in his 50s, wheelchair-bound, was admitted to the neurosurgical ward for breakthrough seizures secondary to hyponatremia and was treated with antiepileptic medications. He was diagnosed with pineal parenchymal tumour of indeterminate differentiation and had undergone a posterior fossa craniotomy and tumour debulking 2 years ago, followed by adjuvant radiotherapy. He developed progressive bilateral lower limb weakness and was diagnosed with spinal metastasis on a recent surveillance magnetic resonance imaging of the spine, and the focus of the neurosurgical team was mainly towards palliative care. Apart from the seizure episodes, he also complained of a 3-month history of intermittent abdominal discomfort with distension, associated with not passing stool for the past 1 week and no flatus for the past three days. The abdomen was distended with no clinical peritonism. He was initially treated with oral laxatives, but his symptoms worsened, resulting in a surgical consult.

INVESTIGATIONS

Initial laboratory investigations showed hyponatremia of 119 mmol/L (normal range 135–145 mmol/L), a normal corrected calcium of 2.25 mmol/L (normal range 2.2–2.7 mmol/L) and mild hyperlactatemia of 2.1 mmol/L (normal range <1.0 mmol/L). There was no leukocytosis or arterial blood gases abnormalities. A supine abdominal radiograph showed a grossly distended right sided large bowel extending from the right lower quadrant of the abdomen towards the epigastrium (Figure 1) suspected dilated caecum. As the radiograph findings were inconclusive, we proceeded to contrast enhanced CT scan of the abdomen, which showed an upward folding of a dilated caecum (maximum diameter of 7.4 cm) towards the midline. The ileocaecal valve was displaced laterally, and the appendix was prominent, measuring up to 0.9 cm in its outer diameter. There were no signs of mesenteric torsion, the small bowel was not dilated,

This article was accepted: 22 November 2023
Corresponding Author: Boon Khang Soh
Email: jaywinlongtimenoc@yahoo.com

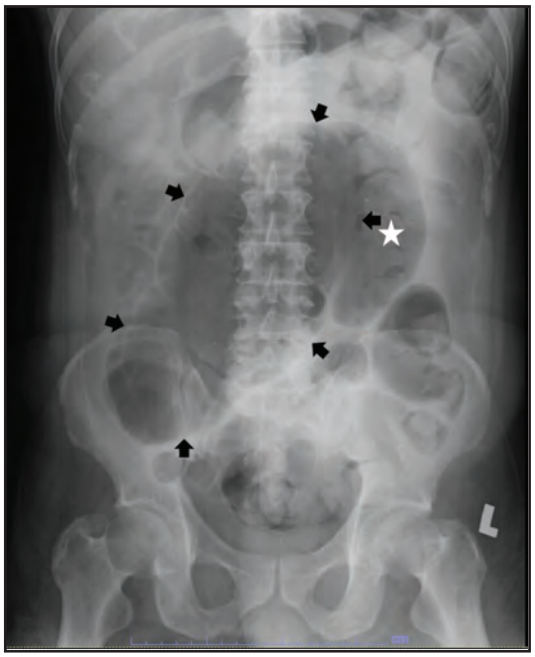

Fig. 1: Supine plain radiograph of the abdomen showing a grossly distended air-filled large bowel extending from the right lower quadrant of abdomen toward the epigastrium (black arrow). Descending colon loops in the left quadrant of the abdomen can also be seen (white star).

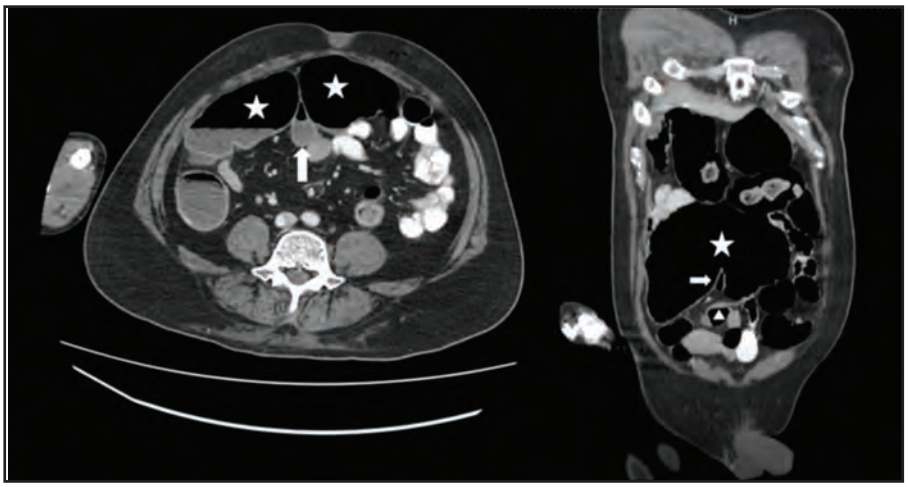

Fig. 2: Axial and Coronal CT Abdomen showing anteromedially migrated dilated caecum (white star) with abnormally located terminal ileum (white arrow) and centrally located appendix (white arrow head).

and bowel wall enhancement confirmed the viability of the caecum. The overall features were suggestive of a caecal bascule (Figure 2).

TREATMENT

The patient was taken to the operating theatre for palliative surgery, where a midline laparotomy was performed. During the operation, there was a grossly distended and mobile caecum folded anteriorly up until the epigastric region. The caecum was otherwise viable with no ischemic changes. The appendix was plastered to the posterior aspect of the caecum, with adhesions noted at the mid-body and faecolith within the lumen. Appendicectomy was performed, and the dilated caecum was decompressed via the appendicular stump. A caecopexy was performed by anchoring the caecum and ascending colon to the lateral abdominal wall with several interrupted polyglactin 910 3/0 sutures. Small bowel was not dilated.

OUTCOME AND FOLLOW-UP

The patient made a good recovery and was discharged on postoperative day 6. During the follow-up in the surgical outpatient clinic 2 months later, he was well with no wound infection or other complications. He was able to pass motion daily and had complete resolution of his abdominal symptoms. However, he became bedbound in the next few months due to cancer progression and passed away in the fifth month after surgery.

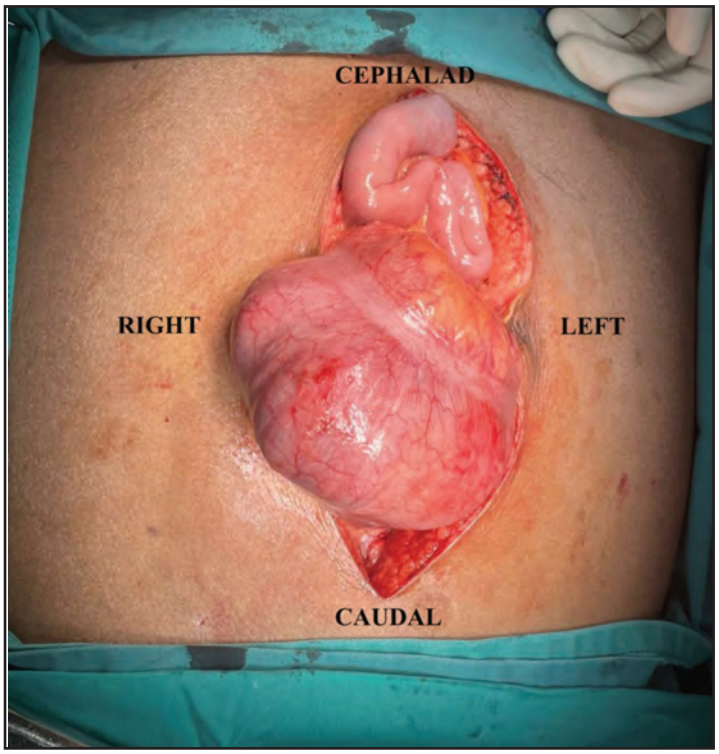

Fig. 3: Intraoperative finding showed a dilated and viable caecum with a viable small bowel located above.

DISCUSSION

One of the suggested aetiologies for caecal bascule is the presence of the mobile caecum with a competent ileo-caecal valve. This prevents caecal contents from flowing back to the small intestine, leading to gaseous and fluid distension of the caecum.[6] Both congenital and acquired anatomical factors have been reported for the development of mobile caecum.,[6] These include congenital malfixation such as failure of fusion between the right colonic mesentery and the lateral peritoneum as well as acquired peritoneal adhesions to the caecum after abdominal surgery.[4,6] Other risk factors include distal mechanical obstruction, colonic pseudo-obstruction (Ogilvie syndrome), neurogenic bowel dysfunction, postoperative ileus, chronic constipation, high fibre intake, chronic use of laxative and previous abdominal surgery.[4] In this context, the combination of risk factors of primary central nervous system tumours, as well as spinal metastasis, chronic constipation due to being wheelchair-bound and previous brain surgery in our patient, may predispose him to reduced colonic motility and subsequent caecal bascule.

The clinical presentation of caecal bascule is highly variable, ranging from recurrent intermittent abdominal pain to acute intestinal obstruction.[4] Abdominal distension and pain are the two most common presenting symptoms.[4] The intermittent nature of abdominal pain is due to occasional episodes of isolated caecal obstruction that resolve spontaneously when the caecum unfolds into its original position.[4] Its presentation is generally less critical compared to other types of caecal volvulus as there is no axial torsion of the mesenteric vasculature, and therefore, lower incidence of vascular compromise of the bowel.[6] However, the 'flap valve' effect of the folded caecum, in the presence of a competent ileocaecal valve, may lead to a closed loop obstruction and ultimately result in bowel ischemia and perforation.[6,9] Due to the nonspecific clinical presentation, a high index of clinical suspicion is needed to prompt further imaging investigations. Plain abdominal radiography is usually the first-line imaging investigation for the evaluation of abdominal pain in most patients. In our case, the diagnosis was suspected from the findings of a grossly distended air-filled right-sided colon from the plain abdominal radiograph, which was thought to be either a caecal volvulus, or some form of mechanical obstruction arising from the right-sided colon. In view of these differentials, a contrast-enhanced CT of the abdomen and pelvis was performed. A CT scan of the abdomen and pelvis is the gold-standard diagnostic imaging modality. It is not only able to diagnose caecal volvulus and its complications but is also useful in differentiating the sub-types of caecal volvulus.[7,9,10]

The management of caecal bascules is primarily surgical intervention in 96% cases[4], with the exact surgical approach based on intraoperative findings. Nonoperative reduction of caecal volvulus using colonoscopy or barium enema should not be attempted as they are rarely successful (<5%) and may cause perforation.[6] A right hemicolectomy is often advocated to prevent recurrence, but caecopexy is equally effective with no reported recurrence.[4]

Therefore, we recommend caecopexy to be performed if the caecum is viable, with resectional surgery reserved for cases associated with ischaemia or perforation.

This case highlights the importance of careful history taking and physical examination in a patient with known advanced malignancy presenting with non-specific abdominal symptoms. Early CT scan should be performed if the diagnosis is not apparent after plain radiography. Early diagnosis and prompt surgical treatment can avoid serious complications and morbidity, thus improving patients' quality of life. Caecopexy is a surgical option in cases of caecal bascule where the caecum is viable.

LEARNING POINTS/TAKE HOME MESSAGES

- Caecal bascule is the anterior folding of mobile caecum on the ascending colon without any torsion, whereby it is the rarest subtypes of caecal volvulus and a rare cause of large bowel obstruction.
- Clinicians should have a low threshold for imaging in patients who present with intermittent abdominal pain and CT scan can be performed to establish the diagnosis, which may not be apparent after conventional radiology.
- Careful history-taking and examination are important in a holistic approach to the management of patients with known advanced malignancy.
- Early diagnosis and surgical intervention can avoid serious complications and morbidity.
- Caecopexy is an appropriate surgical strategy for the treatment of a caecal bascule without bowel ischaemia.

REFERENCES

1. Perret RS, Kunberger LE. Case 4: cecal volvulus. AJR Am J Roentgenol 1998; 171: 855-60.
2. Treves F. The element of pain in intestinal obstruction. Br Med J 1884; 2: 62-4.
3. Weinstein M. Volvulus of the cecum and ascending colon. Ann Surg 1938; 107: 248-59.
4. Lung BE, Yelika SB, Murthy AS, Gachabayov M, Denoya P. Cecal bascule: a systematic review of the literature. Tech Coloproctol 2018; 22: 75-80.
5. Kairys N, Skidmore K, Repanshek J, Satz W. An unlikely cause of abdominal pain. Clin Pract Cases Emerg Med 2018; 2: 139-42.
6. Park JS, Ng KS, Young CJ. Caecal bascule: a case series and literature review. ANZ J Surg 2018; 88: E386-89.
7. Naveed M, Jamil LH, Fujii-Lau LL, Al-Haddad M, Buxbaum JL, Fishman DS, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. Gastrointest Endosc 2020; 91: 228-35.
8. Ooi SK, Tan TJ, Ngu JC. Clinics in diagnostic imaging (171). Caecal volvulus with underlying intestinal malrotation. Singapore Med J 2016; 57: 598-602.
9. Delabrousse E, Sarlieve P, Sailley N, Aubry S, Kastler BA. Cecal volvulus: CT findings and correlation with pathophysiology. Emerg Radiol 2007; 14: 411-5.
10. Rosenblat JM, Rozenblit AM, Wolf EL, DuBrow RA, Den El, Levsky JM. Findings of cecal volvulus at CT. Radiology 2010; 256: 169-75.

CASE REPORT

Application of mesenchymal stem cells in a multi-modal approach in the treatment of stroke

Danaraj Navaratnam, MBBS, Danaraj Navaratnam, MBBS, Danaraj Navaratnam, MB.BS, Angelina Tiah, BSc

SUMMARY

Stroke is a leading cause of death and disability worldwide. Despite advances in acute stroke care, many stroke survivors experience long-term neurological deficits that significantly affect their quality of life. The current standard of care for stroke rehabilitation includes physical and occupational therapy, speech therapy and pharmacotherapy. However, the limitations of these therapies have led to the investigation of alternative approaches, including the use of mesenchymal stem cells (MSCs). MSCs have been shown to promote neuronal survival, stimulate neurogenesis and modulate the immune response following stroke. This case report describes a male in his 40s with a history of right middle cerebral artery stroke in early 2015 likely from spontaneous arterial dissection of the Right ICA. He presented with residual left hemiplegia with spasticity. The patient has received a total of eight transplantations of MSCs, five via intravenous and three via intrathecal route. Patient's motor recovery was assessed during rehabilitation sessions. Post-MSC therapy, patient showed significant improvement in overall tone, power and reflex of upper and lower limb. Patient also displayed stronger and longer endurance and muscle strength. While this case report provides promising preliminary evidence for the use of MSC therapy in the rehabilitation of stroke patients, further research is needed to confirm these findings and to identify the optimal treatment protocol for MSC therapy.

INTRODUCTION

Carotid artery dissection is a condition whereby the layers of the carotid artery are spontaneously separated when a tear occurs in the intimal layer of the carotid artery creating an intramural haematoma. As a result, this potentially compromises blood flow to certain areas of the brain and can lead to a stroke.[1] A stroke especially an ischaemic stroke occurs if there is interrupted or reduced blood supply to the brain leading to lack of delivery of oxygen to the respective cells in the brain, causing cellular death to occur.[2] There are different areas of the brain that are supplied by various blood vessels, compromise of which can lead to neurological deficits in a person.

The only approved pharmacological systemic therapy for acute ischaemic stroke is intravenous thrombolysis (IVT) with alteplase, a recombinant tissue plasminogen activator (rtPA) that is usually recommended to be administered within 4.5 h of symptom onset.[3] Despite the expanded therapeutic time window, many patients still do not qualify for rtPA therapy since they present for evaluation beyond 3-4.5 hours after stroke onset. Initiating rtPA treatment beyond 4.5 hours (i.e., delayed tPA treatment) has been associated with deleterious side effects, notably, haemorrhagic transformation (HT) which could lead to high mortality in stroke patients.[4,5] Less than 5% of ischaemic stroke patients receive this treatment and still suffer post-treatment neurological deficits with no therapy available to promote recovery.[6] IVT can be administered alone or along with endovascular treatment with mechanical thrombectomy (MT), in large vessel occlusion disease. However, this technique is not yet fully developed, and the efficacy and safety of endovascular reperfusion beyond 6 hours remains controversial.[7]

MSCs are multipotent stem cell that have the ability to differentiate into various cell lineages, including chondrocytes, osteoblasts and neuron-like cells.[8] They can be easily isolated from various tissues, such as bone marrow and adipose tissue[9] and are simple to culture and expand. Due to their trilineage differentiation capacity and immunomodulatory properties, MSCs from bone marrow and adipose tissue are preferred sources for tissue engineering and regenerative medicine.[10] Furthermore, they pose low risk of tumorigenesis and require no immunosuppression following allogeneic administration due to their low expression of MHC antigens.[11] MSCs are suitable for transplantation during the acute stage of stroke and have shown substantial neurotrophic effects.[12] In addition, MSCs derived from adult tissues pose no risk of tumorigenesis and their low expression of major histocompatibility complex (MHC)-I and MHC-II antigens eliminates the need for immunosuppression following allogeneic administration.[13] They exert their therapeutic effects through several mechanisms, such as anti-inflammation, anti-apoptosis, angiogenesis and neurogenesis. As a result, they have been the focus in preclinical and clinical studies of various diseases. MSCs derived from human umbilical cord have also been shown to maintain their immunomodulatory and antioxidant activities and can differentiate into neuron-like cells.[14]

Stem cell-based therapies offer promising treatment opportunities as they are well known for their potential for trophic support and regenerative capacity after transplantation into the ischaemic brain. Apart from protecting and repairing damaged brain tissues, MSCs allow the preservation of neural tissue in the acute phase of stroke and the replacement of lost tissue in the chronic stage.[15] In the presence of injury and inflammation, MSCs are directly transplanted or homed to the damaged site. With their potential for tissue regeneration, migration, proliferation, rewiring of neural circuitry, physical and behavioural rejuvenation, these cells offer great regenerative potential and have been tested a treatment for stroke by promoting

This article was accepted: 22 November 2023
Corresponding Author: Danaraj Navaratnam
Email: danarajone@gmail.com

Table I: Progression of left upper and lower limb movement prior and after MSC treatment as per Medical Research Council (MRC) grading of motor power

	Movements	Before MSC therapy	After MSC therapy		
			First follow-up	Second follow-up	4 months post-treatment
Shoulder	Abduction	2/5	2/5	2/5	2/5
	Abduction	3/5	3/5	3/5	3/5
	Flexion	2/5	2/5	2/5	2/5
	Extension	2/5	2/5	2/5	2/5
Elbow	Flexion	2/5	2/5	2/5	2/5
	Extension	1/5	1/5	2/5	2/5
Wrist	Flexion	1/5	1/5	2/5	2/5
	Extension	0/5	1/5	1/5	2/5
Fingers	Flexion	1/5	1/5	1/5	2/5
	Extension	0/5	1/5	1/5	2/5
Hip	Flexion	3/5	3/5	3/5	3/5
	Extension	3/5	3/5	3/5	3/5
Knee	Flexion	3/5	3/5	3/5	3/5
	Extension	4/5	4/5	4/5	4/5
Ankle	Plantarflexion	0/5	1/5	1/5	1/5
	Dorsiflexion	0/5	2/5	2/5	2/5

Table II: Motor function assessments

Test	Before MSC therapy	After MSC therapy		
		First follow-up	Second follow-up	4 months post-treatment
Fugl-Meyer Upper Extremity Scale (FMA-UE)	51/126	80/126	82/126	95/126
Timed up and Go test (TUG)	35.29s	37.37s	35.47s	26.47s
Berg Balance Scale (BBS)	33/56	35/56	35/56	40/56

neurogenesis, rebuilding neural networks and increasing axonal growth.[16,17] This case study focuses on the application of MSCs in a multi-modal approach in treatment of stroke.

MATERIAL AND METHODS

The clinical case study that has been conducted involves the patient following up at Daehan Rehabilitation Hospital Putrajaya to monitor his progress for a period of three consecutive months in 2022. The diagnosis of right middle cerebral artery stroke was confirmed with a neurologist using computed tomography scan (CT scan), neurological deficits post-stroke and clinical history.

The respective inclusion criteria:

1) A confirmed clinical diagnosis of right middle cerebral artery stroke
2) A patient with residual and neurological weakness post-stroke
3) A patient that allows continuity of assessment and treatment for a year
4) A patient to accept stem cells to be used with rehabilitation

The WJ-MSC used in the stroke patients was isolated from Wharton's jelly of the umbilical cord. The stem cell isolation procedure is described in our previous case study on RP.[18] WJ-MSCs were provided by Beike 23 International Stem Cell Laboratory.

Patient received eight WJ-MSC transplantations (5×10^7 cells per session), five intravenously and three via intrathecal method using strict and sterile procedures. This would prove to add further value to the success of MSC transplantation given intravenous route targeting the systemic organs and intrathecal route targeting the cerebrospinal fluid. Further formal evaluation of patient's progress was assessed continuously by a consultant in Rehabilitation Medicine that monitored the progress.

CASE REPORT

A previously healthy male in his 40s was diagnosed with spontaneous arterial dissection of the Right Internal Carotid Artery (ICA) in 2015. Following the stroke event, patient experienced weakness in the left upper and lower limbs, with limited movement in the left upper limb and no movement over the left wrist and fingers. The left lower limb had no movement over the left ankle, with poor core coordination leading to difficulty maintaining an upright position. The patient also had a hemiplegic gait and slow cognitive processing. In addition, there was difficulty integrating motor skills and poor hand-eye coordination. Throughout standard treatment, there was no deterioration of existing neurological condition neither were there any adverse reactions documented. The patient was continuously monitored with rehabilitation, with no major changes in their diet or medication regimen.

RESULTS

Significant improvements in the patient's rehabilitation goals were observed from the initiation of MSC treatment over a period of 6 months from July 2022 till December 2022. After

2 months of intensive rehabilitation with mesenchymal stem cell (MSC) transplantation, the patient showed significant improvement in elbow extension as well as wrist and finger flexion and extension. Patient was also able to isolate muscle movements of the left shoulder as opposed to gross movement prior to treatment. The patient also regained sensation in the left lower limb and was able to extend the wrist and fingers when placed in mid-range. The left ankle was more supple and less rigid, and the patient's ability to transition from sitting to standing had improved. The patient also showed better focus and dexterity in cognitive and visual motor skills. As opposed to the time period during which the patient was solely under conventional rehabilitation, since beginning treatment with MSCs, the patient has demonstrated improvements in sensation, strength, gait and balance, requiring less effort for walking.

