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All submission must be in English. 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
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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.

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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.

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

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- Treatment plan
- Outcome of the treatment plan

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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.

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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.

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

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- 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.

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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.

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EDITORIAL

Dear readers,

I wish to take this opportunity to introduce the first issue of a new Medical Journal of Malaysia Case Reports (MJM Case Reports Journal). Medical Journal of Malaysia (MJM) has been published since the 1960s. Case reports were previously published alongside other research articles in the bimonthly MJM. With the publication of MJM Case Reports, this journal will be able to exclusively focus and highlight the educational and learning qualities case reports can offer. This journal is an online open access journal with a double-blind peer-review process by external reviewers following an internal review by section editors. It is exclusively published in the English language. MJM Case Reports, follows the Vancouver numbered referencing style. In our opinion Case Reports are important scientific documentation of a single clinical observation and have a rich convention in medicine and scientific publication. Case reports represent a relevant form of advancing medical scientific knowledge especially of rare diseases or conditions. They are important learning resources for doctors. They are usually the first encounter that trainees or residents will have in their early career. It will serve as a platform for them to write and learn the technique of scientific writing. Grooming of young talents is essential for the sustainability of the medical profession. It may also be a platform for the senior doctors too busy to do comprehensive research, to contribute their expertise in order to maintain their intellectual productivity. Authors are encouraged to describe the novelty of the case report, its scientific merit, learning outcome and implication for clinical practice.

The decision to publish case reports separately from the MJM is based on the following reasons. Case reports are usually not often cited and this affects the citation index of journals publishing them. Due to this, many journals published by international medical associations have taken the steps to either stop accepting and publishing case reports or have established a separate journal specifically for case reports. During the last several years, the MJM has strengthened its presence not only in Malaysia but also the region. They also play a role in nurturing and improving the skills of junior doctors, general practitioner, clinicians and academics in successful publishing. By doing this, we can enhance the standing of MJM and at the same time allows dissemination of clinical knowledge via case reports in MJM Case Reports.
We welcome submissions from around the region and world. In this first issue you can find reports on various specialties covering subjects related to cardiology, infectious and endocrine diseases, blood disorders, unusual primary and secondary tumours of head and neck as well as reproductive systems, medical together with surgical interventions and pregnancy. Of note, the report of a new generation drug-eluting stent in treating coronary artery disease and the treatment of unusual infections attributed to Mycobacterium avium complex or Pseudomonas oryzihabitans urosepsis would be appealing to most readers. We encourage you to submit case reports of rare or unusual disease, unexpected or unusual presentation of a common clinical condition, new or unreported adverse event and continuous medical education discussing case reports in all aspects of medical therapy and surgery.

We believe, if all the aforementioned responsibilities as authors, reviewers and editors have been carried out, we will achieve our goal to bring your research and clinical experience to a broad range of medical professionals besides contributing to the knowledge pool of evidence-based medicine.

Prof. Datuk Dr. Lekhraj Rampal
MBBS, MPH, DrPH, FAMM, FAMS, FASc, FPHMM
Editor in Chief, MJM Case Reports

CASE REPORT

Acute urinary retention due to severe constipation in a 5-Year-old boy

Yuhi Takagi, MD, George Imataka, MD, PhD, Yuji Kano, MD, Shigemi Yoshihara, MD, PhD

Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan

SUMMARY

We report a 5-year-old Japanese boy with urinary retention due to severe constipation. He presented to the hospital with abdominal pain and inability to urinate for more than 24 h. Physical examination revealed distension above the umbilicus and a palpable cystic mass. Abdominal plain radiography indicated a large mass-like lesion in the lower abdomen. Abdominal computed tomography did not show any mass lesion. However, his bladder was remarkably dilated, and significant faecal impaction was detected. There were no urethral stones that could cause urethral obstruction. There were no abnormalities found in blood or urine. He had severe constipation since he was a baby. Treatment of constipation earlier improved urinary retention. Therefore, we considered constipation to be the cause of urinary retention. Acute urinary retention (AUR) due to a variety of causes is common in adults. However, AUR is rare in children. Paediatricians should be aware that severe habitual constipation may lead to temporary AUR in children.

INTRODUCTION

Acute urinary retention (AUR) is defined as a condition in which the bladder is filled with urine, and urination suddenly becomes completely impossible. Although the bladder detrusor muscle is often normal in patients with AUR, it frequently causes abdominal pain due to increased bladder capacity. Mainly, AUR can be associated with benign prostatic hyperplasia and drugs.[1] Although AUR is relatively common in adult males, it rarely occurs in children. Herein, we report a case of paediatric AUR due to severe constipation.

CASE REPORT

A 5-year-old Japanese boy presented to the hospital with abdominal pain and inability to urinate for more than 24 h. He had no significant medical or surgical history. Physical examination showed distension above the umbilicus and a palpable cystic mass. Thus, he was hospitalised for evaluation of the possible causes of abdominal pain and AUR.

On admission, he was 110 cm tall (0.8SD) and weighed 17 kg (- 0.3SD). On examination, he had a body temperature of 37.4℃, blood pressure of 99/61 mm Hg, pulse rate of 127/min, and respiratory rate of 18/min. In addition, his oxygen saturation was 98% on room air. His abdomen was tight, with significant pain and tenderness in the lower abdomen. Laboratory test results revealed the following: white blood cell count, 14,800/μL (neutrophils: 80%; lymphocytes: 12.5%); haemoglobin level, 11.3g/dL; platelet count, 464,000/μL; blood urea nitrogen level, 10mg/dL; serum creatinine level, 0.27mg/dL (eGFR, 136.8 mL/min/1.73 m2); cystatin C, 0.7mg/dL (eGFR, 140.9 mL/min/1.73 m2); and serum C-reactive protein level, 3.1mg/dL. Urinalysis revealed a pH of 6.5 and proteinuria of 0.15 g/Cr. Haematuria or pyuria was not observed. Moreover, his urine culture was negative. Abdominal plain radiography and computed tomography (CT) were performed at the time of admission. Abdominal plain radiography indicated a large mass-like lesion in the lower abdomen (Fig. 1A). Abdominal CT did not show any mass lesion. However, the bladder was remarkably dilated, and significant faecal impaction was detected (Fig. 1B). However, there were no urethral stones that could cause urethral obstruction.

Based on the information gathered from the patient's family members, it is known that his stools were separate, hard, and nut-like lumps. In addition, his bowel movement occurred only twice a week in a standing position into diapers. Based on the Rome III criteria, he was diagnosed with severe constipation. His stool was graded as type 1 according to the Bristol Stool Form Scale. Furthermore, a presumptive diagnosis of AUR secondary to constipation was made. A urethral catheter was inserted, and 500 mL of clear urine was drained. The patient's abdominal distension and pain immediately improved. Magnesium oxide, probiotics, and sodium picosulfate were prescribed to treat his constipation. During hospitalisation, he was treated with 30mL of glycerine enema solution for three consecutive days. Spinal magnetic resonance imaging (MRI) and voiding cystourethrography (VCUG) were performed to assess the cause of AUR. Lumbar MRI did not show spinal lipoma or meningocele, which are potential causes of neurogenic bladder. There was no vesicoureteral reflux or urethral stricture on VCUG. No other causes of urinary retention were discovered. Therefore, we concluded that his AUR was due to severe constipation.

He was discharged without further recurrence of urinary retention. After discharge, he continued to take magnesium oxide and probiotics. His family members were taught the proper defecation technique (leaning forwards while sitting on a toilet seat of a Western-style toilet with both feet on the floor). At the 1-year follow-up, he had not experienced any episodes of AUR, and constipation had not recurred.

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Table I: Differential diagnosis of urinary retention in children

Mechanical
Urethral stone
Urethral stricture
Bladder diverticulum
Phimosis
Neuroblastoma
Neurologic
Neurogenic bladder
Myelitis
Stroke
Infection and inflammation
Acute prostatitis
Urinary tract infection
Vulvovaginitis
HSV genitalis
Fecal impaction
Adverse drug effect
Anticholinergic drug
Tricyclic antidepressants
Nonsteroidal anti-inflammatory drugs (NSAIDs)

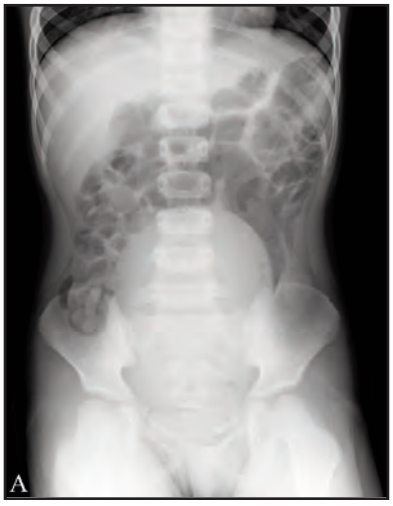

Fig. 1a: Radiography image taken on admission. Findings are suggestive of large masses, such as lesions in the lower abdomen, excluding the intestinal tract.

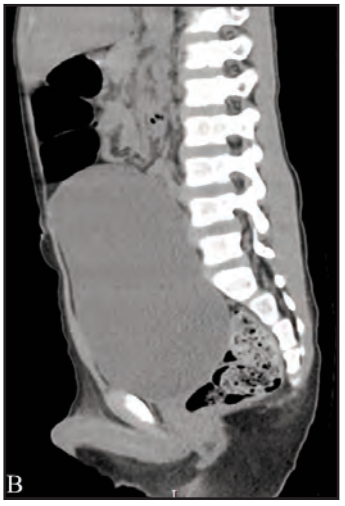

Fig. 1b: Abdominal computed tomography scan (transverse plane). No mass lesion or urethral stone is observed, but the bladder is notably dilated and prominent faecal impaction is evident.

DISCUSSION

Although AUR is common in adults due to a variety of causes, it is rare in children (Table I).[2-4] Our patient underwent thorough examination, including spinal MRI, VCUG, and laboratory tests. These examinations did not reveal the primary cause of the urinary retention. After treatment of constipation, urinary retention resolved and did not recur. Chase et al.[5] evaluated the relationship between AUR and constipation and reported a close relationship between constipation and the urinary system. Based on this report, it is thought that stool mass mechanically presses on the bladder and bladder neck, causing urethral obstruction, which may induce deterioration in vesicoureteral reflux. Moreover, animal studies have shown that rectal dilation reduces bladder contractility.[6] In our case, the patient's urine volume was larger than the expected volume for his age,[7] and it was highly possible that his bladder dysfunction was due to habitual constipation. In addition, his daily urinary frequency was low, which was indicative of bladder and bowel dysfunction.[8]

CONCLUSION

Paediatricians should be aware that severe habitual constipation may lead to temporary AUR in children.

ACKNOWLEDGEMENT

We would like to thank Editage (www.editage.com) for English language editing.

DISCLOSURE

The authors declare no conflict of interest.

INFORMED CONSENT

Informed consent for the publishing of this case report was obtained from the patient's parents.

ETHICAL ISSUES

We have received permission from the parents to publish this case report.

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Intravascular ultrasound-guided treatment of left main stem stenosis with a new-generation everolimus drug-eluting stent

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SUMMARY

Left main stem (LMS) percutaneous coronary intervention (PCI) can be complex and high risk. Since the LMS diameter is usually larger than other coronary arteries, intravascular imaging guided stent sizing and optimisation is especially important. The new-generation everolimus drug-eluting stent (DES), Synergy Megatron DES (Boston Scientific), has a platform that offers improved overexpansion capabilities as well as improved axial and radial strength, which may be more suitable for selected LMS lesions. We present a case where a LMS lesion was successfully treated with Intravascular ultrasound (IVUS)-guided PCI using the Megatron DES platform. This technology safely and effectively facilitates intravascular imaging optimised stent parameters for the improved treatment of large proximal vessels and PCI of LMS lesions.

INTRODUCTION

Left main stem (LMS) stenosis is regarded significant when compared to other coronary arteries since the LMS bifurcates to the left anterior descending and left circumflex vessels, providing blood supply to two-thirds of the left ventricle. Due to the importance of good clinical outcomes following LMS angioplasty, current European guidelines recommend that intravascular ultrasound (IVUS) should be considered in patients undergoing LMS percutaneous coronary intervention (PCI).[1] Since the LMS diameter is usually larger than other coronary arteries, when IVUS is used to evaluate plaque morphology and optimise stent sizing, clinical outcomes can be improved. Current stent technology is limited by the capability of stents to expand beyond a certain limit. Use of post-dilation balloons that exceed the recommended upper limit may pose risk of damage to the stent integrity and lead to long-term complications of PCI.

The Synergy Megatron drug-eluting stent (DES) platform (Boston Scientific) is a new-generation everolimus-coated DES, which offers improved overexpansion capabilities for the treatment of tapered proximal vessels and bifurcations. We present a case where a LMS lesion was successfully treated with IVUS-guided coronary PCI using the Megatron stent.

CASE REPORT

A 42-year-old male had presented with angina and shortness of breath on exertion for two months. He had a history of hypertension and diabetes mellitus and was on medication. Echocardiography showed good left ventricular systolic function with ejection fraction (EF) of 60%. ECG shows sinus rhythm, and blood tests showed normal full blood count and renal function. Cardiac enzymes including troponin were normal. In view of significant coronary risk factors and frequent angina, the patient consented for invasive coronary angiogram.

A coronary angiogram via femoral approach showed severe 60-70% stenosis of the distal LMS (Figure 1) and moderate stenosis at the mid- left anterior descending (LAD) artery, moderate stenosis at the left circumflex (LCX) artery (non-dominant and ectatic vessel), and mild mid-vessel stenosis of the right coronary artery (dominant vessel). SYNTAX scores were calculated to assess the risk of PCI as compared to coronary artery bypass grafting (CABG). The SYNTAX I score was 21 and SYNTAX II score was 14.5 estimating a 4-year mortality risk of 1.9% with PCI (risk of 1.5% with CABG). The decision was made to proceed to LMS PCI.

The left main coronary artery was engaged with a six French-sized guiding catheter (EBU) with a diameter of 3.5cm, and the LAD and LCX were crossed with 0.014 inch hydrophilic guidewires. Further evaluation was done with IVUS (Figure 2). The minimal lumen area (MLA) of the LMS vessel was 5.40mm^2, and the minimal luminal diameter was 2.5mm. The reference luminal area of the distal LMS vessel was 20.9mm^2, and the reference luminal diameter estimated by the external elastic membrane (EEM) was 5.5mm.

The distal LMS was predilated with a non-compliant (NC) 4.0×15mm balloon. A 4.0×15mm Synergy Megatron stent was deployed from the LMS into the proximal LAD. The stent was post-dilated with an NC of 5.5×8mm balloon with good results (Figure 1). Repeat IVUS post angioplasty showed improvement of the left main diameter to 5.5mm and stent cross sectional area of 20.60mm^2 at the distal LMS. The stent struts were well opposed to the LMS and LAD vessel wall (Figure 2).

The patient was hemodynamically stable post-procedure and was discharged after two days. He was put on dual anti-platelet treatment with aspirin and clopidogrel for one year. At follow-up in clinic after one month, the patient was stable with no further angina.

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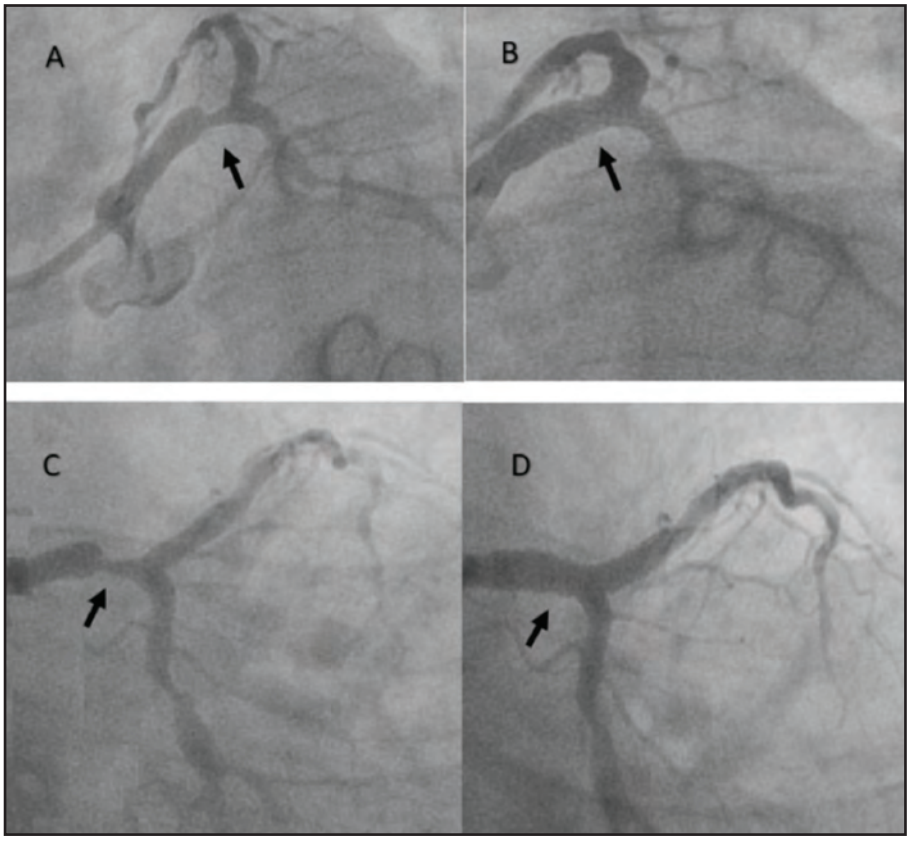

Fig. 1: Pre-procedure angiogram (A) in the spider view showing severe LMS stenosis (arrow) and corresponding post-procedure angiogram after PCI of the LMS (B) showing significant improvement in the stented LMS area (arrow). Pre-procedure angiogram (C) in the caudal view showing severe LMS stenosis (arrow) and corresponding post-procedure angiogram after PCI of the LMS (D) showing significant improvement in the stented LMS area (arrow).

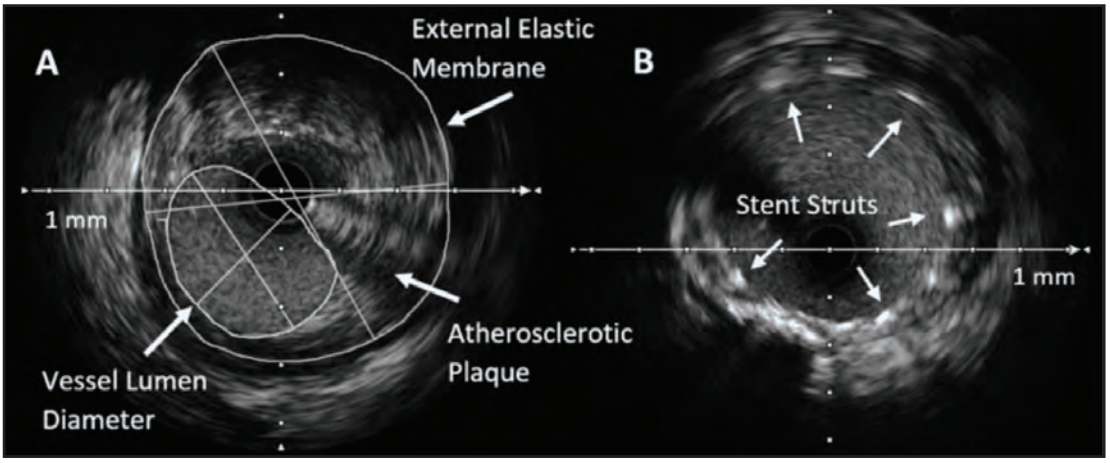

Fig. 2: Pre-procedure IVUS image (A) showing severe LMS stenosis with the inner circle showing vessel lumen, large areas of atherosclerotic plaque, and outer circle showing reference luminal diameter estimated by EEM. Post-procedure IVUS image (B) showing well-opposed LMS stent with arrows showing stent struts.

DISCUSSION

Coronary artery bypass grafting (CABG) currently remains the standard for treatment of LMS stenosis. Previous experience with PCI in treating LMS disease using older generation stents and infrequent use of intracoronary imaging guidance had demonstrated suboptimal outcomes for PCI when compared to CABG. However, newer-generation DES, consistent use of intravascular imaging guidance, and judicious selection of cases for PCI have allowed angioplasty to be a viable alternative to CABG in LMS stenosis.

Current ACC/AHA guidelines recommend calculation of a SYNTAX score for patients with LMS disease. The SYNTAX score estimates the risk of angioplasty based on features of

patient clinical risk profile and anatomical and morphological characteristics of the coronary lesion.[2] The decision for recommending PCI is guided by the calculated risk, and PCI is emerging as an alternative compared to CABG, especially in patients with low SYNTAX score (≤22).[3] In 2018, the European Society of Cardiology and European Association for Cardiothoracic Surgery (ESC/EACTS) jointly published the guidelines on myocardial revascularisation, in which LMS revascularisation with low SYNTAX score was considered class I level of evidence A for both PCI and CABG.[3]

Clinical Evidence for PCI in LMS Stenosis

PCI in LMS is usually considered when evaluation of IVUS shows an MLA <6mm.[2] The evidence comes from a multi-centre prospective study (LITRO study)[4] of intermediate LMS disease. In 354 patients, LMS intervention was deferred in 179 of 186 patients, and intervention was done in 152 of 168 patients based on the MLA cut-off value of 6 mm.[2] During 2-year follow-up, no difference was observed with regard to cardiac death or events. This demonstrated that an MLA of ≥ 6 mm[2] on IVUS is a safe value for deferring revascularisation for intermediate LMS disease.

The first large clinical comparison of PCI and CABG in LMS disease, the SYNTAX trial, randomised 1,800 patients to either the first-generation TAXUS DES (from Boston Scientific) or CABG for treatment.[5] Prior to randomisation, the SYNTAX score was used to quantify anatomical and lesion complexity. Cases were then divided into groups (SYNTAX score of 0–22, 23-32, and >32) based on the complexity of the lesions. It was found that CABG was superior in cases of high risk and complex coronary artery disease (i.e., SYNTAX score of >32).

The EXCEL trial was a non-inferiority study, in which 1,905 patients with LMS disease of low to intermediate complexity (SYNTAX score of <32) were randomised to either PCI using a second-generation everolimus coated DES (from Xience) or CABG.[6] At 3 years, the primary endpoint occurred in 15.4% of patients in the PCI group compared to 14.7% of patients in the CABG group (p=0.02 for non-inferiority), indicating that PCI was noninferior to CABG in the treatment of left main stenosis.

Conversely, the NOBLE trial involving 1,201 patients with LMS disease randomised to either PCI using DES (from BioMatrix) or CABG demonstrated inferiority in the PCI-treated group during a 5-year follow-up (p=0.0002).[7] There were higher MACCE (all-cause mortality, nonprocedural MI, repeat revascularisation, or stroke) rates in the PCI group (28.4% versus 19%).

New-Generation Everolimus-Eluting Stent Platform

The majority of patients with LMS stenosis have a mean vessel diameter of >4mm, suggesting the requirement for post-dilation beyond the nominal diameter of current-generation DES devices in patients requiring LMS angioplasty.[8] Since existing stent technology is limited by expansion capabilities, the use of NC post-dilatation balloons for stent expansion may pose risk of damage to stent structure and integrity. The Synergy Megatron DES platform confers improved overexpansion capabilities, which may be useful particularly for LMS angioplasty. A study of 139 patients undergoing PCI using the Synergy Megatron DES demonstrated very low rates of short-term major adverse cardiovascular events with no cases of acute/subacute stent thrombosis. The technology allows for IVUS-optimised stent parameters and improved treatment of large proximal vessels and bifurcations.[9]

Stent optimisation with larger sizing and optimal minimum stent area (MSA) is important in LMS PCI. Using IVUS optimisation, criteria to achieve 90% MSA in the stented segment of the average reference cross-sectional area are frequently recommended.[10] In the EXCEL trial, a small final LMS MSA was associated with higher major adverse cardiovascular events (small vs. large MSA tertiles; 19.4% vs 9.6%; p=0.01).[6] Similarly, the NOBLE trial demonstrated that long-term complications, such as target lesion revascularisation, were reduced by both the performance of post-PCI IVUS with large MSA compared to small MSA (5.1% vs. 11.6%; p=0.01).[7] It was shown that the Synergy Megatron DES had the capability to achieve a mean LMS MSA that is numerically superior to that in both the EXCEL and NOBLE trials (14.5±3.4 mm[2] vs. 12.5±3.0mm[2] vs. 9.9±2.3mm).[9] The Megatron DES stent also provided a broad overexpansion range (3.5-6.0mm) to overcome the issue of significant mismatch between proximal and distal vessel diameters.

CONCLUSION

PCI is emerging as an alternative to CABG for the treatment of LMS stenosis in patients with a low SYNTAX score. To further optimise the results for PCI in LMS, new-generation stent technology can provide overexpansion capabilities compared to current stents. This case demonstrates the successful use of a new-generation everolimus stent, the Synergy Megatron DES. This technology safely and effectively facilitates intravascular imaging optimised stent Figure 1 parameters for the improved treatment of large proximal vessels and PCI of LMS lesions.

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Concurrent COVID-19 and leptospirosis: A case report on dual infections

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SUMMARY

Malaysia has a long history of fighting tropical diseases including leptospirosis, dengue fever, malaria, enteric fever, and Chikungunya. During the ongoing pandemic of coronavirus disease 2019 (COVID-19), it is crucial for clinicians to have high level of suspicion for detection of COVID-19 co-infection with endemic illnesses, and not to neglect the management of dual infections. We present a case of young man from the East Coast Malaysia, who presented with short history of high-grade fever, non-productive cough, shortness of breath, and haemoptysis, after recently swimming in a river at an oil palm plantation. Both COVID-19 reverse transcription polymerase chain reaction (RT-PCR) and Leptospira microscopic agglutination test (MAT) were positive. He was diagnosed with concurrent COVID-19 and leptospirosis infection. We treated the patient as per national COVID-19 protocol and antibiotic coverage for leptospirosis. Despite the development of acute respiratory distress syndrome (ARDS) with multiorgan impairment during hospitalisation, he responded well to treatment and had a favourable outcome.

INTRODUCTION

Diagnosis of co-infection of *Leptospira spirochete* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is challenging. Both diseases have similar presentations such as fever, malaise, headache, abdominal pain, or vomiting. Due to the COVID-19 pandemic, other differentials could be neglected, and delay in diagnosis would lead to delay in initiating appropriate treatment and eventually poor clinical outcome. To our knowledge, this is the first reported case of concurrent COVID-19 and leptospirosis infection in the region of Asia.

CASE REPORT

We report a case of 16-year-old male student from Terengganu, Malaysia. He is an active smoker with one pack per day, non-alcoholic, and has no known medical illness. He presented with high grade fever, non-productive cough, and shortness of breath for two days. It was associated with large amount of haemoptysis on the day of presentation. He reported history of swimming in a river at an oil palm plantation one week prior, but denied contact with positive COVID-19 patient and denied any known dengue outbreak in his neighbourhood. On examination, he was alert but pale and tachypnoeic. His vital signs on admission were as follows: temperature, 39.8°C; heart rate, 140 beats per minute; blood pressure, 111/75mmHg; and oxygen saturation, 82% on room air. His body mass index was 23. He had otherwise no jaundice, no conjunctival suffusion, no hepatosplenomegaly, and no other bleeding tendency.

Initial resuscitation included 1-litre bolus of normal saline and two pints of pack cells. Intravenous (IV) ceftriaxone 2-gram stat was started in view of high suspicion of leptospirosis. IV tranexamic acid 1-gram stat and IV methylprednisolone 500-milligram stat were given for pulmonary haemorrhage. He was intubated for type-1 respiratory failure. Post-intubation, he developed cardiac arrest due to massive pulmonary haemorrhage. Return of spontaneous circulation occurred after two minutes of cardiopulmonary resuscitation. He was then admitted to intensive care unit (ICU) for further care. In view of ongoing COVID-19 pandemic, COVID RT-PCR sample was sent and turned out to be positive. Leptospira IgM and MAT samples were also sent and came out to be positive, with MAT titre 1:400. A full complement of laboratory studies included complete blood count, renal and liver profile, basic metabolic panel, arterial blood gas, and blood culture. The results of investigations and the trend are shown in Table I. Initial chest X-ray showed bilateral diffuse infiltrates (Figure 1), which improved subsequently (Figure 2).

After ICU admission, IV methylprednisolone another 1-gram stat was given in view of massive pulmonary haemorrhage. He developed severe ARDS and required prone ventilation for 48 hours with protective lung strategy (tidal volume of 6ml/kg and PEEP of 12). He was deeply sedated and paralysed for 48 hours during prone ventilation with continuous infusion of propofol 100mg/hour, midazolam 6mg/hour, fentanyl 100mcg/hour, and atracurium 30mg/hour. Despite all these measures, he developed left tension pneumothorax and a chest tube was inserted. His ventilation subsequently improved and extubated after seven days of intubation. He was put on IV methylprednisolone 150mg daily for four days and subsequently stepped down to IV dexamethasone 8mg OD for six days. He completed IV ceftriaxone 1-gram twice daily for two weeks. He was transferred to general ward after eight days of ICU stay with no neurological deficit and was discharged home after a total of 16 days in hospital.

DISCUSSION

Globally, we have been burdened with COVID-19 caused by SARS-CoV-2 virus since December 2019. According to data released by WHO on 28 February 2020, presentation of

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Table I: Summary of results during ICU stay

Investigation	9/11	10/11	11/11	12/11	13/11	14/11	15/11
Hb (g/L)	7.7	9.0	10.9	9.4	9.9	9.4	10.0
TWC (10^9/L)	22.4	18.6	19.8	18.4	17.3	19.9	23.2
Plt (10^9/L)	259	148	237	208	214	262	352
ALC (10^9/L)	6.37	0.96	0.74	1.31	1.55	2.11	1.57
Na (mmol/L)	139	140	141	146	146	146	141
K (mmol/L)	4.9	4.8	4.5	4.8	5.4	5.0	5.4
Urea (mmol/L)	8.7	19.7	26.1	30.7	27.5	23.9	21.0
Creat (mmol/L)	189	292	275	244	201	164	140
Ca (mmol/L)	1.71		1.95		1.93		
Mg (mmol/L)	0.98		0.84		0.84		
PO4 (mmol/L)	3.22		1.14		1.20		
TB (µmol/L)	7.5		4.1				
DB (µmol/L)	18.4		14.8				
ALT (U/L)	95		156		91		
AST (U/L)	149		118		66		
ALP (U/L)	80		61		61		
Alb (g/L)	29		29		29		
CK (U/L)		1424	3057		2021		
CRP (mg/L)	113.9	184.7	138.6	84.1	60.8	30.4	42.9
LDH (U/L)	853	1561	1025	1643	1708	1625	2118
Ferritin (µg/L)	427.2	879.2	647.8	367.0	542.8	440.5	557.9
D-dimer (ng/ml)	52583	27097	16175	14292	14163	14819	13412
INR	1.38	1.33	1.29	1.14	1.11	1.12	
PT (second)	15.6	15.1	14.6	12.9	12.5	12.7	11.8
APTT (second)	28.4	27.0	29.6	24.8	25.1	23.6	26.7

Note: Haemoglobin (Hb), total white cell count (TWC), platelet (Plt), absolute lymphocyte count (ALC), sodium (Na), potassium (K), creatinine (Creat), calcium (Ca), magnesium (Mg), phosphate (PO4), total bilirubin (TB), direct bilirubin (DB), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin (Alb), creatine kinase (CK), C-reactive protein (CRP), lactate dehydrogenase (LDH), international normalised ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT)

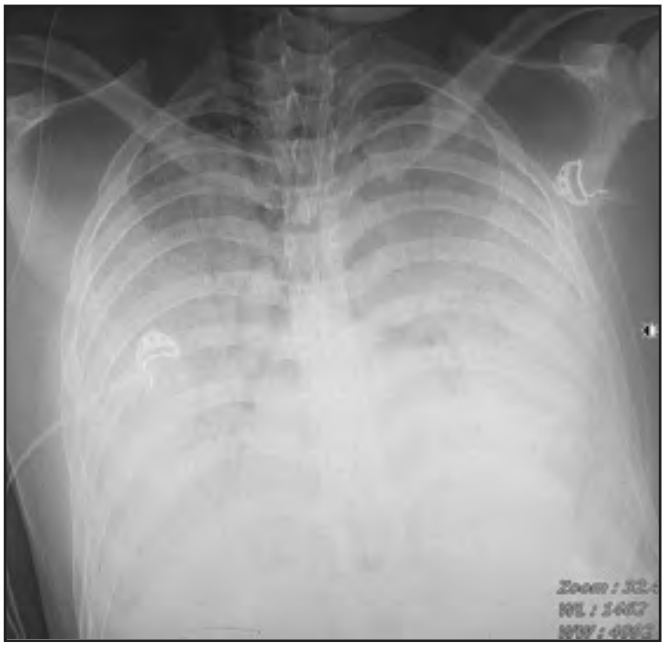

Fig. 1: Chest X-ray with bilateral diffuse infiltrates

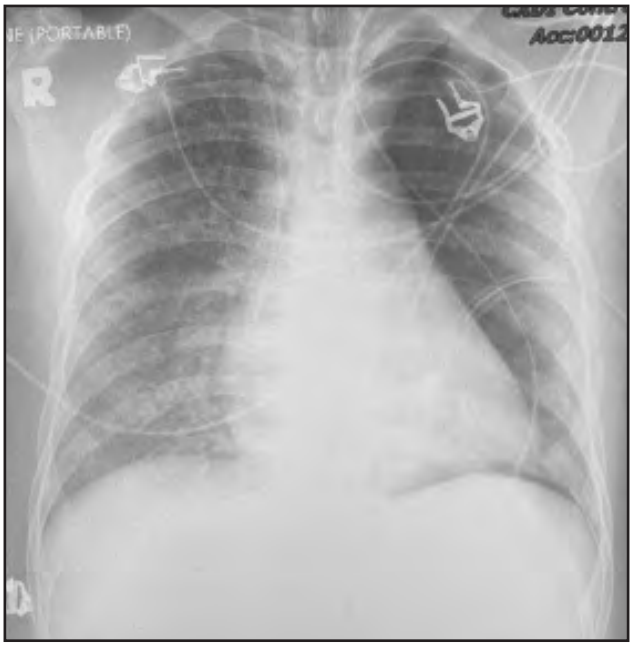

Fig. 2: Chest X-ray on day 7 of ICU admission

COVID-19 includes fever (87.9%), dry cough (67.7%), fatigue (38.1%), and less commonly haemoptysis (0.9%). These presentations of COVID-19 are common to most of the acute febrile illness (AFI), which is an umbrella term used for infectious febrile illness of short duration (<14 days) in tropical and sub-tropical countries.[1] The common causes of AFI include leptospirosis, dengue, malaria, enteric fever, and chikungunya. Leptospirosis is a zoonosis caused by gram-negative spirochetes genus *Leptospira*. Infected reservoir animals, typically rats, will carry the pathogen in their renal tubules and shed the bacteria into their urine.

Leptospirosis is not uncommon in Malaysia. Concurrent COVID-19 and leptospirosis have made the diagnosis of dual infections challenging. Delay in such diagnosis might lead to delay in antibiotic and hence poor outcome.[2] Majority cases of leptospirosis are asymptomatic with only 10% developing severe illness, which is characterised by increased leptospiraemia, multiorgan failure, and increased mortality rate.[3] It is difficult to distinguish between COVID-19 and leptospirosis based on clinical grounds alone, as leptospirosis could also present with fever, dry cough, and fatigue. Conjunctival suffusion, one of the most important signs suggestive of leptospirosis, is not present in this case. In this case, leptospirosis was suspected due to massive pulmonary haemorrhage with a history of swimming in a river at an oil palm plantation. This is supported by the finding of Ludwig et al.,[4] who suggested leptospirosis should be considered in case of rapid multiorgan failure presenting with pulmonary haemorrhage.

Other than similar clinical presentation, laboratory tests of severe leptospirosis and severe COVID-19 share similarity. Presence of acute kidney injury and liver enzyme derangement could be present in both severe leptospirosis and COVID-19. The elevated inflammatory marker levels, such as LDH, ferritin, and D-dimer, could be present due to the cytokine storm from COVID-19 and severe leptospirosis. The higher level of white blood cells, C-reactive protein, and creatine kinase had raised the suspicion of leptospirosis in our patient, as suggested by a study of Li et al.[5] However, elevated level of creatine kinase was also shown to be associated with increased mortality and severity in patients with COVID-19.[6] Hence, the use of rapid diagnostic tests is helpful in early diagnosis and initiation of treatment. In this case, we had sent the samples for both the rapid and diagnostic COVID-19 and leptospirosis testing at presentation, which had aided us in rapid diagnosis and timely antibiotic initiation.

