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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.

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Hyponatremia in the elderly: A primary care challenge

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SUMMARY

Hyponatraemia is common in the elderly. Given the broad differentials for hyponatraemia, a meticulous diagnostic approach and comprehensive laboratory investigations are needed. Fluid status assessment is vital to decide on the next management. Unidentified hyponatraemia may lead to complications such as seizure and coma. Mismanagement or overly aggressive correction of hyponatraemia can lead to morbidity, such as osmotic demyelination syndrome, which might cause mortality. This case report delineates a challenging instance of moderate hyponatraemia in an elderly patient, highlighting the complexities encountered in the primary care setting. The patient initially presented with lethargy and generalised weakness, which worsened during routine follow-ups. History, physical examination, and laboratory investigations lead to the diagnosis of SIADH with no clear cause identified. Treatment primarily consisted of fluid restriction, accompanied by regular electrolyte monitoring. This case underscores the importance of prompt diagnosis and tailored therapeutic interventions to optimise hyponatraemia management in the elderly patients at the primary care settings.

INTRODUCTION

Hyponatraemia has a prevalence of 47.9% among individuals aged 60 years and above.[1] In Malaysia, 6.9% of elderly in primary care have hyponatraemia.[2] The prevalence of hyponatremia among older inpatients in a general hospital in China was 24.7%.[3] Hyponatraemia is defined as a plasma sodium level of less than 135 mmol/L. Sodium is an electrolyte that regulates the balance of water and minerals, conducts nerve impulses, and contracts and relaxes muscles. Mild hyponatraemia may have signs and symptoms such as nausea and vomiting, headache, muscle weakness, spasm, and fatigue.[4] Severe hyponatremia may lead to life-threatening complications such as seizures and coma.[4] It is important to correct hyponatraemia, as it is associated with increased morbidity and mortality.[5] The most common causes of hyponatremia in adults are SIADH, thiazide and antidepressant therapy, and endocrinopathies.[6] The American Family Physician algorithm for hyponatremia assessment provides a structured approach in evaluating hyponatraemia.[7] Assessing fluid status will help to diagnose the underlying condition. In general, hyponatremia is treated with fluid restriction in isovolumic, isotonic saline given in hypovolemia, and diuresis given in hypervolemia. Hypertonic saline is used to treat severe symptomatic hyponatraemia.[8] Chronic hyponatremia is less likely to cause seizures and other severe complications. Correction of chronic hyponatremia should be performed gradually than acute to avoid osmotic demyelination.[4] Recognising and diagnosing hyponatremia is imperative in primary care settings. Hence, this case study is going to discuss the management of an elderly man presented to a primary care clinic with chronic hyponatremia.

CASE PRESENTATION

A 64-year-old man is under six monthly follow-ups in a primary care clinic. He is a known case of hypertension, Parkinson's disease, benign prostatic hyperplasia, and a past episode of major depressive disorder with generalised anxiety disorder but defaulted psychiatry follow-up. During this follow-up, he presented with lethargy and generalised body weakness persisting for the past 5 months. His symptoms had worsened over the past 2 weeks, rendering him unable to climb stairs without assistance. As the presentation is non-specific, a systemic approach to history taking and physical examination is essential in ruling out broad differential diagnoses, including infection, dehydration, stroke, and anaemia. He denied experiencing symptoms of hyponatremia, such as headache, seizure, dyspnoea, nausea, vomiting, diarrhoea, muscle cramp, or paraesthesia. He takes about 2 litres of water per day and has no polyuria or polydipsia. There was no history of excessive fluid intake or fluid loss to rule out psychogenic polydipsia. No history of falls or trauma to the head. He has features of depression, such as low mood, anhedonia, and loss of concentration. His medications were Tab. Madopar (levodopa 200mg/benserazide 50mg) TDS, Tab. bisoprolol 5mg OD, Tab. atorvastatin 40mg ON, Tab. amlodipine 5mg OD, Tab. perindopril 4mg OD, and Tab. vitamin B1/B6/B12, 1 tablet OD. He did not smoke, take traditional medicines, or use alcohol or illicit drugs, and he was not taking diuretics.

During the initial assessment, his BP was 128/64, and other vital signs were stable. Physical examination showed no signs of dehydration and anaemia. There was no evidence of fluid overload, such as raised JVP, pulmonary oedema or bilateral lower limb oedema. He exhibited signs of Parkinsonism, including muscle rigidity, tremors, and reduced arm swing.

Investigations prior to this follow-up revealed moderate hyponatremia with a sodium level of 126 mmol/litre, prompting further evaluation. His sodium level has been ranging between 131 and 134mmol/L since 2007 throughout the follow-ups at primary care. Suggested relevant initial workups in primary care are thyroid function tests, fasting

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Table I: Baseline investigations and results

Date	2 Jan 2024	18 Jan 2024	22 Jan 2024	31 Jan 2024	19 Feb 2024	16 Apr 2024	27 May 2024	1 Nov 2024	Ref range	Units
Na	127	126	129	133	133	131	132	134	136-14	mmol/l
K	4.5	4.4	4.5	4.4	4.7	4.3	4.0	4.5	3.5-5.1	mmol/l
Urea	4.9	4.4	4.9	4.6	4.2	4.7	4.0	7.1	3.2-7.4	mmol/l
Creat	74.6	64.7	71.1	76.1	72.3	71.9	85.1	85.7	64-104	umol/l
LDL	1.98	-	1.92	2.40				2.61	<3.8	mmol/l
Chol	4.17	-	3.91	4.59				4.42	<5.2	mmol/l
TP	67	-	65	69				65	64-83	g/l
AST	22	-	18	22				24	5-34	umol/l
ALT	27	-	20	24				23	0-55	u/l
ALP	84	-	88	85				81	40-150	u/l
FBS	6.05	-	-	-		5.79	5.92		3.9-6.0	mmol/l
T4	-	14.54							9-19.05	pmol/l
TSH	-	0.59							0.35-4.94	uiu/ml
Cortisol	331								>50	nmol/l
Serum osmolality	271								275-295	mosm/kg
Urine osmolality	309								50-1200	mosm/kg
Urine sodium	44								-	mmol/l

blood sugar, fasting serum lipid, and liver function tests. At the same time, serum osmolality is sent to differentiate between isotonic, hypotonic, or hypertonic hyponatraemia. Given the patient's hypotonic hyponatremia (low plasma osmolality) and euvolemia, differentials such as SIADH, Addison's disease, hypothyroidism, psychogenic polydipsia, drug-induced causes, severe potassium depletion, and renal insufficiency need to be considered. Therefore, serum morning cortisol, urine osmolality, and urine sodium were sent. A chest X-ray was done to detect lung malignancy, and it was normal in this patient. A brain CT scan would be necessary if a neurosurgical condition such as subarachnoid haemorrhage or subdural haematoma were suspected.