DISCUSSION

Regenerative medicine aims to provide a solution for diseases that have been deemed incurable. Several diseases, including Parkinson's disease, spinal cord injury, polyneuropathy, myocardial infarction and stroke, have shown positive therapeutic outcomes with regenerative medicine. Despite advances in acute stroke care, many stroke survivors experience long-term neurological deficits that significantly affect their quality of life. The current standard of care for stroke rehabilitation includes physical and occupational therapy, speech therapy, and pharmacotherapy. However, the limitations of these therapies have led to the investigation of alternative approaches, including the use of MSCs.

MSCs have shown promising results in preclinical and clinical studies for the treatment of stroke. MSCs have been shown to promote neuronal survival, stimulate neurogenesis, and modulate the immune response following stroke. Microglia cells switch from a resting form to an activated state and adopt a phagocytic phenotype to secrete pro-inflammatory cytokines after a stroke event has occured.[19] MSCs increase the secretion of anti-inflammatory cytokines, such as interleukin-4 (IL-4), interleukin-10 (IL-10) and tumour necrosis factor (TNF) and reduce the expression of pro-inflammatory cytokines such as interleukin-1 (IL-1), interferon-1 (IFN 1) and TNF. By regulating these cytokines, MSCs affect several pathways involved in immune cells and immune responses, to reduce inflammation.[20] Besides that, MSCs release trophic factors such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, nerve growth factor, vascular endothelial growth factor, and platelet-derived growth factor. Trophic factors are known to induce angiogenesis, increase proliferation of neurons and prevent neuronal apoptosis.[21] The regeneration of blood vessels in the brain is important for stroke patients and with MSCs pro-angiogenic effects, vascular density of ischaemic brain tissue was significantly increased.[22] MSCs allow the growth of axons, synapses and myelin of ischaemic boundary zone, improving neural function which will promoting functional recovery after stroke. MSCs which induce myelination, will in turn increase the number of oligodendrocyte cells. Oligodendrocyte cells are vital in promoting myelin growth and protecting myelin from damage.[23] The stem cell therapy in cerebrovascular conditions depends overall upon their differentiation, inflammation and ability to repair of endogenous processes. Tissue engineering and cellular replacement therapies are at the forefront of regenerative medicine. It is becoming evident that stem cell therapy is an important tool in modern neurology, with potential efficacy in neuro-degenerative disorder.[24]

Clinical studies have investigated the safety and efficacy of MSC therapy in combination with conventional therapies for stroke patients. An open-labelled observer-blind clinical trial was conducted to evaluate the long-term safety and efficacy of autologous MSCs.[25] Post-transplantation with MSCs, clinical improvement in patients was observed in the MSC-treated patient group, which was associated with the serum level of stromal cell-derived factor-1 and the degree of involvement of the sub-ventricular region of the lateral ventricle. No serious adverse effects were observed during long-term follow up of patients. The occurrence of comorbidities was similar in comparison to the control group. Based on pre-clinical findings demonstrating the potential of peripheral blood stem cells (PBSCs), researchers conducted randomised, single-blind controlled studies in patients with middle cerebral artery infarction.[26] Patients meeting the study's inclusion criteria underwent implantation of immune-sorted PBSCs. Notably, no adverse events were reported during the study procedure or the follow-up period. Over a 12-month observation period, clinical outcomes were assessed for both the PBSC-treated group and the control group. These investigations also yielded significant evidence supporting the efficacy of PBSCs in enhancing motor deficits associated with stroke, facilitating the reconstruction of injured corticospinal tracts and restoring electrophysiological activity from the brain to the limbs.

CONCLUSION

In conclusion, the application of MSCs in a multi-modal approach for the treatment of stroke represents a promising therapeutic option. Further clinical trials are needed to determine the optimal dosage, timing and route of MSC therapy for stroke treatment. However, the current evidence suggests that the combination of MSC therapy with conventional therapies can lead to significant improvements in motor cognitive functions and overall quality of life for stroke patients.

ACKNOWLEDGEMENTS

The authors would like to thank 23 Century International Life Science Centre and Daehan Hospital staff involved in this study for their contribution and support.

DECLARATIONS

Stem cells are provided by Beike 23 Century International Stem Cell Laboratory. D Navaratnam and Tiah A are employees of 23 Century International Life Science Centre. NS Khairullah is a visiting Professor at 23 Century International Life Science Centre. Other author declares no conflict of interests.

REFERENCES

1. Hart RG, Easton JD. Dissections of cervical and cerebral arteries. Neurol Clin 1983; 1(1): 155-82.
2. Tadi P, Lui F. Acute Stroke. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
3. The NINDS t-PA Stroke Study Group.Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333(24): 1581-7.
4. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997; 28(11): 2109-18.
5. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 2014; 129(3): e28-e292.
6. Lyden J, Grant S, Ma T. Altered metabolism for neuroprotection provided by mesenchymal stem cells. Brain Circ 2019; 5(3): 140-4.
7. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372(1): 11-20.
8. Williams BA, Keating A. Cell therapy for age-related disorders: myocardial infarction and stroke--a mini-review. Gerontology 2008; 54(5): 300-11.
9. Pinho AG, Cibrao JR, Silva NA, Monteiro S, Salgado AJ. Cell secretome: basic insights and therapeutic opportunities for CNS disorders. Pharmaceuticals (Basel) 2020; 13(2).
10. Faghih H, Javeri A, Taha MF. Impact of early subcultures on stemness, migration and angiogenic potential of adipose tissue-derived stem cells and their resistance to in vitro ischemic condition. Cytotechnology 2017; 69(6): 885-900.
11. Heo JS, Choi Y, Kim HS, Kim HO. Comparison of molecular profiles of human mesenchymal stem cells derived from bone marrow, umbilical cord blood, placenta and adipose tissue. Int J Mol Med 2016; 37(1): 115-25.
12. Walczak P, Zhang J, Gilad AA, Kedziorek DA, Ruiz-Cabello J, Young RG, et al. Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. Stroke 2008; 39(5): 1569-74.
13. Bhatia R, Hare JM. Mesenchymal stem cells: future source for reparative medicine. Congest Heart Fail 2005; 11(2): 87-91; quiz 2-3.
14. Li G, Yu F, Lei T, Gao H, Li P, Sun Y, et al. Bone marrow mesenchymal stem cell therapy in ischemic stroke: mechanisms of action and treatment optimization strategies. Neural Regen Res 2016; 11(6): 1015-24.
15. Wei L, Wei ZZ, Jiang MQ, Mohamad O, Yu SP. Stem cell transplantation therapy for multifaceted therapeutic benefits after stroke. Prog Neurobiol 2017; 157: 49-78.
16. Shi Y, Su J, Roberts AI, Shou P, Rabson AB, Ren G. How mesenchymal stem cells interact with tissue immune responses. Trends Immunol 2012; 33(3): 136-43.
17. Kuriakose D, Xiao Z. Pathophysiology and Treatment of Stroke: Present Status and Future Perspectives. Int J Mol Sci 2020; 21(20).
18. Nor Khairullah S, Nor Fariza N, Roslin AAZ, Angelina T. Subtenon implantation of wharton's jelly-derived mesenchymal stromal cells in retinitis pigmentosa. Med J Malaysia 2022; 77(5): 564-8.
19. Levard D, Buendia I, Lanquetin A, Glavan M, Vivien D, Rubio M. Filling the gaps on stroke research: focus on inflammation and immunity. Brain Behav Immun 2021; 91: 649-67.
20. Zhang Z, Huang S, Wu S, Qi J, Li W, Liu S, et al. Clearance of apoptotic cells by mesenchymal stem cells contributes to immunosuppression via PGE2. EBioMedicine 2019; 45: 341-50.
21. Tanaka E, Ogawa Y, Mukai T, Sato Y, Hamazaki T, Nagamura-Inoue T, et al. Dose-dependent effect of intravenous administration of human umbilical cord-derived mesenchymal stem cells in neonatal stroke mice. Front Neurol 2018; 9: 133.
22. Lee S, Kim OJ, Lee KO, Jung H, Oh SH, Kim NK. Enhancing the therapeutic potential of CCL2-overexpressing mesenchymal stem cells in acute stroke. Int J Mol Sci 2020; 21(20).
23. Venkat P, Zacharek A, Landschoot-Ward J, Wang F, Culmone L, Chen Z, et al. Exosomes derived from bone marrow mesenchymal stem cells harvested from type two diabetes rats promotes neurorestorative effects after stroke in type two diabetes rats. Exp Neurol 2020; 334: 113456.
24. Thwaites JW, Reebye V, Mintz P, Levicar N, Habib N. Cellular replacement and regenerative medicine therapies in ischemic stroke. Regen Med 2012; 7(3): 387-95.
25. Lee JS, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY, et al. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. Stem Cells 2010; 28(6): 1099-106.
26. Chen DC, Lin SZ, Fan JR, Lin CH, Lee W, Lin CC, et al. Intracerebral implantation of autologous peripheral blood stem cells in stroke patients: a randomized phase II study. Cell Transplant 2014; 23(12): 1599-612.

CASE REPORT

A severe case of systemic lupus erythematosus-associated diffuse alveolar haemorrhage post-COVID-19 infection

Whei Chuern Yeoh, MRCP, Ai Lee Lim, MRCP

Rheumatology Unit, Medical Department, Hospital Pulau Pinang, Penang, Malaysia

SUMMARY

Coronavirus disease 2019 (COVID-19) is a life-threatening respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There have been numerous cases of COVID-19 with autoimmune and rheumatic manifestations, including systemic lupus erythematosus (SLE). However, the association between SLE and COVID-19 infection remains unclear. Here, we report a young female who was diagnosed with severe SLE with lupus nephritis and diffuse alveolar hemorrhage 1 month after COVID-19 infection. She was admitted to the intensive care unit and required mechanical ventilation. Despite being given high doses of corticosteroids, cyclophosphamide, intravenous immunoglobulin and initiated on plasmapheresis, she continued to deteriorate and eventually died. Previous case studies have reported newly diagnosed SLEs post-COVID-19 with varied clinical manifestations, ranging from benign and self-limiting features to life-threatening systemic syndromes. More studies are required to understand the mechanisms triggering these immune-related manifestations so that early diagnosis can be achieved and the appropriate therapy administered.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease which can affect many organs. Its pathogenesis is not fully understood, but evidence suggests a multifactorial aetiology, including genetic, environmental and hormonal factors.1

COVID-19 has caused a global pandemic since late 2019. Its clinical spectrum is broad, ranging from asymptomatic infection to life-threatening cytokine storm and multiorgan dysfunction. Previous articles have reported the detection of autoantibodies in COVID-19 patients and development of autoimmune diseases associated with COVID-19 infection.2 However, the role of COVID-19 in autoimmunity remains unclear.

To date, there are only a few reported cases of SLE triggered by or developed after COVID 19 infection. Most of these patients developed mucocutaneous manifestations, vasculitis, serositis, cytopenias and nephritis which mostly improved with immunosuppressive treatments. Here, we describe a case of severe SLE with diffuse alveolar hemorrhage (DAH) post-COVID-19 infection who did not improve despite administration of immunosuppressive agents and plasmapheresis.

CASE PRESENTATION

An 18-year-old girl presented with polyathralgia for three months associated with fever, constitutional symptoms, dyspnoea, facial swelling and frothy urine for 1 week. She had background history of well-controlled bronchial asthma diagnosed at the age of 8 years old. She had just recovered from COVID-19 category 2, 1 month prior without need for admission. She did not have any family history of autoimmune disorder or malignancy.

Her vital signs on admission were stable. On physical examination, she had facial puffiness and minimal pedal edoema bilaterally. Her cardiovascular, respiratory and abdominal examination were unremarkable. Otherwise, she did not have alopecia, malar or discoid rash and oral ulcers. Laboratory investigations revealed pancytopenia, mild acute kidney injury, hypoalbuminemia and raised inflammatory markers (Table I). Her direct Coomb's test was positive, while her full blood picture did not show any features of hematological malignancies or haemolysis. Urinalysis revealed proteinuria and haematuria with the presence of pathological casts. Her quantified 24-hour urine protein was 2.8 g over 24 hours. Tests for human immunodeficiency virus, hepatitis B and C were negative. Her electrocardiogram showed normal electrical activity, while her chest radiograph showed presence of fluid in fissures with mild cardiomegaly. Her complement levels were low and serologies were positive for antinuclear antibodies (1:640, homogenous) and anti-dsDNA. The clinical and laboratory findings led to the diagnosis of SLE (2019 ACR/EULAR score of 26) with hematological and renal involvement. A renal biopsy was performed, which revealed Class IV Lupus nephritis (Activity index 16/24, chronicity index 2/12). She was treated with 500 mg of intravenous methylprednisolone for 3 days and 500 mg of intravenous cyclophosphamide subsequently for active SLE. Her symptoms improved, and she was discharged with tapering oral prednisolone.

She was readmitted 5 days later with fever, dyspnoea, lethargy and worsening bilateral leg swelling. Vital signs on

This article was accepted: 22 November 2023
Corresponding Author: Whei Chuern Yeoh
Email: wchuern53@gmail.com

Table I: Blood investigations during first admission

	Admission Day 1	Admission Day 8	Admission Day 15	References
White blood cells	3.6	6.0	9.9	4–10 × 10^9/L
Hemoglobin	8.6	8.5	7.8	13–17 g/dL
Platelet	89	146	197	150–410 × 10 9/L
Absolute neutrophil	1.9	3.8	3.2	2–7 × 10 9/L
Absolute lymphocyte	1.4	2.0	1.8	1–3 × 10 9/L
Urea	9	10.3	19.61	2.76–8.07 mmol/L
Sodium	137	137	139	136–145 mmol/L
Potassium	4	3.1	4.0	3.4–4.5 mmol/L
Creatinine	157	137	139	44–80 umol/L
Albumin	12		24	32–54 g/L
Bilirubin	8		5.3	< 21 u/L
Alanine transaminase	6		10	<23 u/L
Alkaline phosphatase	44		34	45–87 u/L
Lactate dehydrogenase	306			<279 u/L
Creatinine kinase				<123 u/L
Erythrocyte sedimentation rate	140			0–12 mm/H
C-Reactive protein	1.6			<5 ng/LC
3/C4	0.07/0.02			C3 : 0.90–1.80 g/L C4 : 0.10–0.40 g/L
ANA	1:640 (homogenous)			
dsDNA	Positive			
ENA	Anti-DSF 70: positive Anti-SSa/Ro : positive Anti-Ro52: positive Anti-nucleosome: positive Anti-histone: positive			
Antiphopholipid antibodies	LA: negative aCL: negative B2GP1: negative			

ANA, antinuclear antibody; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; LA, lupus anticoagulant; aCL. anti-cardiolipin antibody; B2GP1, anti-beta 2 glycoprotein 1 antibody; C3, complement 3; C4, complement 4.

Table II: Blood investigations during second admission

	Day 1	Day 3	Day 6	Day 15	Day 25	References
White blood cells	7.4	1.6	2.3	3.9	11.2	4–10 × 10^9/L
Hemoglobin	5.9	4.5	5.5	7.6	7.0	13–17 g/dL
Platelet	120	52	42	50	29	150–410 × 10^9/L
Absolute neutrophil	6.2	1.3	1.7	2.3	10.5	2–7 × 10^9/L
Absolute lymphocyte	0.5	0.3	0.7	0.4	0.6	1–3 × 10^9/L
Urea	15.2	14.1	21.2	25.5	32.8	2.76–8.07 mmol/L
Sodium	139	141	145	142	141	136–145 mmol/L
Potassium	3.9	3.9	3.6	4.3	4.6	3.4–4.5 mmol/L
Creatinine	124	115	116	116	224	44–80 umol/L
Albumin	21	18	29	24	24	32–54 g/L
Bilirubin	13	14	25	28	32	< 21 u/L
Alanine transaminase	15	11	10	22	11	<23 u/L
Alkaline phosphatase	40	28	33	44	47	45–87 u/L
Aspartate transaminase	21	17	20	57	51	<27 u/L
Lactate dehydrogenase	261	331	290	300	290	<279 u/L
Creatinine kinase	22			58	85	<123 u/L
Erythrocyte sedimentation rate						0–12 mm/H
C-Reactive protein	3.2	40		36	216.8	<5 ng/L
PT		10.7	11.0	11.1		9.4–11.0s
INR		1.03	1.06	1.07		0.90–1.10
APTT		21.4	21.9	25.1		22.2–31.0s
C3	0.26					C3: 0.90–1.80 g/L
C4	0.4					C4 : 0.10–0.40 g/L

PT, prothrombin time; INR, international normalised ratio; APTT, activated partial thromboplastin time

admission revealed blood pressure of 131/75 mmHg, pulse rate of 119 beats per minute, temperature of 38.5oc and oxygen saturation of 91% under room air. On physical examination, she appeared tachypnoeic with a respiratory rate of 28 breaths per minute. There were coarse crepitations heard over bilateral lower and middle zones of the lungs, while her cardiovascular and abdominal examinations were unremarkable. Laboratory investigations showed severe anaemia, thrombocytopenia, mild acute kidney injury and hypoalbuminemia (Table II). Polymerase chain reaction for COVID-19 was negative. Her chest radiograph revealed bilateral lower zone to midzone consolidations. She did not have any signs of overt bleeding. She was promptly started on intravenous piperacillin-tazobactam, hydrocortisone, face mask oxygen supplementation and transfused with one unit of packed cell.

Unfortunately, she continued to deteriorate 3 days later as she developed persistent fever, worsening anaemia and desaturation. Repeated chest radiographs revealed worsening infiltrates over bilateral lung fields and she was intubated for respiratory distress. On day 6 of admission, she developed multiple bouts of fresh blood and blood-stained aspirate from her endotracheal tube accompanied by frequent desaturations with progressive increment in ventilatory settings.

She was treated with multiple courses of antibiotics and antifungals, including carbapenems, polymyxin B and fluconazole. There was no evidence of ongoing haemolysis. She was transfused with 11 units of packed cell in total. The presence of positive hemosiderin laden macrophage on tracheal aspirate cytology confirmed the diagnosis of diffuse alveolar hemorrhage and she was initiated on plasmapheresis. She completed six sessions of plasmapheresis. She developed carbapenem-resistant Enterobacteriaceae (CRE) *Klebsiella pneumoniae* bacteraemia after the 6th session of plasmapheresis and shortly oliguric acute kidney injury, requiring continuous renal replacement therapy. She continued to receive IVIG as salvage therapy and methylprednisolone, but her condition did not improve. She eventually passed away after 25 days of admission.

DISCUSSION

Viral infections are one of the triggers for SLE. Many mechanisms have been implicated in virus-induced autoimmunity, including molecular mimicry, innate immunity activation, direct cytotoxicity and others.[3] COVID-19 has been implicated as one of the possible triggers for autoimmune disease, including SLE. Fernandez-Ruiz et al.[4] postulate that a baseline increase in interferon activity in SLE protects against contracting or developing adverse outcomes from COVID-19.[4] Sawalha et al believe that COVID-19 infection in SLE patients leads to a delayed and dysregulated IFN response, causing a hyperinflammatory response and a worse outcome.[5]

DAH is a life-threatening condition caused by bleeding from the pulmonary microcirculation and is characterised by anaemia, haemoptysis, diffuse pulmonary infiltrates on radiograph and hypoxaemia. DAH in SLE is caused by alveolar capillaritis due to deposition of immune complexes in the lungs. Although the incidence of DAH in SLE is only 0.6–5.4%, it carries a mortality rate as high as 85.7%.[6] Older age, longer SLE disease duration, plasmapheresis or mechanical ventilation, concurrent infection, active lupus nephritis, hypoalbuminemia, hypocomplementemia and thrombocytopenia are poor prognostic factors for SLE-associated DAH.[7] There is lack of randomised controlled trials for treatment of SLE-associated DAH. Besides implementing supportive therapy, use of methylprednisolone, cyclophosphamide, intravenous immunoglobulins (IVIGs), plasmapheresis and rituximab have been described in various case reports. Plasmapheresis is an effective therapy for autoimmune DAH as it removes pathogenic immune complexes. A recent large study showed 55% improvement in patients with autoimmune disease associated DAH treated with plasmapheresis.[8] Rituximab has also been described in several case reports to successfully treat DAH. Due to its delayed action, rituximab is often used in combination with other therapies, such as glucocorticoids or cyclophosphamide. Other experimental strategies such as administration of intrapulmonary recombinant Factor VIIa, use of extracorporeal membrane oxygenation support and mesenchymal stem cell transplantation have been described in the literature with varying success.[9]

In our case, we postulate that her previous COVID-19 infection triggered a dysregulated immune response leading to severe manifestations of SLE, including lupus nephritis and DAH in which she responded inadequately to glucocorticoids, cyclophosphamide, plasmapheresis and IVIG therapy. Although infectious complications of plasmapheresis therapy have not been emphasised previously, there is a possibility that our patient was severely immunodeficient after plasmapheresis and cyclophosphamide therapy, rendering her more susceptible to nosocomial infections and a rapid deterioration in her condition.

We identified eight published case reports describing the diagnosis of SLE after COVID-19.[10] Including our case, patients who developed SLE after COVID-19 infection had a mean age of 39 years old and 6 patients were females. The mean duration to diagnosis of SLE post-COVID-19 infection was 22 days. Interestingly, six out of the nine patients had renal failure, five out of nine patients had serositis and four out of nine patients had athritis. None of the patients had DAH except our case. Six out of the nine patients survived while the remaining three patients, including our patient died.

CONCLUSION

In conclusion, we present a patient diagnosed with severe SLE following COVID-19 infection. She developed Class IV lupus nephritis and DAH one month after COVID-19 infection and responded poorly to glucocorticoids, cyclophosphamide, IVIG and plasmapheresis. Our case highlights the need to be aware of the development of severe lupus disease post-COVID-19 infection as prompt diagnosis and appropriate therapy could potentially improve patient outcomes.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for the permission to publish this paper. In addition, we would also like to express our gratitude to the Department of Internal Medicine, Department of Anaesthesiology and Intensive Care Hospital Pulau Pinang.

CONFLICT OF INTEREST

None.