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterised by constitutional symptoms, systemic inflammation, and multiorgan dysfunction, which can lead to multiorgan failure if inadequately treated.[7] Both COVID-19 and increased leptospiraemia will trigger a cytokine storm, which may lead to ARDS and death.[8] High-dose steroids have been used to mitigate the effects of cytokine storm in leptospirosis and COVID-19 with observed benefit in survival. The RECOVERY trial supports the use of steroid in ARDS due to COVID-19.[9] However, there is no well-designed randomised clinical trial to support the effectiveness of high-dose steroid in severe leptospirosis.[10] In our case, we treated cytokine storm with intravenous methylprednisolone and then stepped down to intravenous dexamethasone, which is in accordance with our COVID-19 management guidelines in Malaysia 2020. Additionally, ceftriaxone was started from the beginning, which could lead to the good outcome. A prophylactic anticoagulant, subcutaneous heparin, was only started on day-11 of illness due to persistent haemoptysis.

CONCLUSION

Concurrent infection of leptospirosis and COVID-19 are becoming increasingly common in the background of pandemic COVID-19. Hence, a high index of suspicion should be maintained especially when dealing with acute febrile illness presented with pulmonary haemorrhage and rapid development of multiorgan failure. The suspicion should be further heightened if the patient has epidemiological exposure including water activity. Diagnostic test should be considered early along with other routine laboratory and imaging tests. Early diagnosis and treatment are pivotal as the outcome can be rewarding.

CONFLICT OF INTEREST

None

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CASE REPORT

Primary malignant melanoma of cervix – A rare entity with limited therapeutic option

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SUMMARY

Primary malignant melanoma of cervix (PMMC) is an extremely rare entity, accounting for 2% of the overall incidence of malignant melanoma (MM), which is 1% of all malignancy. We reported a case of PMMC in a 57-year-old woman. She presented with postmenopausal bleeding with no other significant symptoms. General examination was unremarkable with no suspicious mole elsewhere. Speculum and vaginal examination revealed a huge cervical mass with no pigmentation, with clinical stage 1B3 disease. Histopathological examination confirmed MM. She had three cycles of neoadjuvant chemotherapy with cisplatin, vincristine and dacarbazine, after which she underwent radical hysterectomy and pelvic lymphadenectomy. Histopathological examination confirmed stage 1B3 PMMC with close radial margin (1mm margin). She was planning for postoperative adjuvant radiotherapy, but she defaulted on the treatment. She succumbed to disease recurrence nine months after the surgery. There is little consensus on the standard treatment for PMMC. All therapeutic decisions made in this case were based on literature reviews. Surgery remains the mainstay of treatment. Radical hysterectomy may confer survival benefits compared to total hysterectomy alone. While nodal involvement is an important prognosticating factor, the role of regional lymphadenectomy is debatable. Adjuvant therapy with chemotherapy or radiotherapy seems to confer no survival benefits. Radiotherapy was planned for this patient as the margins were close. The prognosis for this condition is generally poor.

INTRODUCTION

Primary malignant melanoma of cervix (PMMC) is an extremely rare entity. Malignant melanoma (MM) accounts for only 1% of all malignancies, of which 3-7% occurs in female genital tract and 2% occurs primarily in cervix. Most of the literatures on PMMC are case reports and case series. In the largest review done by Pusceddu et al.[1], there were only 78 cases of PMMC reported in literatures over 200 years (1889-2009), signifying the rarity of the condition. There is little consensus on the standard treatment for PMMC. In Malaysia, to our best knowledge, PMMC has not been reported, and therefore, we would like to share our experience in managing this rare condition.

CASE REPORT

A 57-year-old para 1 woman was referred from the district hospital, presented with postmenopausal bleeding for one year with no other significant symptoms. She had no prior cervical screening, and nor did she have any medical illness. There was no family history of malignancy.

General examination revealed a well-built woman with no cervical lymphadenopathy and normal abdominal examination. Retrospective examination showed that there was no suspicious mole elsewhere. Speculum examination revealed a huge polypoidal cervical mass >4cm with no pigmentation. The mass replaced the entire cervix. Biopsy was taken. Bimanual vaginal examination showed a hard cervical tumour of >4cm with no vaginal, parametrium or pelvic sidewall involvement. Rectal examination revealed smooth mucosa with external compression anteriorly. She was staged at 1B3 cervical carcinoma.

Staging computed tomography showed heterogeneous enhancing soft tissue mass in the region of the lower uterine body and cervix, measuring 5×7.4×4.2cm. It abutted the urinary bladder with an enlarged left internal iliac node of 1 cm. There was no distance metastasis.

Histopathological examination (HPE) of cervical biopsy showed tumour tissue which exhibited epithelioid to spindle with hyperchromatic nuclei, with some prominent nucleoli. Mitoses were brisk. Some contained melanin pigments. There was no junctional activity seen. The tumour cells stained strongly positive for S100, HMB 45 and Melan A. It was concluded as PMMC as three out of four diagnostic criteria by Morris and Taylor were fulfilled.

Considering the size of the tumour, a multidisciplinary discussion was done with the clinical oncologist and a consensual decision was made for neoadjuvant therapy. She tolerated three cycles of cisplatin, vincristine and dacarbazine chemotherapy. The reassessment CT scan showed stable disease, and she underwent radical hysterectomy and pelvic lymph node dissection (PLND). HPE confirmed stage 1B3 PMMC with close radial margin (1mm margin) and from vaginal cuff (3mm margin). She recuperated well after the surgery with no residual urinary symptoms. She was planned for adjuvant radiotherapy because of unsatisfactory surgical margin, but unfortunately, she defaulted due to the COVID-

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Table I: Summary of the details of review by Pusceddu et al., Yuan et al., and Sun et al., as well as comparison with the index case

Characters	Pusceddu et al.	Sun et al.	Yuan et al.	Index case
Age of diagnosis	65.7% over 50-year-old Median age 59	Age range 38–80 Median age 56.5 Mean age 57	Age range 42–78 Median age 62	57-year-old
Presenting complaints	• Vaginal bleeding (72%) • Vaginal discharge (22%) • Abdominal pain • Dyspareunia, Haematuria, Asymptomatic	• Vaginal bleeding (86%) • Vagina discharge (7%) • Urinary incontinence (7%) • Vaginal bleeding (86%) • Vagina discharge (7%)	• Vaginal bleeding	• Vaginal bleeding
	Main presenting complaint was vaginal bleeding			
Stage at diagnosis	Stage I – 41% Stage II – 34.4% Stage III – 18.0%% Stage IV – 6.5%	Stage I – 50% Stage II – 35.7% Stage III – 7.1%% Stage IV – 7.1%	Stage I – 35.7% Stage II – 42.8% Stage III – 21.5% Stage IV – 0%	Stage 1B3
	Approximately 75 – 80% of cases were diagnosed in early stage			
Treatment modalities	79% (62/78) underwent surgery • Majority had total abdominal hysterectomy – 53/62 (85%) • Local excision in 7/62 (11%) • 1 total pelvic exenteration and one surgery not specified 19 had chemotherapy with 2 neoadjuvant chemotherapy	78.6% (11/14) underwent surgery • 1 had neoadjuvant chemotherapy • 3 – adjuvant chemotherapy • 3 – adjuvant radiotherapy • 3 – BCG, interleukin-2, interferon 3 remaining cases – 2 received no treatment; 1 had chemotherapy and immunotherapy	71.4% (10/14) underwent surgery • 6 radical hysterectomy and 4 total hysterectomy • 8 received PLND • 1 received preop radiotherapy • 1 received preop radiotherapy and chemotherapy 3 only received chemotherapy and radiotherapy 1 received chemotherapy due to physically unfit for surgery	Neoadjuvant chemotherapy (cisplatin, dacarbazine and vincristine) followed by radical hysterectomy and bilateral pelvic lymph node dissection

Survival	• Mean survival – 22.9 months
	• Median survival – 12 months
	• 10.7% survived more than 5 years
	• Majority (85%) died within 3 years
	• 5-year survival rate
	  • I – 18.8%
	  • II – 11%
	  • III and IV – 0%
		• Overall survival – 3–70 months
		• Median survival – 13.7 months
			• Survival >2 years – 50%
			• Survival >5 years – 14.3%
				Survival time – 13 months

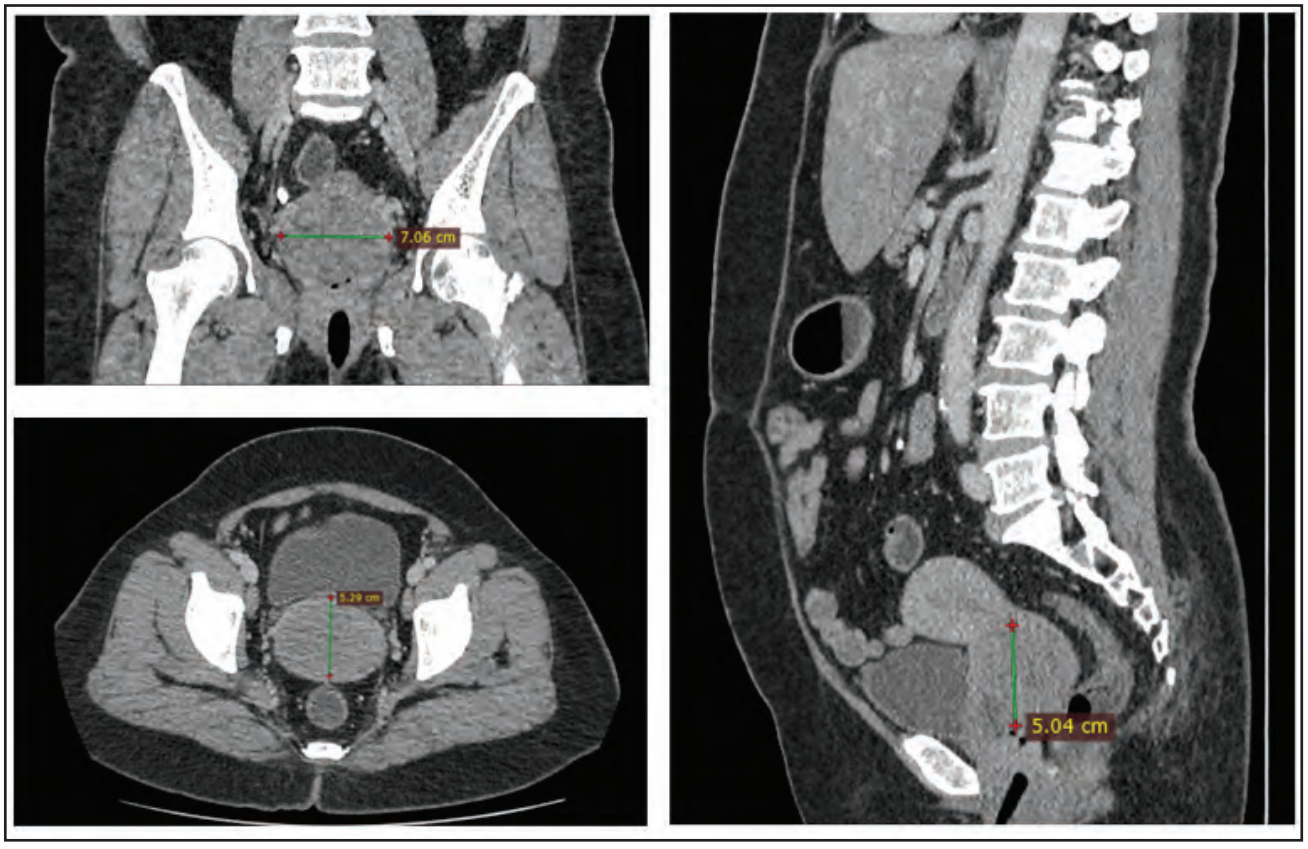

Fig. 1: Computed tomography imaging of the case before treatment

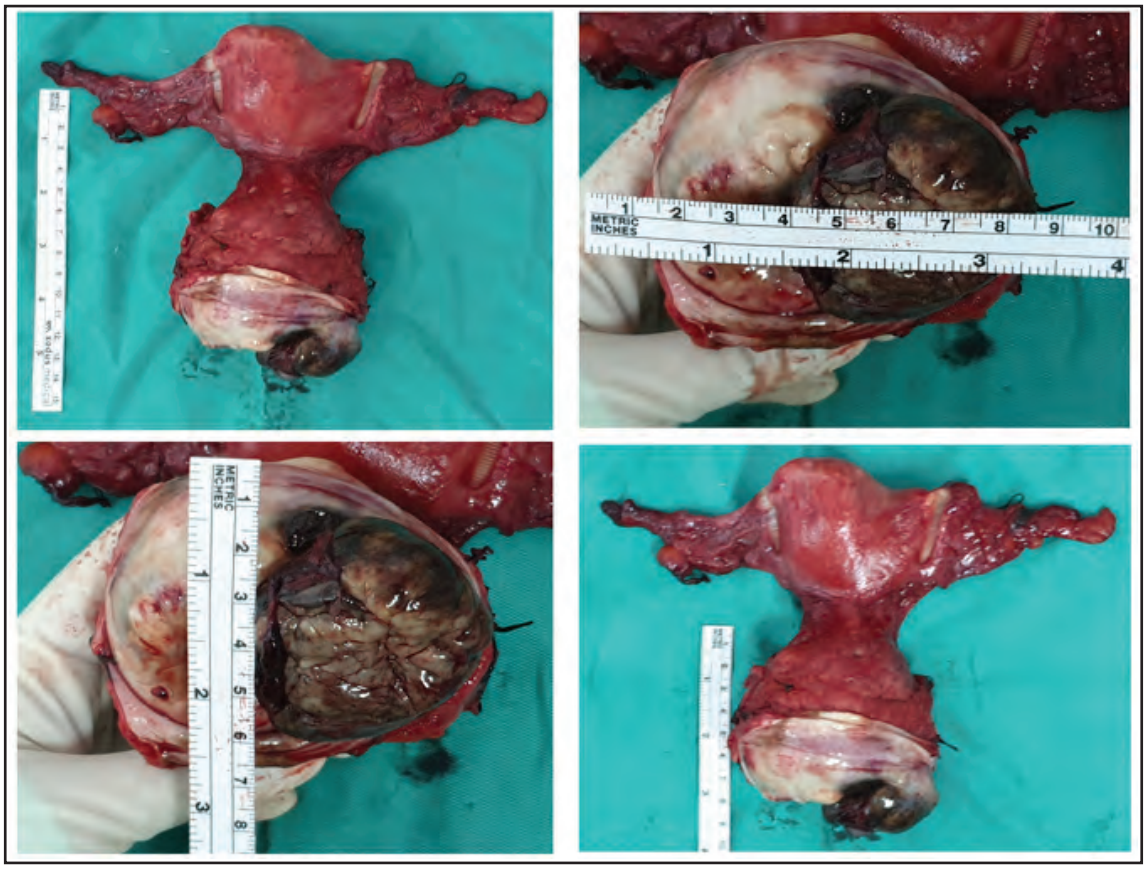

Fig. 2: Images of the resected specimen

19 pandemic. Multiple attempts have been made to contact patient but to no avail. She presented again nine months later with extensive pelvic recurrence with bowel involvement and bilateral obstructive uropathy. She revealed that the reason for defaulting further treatment was because of the fear of COVID-19 infection, and she was not contactable due to poor communication signal in her village. She succumbed to the disease eventually.

DISCUSSION

Managing this case posed a challenge due to our lack of experience in handling such an unprecedented case. We performed a literature search to guide the management of this case. The main literatures included are by Pusceddu et al., Sun et al.,[2] and Yuan et al.[3] Sun et al., performed a review on 14 cases of PMMC diagnosed in Tianjin Medical University Cancer Institute and Hospital from January 1972 to February 2017. Yuan et al., reviewed 14 cases in Cancer Hospital of Chinese Academy of Medical Science from January 1, 1981 to December 31, 2014. The summary of these three literatures is detailed in Table I.

Surgery and lymphadenectomy

In concurring with the general management of MM elsewhere, the mainstay of management of PMMC is surgery. Literature has proven the survival benefits of surgery in PMMC but there is still a lack of consensus on the type of surgery. There are generally two schools with regards to the radicality of surgical treatment. Some authors think that oncological resection to obtain an optimal surgical margin of 2cm is necessary.

On the other hand, in view of the poor prognosis, a more conservative approach can be advocated. In the review by Sun et al.,[2] 11 out of 14 cases had surgery, out of which nine were radical hysterectomy. It was proven that those with surgery had significantly better overall survival compared to those without surgery, regardless of the type of surgery. On top of demonstrating similar findings of better overall survival with surgery (47.9 vs. 7.75 months; p=0.047),[3] Yuan et al concluded that radical hysterectomy conferred longer survival compared to total hysterectomy only (66.8 vs. 19.5 months, p=0.016).

The role of lymphadenectomy in improving survival is still debatable. Historically, Jones et al., suggested prophylactic regional lymph node dissection as 30% of clinically normal lymph nodes contained microscopic metastasis.[4] However, Cantuara et al., advocated lymphadenectomy for grossly involved lymph nodes.[5] The more recent review by Sun et al had only one patient who underwent PLND while Yuan et al had eight patients who received PLND, all of which were negative for metastasis. Both reviews failed to demonstrate the beneficial effect of routine PLND. For our case, we have decided on a more radical surgical approach, including PLND.

Neoadjuvant and adjuvant chemotherapy

There were anecdotal case reports by Min et al.,[6] and Liu et al.,[7] demonstrating successful treatment with neoadjuvant chemotherapy. Min et al reported a case of PMMC with parametrial and iliac lymph nodes involvement, treated with two cycles of cisplatin and dacarbazine, followed by radical hysterectomy, right salpingoophorectomy and pelvic lymphadenectomy. Postoperatively, four cycles of same chemotherapy regime were given concurrently with pelvic irradiation. The outcome was good, with no disease recurrence up to 24 months of follow-up. In another report by Liu et al., where the disease was staged at 1B1 with tumour size up to 4cm, two cycles of cisplatin, dacarbazine and vincristine were given. Subsequently, radical hysterectomy and pelvic lymphadenectomy were performed, followed by postoperative chemotherapy. Patient had survived 30 months of follow-up without recurrence.

The main challenge in this case was the size of the tumour, for which oncological resection might not be achieved with optimal margin. Considering the size, we employed the strategy of neoadjuvant chemotherapy in the hope of shrinking the tumour to get optimal surgical margin without compromising adjacent organs. Unfortunately, the size remained similar after three cycles of neoadjuvant chemotherapy.

Dacarbazine has been the most widely used chemotherapeutic agent for MM with a response rate of 15-20% as a single agent.[8] In combination with cisplatin and vincristine, dacarbazine can achieve a response rate but 25-30%,[9] but this regime is not more superior than dacarbazine alone in prolonging survival. Survival analysis by Sun et al showed that adjuvant chemotherapy did not confer survival benefits.[2]

Radiotherapy

Generally, MM is not a radiosensitive tumour. This treatment modality has been used as adjuvant, neoadjuvant therapy and as palliative intend in some literatures. Sun et al demonstrated no survival benefit from adjuvant radiotherapy.[2] Nevertheless, adjuvant radiotherapy may be considered in cases where there is a close margin or involvement of lymph node or parametrium.

Immunotherapy and targeted therapy

Immunotherapy has been approved for the treatment of metastatic MM as it has been proven to improve survival in that context.[10] For PPMC, reports on the use of immunotherapy have demonstrated contradicting results. Pusceddu et al., reported disappointing results of treatment with Bacille Calmette-Guerin (BCG), interferon, and interleukin-2 in seven cases.[1] Sun et al demonstrated no survival benefit with immunotherapy in the survival analysis.[2] The evidence on targeted therapies against mutations like BRAF, KIT, MEK1/MEK2 and VEGF are emerging and maybe the way forward in the treatment of PMMC. The use of immunotherapy in our patient was out of context due to the cost and indication.

CONCLUSION

PMMC has a poor prognosis. Despite 80% of cases being diagnosed at early stage of Stage I and II, only 10-15% of patients survive more than 5 years,[1,4] with most patients succumbed within three years of diagnosis. The management

PMMC largely depends on the anecdotal experience from case reports and case series, as clinical trials and research are scarce. The behaviour of PMMC is unpredictable, as evidenced by contradicting results of treatment strategies other than surgery. Targeted therapies may have a promising future in the management of PMMC. Hence, research on tumour biology is of paramount importance to understand the disease better. For this patient, it is indeed very unfortunate that the patient has defaulted on her adjuvant treatment. Nevertheless, given the fact that this disease has a very poor prognosis, the adjuvant radiotherapy might not change the outcome.

ACKNOWLEDGEMENT

We would like to thank the family of the deceased for allowing us to publish the case report. Our gratitude goes to Department of O&G, Oncology, Pathology and Radiology of Sarawak General Hospital for its participation in managing the case.

CONSENT

Written informed consent was taken from the patient from the start of managing the case for publication.

CONFLICT OF INTEREST

There was no conflict of interest.

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A challenging issues and situation on maternal cardiopulmonary resuscitation and perimortem caeserian section on COVID-19 patient in 3rd trimester pregnancy

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SUMMARY

Initiating cardiopulmonary resuscitation in pregnant mother with COVID-19 infection can be a challenging situation in many aspects. It needs a simultaneous effective resuscitation and a safety measure to prevent cross-infection to healthcare workers. The aim of this study is to elaborate on issues and challenges in resuscitating a pregnant patient with COVID-19 and the measure to be taken to resuscitate this type of situation. A 34-year-old gravida 3 para 2 woman at 30 weeks period of amenorrhea presented with worsening shortness of breath for 3 days associated with productive cough and intermittent haemoptysis for 1 week prior to admission. She was intubated for severe respiratory distress which later developed into cardiorespiratory arrest. Cardiopulmonary resuscitation (CPR) was commenced with perimortem caesarian section delivery done; however, patient has succumbed to death. There is a need for simultaneous rapid multidisciplinary response in such a complicated situation. This will improve the outcome of the maternal CPR and the risk prevention of infection to healthcare workers.

INTRODUCTION

In the era of COVID-19 pandemic, cardiopulmonary resuscitation (CPR) of a patient with a COVID-19 infection poses a challenging situation for healthcare workers. The situation involving cardiac arrest in pregnancy can be difficult to control, regulate or adapt all aspects of infective control measures when at the same time there is a need to prevent the spreading of the virus to healthcare workers. Most of the updated protocol on COVID-19 regarding resuscitation of a pregnant patient is still the same as those of non-pregnant patients; however, there is a special aspect that has been modified as it involves saving two lives at one time.[1] To add to this chaotic situation, the pressure arises when the decision for perimortem cesarean section is decided during resuscitation in which the delivery needs to be achieved within 5 minutes of cardiac arrest.[2] This article aims to describe the issues regarding maternal resuscitation and CPR in infected COVID-19 patients.

CASE REPORT

We reported a case of 34-year-old gravida 3 para 2 woman at 30 weeks period of amenorrhea (POA) without any comorbidities and otherwise antenatally uneventful who presented to emergency department (ED) with worsening shortness of breath for 3 days associated with productive cough and intermittent haemoptysis for 1 week prior to admission. She also had an intermittent fever for 4 days with diarrhoea but no vomiting or abdominal pain. The patient was initially under home quarantine for the person under investigation as her husband was infected with COVID-19 infection. Upon arrival at ED, she was triaged to the decontamination room and noted to be in severe respiratory distress. She was feverish with a temperature of 38.7°C, blood pressure of 128/78mmHg, heart rate of 123bpm and saturation of 95% under high flow mask oxygen. Lung examination revealed bilateral crepitations in both lower zone.

She was intubated in view of respiratory failure and impending respiratory collapse. Her initial arterial blood gases (ABG) under high-flow mask oxygen 15L/min showed type 1 respiratory failure with pH:7.441, pCO2:24.6, pO2:78, HCO2:16.9 and base excess:-7.4. Other clinical data on admission were as follows: haemoglobin: 12.4 g/dL; white cell count: 8.8 x 10^9; thrombocyte count: 311x10^9; absolute lymphocyte count: 1.06 x 10^9; C-reactive protein (CRP): 185mg/L; urea:3.9 mmol/L and creatinine :148 umol/L. Other parameters such as electrolyte, liver function test and coagulation profile were normal. Her chest radiograph revealed patchy bilateral consolidation of both lungs. The patient was ventilated with a high setting ventilation mode. The ABG post-intubation was worse with a type 2 respiratory failure. The real-time reverse transcription polymerase chain reaction (RT-PCR) test was positive. The impression given was severe COVID-19 pneumonia category 5 with acute respiratory distress syndrome.

One-hour post-intubation, she developed cardiorespiratory arrest and CPR was done with the activation of the obstetric red code. Multiple disciplines, including obstetrics, paediatrics, and anaesthetist simultaneously manage the patient. Lateral uterine displacement was done to relieve aortocaval obstruction while CPR was commenced. In view of the time taken for donning personal protective equipment (PPE) and preparation of perimortem caesarean section set, the delivery of foetus via perimortem caesarean section was only completed at 10 minutes after CPR commenced. Lower segment caesarean section was done with an aseptic

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technique. Unfortunately, the baby was born as fresh stillbirth. Subsequently, the patient had the return of spontaneous circulation; however, she developed another cardiac arrest episode within 1 hour and succumbed to death.

DISCUSSION

COVID-19 infection in pregnancy carries a high risk of severe pregnancy complications such as more severe manifestation, ICU admission or referral to a higher level of care and intubation.[3] Based on the Centre of Disease Control and prevention update, nearly 70% of maternal COVID-19 cases were in the third trimester.[4] The risk of maternal mortality was 1.6% which is 22 times higher compared to the group of non-pregnant women with COVID-19 diagnosis.[3]

There are a few challenging aspects of resuscitation and maternal cardiorespiratory arrest with a COVID-19 infection. Pertaining to this case, she was intubated on admission in view of severe respiratory distress. However, there is limited data specific to the pregnant population with COVID-19 surrounding timing of intubation, use of non-invasive oxygen strategies and mechanical ventilation, as most studies excluded pregnant patients. As such, in the setting of acute respiratory failure requiring invasive mechanical ventilation, principles of care should mirror that of the non-COVID-19 pregnant patient.[5] Following post-intubation strategy, it is still unclear whether uterine decompression with immediate delivery of fetus will improve maternal respiratory status and how the potential benefit balances against the known operative risks in the setting of COVID-19.[6] However, based on fetal consideration, the prolonged hypoxia of the mother will lead to fetal hypoxemia and ultimately acidaemia. This in turn will lead to the risks of prolonged fetal hypoxemia, such as stillbirth and neurologic injury. Thus, the timing of delivery in this critically ill pregnant COVID-19 patient should be based on case-by-case basis following the discussions among obstetric care, maternal–fetal medicine, neonatology, critical care, infectious disease, and obstetric anaesthesiology providers regarding pregnancy management in the setting of worsening maternal respiratory status.[6]

In maternal CPR, the activation of Obstetric red code will lead to various disciplines which include the obstetrician, neonatologist, emergency physician and anaesthesiologist to manage the patient at the same time.[2] However, in the context of COVID-19 cases, particularly pregnant women, this will make the situation very difficult to adhere to infectious control protocol where it is recommended to restrict the number of staff in the room or at the bedside COVID-19 patient at one time.[7] Secondly, compared with non-COVID maternal resuscitation, aerosolize generating procedures such as bagging with a bag valve mask, non-invasive ventilation, tracheal intubation, and chest compression carry a high risk of spreading the infection to medical personnel, especially when they were in close contact with the patient. The safety of the rescuer team member from different disciplines remains as a first priority and should never be compromised. Based on European resuscitation counsel 2020 on COVID-19, there are a few recommendations of PPE that need to be complied with during CPR of COVID-19 patient as it involves multiple aerosols generating procedure.[7] This includes Powered Air-Purifying Respirator (PAPR) or N95 respirator or higher (if PAPR not available), goggles or face shield, gloves, isolation gown (fluid-repellent long-sleeved gown), head cover and shoe cover (in anticipating spillage and vomiting). This strict recommendation provides a challenge to the rescuer in managing maternal with COVID-19 as they need time to complete the entire donning process before starting the CPR. This is more prominent to an obstetrician as they need to be very fast in donning PPE together with preparing equipment for perimortem caesarean section delivery (PMCD) to meet the American Heart Association recommendation that PMCD should begin at 4 minutes to effect delivery at 5 minutes after failed resuscitative efforts.[8] The PMCD is particularly important aspect of maternal CPR as delivery of the fetus will significantly increase venous return and cardiac output to 60%.9 However, in this case, the PMCD is only completed after 10 minutes of CPR due to the prolonged time taken for donning PPE and preparing the PMCD set.

Finally, there are a few changes in anatomical and physiological in pregnancy that make the resuscitation in pregnancy of COVID-19 patient more difficult. The airway in particular has various challenges in pregnancy state such as misplaced cricoid pressure and/or misaligned, increase in intra-abdominal pressure together with reducing in lower oesophageal sphincter tone making it difficult to ventilate and higher risk of aspiration, higher oxygen requirement and reduction in functional residual capacity will make pregnant mother easily desaturate during intubation and reduction of chest compliance due to ribs flaring and splinting of the diaphragm by abdominal content. This factor is particularly important for the operator assigned for intubation as the need to reduce the timing of intubation in order to reduce aerosolised air exposure duration. It is recommended that the intubation is done by senior person with more advanced equipment such as video laryngoscopy. Apart from that, the inferior vena cava is being compressed during pregnancy as the gravid uterus enlarged at the level of umbilicus estimated around 12–14 weeks POA. This will significantly reduce preload to the heart and reduce the efficiency of chest compression. As such, there is a need of additional healthcare worker to do lateral uterine displacement in order to relieve aortocaval compression. This in turn will lead to an increase in cardiac output during CPR.[9]

CONCLUSION

Maternal with COVID-19 infection who need resuscitation or CPR poses a challenging condition for interdisciplinary teams. There is a need to have a proper activation such as Obstetric red code to get a simultaneous rapid team response in such a complicated situation. Thus, a clearer guideline for CPR of pregnant mothers with COVID-19 infection is needed as it deals with a highly contagious environment. This will improve the outcome of the maternal CPR and the risk prevention of infection to healthcare workers.

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CASE REPORT

Primary ovarian rhabdomyosarcoma

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SUMMARY

Sarcomas represent a diverse and extremely complex group of malignancies that can arise from mesenchymal tissue at any site in the body. It is believed rhabdomyosarcoma (RMS) arises from immature cells destined to form skeletal muscles. There are, however, instances where these tumours can occur in locations where skeletal muscles are not typically present. RMS of the ovaries is an extremely rare malignant ovarian tumour. We present a case of 45-year-old woman with progressive abdominal distension and significant weight loss. A fixed pelvic mass and palpable left supraclavicular lymph nodes were discovered during clinical examination. Computed Tomography scans revealed bilateral adnexal masses as well as pelvic and para-aortic lymphadenopathy. A diagnosis of RMS of the ovary was obtained after excisional biopsy of the left supraclavicular lymph node and ultrasound-guided biopsy of the ovarian tumour. We also discuss the difficulties encountered throughout the patient's diagnosis and treatment. She underwent neoadjuvant chemotherapy before cytoreductive surgery after being diagnosed with advanced ovarian RMS. Unfortunately, she died after the first course of chemotherapy due to cancer progression.

INTRODUCTION

The most common soft-tissue sarcoma in childhood is rhabdomyosarcoma (RMS), which usually affects the genitourinary tract, extremities, and head and neck region. The genitourinary tract includes the urinary bladder, prostate, and paratesticular soft tissues.[1] In contrast, primary ovarian RMS is an extremely rare tumour, which can cause diagnostic dilemmas for pathologists and clinicians alike. An accurate diagnosis is crucial, because RMS treatment is different from other tumours that happen in the ovary.[2] Predicting the biological behaviour of primary ovarian RMS is difficult due to a scarcity of evidence.[1] Here, we provide one such case from both a clinical and pathological standpoint.

CASE REPORT

A 45-year-old nulliparous woman with no previous comorbidities presented with 2-month-old lower abdomen pain and distension, as well as considerable weight loss. There had been no changes in bowel or urine patterns in the past.

On general examination, there was a palpable 2×2 cm left supraclavicular lymph node. A fixed pelvic mass equivalent to the size of a gravid uterus at 24 weeks was discovered during an abdominal examination. There were no signs of ascites. Upon pelvic examination, a fixed mass was felt at the right adnexa.

A computed tomography (CT) scan revealed a solid adnexal tumour emerging from the right ovary, measuring 9×11×18 cm (Figure 1a and 1c). There were numerous enlarged lymph nodes (up to 2.5 cm) in both iliac regions, as well as an enlarged left supraclavicular lymph node (Figure 1b) and matted para-aortic lymph nodes from the aortic bifurcation to the renal level (Figure 1c). There was minimal ascites present, but no metastatic lesions in the lungs or liver. CA125, CA19-9, and alpha-fetoprotein (AFP) laboratory tests all came back with increased levels (411U/ml (normal 35), 58U/ml (normal 34), and 21.6IU/ml (normal 5.8), respectively. At this point, we were considering advanced epithelial ovarian malignancy.

An excisional biopsy of the left supraclavicular lymph node was performed, as well as an ultrasound-guided biopsy of the ovarian tumour. Microscopic examination of both specimens showed tissue infiltrated by sheets and clusters of malignant cells with minimal fibrous stroma. The malignant cells display monotonous small to medium size nuclei, inconspicuous nucleoli, and scanty cytoplasm. Mitosis and apoptotic bodies were brisk. The tumour cells were immunopositive for desmin, myogenin (nuclear), synaptophysin, INSM-1, WT-1 (cytoplasmic), and INI1/SMARCB1 (nuclear) while immunonegative for pancytokeratin, epithelial membrane antigen, calretinin, CK20, chromoganin, OCT3/4, CD45, and GATA-3.

Small cell carcinoma of the ovary of hypercalcemic type (SCCOHT), small cell carcinoma of the ovary of pulmonary type (SCCOPT), neuroendocrine carcinoma, and other entities, including epithelial, germ cell, lymphoproliferative disorders, desmotic small round cell tumours, and nephroblastomas have been ruled out by immunochemistry. After a thorough examination of the patient, radiologically, and pathologically, we concluded that it was a primary ovarian rhabdomyosarcoma (RMS).

In view of the advanced disease, she underwent the first cycle of chemotherapy VAC regime (vincristine, actinomycin-D,

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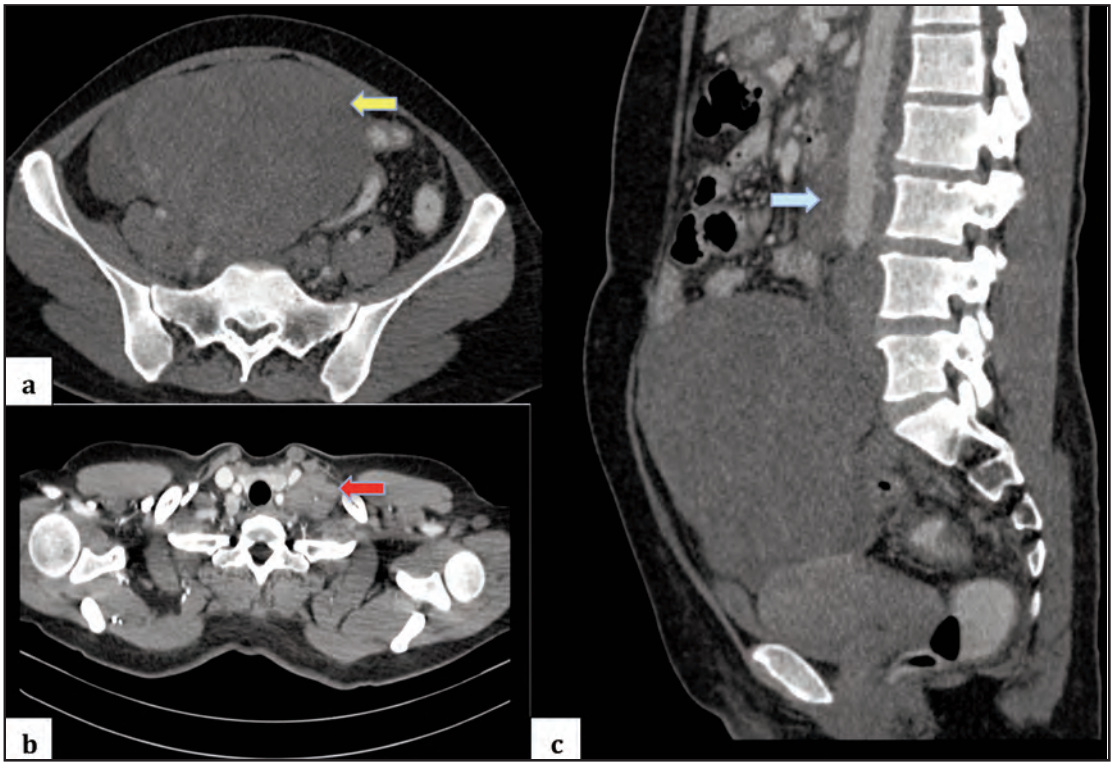

Fig. 1: Computed tomography (CT) imaging
a) Axial CT image showing adnexal mass (yellow arrow) insinuating into the right hemipelvis
b) Axial CT image showing enlarged left supraclavicular node (red arrow)
c) Sagittal CT image showing adnexal mass in relation to the uterus inferiorly and the matted paraaortic nodes (blue arrow)

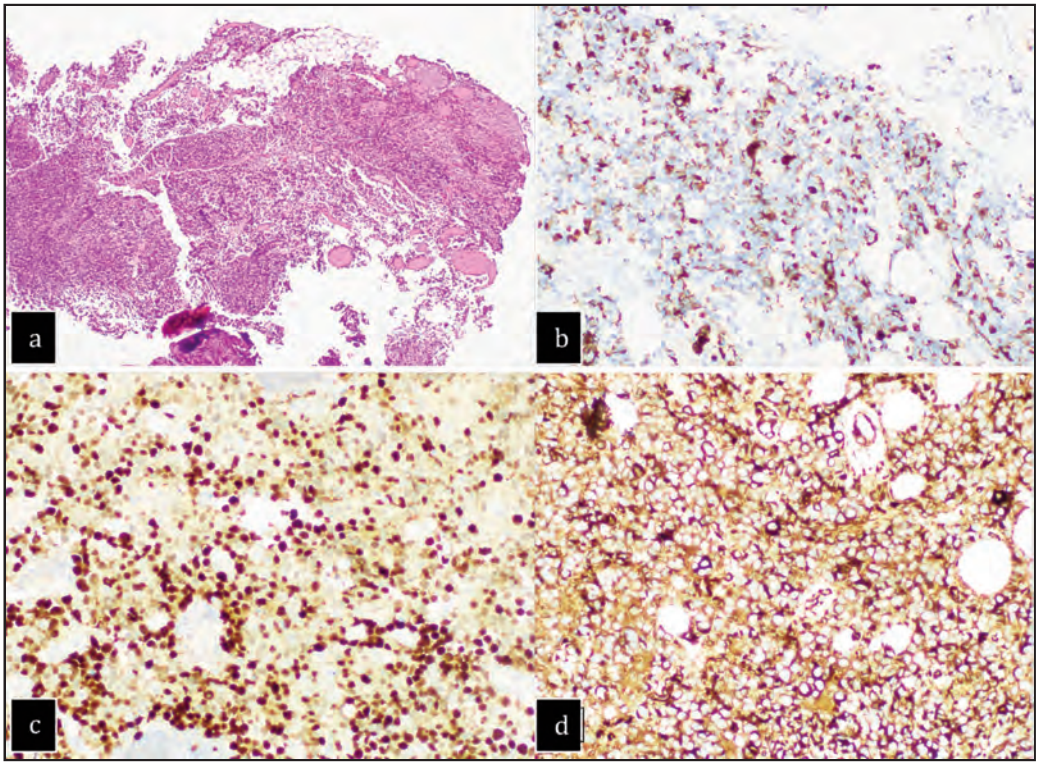

Fig. 2: Microscopic examination findings
a) Diffuse sheets of undifferentiated tumour cells with extensive tumour necrosis (H&E ×40 magnification)
b) Desmin; mesenchymal stain for myogenic differentiation (×200 magnification)
c) Myogenin nuclear positivity. Highlights skeletal muscle differentiation (×200 magnification)
d) WT-1 cytoplasmic positivity (×200 magnification)

and cyclophosphamide). However, her condition deteriorated, and she developed obstructive uropathy and upper gastrointestinal bleeding. Subsequently, she succumbed to death.