Investigations showed low serum osmolality (271mOsm/kg), with raised urine osmolality (309 mOsm/kg) and random urine sodium of 44mmol/L. His serum T4 (14.54pmol/L), TSH (0.59uIU/ml), cortisol (331nmol/L), renal profile, liver function test, and urine albumin creatinine ratio were all normal (Table I). Pseudohyponatremia was ruled out with normal fasting blood sugar and total cholesterol value.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was diagnosed by low plasma sodium (<130mmol/L), plasma osmolality (<275mOsmol/kg), urine Na (>20mmol/L), urine osmolality> plasma osmolality, no oedema or signs of hypovolemia, normal renal, thyroid, and adrenal function with low plasma urea level.

The patient was started on Tab Madopar in 2023, but hyponatremia has been recorded prior to that since 2007. The most common time levodopa causes hyponatremia is when it is newly started or after a dose increase.[9] The patient has tolerated Tab. Madopar well and is not keen to change the medication.

He was given a two-weekly follow-up under the care of family medicine specialists at a primary care clinic in view of moderate hyponatraemia. A fluid restriction regimen with 1 litre/ day was initiated alongside electrolyte monitoring for this patient.

Following fluid restriction of 1 litre/day and no restriction of salt intake, the patient's sodium gradually increased from 127mmol/l to 129mmol/l, then 133mmol/l within one month. The patient's sodium level was stable between 131 and 134mmol/l thereafter. With the increasing trend of sodium, his symptoms of lethargy and generalised body weakness improved. The patient is comfortable with current management.

DISCUSSION

Hyponatraemia is defined as a plasma sodium level of less than 135mmol/L. Mild hyponatraemia is defined as serum sodium concentration (130-135mmol/L), moderate (125-129mmol/L), severe (<125mmol/L). In cases of severe hyponatraemia, a patient may present with seizure or coma. Referral to the hospital for immediate treatment is essential in severe hyponatraemia to prevent the risk of cerebral oedema and hyponatraemic encephalopathy. Plasma sodium concentration depends on the amount of both sodium and water in the plasma. Therefore, hyponatraemia does not necessarily imply sodium depletion. Plasma osmolality is maintained by strict regulation of the arginine vasopressin, also known as antidiuretics hormone (ADH) system, and thirst. If plasma osmolality increases, ADH is secreted and water is retained by the kidneys, thus reducing serum osmolality. If plasma osmolality decreases, ADH also decreases, resulting in diuresis of free water and a return to homeostasis. Failure of regulation of plasma osmolality leads to hyponatraemia. The ability to excrete a water load is delayed in the elderly. Therefore, the elderly are susceptible to alterations of water imbalance due to decreased renal mass, cortical blood flow, and glomerular filtration rate, thus affecting responsiveness to sodium balance.

Managing hyponatraemia in primary care involves initial investigations to facilitate ruling out common differential diagnoses such as hyperproteinaemia, hyperlipidaemia, hyperglycaemia, and hypothyroidism (Figure 1). Assessing fluid status is the key to diagnosis in addressing hyponatraemia. This patient has been diagnosed with

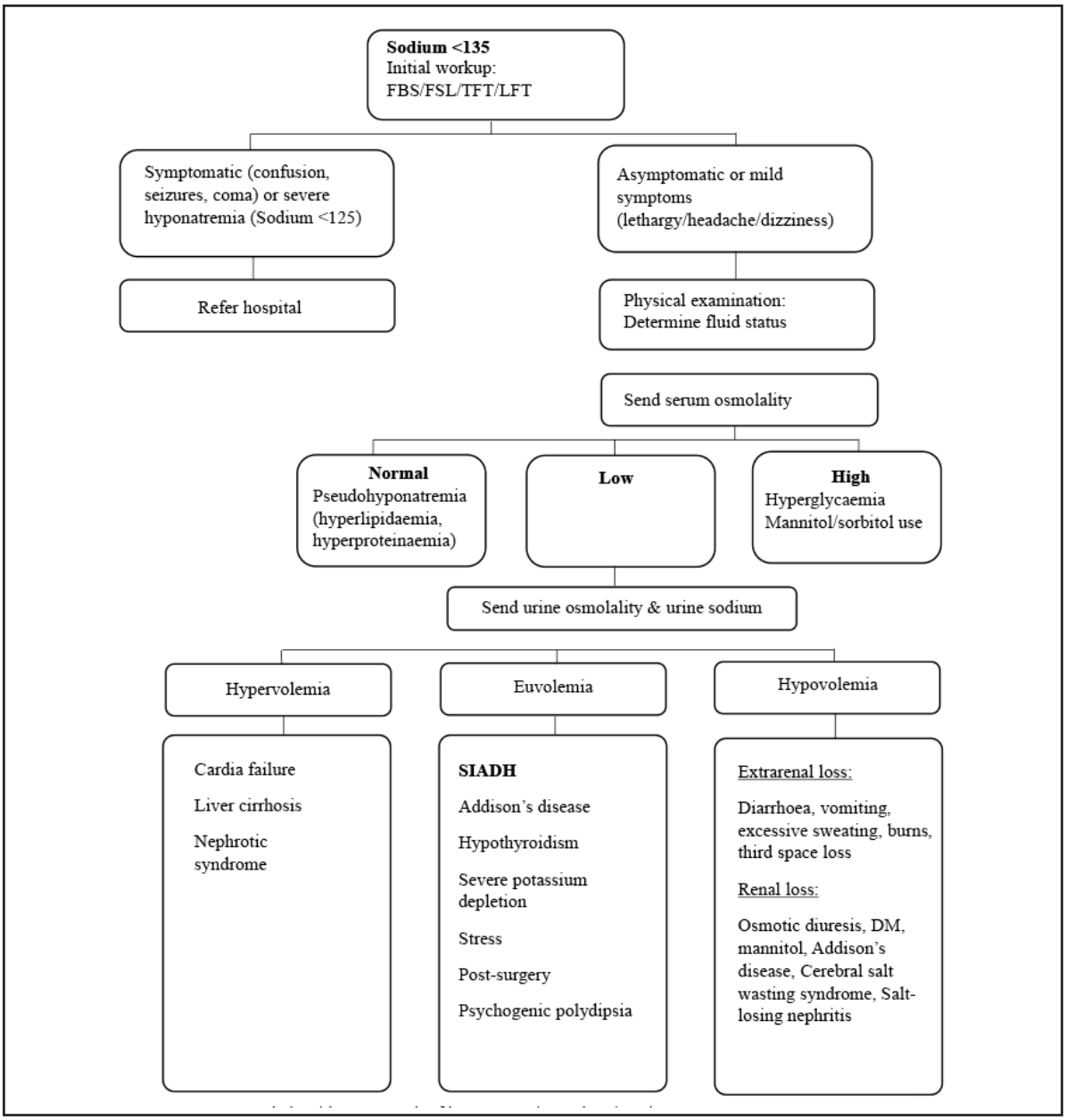

Fig. 1: Suggested algorithm approach of hyponatremia workup in primary care
Abbreviation: FBS = Fasting blood sugar; FSL = Fasting serum lipid; TFT = Thyroid function test; LFT = Liver function test; DM = Diabetes Mellitus; SIADH Syndrome of inappropriate antidiuretic hormone secretion

euvolemic (increased total body water with normal sodium level) hyponatraemia secondary to SIADH, as supported by concentrated urine sodium in the presence of hyponatremia and low plasma osmolality, in the absence of hypovolemia, oedema or diuretics.[4] The patient had no depressive symptoms during subsequent follow-up, thus, antidepressant was not started, considering the patient was already on polypharmacy. Despite the complexities associated with managing this patient's multiple comorbidities and non-compliance issues, a coordinated and patient-centred approach resulted in gradual improvements in his symptoms and overall well-being.