REFERENCES

1. Illescas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, Ruiz C, Costela- Ruiz VJ. Infectious processes and systemic lupus erythematosus. Immunology 2019; 158(3): 153-60.
2. E. Ben-Chetrit. Palindromic rheumatism following COVID-19 infection evolved to rheumatoid arthritis after COVID-19 reinfection. Clin Exp Rheumatol 2021; 39: 1410-12.
3. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and autoimmunity: a review on the potential interaction and molecular mechanisms. Viruses 2019; 11(8): 762.
4. Fernandez-Ruiz R, Paredes JL, Niewold TB. COVID-19 in patients with systemic lupus erythematosus: lessons learned from the inflammatory disease. Transl Res 2021; 232: 13-36.
5. Sawalha AH, Zhao M, Coit P, Lu Q. Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. Clin Immunol 2020; 215: 108410
6. Zamora MR, Warner ML, Tuder R, Schwarz M I. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 1997; 76(3): 192-202.
7. Jiang M, Chen R, Zhao L, Zhang X. Risk factors for mortality of diffuse alveolar hemorrhage in systemic lupus erythematosus: a systematic review and meta-analysis. Arthritis Res Ther 2021; 23(1): 57.
8. Aguirre-Valencia D, Naranjo-Escobar J, Posso-Osorio I, Macia-Mejia M C, Nieto-Aristizabal I, Barrera T, Obando M A, Tobon G J. Therapeutic plasma exchange as management of complicated systemic lupus erythematosus and other autoimmune diseases. Autoimmune Dis 2019; 2019: 5350960.
9. Al-Adhoubi NK, Bystrom J. Systemic lupus erythematosus and diffuse alveolar hemorrhage, etiology and novel treatment strategies. Lupus 2020; 29(4): 355-63.
10. Assar S, Pournazari M, Soufivand P, Mohamadzadeh D. Systemic lupus erythematosus after coronavirus disease-2019 (COVID-19) infection: case-based review. Egypt Rheumatol. 2022; 44(2): 145–49.

CASE REPORT

Non-diabetic hypoglycaemia secondary to non-islet cell tumour. A diagnosis that cannot be missed!: a case report

Najihah Abd Razak, MBBS[1], Mohammad Che Man, MMED Fam Med[1], Shahidah Che Alhadi, MMED Surgery[2]

[1]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Indera Mahkota Campus, Kuantan, Malaysia, [2]Department of Surgery, Kulliyyah of Medicine, International Islamic University Malaysia, Indera Mahkota Campus, Kuantan, Malaysia

SUMMARY

Non-islet cell tumour hypoglycaemia (NICTH) is a paraneoplastic syndrome primarily due to excessive insulin-like growth factor-2 (IGF-2) production. It should be suspected in patients with tumours of any origin and hypoglycaemia. It is potentially misdiagnosed or underdiagnosed due to its rarity, non-classical clinical presentation and ambiguous lab picture. We present the case of a 48-year-old man with no known medical illness brought to the emergency department for altered sensorium, incoherent speech and abnormal movement of bilateral limbs. Initial assessment identified severe hypoglycaemia, and hepatomegaly was detected on physical examination. Five months before the current presentation, he had been seeking medical attention a few times in the primary health center for early morning lethargy and hunger pangs but failed to find clues to his symptoms. He was admitted for observations and further investigations. Subsequent investigations confirm a diagnosis of malignant pancreatic lesion with lymph node, liver and lung metastases. He refused the palliative chemotherapy offered and passed on 3 months later. This case highlights the importance of thorough clinical assessment in the case of non-diabetic hypoglycaemia to prevent the consequences of inappropriate patient management despite poor pancreatic cancer prognoses.

INTRODUCTION

Non-diabetic hypoglycaemia is an uncommon occurrence. There is a paucity of studies on non-diabetic hypoglycaemia incidence. In one retrospective, single-center study of 37,898 non-diabetic, non-critical care hospital admissions, the estimated frequency of a low glucose level (at 3.3mmol/l cut-off) was 50 cases per 10,000 admissions per year.[1] Another single-centre study in Helsinki University Hospital showed the incidence rate of non-diabetic hypoglycaemia encountered was 1082 per 100 000 populations per year.[2]

Hypoglycaemia in non-diabetic patients can occur via two mechanisms: insulin-mediated and independent of insulin. Insulin-mediated mechanisms may occur due to endogenous insulin secretion, such as insulinoma, or exogenous insulin intake, such as accidental ingestion of insulin secretagogue.[3,4] Meanwhile, hypoglycaemia independent of insulin occurs via several mechanisms such as (1) adrenocortical insufficiency, (2) increased glucose utilisation exceeding the glucose production as in those with sepsis, (3) reduced glucose intake together with body fat and muscle depletion as observed in those with malnutrition, (4) inhibition of gluconeogenesis and depletion of hepatic glycogen stores in those with advanced and extensive hepatic destruction or (5) tumoral overproduction of incompletely processed IGF-2 in non-islet cell tumour.[4]

Labelling a non-diabetic patient to have hypoglycaemic disorder requires the presence of Whipple's triad: symptoms and signs consistent with hypoglycaemia, low plasma glucose concentration at the time of symptoms and resolutions of those symptoms and signs after plasma glucose is raised.[4] Cryer et al. recommended documentation of Whipple's triad as the initial step for diagnosing hypoglycaemic disorder. He strongly suggests further evaluation and management only in those who were concluded as having hypoglycaemic disorder to avoid unnecessary investigations, cost and potential harm without benefit to the patient.

We presented a delayed diagnosis of unexplained severe hypoglycaemia in a non-diabetic patient secondary to a non-islet cell tumour. The initial approach in a primary care setting is crucial to prevent delayed or missed diagnoses in the future.

CASE PRESENTATION

This is a case of a 48-year-old man with no known medical illness presented at the emergency department (ED) with altered sensorium, incoherent speech and abnormal movement of bilateral limbs. On initial assessment, severe hypoglycaemia (1.2 mmol/l) was detected, and he was treated with 50 ml of 50% dextrose. His consciousness level improved afterwards, while his incoherent speech and abnormal movement disappeared.

On further history, he had an oesophagogastroduodenoscopy (OGDS) scheduled that morning and had to fast for the procedure. Despite his usual early morning lethargy and hunger sensation, he abstained from eating or drinking. The last thing he remembered was feeling dizzy and sweating while waiting for his relative to pick him up. Collateral history-taking from his relatives revealed that the patient looked unusual when they arrived that morning. He is conscious but looks anxious and sweaty. While on their way to the hospital, they noticed that he could not engage in conversation and had incoherent speech. Shortly after, he

This article was accepted: 23 November 2023
Corresponding Author: Najihah bt Abd Razak
Email: najihah8188@gmail.com

Table I: Endocrine-related blood result during hypoglycaemic episode

Investigations	Result	Reference range
Random plasma glucose	1.2 mmol/L	
C-peptide	60 pmol/L	367–1467
Insulin	<1.3 pmol/L	17.8–173

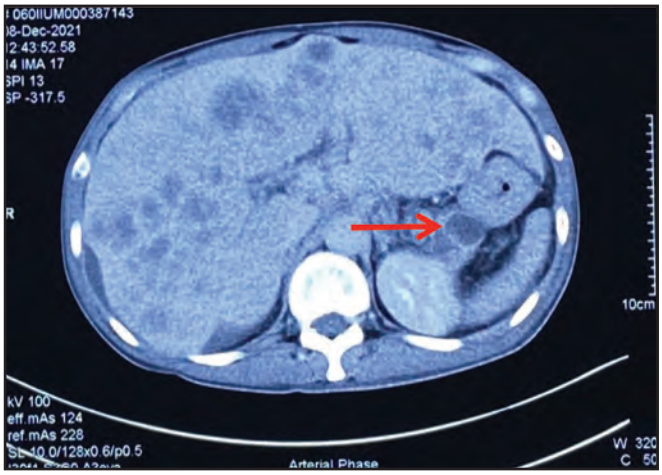

Fig. 1: CT TAP showing multi-loculated cystic lesion (arrow)at the tail of pancreas.

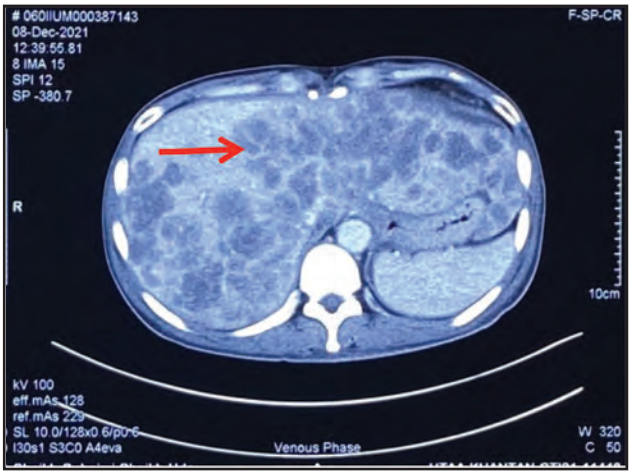

Fig. 2: CT TAP showing extensive (arrow) liver metastases.

was less responsive and started having abnormal movement of his limbs; thus, he was brought to the ED.

Five months prior, he had three visits to health care providers for recurrent early morning lethargy and hunger sensation. He was asymptomatic during each visit. There is no history of diabetes mellitus or bariatric surgery, and he was not taking any medication that could cause hypoglycaemia. There is also no history of poor oral intake, alcohol abuse or illicit drug use and no family history of malignancy. Initial assessments at all clinics revealed normal vital signs and blood glucose. All physicians concluded that his symptoms were likely attributed to hypoglycaemia but needed further investigations and follow-up. He was told to check his blood sugar level during hypoglycaemic episodes and scheduled for blood taking to check for diabetes, renal and liver function and lipid profile. He defaulted on the blood-taking procedure and subsequent follow-up due to his busy schedule. On top of that, he felt relatively well, and his symptoms did not affect his work or daily activities.

Two months after his last visit to the health center, he started losing his appetite and had early satiety and abdominal discomfort. He also experienced hypoglycaemic symptoms more frequently, at any time of the day. Nevertheless, his fourth medical consultation occurred two months after the onset of new symptoms. By this time, he had already lost 4 kg of weight. His fourth visit took place at a district hospital. Given his symptoms and examination findings of hepatomegaly, he was told that he needed further investigations urgently to find out the cause. He was scheduled for an OGDS and abdominal ultrasound the following week. While fasting for his OGDS procedure, he had another hypoglycaemic attack, which led to his latest presentation.

He was admitted for observations and further investigations after his hypoglycaemia was treated in the ED. While in the ward, he had recurrent attacks of severe hypoglycaemia refractory to the glucose supplement. Endocrine input was sought. C-peptide and insulin levels were taken during one of his hypoglycaemic episodes, and the result was consistent with hypoinsulinemic hypoglycaemia, as shown in Table I.

Due to the hepatomegaly finding, he underwent an ultrasound (US) abdomen, which showed multiple liver and pancreatic lesions. The US finding warrants urgent Computed Tomography of Thorax, Abdomen and Pelvis (CT TAP). His CT TAP results suggest a malignant pancreatic lesion with lymph node, liver and lung metastases (Figures 1 and 2). A liver biopsy taken showed metastatic adenocarcinoma of the liver. He was planned for palliative chemotherapy but opted for conservative management and passed on 3 months later.

DISCUSSION

Hypoglycaemia is a typical medical emergency. The symptoms occur when the blood glucose level falls below 4 mmol/L. In a healthy individual, when hypoglycaemia occurs, various effective counter-regulatory mechanisms will take place to restore the blood glucose to its physiological range. Glucagon and epinephrine secretions work synergistically to raise blood glucose via stimulation of hepatic glucose production through glycogenolysis and gluconeogenesis and contribute primarily to immediate response to hypoglycaemia. On the other hand, growth hormone and cortisol work over a more extended period to raise blood glucose via lipolysis and ketogenesis and are not involved in immediate recovery from hypoglycaemia.[5] When the blood glucose concentration falls further below 3 mmol/L despite all these corrective mechanisms, plasma insulin

secretion will be suppressed almost entirely to a level below 18 pmol/L while the C-peptide level will also be deficient (below 200 pmol/L) to prevent the deleterious effect of hypoglycaemia to the brain.[4]

Hypoglycaemia mostly occurs due to complications of therapy with either insulin or other hypoglycaemic agents, but in rare conditions, it can manifest an underlying neoplastic disease. Tumours of any origin can give rise to hypoglycaemia via various mechanisms: excess insulin secretion such as in pancreatic insulinoma or ectopic insulin-producing tumour, massive tumour infiltration of the liver and adrenal gland and secretion of substances which disrupt glucose metabolism such as cytokines, catecholamines, insulin receptor antibodies, insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2).[6] The latter is known as NICTH.

NICTH should be suspected in patients with tumours of any origin with recurrent hypoglycaemia. Early recognition and diagnosis of NICTH are crucial as they can cause persistent and profound hypoglycaemia if left untreated. Early diagnosis is essential as the curative treatment is surgical resection, which is feasible if done early in the illness.

This patient initially presented with early morning lethargy and hunger sensation without any symptoms that point toward underlying malignancy such as loss of appetite, weight loss or mass per abdomen. It was concluded that these two symptoms are attributed to hypoglycaemia. However, the doctors could not demonstrate low glucose readings since the patient had no glucometer at home and presented to the clinic when he was asymptomatic. Despite the setback in establishing Whipple's triad, we should be able to rule in the initial diagnosis of non-diabetic hypoglycaemia when the patient denied having diabetes, thus denying oral hypoglycaemic agents or insulin intake. When non-diabetic hypoglycaemia is suspected, the history should be directed to rule out any alcohol or drug use, underlying liver disease or critical illness, or previous history of bariatric surgery. Suppose the hypoglycaemia occurrence is devoid of relation to any of the stated above. In that case, a doctor should know that they should never skip the physical assessment and must be more vigilant when conducting it as it can be the only clue to the cause of hypoglycaemia.

The hepatomegaly finding can be missed when the physical assessment is not done thoroughly. Early finding of hepatomegaly means early imaging and early intervention. Nevertheless, if the hepatomegaly finding was missed, acknowledging that a specific tumour can cause hypoglycaemia will be reflected in the next step in choosing initial blood investigations. Besides renal and liver function tests, this patient lacks the necessary investigations for non-diabetic hypoglycaemia, such as serum cortisol, insulin, and C-peptide levels.[3,4] These three investigations can be sent from primary care at no added cost for the patient, unlike in a general practitioner setting, which can be costly.

Insulin and C-peptide levels must be taken during a hypoglycaemic event to reflect the underlying disorder accurately, and this patient's major setback was establishing low plasma glucose readings. All three encounters took place when he was asymptomatic. His early morning hypoglycaemia suggested that he had fasting hypoglycaemia. Fasting hypoglycaemia occurs typically after at least 6–8 hours of fasting.[4] It occurs due to a defective counter-regulatory mechanism toward falling blood glucose. A fasting hypoglycaemia state can be achieved by asking the patient to withhold his meal and come to the clinic for blood taking at the initial hypoglycaemic symptoms. This manoeuvre is not only helpful for the blood-taking process; it can also be used to establish Whipple's triad. It confirms someone's hypoglycaemic state from low glucose reading and the disappearance of hypoglycaemic symptoms and signs upon therapeutic intervention (giving meals or intravenous glucose load).

Diagnosis of NICTH would be apparent if all other initial blood investigations were within the range while C-peptide and insulin levels would be suppressed.[3,4] If the diagnosis is still unclear despite preliminary investigations, consultations with an endocrinologist can be sought. This case has taught us several lessons that may be beneficial to share with others. The initial approach to non-diabetic hypoglycaemia in primary care is summarised below (Algorithm 1). Primary care practitioners should utilise the algorithm for managing non-diabetic hypoglycaemia in order to avoid overlooking a critical diagnosis. It is crucial for treating physicians to be aware of when it is necessary to refer patients to a tertiary care centre.

CONCLUSION

In conclusion, thorough clinical assessment and relevant laboratory evaluation are crucial to guide early diagnosis. Consequently, early management can be initiated, and potentially severe complications can be prevented.

ACKNOWLEDGEMENT

We would like to thank the late patient for his permission and cooperation in writing this case report.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Nirantharakumar K, Marshall T, Hodson J, Narendran P, Deeks J, Coleman JJ, Ferner RE. Hypoglycemia in non-diabetic in-patients: clinical or criminal?. PloS One 2012; 7(7): e40384.
2. Vihonen H, Kuisma M, Nurmi J. Hypoglycaemia without diabetes encountered by emergency medical services: a retrospective cohort study. Scand J Trauma Resuscit Emerg Med 2018; 26(1): 1–9.
3. Service FJ. Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metabol Clin North Am 1999; 28(3): 519–32.
4. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabol. 2009; 94(3): 709–28.
5. Tesfaye N, Seaquist ER. Neuroendocrine responses to hypoglycemia. Ann N Y Acad Sci 2010; 1212(1): 12–28.
6. Marks V, Teale JD. Tumours producing hypoglycaemia. Endocr Related Cancer 1998; 5: 111–30.

A Case of pleural solitary fibrous tumour with paraneoplastic hypoglycaemia - Doege-Potter syndrome

Chong Kong Yong[1], Benedict Dharmaraj[1], Diong Nguk Chai[1], Narasimman Sathiamurthy[1], Noraini Mohd Dusa[2]

[1]Thoracic Unit, Department of Surgery, Hospital Kuala Lumpur,50586 Wilayah Persekutuan, Kuala Lumpur Malaysia, [2]Pathology Department, Hospital Kuala Lumpur, 50586 Wilayah Persekutuan, Kuala Lumpur Malaysia

SUMMARY

Pleural-based solitary fibrous tumours (SFT) are rare with incidence of less than 5% reported in literature. It can present as incidental finding on chest imaging or with paraneoplastic symptoms like recurrent hypoglycaemia. Doege-Potter Syndrome refers to solitary fibrous tumour associated with non-islet cell tumour hypoglycaemia (NICTH), as a result of tumour secretion of insulin-like growth factor 2. This is in turn, led by a common driver mutation in solitary fibrous tumours, causes tumorigenesis. Guided core biopsy is often diagnostic of SFT. Pre-operative medical control of hypoglycaemia is often required. Surgery is the definitive treatment, but complete resection might be challenging due to the size and location of the tumour.

INTRODUCTION

Solitary fibrous tumours (SFT) are rare, and they arise from cells in the tissues that support other tissues throughout the body, known as connective tissue. Solitary fibrous tumours of the pleura (SFTP) account for about 30% of all SFTs, while accounting for less than 5% of all pleural based tumours.[1] Patients can be asymptomatic at presentation with incidental finding on the chest imaging, or when symptomatic, present with paraneoplastic symptoms such as recurrent hypoglycaemia. The latter is a manifestation of non-islet cell tumour hypoglycaemia (NICTH), due to tumour secretion of insulin-like growth factors 2 (IGF2). The discovery of the common driver mutation in the pathogenesis of these rare tumours has redefined means for diagnosis by immunohistochemical study and potential molecular targets for adjuvant treatment.[2] Complete surgical resection remains the definitive treatment for SFTP, and surgery can be challenging due to the large size of the tumour.

Here we report a rare case of SFTP associated with NICTH (Doege-Potter syndrome) and discuss its prevalence, pathogenesis, diagnosis, management and follow up of this disease.

CASE PRESENTATION

A 55-year-old previously healthy woman, presented with recurrent hypoglycaemic episodes requiring hospital admissions (serum glucose level ranges 1.9 – 3.9 mmol/L). She also reported weight loss around 10 kg within the past 4 months. During her admission, a large right sided lung mass was noted. There was no respiratory symptom. She does not smoke, and pulmonary TB workup was negative. Physical examination revealed decreased breath sounds on the right and was otherwise unremarkable.

Her chest x-ray (CXR) showed a large opacity occupying the entire right middle and lower zone. Computed tomography (CT) revealed a 14.4 cm x 11.5 cm x 20.0 cm ill-defined heterogenous mass within the right hemithorax with mass effect and compression to right pulmonary artery and lower lobe bronchus (Figure 1).

An ultrasound guided biopsy of the mass was reported as solitary fibrous tumour. Immunohistochemical study shows neoplastic cells which are positive for CD34, STAT6 and CD99, with Ki-67 proliferative index approximately 10%. The cells are negative for CKMNF 116, SMA, CD117 and S100.

Prolonged fasting test was suggestive of NICTH. She had low serum insulin (<1.3 pmol/L), with short synacthen test showed adequate response. Her thyroid function test was normal and blood test for sulfonylurea was negative. She was reviewed by endocrine team and started on raw corn starch and tablet prednisolone 5 mg once daily (OD) for 2 months for her recurrent severe hypoglycaemia. Preop random cortisol was 367 nmol/L.

She subsequently underwent right thoracotomy and excision of the right pleural tumour and intraoperatively, a 1.8 kg, 21 cm × 12 cm tumour with smooth fibrous capsule was excised. On post operative day 3, she was noted to have transient rebound hyperglycaemia, requiring insulin administration. However, it resolved quickly and her blood sugar was back to normal within 1 week post surgery and insulin was taken off. Her post operative recovery was otherwise uneventful and her serum insulin level normalised when checked during her 1 month follow-up.

DISCUSSION AND CONCLUSION

Solitary fibrous tumour is collectively one of the common causes of NICTH, together with carcinomas arising from the gastrointestinal (GI) tract, hepatopancreatic system, fibrosarcomas and haemangiopericytomas.[3] SFTs are rare and they arise from mesenchymal fibroblasts that are found in loose connective tissues of serous membranes in the brain, thorax and abdomen.[4] Up to 30% of SFT can be SFTP.

This article was accepted: 27 November 2023
Corresponding Author: Kong Yong Chong
Email: drchongkongyong@gmail.com

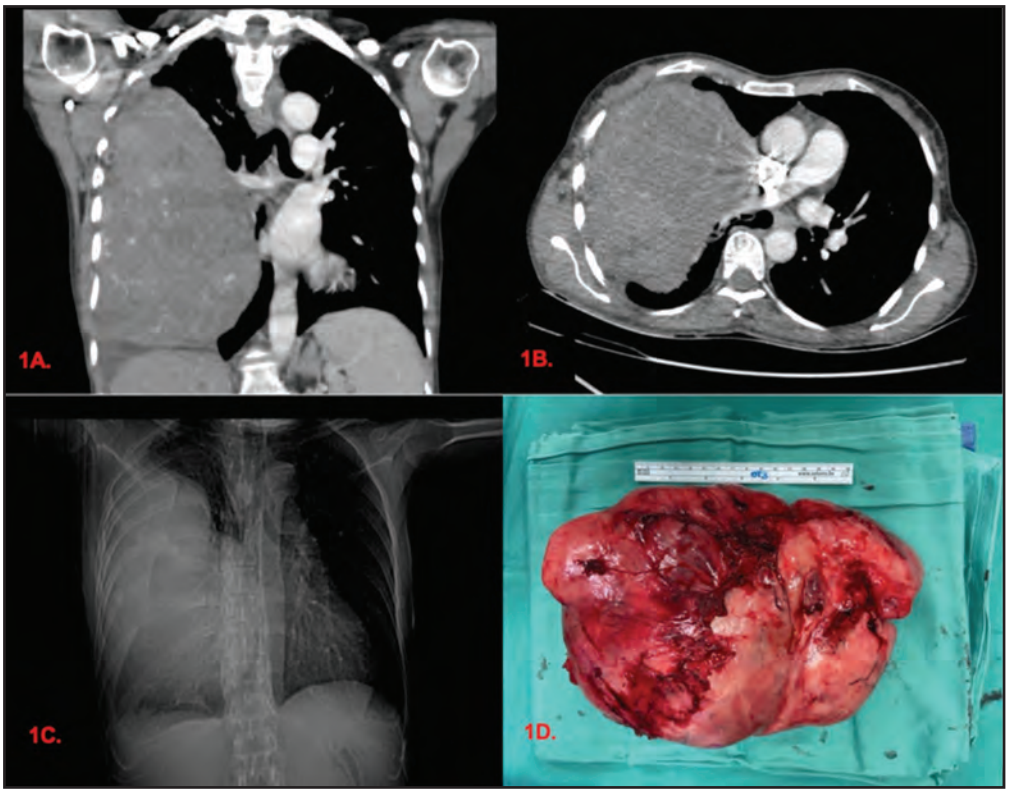

Fig. 1: 1A. Coronal view; 1B. Axial view demonstrating mass compressing on right pulmonary artery. Figure 1C CXR showing mass occupying two third of right lung field. Figure 1D Operative specimen.