DISCUSSION

The most common soft tissue sarcoma in children, accounting for more than half of all soft tissue sarcomas, is RMS. RMS, on the other hand, is extremely uncommon in adults. Soft tissue sarcomas account for less than 1% of all malignancies in adults, while RMS accounts for 3% of these.[3,4] RMS is sporadic in nature, with no known cause or risk factors. The disease, however, is linked to a number of familial syndromes, including Noonan, neurofibromatosis, Beckwith-Wiedemann, Li-Fraumeni, and Costello.[4]

A variety of factors contribute to the different clinical manifestations of RMS, including the location of the origin, the patient's age, and whether or not distant metastases are present. In the course of an initial evaluation of a patient with suspected RMS, it is important to determine the anatomic boundaries of the tumour. All these factors will influence the stage of disease, risk stratification, and eventually the course of treatment.

In conjunction with a thorough physical examination and pelvic ultrasound, a CT scan is useful in assisting the diagnosis and detection of tumours as well as the presence of metastases. Prior to the diagnosis of primary ovarian RMS, a thorough evaluation of the tumour is essential to exclude metastases from other sites or mixed components, such as teratoma, mixed mesodermal tumours, or Sertoli-Leydig cells.[1,2] In our case, clinical and radiological findings did not show any other primary sites. Furthermore, histopathological examination found no evidence of germ cell tumours. Therefore, a final diagnosis of primary ovarian RMS was made.

Guérard et al.,[5] reported that ovarian RMSs are extremely rare and fatal. They documented 14 cases of ovarian RMS ranging in age from 13 months to 86 years, with the majority being over the age of 40. Approximately half of the cases had cancer that had spread beyond the ovary, and survival ranged from 18 days to 15 months after diagnosis. Patient survival appears to be improved through aggressive chemotherapy, radiation, and surgery.

Nielsen et al., subsequently reviewed 13 cases, of which 11 had embryonal histology and 2 had alveolar histology.[6] A follow-up of these patients revealed a poor outcome as 7 of them died within 10 days to 26 months. Cribbs et al., described two paediatric patients with advanced primary ovarian RMS; both underwent complete resection of their primary tumours and were treated with vincristine, doxorubicin, and cyclophosphamide, which resulted in a favourable outcome.[7]

Qureshi et al. reported a case of a 21-year-old woman with pleomorphic ovarian RMS who underwent two surgeries but refused chemotherapy or radiotherapy and was well through the last follow-up.[1] In an article by Ezem et al., a 13-year-old girl was diagnosed with primary ovarian RMS after laparotomy bilateral ovariectomy.[8] Postoperatively, the patient presented with metastatic deposits to the spine. However, she could not afford chemotherapy or radiotherapy. She passed away 93 days after the presentation.

Vanidassane et al. recently described a case of ovarian RMS in a young girl.[2] When an ovarian epithelial tumour was suspected, washings, an omentectomy, and a left salpingo-oophorectomy were performed. Histopathology initially suggested a low-grade myxoid fibrosarcoma. The patient developed a recurrence after a month, and subsequent morphological and immunohistochemical findings confirmed that it was embryonal RMS. A final diagnosis of primary ovarian RMS stage 4 was reached after a thorough pathological, clinical, and radiographic examination. The patient was treated with a high-risk VAC regimen that included vincristine, actinomycin D, and cyclophosphamide. As stated in the case report, the patient is in the midst of treatment.

RMS risk stratification includes histologic classification, pre-surgical stage, and post-surgical clinical group. Surgery, chemotherapy, and radiotherapy are all treatment options. VAC regimen (vincristine, actinomycin D, and cyclophosphamide) and the IVA regimen (ifosfamide, vincristine, and actinomycin D) are the two main chemotherapy regimens used to treat RMS. Ionizing radiation (IR) therapy has been found to be an effective tool in reducing disease recurrence rates, and it is frequently used in patients with advanced stages of cancer. When total resection is not achievable, IR therapy is typically utilised to supplement patient management.[3,4]

CONCLUSION

Primary ovarian RMS is an incredibly rare and lethal form of malignancy. It occurs in a wide range of age groups, usually presents in advanced stages with delayed presentation, and has poor outcomes. Thorough evaluation of the tumour is crucial to rule out metastasis from other sites, as treatment of RMS is different from that of other types of malignant ovarian tumour.

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We would like to thank the family of the deceased for allowing us to publish this case report. Our gratitude goes to the Department of Obstetrics and Gynaecology, Oncology, Pathology and Radiology of Sarawak General Hospital for their participation in managing the case.

CONSENT

Written informed consent was taken from the patient from the start of managing the case for publication.

CONFLICT OF INTEREST

There was no conflict of interest.

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CASE REPORT

COVID-19 with melioidosis and cutaneous mucormycosis – A case report

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SUMMARY

It is generally known that the use of immunosuppressive therapy in COVID-19 infection gives rise to the occurrence of opportunistic infections. We reported a young, immunocompetent patient who presented with COVID-19 pneumonia and multiple erythema nodosum, a week post-trauma and was started on high-dose steroid therapy. Apart from the identification of *Burkholderia pseudomallei* in the blood culture, the skin culture and biopsy yielded *Saksenaea erythrospora*. Possibly compounded by a delay in diagnosis and therapy, the patient did not survive. We describe a COVID-19 pneumonia patient with concomitant melioidosis and cutaneous mucormycosis occurring opportunistically after corticosteroids, leading to an unfavourable outcome.

INTRODUCTION

The role of immunosuppressive therapy in treating severe COVID-19 pneumonia with hypoxia and hyperinflammation is well established,[1] but the treatment itself is well known to predispose patients to a wide range of opportunistic infections,[2] including melioidosis and mucormycosis. Mucormycosis, an angioinvasive fungal infection caused by filamentous fungi of the order Mucorales (Rhizopus (47%), Mucor (18%), Cunninghamella (7%), Saksenaea (5%), Rhizomucor (4%), Absidia (5%), and others (13%)), is a rare but deadly opportunistic infection. Whereas, melioidosis, as it is commonly known, is a tropical infectious disease caused by *B. pseudomallei*. Typically, these two pathogens are primarily transmitted via inhalation or direct contact with contaminated water and soil, especially percutaneous inoculation. Thus far, literature does not describe the coinfection of both organisms in an individual with COVID-19.

CASE PRESENTATION

A 27-year-old Malay man was found unconscious in the roadside drain and was intubated upon arrival at the nearest hospital. Further history from family members revealed that he had a history of recurrent seizures following traumatic brain injury in the past, without proper follow-up care. It was believed that he had a breakthrough seizure while riding a motorbike. Further history revealed that he had been unwell for a week with lethargy, irritability, and cough. He also inhaled narcotic substances. His rapid molecular COVID-19 test of naso-pharyngeal specimen detected SAR-CoV-2 virus.

On examination, there were abrasion wounds seen over his left arm and bilateral lower limbs. The Glasgow coma scale (GCS) was E1VTM1. Other physical findings were unremarkable. The baseline investigation results are described in Table I. In addition, the chest x-ray (CXR) revealed heterogeneous opacity involving multi-lobular areas in both lungs; and the contrasted cranial computed tomography (CT) revealed encephalomalacia over bifrontal areas, with no evidence of brain infection (Figure 1B and 1C). In light of severe COVID-19 pneumonia with presumed superimposed bacterial infection, he was administered intravenous steroid (an equivalent dose of 2mg/kg methylprednisolone) for a week, broad-spectrum antimicrobials (piperacillin/tazobactam), and anti-seizure medication (phenytoin). Anti-viral therapy was not considered as the illness had progressed to a hyperinflammatory state. After four days of hospitalisation, he had recovered from COVID-19 pneumonia and was then extubated with a full GCS.

However, two days later, he became restless and tachypnoeic. His condition subsequently deteriorated to septic shock and respiratory failure. In addition, for the first time, he developed painful, erythematous cutaneous nodules suggestive of erythema nodosum, over his bilateral forearms, legs and periumbilical area (Figure 1A), as well as bullous cellulitis over his left forearm. A skin biopsy was obtained (Figure 1E). The laboratory findings are described in Table 1. Repeated CXR showed patchy consolidation at right basal zone and the thoracic CT depicted grass-ground opacities involving right middle and lower lobe, along with cavitary pulmonary lesions and bronchiectasis at right lower lobe (Figure 1B and 1C). The antibiotic was upgraded to intravenous meropenem. However, he became increasingly septic and eventually succumbed to his illness.

Post-humus, his blood culture grew *Burkholderia pseudomallei,* confirmed by MALTI-TOF MS. The skin biopsy showed the findings of coagulative necrosis of fat lobules and stroma in the subcutaneous layer of skin, suggestive of panniculitis, along with fungal angioinvasion (Figure 1E) and the skin tissue culture grew mucormycosis (Figure 1D). The fungal PCR of the cutaneous tissue showed *Saksenaea erythrospora*.

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Table I: Describes the serial laboratory results taken at different timeframes during the hospitalization. On the first day of hospitalization, the patient had raised septic markers, acute renal failure, transaminitis, and myositis. After four days of initial therapy, the biochemical parameters showed improvement. However, after a week of hospitalization, he developed sepsis with multi-organ failure

Day of admission / Laboratory	1 (baseline)	4	10
WCC (x10^9/L)	23.17	13.70	66.44
Hb (g/dL)	16.2	13.3	11.1
PLT (x109/L)	220	188	288
CRP (mg/dL)	22.9	16.4	30.8
Urea (mmol/L)	7.1	5.5	10.1
Creatinine (umol/L)	137	56	193
ALT (U/L)	144	120	117
ALB (g/L)	42	33	23
CK (U/L)	2116	1142	3206
Ferritin (ng/mL)	566	-	-
D-Dimer (ng/mL)	9499	-	-
PCT (ng/mL)	18.04	-	-

ALB, albumin; ALT, alanine transaminase; AMOX/CLAV, amoxycillin/clavulanic acid; BA, blood agar; CK, creatinine kinase; COVID-19, coronavirus disease; CRP, C-reactive protein; CT, computed tomography; EN, erythema nodusum; GCS, Glasgow coma scale; Hb, haemoglobin; LPCB, lactophenol cotton blue; MAC, MacConkey Agar; MALDI-TOF-MS, matrix-assisted laser desorption/ionization mass spectrometry; PAS, Periodic Acid-Schiff; PCR, polymerase chain reaction; PCT, procalcitonin; PLT, platelet; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDA, Sabouraud dextrose agar; TB, tuberculosis; TMP/SMX, trimethoprim/sulfamethoxazole; WCC, white blood cells.

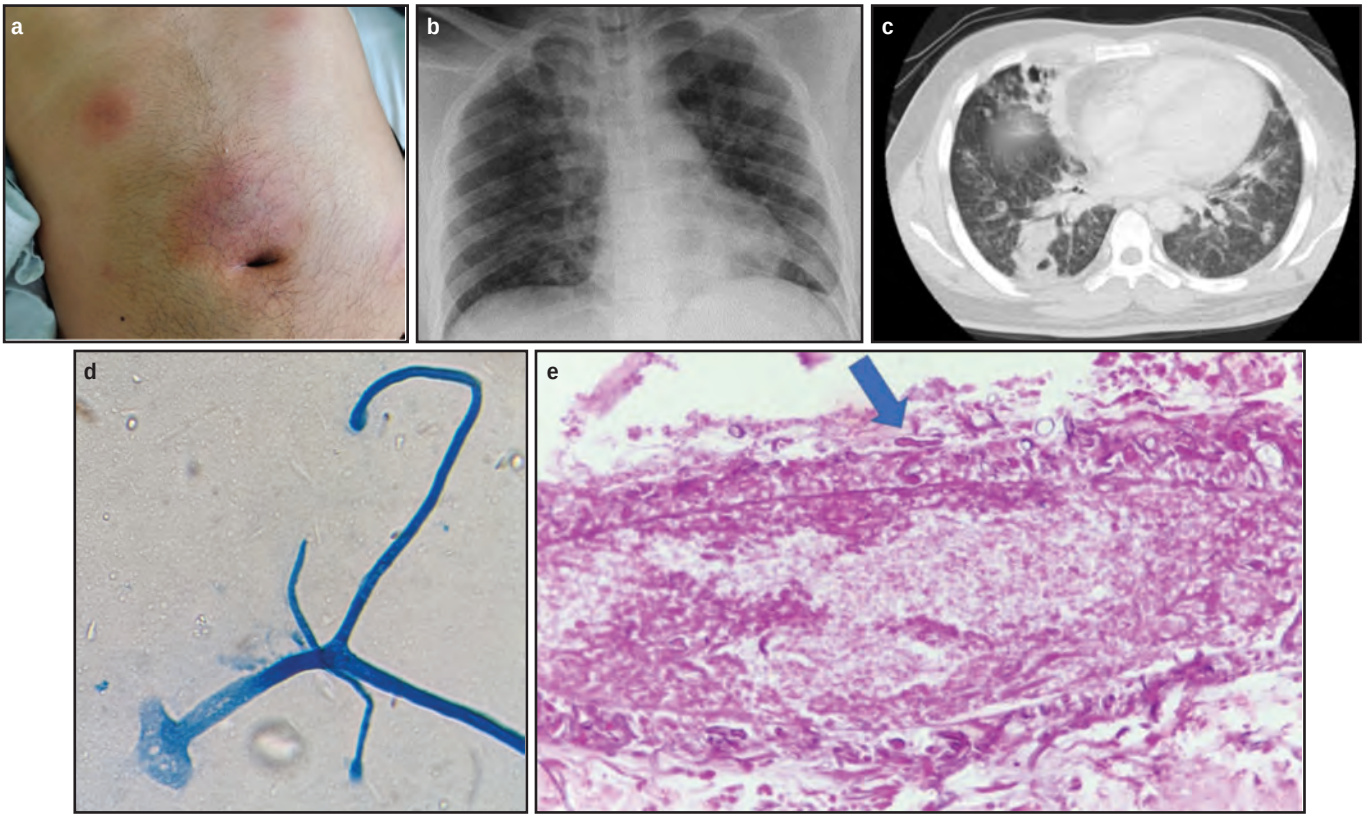

Fig. 1: Describes the clinical, radiological, microbiological, and histological findings in our case. Figure 1A depicts the clinical image of EN found at the anterior abdominal surface. Figure 1B describes the appearance of generalised heterogeneous opacity in the CXR taken at presentation. The image of thoracic CT (as shown in Figure 1C) shows the presence of heterogenous consolidation, tram-track opacities, and cavitations in bilateral lower lobes. Figure 1D shows the finding of fungal growth in skin culture, seen on SDA with LPCB staining, with the presence of a flask-shaped sporangiophore with columellae, suggestive of *Saksaneae sp.* Figure 1E describes the histopathological findings of skin biopsy taken from the left thigh and periumbilical area, with broad, non-septated, thin-walled hyphae detected within the blood vessel walls (shown with a blue arrow), stained with PAS stain

Neither fungal blood cultures nor fungal biomarkers were obtained. The TB workout was negative. The tracheal aspirate culture grew piperacillin/tazobactam-sensitive *Pseudomonas aeruginosa*. The complete diagnosis was revised to COVID-19 pneumonia with melioidiosis bacteraemia and cutaneous mucormycosis.

DISCUSSION

We report this unique case of infection due to two ubiquitous microorganisms that were most likely triggered by extensive immunosuppression using high-dosed steroid. Community-acquired co-infections along with COVID-19 infection are not uncommon.[3] In the background of COVID-19 pneumonia with concomitant coinfection and superinfection, a shorter course of low-dosed steroid, notably intravenous dexamethasone 6 mg daily for up to 10 days, should be considered when indicated.[1,4] In our case, given that he presented with severe hypoxia, it was difficult to distinguish COVID-19-related hyperinflammation from coinfection, and thus, a higher dose of steroid was administered to address the hyperinflammation. Of note, a prolonged use of high-dosed steroid, which is unproven in treating COVID-19 pneumonia, potentially promotes fungi and bacteria to thrive in vivo, leading to severe opportunistic infections.[5,6] The pathogenesis of opportunistic infection in the background of COVID-19 infection can be conceivably explained by immune dysregulation caused by immunosuppressive therapy or post-trauma endothelial injury.[7,8] Consistent with previous studies,[7,9] the risk factors contributing to both melioidosis and mucormycosis in our case include trauma and exposure to immunosuppressive agents used in treating COVID-19.

It was reported that the incidence of mucormycosis had substantially risen during the COVID-19 pandemic.[7,10] The genus Saksenaea, belonging to the class Zygomycetes, is often associated with rapid disease progression and angioinvasion commonly involving the lungs and rhino-cerebral areas.[7] It is traditionally characterised by the presence of flask-liked sporangia with columellae, non-septated sporangiophores, and rhizoids; tiny sporangiospores ranging from 3 to 11µm in diameter are contagiously spread via inhalation or cutaneous inoculation. Noteworthy, the presence of erythema nodosum is suggestive of a disseminated form of the disease.[11] In our case, the patient had probably acquired the disease from inhalation of droplets or spores from a contaminated environment during the time of trauma (he was found in a drain) or while inhaling narcotics. Additionally, direct inoculation from contaminated soil or water has also been described.[12] Fungal biomarkers including serum galactomannan and β-D-glucan are not useful for the diagnosis of mucormycosis, and hence, the tissue biopsy is essential. Diagnosis is confirmed by histopathology or fungal culture of the tissue specimen. Radiological findings of pulmonary mucormycosis (including cavitary lesions, consolidations, or nodules, reversed halo signs) can provide diagnostic clues to suspect mucormycosis. Amphotericin B and posaconazole are the drugs of choice in treating Saksenaea infection.[13] In our case, anti-fungal agent was not considered empirically as his clinical presentation was overshadowed by melioidosis.

Burkholderia pseudomallei, the causative agent of melioidosis, is an aerobic, non-sporulating, gram negative bacillus. With its soil-dwelling property, it is easily spread via skin inoculation and inhalation. Its clinical spectrum ranges from asymptomatic infection to fulminant disease involving multiple organs, including the pulmonary system. In our case, the patient presented with bacteraemia and severe pneumonia (described in Figure 1). Melioidosis pneumonia may mimic any forms of chronic granulomatous disease, including fungal infection, radiologically with diffuse nodular infiltrates, and cavities throughout bilateral lungs. The diagnosis of melioidosis is solely based on blood or tissue culture, with the appearance of grey-translucent colonies seen on BA and MAC. The use of MALDI-TOF MS helps in the rapid detection of melioidosis. Though not widely available, molecular investigation for *B. pseudomallei* may add value to the rapid diagnosis of melioidosis. Generally, the drug of choice during the intensive therapy for melioidosis is ceftazidime with carbapenems as an alternative, followed by the long-term oral eradication phase.

Owing to an atypical clinical presentations and challenges in phenotypic identification, establishing an appropriate diagnosis can be extremely challenging. Thus, it is essential to have a low threshold of suspicion for atypical organisms and to utilise multiple diagnostic tests in immunosuppressed patients to achieve a more rapid and holistic approach. While awaiting laboratory results, atypical imaging characteristics may facilitate the diagnosis of concomitant invasive mycoses or bacterial infection. Nevertheless, the granulomatous diseases, either mucormycosis or melioidosis, manifest with indistinguishable and non-specific imaging appearances, often triggering an extensive diagnostic workup. Furthermore, physicians should use immunosuppressive therapy judiciously in treating COVID-19 pneumonia.

DECLARATIONS

ETHICS APPROVAL

Approval of this study was obtained from the National Medical Research Register, Ministry of Health, Malaysia.

CONSENT FOR PUBLICATION

In consideration of having concerns about the possibilities of disease transmission on papers, an informed verbal consent was obtained from the guardian for publication

COMPETING INTERESTS

None to declare

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CASE REPORT

Recanalisation of the falcine sinus secondary to venous sinus thrombosis

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SUMMARY

The falcine sinus is an ascending midline vein that connects the vein of Galen and sagittal sinus above the level of the confluence of sinuses. It usually involutes after birth. This embryonic vessel is rarely encountered clinically in adults. According to pathogenesis, the falcine sinus can be classified into persistent falcine sinus (PFS) and recanalised falcine sinus (RFS). We present an interest-ing case of an elderly patient with encasement of the internal jugular vein by a thyroid mass, result-ing in secondary cerebral venous thrombosis and recanalisation of the falcine sinus. Following treatment, there is recanalisation of the previously occluded venous sinus pathways with subse-quently reduced enhancement of the falcine sinus. When the falcine sinus is identified on imaging, it is imperative to look for any associated congenital anomalies or causes for the venous sinus ob-struction (e.g., thrombosis or tumours). In this report, we highlight the differences between the two types of falcine sinuses including their pathogenesis and pertinent imaging features.

INTRODUCTION

The falcine sinus is a rare variation of the cerebral venous pathway between the dural layers of the falx cerebri.[1] The sinus can arise from any part of the deep cerebral venous system but most com-monly from the vein of Galen or the straight sinus and drains to the sagittal sinus above the level of the confluence of sinuses.[2] This embryonic vessel normally involutes before or shortly after birth. It is rarely encountered in the adult population. We present an interesting case of an elderly patient with recanalisation of the falcine sinus.

CASE REPORT

An 81-year-old woman with known papillary thyroid carcinoma presented with a worsening head-ache for one month. No neurological deficit was detected on examination. Computed tomography (CT) scans revealed a thyroid mass encasing the right internal jugular vein, resulting in secondary thrombosis of the right internal jugular vein and the sigmoid sinus. CT cerebral venogram con-firmed thrombosis of the right sigmoid sinus and the internal jugular vein (Fig.1). There was re-canalisation of the falcine sinus connecting the vein of Galen to the superior sagittal sinus, with ad-ditional collateral vessels connecting the falcine sinus to the posterior part of the superior sagittal sinus (Fig. 1). There was no evidence of cerebral venous infarction. The patient subsequently un-derwent total thyroidectomy without complication. She has been well and asymptomatic after the surgery. As for the cerebral venous sinus thrombosis, she was prescribed oral anticoagulation thera-py with warfarin for 6 weeks. Two months later, a follow-up CT cerebral venogram showed partial recanalisation of the previously occluded venous sinus drainage pathways with subsequently re-duced enhancement of the falcine sinus (Fig.1d).

DISCUSSION

Falcine sinuses are rarely encountered clinically, only seen in 2.1% of the adult population.[1,3] It usually involutes after birth. There is a variation of the calibre of the falcine sinus ranging from 2 to 17 mm. The morphology of the falcine sinus can vary from an arch-like curved vessel to a straight or branching vessel.[3]

The falcine sinus can be classified into two groups based on the pathogenesis: Persistent falcine sinus (PFS) and recanalised falcine sinus (RFS) which is illustrated in our patient's case.[1]

Persistent falcine sinus: PFS refers to the falcine sinus that does not involute but persists after birth. Figure 2 shows a case example of a 56-year-old woman with PFS. Most PFS are associated with congenital disorders such as malformation of the vein of Galen,[3] absence of the corpus callosum,[4] acrocephalosyndactyly,[4] osteogenesis imperfecta,[3] meningoencephalocele[5] and Chiari II malfor-mation.[1,3] The Manjila classification categorized the PFS based on its relationship with the superior sagittal sinus. It also takes into consideration of associated defects in the brain and other dural ve-nous sinuses (Table 1).[6]

Recanalised Falcine Sinus

The term 'recanalised' in RFS refers to the establishment of flow through a previously involuted falcine sinus.[3] Unlike PFS, which is often associated with other anatomical variants, RFS can be seen in individuals with normal falx and cerebral venous drainage system. RFS is often established following an acquired occlusion of the straight sinus from increased pressure in the cerebral venous system secondary to venous obstruction, e.g., cerebral venous sinus thrombosis (CVST) or tumour compression.[1] The falcine sinus may serve as an alternative venous drainage pathway when throm-bosis or obstruction occurs along the cerebral venous sinus

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Table I: Manjila grading of persistent falcine sinus

Grade	Description
1	Normal falx with PFS disconnected from SSS with or without focal dupli-cation of SSS
2	Hypoplastic falx cerebri posterior to PFS with or without hypoplasia of dis-tal SSS
3	PFS with normal falx; deficient straight sinus with or without dysplastic tentorium cerebelli
4	PFS with hypoplastic falx/SSS associated with deficient straight sinus with or without dysplastic tentorium cerebelli
5	PFS grades 1–4 with additional neurovascular developmental lesions like vein of Galen pathologies and enlarged parietal emissary veins
Subtype A	With atretic parietal/occipital cephalocele
Subtype B	Without atretic parietal/occipital cephalocele

Tenting or peaking of the tentorium can occur in any of the grades. Similarly, an enlarged parietal emissary foramen or a focal duplication of the SSS can appear with or without an atretic parietal/occipital cephalocele. PFS: persistent falcine sinus; SSS: superior sagittal sinus.

Table II: Differences in the imaging features between the persistent falcine sinus (PFS) and the re-canalised falcine sinus (RFS)

Imaging features	Persistent falcine sinus (PFS)	Recanalised falcine sinus (RFS)
Associated with venous sinus disease	No, PFS failed to involute and persisted after birth	Yes, typically associated with intracranial lesion(s) causing venous sinus obstruction including tumours and venous sinus thrombosis secondary to coagulopathy or hypertrophic meningitis
Associated with congenital anomalies of the remaining venous sinuses or other intracranial developmental pathology	Yes, often present (see Table 1 for Manjila grading system of PFS)	Usually absent
Presence of collateral veins around the falcine sinus	Absent	Yes, presence of collateral veins connecting RFS to superior sagittal sinus, depending on the extent of the venous sinus obstruction
Resolution of falcine sinus	No	The RFS may show reduced opacification on CT or MRI venogram following treatment, for example, re-establishment of the normal venous sinus system following anticoagulation therapy or surgical resection of an obstructive intracranial mass

system. When the patient's normal cere-bral venous drainage system is re-establish, the flow through the falcine sinus would be reduced.

Hypertrophic pachymeningitis (HPM) is one of the conditions associated with RFS. It is an un-common condition presenting as chronic inflammation and progressive fibrosis of the dura mater.[6–8] One of the consequences of the inflammatory process in the dura mater is the hypercoagulability state and venous stasis which contributes to CVST.[7,8] HPM can be a secondary manifestation of a number of conditions, including infection (e.g. bacterial meningitis, tuberculous pachymeningitis), neurosarcoidosis, haemodialysis, and mucopolysaccharidoses.[6,8]

Besides CT venogram, the cerebral venous system can be evaluated by magnetic resonance imaging (MRI) which offers a better soft tissue resolution than the CT scan. However, thrombosis of the fal-cine sinus can pose a diagnostic challenge in post-contrast MRI because of the lack of sinus opaci-fication.[3] Traditionally, conventional catheter-based digital subtraction angiography is the preferred modality for the evaluation of the cerebral venous anatomy and drainage pattern.[9] The differences in the imaging features between the PFS and RFS are documented in Table II along with other asso-ciated abnormalities. This may help to guide management.

Clinical Significance of Falcine Sinus

During endovascular or surgical obliteration of the straight sinus, the falcine sinus may assist in ve-nous drainage by establishing an alternative venous sinus pathway.[3] Besides, it is vital in the regula-tion of the intracranial pressure.[3] However, the presence of a falcine sinus could increase the risk of iatrogenic haemorrhage during surgery that involves the falx cerebri.[3] Attention should be paid to the sinus in preoperative planning, especially with tumours that tend to compress the venous sinus.[3] Conversely, the falcine sinus should not be mistaken for a drainage vein of an arteriovenous mal-formation.[3] It is therefore essential to study the cerebral venous sinus system in detail before any endovascular or neurosurgical procedures with attention to the presence of the falcine sinus.

CONCLUSION

The falcine sinus is seldom encountered in the adult population because it usually involutes after birth. Persistent falcine sinus is a variant that persists after birth. Recanalisation of the falcine sinus is often a sequela of acquired venous sinus obstruction leading to increased pressure within the cer-ebral venous system. It is of paramount importance to look for associated congenital disorders or any causes of cerebral venous sinus obstruction when the falcine sinus is identified on imaging.

Declarations of interest
Nothing to declare.
Disclosures: None

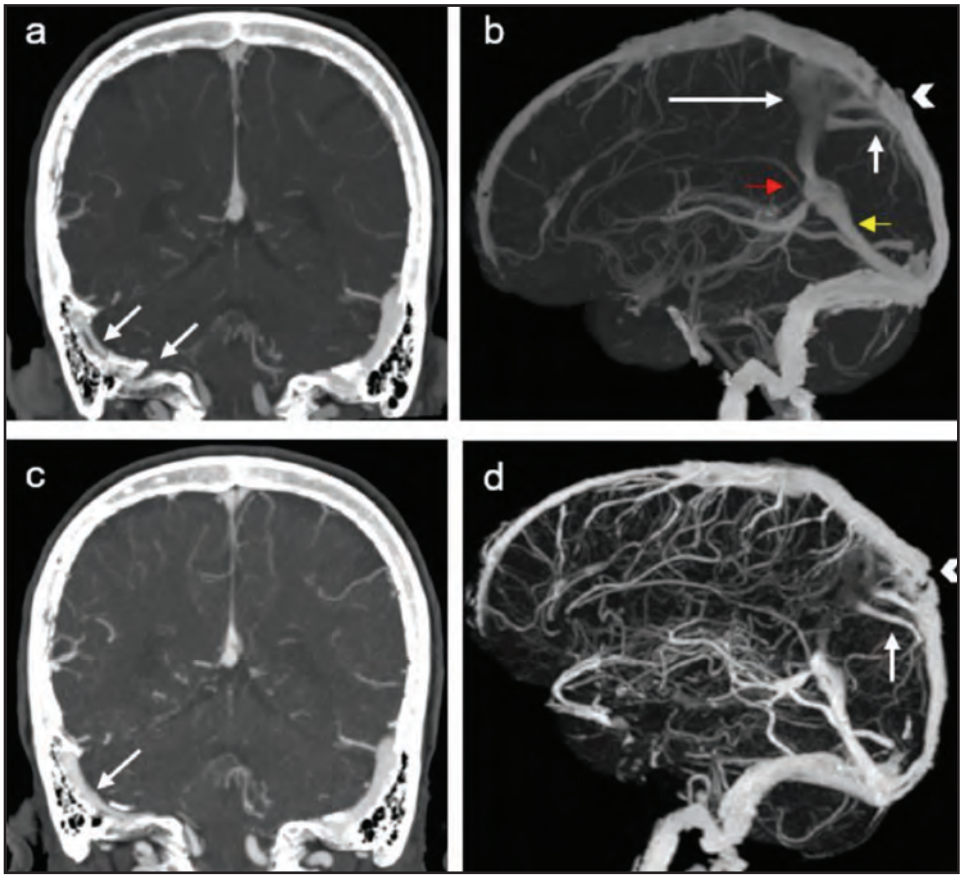

Fig. 1: An 81-year-old woman with known thyroid carcinoma presented with severe headache for 1 month. Coronal CT cerebral venogram image (a) shows filling defects in the right sigmoid sinus and right internal jugular vein (IJV), which is consistent with venous sinus thrombosis (short arrows). Sagittal maximum intensity projection (MIP) CT venogram image (b) shows recanalisation of the falcine sinus (long arrow) connecting the vein of Galen (red arrow) and the straight sinus (yellow arrow) to the superior sagittal sinus. There are two short linear collateral vessels (short arrow) connecting the falcine sinus (long arrow) to the posterior part of the superior sagittal sinus (ar-rowhead). After 6 weeks of anticoagulant therapy, the coronal CT venogram image (c) shows par-tial recanalisation of the right sigmoid sinus and IJV thrombosis. Sagittal MIP CT venogram image (d) shows reduced flow in the falcine sinus. There are persistent short linear collateral vessels (short arrow) connecting the faintly opacified falcine sinus to the posterior part of the superior sagittal si-nus (arrowhead)

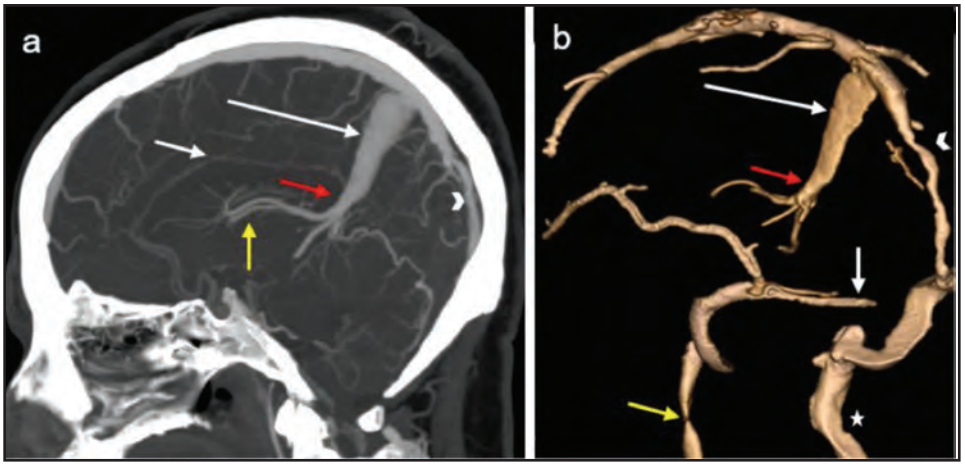

Fig. 2: A 56-year-old woman with a history of Hashimoto's thyroiditis presented with a chronic headache for a few months. Sagittal CT cerebral venogram image (a) reveals a persistent falcine sinus (long arrow) connecting the vein of Galen (red arrow) to the superior sagittal sinus. The paired internal cerebral veins (yellow arrow) fused to form the vein of Galen (red arrow). The inferior sagittal sinus (short white arrow) drains posteriorly into the persistent falcine sinus (long arrow). The posterior third of the superior sagittal sinus is rudimentary (arrowhead). Three-dimensional volume rendering technique (VRT) CT venogram rotated image (b) shows the persistent falcine sinus (long arrow) connecting the vein of Galen (red arrow) to the superior sagittal sinus. There is a rudimentary posterior third of the superior sagittal sinus (arrowhead), and the right transverse sinus is hypoplastic (short white arrow). There is a small calibre right internal jugular vein (IJV) (yellow arrow). As the straight sinus is absent in this case, the venous drainage is preferentially through the persistent falcine sinus (long arrow) and the left transverse and sigmoid sinus into the left IJV (star)

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CASE REPORT

False positivity of fourth generation human immunodeficiency virus rapid diagnostic tests in a malaria patient: a case report

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SUMMARY

Early diagnosis and initiation of treatment is a cornerstone of managing human immunodeficiency virus (HIV) infections and rapid diagnostic tests which provide same-day results are instrumental in bolstering this approach. Fourth-generation (4G) enzyme-linked immunosorbent assays boast near-perfect accuracies; nevertheless, false positives are still possible. We report one such occurrence in a patient with severe *Plasmodium knowlesi* malarial infection. This case report highlights the importance of good history-taking coupled with pre- and post-test counselling when performing HIV screening tests with the 4G HIV rapid diagnostic kits. Clinicians should keep in mind the possibility of false positives and adhere strictly to the WHO standardised testing algorithm to avoid misdiagnosing patients as HIV positive based on a reactive 4G HIV test.