Hyponatraemia is more common in the elderly because they are more likely to have polypharmacy (more frequently thiazides and antidepressants). Levodopa is the effective antiparkinsonian agent. However, Parkinson's disease treatment with levodopa is known to cause SIADH. It is important to correct the underlying cause of hyponatraemia as it increases the risk of falls in the elderly. In general, serum sodium should not be increased by more than 10mmol/L in a 24-hour period in an asymptomatic patient and 12mmol/L in a symptomatic patient. In chronic hyponatremia (defined as a duration of more than 48 hours), overzealous correction should be avoided as it can lead to central pontine myelinosis. Fluid restriction is the mainstay of treatment and

preferred mode of treatment for SIADH. In this case, administration of normal saline is not appropriate, as the sodium may be rapidly excreted while the water is retained, therefore worsening hyponatraemia. We need to take into consideration that taking a high-sodium diet needs to be weighed against the drawback of raised high blood pressure, especially in this patient who has hypertension; hence, close monitoring of blood pressure is required for this patient.

The patient was not referred to the endocrine team, as he was managed by a family medicine specialist with close monitoring of sodium level. Emergency referral is recommended in a patient with a sodium level <125mmol/L or severe symptoms. Consultation with the endocrinologist in patients is required for a patient with a persistent sodium level of 125-129mmol/L.[10]

CONCLUSION

In summary, this case exemplifies the diagnostic and therapeutic challenges posed by moderate hyponatraemia and polypharmacy in elderly patients within the primary care setting. Hyponatraemia, in this case, was attributed to the syndrome of inappropriate hormone secretion with no clear cause identified despite looking for common causes of SIADH (neurological, respiratory, neoplasia, and medication). Doctors in primary care settings may have difficulties treating patients who have hyponatraemia due to the complexity of the diagnostic workup. The diagnostic workup, including assessment of fluid status and blood investigations, is important to aid in confirming the underlying aetiology and guiding appropriate management strategies. While hyponatraemia is common in primary health care, SIADH may be underdiagnosed in primary care due to the complexity of the condition and limited understanding among primary care doctors. It contributes to increased morbidity in the elderly, including a higher risk of falls and altered mental status. Fluid restriction emerged as the cornerstone of treatment for SIADH, with gradual correction of sodium levels observed over subsequent follow-ups.

ACKNOWLEDGEMENT

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DECLARATION

The authors declare no conflict of interest.

REFERENCES

1. Dash SC, Sundary NK, Rajesh B, Pagad T. Hyponatremia in elderly in-patients. J Clin Diagn Res 2019; 13(2): OC01-OC04.
2. Tay CL, Myint PK, Mohazmi M, Soiza RL, Tan MP. Prevalence and documented causes of hyponatraemia among geriatric patients attending a primary care clinic. Med J Malaysia 2019; 74(2): 121-7.
3. Zhang X, Li XY. Prevalence of hyponatremia among older inpatients in a general hospital. Eur Geriatr Med 2020; 11: 685-92.
4. Wilkinson I, Raine T, Wiles K, Goodhart A, Hall C, O'Neill H. Oxford handbook of clinical medicine. 10th ed. Oxford: Oxford University Press; 2017.
5. Corona G, Giuliani C, Parenti G, Norello D, Verbalis JG, Forti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS One 2013; 8(12): e80451.
6. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. Clin Interv Aging 2017; 12: 1957-65.
7. Goh KP. Management of hyponatremia. Am Fam Physician 2004; 69(10): 2387-94.
8. Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. J Am Soc Nephrol 2017; 28(5): 1340-9.
9. Shihabudheen P, Anver P, Uvais N, Mohammed T. Dose-dependent L-dopa/carbidopa-induced hyponatremia presenting with hiccups. J Family Med Prim Care 2020; 9(3): 1749-51.
10. Jacob P, Dow C, Lasker SS, Drake WM, Chowdhury TA. Hyponatraemia in primary care. BMJ 2019; 365: l2172.

Giant gallbladder with stones complicated with cholecardia syndrome: A case report

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SUMMARY

Cholecardia syndrome refers to a complication of gallbladder and biliary diseases (GBDs) caused by acute or chronic cholecystitis, characterised by symptoms similar to coronary heart disease. The severity of cardiac symptoms is positively correlated with the condition of GBDs. Most patients with Cholecardia syndrome have no organic lesions in their hearts, and their cardiac symptoms are relieved or even completely recovered with the effective therapy of GBDs. We report a case of a 71-year-old man who presented with Cholecardia syndrome caused by cholecystitis. The patient presented with angina pectoris mainly characterised by chest distress and pain, and no organic lesions were found on cardiac examination. The cardiac symptoms disappeared completely through the treatment of the gallbladder by relieving spasm with medicines and surgery. The aim of this publication is to remind clinical physicians that when receiving patients with biliary diseases accompanied by cardiac symptoms, detailed history and thorough physical examinations are quite necessary, which could lead to a consideration of Cholecardia syndrome.

INTRODUCTION

Gallbladder diseases (GBDs) are one of the most common digestive diseases. The connections between GBDs and several organs other than the liver have gradually surfaced, accompanied by the changes in people's diet structure and the continuous improvement of medical diagnosis technology. Among them, Cholecardia syndrome, which takes the heart as the important target of GBDs complications, has been paid close attention. However, there are still no systematic reports about its corresponding clinical manifestations and pathogenesis. Cholecardia syndrome often occurs with acute onset of GBDs. The clinical manifestations and electrocardiogram (ECG) changes of Cholecardia syndrome are very similar to those of coronary heart disease. Patients often do not have organic lesions of their heart, and the cardiac symptoms almost always disappear automatically after the treatment of GBDs. In clinical practice, it is necessary to differentiate it from organic heart disease.