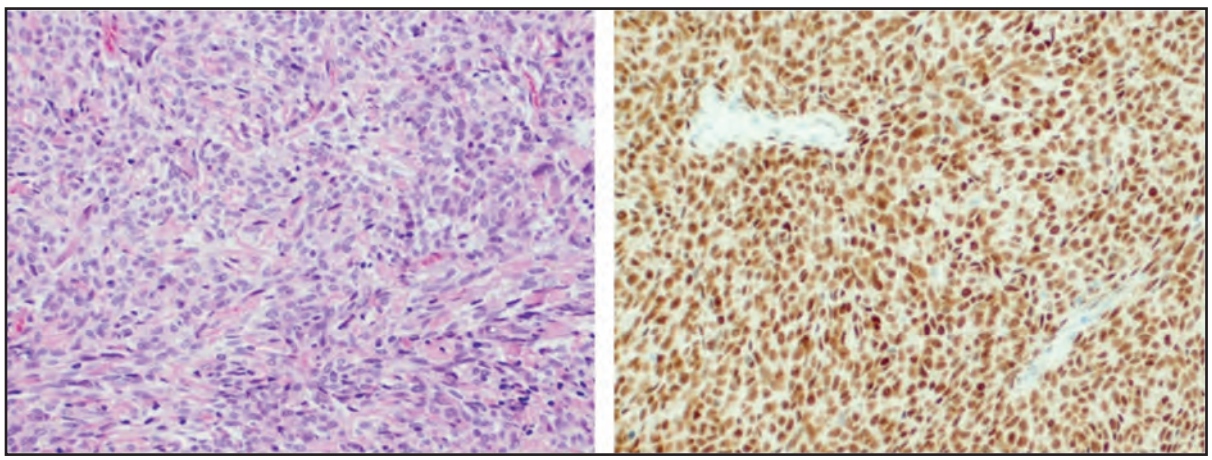

Fig. 2: Histopathological examination of solitary fibrous tumour showing A) Haphazardly arranged spindle to ovoid cells in a variably collagenous stroma (Haematoxylin and Eosin x 200 magnification), B) diffuse nuclear positivity for STAT6 (× 200 magnification).

However, out of all pleural based tumours, SFTP is a rare subset accounting for less than 5%.

SFT manifesting with NICTH is referred to as Doege-Potter syndrome, and SFTP involving the right hemithorax, like in the case of our reported patient, are most commonly associated with this syndrome.[5] The same author reported up to 60% of Doege-Potter syndrome to be associated with malignant SFT, and these are often extra pleural SFTs involving the retroperitoneal or pelvic area, and the meningeal layer.

SFTPs show no sex predilection with equal distribution amongst males and females. They have a peak incidence between 40 and 70 years, with median age at diagnosis in the fifth decade. They are slow growing tumours with low malignant potential. Patient can be asymptomatic until the tumour reaches a large size at the time of diagnosis, with resultant mass effect symptoms. Alternatively in the case of NICTH, patient can present with hypoglycaemic episodes like the ones in this patient.

The NICTH is the result of the tumour secretion of the bigger molecular weighted IGF2. The tumour itself is often well circumscribed and surrounded by fibrous pseudocapsule, with a base that contains big feeder vessels. Grossly, the size of the tumour has been reported to range from a few centimetres to over 40 cm. In this patient, the tumour measures 24 cm x 12 cm x 18 cm, weigh 1.8 kg and has a smooth fibrous capsule. Histologically, haphazardly arranged bland spindled to ovoid cells can be seen embedded in a dense collagenous stroma, with mitosis score of up to 3 per 10 high power fields in the cellular areas. Immunohistochemistry study revealed that the neoplastic cells are positive for CD34, CD99 and STAT6 in our case (Figure 2).

The discovery of the common driver mutation in 2013 for pleural and extrapleural SFTs is a pivotal moment in our understanding of the pathogenesis of these rare tumours. Genetically, it is a result of chromosomal translocation of the NGFI-A binding protein 2 gene (NAB2) to the signal transducer and activator of transcription 6 gene (STAT6).2 This NAB2-STAT6 gene fusion acts as a constituent activator of EGR1 (early growth response 1) targeted transcription and relocates to the nucleus, resulting in cell over proliferations and tumorigenesis. Nuclear STAT6 immunohistochemistry is a sensitive and specific surrogate marker for all fusions.[6]

Workup during initial diagnosis usually starts when patient is brought to the healthcare setup during hypoglycaemic spells. CXR helps to alert the presence of intrathoracic mass, but CT scan is needed to assess the location and relation to adjacent structures beside assessing the tumour size. Magnetic resonance imaging (MRI) may help in delineating diaphragmatic or spine involvement. Positron emission tomography (PET) scan can show presence of distant metastasis in case of malignant SFT.

Guided core needle biopsy is often diagnostic of SFT. However, even the core samples are often inadequate to show enough histological indicators to predict high risk or aggressive tumoral behaviour. These indicators are mainly gathered from histopathological examination and immunohistochemical study of the resected specimen. The definitive management of SFTP is complete tumour resection. Prior to resection, hypoglycaemia can be controlled with dextrose infusion, use of glucocorticoids like dexamethasone, and caloric supplementation.

The surgical principle for malignant SFTP resection is en-bloc resection with a 1 2 cm free margin. Approaches include open thoracotomy and/or sternotomy depending on tumour size and location.[7] Video-assisted thoracoscopic surgery may be used for smaller pedunculated tumour. Due to its often-large size at presentation and depending on the location of the tumour, complete (R0) en-bloc resection might involve partial resection of the adjacent pleura, diaphragm, pericardium or lung, with resultant morbidity. Preoperative embolisation of the feeding vessels for large tumours (>20 cm) is a viable option to reduce the intraoperative blood loss.[8]

SFTs is known to show a variable range of biological behaviour, with up to 15 to 20% showing risk for local recurrence and metastases. It is therefore important for the treating doctors to note that although it is less common for SFTP to be malignant compared to extrapleural SFT, post operative surveillance and follow up should closely take into consideration the World Health Organisation (WHO) risk model for prediction of metastasis of SFTs (original reference[9]). This model takes into account four variables namely the age, tumour size, mitoses and necrosis. A score is assigned under each variable to give a total score that risk stratifies the metastasis-free survival (MFS). It is found that those with low total score (0-3) has a 100% MFS compared to an intermediate/high score (4-7) with 50% MFS at 5 years post operative.[10] Some authors have proposed that increased Ki-67 protein expression, seen on immunohistochemical study, as another reliable indicator for malignant behaviour.

We learned that our patient is in the high-risk category based on the WHO model with a score of 5, and we are following her up long term with close initial surveillance. She is currently disease free within her first-year surveillance. For adjuvant treatment of malignant SFTs, platinum-based chemotherapy like anthracycline has shown limited benefit. Targeted therapy with tyrosine kinase inhibitors has also shown to be ineffective, except for anecdotal report of disease control for refractory NICTH in patient with an unresectable, metastatic SFT.[11] There is no evidence showing radiotherapy to be beneficial in unresectable SFTP. Similarly, in cases of resected SFTPs with margin involvement, tumour recurrence or malignant SFTP, the lack of conclusive evidence favouring adjuvant radiotherapy means any decision on its application should be individualised and guided by multidisciplinary discussion.

There is strong evidence to support long term follow up after complete resection of SFTP. Surveillance imaging should be done at 3 and 6 months after resection, and then yearly thereafter for 10 years.[12] MRI is recommended where possible, to reduce radiation dose.

REFERENCES

1. Ershadi R, Rahim M, Abbasi M, Erfanian R. Giant solitary fibrous tumour of the pleura. J Surg Case Rep 2018; 2018(11): 270.
2. Chmielecki J, Crago AM, Rosenberg M, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumours. Nat Genet 2013; 45: 131-2.
3. Marks V, Teale JD. Tumours producing hypoglycaemia. Diabetes/Metabo Rev 1991; 7(2): 79-91.
4. De Perrot M, Fisher S, Brundler MA, Seine Y, Keshavjee S. Solitary fibrous tumours of the pleura. Ann Thorac Surg 2002; 74: 285-293.
5. Han G, Zhang Z, Shen X, Wang K, Zhao Y, He J, et al. Doeger-potter syndrome: a review of the literature including a new case report. Medicine (Baltimore) 2017; 96(27): e7417.
6. Doyle LA, Vivero M, Fletcher CD, et al. Nuclear expression of STAT6 distinguishes solitary fibrous tumour from histologic mimics. Mod Pathol 2014; 27(3): 390-95.
7. Magdeleinat P, Alifano M, Petino A, et al. Solitary fibrous tumour of the pleura: clinical characteristics, surgical treatment and outcome. Eur J Cardiothorac Surg 2002; 21: 1087-93.
8. Weiss B, Horton DA. Preoperative embolisation of a massive solitary fibrous tumour of the pleura. Ann Thorac Surg 2002; 73: 983-85.

9. Demicco EG, Wagner MJ, Maki RG, et al. Risk assessment in solitary fibrous tumour: validation and refinement of a risk stratification model. Mod Pathol 2017; 30(10): 1433-42.
10. Demicco EG, Fritchie KJ, Han A. Solitary fibrous tumour. In WHO classification of tumours. Soft tissue and bone tumours. 5th edition. Lyon: WHO Classification of Tumours Editorial Board; IARC; 2020: 104-8.
11. Le Jeune S, Des Guetz G, Bihan H, et al. Refractory hypoglycaemia controlled by sorafenib in solitary fibrous tumour. J Clin Oncol 2013; 31: e118-e121.
12. Mercer RM, Wigston C, Banka R, et al. Management of solitary fibrous tumours of the pleura: a systematic review and meta analysis. ERJ Open Res 2020; 6: 00055-2020.

Delayed diagnosis of an advanced abdominal pregnancy with optimal maternal and neonatal outcome: a case report

Dharshini Nadaraja, MBBS, Buvanes Chelliah, MOG, Aruku Naidu, FRCOG, Marvinash Rao, MD

Obstetrics and Gynecology Department, Hospital Raja Permaisuri Bainun, Ipoh, Malaysia

SUMMARY

Abdominal pregnancy is a rare form of ectopic pregnancy with hazardous maternal and perinatal morbidities which increases with advancing gestation. Despite advancement in ultrasound technology, this variant of ectopic pregnancy is still being missed. We present a case of 39-years-old, Orang Asli Gravida six para four at 35 weeks of gestation with two previous caesarean scars, referred to our centre for suspicion of placenta accreta spectrum. Ultrasound findings showed a non-gravid uterus measuring 12 cm × 8 cm × 4 cm with endometrial thickness of 10 mm. Extrauterine gestational sac with viable foetus corresponding to gestational age with estimated weight of 2200 g. The placental mass appears to be attached to the right posterolateral uterine wall and was not in continuity with abdominal wall anteriorly and liver superiorly. Right uterine vessel plexus appears tortuous with turbulent flow within. Magnetic resonance imaging was arranged to facilitate surgical planning and preparation. Exploratory laparotomy was performed. Intraoperatively, uterus, bilateral fallopian tubes and left ovary appears normal. Gestational sac with viable foetus arising from the right adnexal complex with placental attachment seen likely to right mesosalpinx. Laparotomy completed without maternal morbidity. Histopathological examination reported most likely placental implantation site is mesosalpinx or broad ligament.

INTRODUCTION

About 2% of all the pregnancies are ectopic pregnancies and commonly encountered in fallopian tube. Abdominal pregnancy is a rare form of ectopic pregnancy with a reported incidence of one in 10,000 live births, which is about 1% of all the ectopic pregnancy cases.[1] In abdominal pregnancy, the gestational sac will be implanted in the peritoneal cavity outside of the uterine cavity or fallopian tube. Abdominal pregnancy rarely presents at advanced gestation and if it presents it is usually associated with maternal or perinatal morbidity or even congenital anomalies.[1] Since, it is a rare condition that the diagnosis usually made based on complications such as abdominal pain and bleeding or based on high index of suspicion.[1,2] Maternal mortality resulting from uncontrolled haemorrhage during surgical evacuation was reported as high as 20% and perinatal mortality has been reported as high as 40–95%.[2] The challenge in managing an abdominal pregnancy begins with recognising the extra uterine location of the pregnancy during ultrasonography and continues with dilemma of placenta management during the surgical evacuation.

CASE PRESENTATION

We present a case of 39-years-old, Orang Asli, Gravida six Para four with two previous caesarean scars, referred to our centre for suspicion of placenta accreta spectrum at 35 weeks of gestation. She had an uneventful antenatal follow up in local health clinic since 10 weeks period of gestation. Early ultrasound was done but there were no abnormalities detected. Her previous deliveries were uneventful, and she had a history of complete miscarriage which did not require surgical intervention.

On general examination, she looked well, small built, not in pain and had pink conjunctiva. Her vital signs were within the normal limits. Her systemic examination did not reveal any abnormalities. On abdominal examination, her symphysial-fundal height was at 34 cm, and foetus was in transverse lie. Vaginal examination was not done as patient was not in labour. Upon assessment at 35 weeks ultrasound finding (Figure 1A) revealed a small non-gravid uterus measuring 12 cm × 8 cm × 4 cm with endometrial thickness of 10 mm. Extrauterine gestational sac seen with viable foetus corresponding to gestational age with estimated weight of 2200 g. Foetal liquor and dopplers were normal. There was no myometrial tissue seen in between the gestational sac and maternal bladder (Figure 1C). The placental mass appears to be attached to the right posterolateral uterine wall and was not in continuity with abdominal wall anteriorly and liver superiorly (Figure 1B). Right adnexal vessel plexus appears tortuous with turbulent flow within (Figure 1D). Magnetic resonance imaging was arranged to evaluate site of placental attachment, particularly the underlying vessels and organ to facilitate surgical planning (Figure 2). Discussion made with interventional radiologist regarding identification and occlusion of the major feeding vessels, but occlusion of the vessels is not wise before the baby is delivered.

Preoperatively, her blood parameters were at normal limits. Exploratory laparotomy was performed with midline skin incision (Figure 3H). Intraoperatively, uterus, bilateral fallopian tubes and left ovary appears normal. There was no evidence of uterine scar rupture. Right ovary not visualised.

This article was accepted: 30 November 2023
Corresponding Author: Dharshini Nadaraja
Email: dhar2702@gmail.com

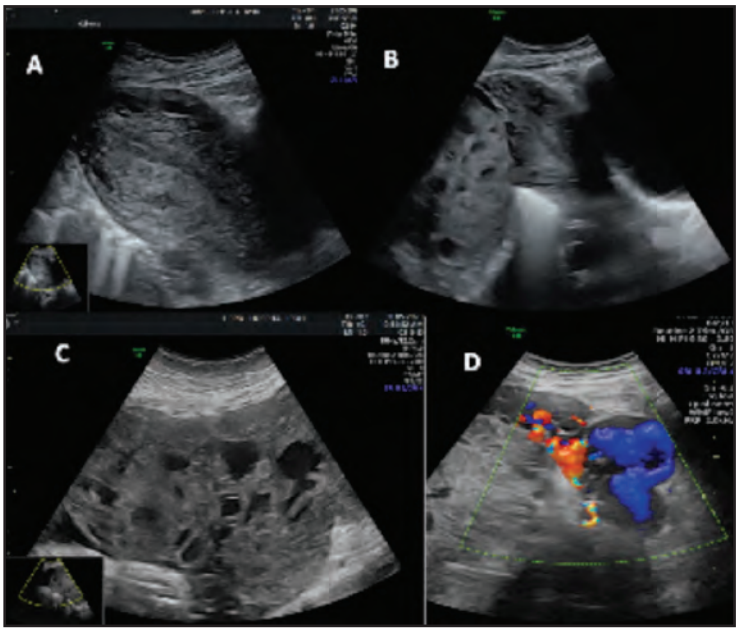

Fig. 1: Ultrasound images (A) Empty uterus; (B) Placental attachment to right posterolateral uterine wall; (C) Loss of intervening myometrium between placenta and anterior abdominal wall; (D) Adnexal vessel plexus with doppler enhancement.

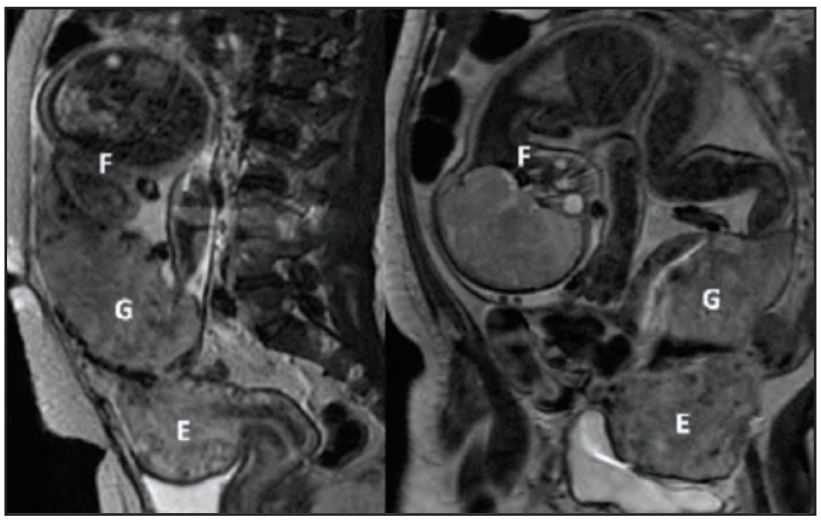

Fig. 2: MRI image. Left sagittal view, right coronal view; (E)uterus; (F) fetus; (G) placenta.

Gestational sac with viable foetus arising from the right adnexal complex with placental attachment seen likely to right mesosalpinx (Figure 3 I, J&K). A healthy newborn weighing 2200 g delivered with good Apgar score. Right infundibulopelvic ligament was clamped, cut and ligated. Placenta was removed completely. Laparotomy completed without maternal morbidity. Estimated blood loss was about 300 mls. Histopathological examination reported most likely placental implantation site is mesosalpinx or broad ligament. Post operatively, patient and baby were discharged home well after three days.

DISCUSSION

An abdominal pregnancy is defined by implantation of the product of conception (gestational sac, foetus and placenta) within the peritoneal cavity but external to the fallopian tubes and myometrium. Potential sites include omentum, pelvic side wall, broad ligament, posterior cul-de- sac, uterine serosa, non-uterine abdominal organs (spleen, bowel, liver), large pelvic vessels and diaphragm. The diagnosis is based on the sonographic or surgical visualisation of the abdominal location of the pregnancy.[3] Advanced abdominal pregnancy defined as abnormal pregnancy after 20 weeks of gestation due to abnormal placentation.[1,3]

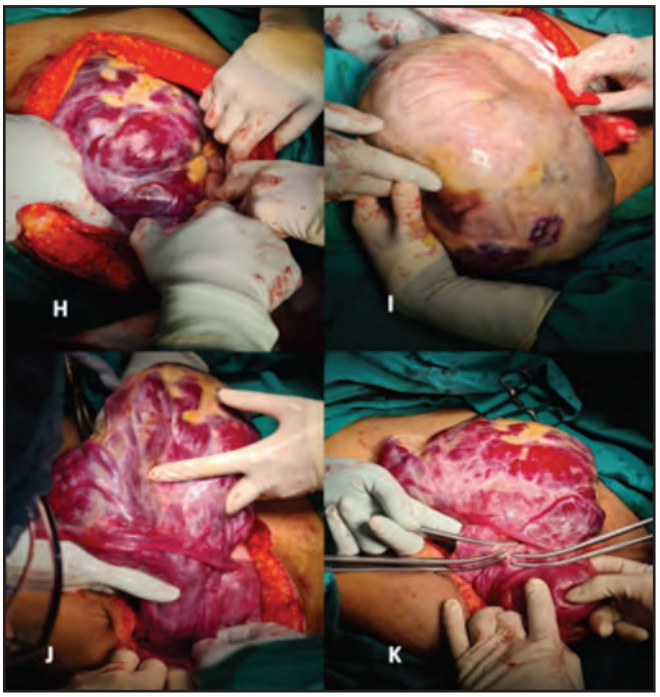

Fig. 3: (H) Image of exploratory laparotomy; (I) Gestational sac with viable fetus; (J & K) Placenta attachment to mesosalpinx with normal uterus.

The risk factor for abdominal pregnancy is in-vitro fertilisation, tubal damage, pelvic inflammatory disease, tubal damage and multiparity.[4] As for this case, the only risk factor was multiparity.

Despite advancement in ultrasound technology, this variant of ectopic pregnancy is still being missed. An advanced abdominal pregnancy may be misinterpreted as intrauterine if the ultra-sonographer does not evaluate the relationship between the pregnancy and myometrium during the examination.

The extrauterine location may not be readily visualised, thus sonographic features that should raise suspicion of an abdominal pregnancy is empty small uterus (often missed), poor definition of placenta, absence of myometrial tissue between the pregnancy and maternal bladder, membranes not visible at internal cervical os and in advanced gestations, the foetus maybe in unusual lie with oligohydramnios.[4]

Magnetic resonance imaging can be useful in confirming diagnosis if there is uncertainty but more importantly for surgical planning.[5] It helps in determining placental attachment site particularly the underlying vessels and organ.

Interventional radiologist can be consulted regarding the occlusion of the feeder vessels supplying the placenta circulation to minimise maternal haemorrhage. Interventional radiologist offer therapeutic options that obviate surgery, therefore reducing mortality and morbidity.[7] Abdominal pregnancy even if advanced are surgically interrupted at diagnosis. Expectant management to gain foetal maturity has been attempted however this approach is not recommended because of high maternal and foetal morbidity from sudden maternal haemorrhage requiring emergency laparotomy in an unplanned environment.