INTRODUCTION

The human immunodeficiency virus (HIV) epidemic continues to be a major public health issue globally, having claimed an estimated 36.3 million lives thus far. Early diagnosis and initiation of treatment remains a cornerstone of managing HIV infections, and rapid diagnostic tests which provide same-day results are instrumental in bolstering this approach.[1] The advent of fourth-generation (4G) enzyme-linked immunosorbent assays has been a huge boon to the establishment of comprehensive HIV testing strategies by the World Health Organization (WHO).[2] These assays test for the p24 antigen in addition to anti-HIV antibodies and boast the ability to identify acute infections earlier and more rapidly than the third-generation assays that only test for antibodies. While 4G assays promise near-perfect accuracies,[3] false-positive 4G HIV test results are nevertheless still possible. Here, we report one such occurrence in a patient with severe *Plasmodium knowlesi* malarial infection.

CASE REPORT

Our patient is a healthy 35-year-old Malay man who works as a hawker by the fringe of a forest. He presented to us with a 4-day history of fever, chills and rigors, headache, abdominal pain, and reduced oral intake. Physical examination revealed that he was febrile (temperature 39.8℃) and slightly hypotensive (111/70mmHg); his other vital signs were otherwise not deranged (heart rate 91 beats/min, SpO_2 98% at room air). Remaining physical findings were likewise unremarkable. Laboratory investigations demonstrated bicytopaenia (haemoglobin 13.1g/dL, platelets 20×10^9/L) with raised creatinine levels (156µmol/L). An urgent peripheral blood film revealed features consistent with malarial infection, and this was confirmed with blood film for malarial parasite identification of *Plasmodium knowlesi* (parasite count 36,320 asexual/0 sexual per µL). Dengue serology was negative.

The patient's condition deteriorated in the emergency department while awaiting laboratory results. He went into septic shock, necessitating inotropic support briefly with a 1-day stay in our intensive care unit for close monitoring. Artesunate and arthemeter/lumefantrine therapy was quickly initiated with good response, and the patient was discharged uneventfully after another 4 days in the general ward.

Due to the initial severity of clinical presentation, inpatient HIV screening was done to assess for HIV co-infection. His 4G HIV test (ARCHITECT HIV Ag/Ab Combo assay; Abbott Laboratories; Wiesbaden, Germany) and particle agglutination test returned weakly positive thrice; however, subsequent HIV polymerase chain reaction (PCR) did not produce any detectable viral load. Further history taking regarding high-risk behaviours were strongly denied by the patient. A second HIV PCR test repeated at three months follow-up after discharge was also negative. The patient was counselled accordingly regarding the false-positive HIV results and subsequently discharged from our care.

DISCUSSION

Fourth-generation (4G) HIV tests differ from third-generation tests in their ability to detect the p24 antigen, on top of anti-HIV antibodies. Detection of the p24 antigen allows for improved diagnostic accuracy, especially in the acute phase

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where antibodies have yet to develop. The assay used in this case study, ARCHITECT HIV Ag/Ab Combo assay, has a reported sensitivity of 100%, specificity 99.77%, positive predictive value 81.25%, and negative predictive value 100%.[3]

The phenomenon of false-positive HIV results has been implicated in several conditions, including African trypanosomiasis, schistosomiasis, systemic lupus erythematosus, and influenza vaccinations; the assays used in these reports were often of the earlier generations.[4-6] Nevertheless, false positives may still occur with 4G HIV tests despite their improved accuracies.[7,8] Such an incidence in malaria specifically has been recorded in the literature previously,[9] though ours is the first case involving *P. knowlesi* to the best of our knowledge.

Malarial infections, along with other parasitic infections, are hypothesised to cause false-positive HIV results via activation of a marked immunological response in the host. The introduction of *P. knowlesi* antigens into our patient triggered his CD5+ B-lymphocytes to produce broad-spectrum antibodies. These non-specific polyclonal antibodies then cross-reacted with the p24 antigens in the ARCHITECT 4G HIV test, producing chemiluminescence which was consequently interpreted by the system as "reactive". Other probable risk factors for such a false-positive result in our patient include his younger age, poor socioeconomic status, and dietary limitations.[7]

There are a number of lessons to be drawn from our reported case of a false-positive HIV 4G test result. It serves as a reminder that 'reactive HIV test' does not necessarily equate to 'HIV positive'. It also underscores the importance of following up initially reactive samples with a confirmatory nucleic acid amplification test as prescribed in WHO's standardised testing algorithm.[2] Had the algorithm not been followed, our patient would have been misdiagnosed as HIV positive.

With regards to the bedside approach, such a possibility of false positives illustrates the significance of pre- and post-test counselling for HIV, especially given the persisting societal stigma associated with this viral infection. Targeted and concise history taking in relation to high-risk behaviours is also crucial as part of the consultation prior to pre-test counselling. In this case, the initial positive rapid test results caused a considerable amount of marital discord between the patient and his newly wed wife. Notwithstanding that, we managed to elicit that the patient had no risk factors, and so we are able to somewhat reassure the patient and his wife of the probable false results during the post-test counselling prior to hospital discharge.

CONCLUSION

We report a false-positive HIV 4G test result in a patient with severe *Plasmodium knowlesi* malarial infection. Clinicians should keep in mind such a possibility when managing a patient who had a reactive test result but lacked apparent risk factors. Good history-taking and strict adherence to the WHO standardised testing algorithm are essential to ensure that such patients are not misdiagnosed with an HIV infection. Pre- and post-test counselling sessions are necessary to ameliorate the patient's (and spousal) anxiety and distress upon learning of their initial results.

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CASE REPORT

Glottic neurofibroma in a background of juvenile onset respiratory papillomatosis and obstructive sleep apnoea: A baffling discovery

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SUMMARY

Laryngeal neurofibromatosis and papillomatosis are relatively uncommon, the former being extremely rare cause for an obstructed paediatric airway. Here, we would like to report a case of synchronous occurrence of laryngeal papilloma with neurofibroma in a child who presented with a life-threatening obstructed upper airway. The management primarily revolved around acute airway management and airway surveillance.

INTRODUCTION

It is uncommon to find both laryngeal neurofibromatosis and papillomatosis to exist synchronously within the airway. Juvenile laryngeal papilloma is known to be closely related to human papillomavirus (HPV) infections. However, laryngeal neurofibroma can either be attributed to a genetic inheritance, i.e., in neurofibroma type 1 and type 2 or as a sporadic occurrence resulting in isolated solitary lesions. To our knowledge, this dual synchronous occurrence, which presented as an airway emergency, has not been reported in literature thus far. Therefore, this case report details the co-existence of both these pathologies in a child with obstructive sleep apnoea who presented with an acute life-threatening respiratory distress.

CASE REPORT

A 7-year-old boy of mixed African-Malay descent, with underlying autism and morbid obesity (weight 134 kg, height 158 cm, Body mass index of 53) presented to the Sarawak General Hospital emergency department with features of impending respiratory collapse. Patient complained of productive cough with dyspnoea, orthopnoea, and progressive reduced effort tolerance for 5 weeks. He also had hoarseness since age 1 accompanied with noisy breathing since age 3, for which the latter was treated as bronchial asthma by a general practitioner, and there were no prior hospitalisations. Patient was drowsy on arrival, with presence of audible wheeze and reduced air entry upon auscultation. There were no abnormal skin lesions, e.g., café au lait spots, no bone deformities, and no obvious masses.

Blood gas analysis showed type II respiratory failure, and chest X-ray showed blunting of bilateral costophrenic angles and cardiomegaly. Bedside echocardiogram revealed dilated right heart with poor contractility. A working diagnosis of acute exacerbation of asthma and congestive heart failure secondary to chronic obstructive sleep apnoea was deduced, and initial treatments were instituted. As a result of failed non-invasive ventilation, he was intubated in the operation theatre in the presence of the otolaryngology team in the advent of anticipated difficult airway. He was preoxygenated with bilevel positive airway pressure and administered with total intravenous anaesthesia. Patient was placed in a ramped position and successfully intubated with cuffed endotracheal tube size of 6.5 mm assisted by C-MAC videolaryngoscope. Direct laryngoscopy and rigid tracheoscopy were performed by the otolaryngologist displayed presence of papilloma-like lesions at bilateral false cord, arytenoids, and laryngeal surface of the epiglottis including the anterior and posterior commissures (Figure 1a, 1b). There was no infraglottic involvement, and the glottic inlet was stented by the endotracheal tube. No tracheobronchomalacia seen. Debulking of the mass was done with cold instrument with multiple specimens sent for histopathological examination.

He underwent adenotonsillectomy at day 7 post-op, and two days later, he was extubated to bilevel positive airway pressure and continuous positive airway pressure subsequently. Flexible nasopharyngeal scope evaluation during extubation showed bilateral mobile vocal cord movement. Throughout this period, he developed lower limb deep vein thrombosis, nosocomial infection, and pressure sore as a result of prolonged immobilisation and underlying co-morbidities.

Histopathological examination of the specimens from the supraglottis and larynx revealed two different pathologies: squamous papilloma involving both false cords, arythenoids and laryngeal surface of epiglottis and neurofibroma at the anterior commissure. The squamous papillomatous lesions displayed proliferative well-differentiated squamous epithelium overlying the fibrovascular cores. These fibrovascular cores were infiltrated with mixed inflammatory cells and many ectatic blood vessels. The presence of intraepithelial neutrophils, with some areas showing reactive atypia, was observed. These squamous epithelial cells were negative for p16 (Figure 2a). The neurofibroma involving the

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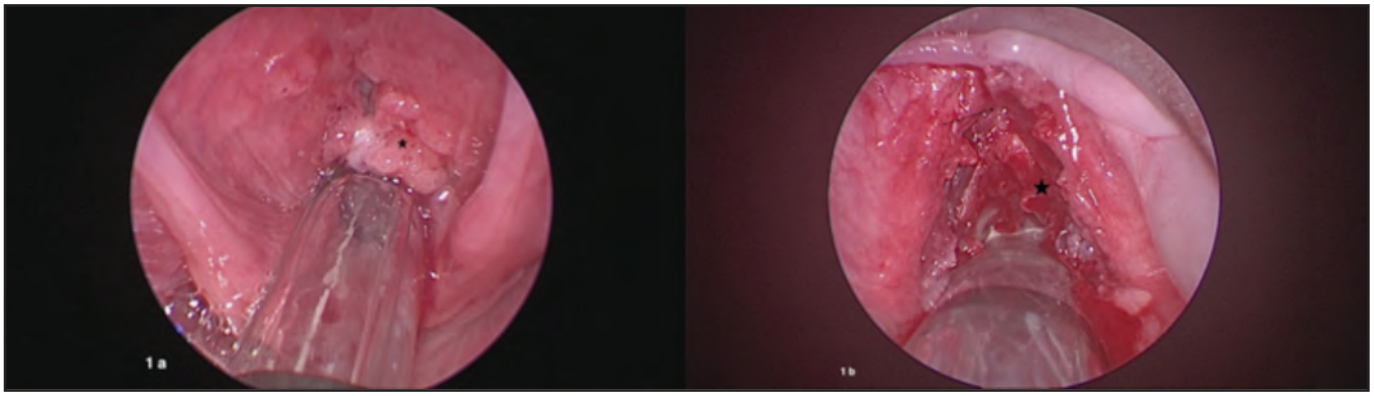

Fig. 1: (a) Intra-operative direct laryngoscopy 0-degree endoscopic view: Papillomatous lesions at bilateral false cords; asterisk denotes left false cord and arytenoids obstructing glottic inlet
(b) Post-debulking of the lesion showing the anterior commissure (marked by thin arrow) and right vocal fold (marked by black star)

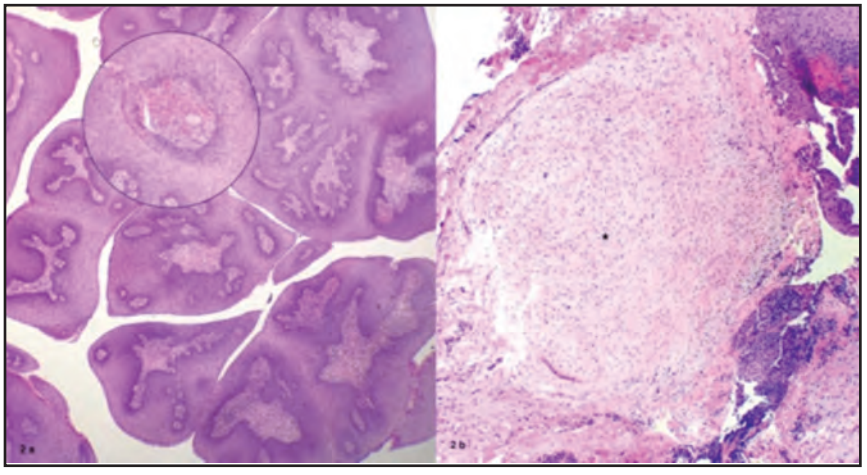

Fig. 2: (a) Haematoxylin and Eosin stain: Papillomatous lesions displaying proliferative well-differentiated squamous epithelium with arborising fibrovascular cores. Fibrovascular cores are infiltrated by mixed inflammatory cells with ectatic blood vessels; magnified lens
Original magnification x100
(b) Haematoxylin and Eosin stain: Neurofibroma with features of hyperplastic overlying squamous epithelium. Hypocellular proliferation of spindle cells with wavy bland nuclei. Cells are arranged in lose fascicles intermixed with bundles of collagen, denoted by black asterisk. Cells are positive for S100 stain
Original magnification x100

anterior commissure showed the presence of a poorly circumscribed lesion composed of hypocellular proliferation of spindle cells with wavy band nuclei. The cells were arranged in loose fascicles intermixed with bundles of collagen, which stained positive for S100 (Figure 2b).

He was discharged home with continuous positive airway pressure at eight weeks post-op, with only hoarseness evident. There was no stridor throughout the post-operative period. The final diagnosis upon discharge was severe obstructive sleep apnoea contributed by laryngeal papilloma and laryngeal neurofibroma causing severe respiratory distress. He is currently undergoing serial airway assessment to monitor disease progression and outcome.

DISCUSSION

Laryngeal papillomatosis (LP) was first described in children by Sir Morel Mackenzie in 1800, and later, Chaveliar Jackson introduced the term *'juvenile laryngeal papillomatosis'* (JLP) in 1940.[1] This benign laryngeal disease poses a management challenge owing to its tendency to recur and its unpredictable course. LP can be divided into two subtypes: juvenile and adult-onset LP, with the former displaying a more aggressive behaviour. The incidence of laryngeal papillomatosis is 4.3 per 100,000 children and 1.8 per 100,000 adults.[2] Juvenile LP shares a commonality with other respiratory disorders, resulting in frequent misdiagnoses as asthma or laryngotracheobronchitis in the emergency room.[3] Its presentation at a young age makes formal lung function test not feasible, thereby contributing towards challenges in making a correct diagnosis. The mean age of diagnosis is

2–9.[4] years, whereby children presenting later may have worsening dysphonia, stridor followed by respiratory distress4, as seen in our patient. Role of early laryngoscopic examination by the otolaryngologist is paramount in reaching a diagnosis, owing to the characteristic features of these papillomas, thereby preventing treatment delay. Histologically, papillomas are warty lesions with finger-like projection of stratified squamous epithelium with abnormal keratinisation and basal hyperplasia.

Highly sensitive real-time polymerase chain reaction is used to detect the presence of HPV. False negative results may occur when there is a low viral load. P16 (IKN4A) antibody expression as a biomarker is routinely used in combination with PCR to detect HPV. However, Huebbers et al reported a case of recurrent laryngeal papilloma linked to HPV, with no positivity to p16,[5] similar to this case.

Therefore, immunohistochemical detection of p16 alone is insufficient to prove the presence of HPV. As a result of poor laboratory resources and accessibilities in developing countries, the use of single methods to detect HPV, as done in our centre, may contribute to the false negative status.

JLP is commonly linked to HPV 6 and 11 subtypes, via intrapartum transmission. Despite this, its prevalence in pregnant mothers is only about 2%. Therefore, HPV infection may not be wholly responsible, and recent studies have shown immune response and some genetic susceptibility linked to the development of JLP.[6] Gelder et al found significant association with HLA DRB1x0102/0301 and DQB1*0201/0202 and increased inclination to JLP.[7] This may support the HPV-negative squamous papilloma presented in the biopsies from our patient.

Treatment of recurrent laryngeal papilloma is challenging and entails surgical and adjuvant therapies. Surgery aims to remove papillomas while preserving normal laryngeal tissue. It consists of repeated endoscopic microlaryngeal debulking surgeries with cold instruments, powered instruments such as microdebriders, lasers, or coblators. depending on the availability of resources and surgeon's preference.

Adjuvant therapies have been tried such as alpha interferon, bevacizumab, cidofovir, immunotherapy, and quadrivalent HPV vaccine to further improve the treatment outcome. Quadrivalent HPV vaccinations have shown to decrease the number of surgeries and increase the duration between surgeries.[8]

Laryngeal neurofibromas (LN) are benign tumours arising from Schwann cells and perineural cells and are extremely rare cause of paediatric upper airway obstruction. To the best of our knowledge, LN occurrence in the background of laryngeal papilloma, as reported in this index patient, has not been reported to date.[8]

Neurofibromas are classified as neurofibromatosis-1 (NF-1), neurofibromatosis-2 (NF-2), and spontaneous solitary lesions. The estimated prevalence of NF-1 is cited as 1 in 3000 patients and is transmitted in an autosomal dominant fashion; however, 30–50% patients are associated with spontaneous mutations with no family history.[9] They present in childhood with café-au-lait spots, learning disabilities, endocrine abnormalities, Lisch nodules, skeletal defects, axillary or groin freckling, or multiple cutaneous neurofibromas. NF-2 occurrence is also rare and typically presents in third decade of life.

There are only 62 paediatric laryngeal neurofibromas that have been reported worldwide.[6] Owing to their slow growth, patients may remain symptom-free for years or present at birth. The mean age of presentation is 4.1 years (0.8–12 years) with stridor being most common feature (44%) followed by hoarseness (12%). Most common site involvement in the larynx is the aryepiglottic folds and arytenoids as they are rich in terminal nerve plexuses. Features such as mimic papillomas until surgery reveal unanticipated histology. There is limited occurrence of neurofibroma in the vocal cord, which was reported in adults and not in children.[6] Here in our case, the anterior commissure of the glottis revealed the presence of a neurofibroma, thus postulating the possibility of an isolated spontaneous solitary neurofibroma, which is extremely rare. Tumour is believed to arise from the superior laryngeal nerve and/or from anastomosis with the recurrent laryngeal nerve. Histological features include slender spindle cells in collagenous stroma adjacent nerve fibres and axons and stain for S100 due to neurogenic origin.[6]

Treatment of LN depends on the site, size, and severity of presenting symptoms. Due to its infiltrative nature and poor margin control, the likelihood of recurrence is high as with papillomas. Therefore, mainstay of treatment includes surgical procedures that preserve laryngeal function while providing an adequate airway. Endoscopic approach either using cold-steel instruments or laser is used to address small, localised lesion. Large infiltrative lesions may require an open approach for a wider exposure, sometimes requiring tracheostomy.[6]

CONCLUSION

The irony of similar clinical presentation and behaviour of both JLP and LN as seen in this case were indeed challenging. Bearing in mind that both lesions tend to recur and may contribute to an obstructed airway, close monitoring with airway surveillance and follow-up is indeed at its utmost precedence.

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CASE REPORT

Scrotal cystocele versus incarcerated inguinal hernia: Perils of misdiagnosis

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SUMMARY

Scrotal cystocele or sliding bladder hernia occurs when part of the bladder herniates into an inguinal hernia, forming part of its wall. While some patients may present with urinary tract symptoms that can raise suspicion of such diagnosis, others may be completely asymptomatic, leading to an initial misdiagnosis, which if not picked up, can lead to avoidable complications. We report a case of a 49-year-old man, who presented with clinical signs of an incarcerated right inguinal hernia and was put up for open right hernioplasty. Intra-operatively, a diagnosis of sliding bladder hernia was made through the discovery of the Foley's catheter balloon within the hernial sac. An on-table urology referral was made, and through cystoscopy and cystography, the diagnosis of sliding bladder hernia was confirmed. Using fluoroscopy guidance, the Foley's catheter balloon was reinserted into the herniated part of the bladder and inflated, and using it as a guidance for dissection, the excess peritoneum and preperitoneal fat is dissected away from the bladder, allowing reduction of the bladder into the peritoneal cavity. This is then followed by a herniorraphy to repair the posterior wall defect leading to the sliding hernia. In our case, a mesh was not used as a breach of asepsis was a concern, owing to the manoeuvers and manipulation performed in order for cystoscopy and cystogram to be carried out.

INTRODUCTION

Sliding inguinal hernia occurs when part of the intra- or retroperitoneal organ forms part of the hernial sac wall. When the urinary bladder is involved, it is termed a sliding bladder hernia or scrotal cystocele.[1] While rare, knowledge of such hernias needs to be kept at the back of a surgeon's mind, as most cases are only diagnosed intra-operatively.[2] If proper precautions are not taken, injury to the urinary bladder may occur, which not only will increase the complexity of the surgery, but also can lead to post-op complications that can lead to increased morbidity among patients. Up to 16% of sliding bladder hernias are diagnosed post-operatively due to complications following the operation. The surgical approach of such hernias are similar to most other inguinal hernias, which is to explore the inguinal canal, identify and reduce the sac content (bladder), and perform a hernia repair. We report a case of irreducible sliding bladder hernia, with the absence of any urinary tract symptoms, thus mimicking an incarcerated indirect inguinal hernia. Intra-operative diagnostic and surgical techniques used to clinch and facilitate the management of this patient will be further discussed.

CASE REPORT

A 49-year-old obese man presented with a sudden pain in his right inguinal swelling associated with right scrotal enlargement.

On further history, patient claims that he has had this inguinal swelling since he was a child, which was not reducible, but did not seek any medical attention until 6 years ago, when it started becoming symptomatic with on and off dragging pain. He was initially planned for surgery, but it was delayed due to the ongoing CoVID-19 pandemic.

Otherwise, he denies any obstructive symptoms, still able to pass flatus and passing stool as usual. He denies any frequency of urination, dysuria, strangury, nocturia, pis en deux, or hesitancy. He does not have any history of heavy lfiting, chronic cough, and does not have any previous abdominal surgery done.

Examination of this patient showed a right inguinal hernia, with extension into the scrotum. Cough impulse was negative, and the swelling is irreducible and non-tender to touch. There is otherwise no overlying skin changes, and both testes are palpable within the scrotum. Abdominal examination was otherwise soft and non-tender. Initial blood works were unremarkable, and blood gases showed no acidosis with a normal lactate level of 0.7. Chest X-ray showed no air under diaphragm, and abdominal X-ray showed no dilated bowels.

An initial diagnosis of incarcerated right inguinal hernia was given. The patient was admitted, started on analgesia and put up for right inguinal hernioplasty under emergency setting.

Intraoperatively, upon entering the inguinal canal, a hernia sac was noted protruding out of the Hesselbach triangle. During the assessment of the sac content, it was noted that the Foley's catheter balloon was palpable within the sac, thus an impression of a sliding hernia containing part of the bladder was made. An attempt to reduce the hernia content was made, but unsuccessful as part of the bladder herniated

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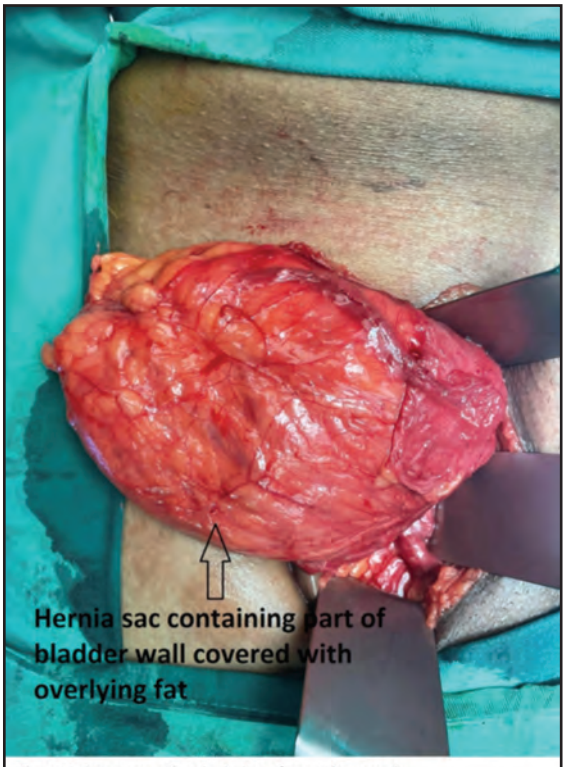

Figure 1: Intra-operative depiction of scrotal cystocele

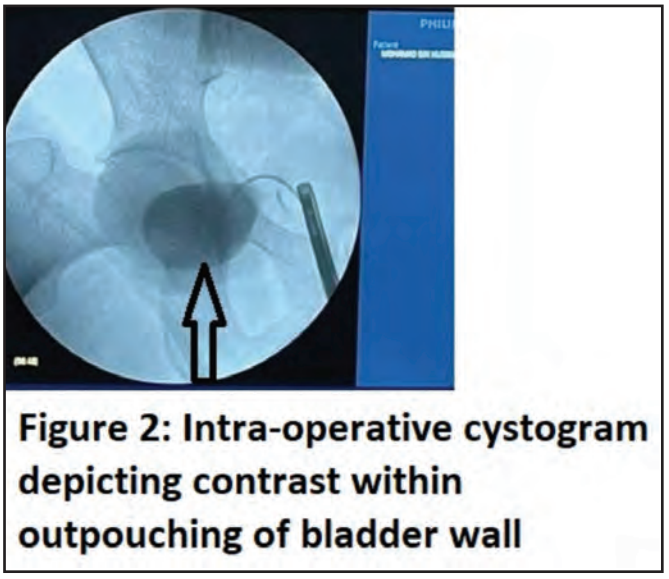
Figure 2: Intra-operative cystogram depicting contrast within outpouching of bladder wall

together with excessive peritoneum with its preperitoneal fat. A urological consult was made on the table and was attended by the urologist oncall. A rigid cystoscopy was done, showing a normal urethra with non-occlusive prostate. The right bladder wall was seen herniating into the hernia sac. This was followed by a cystogram demonstrating the herniation of the bladder wall. Bladder capacity was approximately 200ml, whereas hernia sac is approximately 100ml, and both ureterovesical orifices are seen on cystoscopy. The urological team proceeded with a right retrograde pyelogram, and the pyelogram showed no hydronephrosis or hydroureter. However, the distal ureter appears in close contact with the hernia sac, hence a right ureteric stent was done using a Boston stent size 24Fr/6cm. A urinary balloon catheter was then placed into the hernia sac via guidewire guidance and inflated using 30cc water as a guidance during dissection. Methylene blue solution was then used to inflate the bladder, to confirm no leak or perforation was seen.

The hernia sac was then identified, and the overlying fat was dissected and released away from the bladder wall. The bladder was reduced into the pelvis and excessive peritoneum excised and sutured. This is followed by a herniorraphy with Prolene 2/0 using Bassini's repair.

On post-operative day 1, hematuria was seen within the urinary bag, which cleared up on post-op day 3. Patient's vital signs remained stable and his pain remained well controlled with adequate analgesia, and he was subsequently discharged well on post-operative day-7.

He was later seen in our outpatient department 2 months post-operatively, with a well healed wound and no recurrence of hernia evident. He was subsequently discharged from our care.

DISCUSSION

Sliding inguinal hernia is defined as an inguinal hernia in which part of its wall is formed by an intraperitoneal or retroperitoneal organ Scrotal cystocele, or sliding bladder hernia, occurs when the urinary bladder forms part of the hernial sac wall.[1] It is a rare occurrence, and a retrospective study in 2006 involving 1950 patients with inguinal hernias revealed that only 0.36% had sliding bladder hernia.[3]

While most cases are asymptomatic and are diagnosed intra-operatively, some cases present with urinary tract symptoms.[2] In cases in which a large portion of the bladder is herniated into the scrotum, patients may describe a two-stage urination, the first of which is spontaneous and the second following manual compression of the scrotum.[4] Some may also describe a reduced hernia size following urination.[4] And some cases, especially large sliding bladder hernia can lead to complications including obstructive uropathy, vesicoureteric reflux, hemorrhage, incarceration, or even necrosis of the bladder.[2] While the association between sliding bladder hernia and bladder cancer is not properly established, a review of 190 cases in 2004 demonstrated that approximately 11.2% of such hernias were associated with urological malignancies.[5]

Most cases of sliding bladder hernia are found either on radiography or intra-operatively.[5] Only less than 7% of sliding bladder hernias are diagnosed pre-operatively, and 16% are diagnosed post-operatively following complications,

whereas the rest are diagnosed intra-operatively.[4] Intra-operative discovery and diagnosis may follow incidental findings during hernia repair, or following injury to the bladder.[5] In fact, literatures have reported up to 12% risk of injury to the bladder in hernia repair of this variety.[4] In our case, the identification of a Foley's catheter balloon within the hernia sac intra-operatively led to the suspicion of a scrotal cystocele. In cases where sliding bladder hernia is suspected before operation, cystography remains the gold standard, which can show an indentation of the bladder wall,[6] such findings often mimic and can be confused as a bladder diverticulum.[4] This is utilized in the intra-operative management of our patient, which along with cystoscopy, helped confirm the diagnosis of scrotal cystocele. Ultrasonography may also be utilized to differentiate a bladder hernia from other possible differential diagnosis, including hydrocele, epididymal cyst, scrotal abscess, and spermatocele.[7] CT scan can be useful in allowing a rapid and accurate diagnosis and evaluation of ureteric herniation, which could be imperative in guiding the operative approach.[8] The authors, however, do not recommend the routine use of these imaging modalities for all cases of inguinal hernia. This is due to the fact as mentioned, scrotal cystocele is a rare occurrence (0.36% of all inguinal hernias), and the cost benefit analysis will put this out of favour. However, we would recommend further imaging if patient presents with symptoms that can suggest the presence of this diagnosis i.e., two stage urination, reduction of hernia following urination or recurrent urinary tract infection.

As expected, pre-operative diagnosis of this hernia allow modifications to the surgical techniques and allow precautionary steps to be taken in order to reduce the risk of such injuries.[9] In our case, no pre-operative imaging asides from abdominal X-ray was done, as we suspected an incarcerated inguinal hernia with bowel or omental content, and further imaging was not done in hopes of not delaying the operative management of this patient.

To date, there are no literatures that are available that discuss regarding intra-operative clinical features that could suggest or point towards the diagnosis of sliding bladder hernia. In our case, the presence of the Foley's catheter balloon within the herniated sac led to our suspicion and eventual diagnosis of a scrotal cystocele. However, other findings we find that may point towards this uncommon diagnosis is the presence of thick adipose tissue within the hernia sac. While this can be confused with the omentum, from what we observed intraoperatively, this fatty layer appears less vascular, and is not easily reducible back into the peritoneal cavity.

The standard management in sliding bladder hernia is surgical repair, through exploration of the inguinal canal, identification of the bladder, and reducing it into the pelvic cavity with or without resection of the herniated bladder wall. While resection of the involved bladder wall used to be a norm in past practice in large hernias cases, current literatures favour against such practices as it is deemed "unnecessary" and will only impose extra risk and potential complications to such patients.[4] However, in cases where there is a true herniation of bladder diverticulum, bladder wall necrosis or if the hernia occurs with a combination of a suspected malignancy, bladder resection is recommended.[2] Hernia repair is then performed, and the technique used is largely up to the surgeon's preference and choice.[9] In the patient discussed in this case report, bladder resection was not carried out, as the herniated content is not a true diverticulum, but is rather a part of the bladder wall.. A choice of herniorraphy was used instead of hernioplasty in our patient, as due to the manoeuvres and exposures required for performing on table cystoscopy and cystography, there is a concern of breach of asepsis, thus the worry of infected mesh if hernioplasty was performed.

In our case study, a rigid cystoscopy and cystogram were performed to assess the proximity of the right ureteric orifice to the herniated bladder and to look for the presence of a bladder diverticulum, which is an indication for diverticulectomy.[2,4] A similar approach was reported in a case report in 2017, whereby an on-table cystoscopy was performed on a patient with a sliding hernia containing a bladder diverticulum in order to assess the location of the diverticular orifice.[10] The authors would, however, like to point out that the usage of intra-operative cystoscopy and cystogram need not be performed routinely in all cases of sliding bladder hernia, but if difficulty arises, as in our case, it is useful in confirming the diagnosis and differentiating it from a bladder diverticulum.

CONCLUSION

While rare, the occurrence of sliding bladder hernia, also known as a scrotal cystocele, should always be kept in the back of a surgeon's mind, as it can be oftentimes be missed. If this diagnosis is missed intra operatively, complications, particularly inadvertent bladder injury can occur, resulting in increased morbidity among patients. While most patients are asymptomatic, certain features including two-stage voiding and a reduction in hernia size following voiding could suggest the possibility of a sliding bladder hernia. If this diagnosis is suspected pre-operatively, certain investigations including an ultrasound, cystogram, or a CT scan can guide the intra-operative approach of such patients. Intra-operatively, the presence of a thick fat layer within the hernial sac that is not easily reducible into the peritoneal cavity should raise the suspicion of this diagnosis. The principle of the intraoperative management of sliding bladder hernia remains the reduction of the herniated bladder, and repair of the hernia, with or without a mesh. Resection of the bladder wall is only reserved in certain situations, where there is a true bladder wall diverticulum, or in cases in which complications such as incarceration and necrosis have occurred.

**Patient has consented for the use of his case and photographs for the purpose of this publication.

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CASE REPORT

Primary cold agglutinin disease: A case report

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SUMMARY

Cold agglutinins are circulating autoantibodies directed against the i-antigen on red blood cells, causing complement-mediated extravascular haemolysis at a thermal amplitude of 3-4°C in vitro. Clinically, however, these autoantibodies may be active and cause haemolysis at higher temperatures such as in acral areas of the body. We report a 69-year-old Chinese man who presented to the emergency department with non-specific chest discomfort and acrocyanosis of his toes which was resolved with warming blankets. Interestingly, his routine blood investigation samples within the point of care were repeatedly rejected due to sample haemolysis. The constellation of clinical signs and laboratory findings prompted us to suspect the presence of cold agglutinins. He was ultimately diagnosed to have a primary cold agglutinin disease based on supporting biochemical, molecular, and histopathological evidence. As he did not have symptomatic anaemia nor any disabling cold-induced symptoms, no targeted B cell therapy was commenced. He is currently being managed supportively and is under our close follow-up. He remains well and asymptomatic to this date.

INTRODUCTION

Primary cold agglutinin disease is a rare cause of haemolytic anaemia. It accounts for 15-20% of autoimmune haemolytic anaemias (AIHAs) and refers to the presence of cold agglutinins, attributed to an indolent B cell lymphoproliferative disorder which is distinct from a classical non-Hodgkin's B cell lymphoma. Specifically, cold agglutinins are antibodies that recognise antigens on red blood cells at temperatures below normal core body temperature, leading to agglutination of red blood cells resulting in haemolysis via the complement-mediated pathway. Patients with cold agglutinin disease typically present with haemolysis and cold-induced symptoms such as the Raynaud phenomenon, acrocyanosis, and livedo reticularis. A thorough workup to rule out secondary causes of cold agglutinins is necessary before diagnosing a patient with primary cold agglutinin disease.

CASE REPORT

A 69-year-old man, chronic smoker with hypertension, presented with sudden onset of central chest pain for a day, pressing in nature associated with diaphoresis and shortness of breath. He was admitted and treated for unstable angina. During his admission to our cardiology ward, we noticed an incidental finding of a painless bluish discolouration on his toes. On further history, the patient mentioned that the bluish discolouration started on the day of admission, and he had never noticed any such changes before this. Apart from that he also complained of dark urine for two days and a non-productive mild cough for two days. He denied any symptoms to suggest a connective tissue disease, nor any constitutional symptoms such as fever, loss of weight, or night sweats. On examination, he was an average built Chinese man, with no palpable cervical, axillary, or inguinal lymph nodes. His cardiovascular examination was unremarkable, and he had no hepatosplenomegaly. His peripheral pulses were all present. He had no stigmata of peripheral vascular disease; however, he had persistent acrocyanosis, especially over his bilateral toes. His blood investigations agglutinated immediately after phlebotomy, thus making it difficult for the laboratory to process. The constellation of these symptoms and signs led to the suspicion of cold agglutinin disease.