CASE PRESENTATION

A 71-year-old man, with a history of hypertension for ten years, takes 5mg amlodipine besylate orally every day, and his blood pressure (BP) is well controlled at ordinary times. He has neither a history of diabetes nor coronary heart disease. He suffered precordial pain radiating to the left back and left upper limb, chest distress, dyspnoea, and sweating, accompanied by nausea and acid reflux for a week. The symptoms often occurred 2 hours after dinner and lasted for 4-6 hours, which could not be alleviated by taking nitroglycerin. The patient came to the emergency department at the onset of the symptoms, with a pulse rate of 78/min and a BP of 136/89 mmHg. There was no scleral icterus and no protrusion in the precordial area. The lung auscultation was normal bilaterally. There was a regular rhythm with no pathological murmurs in the area of each heart valve. The abdomen was flat, and there was tenderness in the right upper quadrant, accompanied by rebound pain and local muscle tension. The Murphy sign was positive, and the fundus of the gallbladder could be palpated at the right subcostal. The patient had a fever of 38.1℃ without rigour. His white blood cell count (WBCs) was 16.7 x 10^9/L, C-reactive protein (CRP) was 225mg/L, haemoglobin level was 125g/L, platelet count (PLTs) was 166 x 10^9/L, total bilirubin level (TB) was 20μmol/L, glutamic-pyruvic transaminase level (GPT) was 41U/L, glutamic oxaloacetic transaminase level (GOT) was 36U/L, γ-glutamyl transferase level (GGT) was 209U/L, cardiac troponin level T (cTnT) was 0.012ng/ml, creatine kinase isoenzyme level (CK-MB) was 2.93ng/ml, N-terminal pro-brain natriuretic peptide level (NTproBNP) was 320pg/ml. The abdominal CT scan is shown in Figure 1, and the chest CT scan was normal. The abdominal ultrasound showed the gallbladder effusion and enlargement with a giant gallstone, and the length of the gallbladder was 172mm with 63mm in width, which presented with cholecystitis by the wall of the gallbladder 6mm in thickness. The ECG showed ST segment changes of II, III, AVF, and V2-V6 (horizontal or slightly elevated, Figure 2a). Nevertheless, there were no significant abnormalities found in cardiac ultrasound, coronary CTA, and coronary angiography. After the application of scopolamine or triphenyl phenol, the above symptoms of the patient were relieved. During hospitalisation, the above symptoms occurred intermittently, and the ECGs rechecked during the onset were the same as Figure 2a. When there were no symptoms, the ECG showed as Figure 2b (lowering of T-wave of II, III, and AVF). Both ECGs in figures 2a and 2b were done before surgery. On the 5th day after admission, laparoscopic cholecystectomy (LC) was performed, and it was confirmed that the anterior wall of the gallbladder was perforated with wrapping of the greater omentum. The biggest size of the gallbladder stone was 68 x 54 mm, and the bile culture was negative. The patient did not

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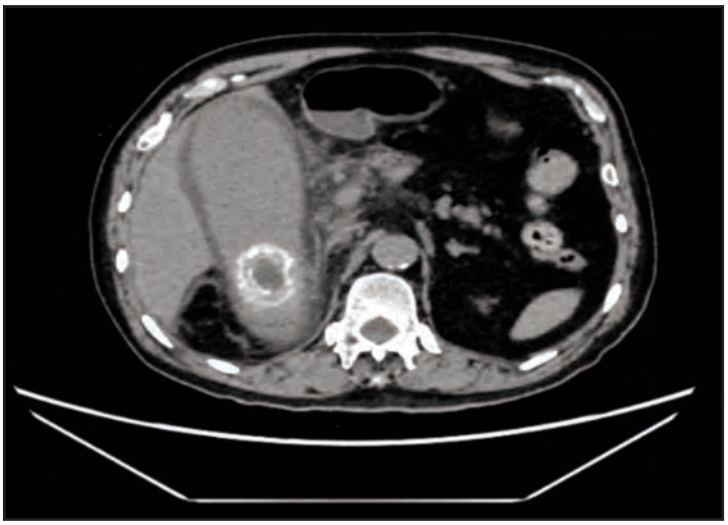

Fig. 1: Abnormal CT findings of a giant gallbladder with an impacted stone

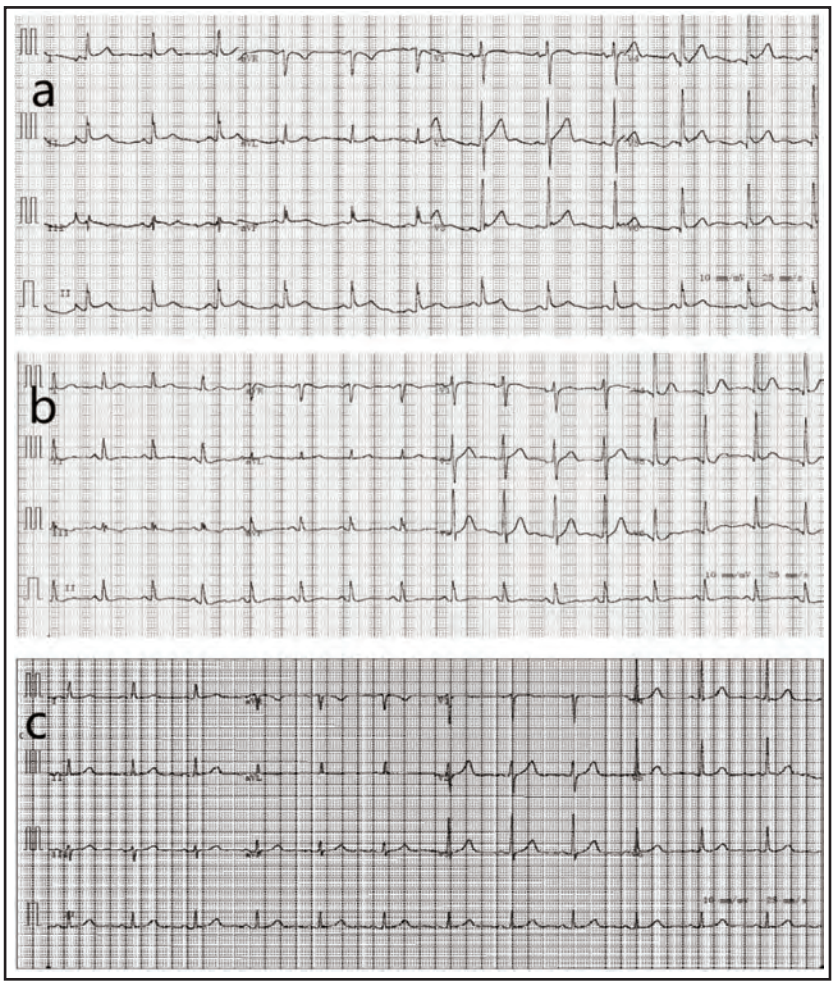

Fig. 2: a) ECG upon onset of symptoms, which showed ST segment changes of II, III, AVF, and V2-V6 (horizontal or slightly elevated); b) ECG before surgery, when the patient did not suffer from cardiac symptoms; c) normal ECG during follow-up

complain of any discomfort from the aforementioned symptoms from post-operation to the six-month follow-up, and the ECG follow-up was normal, as in Figure 2c.