The management of placenta during surgery can pose problem. In this case, it was easily removed because of its location. Individualised management is deemed appropriate. Removing the placenta at surgery may lead to life threatening maternal haemorrhage if site of implantation is on vital organs or large vessels as the normal myometrial mechanism that control placental site haemorrhage is absent. The safe option when the placenta is attached to small or large bowel or mesentery is to leave the placenta in-situ, and close follow-up for haemorrhage and infection is essential and the placenta will slowly regress.[1,4,6]

In some case reports, they have reported about 40% risk of foetal congenital anomalies and only about 50% of the baby survives 1 week post-delivery. In this case, there was no foetal anomalies detected.[1,5]

CONCLUSION

The diagnosis and management of an advanced abdominal pregnancy still poses challenges to obstetricians, even in the era of increased access to advanced diagnostic imaging modalities. High index of suspicion and planned surgical intervention is essential to improve maternal and foetal outcome.

ACKNOWLEDGEMENT

We would like to thank Radiology Department, Hospital Raja Permaisuri Bainun, Ipoh for their participation in managing this case.

CONSENT

Written and informed consent was taken from patient prior to publication of the case.

CONFLICT OF INTEREST

There was no conflict of interest.

REFERENCES

1. Baffoe P, Fofie C, Gandau BN. Term abdominal pregnancy with healthy newborn: a case report. Ghana Med J 2011; 45(2): 81–3.
2. Nwobodo EI. Abdominal pregnancy; a case report. Ann Afr Med 2004; 3(No.4): 195-96.
3. Chen Y, Peng P, Li C, Teng L, Liu X, Liu J, et al. Abdominal pregnancy: a case report and review of 17 cases. Arch Gynecol Obstet 2023; 307: 263-74.
4. Gure T, Sultan S, Alishum R, Ali A, Dibaba B, Usmael I, et al. Term abdominal pregnancy with live baby: case report from hiwot fana specialised university hospital, eastern Ethiopia. Int Med Case Rep J 2021; 14: 689-95.
5. Mengistu Z, Getachew A, Adefris M. Term abdominal pregnancy: a case report. J Med Case Rep 2015; 9: 168.
6. Dorman DB. Full-term abdominal pregnancy. N Engl J Med 1951; 245: 207-10.
7. Thabet A, Kalva SP, Liu B, Mueller PR, Lee SI. Interventional radiology in pregnancy complications: indications, technique, and methods for minimising radiation exposure. Radiographics 2012; 32(1): 255-74.

COVID-19 and Phlegmasia cerulea dolens: a case report and review of the literature

Yap Wai Leong, MMed[1], Norfarahin Hasim, MD[1], Mimi Azliha Abu Bakar, MMed[1,2], Mohd Hashairi Fauzi, MMed[1,2], Tuan Hairulnizam Tuan Kamauzaman, MMed[1,2], Kamarul Aryffin Baharuddin, MMed[1,2]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia, [2]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan

SUMMARY

COVID-19 affects respiratory system and may also lead to severe deep vein thrombosis (DVT), known as phlegmasia cerulea dolens (PCD). We report the case of a 35-year-old woman who presented with a two-day history of pain and swelling in her left lower extremity. She had a history of COVID-19 infection three weeks prior to presentation. Ultrasound doppler showed acute left DVT extending from the left external iliac to the popliteal vein. PCD was diagnosed based on her physical examinations and doppler ultrasound reports. We also searched published case reports related to PCD and tabulated 13 cases for discussion. Most of the patients were more than 50 years old and had increased hypercoagulable states. Half of the patients had acute pulmonary embolism, and the case fatality rate was approximately 25%. The anticoagulant was the initial treatment of choice, but most patients needed surgical intervention.

INTRODUCTION

Phlegmasia cerulea dolens (PCD) is a rare and severe form of deep vein thrombosis (DVT).[1] PCD often manifests as a triad of pain in the affected limb, oedema and cyanosis.[1,2] Diagnosis is made based on physical examination findings and doppler ultrasonography.[3] Life-threatening sequelae of PCD include acute pulmonary embolism (PE), limb amputation, and death.[3]

The first case of SARS-CoV-2 was reported in December 2019,4 and the World Health Organisation (WHO) declared the disease, later known as COVID-19, a global pandemic in March 2020.[4] It is known to be associated with thromboembolic events.[1,2,5–7] We describe a rare thromboembolic event that led to PCD in a COVID-19 patient. A review of the literature involving similar cases that have occurred worldwide is also highlighted, including the interventions.

CASE PRESENTATION

A 35-year-old woman with type 2 diabetes mellitus (DM) and hypertension presented to the Emergency Department (ED), Hospital Universiti Sains Malaysia with a two-day history of pain and swelling of the left lower extremity (LLE).

Based on further history, she has been taking a combined oral contraceptive pill (COCP) for the past year after her last pregnancy. She also had undergone an emergency lower segment caesarean section for breech presentation. Three weeks prior to this presentation, she was treated for a category 2 COVID-19 infection and was discharged well.

On arrival at the ED, she was alert and conscious. Her vital signs were blood pressure of 152/98 mmHg, heart rate of 121 beats per minute, afebrile (36.4°C) and oxygen saturation of 98% in room air. On examination, her entire LLE was swollen, tender to palpation, appeared cyanotic and shiny with pitting oedema up to the mid-shin. Her distal pulses and sensation were intact. There was also a discrepancy in her calves' circumferences. Her right calf was measured at 40 cm, while her left calf was measured at 45 cm (Figure 1).

A formal doppler ultrasound of the LLE was performed, and the radiology team found dilated deep veins of the left lower limb with non-compressible distal left external iliac, left common femoral, proximal and midpart of left superficial femoral and left popliteal veins, with the presence of echogenic thrombus and no colour doppler flow seen within (Figure 2 and 3). It was reported as an acute left DVT extending from the left external iliac to the left popliteal veins.

Based on the clinical examination findings and LLE ultrasound doppler report, she was diagnosed with LLE PCD, aligned with the same diagnosis from the medical team. She was started on intravenous heparin with a loading dose of 80 IU per kg, followed by infusion of 18 IU per kg per hour in the ED. The medical team opted for subcutaneous injection of fondaparinaux 7.5 mg once a day (OD) and changed to oral rivaroxaban once available with a dose of 15 mg BD for 3 weeks, followed by 20 mg OD for 6 months.

She was well during the hospital stay and was counselled for intrauterine contraceptive devices by the Obstetrics & Gynaecology (O&G) team for her future contraceptive option. She was discharged well and was given a clinic and an LLE doppler ultrasound appointment 6 months after discharge for reassessment.

DISCUSSION

This is the first COVID-19 patient with PCD reported in an Asian country, and it involves Malay ethnicity. The patient was on oral contraceptive pill (OCP), which is a known risk factor for thromboembolic events. Complicated by the

This article was accepted: 30 November 2023
Corresponding Author: Kamarul Aryffin Baharuddin
Email: amararyff@usm.my, amararyff@yahoo.com

Table I: Summary of Case Reports

Study / Case Report	Setting during the diagnosis	Ethnic (Country)	Gender	Age (years)	Extremity involved	Comorbids	COVID-19 category	Onset to PCD	Other risk factor/s for thromboembolism	Lung findings	Associated with pulmonary embolism	Inter-vention	Out-come
Akkari 2020[8]	NA	African American (USA)	Male	61	Left lower extremity	Nil	5	Asymptomatic	Nil	CT chest bilateral patchy ground-glass opacities	Yes, CT chest left main pulmonary artery PE	Emergent fasciotomy	Expired
Bamgboje 2020[4]	Ward	Caucasian (USA)	Male	61	Both lower extremities	HPT	4	7 days	APLS	Chest X-ray on admission showed bibasilar pulmonary infiltrates compatible with pneumonia	No	Heparin	Discharged
Chun 2020[10]	Vascular Surgery	Caucasian (USA)	Male	51	Left lower extremity	Congenital tricuspid atresia, pulmonic stenosis, recurrent paroxysmal AF on long term warfarin	5	2 days	APLS	NA	No	Surgical - lower extremity venography, placement of a retrievable filter, and mechanical thrombectomy	Left BKA on hospital day 39 and discharged 9 days later, with warfarin therapy
Hembd 2021[5]	Plastic Surgery	Caucasian (USA)	Female	54	Right upper extremity	DM, refractory ph-like lymphoblastic leukemia with indwelling PICC line, chemotherapy related pancytopenia	2	9 days	Leukemia	NA	NA	Heparin and bedside fasciotomy	Expired
Jan 2021[9]	Outpatient department	Caucasian (USA)	Male	42	Left lower extremity	NA	2	2 weeks	History of DVT	CTA pulmonary infarcts bilaterally, multiple mixed cavitating and non-cavitating lesions in both lungs associated with ground glass haze and small left pleural effusion, multiple large mediastinal and upper abdominal lymph nodes, hilar lymph nodes eroding walls of bilateral pulmonary arteries.	Yes, CTA	Surgical thrombectomy	Anticoagulant and discharged

cont..... pg 253

cont from..... pg 252

Table I: Summary of Case Reports

Study / Case Report	Setting during the diagnosis	Ethnic (Country)	Gender	Age (years)	Extremity involved	Comorbids	COVID-19 category	Onset to PCD	Other risk factor/s for thromboembolism	Lung findings	Associated with pulmonary embolism	Inter-vention	Out-come
Morales 2020[6]	ED	Caucasian (USA)	Male	55	Right lower extremity	MVA with multiple surgeries complicated with DVT and IVC filter placed, hypertension	2	3 weeks	APLS	Chest x-ray revealed bilateral patchy infiltrates	Yes, CT chest subsegmental PE in the medial right middle lobe	Medical - IV alteplase 50mg and heparin	Admitted to ICU, continued on heparin, transitioned to oral anticoagulant, discharged on day 7
Visveswaran 2021[2]	Paediatric department	Caucasian (USA)	Female	12	Left lower extremity	Nil	1	5 days	APLS	Pulmonary angiography confirmed extensive emboli in the superior, middle, and inferior segments of the right lung; the lingular segment of the left lung; and interlobular pulmonary arteries	Yes, Echocardiogram revealed severe right ventricular dilation with severe hypokinesis	Heparin and percutaneous mechanical venous thrombectomy	Discharged with enoxaparin
Moraes 2021[1]	ED	Caucasian (USA)	Male	47	Left lower extremity	DM HPT	2	7 days	Nil	V/Q scan revealed multiple, large, segmental perfusion defects in the bilaterallungs	Yes, Bedside echocardiogram revealed evidence of acute right heart strain with a dilated right ventricle and paradoxical septal wall motion	Catheter directed alteplase by IR, IVC filter placement	Discharged with rivaroxaban
Orso 2021[7]	ICU	Caucasian (Italy)	Male	64	Both lower extremities	Obese, HPT, AF, type 2 DM, CKD, OSA, chronic venous insufficiency	5	NA	Nil	Lung and cardiac ultrasound were compatible with severe interstitial pneumonia and with no signs of pressure overload of the right heart	NA	Heparin and iloprost, CVVH	Expired
Abdulmutaali 2021[11]	Internal Medicine	Arab (Saudi Arabia)	Female	62	Left lower extremity	DM, HPT	2	5 days	Nil	NA	Yes, computed tomography of the patient's chest showed bilateral PE	Heparin, fasciotomy and AKA	Discharged with anticoagulant

cont..... pg 254

cont from..... pg 253

Table I: Summary of Case Reports

Study / Case Report	Setting during the diagnosis	Ethnic (Country)	Gender	Age (years)	Extremity involved	Comorbids	COVID-19 category	Onset to PCD	Other risk factor/s for thromboembolism	Lung findings	Associated with pulmonary embolism	Inter-vention	Out-come
Avdeev 2021[3]	ED	Caucasian (Russia)	Female	61	Right upper extremity	Type 2 DM HPT	2	3 days	Nil	NA	NA	Heparin and emergency percutaneous mechanical thrombectomy	Discharged with apixaban
Alghamdi 2022[13]	ED	Arab (Saudi Arabia)	Male	58	Left lower extremity	Nil	3	3 days	May-Thurner syndrome	Bilateral peripheral patchy opacities	No	Heparin, IVC filter, catheter-directed alteplase, aspiration	Discharged with anticoagulant
Cohen 2023[12]	NA	Caucasian (USA)	Male	44	Bilateral lower extremities	DM	NA	NA	DVT, PE with IVC filter, PAD	NA	Past history of PE	Heparin, catheter-directed alteplase, followed by thrombectomy and suction	NA
Current case	ED	Malay (Malaysia)	Female	35	Left lower extremity	DM, HPT HPL	2	4 weeks	COCP	NA	No	Fondaparinaux and rivaroxaban	Discharged with anticoagulant

COVID-19 category (CAT): CAT 1=asymptomatic; CAT 2=symptomatic, no pneumonia; CAT 3=symptomatic, pneumonia; CAT 4=symptomatic, pneumonia, requiring supplemental oxygen; CAT 5=critically ill with multi-organ involvement.

Abbreviation: AF=atrial fibrillation; AKA=above knee amputation; APLS=antiphospholipid syndrome; BKA=below knee amputation; CKD=chronic kidney disease; COCP=combined oral contraceptive pill; CT=computed tomography; CTA=CT angiography; CVVH=continuous veno-venous hemofiltration; DM=diabetes mellitus; DVT=deep venous thrombosis; ED=emergency department; HPL=hyperlipidemia; HPT=hypertension; ICU=intensive care unit; IV=intravenous; IVC=inferior vena cava; MVA=motor vehicle accident; NA=not available; OSA=obstructive sleep apnea; PCD=phlegmasia cerulea dolens; PE=pulmonary embolism; PICC=peripheral inserted central catheter; PAD=peripheral arterial disease; USA=United States of America.

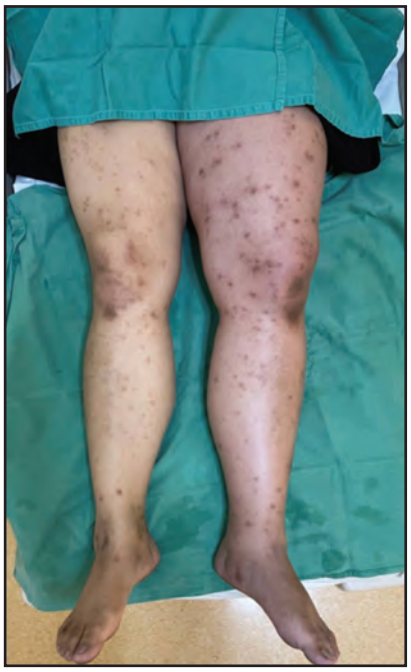

Fig. 1: Swollen, shiny and bluish discoloration of left lower extremity extending from thigh until the foot.

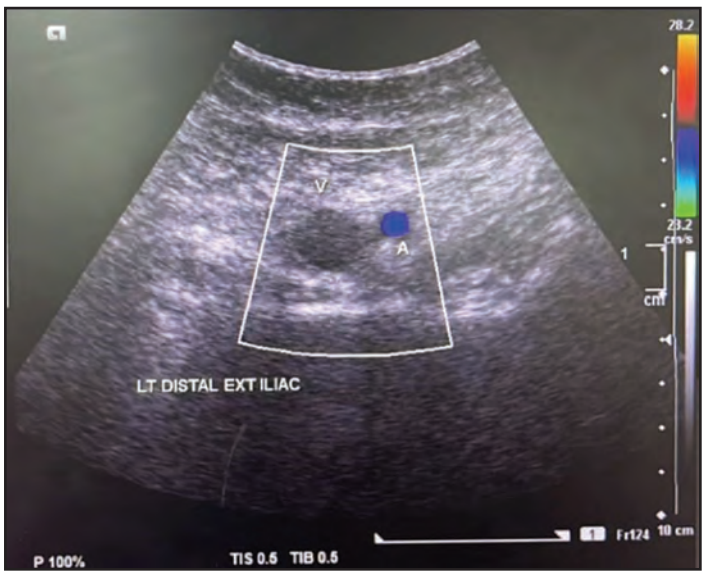

Fig. 2: Colour doppler flow not seen within visualised left distal external iliac vein with presence of echogenic thrombus within.

COVID-19 infection, she developed PCD a month later. Based on the published case reports, there were variations in the onset of PCD among post-COVID-19 patients, as summarised in Table I. Most of the cases were reported in the USA.[1,2,4–6,8–10] The outcome of patients also varied, in which three patients passed away due to PCD and its complications.[5,7,8]

There was no specific gender preference, and most of the cases involved patients who were more than 50 years of age. There was only one paediatric patient who had PCD involving the LLE.[2] LLE is more commonly affected, possibly due to the compression of the left common iliac vein by the right common iliac artery. Based on the series of previous case reports (refer Table I), it appears that there is no specific COVID-19 category that is associated with developing PCD. Diabetes and hypertension are common comorbidities. The onset of COVID-19 until the diagnosis of PCD varies from as early as two days to as long as 1 month, as reported in the current case. However, PCD can also manifest in an asymptomatic COVID-19 patient,8 and some of whom exhibit no risk factors for thromboembolism.[1,3,7,8,11] Among the COVID-19 patients, the most common risk factors for thromboembolism is antiphospholipid syndrome (APLS),[2,4,6,10] followed by a history of DVT,[9,12] leukaemia,[5] May-Thurner syndrome13 and COCP. In addition to this, many COVID-19 patients show elevated D-dimer levels and hypercoagulable states, contributing to an increased incidence of thromboembolic events.[12] Viral illnesses such as SARS-CoV-2

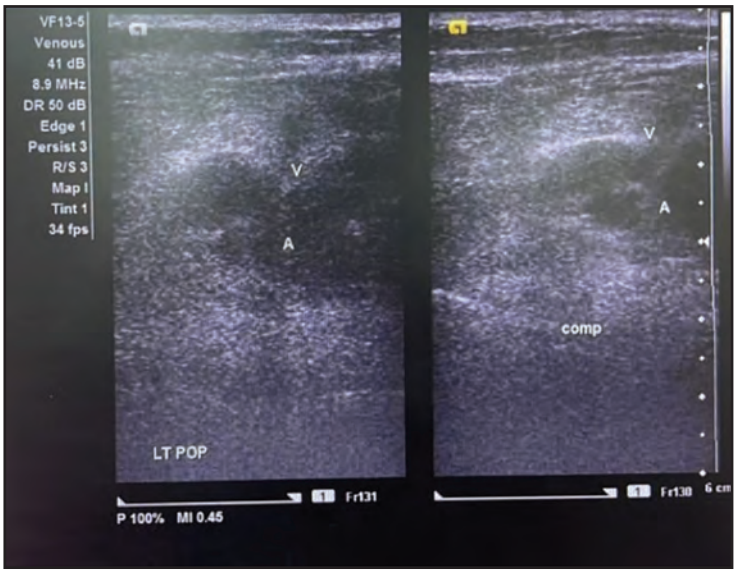

Fig. 3: Non compressible left popliteal vein with presence of echogenic thrombus within.

also have been linked to transiently elevated antiphospholipid antibodies, further augmenting the hypercoagulable state.[13]

Lung findings reported in the cases were ground-glass opacities,[8,9] bilateral pulmonary infiltrates,[4,6] and severe interstitial disease.[7] Six cases eventually led to acute pulmonary embolism (PE), four of which reported the involvement of bilateral lungs.[1,2,9,11] Most cases were administered heparin before proceeding to other modes of treatment. Four cases reported the use of alteplase in treating PCD.[1,6,12,13] Surgical interventions in PCD were emergency mechanical thrombectomy in five cases,[2,3,9,10,13] emergency fasciotomy in three cases,[5,8,11] and filter insertion in two cases.[1,10] In this case, our patient responded well to the treatment and was discharged alive. She did not develop any PE, and no surgical intervention was required.

CONCLUSION

COVID-19 patients have higher hypercoagulable states and may lead to phlegmasia cerulea dolens (PCD) and its complications. Half of the patients had acute pulmonary embolism (PE), and anticoagulants were the initial treatment of choice during presentation. Surgical interventions such as fasciotomy and thrombectomy may be required if the condition worsens.

REFERENCES

1. Moraes B, Hashemi A, Mancheno K, ObanDo M, Marra E, Obano M, et al. Hypercoagulability due to COVID-19 leading to impending phlegmasia cerulea dolens and sub-massive bilateral pulmonary embolism. J Cureus 2021; 13(8): 1-5
2. Visveswaran GK, Morparia K, Narang S, Sturt C, Divita M, Voigt B, et al. Severe acute respiratory syndrome coronavirus 2 infection and thrombosis: phlegmasia cerulea dolens presenting with venous gangrene in a child. J Pediatr 2020; 226: 281–84.e1.
3. Avdeev SN, Nekludova GV, Tsareva NA, Yaroshetskiy AI, Merzhoeva ZM, Nuralieva GS, et al. Pain, swelling and blue discolouration of right hand in a COVID-19 patient. Ann Emerg Med 2021; 77(6): 657.
4. Bamgboje A, Hong J, Mushiyev S, Pekler G. A 61-year-old man with SARS-CoV-2 infection and venous thrombosis presenting with painful swelling and gangrene of the lower limb consistent with phlegmasia cerulea dolens. Am J Case Rep 2020; 21: e928342–1.
5. Hembd A, Kim H, Lahsaei P, Haddock NT, Teotia SS. Upper-extremity phlegmasia cerulea dolens with compartment syndrome in coronavirus disease 2019 sepsis. J Hand Surg 2022; 47(7): 693.e1-.e3.
6. Morales MH, Leigh CL, Simon EL. COVID-19 infection with extensive thrombosis: a case of phlegmasia cerulea dolens. Am J Emerg Med 2020; 38(9): 1978.e1.
7. Orso D, Mattuzzi L, Scapol S, Delrio S, Vetrugno L, Bove T. Phlegmasia cerulea dolens superimposed on disseminated intravascular coagulation in COVID-19. J Acta Bio Medica: Atenei Parmensis 2021; 92(4): 1-4
8. Akkari R, Schwartz B. Phlegmasia cerulea dolens: an atypical COVID-19 presentation. Chest 2020; 158(4): A2090.
9. Jan A, Khizar HM. Phelgmasia cerulea dolens (PCD) as a complication of COVID-19: case report. CTSNet, Inc. Media; 2021.
10. Chun TT, Jimenez JC, Pantoja JL, Moriarty JM, Freeman S. Phlegmasia cerulea dolens associated with acute coronavirus disease 2019 pneumonia despite supratherapeutic warfarin anticoagulation. J Vasc Surg Cases Innov Tech 2020; 6(4): 653–56.
11. Abdulmutaali W, Alamri M. Extensive thrombosis (DVT/PE) with phlegmasia cerulea dolens/amputation and compartment syndrome with COVID-19: a case report. IJMDC 2021; 5(4): 1100–102.
12. Cohen S, Lynch J. COVID-19-Induced phlegmasia cerulea dolens. Cureus 2023; 15(1): e33644. doi: 10.7759/cureus.33644.
13. Alghamdi L, Alattab N, Alwohaibi A, Alotaibi YH, AlSheef M. Phlegmasia cerulea dolens secondary to COVID-19 and May-Thurner syndrome: a case report. Cureus 2022; 14(1): e21301.