His blood parameters on presentation are shown in Table I. His peripheral blood smear showed marked agglutination of red blood cells, with polycythaemia. Cold agglutinin titre of 1:1024 at 4°C confirmed our suspicion of cold agglutinin disease. Infectious screening for viral hepatitis, HIV, Epstein Barr virus (EBV), and cytomegalovirus (CMV) was negative. His serum mycoplasma serology was positive with a titre of 1:320. Autoimmune workup was negative. Serum protein electrophoresis showed IgM Kappa paraproteinemia in the gamma region. His bone marrow biopsy showed 15 small to medium sizes of paratrabecular lymphoid follicles, consisting of a mixture of B (C79a/CD20 positive cells) and T cells (CD3 and CD5 positive cells) that are negative to CD10 and CD38. There were no light chain restrictions noted in the trephine biopsy sample.

However, further Immunophenotyping of the marrow aspirate showed a mature B lymphoid population with increased kappa chain expression.

Details of the investigations are shown in Table II.

DISCUSSION

Cold agglutinins are autoantibodies that are usually of the IgM type with kappa light chain restriction, while IgG and IgA lambda light chain phenotypes are rarer occurrences. A population-based retrospective study conducted in 2006 in 86 patients with cold agglutinin disease in Norway revealed that monoclonal IgM was detected in 90%; IgG and IgA in 3.5% each; with kappa light chains in 94%.[1] The binding of multiple RBCs by the pentameric IgM molecule is the basis for agglutination and haemolysis by these antibodies. Even a small amount of antibodies, perhaps as few as 25 per RBC, can produce obvious agglutination.[2]

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Table I: Initial blood investigations

	19 Sept 2021	20 Sept 2021	22 Sep 2021	4th Oct 2021
White blood cell ($\times 10^3$)	8.9	9.0	5.8	5.5
Haemoglobin (g/dl)	18.6	20.2	18.3	16.5
Mean cell volume (fl)	96	96.4	96.3	97
Mean cell Hgb concentration (g/dl)	35	36.8	36.9	38.7
Reticulocytes ($\times 10^3$/ul)	147	134	128	
Platelets ($\times 10^3$)	222	186	197	246
Lactate dehydrogenase(u/l)	-	571	621	
Total bilirubin (umol/l)	73	90	59.7	25.2
Direct bilirubin(umol/l)	14.3	20	17.2	
Indirect bilirubin(umol/l)	59	70	43	
Direct antiglobulin test				
i)Anticomplement	i) 2+			
ii)IgG	ii) Negative			
Mycoplasma antibody titre	1:320			Equivocal

Table II: Details for further tests

Date	Test	Results
22nd September 2021	Cold Agglutinin titre	@ 37°C : 1:2 @ 20°C : 1:8 @ 4°C: 1:1024
22nd September 2021	Serum electrophoresis	Total protein (serum): 63.81g/L Paraprotein (serum): 2.68g/L SPE shows IgM Kappa paraproteinaemia at the gamma region.
22nd September 2021	Urine electrophoresis	Total protein (urine) 0.04g/L Paraprotein (urine) Absent
22nd September 2021	Bone marrow immunophenotype	17.1% lymphoid population gated at CD45 positive andlow side scattered region, with the presence of 10.0% T cells and 4.3% B cells. The B-cells are positive for CD19, CD20, CD200, CD23 (heterogenous), CD79b and are negative for CD5, CD10, CD38, CD43, CD3. Kappa:Lambda ratio is 4.1:1 (increased kappa light chain expression). **Conclusion** Presence of 4.3% mature B-lymphoid population with increased kappa light chain expression.
	Workup for Polycythaemia vera	JAK2 Mutation not detected Mutation of Calreticulin gene(Exon9) is not detected.
24th Feb 2022	CT thorax/abdomen/pelvis.	No evidence of solid organ malignancy

There are primary and secondary causes of cold agglutinins. Secondary causes of cold agglutinins are due to viral/bacterial infections, autoimmune disorders, and overt lymphoid malignancies. This entity is known as secondary cold agglutinin syndrome. For the purposes of this report, only primary CAD will be discussed in more detail.

In the past, primary CAD was once believed to be due to a classical B cell lymphoma. However in a study by Randen et al.,[3] done between 1995 and 2012, they postulated that by restudying the bone marrow of 54 of patients diagnosed to have cold agglutinin disease, there is reason to believe that there are unique pathological and genetic features that distinguish the disease from the classical well-characterised B-cell lymphoma type such as marginal zone lymphomas and lymphoplasmacytic lymphomas.

The bone marrow findings in our patient are consistent with a primary cold agglutinin disease as the bone marrow aspirate, and trephine biopsy did not reveal any classical features of a B cell lymphoma.

Primary CAD usually presents in the seventh decade of life and predominantly affects women. The median age of onset is 66-72 years old, with a male to female ratio of 0.55.[4] It has a prevalence of 5-20 cases per million and an incidence of 0.5-1.9 cases per million per year, showing considerable variation with climate. CAD accounts for 15-30% of AIHAs.[5] Delays in diagnosis are common, owing to the rarity of the disease and insufficient recognition. The most common presenting symptoms are cold-induced circulatory symptoms such as acrocyanosis, Raynaud's phenomenon, distal ulcers, and livedo reticularis, occurring in 90% of patients in cold countries. Haemolysis is also common, its severity ranging

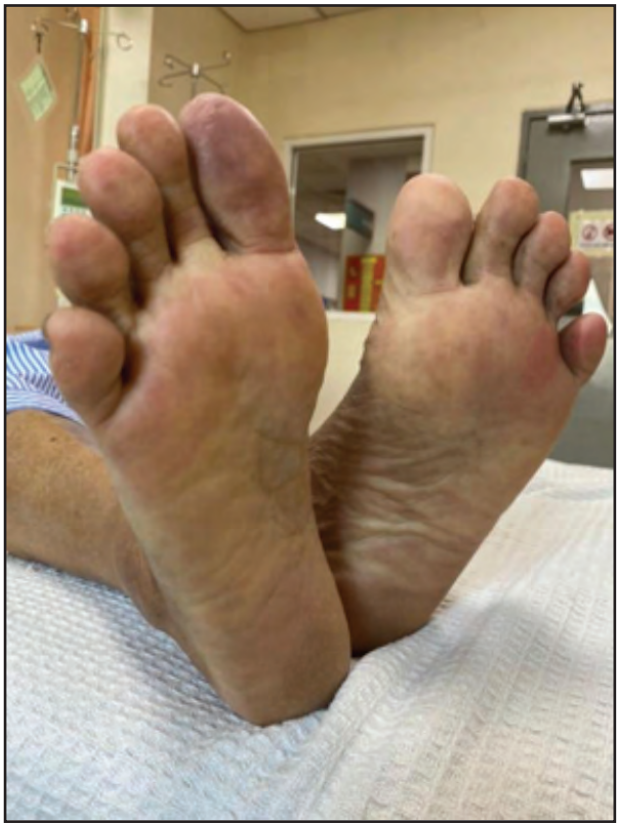

Fig. 1: Acrocyanosis of patient's toes

from compensated haemolysis without anaemia to severe haemolytic anaemia requiring transfusion. Mean haemoglobin is 9.3g/dL; however, there are patients who present with normal haemoglobin, indicating compensated haemolysis.[5]

In contrast with many other case reports on Cold agglutinin disease, our patient presented with macrocytic hyperchromic red blood cells, and polycythaemia. RBC agglutination in cold agglutinin disease can spuriously cause macrocytosis; however, polycythaemia is a rare finding in cold agglutinin disease. From our literature search, there is no reported case of Cold agglutinin disease presenting with polycythaemia. In our patient, we postulate that he has underlying chronic secondary polycythaemia due to his chronic smoking habit.

It is important to note that not all patients require definitive chemotherapy with B cell-reducing agents. Many patients are advised for lifestyle modifications like avoiding cold climates for an example. Chemotherapy is indicated only if the patient has disabling symptomatic anaemia or disabling cold-induced symptoms. The rationale of B cell-reducing agents such as Rituximab derives from the fact that the primary cause of CAD is a B cell lymphoproliferative disorder. There are also second-line treatment options such as the complement C1 inhibitor, sutimlimab. Of particular relevance for general physicians is to note that corticosteroids should not be used, as it only achieves remission in <20% of patients, and in responders, an unacceptably high maintenance dose is required to maintain remission.[6]

This patient is currently being treated conservatively as he does not have disabling anaemia or disabling cold-induced symptoms and is followed up as an outpatient.

CONCLUSION

To the best of our knowledge in Malaysia, there has only been one case report on primary cold agglutinin disease published in 1999. The authors from Universiti Kebangsaan Malaysia postulated that their patient had a low-grade non-Hodgkin's lymphoma. However, they also acknowledged that the patient did not fulfil the classical diagnosis of the more well-defined lymphomas.[7] To date there has also not been any population-based studies in Malaysia published. The majority of the data quoted in this report are based on population-based retrospective reviews of patients in Scandinavia. This is perhaps due to the fact that Malaysia has a tropical climate, and therefore the cold agglutinin disease may go unrecognised, especially in patients who are not exposed to cold environments.

However, it is a disease that should be recognised owing to the potential for transformation to an aggressive lymphoma and also the possibility of disabling symptoms such as anaemia and cold-induced symptoms.

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Disseminated *Mycobacterium avium* complex infection diagnosed from bone marrow biopsy and culture in a patient with human immunodeficiency virus – A case report

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SUMMARY

***Mycobacterium avium* complex (MAC) is one of the common non-tuberculous mycobacterium (NTM) organisms that typically affects patients with severe acquired-immunodeficiency syndrome with CD4 count of less than 50 cells/mm³ as an opportunistic infection. Here, we present a case of disseminated MAC diagnosed via bone marrow biopsy and culture in a severely immunocompromised patient with human immunodeficiency virus. An 18-year-old male, newly diagnosed human immunodeficiency virus who was poorly compliant with highly active antiretroviral therapy, presented with lethargy, prolonged fever, chronic diarrhoea, and significant weight loss. Biochemically, he had persistent spiking fever and bicytopenia and therefore a bone marrow trephine biopsy was obtained. Report of the bone marrow biopsy revealed granulomatous inflammation, Ziehl-Neelson stain was positive for acid-fast bacilli. Bone marrow aspirate culture detected MAC, but the sensitivity test was not available until few weeks later. He was empirically treated for disseminated NTM with Azithromycin, Ciprofloxacin, and Ethambutol while awaiting sensitivity report from the marrow blood culture. Unfortunately, the patient continued to deteriorate despite HAART and NTM treatment. Eventually, he succumbed to the disease after 3 weeks of treatment.**

INTRODUCTION

Mycobacterium avium complex (MAC) infection is an opportunistic infection commonly found in patients who are in an immunocompromised state. It can be caused by either *Mycobacterium avium* or *Mycobacterium intracellulare*. The advent of effective antiretroviral treatment (ART) in the modern era has resulted in a marked decline in MAC infection in human immunodeficiency virus (HIV) patients. In the United States, a large-scale observational retrospective cohort study from 1992 to 2015 reported a significant reduction in incidence from 65.3/1000 in 1992, which was prior to the beginning of highly active antiretroviral therapy (HAART) era in 1996, to 2.0/1000 in 2015.[1] However, the disease is prevalent among patients who presented late with advanced acquired-immunodeficiency syndrome (AIDS) disease and in those patients who were not on HAART. Till date, there have been no reported cases of MAC in bone marrow in Malaysia. Here, we report a case study of disseminated MAC (dMAC) infection in a HIV patient diagnosed by bone marrow biopsy and trephine.

CASE PRESENTATION

An 18-year-old male student was diagnosed with HIV in August 2021 through sexual transmission. He was warded from July 2021 to September 2021 for a splenic microabscess, which resolved after 31 days of intravenous (IV) Ampicillin-Sulbactam 3 g thrice a day. At that time, his CD4 count was 2 cells/mm³ and a CD8 count of 183 cells/mm³; serial blood cultures yielded no organisms. He was initiated with ART, which includes oral Emtricitabine-Tenofovir once daily and Efavirenz 600 mg once daily. Trimethoprim-sulfamethoxazole 2 tablets, once a day was prescribed for prophylaxis of *Pneumocystic carinii* infection.

He presented to us one month later, in October 2021, with progressive generalised body weakness, prolonged fever, and loose stool for the past month, which was 3 episodes per day and weight loss of 5 kg. He reported poor adherence to the ART medications. On examination, the patient was tachycardic with a pulse rate of 136 beats per minute and a body temperature of 38.6°C. He was cachexic, lethargic with pale conjunctiva, and clinically appeared dehydrated. Cardiovascular and lung examinations were unremarkable. Abdominal examination showed an enlarged liver measuring 16 cm, Traube's space was dull, and multiple shotty inguinal lymph nodes bilaterally.

On admission, complete blood count revealed persistent bicytopenias: haemoglobin 5.9 g/dL, total white cell count $1.82 \times 10^3/\mu L$, and platelet $405 \times 10^3/\mu L$. The peripheral blood film showed hypochromic microcytic anaemia and leukopaenia, with lymphopenia and neutropenia likely secondary to underlying infection; no blast cells were seen. The liver enzymes were raised with aspartate transaminase (AST) -236 U/L, alanine transaminase 202 U/L, and alkaline phosphatase 829 U/L. Inflammatory markers were raised with C-reactive protein 168 mg/L and erythrocyte sedimentation rate 118 mm/h. Stool samples were sent for culture, ova and cyst, and *Clostridium Difficile* toxins, and the results were negative. The chest and abdominal radiographs were normal. Sputum samples sent for Acid Fast Bacilli smear and *Mycobacterium* Tuberculosis (MTB) cultures as well as

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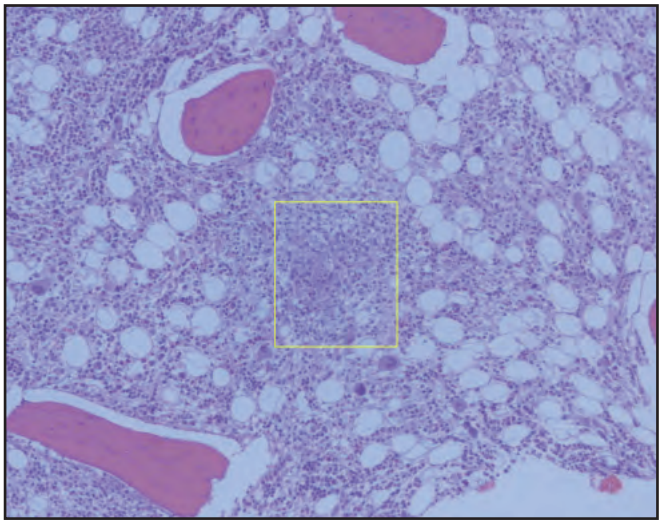

Fig. 1: A small foci of epithelioid granuloma surrounded by epitheloiod histiocytes (H&E stain, x20obj)

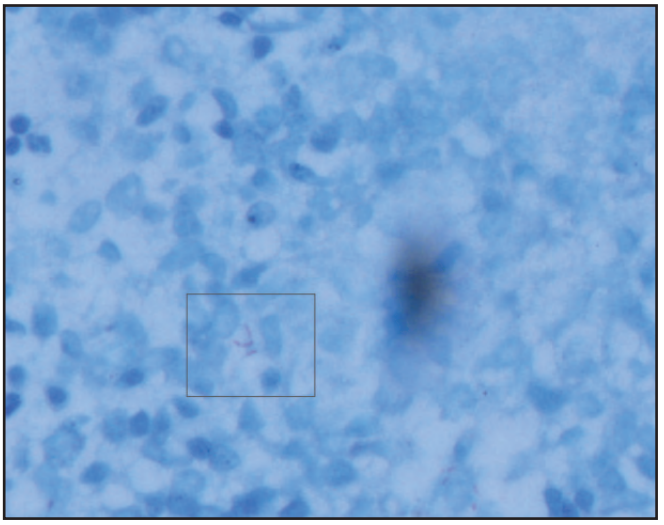

Fig. 2: Acid fast bacilli seen in the bone marrow (x60 obj)

Figure 1 and 2 are the slides of bone marrow trephine biopsy

GeneXpert MTB were negative. Hepatitis B and Hepatitis C serology as well as Rapid Plasma Reagin test were negative. With the evidence of hepatomegaly, persistent temperature spikes, severe bicytopenia, and persistent raised alkaline phosphatase, bone marrow trephine biopsy was obtained due to high clinical suspicion of haematological malignancies.

Findings of bone marrow biopsy revealed tuberculous granulomatous inflammation; Ziehl-Neelson stain was positive for acid-fast bacilli (Figures 1 and 2). Preliminary report yielded non-tuberculous mycobacterium (NTM) species. The case was discussed with the infectious disease consultant and the patient was given empirical treatment with Azithromycin, Ciprofloxacin, and Ethambutol while awaiting the susceptibility report. Rifampicin was not initiated in view of transaminitis.

The bone marrow aspirate culture detected MAC and this microorganism was identified through the Line Probe Assay. Susceptibility testing using the broth microdilution method showed a minimum inhibitory concentration (MIC) of <0.12 for rifampicin, < 0.5 for ethambutol, 2.0 for ciprofloxacin, and 0.25 for clarithryomycin. Despite undergoing treatment for disseminated MAC infection for 3 weeks, there was no clinical improvement and was complicated with septic shock due to hospital-acquired infection. Despite adequate resuscitation and timely administration of broad-spectrum antibiotics, in his case, he was given parenteral Piperacillin-Tazobactam. Unfortunately, his condition continued to deteriorate, eventually succumbed to the disease.

DISCUSSION

MAC is one of the common NTM organisms that are ubiquitous in the environment. Its niche includes water, soil, and dust. The mode of transmission is usually via ingestion, inhalation, or dermal contact with the environment.[2] It typically affects patients who are immunocompromised, such as those with haematological malignancies, patients receiving immunosuppressants after solid organ transplantation, as well as severe AIDS with CD4 count <50 cells/mm^3 as an opportunistic infection.

The disease has a long incubation period with an insidious onset. It presents as either a disseminated or localised syndrome, i.e. lymphadenitis, osteomyelitis, pericarditis, cutaneous or soft tissue abscesses, or central nervous system involvement. Disseminated MAC with multiorgan involvement can be found in as high as 20–40% of patients with advanced immunosuppressed states who were not on effective ART or undiagnosed HIV patients.

Clinical presentation of MAC is vague and includes prolonged fever, night sweats, significant weight loss, fatigue, diarrhoea, and abdominal pain. Lack of specific symptoms often make the clinical suspicion of NTM infection difficult. Disseminated MAC may present as pancytopenia or leukopaenia due to bone marrow infiltration as well as elevated alkaline phosphatase. In patients who are on HAART, MAC disease can present as immune reconstitution syndrome (IRIS), which is a systemic inflammatory response that is indistinguishable from active MAC disease, often with absent bacteremia. MAC-associated IRIS often presents as a localized abscess and lymphadenitis. The immune response is related to a temporary increase in CD4 counts and a rapid reduction in HIV ribonucleic acid counts.

The diagnosis of dMAC is based on clinical features and is confirmed by the isolation of MAC organisms from sterile cultures such as blood, lymph nodes, bone marrow biopsy, or other sterile tissue or body fluid samples. Although blood culture remains the gold standard in detecting dMAC as it is a less invasive procedure and has almost 100% sensitivity, the downside of blood culture is its long turnaround time, which takes up to 6 weeks. On the other hand, bone marrow trephine biopsy is able to detect acid-fast bacillus (AFB) -stain

positive and granulomatous formation early in dMAC, enabling early initiation of treatment for its rapid diagnostic strategy. However, further staining is required to identify the type of acid-fast microorganism. In our case, we were able to detect AFB from the bone marrow biopsy within a few days of the procedure and the marrow aspirate culture later identified MAC using Line Probe Assay. This enabled early initiation of empirical treatment.

The infiltration of MAC organisms into the bone marrow indicates rapid disease progression and reflects severe immunocompromise.[3] A study by Hussong et al. concluded that bone marrow biopsy staining has an important value as it allows rapid recognition of AFB microorganisms with a mean time of 1.1 days as compared to bone marrow aspirate culture and MTB blood culture, which took 19 days and 16 days, respectively.[4] The study concluded that routine staining of core biopsy from bone marrow allows prompt identification and early initiation of antimicrobial treatment, which may improve the survival outcome for these patients. Prior to the availability of ART, MAC infection was the most common opportunistic infection and contributed substantially to the mortality and morbidity in severely compromised HIV patients with CD4 counts 50 cells/μL.[5] However, since the advent of ART, the incidence of MAC infection has decreased exponentially, although patients with low CD4 counts are still at risk.[6]

The current standard treatment for MAC infection is multidrug therapy, which consists of Clarithromycin or Azithromycin, Ethambutol, and Rifabutin in combination. Alternative drugs include fluoroquinolones or Amikacin. Primary prophylaxis for MAC is no longer recommended in today's practice, regardless of CD4 count.[7] Once a diagnosis is made, the treatment duration for MAC is a minimum of 12 months. After the 12-month therapy, secondary prophylaxis, either using Clarithromycin or Azithromycin, should be continued until the CD4 count reaches at least 100/mm^3. In our case report, our patient was treated empirically with Azithromycin, Ciprofloxacin, and Ethambutol while waiting for the culture sensitivity report.

Disseminated MAC carries a high mortality rate in patients with AIDS and the prognosis is poor. Kobayashi et al reported a mortality rate of 29% ($p = 0.022$) from a single-center study on HIV patients with dMAC who were on ART, particularly those with MAC bacteremia and low CD4 count.[8] Our patient succumbed to the illness despite 3 weeks of combination treatment consisting of empirical antibiotics with ART. This is likely due to rapid disease progression and severe sepsis from the infection.

CONCLUSIONS

The diagnosis of MAC is challenging as the clinical features are generally nonspecific. Patients with AIDS who presented with fever, persistent anemia, and high alkaline phosphatase should raise a high clinical suspicion for dMAC infection. Isolation of MAC from blood cultures has a long waiting period for susceptibility as mycobacterium is a slow-growing microorganism. More studies need to be done to evaluate the role of routine trephine biopsy for prompt diagnosis of dMAC in severely immunocompromised patients.

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CASE REPORT

Acute suppurative thyroiditis with *Klebsiella pneumoniae* thyroid abscess and concomitant pneumonia

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SUMMARY

Thyroid abscess is an uncommon infectious pathology. The thyroid is highly resistant to infection due to its high iodine content, capsular encasement, and rich in vascularity. Acute suppurative thyroiditis represents <1% of the thyroid diseases that could be potentially life-threatening. We report a case of a 64-year-old Indian lady with underlying long-standing type 2 diabetes mellitus presented with painful anterior neck swelling and diagnosed with *Klebsiella pneumoniae* thyroid abscess. Unfortunately, despite surgical drainage, she succumbed to death due to overwhelming sepsis and renal failure. Thyroid abscess in adult is rare but potentially life threatening. Physicians must have a high index of suspicion when dealing with immunocompromised or diabetic patients with sepsis. Early diagnosis with appropriate medical and surgical treatment can improve patient's outcome.

INTRODUCTION

Acute suppurative thyroiditis (AST) is extremely rare and it accounts for <1% of thyroid diseases.[1] Due to the encasement of the gland, its rich blood supply, high iodine content, and good lymphatic drainage, the thyroid gland is relatively resistant to most infections. Pre-existing thyroid gland pathology such as Hashimoto's thyroiditis, large goitre, and thyroid cancer; retained foreign body and local anatomic abnormalities, such as pyriform sinus fistula and thyroglossal duct, are predisposing factors for AST.[2] It is usually caused by hematogenous spread or direct inoculation of a pathogen. Treatment includes systemic antibiotics targeting the causative organism although the gold standard remains surgical drainage. Here, we present a case of thyroid abscess caused by *Klebsiella pneumoniae* with concomitant pulmonary infection.

CASE REPORT

A 64-year-old lady with diabetes presented to us with progressive painful anterior neck swelling for the past 4 days. It was associated with odynophagia, dysphagia, hoarseness of voice, and breathlessness. Two weeks prior to this, she experienced high-grade fever with chills and rigors along with dysuria. Physical examination was unremarkable, and there was no neck swelling. Her C-reactive protein level was elevated at 166.8 mg/L (<5mg/L). She was initially treated as urinary tract infection and her blood culture grew *Klebsiella pneumoniae*; however, her urine culture isolated *Escherichia coli*. Ultrasound abdomen did not show any intraabdominal abscesses and ophthalmology examination had no evidence of endophthalmitis. She completed two days of intravenous piperacillin-tazobactam 2.25g four times a day and de-escalated to five days of intravenous cefuroxime 1000mg three times a day after culture and sensitivity results of both blood and urine samples were available and discharged with seven days of oral cefuroxime 500mg bd. Despite that, she had persistent fever at home and subsequently developed painful anterior neck swelling. On examination, the patient appeared toxic looking, tachycardic with the heart rate of 124 beats/minute, normotensive with blood pressure of 134/71 mmHg, tachypnoeic with respiratory rate of 24/minute and stridor, and febrile with temperature of 39.8°C. She had a firm, tender, non-fluctuant, warm, and erythematous anterior neck swelling extending from mandible to clavicle measuring 7cmx5cm which moved with swallowing. There was no cervical or supraclavicular lymphadenopathy. Otherwise, she had no other thyrotoxic signs such as tremors, sweaty palms, thyroid eye signs, or pretibial myxoedema. Her respiratory examination showed coarse crepitations over the right lower zone.

Laboratory studies showed leucocytosis with white blood cells of 20.7 x 10^9/L (4—11 x 10^9/L), and raised C-reactive protein of 368 mg/L (<5 mg/L). The erythrocyte sedimentation rate was >120 mm/h (0—20 mm/h). Blood sugar level was elevated, 25 mmol/L with blood ketone of 0.3 mmol/L. She was clinically euthyroid; however, serum-free thyroxine (FT4) was 38.6 pmol/L (7.9—14.4 pmol/L), and thyroid-stimulating hormone concentration (TSH) was 0.268 mU/L (0.34—5.6 mU/l). Her anti-thyroglobulin level was < 0.9 U/mL (<1.0 U/ml) and anti-thyroid peroxidase antibody was mildly elevated with the level of 78.15 (<10 u/mL). Her electrocardiogram showed sinus tachycardia with no ischaemic changes or arrythmia. Her other significant laboratory findings are seen in Table I. Her chest radiograph showed right middle and lower zone consolidation consistent with lobar pneumonia.

She was started on intravenous meropenem 1000mg twice a day, insulin infusion, and low dose beta blocker and admitted to intensive care unit. The flexible indirect laryngoscope examination revealed narrowing of the subglottic region and she was intubated for airway protection. Post intubation, computed tomography (CT) scan of the neck showed anterior

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Table I: Laboratory results

Investigations	Day 1	Day 2	D3 (Post op D1)	Reference range
Hb (g/dL)	9.7	8.5	8.5	12–15 g/dL
WBC (10^9/L)	20.7	14.9	13.9	4—11 x10^9/L
Platelets (10^9/L)	327	294	323	150–450 x 10^9/L
Na (mmol/L)	119	124	131	136—146 mmol/L
K (mmol/L)	4.8	5.5	4.3	3.5—5 mmol/L
Urea (mmol/L)	12.4	15.8	20.5	2.8—7.2 mmol/L
Creatinine (umol/L)	216	272	313	45—84 umol/L
FT4 (pmol/L)	38.6	ND	ND	7.9—14.4 pmol/L
TSH (mU/L)	0.268	ND	ND	0.34—5.6 mU/L
ESR (mm/h)	>120	ND	ND	0—20 mm/h
CRP (mg/L)	368	ND	ND	<5 mg/L
HbA1c (%)	10.4	ND	ND	<6.5%

Hb: haemoglobin
WBC: white blood cell
Na: sodium
K: potassium
TSH: thyroid stimulating hormone
ESR: erythrocyte sedimentation rate
CRP: C-reactive protein

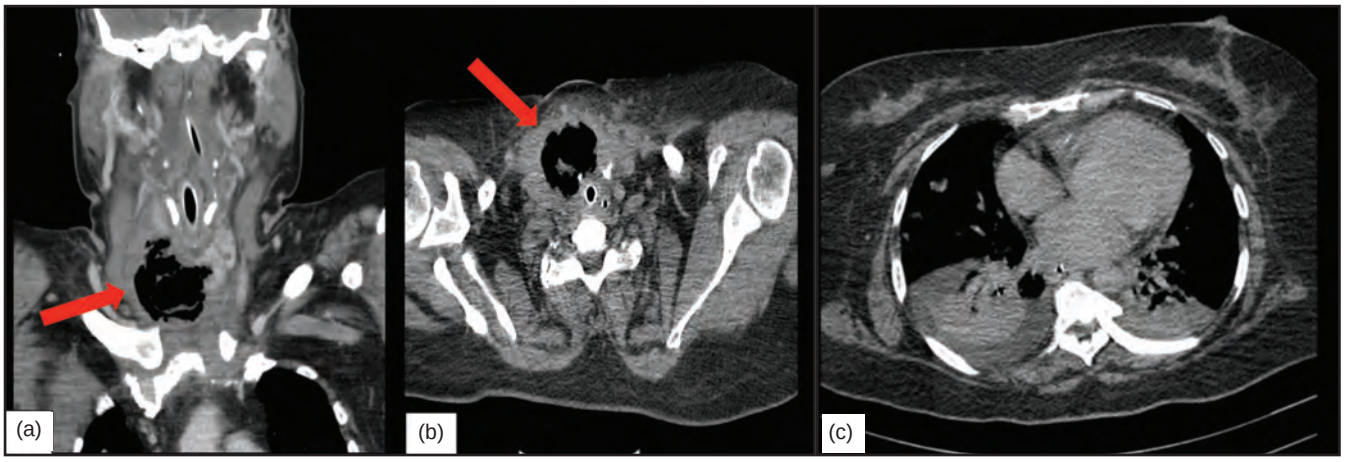

Fig. 1: Computer tomography (a) Coronal view and (b) axial view of the neck showing anterior neck collection (red arrow) measuring 5.7x7.4x6.3 cm (APxWxCC) with large air locules arising from the right thyroid gland with extrathyroidal extension and compression on trachea. CT of the thorax (c) showing extensive patchy collapsed consolidations seen in both lungs (right> left), most severely affecting the right lower lobe with minimal pleural effusions

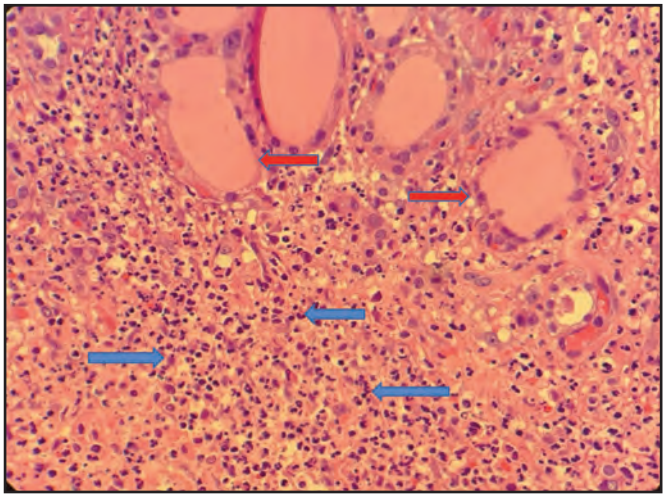

Fig. 2: Microscopic image: Hematoxylin & Eosin (H&E) X 400: Destructions of thyroid follicles (red arrows) by acute inflammatory cells with localized collection of neutrophils (blue arrows)

neck collection measuring 5.7x7.4x6.3 cm (APxWxCC) with large air locules arising from the right thyroid gland with extrathyroidal extension (Figure 1a, 1b). There were also extensive patchy consolidations in both lungs, most severely affecting the right lower lobe (Figure 1c). The diagnosis of AST with thyroid abscess and concomitant pulmonary infection was made and she underwent surgical drainage on day 3 of admission. Intraoperatively, the surrounding muscles appeared oedematous, and the thyroid tissue appeared unhealthy and sloughy with pus within. The pus and tissue culture isolated *Klebsiella pneumoniae* which showed the same antibiotics susceptibility pattern to amoxicillin-clavulanic acid, ampicillin-sulbactam, cephazolin, cefuroxime, and gentamicin. The histopathological examination showed fibro-fatty thyroid tissue with localized collections of neutrophils, lymphocytes, and foamy macrophages. There were areas of haemorrhages and cystic degenerations with focal chronic inflammatory cells infiltration and multinucleated giant cells suggestive of thyroid abscess. There is no cellular atypia or evidence of malignancy seen

(Figure 2). Her tracheal aspirate and repeated blood culture (both aerobic and anaerobic bottles) isolated *Klebsiella pneumoniae* which have a similar sensitivity as well. The recent *Klebsiella pneumoniae* bacteraemia had triggered hematogenous dissemination to the thyroid and lungs, resulting in thyroid abscess and pneumonia formation. Unfortunately, the patient succumbed to overwhelming sepsis and renal failure two days after surgery.

DISCUSSION

The major pathogens that can cause thyroid abscess are *Staphylococcus* and *Streptococcus* species accounted for about 35%–40% of the cases. Gram-negative organisms such as *Klebsiella, Escherichia coli, Salmonella,* and *Acinetobacter sp* cause about 25% cases, whereas anaerobes around 9% to 12%. The rest are fungal and *Mycobacterium tuberculosis* etiologies.[3] Mycobacterial and fungal cases tend to be more common in immunocompromised patients and are chronic in nature, while bacterial causes are more acute.[4]

The clinical presentation of AST is typically a short non-specific prodrome followed by fever, intense pain, and erythema around the neck, resulting in dysphagia and odynophagia. Occasionally, thyroid abscess manifests as a medical emergency, with laryngeal oedema or tracheal compression, necessitating early intubation. Thus, a patient with stridor should undergo immediate endoscopic evaluation with a flexible endoscopy, to exclude laryngeal or tracheal compression. Our patient presented with painful enlarging anterior neck swelling with airway compromise as evidenced by stridor and subglottic narrowing in flexible laryngoscopy examination which required early intubation to prevent respiratory collapse.

The differential diagnosis of AST includes subacute thyroiditis, Hashimoto's thyroiditis, acute suppurative lymphadenitis, rapidly enlarging thyroid carcinoma and cyst, infected thyroglossal duct cyst or branchial cleft cyst, anterior neck abscess or cellulitis. Clinical examination, history, and diagnostic imaging, such as ultrasound and computed tomography (CT) scan, can distinguish these entities. Ultrasound often demonstrates a heterogeneous echotexture of the thyroid gland with a superimposed anechoic or hypoechoic mass, while CT findings of abscesses vary depending on the stage of infection with heterogeneous enhancement of the thyroid gland.[5] Furthermore, CT scan is able to provide information on extra thyroidal involvement and demonstrate anatomical defect such as pyriform sinus fistula and thyroglossal duct which are associated with AST. Thyroid abscess associated with pyriform sinus fistula usually occurs in young children and predominantly involves the left lobe more than the right,[4] however it was not seen in our patient. The CT scan of the neck and flexible indirect laryngoscope did not visualise any pyriform fossa fistula and the thyroid abscess is mainly arising from right thyroid gland.

The risk factor for developing AST in this patient was poorly controlled diabetes. *Klebsiella* infection tends to occur in people with diabetes mellitus and AST secondary to *Klebsiella pneumoniae* has been mostly described in diabetics.[2,6] Chemotaxis and phagocytosis are impaired among diabetic patients.[7] Poorly controlled blood sugar levels enhance the severity of AST. Besides that, recent admission with *Klebsiella pneumoniae* bacteraemia may cause hematogenous spread to the thyroid gland. This patient was treated with 2 days of intravenous piperacillin-tazobactam and de-escalated to 5 days of intravenous cefuroxime after culture sensitivity results were available and discharged with 7 days of oral cefuroxime during the first admission. The initial choice of antibiotics was based on the patient's background of poorly controlled diabetes mellitus, hence a broad-spectrum agent with anti-pseudomonal activity like piperacillin-tazobactam was chosen. Once the sensitivity results were available, the antibiotic therapy was de-escalated to intravenous cefuroxime. The duration of antibiotic for uncomplicated *Klebsiella pneumoniae* bacteraemia is 7–14 days. However, in poorly controlled diabetics, the intravenous antibiotics duration should be at least 14 days. Despite 14 days of antibiotic, the patient remained unwell and developed persistent fever at home. This should raise the suspicion that the source of infection remained unrecognised. In addition, her urine culture which isolated *Escherichia coli* was different from the blood culture. Hence, a repeated blood and urine cultures should be performed during the first admission to determine the causative pathogens and antibiotics susceptibility pattern. More thorough examination including CT scan of the whole body should be done to identify the source of infection. Furthermore, *Klebsiella pneumoniae* is known to cause disseminated infection to the lungs, eyes, skin, liver, muscle, kidney, prostate, and cerebrospinal fluid particularly in immunocompromised or diabetics. Delayed in identifying the source of infection and inadequate duration of intravenous antibiotics in this patient had caused disseminated infection and overwhelmed sepsis with multiorgan failure.