DISCUSSION

Cholecardia syndrome refers to the clinical syndromes of angina pectoris, arrhythmia, and abnormal ECG caused by GBDs. Desai et al.[1] first used the term "cholecardia" to describe heart dysfunction caused by excess bile acid in 2017. The symptoms such as angina pectoris, chest distress, and palpitation caused by Cholecardia syndrome are characterised by a long attack time, which can last for several hours, often accompanied by arrhythmia.[2] ECG shows myocardial ischaemia changes, and the heart symptoms are often severe. Especially after eating a fatty diet, the onset of symptoms begins, always accompanied by cholecystitic presentation such as nausea, vomiting, abdominal distension, and pain in the right upper abdomen. Nitroglycerin almost failed to relieve the symptoms; however, atropine, hyoscyamine, and phloroglucinol can relieve it.[3]

The main pathogenesis of Cholecardia syndrome is unknown nowadays. Cholelithiasis and coronary heart disease have many common predisposing factors in aetiology, such as abnormal lipid metabolism, especially the increase of cholesterol, which is the basis of gallstone disease and atherosclerosis. Obesity, diabetes, less physical activity, and eating too much animal fat or foods rich in cholesterol are common predisposing factors. It is believed that biliary hypertension can cause coronary artery constriction, then coronary blood flow reduced, and finally lead to myocardial ischemia and angina pectoris in certain conditions. The fact that the heart is innervated by the T2 to T5-6 spinal nerves, and the gallbladder is innervated by the T4-5 to T9 spinal nerves. But the distribution of sensory nerve innervation is diffuse, intersecting at T4-5 and overlapping at T4-5. Therefore, when the pressure inside the bile duct increases or bile duct spasms or stimulated by bile acid salt, the spinal cord (T4-8) nerve reflex can be regulated resulting in excitation of vagus nerve.[4] After excitation of the vagus nerve, myocardial activity and myocardial oxygen consumption decreases, and partial pressure of oxygen in myocardial tissue increases. This indirectly causes coronary artery contraction, offsetting the vasodilation effect of the vagus nerve on coronary arteries.[5] Indirect constriction of coronary arteries leads to a decrease in coronary blood flow, which suppresses myocardial contraction and reduces cardiac output. The blood pressure then drops, and coronary blood flow reduces. Myocardial hypoxia results in angina pectoris, arrhythmia and abnormal ECG, which are the main mechanisms of Cholecardia syndrome. Studies have shown that certain efferent fibres in the vagus nerve of the abdomen, other than cholinergic ones, can promote the release of certain humoral factors in the organ.[5-7] These vasoactive factors can directly affect the function of the heart. Biliary tract infection has serious interference on myocardial metabolism, mainly concentrated in two aspects: one is the influence of the infection factors themselves; The second is the indirect impact caused by liver dysfunction. The biliary suppurative inflammation is a mixed infection. The types of bacteria are extremely complex. Once the biliary hypertension is formed, it is easy to spread and become sepsis. The damage to the myocardium is not only due to bacterial toxicity, but also includes body temperature, electrolytes, internal environment, serum pH, serum osmotic pressure and interference with immune response.

Cholecardia syndrome often occurs with acute onset of GBDs. Patients often do not have organic lesions of their heart, and the cardiac symptoms almost always disappear automatically after the treatment of GBDs. Therefore, the focus of treatment should be on treating GBDs, and the related cardiovascular manifestations generally do not require special management. Patients should undergo surgical therapy actively if their conditions are not too bad. According to research, cardiac symptoms completely disappeared after surgery in 90% of patients with Cholecardia syndrome.[7] Therefore, Cholecardia syndrome is not a contraindication but an indication for surgery. Patients who cannot undergo surgery should choose ultrasound-guided percutaneous transhepatic gallbladder drainage (PTGBD), or endoscopic retrograde cholangial pancreatography (ERCP), or percutaneous transhepatic cholangial drainage (PTCD).[8,9] In this condition, coronary vasodilators and antiarrhythmic drugs should be administered appropriately.

CONCLUSION

Detailed history and thorough physical examinations are quite necessary, which could lead to a consideration of Cholecardia syndrome. For patients with chest pain and dynamic ECG changes, acute coronary syndrome still needs to be differentiated, which is combined with coronary CTA or coronary angiography. For patients with a clear diagnosis, dynamic follow-up of ECG and myocardial enzyme spectrum is still necessary after biliary therapy.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

REFERENCES

1. Desai MS, Mathur B, Eblimit L, Vasquez H, Taegtmeyer H, Karpen SJ, et al. Bile acid excess induces cardiomyopathy and metabolic dysfunctions in the heart. Hepatology 2017; 65 (1): 189-201.
2. Mainali A, Adhikari S, Chowdhury T, Shankar M, Gousy N, Dufresne A. Symptomatic sinus bradycardia in a patient with acute calculous cholecystitis due to the cardio-Biliary reflex (Cope's sign): a case Report. Cureus 2022; 14(6): e25585.
3. Daliparty VM, Amoozgar B, Razzeto A, Ehsanullah SUM, Rehman F. Cholecystitis masquerading as cardiac chest pain: a case report. Am J Case Rep 2021; 22: e932078.
4. Vasavan T, Ferraro E, Ibrahim E, Dixon P, Gorelik J, Williamson C. Heart and bile acids- Clinical consequences of altered bile acid metabolism. Biochim Biophys Acta Mol Basis Dis 2018; 1864(4 Pt B): 1345-55.
5. Vacca G, Battaglia A, Grossini E, Mary DA, Molinari C. Reflex coronary vasoconstriction caused by gallbladder distension in anesthetized pigs. Circulation 1996; 94(9): 2201-9.
6. Papakonstantinou PE, Asimakopoulou NI, Kanoupakis E, Maragkoudakis S, Panagiotakis S, Gikas A. Cope's sign and complete heart block in a 78-year-old patient with biliary colic. Int Emerg Nurs 2018; 37: 3-5.

7. Li Y, Li J, Leng A, Zhang G, Qu J. Cardiac complications caused by biliary diseases: A review of clinical manifestations, pathogenesis and treatment strategies of cholecardia syndrome. Pharmacol Res 2024; 199: 107006.
8. Zachäus M, Bartels M, Flade A, Schubert-Hartmann A, Lamberts R, Sepehri-Shamloo A, et al. Endoscopic ultrasound drainage of the gallbladder in acute cholecystitis in patients at high surgical risk. Zentralblatt fur Chirurgie 2023; 148(2): 140-6.
9. Park SW, Lee SS. Current status of endoscopic management of cholecystitis. Dig Endosc 2022; 34(3): 439-50.