Hoarseness of voice: a case report on three different underlying causes

Magaletchumi Chelladorai, MBBS[1,2], Leelavathi Muthupalaniappen, MMed (Fam Med)[2,3]

[1]Ministry of Health Malaysia, Pusat Pentadbiran Kerajaan Persekutuan, 62000 Putrajaya, Malaysia, [2]Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Jeffrey Cheah School of Medicine and Health Sciences, Department of General Practice, Monash University, Sunway Campus, Bandar Sunway, Malaysia

SUMMARY

Hoarseness of voice is the alteration in the normal voice quality which may be due to structural or functional causes. It is a common condition, and it is mostly benign and self-limiting e.g., in post viral upper respiratory tract infections. However, persistent or progressive dysphonia needs to be evaluated to identify the underlying cause. Persistent hoarseness of voice is commonly feared to be due to malignancy. In this case report, we describe three patients with persistent hoarseness of voice who were investigated and found to have malignant and non-malignant aetiologies.

INTRODUCTION

Hoarseness of voice or dysphonia is a common condition that affects all age groups. Hoarseness is the symptom of altered voice reported by patients while dysphonia is the term used by the physician to describe altered voice.[1] The altered voice is often described as rough, weak or strained affecting the pitch, quality, loudness or effort of speech. There are many aetiologies for hoarseness of voice such as voice overuse, laryngitis of any cause, inhaled corticosteroid, hypothyroidism, vocal cord lesion or malignancy.[1]

Laryngopharyngeal reflux (LPR) and allergic rhinitis (AR) are some of the common non-malignant causes of hoarseness of voice. The symptoms of both these conditions often overlap. AR commonly presents with frequent sneezing, blocked nose, itchy red eyes, cough and hoarseness of voice while LPR mainly presents with hoarseness of voice, lump in the throat sensation, chronic cough, sore throat, postnasal drip (the need to frequently clear the throat) and difficulty in swallowing. The incidence of dysphonia in AR is about 44% while almost 100% of people with LPR will experience dysphonia.[2] Both these conditions occur due to inflammation of the upper aerodigestive tract and larynx. The inflammation of the larynx in AR is IgE mediated while in LPR, it is due to gastric acid reflux.[3]

Laryngeal carcinoma is a common malignant cause for hoarseness of voice. It is responsible for almost one third of the malignancies occurring in the head and neck region and accounts for about 1 to 5% of malignancies in Malaysia. People with history of tobacco use, alcohol consumption and oncogenic human papilloma virus (HPV) infection are at risk to develop laryngeal carcinoma.[4] Early detection of laryngeal carcinoma is vital as the 5-year survival for early-stage disease is about 60 to 80% and reduces to 40 to 50% for late-stage presentations.

Among the functional causes of voice hoarseness, puberphonia is a rare disorder which occurs in about 1 in 900,000 cases where the pubertal voice changes or voice break fails to occur resulting in a persistently high pitch voice despite adequate vocal cord growth.[5] Patients commonly complain of high-pitched voice beyond puberty which may be associated with intermittent hoarseness, unable to shout, experience vocal strain or fatigue. Other causes of puberphonia are non-fusion of the thyroid cartilage, increased laryngeal muscle tension, emotional stress, psychogenic factors and delayed puberty.

Since there are many causes for persistent hoarseness of voice, a sound knowledge of this condition is important as it can guide physicians towards a more systematic approach to the underlying aetiology and advocate appropriate management for these patients. We describe three patients of different age groups, who presented with different causes of dysphonia, how they were diagnosed and managed by a multidisciplinary team of experts.

CASE PRESENTATION

Case 1

A 45-year-old housewife presented with first episode of hoarseness of voice, associated with frequent sneezing and blocked nose for 8 weeks after an episode of upper respiratory tract infection (URTI). She also complained of a lump-like sensation on swallowing and frequently cleared her throat. Other symptoms such as reflux, cough, sore throat, dysphagia, difficulty in breathing, hearing loss, ear pain, discharge or vertigo were all absent. Past medical history revealed that she had frequent episodes of sneezing and nasal congestion since childhood. She had no other medical illness or allergies. She was a non-smoker and did not consume alcohol.

Clinically her voice was noted to be rough. The oropharyngeal examination showed mild congestion of pharynx. Neck and lung examination were unremarkable. She was referred to otolaryngologist for laryngoscopy examination to exclude any laryngeal pathology as a cause for prolonged hoarseness of voice. A flexible nasopharyngoscopy showed bilateral inferior turbinate hypertrophy with clear post-nasal discharge, cobblestoned posterior pharyngeal wall with diffuse laryngeal oedema, post commissure hypertrophy, oedematous arytenoids and thick endo-laryngeal mucus. With these findings, she was diagnosed to have chronic laryngitis secondary to AR and

This article was accepted: 02 December 2023
Corresponding Author: Leelavathi Muthupalaniappen
Email: drleelaraj@yahoo.com

LPR. She was advised on lifestyle modifications to prevent acid reflux and was prescribed with loratadine 10 mg daily and momethasone nasal spray two puffs daily for AR. Esomeprazole 40 mg twice daily was prescribed for LPR. She was also referred to the speech and language pathologist (SLP) for advice on vocal hygiene. Her symptoms improved gradually after 8 weeks of treatment.

Case 2:
A 55-year-old retired man presented with a 6 month history of persistent hoarseness of voice after an episode of URTI. The URTI symptoms cleared after 2 weeks of treatment however the hoarseness of voice persisted. Other symptoms such as dysphagia, odynophagia, difficulty in breathing, neck swelling, haemoptysis, hearing loss, reflux symptoms and symptoms of hypothyroidism were all absent. Appetite and weight were normal. He had diabetes, hypertension and dyslipidaemia, for which he was on medication for the past 10 years. He did not consume alcohol but had a 30 pack-year history of smoking.

On examination, his vital signs were stable. His voice was notably deep. The oropharyngeal, neck and respiratory system examination were all unremarkable. He was referred to the otolaryngologist for evaluation of persistent hoarseness of voice. A flexible laryngoscopy revealed an infiltrative lesion on the right true and false vocal folds extending to the right piriform sinus suggesting malignancy. Contrast enhanced computed tomography (CECT) of the neck and thorax showed stage 4 glottic carcinoma (T4aN0M0). Biopsy of the lesion confirmed a moderately differentiated squamous cell carcinoma. He underwent surgery for total laryngectomy with bilateral neck lymph nodes dissection. Patient was scheduled for post-surgery radiotherapy however, he succumbed to the disease three months later.

Case 3:
A 19-year-old student complained of intermittent high and low-pitched (hoarseness) voice for 3 years. He was unable to control his voice fluctuations and it embarrassed him. There were no other symptoms such as cough, breathing difficulties, throat pain, difficulty in swallowing, reflux symptoms, voice strain or any ear related symptoms. Family history for malignancy, voice or laryngeal disorders were all absent. He was a non-smoker and did not consume alcohol.

On examination, his vital signs and oropharyngeal examination were all normal. He was referred to the otolaryngologist to rule out any pathology of the larynx. A flexible nasolaryngoscopy examination revealed a normal laryngeal anatomy and vocal cord mobility. With the history of persistent high pitch voice and intermittent hoarseness beyond 2 years from the onset of pubertal voice change, in the absence of laryngeal pathology suggested a functional cause leading to the diagnosis of puberphonia. He was then referred to the SLP team where he underwent biweekly voice training. After 4 months of therapy, there was some improvement with the voice pitch and control.

DISCUSSION

Hoarseness of voice which fails to resolve or improve within 4 weeks warrants laryngeal examination. A patient can be referred for laryngeal examination earlier if a serious underlying pathology is suspected.[1] Having alarm features such as history of smoking, haemoptysis, fever, night sweats, ear pain (otalgia), noisy breathing (stridor), painful swallowing (odynophagia), difficulty in swallowing (dysphagia), neck mass, loss of appetite and weight require urgent assessment by the otolaryngologist.[1,6] Details of the underlying causes for persistent hoarseness of voice in the three cases described above are discussed in detail.

Allergic Rhinitis and Laryngopharyngeal Reflux
AR is associated with inflammation (IgE mediated) of the larynx resulting in symptoms such increased mucus secretion, hoarseness of voice, nasal congestion or obstruction. LPR on the other hand, occurs when gastric acid comes in contact with the laryngeal mucosal which may be due to dysfunction of the oesophageal sphincters (lower or upper), oesophageal peristalsis or resistance factors.[1] The acid, causes damage to the laryngeal mucosa resulting in symptoms such as hoarseness of voice, a sensation of lump in the throat, chronic cough, sore throat, postnasal drip and difficulty swallowing. A mention of gastroesophageal reflux disease (GERD) here, is also important as some of its symptoms and risk factors such as, consumption of coffee, alcohol, acidic or fatty food, large meal, smoking and obesity may overlap with LPR leading to possible misdiagnosis of this condition. However, hoarseness of voice is mostly absent in GERD.[3] The reflux symptom index (RSI) by Belafsky et al, is a simple questionnaire tool which can be used help to identify, assess severity and response to treatment in patients with LPR.[3]

Further, on assessment using the laryngoscope examination, a person with AR would show cobblestone appearance of the posterior pharyngeal wall, while those with LPR would most commonly (85%) show posterior laryngeal hypertrophy, granulomatous appearance, erythema, oedema of the vocal cords and thick laryngeal mucous.[7]

The mainstay of AR management includes oral antihistamine and intranasal corticosteroid. Management of GERD and LPR is almost similar which involves the initial lifestyle modifications such as low-fat diet, low acidic diet, small meals, refraining from lying down within 3 hours after meals, elevating the head end of the bed, reducing, or avoiding alcohol intake, stop smoking and weight reduction if patient is obese. Voice rest is a useful supportive measure, which includes abstaining from talking, whispering or singing. Vocal hygiene, which involves refraining from excessive throat clearing, avoid heavy lifting, straining at stool, avoiding irritants such as smoking, caffeine and alcohol is also advised.

The current clinical practice guideline on hoarseness (dysphonia) does not advocate the use of anti-reflux medication for clinically diagnosed LPR. However, there is a suggestion that, in the absence of alarm symptoms or voice abuse, a non-resolving dysphonia after 4 weeks of conservative measures based on education and preventive

strategies warrants a laryngoscopy evaluation for diagnosis and treatment.[1] The main medical management for GERD and LPR is similar, which is with a proton pump inhibitor (PPI). However, LPR requires more aggressive and longer treatment with PPI compared to GERD because the laryngeal structures are more vulnerable to damage even at a higher pH compared to the oesophagus. This is because the larynx lacks the protective acid diluting effect of the saliva in this region. Hence, it may take 3 to 6 months of treatment before laryngeal symptoms to resolve.[8] If LPR symptoms resolve within 6 to 8 weeks of therapy, then PPI can be titrated down and stopped. Other medications such as H2-receptor antagonists and alginates may also be used to treat LPR. Surgical intervention may be considered in cases where lifestyle modification and medical therapy have failed.[8]

Laryngeal Carcinoma

Laryngeal carcinoma can be classified anatomically as supraglottic, glottic and subglottic types. Squamous cell carcinoma is the commonest cell type. Patients with localised lesions classically present with hoarseness of voice, pain on swallowing (odynophagia) and ear pain (referred otalgia).[4] Those with advanced lesions, may present with cervical lymphadenopathy and airway compromise. Treatment modalities for laryngeal carcinoma include single-modality radiotherapy or transoral laser microsurgery (TLM) for early-stage tumour or total laryngectomy with neck dissection followed by chemotherapy for disseminated metastasis.[4] Our patient in case two, presented late, after 6 months of persistent change in voice and had developed advanced laryngeal carcinoma (stage 4) which has a poorer prognosis. Those who undergo treatment with surgery or radiotherapy may experience a negative impact on their speech, swallowing or airway patency hence, they must be informed (informed consent) regarding the possible functional sequelae of treatment and followed up with post treatment rehabilitation with a SLP.

Puberphonia

"Voice break" is the change in voice during puberty. It is the transition from the high pitch voice during childhood to a lower pitch to form the deep voice of adulthood. This change is more pronounced in males compared to females. Normally pubertal voice change occurs between the ages of 12 to 16 years in boys and between the ages 10 to 14 years in girls.

Pubertal voice development would normally complete within 2 years of onset in voice change. Adolescent males presenting with a persistently high-pitched prepubertal voice beyond 2 years of onset in voice change, warrants an otolaryngology review to rule out structural abnormalities of the vocal cords. In the absence of a structural pathology, referral to a SLP is required for voice assessment and therapy. Voice therapy is a conservative approach designed to eliminate harmful vocal behaviour and assist in vocal cord healing and control. The objective of voice training is to achieve laryngeal relaxation and voice pitch control. This is done by using techniques such as reading aloud and singing. Findings from a retrospective study show improvement in voice pitch by 78.9% and voice quality by 35.2% over one to ten months of voice therapy. However, successful voice therapy takes a long time and requires the combined effort of a motivated patient and a dedicated therapist.[8] Failing conservative approach, suitability of a surgical approach may be considered after discussion with an otolaryngologist.

CONCLUSION

Hoarseness of voice occurs most commonly due to laryngitis secondary to upper respiratory tract infection, in which case it usually recovers spontaneously within 1 to 2 weeks. Patients with persistent hoarseness of voice, not resolving within 4 weeks or with any red flag signs such as being a smoker, difficult or painful swallowing, noisy breathing, ear pain, haemoptysis, neck mass or constitutional symptoms warrant early referral to otolaryngologist for further evaluation and to rule out any underlying malignant pathology. Other non-malignant causes such as allergic rhinitis and puberphonia should be considered among people presenting with hoarseness of voice, based on the presence of other medical conditions and the time of onset of this condition e.g. at puberty. Hence, a detailed history is pertinent. The multidisciplinary team approach with an otolaryngologist and speech and language pathologist is essential to be able to identify the underlying causes of hoarseness of voice and to be able to manage as shown in the case report to help patient attain their normal voice.

ACKNOWLEDGEMENT

The authors would like to thank the three patients for permission to write this case report. We also extend our gratitude to the otolaryngology and speech and language pathology team for the joint management of these patients.

DECLARATION

The authors declare no actual or potential conflict of interest in relation to this article

REFERENCES

1. Stachler RJ, Francis DO, Schwartz SR, Damask CC, Digoy GP, Krouse HJ et al. Clinical practice guideline: hoarseness (dysphonia) (Update). Otolaryngol Head Neck Surg 2018; 158: S1-S42. [published correction appears in Otolaryngol Head Neck Surg. 2018 Aug;159(2):403].
2. Govindaiah RC, Baldwin JL, Sanders GM. Incidence and potential etiologies of dysphonia in patients with allergies and or asthma. J Allergy Clin Immunol 2004: 113(2): S275.
3. Brown J, Shermetaro C. Laryngopharyngeal reflux. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [cited September 2023]
4. National Comprehensive Cancer Network (NCCN). 2022. NCCN clinical practice guidelines in oncology—Head and neck cancers [cited September 2023]. Available from: file:///C:/Users/JABPPUKM/Downloads/head-and-neck_1_2022_101521%20(2).pdf
5. Bhattarai B, Shrestha A, Shah, SK. Psychosocial impact on puberphonic and effectiveness of voice therapy: A case report. J Coll Med Sci Nepal 2010; 6(1): 57-62.
6. Cooper L, Quested RA. Hoarseness: An approach for the general practitioner. Aust Fam Physician. 2016; 45(6): 378 81.
7. Joshi AA, Chiplunkar B. Laryngopharyngeal reflux. Int J Head Neck Surg 2022; 13(1): 8-17.
8. Alwis A, Rupasinghe R, Kumarasinghe I, Weerasinghe A, Perera R, Jayasuriy C. Efficacy of voice therapy in patients with puberphonia- a 15-year experience. Ceylon J Otolaryngol 2018; 7(1): 8-11.

CASE REPORT

When the unusual strikes: an uncommon occurrence of pyogenic liver abscess induced by *Parvimonas micra*

Priyadarsini Appalaramoo, MBBS, Anim Md Shah, FRCP

Department of Medicine, Hospital Sultan Abdul Aziz Shah, University Putra Malaysia, Serdang, Selangor, Malaysia

SUMMARY

Liver abscesses is one of the common infections affecting the immunosuppressed patients, with *Klebsiella pneumonia* or Escherichia coli being the most likely organisms found. We present a case of liver abscess with a rare organism, *Parvimonas micra* which is typically found in the oral cavity. Four-phase computed tomography of the liver showed multiloculated rim enhancing hypodense lesions, typical of an abscess and patient was treated successfully with intravenous metronidazole, without needing surgical drainage. Early identification of pathogen and the administration of the correct antibiotics proved beneficial to ensure effectiveness of therapy and reducing morbidities.

INTRODUCTION

Parvimonas micra (P. micra), an anaerobic gram-positive coccus is a commonly known commensal of oral pathogen, and it is rarely encountered outside of the oral cavity. However, when a person is infected with *P. micra* in other organs such as the spine, joints and the heart, it has shown to have a more detrimental effect.[1] This case highlights the significance of a prompt diagnosis and the use of appropriate diagnostic methods to further aid the management of such infrequent occurrences.

CASE PRESENTATION

We report a case study involving a 53-year-old Malay man with multiple medical comorbidities including hypertension, hyperlipidaemia, benign prostatic hyperplasia (BPH), gout and chronic kidney disease stage IV. His initial presentation was with a 3-day history of intermittent fever associated with chills and rigors. It was complicated with bouts of vomiting which resolved after 1 day, but he continued to have reduced oral intake. He was otherwise well and denied having any other health concerns. During his initial arrival at our emergency department, he presented with signs of dehydration, recording a blood pressure reading of 99/62 mmHg, coupled with a tachycardic pulse rate of 108 beats per minute. He was afebrile and maintained normal oxygen levels under room air. On clinical examination, he was lethargic and dehydrated with dry mucosa membrane. He was started on 1 L of intravenous drip of 0.9% sodium chloride for 1 hour. After receiving fluid resuscitation, his general condition improved, especially the blood pressure readings. Subsequently, he was admitted to the general medical ward for further management.

A complete blood count revealed an elevated lymphocyte count of 17.12 x 10^9/L with a predominant neutrophil count of 14.68 accounting for approximately 85%. Haemoglobin levels were measured at 11.7g/dL and a slightly low platelet count of 141 x 10^9/L. Screening of coronavirus disease 2019 (COVID-19) through a rapid antigen testing was negative. As for his biochemical parameters, there was evidence of mild hyponatremia with a reading of 132 mmol/L while potassium level was within the normal range. Due to his underlying chronic kidney disease, both his blood urea nitrogen and creatinine levels were elevated, measuring 16.2 mmol/L and 270 µmol/L respectively. At this point, procalcitonin result was unavailable, but his inflammatory marker c-reactive protein (CRP) was elevated at levels of 305 mg/L. Additionally, his liver enzymes were also significantly elevated of which alanine transaminases levels measured at 76 U/L (normal range 0-55), aspartate aminotransferase levels at 305 U/L (normal range 1-5) and alkaline phosphatase levels of 145U/L which falls in the normal range. Unfortunately, there were no baseline liver function test available for comparison. His subsequent serial blood investigation results will be shown in table below. Based on these clinical findings and laboratory investigation results, a preliminary diagnosis of occult sepsis and transaminitis due to underlying sepsis were made. An abdominal ultrasound abdomen was performed, which unveiled a mixture of heterogenous mixed cystic and solid lesions that could possibly represent abscesses. For further evaluation, a four-phase computed tomography (CT) of the liver was done which revealed multiloculated rim enhancing hypodense lesion with central fluid density occupying segments VI/VII of the liver, with measurements of approximately 6.8 cm x 8.4 cm x 6.8 cm (AP x W x CC). There were no filling defects seen and absence of arterial enhancement noted. Additionally, there was a partial loss of the liver margin at this region with adjacent fat streakiness. Rest of the liver was homogenous. These findings pointed towards the presence of partially liquefied liver abscesses. To further aid in our diagnosis, two sets of blood cultures were taken and sent for microbiological analysis.

While waiting for definitive culture results, we initiated him with a broad-spectrum antibiotic i.e., piperacillin-tazobactam administered at a dose of 2.25 g four times daily (renal adjusted dose based on his creatinine clearance <30) which he completed over 13 days. Subsequently, results of peripheral cultures were available, revealing the presence of *P. micra* which is a gram-positive anaerobic organism. Sensitivity testing indicated susceptibility to metronidazole, ampicillin/sulbactam and penicillin. Following this, we

This article was accepted: 04 December 2023
Corresponding Author: Anim Md Shah
Email: animshah@upm.edu.my

Table I: Trends in inflammatory and biochemical parameters during the patient's hospitalisation

Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Haemoglobin (g/dL)	11.7	10.7	10.4	10.8	10.2	10.6	10.5
White cell counts (x109)	17.12	13.75	17.6	21.03	11.7	12.4	7.24
Platelet (x109)	141	104	118	371	251	429	352
Haematocrit (%)	35.9	33.1	32.3	33.1	32.4	32.6	32.6
Sodium (mmol/L)	132	137	132	134	136	138	140
Potassium (mmol/L)	3.9	3.3	4.2	4.9	5.4	4.5	4.4
Urea (mmol/L)	16.7	8.6	9.5	6.6	6.6	4.6	3.0
Creatinine (µmol/L)	270	152	174	153	159	156	149
Total protein (g/L)	67				60	65	
Albumin (g/L)	31				23	25	
AST (U/L)	81				21		
ALT (U/L)	76				33	22	15
ALP (U/L)	145				152	145	125
Bilirubin (µmol/L)	20.2				14.2	10.5	
INR							
Prothrombin time (s)							
Activated partial thrombin time							
C-Reactive Protein (mg/L)	305	387	149		125	52	21

**AST- Aspartate transaminase, ALT – Alanine transaminase, ALP – Alkaline phosphatase

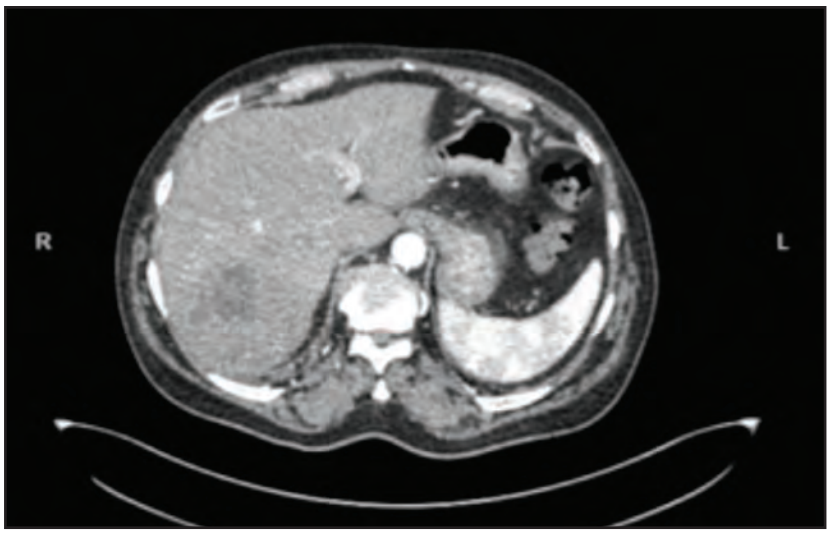

Fig. 1: Multiloculated rim enhancing hypodense lesion with central fluid density seen in four phase liver computed tomography.

changed his treatment to intravenous metronidazole 500 mg three times daily. Considering the common occurrence of *P. micra* in the oral cavity, we arranged an extensive dental assessment for this patient. The assessment did not reveal any possible potential of source of infection originating from the dental cavity. The only notable findings were a few loose teeth for which patient was scheduled for dental extraction. Patient was then discharged well after the completion of his intravenous antibiotics and was scheduled for regular follow up at our outpatient clinic. No other complications noted during his post discharge period, and he was recovering well.