Thyroid function is usually normal in AST, but diffuse inflammation of the thyroid gland and the disruption of follicles with the release of preformed thyroxine and triiodothyronine into circulation can lead to transient thyrotoxicosis.[2] Yu et al.[8] reviewed 191 cases of AST and reported most patients (83.1%) with bacterial infections were euthyroid, whereas those with fungal or mycobacterial infections tended to be hypothyroid (62.5%) and hyperthyroid (50%), respectively. Although this patient had elevated free thyroxine level, the TSH level was not very much suppressed. Non-thyroidal illness can also present with discordant thyroid function test. Free T4 and free T3 typically low or low-normal, with normal or low (but rarely fully suppressed) TSH. However, elevated FT4 may also be found, and it is not uncommon for the same sample to yield markedly discordant FT4 concentrations when run on different assay platforms. She was only given beta blocker for symptomatic control and no other antithyroid drug was initiated. Antithyroid drugs have no role in the management of destructive thyroiditis as the excess thyroid hormone levels result from the release of preformed thyroid hormones from inflamed tissue. In some patients, thyroiditis can result in permanent thyroid gland destruction, and it may be severe enough to cause permanent hypothyroidism. Thus, follow-up thyroid function studies are recommended specially in cases of more diffuse thyroiditis.

AST requires immediate parenteral antibiotic therapy before the formation of thyroid abscess. In the presence of thyroid abscess, surgical drainage is generally necessary in addition to antibiotic therapy. Complications of thyroid abscesses include tracheal or oesophageal perforation, descending necrotizing mediastinitis, extension into the deep spaces of the neck, airway obstruction, internal jugular vein thrombosis, and sepsis.[9] Mortality with suppurative thyroiditis is reported to range from 3.7 to 12.1%[10] and tends to be higher in immunocompromised patients. Berger et al. reported that with no therapy, the mortality rate in bacterial thyroiditis is almost 100%. Early diagnosis and treatment are essential to decrease the morbidity and mortality associated with suppurative thyroiditis and thyroid abscess.

CONCLUSION

Thyroid abscess in adult is rare and potentially life threatening. Physicians must have high index of suspicion when dealing with immunocompromised or diabetic patients with sepsis. Early diagnosis with appropriate medical and surgical treatment can improve patient's outcome. It is also important to recognize AST with abscess formation in the differential diagnosis of anterior neck pain in diabetic patients.

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CASE REPORT

An unusual pathogen in a typical clinical scenario: *Pseudomonas oryzihabitans* urosepsis in a patient with Myelodysplastic syndrome

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SUMMARY

Neutropenia is a common clinical occurrence in the background of malignancies, either as a direct result of defective haematopoiesis due to the illness or as a result of antineoplastic therapies. Opportunistic infections with low-virulence organisms are not uncommon among immunocompromised patients. Within this patient subset, opportunistic infections with *Pseudomonas oryzihabitans (P. oryzihabitans)* are considered rare. In this first reported case of P. oryzihabitans infection in Malaysia, we describe its clinical presentation in a susceptible patient, the management, and its subsequent clinical course. Comparing against a brief overview of the literature, we explore the mechanisms driving immunosuppression, leading to susceptibility of opportunistic infections among patients with myelodysplastic syndrome. We also feature the use of matrix-assisted laser desorption-ionisation time of flight mass spectrometry (MALDI-TOF MS) as a promising platform to revolutionize microorganism identification and diagnosis.

INTRODUCTION

Pseudomonas oryzihabitans (formerly known as *Flavimonas oryzihabitans*) is a gram-negative rod-shaped aerobic bacillus, an uncommon pathogen which acts as an opportunistic pathogen in immunocompromised patients.[1] It has been reported in both humans and as a zoonotic pathogen.[2] In this case, we detected this relatively unusual pathogen in a patient with a background of myelodysplatic syndrome (MDS) and numerous other chronic co-morbidities.

CASE REPORT

A 73-year-old female with a recent diagnosis of myelodysplastic syndrome presented with an acute episode of dysuria following 3 days' duration of abdominal distension and suprapubic discomfort. She denied having fever, hematuria, difficulty in breathing, or gastrointestinal losses. She has multiple co-morbidities, including type 2 diabetes, hypertension, dyslipidemia, and neurogenic bladder due to T12-spinal cord injury following a motor vehicle accident more than two decades ago.

She was bed bound and highly dependent on her daughter on most daily activities. Further medical history reveals a recent diagnosis of myelodysplastic syndrome 4 months prior to her current admission, where her bone marrow aspiration and trephine biopsy (BMAT) reported hypercellular marrow with trilineage myelodysplasia. Whilst awaiting cytogenetic study results, management for her myelodysplastic syndrome has been largely supportive, where blood products transfusions were arranged to address her anaemia and thrombocytopenia.

Upon examination, she appeared alert but pale, with no apparent signs of respiratory distress. She was afebrile but tachycardic, with a heart rate of 117. Her blood pressure reading and oxygen saturation under room air were otherwise normal. An indwelling urinary catheter with the attached urine bag contained heavily sedimented urine, with no evidence of gross hematuria. A physical examination revealed a soft abdomen with mild tenderness over the suprapubic region, with no masses palpable. Cardiovascular and respiratory examinations were unremarkable.

Investigations revealed pancytopenia, with a haemoglobin reading of 6.7g/dL (normochromic, normocytic picture), absolute neutrophils count (ANC) of 270 cells/mm^3, and platelet count of 23 x10^9/L. Urinalysis showed a positive leucocyte and nitrite picture. Renal profile and liver function tests were normal. Ultrasound of kidney, ureter, bladder (KUB) identified bilateral renal parenchymal disease, with no features of hydronephrosis or pyelonephritis. Inflammation was evidenced by an elevated C-reactive protein reading of 53 mg/L.

She was empirically treated with intravenous ceftriaxone 2g daily for the urinary tract infection. The initial urine culture on admission showed mixed growth due to contamination. On day two of admission, her blood culture yielded *P. oryzihabitans* that was sensitive to piperacillin-tazobactam, imipenem, and meropenem; but with intermediate sensitivity to cefepime and resistant to ceftazidime. Based on the working diagnosis of *P. oryzihabitans* blood stream infection secondary to urinary tract infection, her intravenous antibiotics was switched to a 6-hourly regime of 4.5g intravenous piperacillin-tazobactam.

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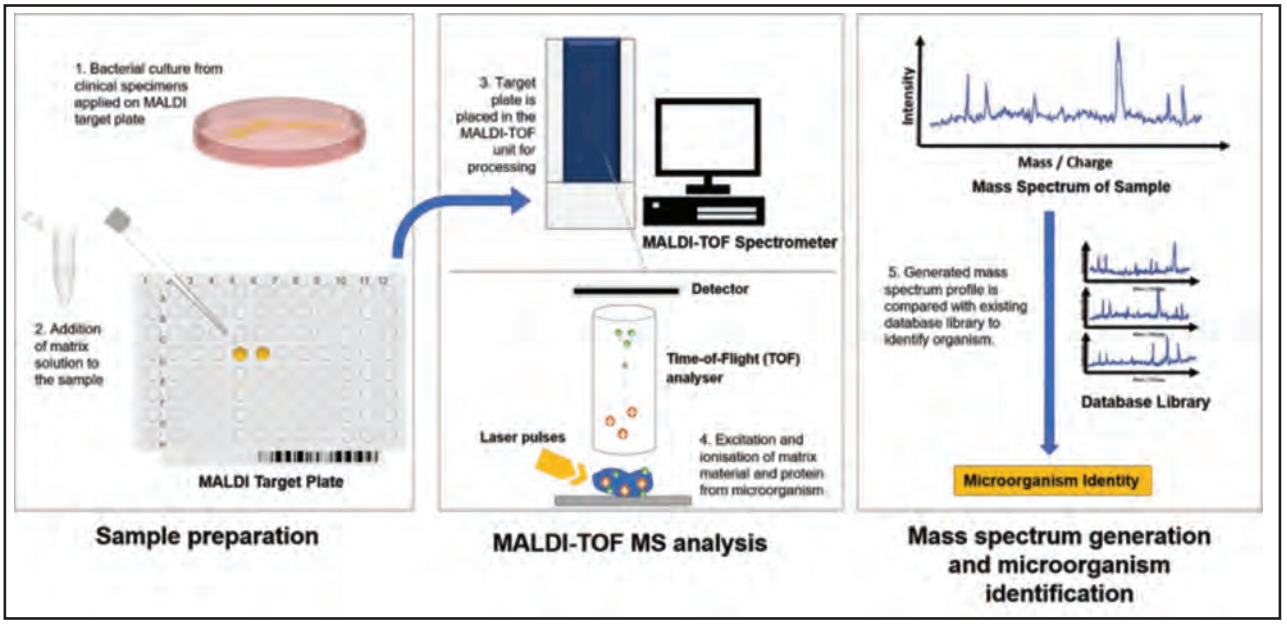

Fig. 1: Workflow of the matrix-assisted laser desorption-ionisation time-of-flight mass spectrometry (MALDI-TOF MS) in microorganism identification

Throughout admission, she remained afebrile, but the neutropenia persisted. Haematology team initiated a course of oral danazol 200mg twice daily as a therapy for her persistent pancytopenia. Patient also received one unit of packed cell transfusion on day 6 of admission to address her symptomatic anaemia. Following completion of the 2-week antibiotic regime, with the absence of fever, suppression of inflammatory markers, and no further isolation of P. oryzihabitans, patient was discharged home.

DISCUSSION

P. oryzihabitans is a yellow-pigmented, aerobic, non-fermenting, gram-negative organism.[1] Indigenous to rice paddies, it is commonly found as a soil and saprophytic organism that thrives in damp environments.[1] Since its discovery in the 1980s, *P. oryzihabitans* have been increasingly implicated as a causative organism in bacteremia, septicemia, and peritonitis; among individuals who are immunocompromised, particularly in haematological malignancies, acquired immunodeficiency syndrome, or individuals on steroid treatment.[3,4] There were also reports of *P. oryzihabitans* infection causing peritonitis and septicaemia among individuals on peritoneal dialysis with long-term in-dwelling catheters.[3] Several *P. oryzihabitans* outbreaks in the hospital setting have also been reported in the literature, noting that *P. Oryzihabitans* was frequently isolated in various sites, such as sink drains, respiratory therapy equipments, and containers of saline gauzes.[5]

MDS is a group of heterogenous clonal disorder of the haematological system. It is characterized by ineffective haematopoiesis and differing degrees of peripheral cytopenia, with a risk of transformation to acute myeloid leukemia (AML).[6] Infections pose a major threat to all MDS patients alike, regardless of treatment status. This can be ascribed to functional defects in the myeloid lineage, with or without neutropenia, which is also complicated further by treatments.[7] Immune dysregulation in MDS is complex, accompanied with an increased release of pro-inflammatory cytokines such as tumour-necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), transforming growth factor-beta (TGF-β), and interleukins (IL-6, IL-10) in the bone marrow microenvironment.[6] Besides immunosuppression, majority of patients diagnosed with MDS are affected by anaemia and anaemia-related symptoms, which can be debilitating and thus result in a poor health-related quality of life (HRQoL).[8] Transfusion dependence, apart from its costs, has also been recognised as a negative prognostic factor leading to reduced overall survival among patients with MDS.[8]

Bacteria is the most common type of pathogen implicated in MDS-related infections.[7] To date, cases of P.oryzihabitans infections have been shown to respond well to treatment, with the eradication of the organism whenever suitable antimicrobial therapy is initiated.[3,5] Although the patient in our case responded well to treatment, it is also worth noting that the intravenous piperacillin-tazobactam required was a broad-spectrum antibiotic that is reserved for severe infections involving resistant microorganisms. As opposed to the sensitivity patterns of *P. oryzihabitans* described in earlier studies, the *P. oryzihabitans* isolated in this case exhibited resistance against the cephalosporin groups, further warranting the importance of judicious antibiotics prescription to treat such infections among the at-risk groups. For patients with a baseline neutrophil of less than 500 x 10^9/L, some studies have suggested the use of antibacterial prophylaxis before commencing therapy with demethylating agents.[7] However, proper risk-benefit analysis of prophylactic antibiotics needs to be done, considering the issue of antibacterial resistance and risk of selecting resistant bacteria.

In this case, a rapid and accurate identification of *P. oryzihabitans* was made possible as a result ofthe MALDI-TOF MS (refer Figure 1) use in the microbiology laboratory, which allowed the timely prescription of appropriate antibiotics administration to treat the patient. With MALDI-TOF MS, the turnaround time for microorganism identification was dramatically shortened from several hours to less than 20 minutes. The MALDI-TOF MS involves ionizing biological samples and separating the particles based on their mass-to-charge ratio and detection of their time-of-flight in a detector.[9] Subsequently, the resulting spectrum can be compared to an existing spectra database from known organism, which allows prompt identification of organism with high accuracy.[9] Moreover, the superiority of MALDI-TOF MS over traditional detection techniques has also been shown to contribute to the increased reporting of some relatively rare species.[10] In the long run, the MALDI-TOF MS technique represents a cost-effective, straightforward, and robust microbial identification method, allowing proper guidance in managing infectious diseases.[9]

CONCLUSION

Although rare, findings from our case and the existing literature suggest the potential of *P. oryzihabitans* as a pathogen in the clinical setting, especially among patients with underlying haematological malignancies and immunosuppression. This emphasizes the need for vigilance and clinical suspicion in this group of patients, prompting the role of appropriate antibiotic in clinical settings. With the increasing use of MALDI-TOF mass spectrometry platform in clinical laboratories, we expect to see significant improvements in accurate identification of microorganisms, thus speeding up diagnoses and reducing the time to appropriate therapy.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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Levothyroxine absorption test: An underutilized tool

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SUMMARY

A subset of hypothyroid patients who are refractory to standard thyroid hormone replacement treatment is commonly encountered causing patients to be prescribed with high doses of levothyroxine. However, it remains a challenge to clinicians to distinguish nonadherence from malabsorption in patients with uncontrolled hypothyroidism despite the administration of high doses of levothyroxine. Here, we present a case of a 55-year-old woman with refractory hypothyroidism who was subjected to the levothyroxine absorption test (LT4AT).

INTRODUCTION

The levothyroxine absorption test (LT4AT) is typically performed by administering a single large oral dose of levothyroxine (LT4) with serial measurements of FT4. It is performed on patients with uncontrolled hypothyroidism despite the administration of high doses of oral LT4. This test is performed to effectively distinguish the cause of uncontrolled hypothyroidism due to poor compliance secondary to nonadherence or malabsorption of the drug.[1] In most patients, hypothyroidism is readily treated with oral LT4 replacement with doses ranging from approximately 0.8 - 2.1 µg/kg.[2] However, it becomes a challenge for clinicians involved in predicaments where patients have an inadequate response to a seemingly appropriate dose of levothyroxine (LT4) in the absence of known conditions or medications that impair LT4 absorption. This case report aims to distinguish nonadherence in a patient with refractory hypothyroidism despite the administration of high doses of levothyroxine by performing LT4AT and highlighting its importance in the diagnosis of LT4 pseudomalabsorption. The term pseudomalabsorption of levothyroxine is frequently used when important organic causes, concomitant medications, intrinsic gastrointestinal disorders, pharmacodynamics-modifying drugs have been ruled out.[3]

CASE REPORT

A 55-year-old female on daily intake of LT4 of 250 ug was classified by the treating physician as refractory hypothyroidism. She weighs 69 kg and LT4 dosage requirement is 1.6 µg/kg body weight. Her thyroid-stimulating hormone (TSH) remains high (>150 mu/L) despite increasing the LT4 dosage as shown in Figure 1. She claims to take the medication accordingly as instructed and took no other medications that were potential to alter the absorption of LT4. All biochemical tests including haemoglobin were within normal range. She was referred to the pharmacist for evaluation of compliance. The patient expressed her frustration about the treatment not being any help to her condition and subsequently agreed to undergo further testing. She was subjected to the LT4AT after having fasted for 8 hours and omitting her daily LT4 dose for the day. A protocol by Lima et al.[4] was used with a slight change in the time of blood collection measurement of TSH and FT4. Blood for serum FT4 at 0, 60, 120, 180, 240, 300, 360 minutes and serum TSH at 0 and 360 minutes were taken after administration of 1000 µg of LT4 orally. The results of her TSH and FT4 were as in Figure 2.

Her results showed an increase in FT4 initially for the first 180 minutes and a plateau till the end of 360 minutes. The FT4 increment was 2.7 times higher than the baseline. In this patient the FT4 increment from baseline (5.0pmol/L) at 3 hour is 13.7 pmol/L (1.06ng/dL). The TSH level fell accordingly and was compatible with normal absorption. Thus, inadequate levothyroxine absorption was therefore excluded. This finding excluded her from the need of a potentially exhaustive search for an organic underlying cause.

DISCUSSION

Hypothyroidism is characterized by low levels of thyroid hormones in the blood. It is common in women with a female-to-male ratio of 6:1.[5] Primary hypothyroidism occurs when there is a destruction of the thyroid gland due to autoimmunity which is the commonest cause, resulting in low thyroid hormones. It accounts for more than 90% of cases of hypothyroidism and effective hormone replacement can be achieved in most patients clinically with a daily intake of LT4. The ingested LT4 absorption occurs primarily in the duodenum and jejunum in approximately 62% to 81% within 3 hours of oral ingestion. Optimal dissolution of the drug particles and proper ionization of thyroxine requires low gastric pH[6]. LT4 undergoes hepatic metabolism and is partially deconjugated and resorbed in the intestinal tract.

Patients with clinical and biochemically uncontrolled thyroid function, even in the use of adequate doses of oral LT4, represent a challenge in clinical practice. When compared to other minimally invasive test available to rule out malabsorption such as esophagogastroduodenoscopy (OGDS) and colonoscopy, LT4AT is definitely cost effective and widely available in most laboratories. The LT4AT is an important test to consider for distinguishing between nonadherence and true intestinal pseudo malabsorption (after excluding gastrointestinal and liver diseases,

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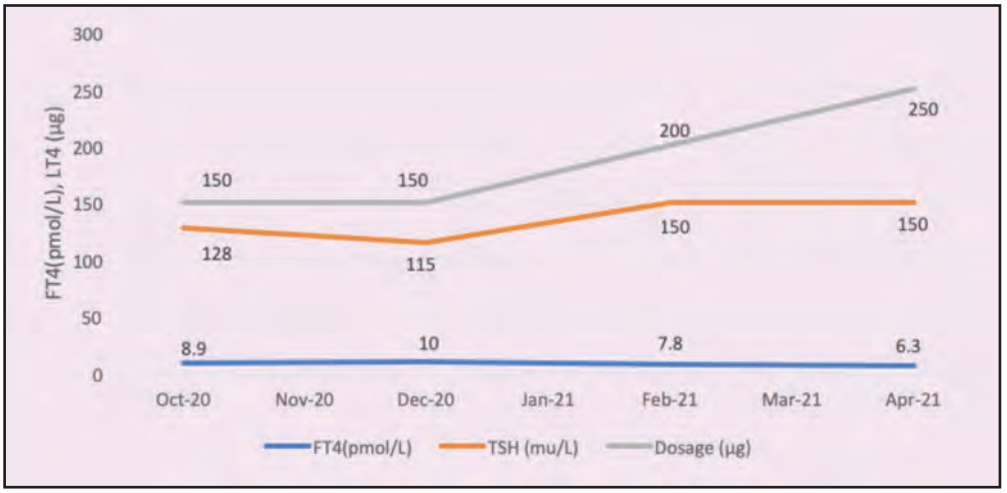

Fig. 1: Thyroid function trend prior to LT4AT

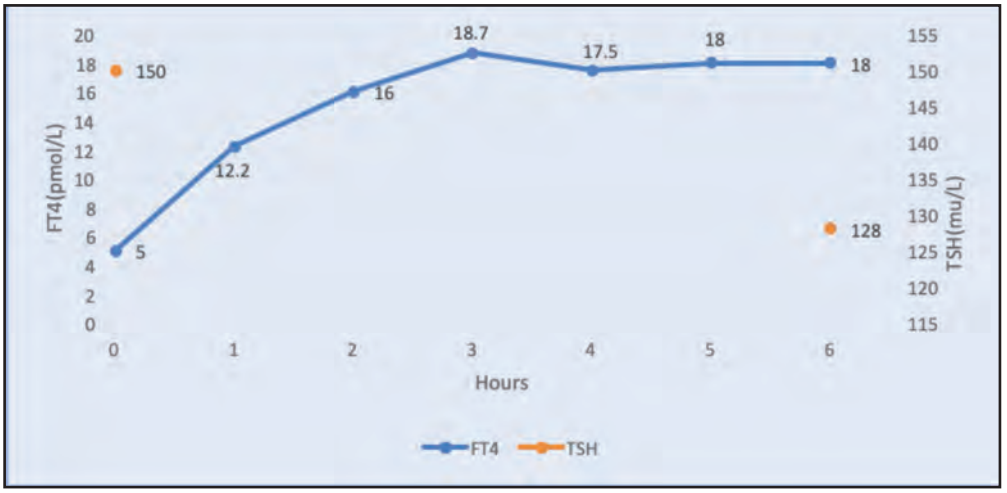

Fig. 2: Levothyroxine absorption test curve

medication and dietary interference), the latter of which is very rare. If nonadherence is suspected, the options to confirm the possibilities are limited especially when patients do not report such behaviour.

There is no gold-standard method for the LT4AT with various protocols advocated in the literature. In most case reports, LT4AT was conducted under the supervision of LT4 ingestion with a dose of 1000 µg orally. Observation of the patient for at least 60 minutes after ingestion is important to evaluate if the patient develops any symptoms and to ensure compliance. In patients with hypothyroidism, the FT4 usually increases 1 hour after LT4 intake and achieves a peak at 2 hours.[7] Several small studies reported good absorption of levothyroxine in such patients; however, there was no suggestion for any cut-off for LT4 increment to rule out pseudomalabsorption.[7] For the interpretation of LT4AT, many authors suggest that an increment of at least 2.5 times from the baseline of FT4 is suggestive of pseudomalabsorption.[6] According to Ghosh et al., the cut off of free T4 increment at 3 hours from baseline above 0.40 ng/dL (5.14 pmol/L) had a sensitivity of 97% and specificity of 80% (AUC 0.904, $p < 0.001$) to exclude true malabsorption.[8]

Another way of interpreting LT4AT testing suggested by some authors was by calculating the LT4AT using the volume of distribution (Vd) to estimate the amount of drug absorbed. Vd (liters) is measured as Vd=0.442 x body mass index (BMI). Based on this, the percentage of drug absorption can be estimated by the formula of LT4 absorbed (%) = peak TT4 (µg/ dL) x Vd (dL)/ administered dose of LT4 x 100. A normal absorption is taken as ≥60%.[9]

Based on Sun Ge et.al study, FT4 and TT4 correlated highly, in patients who were severely hypothyroid. FT4 may be used as a qualitative assessment of suspected malabsorption using an oral LT4 absorption test for the evaluation and management of hypothyroidism dosage of FT4 in association with TSH is widely recommended.[10]

In this patient, adequate absorption of LT4 was demonstrated with a subsequent prominent spike in FT4 levels and

concomitant suppression of TSH suggested of pseudomalabsorption. She was counselled on how current symptoms could be attributed to poor disease control due to irregular administration of vital medications. She was advised on regular administration of LT4 for better symptom control which she was agreeable as she realised that her adherence made improvement to her thyroid function test. Further plans were to monitor and further analyse her for a psychiatric condition if non-compliance still exist.

CONCLUSION

For patients with suspected 'pseudomalabsorption' of levothyroxine, the thyroxine absorption test may aid clinicians in establishing poor compliance with objectivity and confidence. The lack of uniformity in practice or interpretation of this test may have led to it being underutilized. We report a case of pseudo malabsorption where a rapid 6-hour thyroxine absorption test allowed us to objectively prove adequate LT4 absorption, leading to a reduction in LT4 dosing, without the need for potentially more invasive testing. Concurrently, this would establish a clearer view and awareness to the patient regarding the need of adherence for finer disease control. A standard protocol of LT4AT is needed with a clear objective and selection of patients to help in the management of hypothyroid patients.

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CASE REPORT

Cutaneous thrombosis in pregnancy: A case report

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SUMMARY

Antiphospholipid syndrome (APS) is a multisystem, autoimmune disease, which is characterized by thrombosis which may lead to obstetric complications such as uteroplacental insufficiency and pregnancy loss. Antiphospholipid antibodies promote activation of endothelial cells, monocytes, and platelets, causing an overproduction of tissue factor and thromboxane A2. These factors, together with the typical changes in the hemostatic system during normal pregnancy, result in a hypercoagulable state which is responsible for the thrombosis that is presumed to provoke pregnancy complications associated with APS. Obstetric care is based on combined medical-obstetric high-risk management and treatment with antithrombotic agents. We here report a case of APS involving a 23-year-old presented at 24 weeks of her third pregnancy. She had a history of oligohydramnios and an ectopic pregnancy. She had progressive cutaneous thrombosis at 24 weeks of gestation and oligohydramnios at term. She was prescribed enoxaparin and aspirin. She delivered a healthy baby boy without any postnatal complications. Both the enoxaparin and aspirin were continued up to six weeks postpartum. Her lupus anticoagulant antibody was tested positive.

INTRODUCTION

Thrombosis in pregnancy is a major cause of peripartum morbidity and mortality. Data suggests that at least 50% of cases of venous thromboembolism in pregnant women are associated with thrombophilias.[1] Antiphospholipid syndrome (APS) is the most frequent treatable cause of recurrent pregnancy loss. Recurrent miscarriages occurred in 26.4% of women with APS.[2] In another larger cohort, preeclampsia, premature birth, or fetal loss are seen in 10–20% of pregnancies with APS.[3]

Diagnosing and managing patients with APS is a challenge for most clinicians. Here, we report a case of APS who presented with cutaneous thrombosis and oligohydramnios in pregnancy.

CASE REPORT

A 23-year-old female, G3P1+1 was hospitalised at 24 weeks of gestation for a one-week history of painful bullae which ulcerated on her right 2nd, 3rd, 4th, and 5th toes. Her firstborn, a girl, was delivered via emergency lower segment caesarean section (EMLSCS) for failed induction of labour at 37 weeks of gestation, which was complicated by oligohydramnios and reduced fetal movement. The birth weight was 3.0kg. The cause of oligohydramnios was not established. Her postnatal period was uneventful. Her second pregnancy was a tubal ectopic pregnancy, which was managed by laparoscopic removal of the product of conception.There was no family history of any blood coagulation disorders or autoimmune diseases.

On examination, her vital signs were normal. She had a gravid uterus of 24 weeks size. Her pulse rate was regular. All the peripheral pulses were palpable and equal. There were multiple haemorrhagic bullae on her right foot affecting the dorsal aspect of 2nd to 5th toes (Figure 1a and 1c).The capillary refill time was normal. The calves were not swollen or tender. Examination of the cardiovascular, respiratory, and neurological systems was normal. There were no clinical features to suggest systemic lupus erythematosus (SLE) or other connective tissue diseases. During the hospitalisation, she developed more areas of painful non-blanchable reticulated purpuric macules and patches on distal aspects of both legs, which then became superficially ulcerated.

The differential diagnoses that were considered included cutaneous thrombosis and cutaneous vasculitis. The possible underlying causes such as APS, various inherited or acquired thrombophilia disorders, and SLE were investigated.

A full blood count, renal, and liver function tests, coagulation screen, urinalysis,and immunologic profile including antinuclear antibody (ANA), C3, and C4 were also normal. Hepatitis viral screening, p- and c-antineutrophil cytoplasmic antibody (ANCA) did not reveal any abnormalities. Lupus anticoagulant (LA), anti-cardiolipin antibodies (ACL), and anti–β-2-glycoprotein I (aß2GPI) for IgG were not detected in her thrombophilia screen at 24 weeks of gestation. Doppler ultrasound showed no sonography evidence of right lower limb deep vein thrombosis. Echocardiogram and uterine artery doppler at 24 weeks were normal.

A skin biopsy of a purpuric patch on the right calf showed normal epidermis within travascular thrombi inall small and medium vessels of dermis and hypodermis, associated with haemorrhage and minimal inflammatory cells(Figure 2a–c). Immunofluorescence study showed no depositions of IgG, IgM, C3, and C1 around the vessels or at the dermo-epidermal junction. She was confirmed to have cutaneous thrombosis.

Low molecular weight heparin (LMWH) of subcutaneous enoxaparin 80mg twice a day and oral aspirin 150mg daily

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Table I: Vasculopathy in antiphospholipid syndrome: summary of vascular involvement.(Adapted from Sal,a S et al..[4])

Organ	Clinical manifestation	Vascular pathology
Brain	Multi-infarct dementia, seizures	Endothelial proliferation
Coronary artery	Valve abnormalities (valve thickening and vegetations), occlusive arterial disease (atherosclerosis and myocardial infarction), intracardiac emboli, ventricular dysfunction	Endothelial proliferation
Lung	Pulmonary hypertension	Plexiform lesions (i.e. endothelial proliferation)
Renal artery	Hypertension	Smooth muscle cells
Intrarenal vessels	APS nephropathy	Endothelial and smooth muscle cells proliferations
Placenta	Placenta-mediated complications	Decidual vasculopathy (i.e. endothelial proliferation)
Peripheral artery	Peripheral artery disease, critical ischaemia	Endothelial and smooth muscle cells proliferations
Skin	Livedo, livedoid vasculopathy	Endothelial proliferation

Table II: Classification criteria for definitive antiphospholipid syndrome (adapted from the revised Sapporo classification criteria[12]).

Vascular thrombosis	≥ 1 clinical episode of arterial, venous or small vessel thrombosis. Thrombosis must be objectively confirmed. For histopathological confirmation, thrombosis must be present without inflammation of the vessel wall.
Pregnancy morbidity	1. ≥1 unexplained death of a morphologically normal fetus ≤ 10 weeks gestation. 2. ≥1 premature delivery of a morphologically normal fetus <34 weeks gestation because of: • severe preeclampsia or eclampsia defined according to standard definition • recognized features of placental insufficiency* 3. ≥ 3 unexplained consecutive miscarriages <10 weeks gestation, with maternal and paternal factors (anatomic, hormonal or chromosomal abnormalities) excluded.
Laboratory criteria to	The presence of APLA, on two or more occasions at least 12 weeks apart and no more than 5 years prior clinical manifestations, as demonstrated by ≥1 of the following: 1. Presence of lupus anticoagulant in plasma. 2. Medium to high-titer anticardiolipin antibodies (>40GPL or MPL, or >99th percentile) of IgG or IgM isoforms. 3. Anti-β2 glycoprotein-I antibody (anti-β2GP I) of IgG or IgM present in plasma.

APS, antiphospholipid syndrome; APLA, antiphospholipid antibodies; GPL, grams per liter: MPL, micrograms per liter.
* Features of placental insufficiency include abnormally thin placenta (less than 1 cm), circumvallate placenta (1% of normal placentas), amnion cell metaplasia, amnion nodosum, increased syncytial knots, calcifications, infarcts due to focal or diffuse thickening of blood vessels, villi capillaries occupying about 50% of the villi volume or when <40% of capillaries are on the villous periphery. Placental insufficiency can lead to intrauterine growth retardation, oligohydramnios, fetal heart rate abnormalities indicating fetal hypoxia and eventually fetal death.
The classification criteria for definitive antiphospholipid syndrome requires that a patient fulfills the laboratory and clinical criteria. As outlined previously, the laboratory criteria include the presence of persistent antiphospholipid antibodies, whereas the clinical criteria include manifestations such as thrombosis and/or pregnancy morbidity.

was initiated. The initial necrosis on the lower limbs gradually improved (Figure 1b and 1d) while she developed new reticular purpuric patches on her right elbow, left thigh, and bilateral shins. In addition, focal areas of painful ulceration and necrosis developed on the purpuric patches. Compliance to medications was reinforced repeatedly to the patient. These lesions improved albeit slowly with the continuation of both enoxaparin and aspirin at the same dose.

She was under close follow-up by a team comprised of materno-fetal obstetrician and haematologist. The fetal growth was according to gestation. However, towards the end of pregnancy, she had oligohydramnios without history of leaking liquor. A healthy baby boy weighing 3.8kg was delivered via EMLSCS at 39 weeks of gestation. Postnatally, there was a rapid resolution of her skin lesions. She continued the subcutaneous enoxaparin and aspirin until 6 weeks postpartum without any bleeding complications. An intrauterine contraceptive device was inserted as a contraceptive measure.

Her thrombophilia screening was repeated 4 months after the anticoagulant and antiplatelet were discontinued. Her LA was positive. ACL and aß2GP1 were not detectable. Protein C, protein S, and antithrombin activity levels were within normal ranges. Her LA was however undetected on repeated test at 10 months post anticoagulant therapy. She was finally diagnosed to have APS. She was planned to re-initiate LMWH from fetus viability until 6 weeks postpartum in future pregnancies.

DISCUSSION

APS is the most important acquired autoantibody-mediated thrombophilia. It is a systemic condition affecting multiple organs as shown in Table I.[4] In a study of 200 patients with APS, dermatologic manifestations were observed in 49%.[5] Cutaneous manifestations were the initial presenting complains in about a third of them.There are myriad of dermatological manifestations in APS. The most commonly documented rash associated with APS syndrome was livedo reticularis, which typically affects the lower limbs. Other

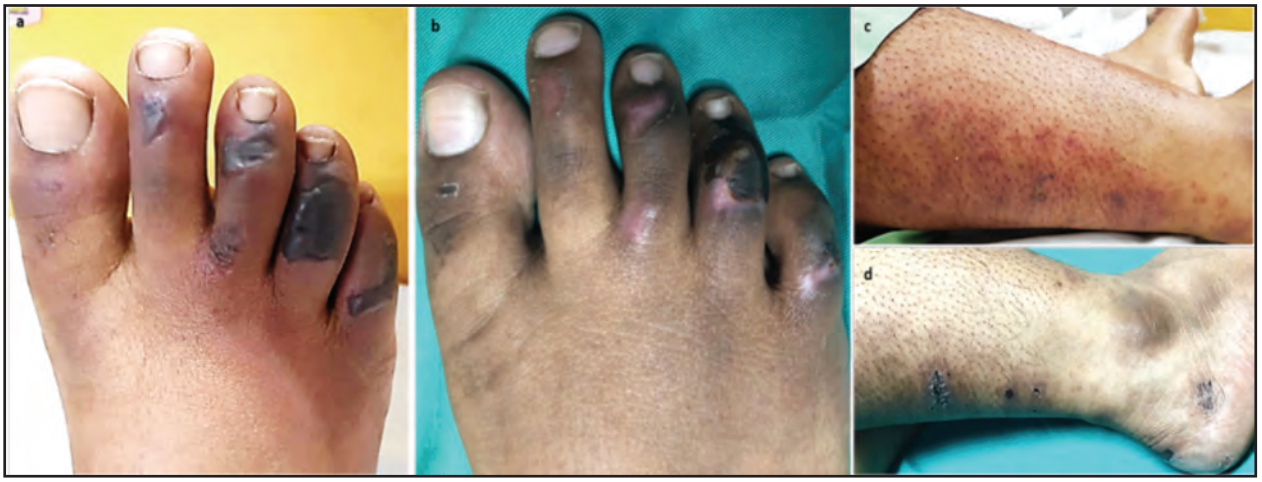

Fig. 1: (a, c)Multiple haemorrhagic bullae on toes and non-blanchable purpuric patches on calves at first presentation;(b, d)Healing ulcers on toes with porcelain white, atrophic, stellate scars (atrophie blanche), reduced swelling, resolved reticular purpuric patches and netlike pattern of hyperpigmentation seen on the calf on follow-up at 28 weeks of gestation

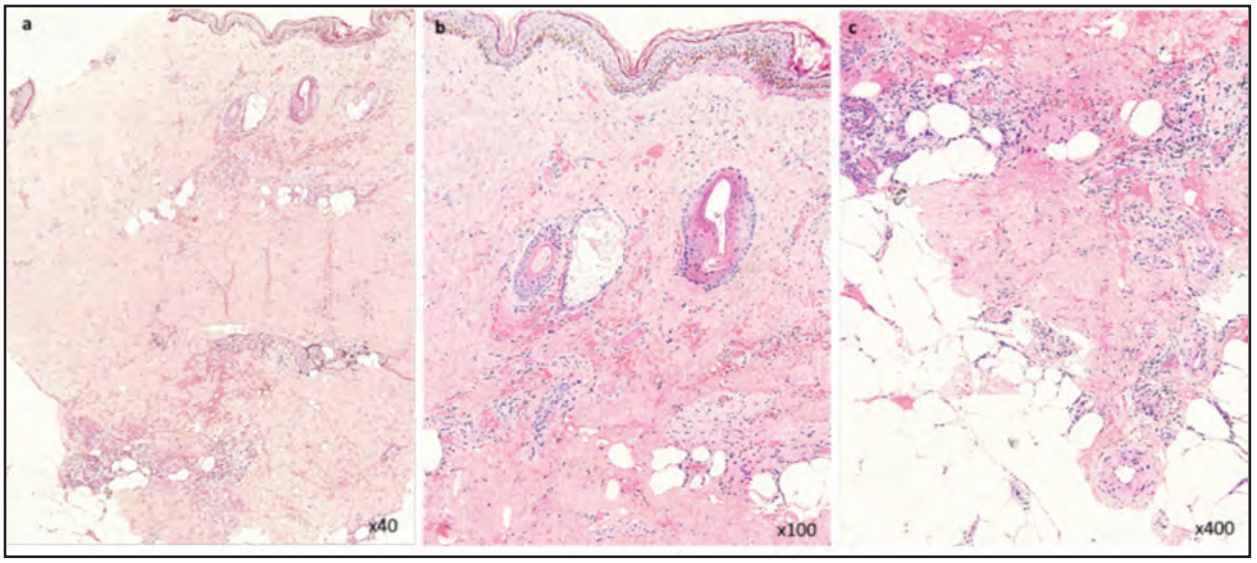

Fig. 2: (a-c) Histopathology of skin biopsy stained with hematoxylin and eosin showed the presence of subepidermal fibrin collection. The superficial dermis exhibits scattered neutrophilic infiltration, nuclear ducts, and extravasated red blood cells. There are numerous thrombosed blood vessels in the superficial dermis extending to deep dermis and hypodermis

dermatological manifestations of APS are skin ulcerations, digital gangrene, superficial venous thrombosis, pseudovasculitis lesions, purpura, palmar or plantar erythema, nodules, pustules, malignant atrophic papulosis-like lesions, superficial skin necrosis, superficial phlebitis, multiple subungual splinter haemorrhages, primary anetoderma, extensive cutaneous necrosis, and white-atrophy-like lesions.[6]

Adverse pregnancy outcomes in APS include recurrent early abortions, fetal death, intrauterine growth restrictions, premature birth due to preeclampsia, and other placenta-mediated complications. These conditions result in fetal hypoxia, an indicator of uteroplacental insufficiency. Our patient had oligohydramnios in both her pregnancies. The first pregnancy was an early term delivery. There was fetal distress as evidenced by reduced fetal movement. This could reflect uteroplacental insufficiency, suggesting that spiral artery vasculopathy may be the contributary factor. Regrettably, the placenta of her both pregnancies was not examined histologically after delivery.