The eldest survivor in Malaysia: Pulmonary agenesis with isolated dextrocardia in late adulthood

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SUMMARY

Pulmonary agenesis is a rare congenital anomaly. It is frequently associated with other congenital anomalies and is present during early childhood. The exact aetiology of pulmonary agenesis is not fully understood. In this case report, we present a rare case of type 1 right pulmonary agenesis with isolated dextrocardia in an elderly man, diagnosed at 68 years old. He was well antenatally with no previous history of hospitalisation or respiratory-related health issues. Upon his short presentation with upper respiratory tract symptoms, a chest radiograph performed shows unilateral right hemithorax opacity with crowding of the right ribs. Subsequent contrast-enhanced computed tomography (CT) of the thorax confirmed features of right pulmonary agenesis with isolated dextrocardia. Despite having the type of congenital pulmonary underdevelopment with the worst prognosis, this man has survived into his late adulthood without any significant symptoms. To the author's knowledge, diagnosing pulmonary agenesis with isolated dextrocardia at this age is the oldest age that has been reported in Malaysia. This case highlights features of pulmonary agenesis as well as the importance of considering this rare condition as a differential diagnosis for unilateral hemithorax opacity in adult chest radiographs. The advancement of CT nowadays has allowed us to utilise various imaging techniques to avoid invasive methods such as bronchoscopy, bronchography, or angiography to establish this diagnosis.

INTRODUCTION

Pulmonary agenesis is a rare congenital anomaly with a prevalence of 24-34 out of 1,000,000 live births and a slight female preponderance.[1] It is a condition where there is unilateral absence of developed pulmonary vessels, bronchi, and parenchyma.[2] This diagnosis is usually made during childhood, with approximately a fifty percent survival rate due to concomitant anomalies.[3] The incidence of right and left lung pulmonary agenesis is equal in reported cases, but right pulmonary agenesis manifests a worse overall prognosis compared to left pulmonary agenesis.[4]

The first description of this condition was narrated back in 1673 by De Pozze as an incidental finding during the autopsy of an adult female.[5] As this is a congenital anomaly, most of the cases reported are diagnosed within the paediatric population, as these patients are usually symptomatic either from the pulmonary agenesis itself or other concomitant anomalies. To date, the oldest age reported for the first diagnosis of pulmonary agenesis in Malaysia is 40 years old, as per Sulaiman et al., in their article published in June 2020.[6]

In this case report, we present a case of type 1 right pulmonary agenesis with isolated dextrocardia, first diagnosed at the age of 68 years old, which is the oldest reported age in Malaysia.

CASE PRESENTATION

Mr. R, a 68-year-old man, is a retired farmer who has lived in a small village his entire life. He has underlying type 2 diabetes mellitus and hypertension, which are well controlled with oral medication under community health clinic follow-up. He is also a chronic smoker with 12 pack-years. There was no previous history of surgery or hospitalisation.

Mr. R presented to the emergency department in July 2017 for a short two-day history of dry cough and shortness of breath. He has no documented fever. Upon examination, he was not tachypnoeic or appeared to be in distress. He was well perfused with a capillary return time of less than 2 seconds. His vital signs were all within normal limits, with a heart rate of 70 bpm, a respiratory rate of 18, and oxygen saturation of 97% under room air. However, on auscultation, there was reduced right lung breath sound with rhonchi on the left lung. Otherwise, his laboratory investigations, namely the full blood count, renal profile, and electrolytes, were normal.

An erect frontal chest radiography was performed in view of reduced right lung breath sounds on auscultation. Surprisingly, his chest radiograph (Fig. 1) shows unilateral right hemithorax opacity with crowding of the ribs, which did not fit into his relatively stable presentation. The tracheal and mediastinal were deviated to the right in keeping with right lung volume loss. The right main bronchus was not well visualised in this radiograph. On the other hand, the left main bronchus was patent, and the left lung field was clear. There was an absence of a left cardiac silhouette on his radiograph. An additional remark on this radiograph is that the stomach bubble was seen in a normal position, inferior to the left hemidiaphragm.

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Table I: Differential diagnosis to be considered for complete opaque hemithorax.

Non-displaced mediastinum	Displaced mediastinum towards opacity	Displaced mediastinum away from opacity
• Consolidation • Pleural effusion • Chest wall/pleural mass	• Total lung collapse • Pneumonectomy • Pulmonary hypoplasia/agenesis • Malignancy	• Large pleural effusion • Large pulmonary mass • Diaphragmatic hernia

An initial diagnosis of bronchiolitis was made, and Mr. R responded well to salbutamol nebulisation. He was subsequently discharged from the emergency department with prophylactic antibiotics. An outpatient computed tomography (CT) thorax and respiratory clinic referral was made for further investigation.

The contrast-enhanced CT thorax (Fig. 2) shows the absence of the right lung parenchyma, right main bronchus, and right pulmonary vessels. The heart was situated on the right side of the thorax with its apex pointing to the right, suggestive of dextrocardia. The ascending aorta was seen arising from the left ventricle and coursing to the left to resume normal position of the descending aorta. The trachea and oesophagus were intact but deviated to the right. There was hyperplasia of the left lung with a normal left main bronchus and pulmonary vessels. No focal lung nodule or lesion noted within. Other negative findings include no pleural effusion, bronchiectasis, or mediastinal lymphadenopathy. The visualised upper abdominal organs were in normal position in keeping with situs solitus.

To further visualise the structures of the heart and great vessels, we have reconstructed volume rendering images to provide a 3-dimensional visualisation, as seen in Figure 3. This volume rendered images help to ascertain the absence of the right pulmonary vessel, which are the main differentiating features of pulmonary agenesis. Overall features of this CT thorax are suggestive of type 1 pulmonary agenesis with isolated dextrocardia. Fortunately, Mr. R was discharged well and does not require any long-term follow-up or further intervention.

DISCUSSION

Pulmonary agenesis is a rare congenital anomaly that is usually present in childhood. Uncommonly but possible, patients may present late in adulthood without developing significant symptoms to seek medical treatment earlier in life, such as in this case where Mr. R has survived with one lung until his late adulthood.

The exact aetiology of pulmonary agenesis is not fully understood. It has been postulated to occur due to arrested development of the lung during the 4th gestational week, where the embryogenesis of the pulmonary system begins via formation of the respiratory diverticulum from the laryngotracheal bud. The intrauterine development of the lung has been divided into five phases throughout the entire pregnancy, namely the embryonic, pseudoglandular, canalicular, saccular, and alveolar phases.[7] Some hypothesised that during the 4th week of gestation, abnormal blood flow in the dorsal aortic arch causes pulmonary agenesis.[5] Genetic factors, viral agents, and dietary deficiency of vitamin A or folic acid or maternal use of salicylates have been suggested as contributing factors.[7]

Pulmonary agenesis is rare, and therefore recognising its radiological features will be challenging, particularly when it's not in the common age group. Understanding the differential diagnosis for unilateral complete opaque hemithorax is essential when it comes to chest radiographs. According to Chapman & Nakielny's Aids to Radiological Differential Diagnosis,[8] the differential diagnosis of complete opacity of unilateral hemithorax can be further narrowed depending on the mediastinal displacement, as stated in Table I.

In our case, Mr. R's chest radiograph showed right hemithorax opacity with displaced mediastinum towards opacity, which narrowed down the differential to total lung collapse and pulmonary agenesis, as he had no previous surgery.