DISCUSSION

P. micra originally classified as Peptostreptococcus micros is an emerging gram-positive anaerobic pathogenic bacterium that is a part of the normal flora of the oral cavity and can be found in other various mucous membranes which include the gastrointestinal tract, genitourinary tract and skin. Although *P. micra* is frequently encountered within the human dental cavity, *P. micra* can also cause bloodstream and spinal infections, lung and/or liver abscesses and sepsis.[1,2] Individuals infected with *P. micra* usually exhibit a typical presentation of lower back pain, although in most cases, patients will not have these presentation. In this case study, the patient presented with non-specific constitutional symptoms such as fever, vomiting and reduced oral intake with a raised inflammatory marker.

Our patient was diagnosed with liver abscesses. Liver or hepatic abscesses can be divided into few different classes which include bacterial, amoebic and fungal, with the highest occurrence seen in bacterial cases (approximately 80% of the cases). *P. micra* usually manifest in immunocompromised populations and our patient has an underlying chronic kidney disease and hypertension.

Diagnosing *P. micra* can be a challenge and choosing the appropriate test is crucial to minimise patient's exposure to unnecessary radiation. The preferred initial test of choice is abdominal ultrasonography (US), showing the presence of hyper or hypoechoic lesions with occasional septations. To further aid in the diagnosis, a contrast-enhanced CT can be done. Rim enhancement and oedema, although atypical, are highly specific for infection. Whenever feasible, a CT guided needle aspiration should be done to precisely identify the causative organism, essential for both diagnostic and therapeutic purposes. Additionally, in recent times more advanced methods are available. A technetium scan offers 80% sensitivity (lower than CT), with gallium and indium exhibiting sensitivities of 50 to 80% and 90%, respectively.[3]

The presence of a substantial liver abscess in this case study, as evident from the liver's four-phase CT constitutes to a unique and distinctive presentation linked to *P. micra*.[4] Only a few cases of *P. micra* causing pyogenic liver abscess have been reported. Ha et.al reported two cases both occurring in South Korea involving solitary liver abscess, while Kim Ey et al reported a case of concurrent liver and brain abscesses.[5-6] There were also other several instances of P. micra triggering severe infections in other organs that have been reported; such as spondylodiscitis, epidural abscess and lung abscess.[7,8] In 2013, there is only one case report of hepatic abscess infected with *P. micra* reported, underscoring this rarity.[4]

First line of treatment for pyogenic liver abscess remained the administration of a broad-spectrum intravenous which then can be narrowed down based on culture sensitivity. Duration of treatment ranged between few weeks to 6 months.[9] Nevertheless, currently, there is not a single universally accepted standard antibiotic regimen for treating *P. micra* infections. However, it has been reported that *P. micra* typically responds to antibiotics such as penicillin, imipenem, clindamycin and metronidazole although metronidazole-resistant strains of P. micra have been reported.10 In the context of this case, metronidazole is prescribed only after obtaining the culture susceptibility results and patient responded well.

CONCLUSION

Irrespective of the causative microorganism, under-diagnosed or late initiation of treatment of hepatic abscesses might be fatal. Therefore, it is of utmost importance to initiate appropriate treatment promptly and to drain if large abscesses encountered. Responsiveness of treatment can be monitored through inflammatory markers and clinical features of sepsis. The best approach to P. micra infection involves treatment with metronidazole, clindamycin or penicillin guided by the individual's susceptibility test results. Given the rarity of this infection, exact timeline of antibiotics administration does not yet exist, and duration is solely based on clinical judgement of physicians.

ACKNOWLEDGEMENTS

We would like to thank the patient for agreeing to be a part of this case report, and to all the staff in Hospital Sultan Aziz Shah who were a part of his care.

DECLARATIONS

There are no competing interest exists between the authors.

REFERENCES

1. Watanabe T, Hara Y, Yoshimi Y, Fujita Y, Yokoe M, Noguchi Y. Clinical characteristics of bloodstream infection by Parvimonas micra: retrospective case series and literature review. BMC Infect Dis 2020; 20: 578.
2. Gorospe L, Bermudez-Coronel-Prats I, Gomez-Barbosa CF, Olmedo-Garcia ME, Ruedas-Lopez A, Gomez del Olmo V, et al. Parvimonas micra chest wall abscess following transthoracic lung needle biopsy. Korean J Intern Med 2014; 29(6): 834–7.
3. Rassam F, Cieslak KP, Beuers UHW, van Gulik TM, Bennink RJ. Stress test of liver function using technetium-99m-mebrofenin hepatobiliary scintigraphy. Nucl Med Commun 2019; 40(4): 388-92.
4. Chaucer B, Smith N, Beatty D, Yadav M. Multiple Hepatic Abscess from Parvimonas micra: an emerging gastrointestinal microbe. ACG Case Rep J 2018; 5: e70.
5. Ha J, Choi SP, Lee WH, Yoo SS, Kim HJ, Kim TH, et al. A clinical study on pyogenic liver abscesses: the changes in the clinical features during the recent 12 years. Korean J Med 2008; 74(1): 37-50.
6. Kim EY, Baek YH, Jung DS, Woo KS. Concomitant liver and brain abscesses caused by Parvimonas micra. Korean J Gastroenterol 2019; 73(4): 230-34.
7. Endo S, Nemoto T, Yano H, Kakuta R, Kanamori H, Inomata S, et al. First confirmed case of spondylodiscitis with epidural abscess caused by *Parvimonas micra*. J Infect Chemother 2015; 21(11): 828-30.
8. Yun SS, Cho HS, Heo M, Jeong JH, Lee HR, Ju S, et al. Lung abscess by Actinomyces odontolyticus and Parvimonas micra co-infection presenting as acute respiratory failure: a case report. Medicine (Baltimore) 2019; 98(35): e16911.
9. Strobel S, Whitaker D, Choi E, Lindow J, Lago K. P. micra and F. necrophorum: hepatic abscesses in a healthy soldier. Case Rep Infect Dis 2022; 2022: 5500365.
10. Sawai T, Koga S, Ide S Yoshioka S, Matsuo N, Muhae H. Aniliopsoas abscess caused by Parvimonas micra: a case report. J Med Case Reports 2019; 13: 47.

Variation of hearing function in children with Apert Syndrome: A case report of three patients

Semiramis Zizlavsky, MD, PhD[1], Indira Sari, MD[1], Fikry Hamdan Yasin, MD[1], Ghaisani Fadiana, MD[2], Mohamad Yanuar Amal, MD[3], Ayu Astria Sriyana, MD[1]

[1]Department of Otorhinolaryngology Head and Neck Surgery (ORL-HNS), Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [2]Department of Pediatrics, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, [3]Departement Radiology, Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

SUMMARY

Introduction: Apert syndrome is a rare disorder characterised by craniosynostosis, midfacial hypoplasia and symmetrical syndactyly of both hands and feet. Hearing loss is also a common symptom in patients with Apert syndrome. This case series aims to describe the clinical characteristics of hearing loss in patients with Apert syndrome. Case report: We present three children with Apert syndrome: (1) a 3-year-old boy with bilateral profound sensory neural hearing loss (SNHL), (2) a 2-year-old girl with otitis media effusion (OME) and mild conductive hearing loss (CHL) and (3) a 4-month-old boy with prolonged interpeak wave latency of wave I-III in the right ear based on brainstem evoked response audiometry (BERA) examination. Conclusion: As hearing loss is a common complication in patients with Apert syndrome, early and periodic screening of hearing function and speech and language development are imperative in these patients.

INTRODUCTION

Type 1 acrocephalosyndactyly, commonly known as Apert syndrome, is a rare craniosynostosis affecting about 9.9 to 15.5 infants per 1,000,000 live births. This syndrome, caused by the mutation of fibroblast growth factor receptor 2 (FGFR2) and inherited in an autosomal dominant manner, is classically characterised by craniosynostosis (fusion of premature cranial sutures), midfacial malformation and syndactyly of the hands and feet.[1–3]

Patients with Apert syndrome usually presents with acrocephaly, frontal bossing, midfacial retrusion, shallow orbits, proptosis, hypertelorism, down-slanting palpebral fissure, strabismus, flat nasal bridge, septal deviation and low-set ears. In addition, oropharyngeal examination may reveal bifid uvula, dental crowding, and orofacial clefts – including submucous cleft palate, cleft palate and pseudo cleft. These patients may be distinguished from other craniosynostosis syndromes by their unique hand deformities comprising of three syndactyly types: spade (type I), mitten (type II), and rosebud (type III).[4,5]

Otologic and audiologic symptoms are common in Apert syndrome. These include malformations of the outer, middle and the inner ear resulting in hearing loss. This warrants the need to perform prompt comprehensive audiologic investigation in children with Apert syndrome. These examinations may include impedance audiometry, pure tone audiometry, otoacoustic emission (OAE), brainstem evoked response audiometry (BERA) and auditory steady state response (ASSR) tests. Computed tomography (CT) scan of the temporal bone may also help visualise the middle and the inner ear and exclude other potential causes of hearing loss.[2,3]

Although there were several studies that reported the variation of hearing impairment in patient with Apert syndrome, our case report aims to add more information regarding anatomical finding, variation, and degree of hearing impairment in Apert syndrome. We reported three Apert syndrome patients with variation and clinical findings in hearing assessment.

CASE PRESENTATION

First Case

A 3-year-old boy diagnosed with Apert syndrome presented to the ear, nose and throat (ENT) clinic for audiologic investigation. The patient had delayed speech and was only able to say a few simple words with poor articulation. He was only able to respond when called with loud voice but was able to understand commands through sign language. The child was delivered vaginally at term with a birth weight of 3000 grams. There was no history of icterus, neonatal intensive care unit stay or ototoxic drug use. At birth, the patient had flat head syndrome and syndactyly of both hands and feet. The child had a history of front orbital advancement (FOA) surgery at the age of 24 months and syndactyly repair at the age of 35 months. He also had motor developmental delay in which the patient could walk only at the age of three years.

Physical examination revealed craniosynostosis, midfacial retrusion, hypertelorism, downslanting palpebral fissures, flattened nasal bridge and low-set ears (Figure 1). Patient also present with syndactyly of the hands and feet. The nasal cavities were narrow with inferior turbinate oedema, without secretions or septal deviation. Oropharyngeal examination revealed bifid uvula and pseudo cleft with adenotonsillar hypertrophy. Patient had normal ear canal with intact

This article was accepted: 04 December 2023
Corresponding Author: Semiramis Zizlavsky
Email: semiramiszizlavsky@gmail.com

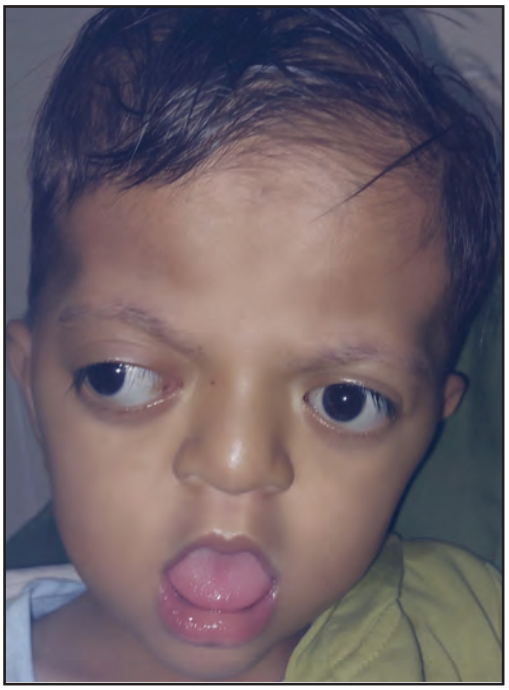

Fig. 1: Clinical findings of the first case showing craniosynostosis, midfacial retrusion, hypertelorism, and downslanting palpebral fissures, flattened nasal bridge, and low-set ears.

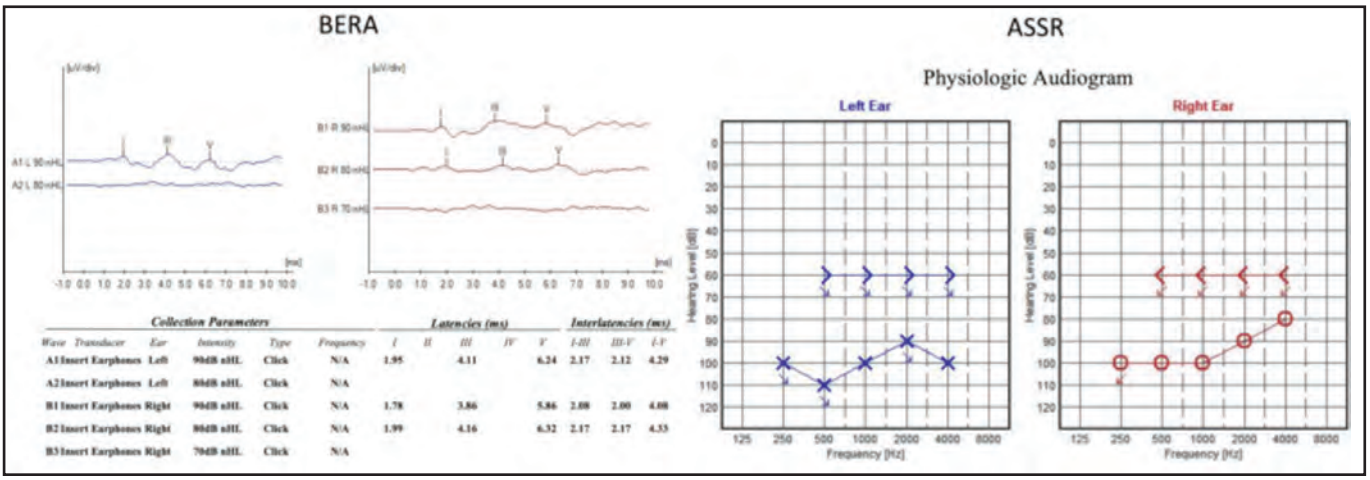

Fig. 2: Results of brainstem evoked response audiometry (BERA) and auditory steady state response (ASSR) tests of the first patient.

tympanic membrane in both ears. Non-contrast CT scan revealed diameter of internal auditory canal (IAC) were 2.08 to 2.93 mm in the right ear and 2.68 to 3.01 mm in the left ear and bilateral high jugular bulb.

Tympanometry showed type A tympanogram in both the ears. A BERA with click stimuli (2000 to 4000 Hz) showed that wave V was detected at 80 dBnHL on the right ear and at 90 dBnHL on the left ear. ASSR test (500 to 4000 Hz) revealed right and left AC >90dB and BC undetected more than 60 dB (Figure 2).

The patient was diagnosed with Apert syndrome with type III syndactyly (rosebud) based on the clinical findings, bilateral profound sensory neural hearing loss (SNHL), delayed speech, global developmental delay, bifid uvula and adenotonsillar hypertrophy. Based on the examinations, the patient was suggested to use hearing aids, undergo tonsiloadenoidectomy and consult to speech therapy.

Second Case

A 27-months-old girl with Apert syndrome presented to the ENT clinic for hearing examination. The patient also had delayed speech in which she was only able to say four simple words ("mama", "papa", "num" and "mam") and had type II syndactyly (mitten) in both hands and feet. She was able to respond when called and show signs of interest to the environment by pulling the mother's hands. The patient was born to an uneventful pregnancy by normal vaginal birth at term with a birth weight of 3500 gm. The patient was born

with flat head syndrome, cleft palate and syndactyly. The child underwent palatoplasty at the age of 9 months, FOA surgery at the age of 20 months, and syndactyly repair at the age of 23 months.

The patient had normal motor development with craniosynostosis, midfacial retrusion, hypertelorism, proptosis, downslanting palpebral fissures, low-set ears and repaired cleft palate. Patient had normal ear canal with intact dull tympanic membrane in the both ears.

Non-contrast CT scan showed dysplasia of the lateral semicircular canal of the right ear. Diameter of IAC were 4.38 to 5.59 mm in the right ear and 3.98 to 5.74 mm in the left ear. Tympanometry revealed type B tympanogram in both ears, suggesting the presence of OME. A BERA with click stimuli revealed that wave V was detected at 30 dBnHL in both the ears, while with tone burst stimuli at 500 Hz showed that wave V was detected at 20 dB in both ears. The patient was diagnosed with Apert syndrome with type II syndactyly (mitten) based on clinical findings, otitis media effusion (OME) and mild conductive hearing loss (CHL). The patient advised to visit outpatient clinic regularly to evaluate middle ear condition and hearing function.

Third Case

A 4-month-old Apert syndrome boy presented to the ENT clinic for hearing evaluation. The parents complained that the patient had brachycephaly, proptosis, lagophthalmos and syndactyly in both hands and feet. The child was born to an uneventful pregnancy by a caesarean section after 36 weeks of gestation with a birth weight of 2875 gm. The patient had uneventful postnatal period, had no history of ear discharge, could respond to sound and could raise his head at the age of 3 months. The patient was diagnosed with Apert syndrome with bilateral type II syndactyly (mitten) in both hands and feet, tetralogy of Fallot, right undescended testis and spina bifida.

Physical examination revealed brachycephaly, wide fontanelle, high forehead, midfacial retrusion, exophthalmos, hypertelorism, downslanting palpebral fissures and low-set ears, while oropharyngeal examination revealed pseudo cleft. Patient had normal ear canal with intact tympanic membrane in both the ears. Non-contrast CT scan showed dilated endolymphatic space in the ampulla of semicircular canal in both ears.

Tympanometry test revealed a bilateral type A tympanogram and OAE test showed normal findings. A BERA with click stimuli revealed that wave V was detected at 30 dBnHL and with tone burst stimuli at 500 Hz showed that wave V was detected at 20 dBnHL in both ears. We found the latency of wave I-III at 60 dBnHL was lengthened in the right ear (2.91 ms). The patient was diagnosed with Apert syndrome with type II syndactyly (mitten) based on the clinical findings. The patient was advised to visit ENT outpatient clinic regularly to evaluate hearing function.

DISCUSSION

The clinical features found in our three patients, including craniosynostosis, midfacial retrusion, down slanting palpebral fissures and syndactyly, are consistent with the diagnosis of Apert syndrome. In addition, all three cases also exhibited ear malformations such as bilateral high riding jugular bulb, dysplasia and dilatation of semicircular canal and low-set ears. This is consistent with previous literature stating that ear malformations in patients with Apert syndrome may involve the outer ears (low-set ears, posteriorly rotated ears, micro or macrotia, abnormal pinna morphology and narrowing of external auditory canal, the middle ear (Eustachian tube dysfunction, CHL, chronic recurrent OME, stapes fixation and ossicular malformations), and/or the inner ear (dilated cochlear aqueduct, dilated vestibulum, cochlear hypoplasia, high-riding jugular bulb, superior and posterior semicircular canal dehiscence, and mastoid cell opacification).[2,3,6]

With the involvement of ear organs in the pathophysiology of Apert syndrome, patients with Apert syndrome may suffer from hearing loss, of which the most common type of hearing loss is CHL. However, cases with mixed-type hearing loss or SNHL have also been described in Apert syndrome. This is proven by findings from a case series involving 125 patients with Apert syndrome which found that about 80% of these patients suffered from hearing loss, 93% of which suffered from CHL, 5% from mixed-type hearing loss, and 2% from SNHL.[7] Our second case had mild CHL with OME from the tympanometry, BERA. It is consistent with literature that found CHL in Apert syndrome may be attributed to chronic persistent OME, tympanic membrane ossification, congenital ossicular anomalies (e.g., stapes fixation, ossicular erosions).[1,2,6,7] As stated by Rajenderkumar et al.[2], chronic persistent OME, which happens in nearly all patients with Apert syndrome (93%), is responsible for mild-to-moderate CHL in more than 56% cases. On the other hand, the stapes fixation observed in Apert syndrome patients may be elaborated by the fact that the syndrome is characterised by the disturbance of the development of the branchial arches, which are the precursors of the ossicles.[2]

While CHL is commonly found in patients with Apert syndrome, SNHL is rarely reported in this syndrome. Our first case showed profound sensorineural hearing loss without any cofounding factors related to SNHL in pre-postnatal history. Zanetti et al.[1] postulated that SNHL in Apert syndrome may arise from auditory nerve compression due to skull base defect or narrow internal auditory canal, while Church et al.[8] added that the hearing loss may be caused by brainstem compression, Alnord-Chiari malformation, or auditory nerve stretch. This is based on the finding that, according to BERA with click stimuli, wave II was either absent or abnormal in all cases, while the interpeak latency of wave I-III was lengthened in 91% of the patients and those of wave III-V was lengthened in 27% of the study's patients – suggesting a decrease in nerve conduction velocity when the impulse passes through internal auditory canal and posterior fossa.[8] We found prolonged interpeak latency of wave I-III in our third case, which suggesting a possibility of decrease in nerve conduction velocity. The normal diameter of IAC varies from 4 to 8 mm based on several publications, although it is

considered stenotic if smaller than 2 mm.[9] First and third case has smaller diameter than normal IAC variation (< 4 mm). Other possibility of this prolonged interpeak latency of wave I-III is delayed maturation of auditory nerve pathways.

All in all, these findings highlight that hearing loss is common in Apert syndrome, thus emphasizing the importance to perform hearing screening and evaluation in Apert syndrome patients to promptly detect abnormalities that are overlooked with radiological imaging.[8] This is saliently important to enable prompt intervention and early speech-language therapy to prevent progressive hearing loss and cognitive and developmental delay in these patients.