Besides skin and obstetric manifestation, APS is a major risk factor for arterial thrombotic events such as ischaemic stroke and myocardial infarction.[4] Rarely, catastrophic antiphospholipid syndrome (CAPS), also known as Asherson's syndrome may occur. It is characterized by multiorgan failure due to multiple small vessel thrombosis associated with thrombotic microangiopathy. It occurs in less than 1% of APS.[3] CAPS was triggered by an identifiable factor mainly infections, trauma or surgery, anticoagulation withdrawal, malignancies, lupus flares, and/or pregnancy in

50% of patients. In pregnancy, CAPS usually follows HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, which can be associated with preeclampsia or eclampsia. Close monitoring of patient's full blood count, liver function test, and blood pressure is vital in the management of such patients.

Testing for APLA should be considered in recurrent pregnancy loss or stillbirth. In the original 1999 Sapporo classification, the diagnosis of APS is established when the APLA is present together with any of these three clinical criteria: (1) three or more consecutive unexplained miscarriages before the 10th week of gestation, (2) one or more unexplained death of a morphologically normal fetus at 10 weeks of gestation or later, or (3) one or more premature births of a morphologically normal fetus at 34 weeks of gestation or earlier, associated with severe pre-eclampsia or placental insufficiency.[7] As illustrated in Table II, the revised Sapporo classification (The Sydney criteria), were proposed in 2006 for the classification of true APS. In this revised classification, the clinical criteria remained unchanged, but the laboratory criteria were revised. IgG or IgM anti-β 2GPI antibody test were added to the laboratory criteria. In addition, the follow-up interval was prolonged from 6 weeks to 12 weeks.

Our patient initially tested negative for LA. A normal coagulation factor or inhibitors test results in the acute setting of thrombosis should be interpreted with caution. Aboud et al. proved that testing at the time of a thrombotic event may result in 'false-negative' LA result.[8] Testing is more accurate once the prothrombogenic mechanism is arrested and acute phase reactants lowered. Thus, the best time for an accurate assessment of thrombophilia is at least six months after an acute thromboembolic episode and at least four to six weeks after stopping antithrombotic therapy. Testing should be repeated at least 12 weeks apart, and the diagnosis of thrombophilia is confirmed if at least two or more subsequent test results are positive.

APLA fluctuates over time. Our patient was retested at 4 months and 10 months after completing her anticoagulant treatment. The test showed positive LA initially but was undetected at 10 months post anticoagulant. Loss of positivity of APLA post-thrombosis has been observed in clinical practice, especially those with secondary APS. If it occurred just at the time of thrombosis, it might reflect loss due to deposition in the thrombosis. This shows how difficult it is to define a patient as 'positive' or 'negative' for the APL markers, given the fluctuations over time, and high false-negative and false-positive rates for LA detection.[8] Thus, an overall interpretation of all LA testing, combined with the patient's clinical information is required to make an appropriate diagnosis. Therefore, patients with thrombotic events need to be treated with anticoagulants immediately although the cause of thrombosis may or may not be confirmed later.

The current recomended treatment of thrombotic and obstetric APS is antithrombotic agents. The anticoagulant of choice during pregnancy is LMWH, although adjusted-dose unfractionated heparin (UHF) can also be used. Warfarin is usually avoided after the first trimester because of concern for warfarin embryopathy. Anticoagulation should be continued throughout delivery and for six weeks postpartum In the postpartum period, either continuation of LMWH or bridging to warfarin with the aim to achieve a therapeutic International Normalized Ratio (INR) of 2 to 3 are acceptable options. The combination of aspirin and LMWH has resulted in a live-birth rate of over 70%.[9]

Our patient was started on LMWH and was continued until 6 weeks postpartum. Low-dose aspirin was also prescribed to reduce the theoretic potential for adverse effects on the placental microcirculation. Both aspirin and LMWH are safe for the fetus in pregnancy. For future pregnancies, patients with previous thrombosismay be put on long-term anticoagulants prior to conception.

Pregnancy outcome is optimized when pregnancy is planned in patients with APS. Patients are generally advised to use contraception to avoid pregnancy if they have severe disease-related damage, during active disease and while on teratogenic medications such as warfarin.[10] Given the additive effects of multiple risk factors, combined hormonal contraceptives are not advised for use in APS patients.[10] Progesterone-only contraceptives likely represent the best option for APS patients, as there is little-to-no demonstrated an increased risk for thrombosis.[10] The risks and benefits of each method need to be explained to patients with APS in the childbearing age.[10]

CONCLUSION

In summary, we described a young mother who presented with cutaneous thrombosis at the end of second trimester of pregnancy with recurrent oligohydramnios, whom later confirmed to have APS. The use of LMWH in combination of aspirin has resulted a favourable maternal and fetal outcome in our patient. This case highlights the importance of a skin biopsy of the skin lesions which allowed early diagnosis of thrombosis when thrombophilia screening during pregnancy and active thrombotic event is usually false negative. Initiation of appropriate antithrombotic treatment will improve the pregnancy outcome and prevent potential complications of the disease.

CONFLICT OF INTEREST

None

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Haematidrosis in young Lass: An omen of stress

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SUMMARY

Haematidrosis, also known as hematohidrosis, is an unusual disorder in which healthy skin secretes blood. Scarce case reports mainly occurred in adolescent Asian girls. It is common to misdiagnose haematidrosis as a consequence of self-harm because it is often triggered by severe stress or psychiatric disorders. Early diagnosis will enable rapid treatment and intervention of the underlying diseases and stress, making it essential to understand this disease and its clinical features. We describe a case report of a 16-year-old Malay girl who presented to the clinic with a 1-month history of episodic sweating blood from her forehead and occasionally bloody tears. Specific investigation to establish the diagnosis is still a dilemma, but a more significant challenge in primary care is identifying and managing a teenage patient's stressor.

INTRODUCTION

Haematidrosis (ICD-10 2016 diagnosis code L74.8) is an eccrine sweat disorder and a rare clinical condition of sweating blood presented spontaneously from non-traumatized skin. Sweat glands have not been definitively implicated in this condition. It usually occurs when a person suffers from extreme stress, for example, being bullied by peers. A few cases of haematidrosis were reported in the literature, and none has been reported in Malaysia.[1] The existing literature is scarce and often based on clinical events; therefore, incidence and prevalence are unknown.[1,2] Most cases include bleeding from the eyes, ears, and nose, although there have also been reports of bleeding from the umbilicus, trunk, and extremities.[1] The actual cause and pathophysiology of the disease are still unknown. Haematidrosisis blood oozing out of unbroken skin in the same way as sweat does. It affects the face, ears, nose, and eyes, linked to other psychological concerns, including fear and mental stress.[1,2]

Haematidrosis remains a diagnosis of exclusion after ruling out other conditions such as bleeding disorders, self-inflicted skin lesions, chromhidrosis (another rare skin condition characterized by the secretion of yellow, blue, green, or black-coloured sweat), or pseudochromhidrosis (a condition where normal sweat becomes coloured by exogenous factors). There is no specific laboratory investigation to diagnose haematidrosis. However, in some cases, red blood cells in the secreted liquid distinguish haematidrosis from chromhidrosis and pseudochromhidrosis.

CASE REPORT

A 16-year-old Malay girl with no prior medical illness presented to a health clinic in Kuantan, Pahang, with a complaint of bleeding intermittently from her face and palm for one month, without any underlying trauma. No other areas involved in bleeding episodes such as the axilla, areola, and anogenital skin. No similar episodes were experienced by her before. She reported no visible broken skin; bleeding episodes began without warning and were unprovoked. It was not preceded with feeling of warmth or burning sensation over the skin. She also experienced between two to three daily episodes of bleeding that occurred during sleep and when awake. Each episode lasted for 3–5 minutes and was usually self-limited. The patient described an occasional tingling sensation over her forehead during the bleeding episode. The sweat was bloody in appearance and does not involve other colours such as brown, black, blue, green, or yellow. It also did not stain the skin. There was no other associated bleeding tendencies, such as gum bleeding, hematemesis, menorrhagia, bruises, or anaemia symptoms. There was no family history with bleeding disorder or similar presentation. Other aspects of her history at that stage were noted to be non-contributory as there was no history of prolonged fever, joint pain, alopecia, dye exposure, chemical product, medication, and supplementation history.

Upon examination, she appeared comfortable with no psychomotor agitation or retardation. Her vital signs were stable. She was not pale nor tachycardic. Examination over the face, scalp, eyes, and other parts of her body revealed no wound, swelling, lump, abnormal vascular lesion, skin pigmentation, or staining. Other physical examinations were unremarkable; specifically, there were no signs of self or secondary inflicted injuries (scars, scratches, or wounds), and a possible diagnosis of haematidrosis was made. Figures 1 and 2 show bleeding episodes at home which were recorded and witnessed by her parents.

Recognizing that haematidrosis could signify a hidden psychological finding, she was approached by applying CRET *(Confidentiality, Rapport, Empathy, and Trust)* throughout the consultation. An important assessment tool to engage a teenage patient was utilized. HEADSS, which consists of psychosocial assessment of *Home, Education/eating/exercise, Activities/peer relationships, Drugs/cigarette/alcohol, Sexuality, and Suicide/self-harm* revealed that this young girl was having issues at home and school. She admitted to having depressive symptoms and did not fulfil the DSM-5 criterion for major depression due to peers and parental factors. She also complained of persistent low mood in the past two months

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Table I: Investigations

		Normal value
Haemoglobin (g/L)	13.2	12.5–16.0
Platelet (10^9/L)	291	150-300
White cell count (10^9/L)	9.71	4.0-10.0
Differential count (10^9/L):		
Lymphocyte	2.3	1.0-4.0
Neutrophil	5.0	2.0-7.5
Peripheral smear	Normochromic normocytic red blood cell	
Prothrombin time (s)	10.3	sec.
International normalized ratio (s)	1.0	1.0-1.2
Activated partial thromboplastin (s)	28.5	25.0-35.0
ISTH SCC Bleeding score	1	<6 (female)

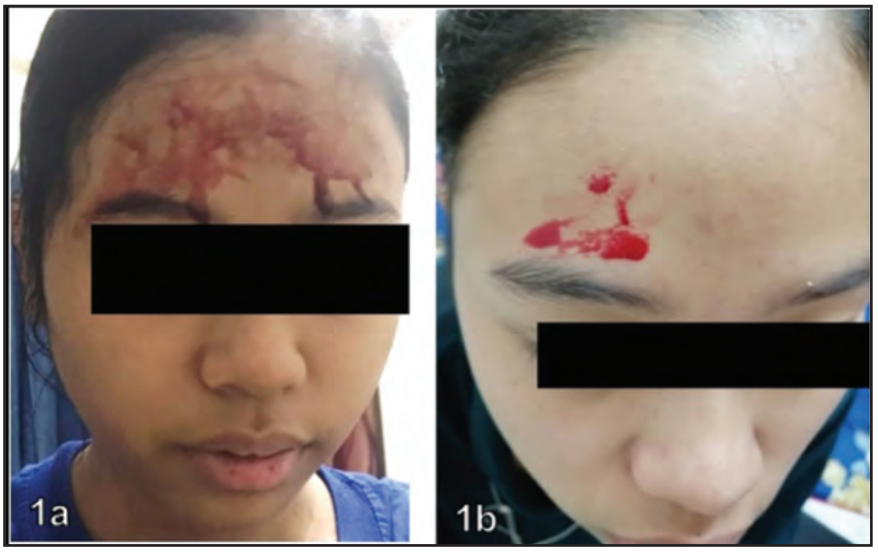

Fig. 1: (a) Bleeding sweats from the forehead and (b) no bleeding seen after wiping the forehead

Fig. 2: (a) Bleeding tears and (b) bleeding sweats from the forehead

before the bleeding episode occurred. It was associated with anhedonia (loss of interest), hopelessness, and poor sleep—otherwise, no suicidal thoughts or self-harm behaviour. The patient felt intimidated and was experiencing significant psychological stress due to peer bullying at her new school, which occasionally involved physical abuse. This problem was triggered since her family moved to Kuantan from Kuala Lumpur. She also felt that her parents were authoritarian and that they paid more attention to her other siblings.

At the clinic, she was counselled on relaxation techniques and coping skills. She was referred to Hematology Department where the diagnosis of haematidrosis was confirmed clinically. She was planned for fluid serology and skin biopsy but was not proceeded.

Her blood investigations are shown in Table I, and all results were normal.

She was also referred to psychiatry team, which diagnosed her with mild depression and was prescribed medication to help with her sleep, but her mother refused the medication. She defaulted hospital follow-up as her parents opted for alternative treatment and breathing and relaxation techniques. After 6months, her symptoms eventually resolved. Her mother claimed it was due to the alternative treatment using only healing water given by a pious man.

DISCUSSION

Haematidrosis is a rare condition in which capillary blood vessels enter the sweat gland, possibly rupturing and causing them to exude blood. It occurs under extreme physical or emotional stress and aetiology proposed by a few authors.[1,3] There are various causative factors, for instance, systemic disease, excessive exertion, psychogenic, and unknown causes.[2,4] According to a case series by Kluger et al. in 2017 for 10 years,it was revealed that only 25 cases were reported, and most patients were women (84%) with the median age in youth (13 years old) and mainly in Asia.[1] The researcher also found that forehead was the most common site of bleeding (40% in cases), and possible triggering factors were identified in 56% of the cases; most of these (86%) were stress, and others were platelet dysfunction and epilepsy.[1] Our case report has similar characteristics as the majority of other cases reported.

Treatment of haematidrosis depends on the aetiology. In a recent case series, few patients were treated with beta-blockers, anxiolytic medications, and antidepressants.[2,5] About 50% of the patients were treated with beta-blockers, and the treatment was effective 94% (17/18) of the time in reducing or resolving symptoms.[2,6] Psychological therapy, counselling, and relaxation techniques are all included in the treatment plan.[1,2,6] Psychotherapy primarily involved relaxation techniques, cognitive behavioural therapy and parental education to reduce stress. Referral to the haematology team was also done to identify possible underlying haematological disorder(s). As part of the natural history of this condition, the symptoms of haematidrosis usually resolve when the causal agent is removed. In this case, the remission occurred spontaneously without medical therapy. There is a misconception by parents that the disease had been cured due to taking the healing water. Therefore, it is the role of the primary care physician to correct the misconception and re-educate the patient and the family.

Shafique et al., 2021, proposed an algorithm for the evaluation and management of patients with potential haematidrosis.2 Without an actual laboratory test, it is crucial to rule out bleeding diseases or connective tissue illnesses in which vascular fragility might cause bleeding. According to the proposed algorithm, haematidrosis remains a diagnosis of exclusion while investigating patients with suspected haematidrosis.[2] Further examination, such as the platelet function test, could not be done in this case because the mother opted for alternative treatment with conventional care.

Knowing the aetiology of psychosocial stressors requires the HEADSS framework as an integral part of history, it is relevant when the psychosocial assessment of a teenage patient is a concern. Approaching via CRET and HEADSS, besides psychosocial assessment and as an engagement tool, stressor(s) (negative factors) and positive factor(s) could also be identified. Similarly, HEADSS is used to assess the teenager's progress during follow-up. The psychiatric referral was done as a shared care mainly to identify undetected underlying significant psychiatric issue(s). Mild depression can be managed in primary care, collaborating with occupational therapists and counsellors.

CONCLUSION

This case highlights the rarity of the condition and the dilemma in diagnosis as no gold standard investigation is available to confirm the diagnosis of haematidrosis. It is an interesting bleeding phenomenon where a psychological trigger (rivalry, bullying, punishment) leads to a sequence of events culminating in bleeding from intact skin. Referral to other related departments must be arranged to exclude other conditions to confirm the diagnosis. CRET and HEADSSS frameworks were used to engage and explore her psychosocial state, and they revealed mild depression precipitated by peers' bullying and family conflict. Non-pharmacological therapy (relaxation technique, coping skills, supportive counselling) was rightfully instituted at the primary care level, and psychiatry input was also sought. HEADSS approach was able to identify the stressor, and eventually, health care personnel will be able to alleviate the stressor by focusing on the area involved through an appropriate solution given. Therefore, HEADSS is the right tool for facilitating clinical management in a case of haematidrosis in adolescents in line with the detailed investigation to rule out other causes of bleeding.

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CONFLICT OF INTEREST

None to declare.

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A rare case of metastatic colorectal adenocarcinoma to the thyroid gland after 7 years: An upper airway emergency in a thin neck

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SUMMARY

Upper airway obstruction is an Ear, Nose, and Throat (ENT) emergency, a life-threatening condition that requires immediate intervention. An 87-year-old female post right hemicolectomy for colon adenocarcinoma 7 years ago presented with stridor. It was a rare case of metastatic colorectal adenocarcinoma to the thyroid causing bilateral vocal fold immobility. Emergency tracheostomy and debulking of thyroid were performed with much difficulty despite the patient's thin neck, due to the distorted laryngeal anatomy caused by the thyroid malignancy. In this case report, we highlight the challenges in acute airway management and role of surgical debulking to management in future cases.

INTRODUCTION

Upper airway obstruction (UAO) is a potentially fatal Ear, Nose & Throat (ENT) emergency that requires immediate intervention. UAO is defined as an anatomic narrowing or blockage of any portion of the airway above the thoracic inlet resulting in decrease ability for ventilation.[1,2] Bilateral vocal fold immobility (BVFI) is a cause of UAO as the vocal cords assume a paramedian static position following injury to the recurrent laryngeal nerve (RLN). This may occur following thyroidectomy or neck malignancy.[3] We describe a rare case of BVFI secondary to inapparent metastatic colorectal adenocarcinoma to the thyroid. The challenges in acute airway management and role of surgical debulking are highlighted for better management in future cases.

CASE REPORT

An 87-year-old female with a background of colon carcinoma with a hemicolectomy 7 years prior presented with progressive noisy breathing and breathlessness for 2 weeks. Her voice was getting increasingly breathy and easily fatigable over the past year. This was associated with a non-productive cough and blood-stained saliva.

She also complained of a 6-month history of progressive dysphagia, choking on solid food. She could only tolerate a soft or liquid diet (e.g.,porridge or soup). She was, however, still independent of all her activities in daily life.

She saw a physician once 6 months ago and was found to have multiple bilateral parenchymal opacities measuring 2–3mm in size on chest X-ray. Metastatic lung disease was suspected however, at that time, she elected not to have further treatment.

She has hypertension and dyslipidaemia. She previously had a right hemicolectomy for a T3N0M0 moderately differentiated adenocarcinoma of the proximal transverse colon. Although there was a perineural invasion, there was no lymphovascular invasion. The tumour was completely excised with clear margins. She refused adjuvant chemotherapy or radiotherapy.

On observation, she had biphasic stridor. Her dysphonia grade was three on the GRBAS scale (grade, roughness, breathiness, asthenia, strain) scale with a predominant breathy component. Her maximum phonation time was only 3 seconds. She was unable to count 1–10 in a single breath and she had poor cough effort.

Physical examination of her neck revealed a thin, slender neck with no neck masses palpable or cervical lymphadenopathy (Figure 1A). Trachea was central and the laryngeal framework was intact. There was, however, loss of laryngeal crepitus.

Flexible nasopharyngolaryngoscopy showed bilateral vocal folds in paramedian position with a slit-like airway. There was a pooling of saliva in the piriform sinuses; however, no lesions were seen in the supraglottic and glottic region. Repeat chest radiograph confirmed metastatic lung cancer with cannonball lesions. Lateral neck radiograph showed narrowing of the subglottic trachea at the level of C7 and below (Figure 1B).

The initial impression was metastatic adenocarcinoma to the lungs or a second primary malignancy such as an upper oesophageal carcinoma causing RLN palsy.

She underwent an emergency tracheostomy under local anaesthesia (LA) due to concerns of difficult intubation due to BVFI, as well as the risk of airway collapse, and prolonged ventilation due to poor lung condition if she was put under

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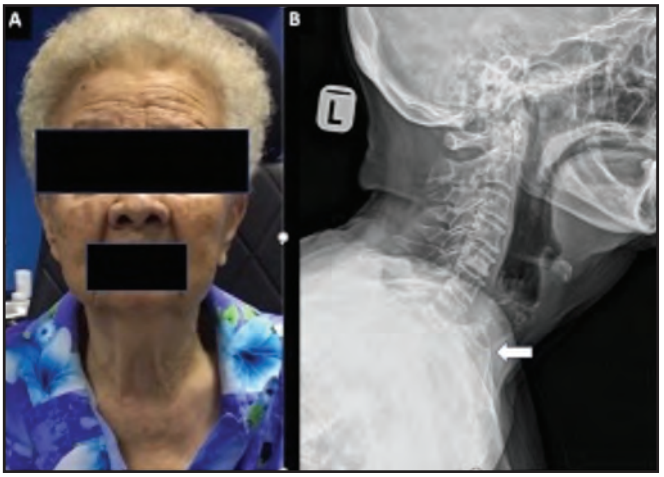

Fig. 1: (A) Patient with a thin neck with no anterior neck swelling palpable (printed with consent). (B) Lateral neck x-ray showing a narrowed subglottic area at level C7 (white arrow)

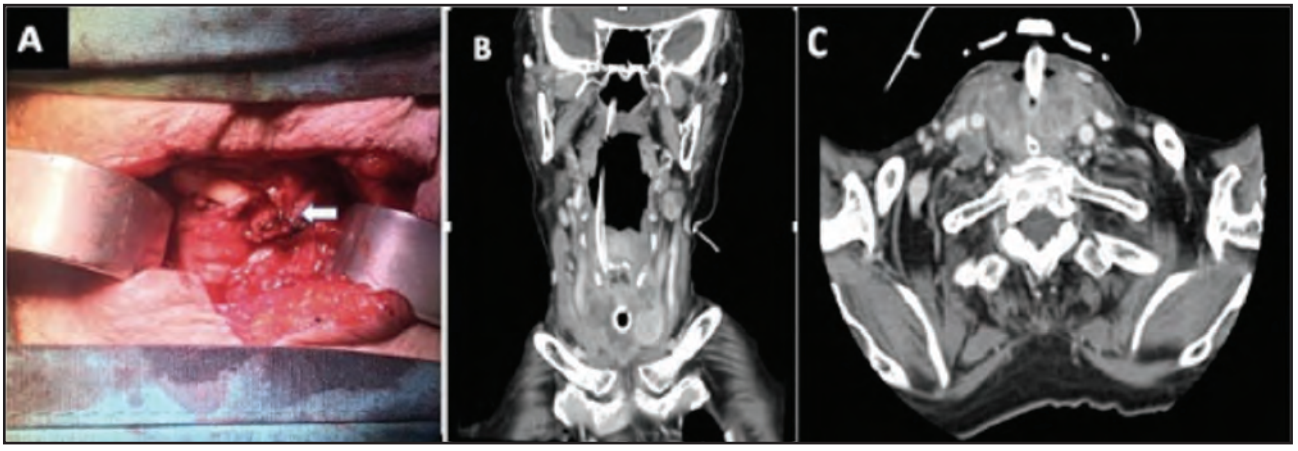

Fig. 2: (A) Intraoperative picture of trachea showing cricoid and tracheal rings one to three after debulking of thyroid tumour (white arrow). (B) Coronal CECT view of right hypodense tumour and left hyperdense thyroid nodule with tracheostomy *insitu*. (C) Axial CECT view of tumour surrounding trachea causing tracheal narrowing at level C7 with tracheostomy *insitu*

general anesthesia (GA) via intubation. Intraoperatively, there was a thick, hard, calcified mass firmly adherent and wrapped around the thyroid cartilage, cricoid, and trachea, conforming to these structures. The mass was identified as a calcified thyroid gland, around 1cm in thickness, and there was no plane of dissection. This distorted the laryngeal anatomy causing difficulties identifying the trachea. After dissecting superiorly to delineate the superior thyroid notch and inferiorly to the level of the sternal notch, a low tracheostomy was not possible. A hypodermic needle and syringe partially filled with normal saline was used intermittently to aspirate air from the lumen ofthe trachea to ensure that it was still midline and to ascertain the depth from the plane of our dissection. Partialdebulking of the mass or an isthmectomy was performed to create a window to expose the cricoid cartilage and upper tracheal rings (Figure 2A) and a size 7.5mm single lumen cuffed tracheostomy tube was inserted. Of note, there was tracheomalacia at rings two to four.The patient was supplemented with oxygen via a face mask throughout the procedure. Once the tracheostomy was completed, the patient was put under GA. Biopsy of the calcified thyroid gland was sent for histopathology examination.A rigid esophagoscopy was initially planned but it was not performed as the patient was not fit for further procedures.

Postoperatively, she was extubated, put on tracheal mask oxygen support for few days and nursed in general ward. She did not require intensive care unit admission. She was treated with amoxicillin / clavulanic acid 1.2g three times a day for aspiration pneumonia which was caused by the emergency tracheostomy under LA. She also had a left lung pigtail drain inserted for malignant pleural effusion. Cytology of the pleural fluid showed atypical cells. CEA and CA19-9 were elevated.An upper flexible oesophagoscopy and a percutaneous endoscopic gastromy (PEG) tube insertion was scheduled postoperatively but cancelled due to general frailty.

Postoperative contrast-enhanced computed tomography (CECT) scans of her brain, neck, thorax, abdomen, and pelvis revealed metastases to the thyroid gland, cervical lymph

nodes, brain, lung, pleural space, and liver. In the neck, there was a large hypodense right thyroid lobe and isthmus with central necrosis (Figure 2B). There was evidence of extracapsular spread and the lesion surrounded the trachea, causing narrowing of the trachea at the level of C7 (Figure 2C). Posterior to the trachea, there was no clear plane between the tumour and oesophagus at the level of T2; however, there was no overt infiltration of tumour into the lumen of the oesophagus. At that level, the oesophagus was compressed by the tumour. There was the presence of necrotic lymph nodes largest at right level II (1.6cm). There was, however, no evidence of local recurrence in the bowel.

Histopathological examination confirmed metastatic adenocarcinoma to the thyroid gland from colorectal origin. The thyroid gland was completely infiltrated by malignant cells which were positive for gastrointestinal immunohistochemical markers cytokeratin 20 (CK20) and negative for cytokeratin 7 (CK7) and transcription termination factor 1 (TTF-1).

She spent 3 weeks in hospital and was discharged home for hospice care.

DISCUSSION

Thyroid metastases are rare withan incidence of 0.36–2% of all thyroid malignancies.[4-5] The most common site of origin for thyroid metastases is from renal cell carcinoma followed by lung, breast, and then only from the gastrointestinal tract carcinomas.The incidence of thyroid metastases from colorectal carcinoma (CRC) is therefore low and has been reported to be 0.1% in a retrospective audit of 5,862 cases of thyroid metastases detected over a 10-year-period.[6] The principal ways for metastases in colorectal cancer are direct invasion, hematogenous spread, lymphatic spread, and implantation metastasis.However, despite its rarity, one should consider the possibility of an undiagnosed thyroid malignancy in a stridorous patient when faced with the difficulty in identifying normal tracheal rings during tracheostomy.

Thyroid gland and RLN are commonly mentioned together due to their anatomical proximity. The right RLN branches from the right vagus nerve or cranial nerve X (CNX) in front of the first part of the subclavian artery and then hooks below and behind the artery. The right RLN subsequently enters the trachea-oesophageal fascia (TOF) at a level inferior to C7 to T1.[7]

In contrast, the left RLN branches from the left CNX on the left side of the arch of aorta before it hooks around ligamentum arteriosum on the lower surface of the aortic arch in the thorax. The left RLN enters at level inferior to T2.[7] Both RLNs ascend within the trachea-oesophageal groove with the right RLN located more anteriorly and laterally compared to the left RLN, on the medial surfaces of the thyroid lobe.[7] Each RLN passes deep to the inferior constrictor muscle before it enters the larynx. The RLN innervates all the laryngeal muscles except the cricothyroid muscle and the sensation below the vocal cord level.

In the patient above, the CRC had metastasized to the right thyroid gland and the isthmus with extracapsular spread. Based on the CECT of the neck, the tumour had significantly encased and caused narrowing of the trachea at the level C7 with no erosion of the thyroid cartilage seen. Posteriorly, there was no clear fat plane with the trachea at T2 level and tumour compressed the oesophagus. This correlates to the involvement of the trachea-oesophageal groove at the level C7 to T2 which explains the BVFI causing UAO, stridor, hoarseness, and aspiration. Other causes of worsening respiratory distress could include enlargement of thyroid tumour due to haemorrhage or progression of cancer causing rapid increase of external pressure on the trachea or intratracheal invasion of thyroid tumour. In contrast, it was initially thought that the BVFI was due to lung metastases involving both sides of the RLN.

Malignancy of the thyroid gland often causes tethering of the soft tissues due to fibrosis thereby making it difficult to obtain a good laryngoscopic view of the larynx during orotracheal intubation.[8] Although there was a role for awake fibreoptic intubation, this was not possible for this patient due to her severe metastatic lung disease which would put her at a high risk for a complete airway obstruction or a prolonged ventilation period subsequently. Therefore, in our case, we performed a tracheostomy under LA.

Surgically, this was a difficult case due to poor anatomical landmarks. Therefore, a total or subtotal thyroidectomy would have helped delineate the anatomy better. However, given the patient's comorbidities and the emergency airway obstruction requiring quick airway secure, we performed an isthmectomy and partially debulked the thyroid mass instead to enable us to access the trachea. This was possibly the most appropriate decision at the time to secure the airway, given the urgency of situation.

In a caseseries by Testini et al,[9] they have advocated for an emergency thyroidectomy with or without an emergency tracheostomy for airway obstruction caused by a thyroid mass.[9] This is to relieve the compression on the trachea. In their series, tracheostomy was reserved for patients with tracheomalacia or when there was tracheal infiltration of tumour.[9] The rationale was that a tumour of the thyroid gland would completely obscure the landmarks of the thyroid cartilage and trachea and this would carry a high risk of bleeding when performing a tracheostomy alone. Therefore, if a subtotal, near-total or total thyroidectomy was unable to be performed at the same setting, a debulking of thyroid tumour would be appropriate to gain access for a tracheostomy and relieve the airway obstruction.[9]

Another method of a tracheostomy was to combine the use of a rigid bronchoscopy and percutaneous tracheostomy.[10] This technique involved tracheal intubation usinga rigid bronchoscopein a dark light off operation theatre. A 30-degree telescope wasintroduced and facedanteriorly. The xenon light intensity was set to the maximum level. Anopen surgical collar incision was made following a standard skin preparation. A partial debulking of tumour might be required if the pre-tracheal mass was thick until the illumination was visualised. A 23 Gaugehypodermic needle

was inserted into the trachea with an illumination guide. Once the endoscopic control has confirmed needle position in the midline of trachea, percutaneous tracheostomy would proceed. The advantages of this technique are the airway is under control throughout the procedure, it allows reopening of airway in the case of partially obstructing endoluminal tracheal tumour, it provides suctioning of the blood and secretion adequately, and the positioning of tracheostomy tube can be performed under direct visualisation.[10] Therefore, this technique should be considered as a management of upper airway in an obstructing tumour.

CONCLUSION

This was a rare presentation of BVFI due to metastatic CRC to the thyroid. Although rare, surgeons should be aware of its possibility in spite of a patient's thin neck. This is to avoid the undesirable consequences of discovering an advanced thyroid malignancy intraoperatively. When there is difficulty identifying the tracheal rings during a tracheostomy intraoperatively, one should always consider the diagnosis of a thyroid malignancy. This will ensure that the operating team is well-prepared to handle a potentially hazardous airway when a patient presents with obstructive symptoms.

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May–Thurner Syndrome: A case of an extensive left lower limb deep vein thrombosis and delirium precipitated by acute urinary retention

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SUMMARY

May–Thurner syndrome (MTS) is an anatomical variant in which the left common iliac vein is compressed by the right common iliac artery against the fifth lumbar vertebrae. It predisposes patients to left leg venous congestion, deep vein thrombosis (DVT), and recurrent cellulitis. We describe a case of a 78-year-old man who developed an extensive left lower limb DVT and delirium after an episode of acute urinary retention due to underlying benign prostatic hyperplasia (BPH). His computed tomography (CT) was suggestive of MTS. While MTS predisposed him to develop DVT, his DVT was precipitated by venous compression due to acute urinary retention. Similarly, his delirium was precipitated by acute urinary retention and by disorientation due to environmental change and poor vision. Underlying dementia was suspected, and an outpatient dementia workup was arranged. His delirium resolved following treatment of his urinary retention and rehabilitation. He was given anticoagulation, treated for BPH, and weaned off his bladder catheter. Endovascular management with antithrombotic therapy post-stenting is the management of choice for patients with left leg DVT and MTS, but while this patient was referred to the vascular surgeon, he was not planned for endovascular therapy due to evidence of a resolved DVT on repeat Doppler ultrasonography. He was put on life-long anticoagulation with warfarin.

INTRODUCTION

May–Thurner syndrome (MTS) also known as iliocaval venous compression syndrome is an anatomical variant in which the left common iliac vein is compressed by the right common iliac artery against the lower lumbar vertebrae. This may predispose to venous outflow obstruction and increase the risk of left lower limb deep vein thrombosis (DVT)[1] and recurrent unilateral cellulitis.[2] Bladder distension due to urinary retention has also been reported as a provoking factor for DVT[3] and is known to precipitate delirium.[4] Here, we report a case of a patient with MTS, with underlying benign prostatic hyperplasia (BPH), who developed extensive left lower limb DVT and acute delirium after an episode of acute urinary retention.

CASE REPORT

A 78-year-old man presented to the emergency department with a 3-day history of painful left lower limb swelling, and altered behaviour. Before the onset of symptoms, he was ambulatory, independent in his basic activities of daily living, had no history of fever or trauma to the lower limb, and no identifiable risk factors for thromboembolism such as immobilisation, constitutional symptoms, medications, smoking, or family history. He had underlying hypertension, dyslipidemia, bilateral eye cataracts, and glaucoma. He also had a history of lower urinary tract symptoms (urgency, nocturia, dribbling, incomplete voiding) with a previous history of recurrent episodes of acute urinary retention.

Physical examination revealed left leg oedema, warmth, and tenderness. Abdominal examination revealed a palpable bladder. The prostate was clinically enlarged. There was no lymph node palpable. Full blood count, liver function test, and coagulation profile were normal. Renal profile was impaired (Urea 10.1mmol/L, Creatinine 195mmol/L), and D-Dimer was positive (>20ug/mL). Ultrasound Doppler over the left lower limb showed an extensive left lower limb DVT involving the common femoral, superficial femoral, and popliteal veins. Abdominal ultrasound revealed prostatomegaly. Prostate-specific antigen, alpha-fetoprotein, carcinoembryonic antigen, and CA-19-9 were all normal.