Prenatal diagnosis of pulmonary hypoplasia or agenesis is usually done by ultrasound or magnetic resonance imaging (MRI) to reduce radiation dose to the foetus.[9] On the other hand, diagnosing pulmonary hypoplasia or agenesis in adults can be achieved effortlessly via contrast-enhanced CT thorax. The advancement of CT nowadays allows not only soft tissue and lung window views, but also reconstruction of volume rendering images to better appreciate the great vessels and airways. Hence, there is no need for more invasive pulmonary angiography, bronchoscopy, or bronchography to delineate the pulmonary vessels and bronchus pattern.

Pulmonary hypoplasia has been classified into three types by Boyden, which was then modified by Schneider in 1912, as stated below.[2]

- Type 1 (Agenesis): Complete absence of lung and bronchus with no vascular supply to the affected side.
- Type 2 (Aplasia): Rudimentary bronchus with complete absence of pulmonary parenchyma.
- Type 3 (Hypoplasia): Presence of variable amounts of bronchial tree, pulmonary parenchyma, and supporting vasculature.

In our case, Mr. R's CT showed complete absence of right lung parenchyma and right pulmonary vessels with no rudimentary bronchus, in keeping with type 1 pulmonary agenesis.

Pulmonary agenesis is often associated with a wide range of congenital anomalies in half of the affected individuals. For instance, the cardiovascular (patent ductus arteriosus, patent foramen ovale), gastrointestinal (tracheoesophageal fistula, imperforate anus), genitourinary, or musculoskeletal system (limb or vertebral anomalies). Depending on the severity of

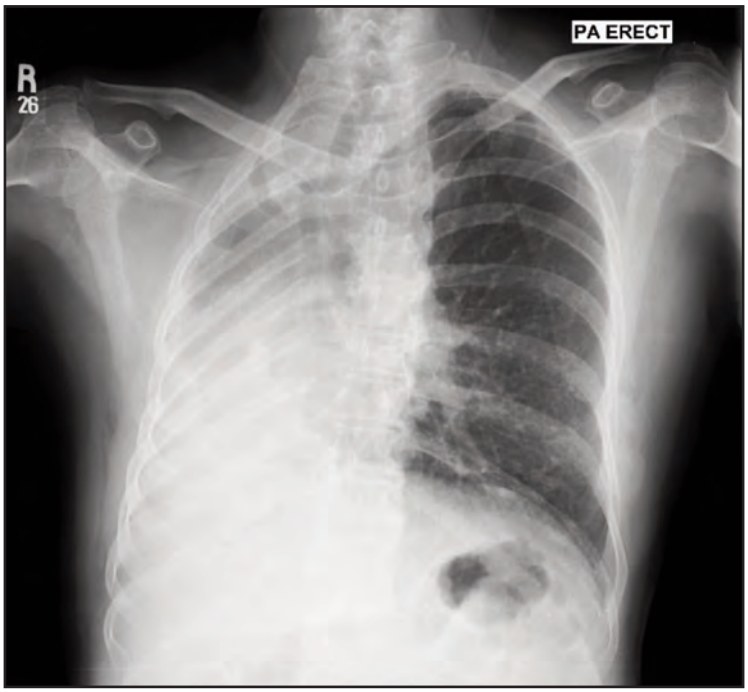

Fig. 1: Erect frontal chest radiograph. Complete opaque right hemithorax with crowding of right ribs. Tracheal and mediastinal shift to the right, resulting in the absence of normal left cardiac silhouette. Normal stomach gas bubble position in the left hypochondriac.

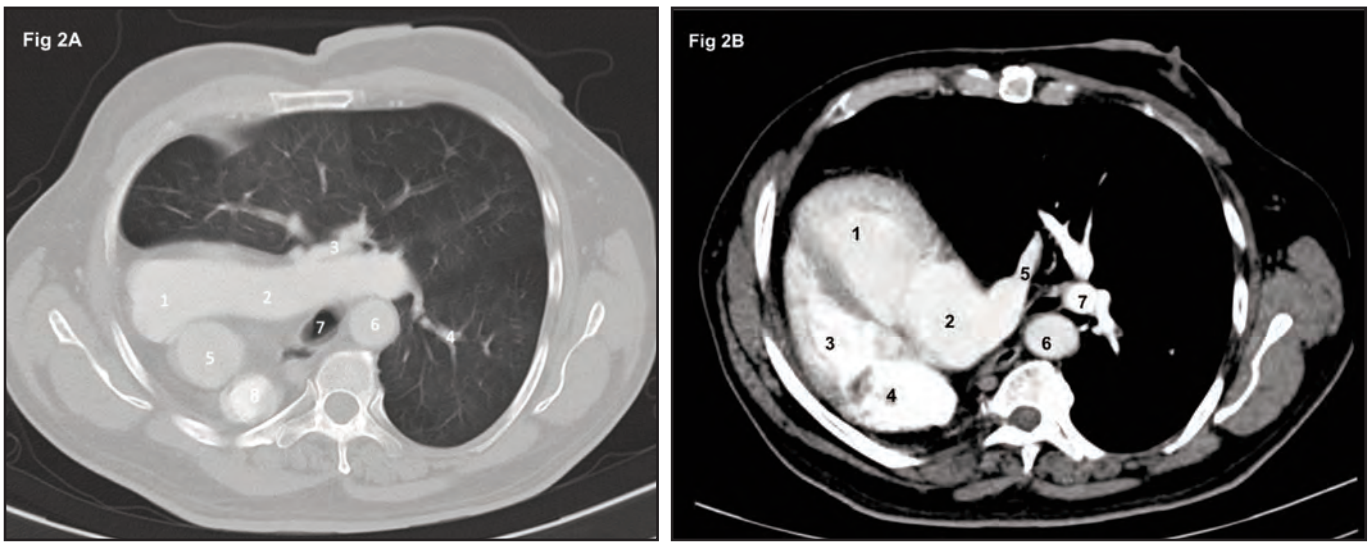

Fig. 2: A) Axial image of CECT Thorax at the level of mid thorax showed mediastinum deviated to the right hemithorax with absent right lung and hyperplasia of the left lung. 1. Pulmonary trunk, 2. Left main pulmonary artery, 3. Left upper lobe pulmonary artery, 4. Left lower lobe pulmonary artery, 5. Ascending aorta, 6. Descending aorta, 7. Trachea, 8. Superior vena cava, B) Reconstructed axial image of CECT Thorax at the level of the heart showed the apex pointing to the right in keeping with dextrocardia. 1. Left ventricle, 2. Left atrium, 3. Right ventricle, 4. Right atrium, 5. Left inferior pulmonary vein, 6. Descending thoracic aorta, 7. Left segmental pulmonary artery.

the accompanying comorbid anomaly, variable clinical findings can occur. Fortunately, Mr. R does not possess any of these congenital concomitants, which is probably the reason he survived asymptomatically until his late adulthood. There is no definite treatment for pulmonary underdevelopment to the current date, and the management is mainly supportive therapy.