REFERENCES

1. Zanetti D, Piccioni M. Otologic features of apert syndrome : a case report. Mediterr J Otol 2006; 2: 83-7.
2. Rajenderkumar D, Bamiou D, Sirimanna T. Management of hearing loss in Apert syndrome. J Laryngol Otol. 2005; 119(5): 385-90.
3. Huang F, Sweet R, Tewfik TL. Apert syndrome and hearing loss with ear anomalies: a case report and literature review. Int J Pediatr Otorhinolaryngol 2004; 68(4): 495-501.
4. Meara J, Editor. Apert syndrome: A guide to diagnosis and treatment. Boston (MA): Boston Children's Hospital; 2022. 1-28 p.
5. Saritha S, Sumangala S, Supriya G, Kumar M. Apert syndrome acrocephalosyndactyly: a case report. Int J Res Med Sci 2013; 1(1): 36.
6. Rajenderkumar D, Bamiou DE, Sirimanna T. Audiological profile in Apert syndrome. Arch Dis Child 2005; 90(6): 592-3.
7. Zhou G, Schwartz LT, Gopen Q. Inner ear anomalies and conductive hearing loss in children with apert syndrome: An overlooked otologic aspect. Otol Neurotol 2009; 30(2): 184-9.
8. Church MW, Parent-Jenkins L, Rozzelle AA, Eldis FE, Kazzi SNJ. Auditory brainstem response abnormalities and hearing loss in children with craniosynostosis. Pediatrics 2007; 119(6): e1351-e1360.
9 Marques SR, Ajzen S, D Ippolito G, Alonso L, Isotani S, Lederman H. Morphometric analysis of the internal auditory canal by computed tomography imaging. Iran J Radiol. 2012; 9(2): 71-8.

The Great Masquerader: A successful pulmonary vein isolation with cryoablation for paroxysmal atrial fibrillation manifesting with recurrent syncopal episodes

Mohd Ridzuan Mohd Said, MMED[1], Murshidah Ainun Mukhtar, MMED[2], Mohd Al-Baqlish Mohd Firdaus, MMED[1], Kantha Rao Narasamuloo, MRCP[3], Saravanan Krishinan, MRCP[3]

[1]Department of Medicine, International Islamic University of Malaysia, Pahang, Malaysia, [2]Department of Medicine, Hospital Canselor Tuanku Muhriz, Kuala Lumpur, Malaysia, [3]Department of Cardiology, Hospital Sultanah Bahiyah, Kedah, Malaysia

SUMMARY

Atrial fibrillation (AF) is the most common arrythmia observed in clinical practice. Early detection of AF is paramount to prevent fatal complications such as cardiomyopathy, heart failure, and stroke. Manifestation of AF varies, including being either asymptomatic or having transient palpitation, especially for paroxysmal AF. Pulmonary vein isolation (PVI) with either radiofrequency or cryoballoon ablation is the cornerstone treatment for AF, especially for those who remain symptomatic despite being on optimal treatment. Here we report a case of successful PVI with cryoablation for symptomatic paroxysmal atrial fibrillation manifesting with recurrent syncopal episodes.

INTRODUCTION

Atrial fibrillation (AF) is associated with significant morbidity, especially during the later stage and manifests in various forms including being asymptomatic to debilitating decompensation state.[1] We reported a case of paroxysmal AF presented with recurrent syncopal episodes and successful treatment with pulmonary vein isolation (PVI).

CASE PRESENTATION

A 59-year-old non-smoker gentleman with underlying dyslipidemia and mild coronary artery disease presented to the emergency department with recurrent syncopal episodes. He complained of multiple syncopal episodes within the last six months, preceded by giddiness and associated with progressive exertional dyspnea. Most of the symptoms were brief and lasted for a few seconds. He presented to his regular general practitioner twice for his symptoms and was subsequently referred to our emergency department. Initial electrocardiogram (ECG) showed normal sinus rhythm with no evidence of arrhythmia, axis deviation or prolonged PR/QTc intervals (Figure 1A).

On physical examination, minimal bilateral pedal oedema was observed and auscultation of the chest revealed clear lung fields with no murmur. In addition, neurological examination was unremarkable, no abnormal gaze and postural hypotension were detected. Blood investigation revealed normal counts of haemoglobin, 13.4 g/dL, and creatinine of 87 umol/L. In addition, other electrolytes including urea, potassium and calcium, and thyroid function tests were within the normal range. Bedside echocardiogram was performed and preserved left ventricular ejection fraction was reported. There was no regional wall motion abnormality, and all heart chambers were within normal range.

He was admitted and had a non-contrast computed tomography of the brain which revealed no acute ischaemic events. Subsequently, he underwent a 24-hour holter monitor which showed paroxysmal atrial fibrillation (Figure 1B) with 33% burden. In addition, a bradycardia episode was reported with pause of 1.84 seconds and the episode happened in the afternoon (Figure 1C). In term of symptoms, he recorded transient giddiness from his diary which occurred concurrently with the bradycardia episode. He was instructed to record any symptoms while attached to the 24-hour holter monitor. From his diary, we observed another episode of symptomatic transient bradycardia episode that evening lasted 1.74 seconds.

Hence, dabigatran was commenced, and he was subjected to cryoablation procedure (Medtronik, MN) with concurrent electro-anatomical mapping via Ensite High–Density Mapping System (Abbott, MN). Two punctures were made in the femoral vein, and size 7 French femoral sheaths were inserted. A steerable electrophysiology catheter was cannulated into the coronary sinus to serve as an anatomical landmark during transseptal puncture. Subsequently, the 7 French femoral sheath was replaced with an SL 1 catheter (Abbott, MN), and proceeded with trans-septal puncture using the BRK 1 needle (Abbott, MN) (Figure 2A).

Once access to left atrium was obtained, the SL 1 catheter (Abbott, MN) was exchanged for a cryo-delivery sheath (Medtronik, MN) using an Amplatz Super Stiff guidewire (Boston Scientific, Marlborough, MN). Subsequently, each pulmonary vein was mapped using Ensite High–Density Mapping System (Abbott, MN) while creating its geometry (Figure 3). Pulmonary vein potential was identified and the active right inferior pulmonary vein with fibrillating potentials was noted. Subsequently, a cryoballoon (Medtronik, MN) was advanced into the pulmonary vein and proceeded with ablation of the left sided pulmonary veins (Figure 2B) followed by right sided pulmonary veins (Figure

This article was accepted: 28 December 2023
Corresponding Author: Mohd Ridzuan Mohd Said
Email: ridzuan.said85@gmail.com

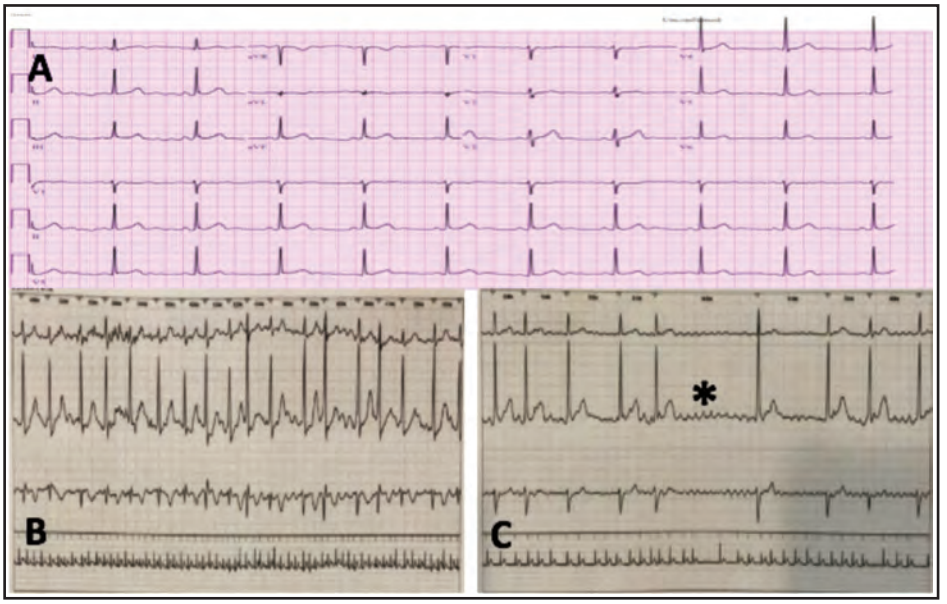

Fig. 1: ECG and 24-hour holter monitoring. (A) Sinus rhythm with rate of 54 beats per minute. (B) Atrial fibrillation episodes with irregularly irregular rhythm. (C) Tracing of bradycardia episode with 1.84 seconds and F wave (*).

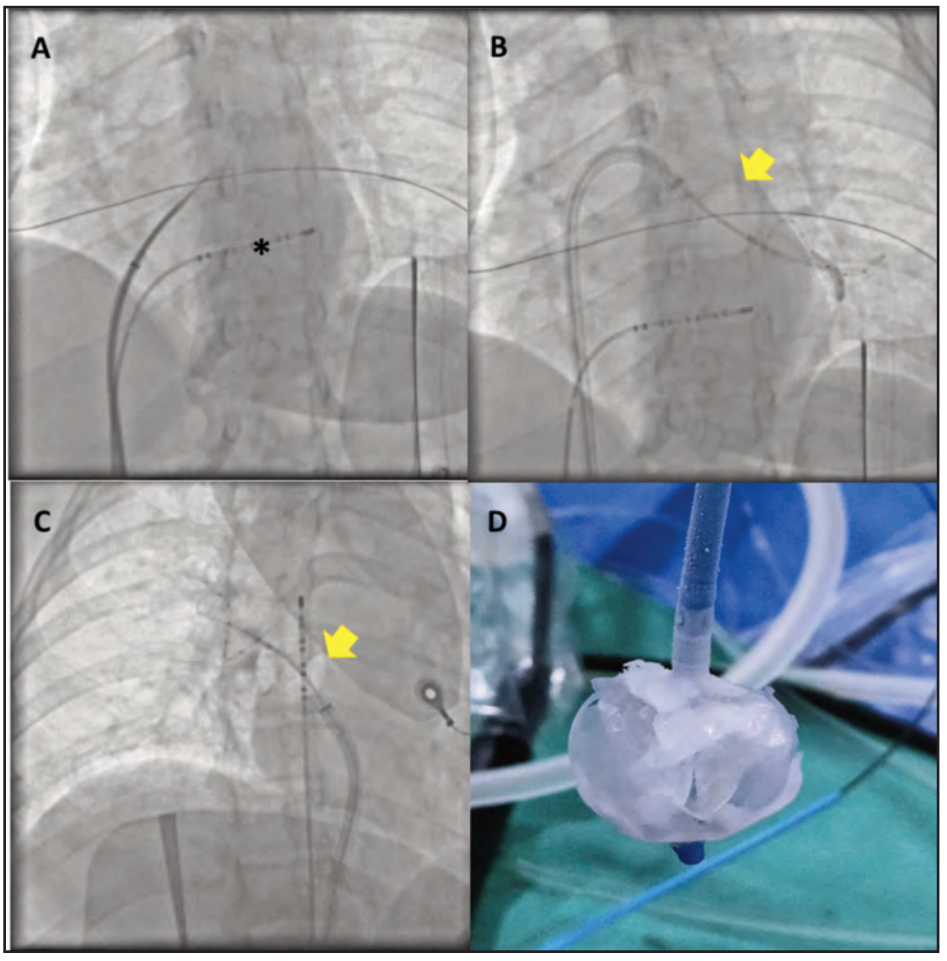

Fig. 2: Procedural steps during cryoablation. (A) Trans-septal puncture with BRK 1 needle (Abbott, MN) over SL 1 catheter (Abbott, MN) with steerable electrophysiology catheter (*) providing anatomical landmark. (B) Inflated cryoballoon (yellow arrow) on Left Inferior Pulmonary Vein during cryoablation. (C) Inflated cryoballoon (yellow arrow) on Right Superior Pulmonary Vein during cryoablation (D) Frozen cryoballoon at – 40○C.

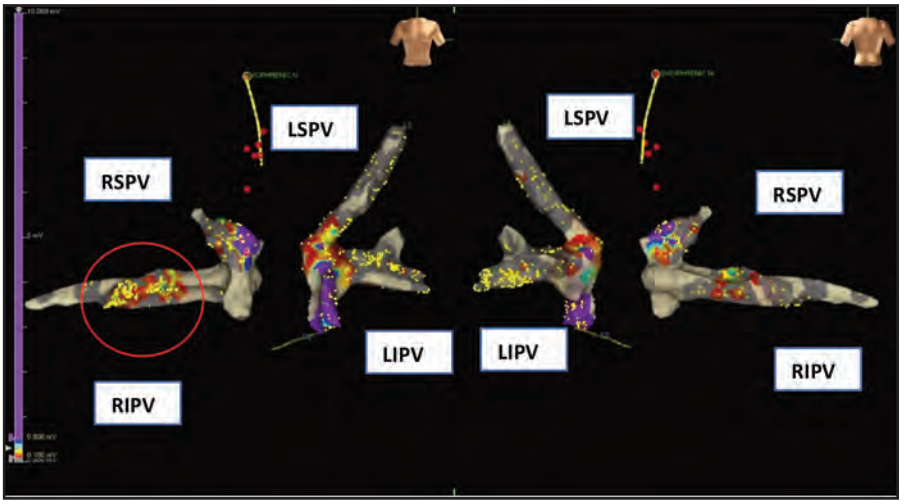

Fig. 3: Electro-anatomical mapping of each pulmonary vein. Active right inferior pulmonary vein and potentials are highlighted with red circle. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein.

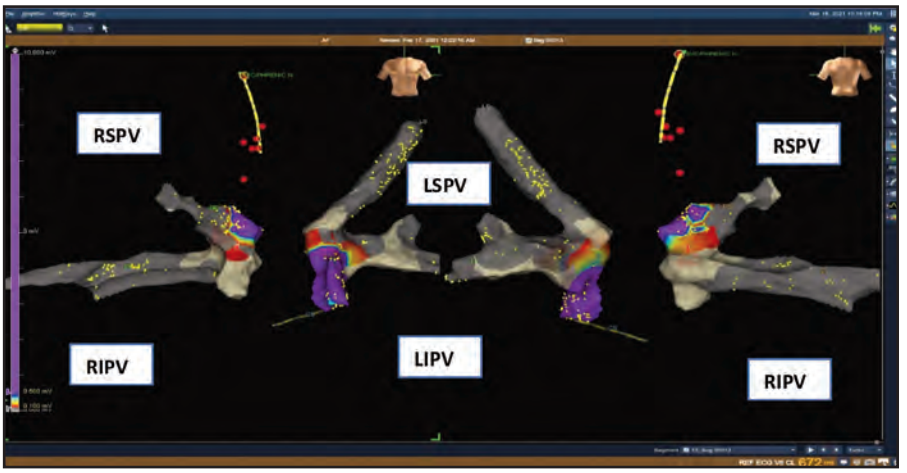

Fig. 4: Electro-anatomical mapping of each pulmonary vein post cryoablation. Grey area indicated no potential and suggests complete isolation of pulmonary vein. RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein.

2C). All pulmonary veins were isolated with the freezing temperature of -40°C to 50°C (Figure 2D) for 180 seconds. Post ablation, all the veins were re-mapped and complete isolation was noted especially at the right inferior pulmonary vein (Figure 4).

The procedure was uneventful, and he was discharged without complications. Repeated 24-hour holter monitoring after 6 months post-procedure showed no evidence of atrial fibrillation and the patient remained asymptomatic during his follow-ups.

DISCUSSION

Atrial fibrillation (AF) is characterised by high frequency excitation of the atrium that results in both dyssynchronous atrial contraction, irregularity of ventricular excitation and defined as recurrent AF (≥ two episodes) that terminates spontaneously within seven days.[1] Symptoms of AF can range from asymptomatic to a decompensated state but approximately 1.6% of individuals with AF may experience syncopal episodes as part of their symptomatology as demonstrated in our clinical vignette.[2]

More than 50% patients will either progress to persistent AF or face death. Hence, early intervention is imperative as it can improve clinical outcome.[1] In addition, increasing age, valvular diseases including mitral regurgitation and aortic stenosis, left ventricular hypertrophy and left atrial dilatation are associated with progression to persistent AF.[3]

Hence, catheter ablation with pulmonary vein isolation is an essential tool for treating AF and it has been the cornerstone strategy for managing paroxysmal atrial fibrillation. Catheter ablation aims to eliminate the trigger that initiates AF, or alter the arrhythmogenic substrate.[1] Previously, radiofrequency ablation is used to treat AF but with current medical advancement, cryoballoon ablation with the aims of

pulmonary veins isolation (PVI) is preferred and it shows non-inferiority to radiofrequency ablation.[4] Moreover, arrhythmia recurrence is reported significantly reduced with an initial strategy of catheter cryoballoon ablation compared with antiarrhythmic drug therapy alone.[5]

Cryoablation targets complete electrical isolation of the four major pulmonary veins (PV) that is the left inferior, left superior, right inferior and right superior as confirmed by the entrance and exit block.[6] The combined common left PVs were likewise ablated to achieve similar blockage within the constituent PVs.[6] In addition, the procedure has a shorter duration with lower left atrial dwell time compared to conventional radiofrequency ablation.[4] Besides its efficacy, the STOP AF trial demonstrated a persistent benefit of cryoballoon-based ablation for paroxysmal AF with less serious adverse event rate.[6]

Back to our patient, he was diagnosed with paroxysmal AF with arrhythmia related recurrent syncopal episodes. However, the decision to proceed with rate control, rhythm control or even pacemaker for bradycardia episode is typically based on a comprehensive evaluation of the patient's overall health, and the impact of their AF. Our aim for his comprehensive management was to achieved prolonged rhythm control while eliminating his symptoms and this was achievable with cryoablation. Chemical cardioversion is a viable choice, although it comes with the potential for adverse drug effects.[2] Alternatively, implanting a pacemaker is another option, but it carries the risk of long-term complications such as pacemaker-mediated cardiomyopathy, infection related to cardiac implantable electronic devices, and the need for recurrent box exchanges. Right peripheral nerve palsy (PNI) is the most common complication associated with cryoballoon ablation and persistent PNI lasting after the procedure is reported to be as high as 8.3%.[1,7] Furthermore, oesophageal injury is also observed after cryoablation and radiofrequency ablation.[1,7] Thus, close observation post ablation is pivotal to avoid any complications. Fortunately, our patient had successfully undergone the procedure without any complication.

In addition, our patient presented with atypical manifestation of AF such as recurrent syncopal episode and his episodes were likely explained by transient paroxysmal AF with pauses. Therefore, holter was an essential tool for detection of paroxysmal arrhythmia. However, it offers limited detectability within designated monitoring time. With advancement of loop recorders, photoplethysmogram on smartwatch or smartphone, more arrhythmias could potentially be detected leading to early management.[1]

CONCLUSION

Cryoballoon ablation is a relatively safe, effective and useful tool for the treatment of paroxysmal AF with high rate of successful PVI and long-term freedom from AF. In addition, manifestation of paroxysmal AF may vary and recurrent syncopal episodes warrant extensive investigation including holter monitoring.

REFERENCES

1. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Heart Rhythm 2012; 9(4): 632-696 e621. https://doi.org/10.1016/j.hrthm.2011.12.016
2. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347(23):1825-1833
3. Padfield GJ, Steinberg C, Swampillai J, Qian H, Connolly SJ, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. Heart Rhythm 2017; 14(6): 801-807. https://doi.org/10.1016/j.hrthm.2017.01.038
4. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med. 2016; 374(23): 2235–45.
5. Andrade JG, Wells GA, Deyell MW, Bennett M, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. N Engl J Med. 2021; 384(4): 305-315. https://doi.org/10.1056/NEJMoa2029980
6. Packer DL, Kowal RC, Wheelan KR, Irwin JM, et al. Cryoballoon Ablation of Pulmonary Veins for Paroxysmal Atrial Fibrillation. Journal of the American College of Cardiology. 2013; 61(16): 1713-1723. https://doi.org/doi:10.1016/j.jacc.2012.11.064
7. Knight BP, Novak PG, Sangrigoli R, Champagne J, et al. Long-Term Outcomes After Ablation for Paroxysmal Atrial Fibrillation Using the Second-Generation Cryoballoon. JACC: Clinical Electrophysiology. 2019: 5(3): 306-314.

Acknowledgement
December Issue 2023

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Dr Ai Lee Lim
2. Dr Ahmad Shamsuri Muhamad
3. Dr Ahneez Abdul Hameed
4. Dr Alexis Wong
5. Dr Anand Sachithanandan
6. Dr Andrew Chang Kean Wei
7. Dr Anirban Ghosal
8. Prof Dr Andrew Kiyu
9. Dr Asra Al Fauzi
10. Dr Azantee Yazmie
11. Dr Azmi Alias
12. Dr Azwanis Abdul Hadi
13. Prof Dr Baharudin Abdullah
14. Dr Baharul Hakim Said Daliman
15. Prof Dr Chew Keng Sheng
16. Dr Chua Hock Hin
17. Dr Elaine Hui Been Ng
18. Dr Esha Das Gupta
19. Dr Fa'iza Abdullah
20. Dr Glen Alvin
21. Dr Gurmit Singh
22. Dr Harwant Singh
23. Dr Hasni Mahayidin
24. Dr Hayani Abdul Wahid
25. Dr Huda Sahib Abdul Mohammed Al-Rawazq
26. Dr Intan Nureslyna
27. Dr Jothinathan Muniandy
28. Dr Karimah Hanim bt Abd Aziz
29. Dr Koh Ewe Jin
30. Dr Kumar Harirajah
31. Dr Lee Yew Kong
32. Dr Mohamed Mohamed
33. Dr Mohammad Shukri Jahit
34. Dr Mohd Aizuddin Abd Rahman
35. Dr Mohd Firdaus Che Ani
36. Dr Mohd Radzniwan A Rashid
37. Dr Narendran Balasubbiah
38. Dr Navin Kumar Devaraj
39. Dr Navinakathiresu Muthukumarasamy
40. Dr Ng Rong Xiang
41. Dr Pragnesh M Bhatt
42. Dr Rafidah binti Atan
43. Dr Ren Yi Kow
44. Dr Rosnelifaizur Ramely
45. Dr Ruhaila Abdul Rahim
46. Prof Dr Dr Rukman Awang Hamat
47. Dr Sabarul Afian Mokhtar
48. Dr Salman Amiruddin
49. Dr Sanihah Abdul Halim
50. Dr Saraswathi Bina Rai
51. Dr Shelina Oli Mohamed
52. Dr Shireen Anne Nah
53. Dr Thanalactchumy Chandrabose
54. Dr Valyakalayil Daniel Philip
55. Dr Vasu Pillai A/L Letchumanan
56. Dr Yong Meng Shien