He was diagnosed with left leg DVT with acute delirium, precipitated by urinary retention and disorientation due to an unfamiliar environment and poor vision. A urinary catheter was inserted, and medication for BPH (tamsulosin and dutasteride) was started. He was transferred to the Geriatric subacute cubicle for delirium and medical management. His delirium gradually resolved following the resolution of his urinary retention, and with rehabilitation. His renal function normalised during the admission, and he was weaned off the urinary catheter. His DVT was treated with warfarin with an initial course of enoxaparin. He was discharged with an early appointment for a computed tomography (CT).

Since discharge, he had received one course of outpatient treatment for left lower limb cellulitis, and his left lower limb erythema, pain, induration, and oedema have gradually resolved. CT findings were suggestive of MTS. The case was referred to a vascular surgeon for endovascular treatment and stenting. A repeat Ultrasound Doppler demonstrated resolution of the DVT. There were no plans for endovascular intervention due to the evidence of a resolved DVT, but he was put on life-long anticoagulation with Warfarin. He is also currently being worked up for suspected dementia.

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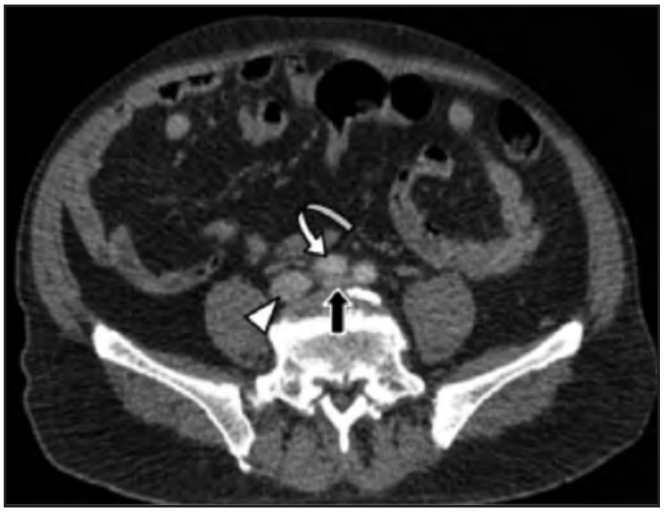

Fig. 1: Axial contrast-enhanced CT image showed slit-like appearance of left common iliac vein (black arrow) due to compression by the overlying right common iliac artery (curved white arrow). The right common iliac vein (white arrowhead) was normal in calibre and patent

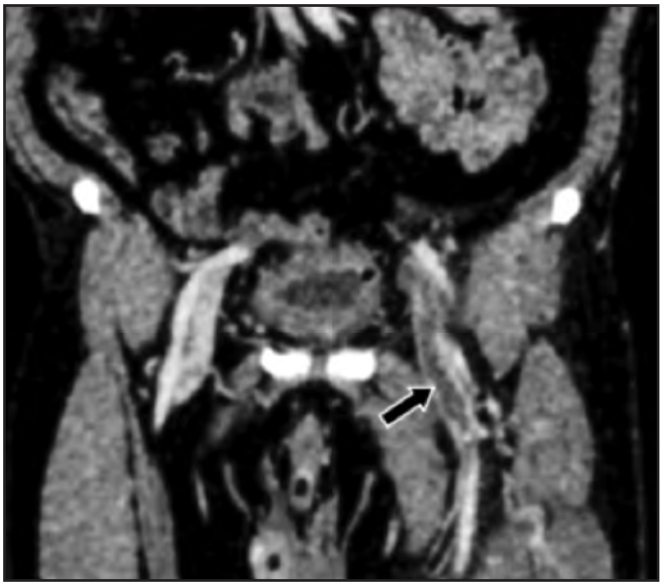

Fig. 2: Coronal contrast-enhanced CT image showed long segment thrombosis of the left external iliac and common femoral vein (black arrow) as is typical of a DVT with underlying May–Thurner syndrome

DISCUSSION

MTS may be a relatively common finding. A retrospective review of abdominal CT scans in asymptomatic patients found that 24% of patients had greater than 50% compression of the left iliac veins with the most commonly compressed structure being the left common iliac vein.[3] In a population-based study, it was found that 55.9% of all DVTs occur on the left side, and this tendency was not influenced by obesity, age, sex, surgery, injury, or oral contraceptive use.[5] This suggests that left common iliac vein occlusion by the right common iliac artery maybe is the only plausible explanation for this predominance. However, clinically recognized MTS accounted for only 2–5% of all DVTs,[6] which might suggest an under-diagnosis of MTS.

MTS may be asymptomatic, but patients are predisposed to developing lower limb oedema, varicosities, venous claudication, venous eczema, venous ulceration, DVT, and recurrent cellulitis.[2,7] Any insult which contributes to Virchow's triad of stasis, hypercoagulability, and endothelial dysfunction may provoke an episode of DVT in patients with MTS. In this case, the patient was asymptomatic until the onset of urinary retention. Bladder distension due to urinary retention has been reported as a provoking factor for DVT.[8]

What triggered a suspicion of MTS in this patient was the finding of an extensive left lower limb DVT, with absence of conventional risk factors for DVT. MTS should be suspected in any patients with venous insufficiency, recurrent cellulitis, or extensive DVT affecting the left lower limb. It should be noted that symptomatic MTS occurs more frequently in younger women compared to men, at a ratio of 2:1,[9] so in there should be an index of suspicion of MTS in this demographic group. The reasons for this predisposition are unclear. It might be due to a combination of pregnancy, hormonal changes, or oral contraceptive pill use predisposing to thrombosis, leading to detection of this anatomical variant.

Several imaging modalities can be employed to diagnose MTS.[5] Colour Doppler ultrasonography can be used as an initial, non-invasive imaging modality. It can help to identify DVT, which is a common complication of MTS. However, it is difficult (but possible) to demonstrate common iliac vein compression through ultrasound due to limitations such as body habitus and overlying bowels. CT was found to have high sensitivity and specificity in confirming a diagnosis of MTS. Magnetic resonance venography (MRV) has high sensitivity and specificity for detecting MTS and can be done without contrast or radiation. However, MRV has the disadvantages of higher cost, more time consumption, and limited availability.

In patients with MTS and DVT, therapeutic doses of anticoagulation should be started upon diagnosis. Endovascular treatment should be performed in combination with anticoagulation. Endovascular intervention should include catheter-directed thrombolysis or pharmaco-mechanical thrombolysis followed by angioplasty and stenting of the affected iliocaval segment.[8] In this case, management was limited to anticoagulation as a repeat Doppler ultrasound has demonstrated the resolution of the DVT.

The optimal duration of anticoagulation following an episode of DVT with MTS is unclear, especially in patients who did not undergo endovascular treatment. In a recently published case series of eight patients, where only two received endovascular stenting, left lower limb DVT recurred in one out of three patients who received 6 months of anticoagulation and one out of five patients who were given

life-long anticoagulation.[10] However, these two patients had additional thrombotic risk factors.

The focus of our case report is on MTS, but delirium is an important clinical condition that is worth mentioning. This patient had several predisposing factors for developing delirium: his age, visual impairment due to bilateral cataracts with glaucoma, and we suspect he had underlying dementia. His delirium was precipitated by acute urinary retention and disorientation to his environment during the acute admission. Known precipitating factors for delirium include acute illness/injury, environmental change, physical discomfort, use of physical restraint, and iatrogenesis. It is important to look for and treat these precipitating factors to treat delirium. There are currently no local clinical practice guidelines on the management of delirium, but the Malaysian Society of Geriatric Medicine has published a position statement on delirium which could serve as a reference.[4]

CONCLUSION

MTS predisposes to left lower limb DVT, venous congestion, and recurrent cellulitis. Patients presenting with extensive, unilateral left-sided DVT should be evaluated for MTS. Urinary retention due to BPH may provoke DVT in patients with MTS.Treatment of DVT with underlying MTS involves a combination of anticoagulation and endovascular therapy.

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CASE REPORT

Bilateral temporomandibular joint reconstruction with alloplastic condylar prosthesis: a case report

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SUMMARY

Trauma, pathology, and degenerative disease are common causes of structural damage to the temporomandibular joint (TMJ). The primary goal of TMJ reconstruction is to reestablish mandibular form, function and prevent further morbidity associated with non-functioning TMJ. Reconstruction of the condyle can be done with various material and techniques to achieve a functional and aesthetic outcome for the patient. We present a case of a 20-year-old male who was referred to our center for management of bilateral TMJ ankylosis post trauma. Patient sustained comminuted anterior mandible fracture with bilateral condylar fracture, however only the anterior mandible was reduced and fixed with titanium reconstruction plates. Post open reduction and internal fixation, the patient was noted to have progressively limited mouth opening, difficulty in both mastication and speech. Alloplastic condylar prothesis is an option in this patient as his TMJ structure was damaged due to trauma. Bilateral gap arthroplasty with interposition temporalis graft was performed prior to placement of alloplastic titanium condylar (Synthes®) Head Add - on system. Currently, post-operative 1 year, patient has a good mouth opening of 30mm, with improved function and aesthetics. We present this case to highlight that with detailed and methodical treatment planning, alloplastic titanium condylar prothesis is a safe and effective choice in the reconstruction of TMJ.

INTRODUCTION

Temporomandibular joint ankylosis (TMJA), can be classified by location, type of tissue (fibrous or bony), and extent of fusion (complete or partial). Multiple aetiologies account for hypomobility and TMJA, which ultimately leads to progressively decreased translation and rotation movement of the joint. Trauma is the most common cause, and other causes include otitis media, mastoiditis, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, scleroderma, irradiation, previous surgery, internal derangements, and perinatal events.[1] Patients with a fibrous or bony ankylosis may have a facial asymmetry, restricted range of motion, malocclusion, anterior open bite from a shortened ramus, or possibly midface abnormalities, including those of the piriform rim and orbits. The current treatment for ankylosis must be tailored based on the cause and other patient factors. Compressive management of TMJA starts with surgical intervention followed by physiotherapy. The scope of surgery includes gap arthroplasty, with or without interpositional tissue or joint reconstruction using autogenous grafts or alloplastic material.[2]

In maxillofacial trauma, it has been postulated that the formation of TMJA is secondary to organization and ossification of haematoma that arise from the fractured condylar head of mandible. Besides these local causes, poor reduction of condylar segments and conservative management (non-surgical) of condylar fractures has been shown to cause TMJA. When TMJA is present at an early age, there is significant disturbance toward the growth of the mandible, usually leading to patients presenting with limited mouth opening and asymmetrical face. This leads to physiological stress, lack of good oral hygiene and eventually loss of multiple tooth due to decay. Cumulatively, this leads to reduced quality of life for TMJA patient.

The main aim of any TMJA is to restore mouth opening, restore adequate ramus height, prevent further recurrence and symmetric growth of the mandible in the growing patient. TMJA management protocol by Kaban et al,[3] is generally used to guide the surgeon in achieving optimal results. The use of autogenous bone graft to reconstruct the TMJ has always been the gold standard, however here we describe an alternative option, using titanium alloplastic condylar prosthesis in TMJA.

CASE REPORT

A 20 -year- old gentleman, was referred for management of progressive limited mouth post open reduction internal fixation of mandible. Patient was involved in a motor vehicle accident, where he sustained high Le Fort 1 with palatal split, right orbital floor blow out fracture, comminuted fracture of bilateral parasymphysis of mandible and bilateral high sagittal intracapsular condylar fracture. Following the accident, open reduction internal fixation of Le Fort 1 with palatal split, right orbital floor blow out fracture, comminuted fracture of bilateral mandible 10 months prior to the initial referral. Over the months, despite aggressive post-operative physical therapy his mouth opening worsened to 4mm (inter incisor distance). Baseline computer tomography imaging showed bilateral sagittal fracture of the mandibular condyle, with dislocation of the medial segment of fracture, with widening of the intercondylar distance. The distal aspect of bilateral condyle appears to have moved

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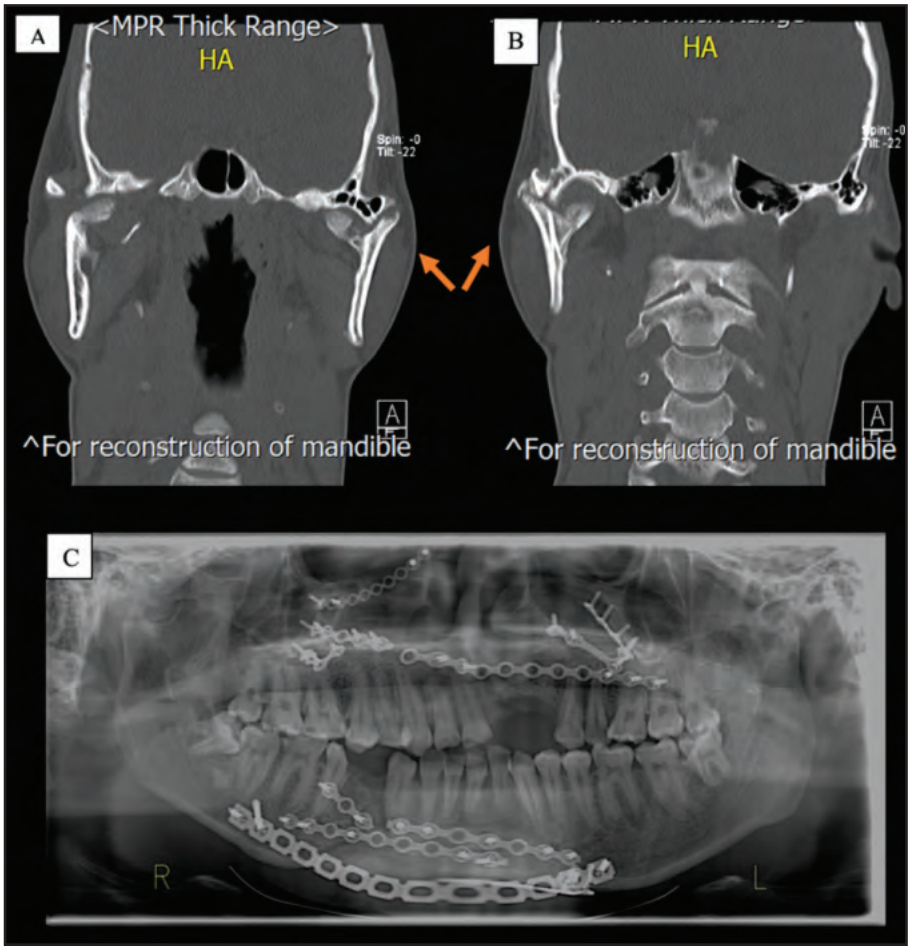

Fig. 1: A & B: Dislocation of the medial segment of fracture, with a widening of the intercondylar distance and the distal aspect of bilateral condyle, appears to have moved superolateral leading to widening of the midface clinically (arrow) (C): Orthopantomogram showing bilateral ill-defined condyle, loss of bilateral synovial cavity, and reconstruction plate over the lower border of mandible.

superolateral (Figure 1A & B), with significant flaring of the ramus leading to widening of the midface clinically. Panoramic Imaging taken shows bilateral ill-defined condyle, loss of bilateral synovial cavity, multiple titanium plate at anterior mandible and reconstruction plate over the lower border of mandible (Figure 1C). The proposed surgical plan for him was bilateral gap arthroplasty with interposition temporalis muscle, coronoidectomy, and reconstruction of condylar head with stock alloplastic titanium condylar prosthesis (Synthes ®) due to financial constraints. Extended pre-auricular incision was done to expose bilateral TMJ area. Intraoperatively, noted type IV TMJA[4], where there was extensive ankylosis, with complete disappearance of temporomandibular joint and fusion with the zygomatic arch (Figure 2A).

Bilateral condylectomy and coronoidectomy were performed followed by contouring of excessive bone to prepare a neo-glenoid fossa. Inferior attachment of the temporalis muscle was mobilized to be used as interpositional flap over the neo-glenoid fossa and anchored to underlying bone (Figure 2B). Intermaxillary fixation was placed, to ensure optimal occlusion prior to placement of condylar prosthesis. Synthes condylar head add-on with fixation plate used to reconstruct the TMJ with the desired vertical height (Figure 2B). Post-operative recovery was uneventful. Post-operative skull imaging displays a symmetrical appearance of both TMJ prosthesis secured to ramus of mandible (Figure 2C). Patient was put back on physical joint therapy incorporating TheraBite ® jaw motion rehabilitation system, to restore jaw mobility. Post-operative 1 year, his mouth opening was maintained at 35mm (Figure 2D).

DISCUSSION

Correction of TMJA is one of the most challenging procedures in oral and maxillofacial surgery. Apart from the complex anatomy surrounding the TMJ, in order to achieve adequate ramus height, multiple graft sources have been used over the years, including costochondral, sternoclavicular, fibular, iliac crest, and metatarsophalangeal tissue. The most widely used graft, particularly in children, is the costochondral graft. Unfortunately, the costochondral graft has been shown to have an unpredictable growth pattern and results in more complications. Regardless of these problems, the costochondral graft is still considered by some to be the

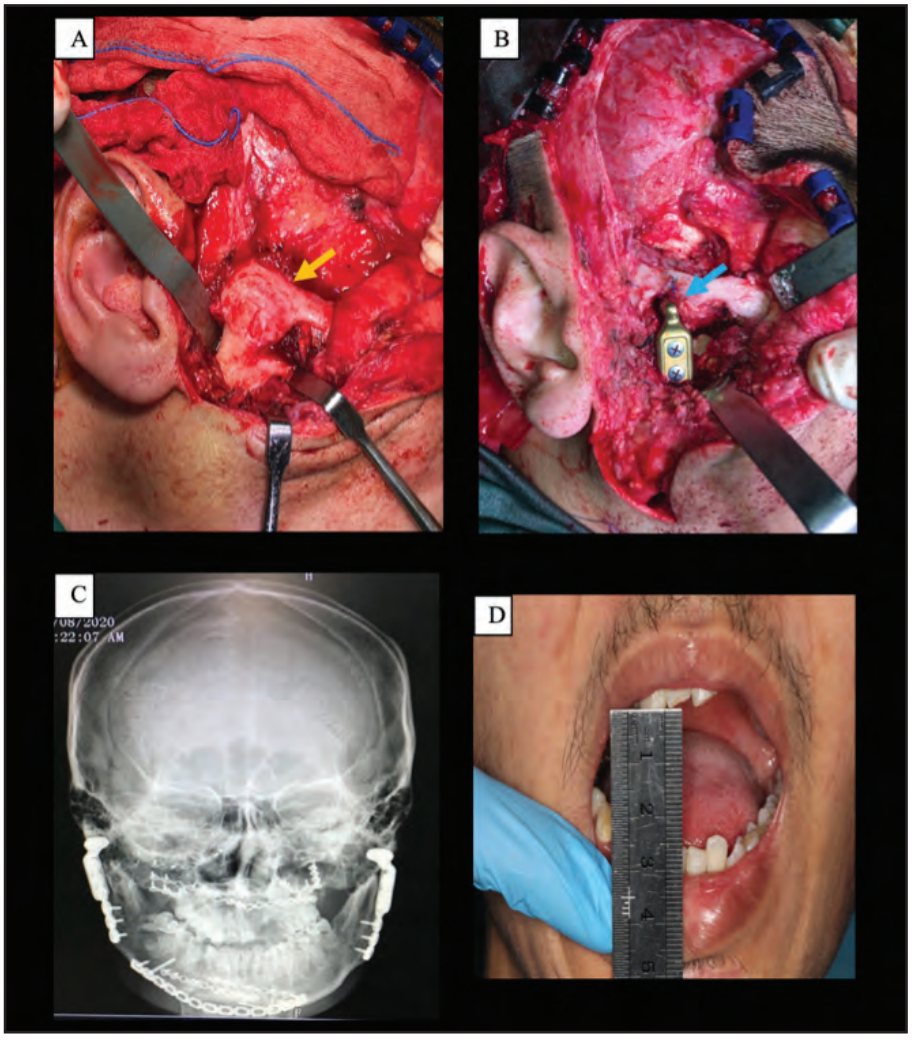

Fig. 2: A Exposed right TMJ with extensive ankylosis and with complete disappearance of temporomandibular joint space with fusion into the zygomatic arch (Arrow). B: Neo- glenoid fossa with temporalis muscle acting as interpositional flap (arrow) with condylar prothesis. C: Post-operative skull posteroanterior view shows, symmetrical TMJ prosthesis secured to ramus of mandible D: Post-operative 1 year, mouth opening at 30mm.

operative management of choice in children and adults who have not had prior surgery.[5] Besides free grafts, distraction osteogenesis of the ramus in order to create adequate ramus height is an option to achieve adequate mouth opening and functional jaw movements.[6] However, the cost of the distraction device is quite expensive and subjects the patient to multiple sessions of surgery. Performing gap arthroplasty with no reconstruction of the condyle and interposition flap is another option discussed in the literature, however we believe that this will cause loss of ramus height which will lead to anterior open bite with the risk of ankylosis in the future.

Alloplastic condylar prosthesis can be an excellent option in achieving adequate ramus height and preventing the risk of ankylosis in the future. Alloplastic condylar prothesis available in the market can be divided into stock and custom made patient specific implant. The idea of using alloplastic condyle was first done by Carmochan using wood in the 1840.[7] The advantages of using alloplastic condylar prothesis are lack of donor site related complication, leading to reduced post-operative stay and reduction in operative time. Besides that, the ability to start physiotherapy immediately post operatively, is a major advantage as it returns the jaw to normal function, reduces scar tissue formation, and allows for immediate optimal range of motion. Three-dimension stability of alloplastic prothesis is superior when compared to risk of resorption in autogenous graft, and this allows for long term stable occlusion. As for the customizable prosthesis, the ability to create a specific size condylar head and glenoid fossa based on the patient anatomy is an added advantage. The disadvantages of using alloplastic material are the potential wear and debris formation which is usually associated with pathological response which will lead to potential re-surgery. Besides that, the size of the condyle head may be a mismatch to the underlying glenoid fossa, leading to unstable occlusion. The financial cost of purchasing the prothesis needs to be factored in when discussing it with the patient. Finally, the risk of foreign body reaction, which may lead to re surgery with complete removal of prosthesis is a possibility. After deliberating with the patient regarding the multiple options available together with its advantages and

disadvantages, patient decide for stock alloplastic condylar prosthesis because it entailed a single surgical session and site, as well as being affordable for the patient.

In future management of post trauma TMJA, we believe prevention is the best option. In this particular case, we postulate that the combination of high intracapsular sagittal fracture with bilateral comminuted parasymphysis fracture leads to the formation of TMJA. This was further complicated with lateral flaring of the ramus due to the placement of reconstruction plate over the lower border of mandible. All these combinations lead to condylar fracture to be displaced laterally, where it then forms ankylosis with the zygomatic arch. This is similar to what is proposed by He et al,[8] where they postulated that TMJA can be traumatically induced in patient with condylar fracture, no/inadequate reduction of condyle fracture, fracture condyle/ residual ramus displaced laterally or superior to the glenoid fossa, and mandibular hypomobility secondary to pain, head injury, mechanical restriction due to lateral displacement, and duration of maxillomandibular fixation. Management of anterior mandibular fracture with a concomitant high intracapsular fracture should have a high index of suspicion to the formation of TMJA and preventive steps should be taken to avoid the formation of TMJA.

Currently, there is no single surgical procedure or reconstruction option that provides absolute success in TMJA management. A systematic review and meta-analysis of surgical outcome in TMJA showed similar clinical outcomes in a patient treated with autogenous material or alloplastic prosthetic device. However, we believe compressive, immediate management of mandibular fractures will help prevent TMJA in trauma patients.

CONCLUSION

The use of stock (Synthes ®) add-on condylar prosthesis was successful in reestablishing mandibular form, function and to prevent further morbidity associated with non-functioning temporomandibular joint. However long term periodic post-operative review and serial imaging will require to monitor the new joint space and signs of glenoid fossa erosion. A proper TMJ prosthesis which consist of glenoid fossa and condyle is still required in a long term measure. Due to financial constraint patient opted for this option and will consider it later for re-operation.

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DECLARATION

The authors declare no conflict of interest.

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CASE REPORT

Extensive primary maxillary mucocele treated by combined external and endoscopic approaches

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SUMMARY

A mucocele is an epithelial lined mucus-containing sac completely filling a paranasal sinus cavity and capable of expansion. The common presentation of maxillary mucocele is nasal block, followed by cheek pain or pressure, nasal drainage and proptosis. Mucocele should be differentiated from a retention cyst by its histological appearance and imaging. Computed tomography scan and MRI are essential to confirm the diagnosis of mucocele, determine the location of the lesion, and evaluate possible involvement of the orbit or skull base. The management of mucoceles is by surgical removal of all their mucosal linings. Mucocele formation is usually due to an identifiable cause resulting in blockage of the common paranasal sinuses drainage. Primary mucocele in the maxilla is infrequently encountered. We presented a case of an extensive unilateral maxillary mucocele in a 36 years old lady without any predisposing factors, treated by combined endoscopic and Caldwell-Luc approaches. It is important for all clinicians to be aware that mucoceles may occur without any predisposing factors to avoid misdiagnosis.

INTRODUCTION

Maxillary mucocele may arise as a result of chronic nasal infection, previous trauma, allergy, sinonasal disease or prior sinus surgery.[1] But 64 % of the cause remains unknown.[1] Most reported origin of primary mucocele was the ethmoidal sinus, while secondary mucocele mostly from the maxillary sinus.[2] General occurrence of paranasal mucocele is commonest in frontal, followed by ethmoid, maxillary and sphenoid sinus.[3] The incidence is reported commonly in 40 to 60 year old without any gender predilection.[3,4] The frontonasal duct which is smaller as well as developmentally more variable, tends to be obstructed most as compared to the wider and consistent natural ostia of the maxilla.[3] Primary maxillary sinus mucocele is a rare condition and unlike the normal development of mucocele which is due to obstruction of sinus ostia, has no predisposing factors. The common presentation of maxillary mucocele irrespective of type is nasal blockage, followed by cheek pain or pressure, nasal discharge and proptosis.[1,2] Any patients having symptoms and signs suggestive of sinonasal conditions such as sinusitis should be referred to tertiary care for further expert evaluation which can include nasoendoscopic examination and sinus computed tomography scan. Sinus computed tomography scan is especially indicated when a tumour is suspected or in patients that don't respond to conservative management.

CASE REPORT

A 36 years old lady with no underlying medical illness, presented with presented with left sided blood-stained nasal discharge and nasal blockage. There was no history of trauma and no symptoms of upper respiratory tract infection. She has no history of allergic rhinitis symptoms such as frequent sneezing or rhinorrhea. There was no facial pressure or anosmia. She did not experience any epiphora, double vision or orbital pain. There was no surgical history to the nose or paranasal sinuses. She was not on any medications. The nasoendoscopic examination revealed engorged inferior turbinate of left nasal cavity. The septum showed no deviation or spur. There was no bleeding point seen at the postnasal region, septum or turbinal area both anteriorly and posteriorly. Bilateral otoscopy was normal. The oral cavity and oropharynx were normal, and the neck examination was unremarkable. The blood-stained nasal discharge most probably originated from the dry nasal mucosa of the left side of nose due to narrow nasal space from the enlarged left inferior turbinate. She was started with intranasal steroid spray, oral antihistamine and alkaline nasal douching. She was seen again for a few times after the first consultation, with similar symptoms and examination findings. About 5 months after the initial visit, the patient complaint of left nasal blockage. She denied left facial pain, left epiphora or left protrusion of eye. There was no palatal or alveolar mass and she denied any recent loosening of tooth over the left upper alveolus. The examination showed narrowing of the left ostiomeatal complex with left turbinate engorgement abutting the septum. Otherwise the eyes and intra-oral examination were unremarkable. Computed tomography of paranasal sinuses (CTPNS) showed an expanded left maxillary sinus with isodense mass occupying the entire left maxillary sinus, measuring 5.0 x 3.7 x 3.8 cm in dimension, with small peripheral calcification (Figure 1A). The mass caused thinning and medial bowing of the medial wall of the left maxillary sinus, compressing the inferior and middle turbinates. Concurrently, the intramaxillary lesion

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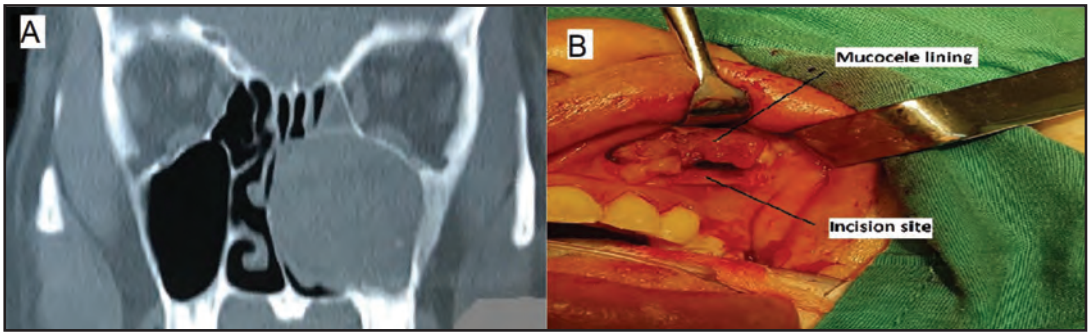

Fig. 1: The coronal view of sinus computed tomography scan showing heterogenous soft tissue density occupying the left maxillary sinus and extending into the left nasal cavity, with erosion of the medial bony wall of the maxillary sinus (A). The sublabial incision for left Caldwell Luc approach, superior to the canine fossa and extended laterally, showing part of the mucocele lining for complete removal (B)

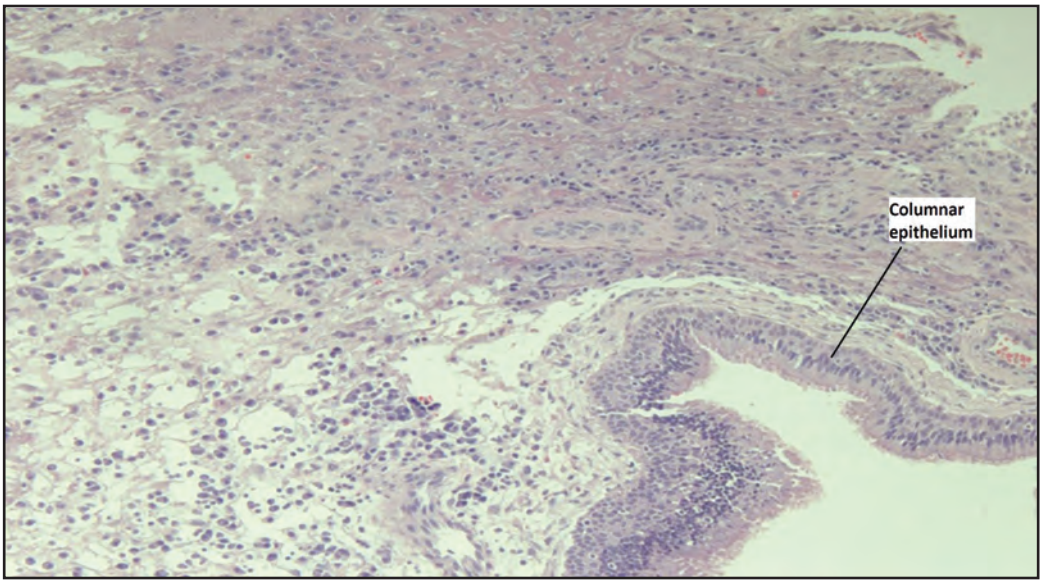

Fig. 2: Histopathological examination with hematoxylin and eosin staining (x 4 magnification) showing wall formed by hyaline connective tissue, with cystic areas lined by columnar epithelium

expanded through the medial wall to narrow the left nasal cavity due to the mass effect. The left ethmoidal sinuses showed mucosal thickening, while the frontal sinuses and sphenothemoidal recesses were patent. There was no left intraorbital, intracranial, nasopharyngeal or subcutaneous extension of the mass. She underwent left nasal middle meatal antrostomy and left Caldwell-Luc approach under general anaesthesia (Figure 1B). Intraoperatively, noted that both the left middle and inferior turbinate were medialized due to the left maxillary mass effect. On identification of the left maxillary ostium, it was noted that the antrum was widened but not draining the maxillary content as it was obliterated by the intramaxillary mass. The medial was thinned out and appeared soft. The left maxillary sinus ostium was further widened via middle meatal antrostomy, and the left maxillary sinus mass was visualized. It appeared as cystic looking, glistening, whitish greyish in colour, and fully occupying the whole maxillary sinus. After approaching the medial wall of maxillary sinus via middle meatal antrostomy, the mucocele ruptured and clear mucoid content seen. The content was decompressed, the mucocele lining was delivered in piece meal using forceps and angled microdebrider. The surgery was completed using Caldwell-Luc approach to access the anterior and inferior maxillary walls. Bilateral noses were packed with merocele and removed after 48 hours. The patient was discharged well after nasal packing removal and appointment given a week after the surgery for nasal toileting. She was instructed to do regular nasal douching with saline to remove the nasal crusting and blood clot. On follow-up at the outpatient clinic, she remained asymptomatic without any post-operative complications including synechiae seen. The nasoendoscopic examination showed left maxillary sinus was clear from the disease, and the left inferior and middle turbinate were normal. The histopathological examination showed the mass was formed by hyaline connective tissue, with cystic areas lined by columnar epithelium consistent with a diagnosis of mucocele (Figure 2). On follow at 24 months post operatively, she was well and there was no medialization of the left lateral nasal wall. The maxillary sinus remained clear.

DISCUSSION

The differential diagnosis of paranasal sinuses benign cystic mass presenting in the nasal cavity includes retention cyst, mucocele, chronic rhinosinusitis with nasal polyps, mycetoma, maxillary mucosal cyst and odontogenic cyst.[5,6] Occasionally, epidermoid cyst may also arise from the maxillary sinus.[7] Mucocele should be differentiated from a retention cyst by its histological appearance and CT imaging.[1] Mucoceles grow under the periosteum, while retention cysts grow under the mucosa of the sinus. Thus, retention cysts are non-expanding, well circumscribed, mucosa covered masses, whereas mucoceles exhibit an osteolytic capacity with a tendency to expand along the least resistance route.

Plain paranasal sinuses X-ray does not play much role in diagnosing maxillary mucocele, unless for frontal sinus mucocele which readily can be seen.8 CT scan and, in selected cases, magnetic resonance imaging (MRI) are essential to support the clinical suspicion of mucocele, determine the location of the lesion, and evaluate possible involvement of the orbit or skull base.[4] CT in the axial and direct coronal planes is the optimum modality in visualization of the bony expansion which occurs in mucocele formation. The CT scan appearance of a maxillary mucocele is an expansile mass with homogeneous substance that has an attenuation of 10 to 18 Hounsfield unit (HU). In contrast, long standing chronic mucoceles may have a larger protein content and the attenuation is higher (20–40 HU). On contrast study, there be will enhancement of the lining membrane of the mucocele. However, contrast enhancement is best reserved for MRI especially when secondary mucocele is suspected owing to sinonasal tumor.[8]

The management of mucoceles is by surgical removal of all their mucosal linings.[9] Endoscopic approach is advocated for the removal of maxillary mucocele.[10] Greatest advantages of this minimally invasive approach are reduced intraoperative pain, reduce postoperative cheek swelling and numbness and therefore shortened the hospital stay. However, an extensive maxillary mucocele may require a combined external and endoscopic approaches to ensure complete removal and prevent recurrence. Even though Caldwell Luc surgery is almost historical in the era of endoscopic sinus surgery, there are few conditions where the Caldwell Luc approach is useful as an access to the maxillary sinus; when the mucocele is located too far lateral in the maxillary sinus, severe thickening of medial bony wall of the maxillary sinus and when there is compartmentalization of the mucocele.[2,10] Another indication for an external approach is when the mucocele is located at the anterior wall of the maxillary sinus or extended into the pterygomaxillary fossa.[10] Planning of approach to maxillary mucocele prior to surgery is important in regards with the extension of the mucocele, surgeon familiarity of the technique and facilities available. In our patient, we successfully removed the maxillary mucocele by combining both endoscopic and Caldwell Luc approach. In recurrent cases, endoscopic removal can be attempted by employing either a wide middle meatal antrostomy, if that has not be done, or a modified prelacrimal recess approach to ensure complete removal. Though rarely done, external approaches with marsupialization have been described.[1]

CONCLUSIONS

It is important for all clinicians to be cognizant that mucoceles may occur without any predisposing factors to avoid misdiagnosis. Primary maxillary mucocele is a rare entity, where the exact aetiology is still unknown. Symptoms are mostly of mass effect in the maxillary sinus, together with symptoms related to its surrounding structures. Endoscopic approach is advocated but a combined approach of endoscopic and external are required for extensive lesion. As maxillary mucoceles can recur and in cases where histopathological examination has not excluded malignancy, regular tumour surveillance on follow-up is essential for early detection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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