CONCLUSION

This case is a type 1 pulmonary agenesis with isolated dextrocardia reported and diagnosed at the oldest age in Malaysia, discovered during a work-up for bronchitis. This case is a rare presentation that reminds all clinicians to include this differential diagnosis in their minds in the future. Recognising pulmonary agenesis in adult patients can be challenging with chest radiographs alone, but the current

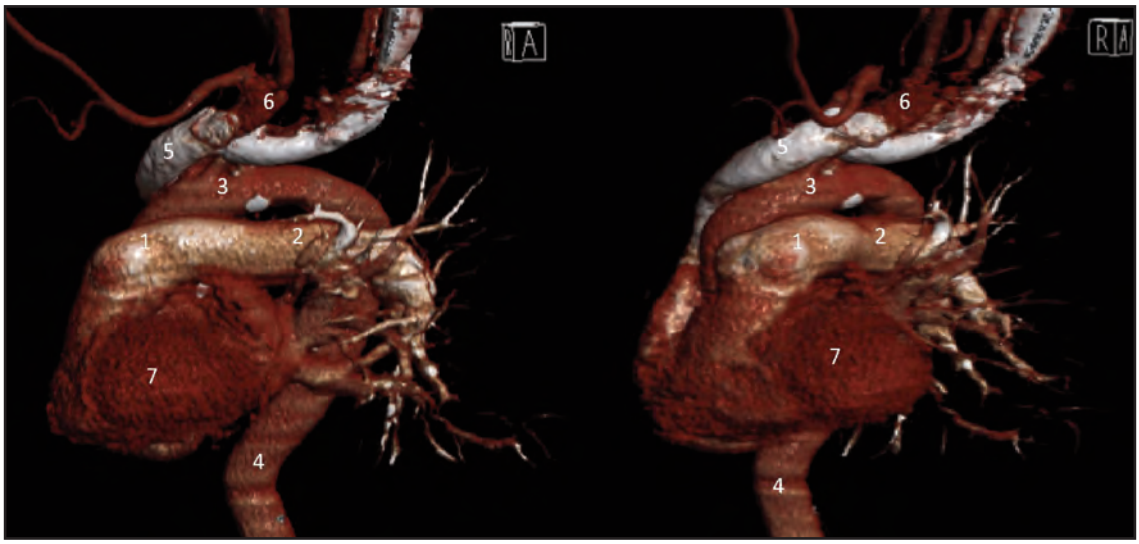

Fig. 3: Reconstructed volume rendering images of the heart and great vessels showing the absence of the right main pulmonary artery. Annotation: 1. Pulmonary trunk, 2. Left main pulmonary artery, 3. Arch of the aorta, 4. Descending thoracic aorta, 5. Superior vena cava, 6. Brachiocephalic trunk, 7. Heart (right ventricle).

advanced CT imaging tools, such as volume-rendered images, will aid in the diagnosis of this condition. It is not necessary to further investigate with more invasive methods such as bronchoscopy, bronchography, or angiography to establish this diagnosis.

DECLARATION

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

REFERENCES

1. Kumar B, Kandpal DK, Sharma C, Sinha DD. Right lung agenesis. Afr J Paediatr Surg 2008; 5(2): 102-4.
2. Boyden EA. Developmental anomalies of the lungs. Am J Surg 1955; 89(1): 79-89.
3. Sbokos CG, McMillan IK. Agenesis of the lung. Brit J Dis Chest 1977; 3: 183-97.
4. Say B, Carpenter NJ, Giacoia G, Jegathesan S. Agenesis of the lung associated with a chromosome abnormality (46,XX,2p+). J Med Genet 1980; 17(6): 477-8.
5. De Pozze S, Brescia MA, Amermon EE, Sharma KK. Agenesis of the left lung. Arch Pediatr 1960; 77: 485-90.
6. Sulaiman W, Subramaniam R. Left lung agenesis in an adult–a rare anomaly. Asian J Med Health Sci 2020; 3(1): 72-6.
7. Roque AS, Burton EM, Boedy RF, Falls G, Bhatia JS. Unilateral pulmonary agenesis without mediastinal displacement. South Med J 1997; 90(3): 335-7.
8. Davies SG, editor. Chapman & Nakielny's Aids to Radiological Differential Diagnosis. 6th ed. Edinburgh: Saunders Ltd.; 2013.
9. Alamo L, Gudinchet F, Reinberg O, Vial Y, Francini K, Osterheld MC, Meuli R. Prenatal diagnosis of congenital lung malformations. Pediatr Radiol 2012; 42(3): 273-83.

Leukaemic retinopathy: An uncommon initial presentation of chronic myeloid leukaemia in a paediatric patient

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SUMMARY

An 11-year-old girl presented with unilateral eye redness and blurred vision, accompanied by a one-month history of abdominal distension. Ocular examination revealed reduced visual acuity, bilateral optic disc swelling, dilated and tortuous retinal vessels, multiple retinal haemorrhages, and yellowish retinal deposits suggestive of leukaemic retinopathy. Systemic examination and haematologic investigations confirmed the diagnosis of chronic myeloid leukaemia. The patient was commenced on chemotherapy, after which her ocular findings and visual acuity progressively improved. This case emphasises the importance of recognising ocular signs such as disc swelling, haemorrhages, and retinal deposits as potential early indicators of underlying systemic malignancies, particularly in paediatric patients. Prompt ophthalmic evaluation and timely referral can facilitate early diagnosis and significantly improve both visual and systemic outcomes.

INTRODUCTION

Ocular manifestations of CML are relatively uncommon but can serve as early and sometimes critical indicators of the disease.[1] In some cases, ophthalmologists may be the first to detect underlying haematologic malignancy during routine eye examinations, where ocular signs are either incidental or the primary complaint. These ocular findings may occur at initial diagnosis or signal disease relapse.[1]

CML is a clonal myeloproliferative neoplasm arising from haematopoietic stem cells, characterised by the presence of the Philadelphia chromosome and the BCR-ABL1 fusion gene.[2] While it predominantly affects older adults with a median age of diagnosis around 64 years, paediatric and adolescent cases are rare. CML accounts for approximately 2% of all leukaemia in children under 15 years and 9% in adolescents aged 15–19 years.[3] The annual incidence in these age groups is estimated at 1 per million and 2.2 per million, respectively.[3]

A hallmark laboratory feature of CML is hyperleukocytosis, which can lead to leukostasis, a condition marked by impaired microcirculation due to excessive, bulky, and adhesive leukocytes. In the eye, this can manifest as leukostasis retinopathy, a rare but vision-threatening complication of CML.[4] This condition results from microvascular occlusion and ischaemia, leading to a variety of retinal findings such as haemorrhages, venous dilation, cotton wool spots, and optic disc swelling.[4] This case report describes a rare ocular presentation as the initial clinical manifestation of CML in an 11-year-old girl. It underscores the diagnostic challenges posed by atypical presentations in paediatric patients and highlights the vital role of ophthalmic evaluation in the early detection of systemic malignancies.

CASE PRESENTATION

An 11-year-old girl presented with redness and blurred vision in her right eye, which had been occurring for one week. The onset of redness was sudden and followed several bouts of coughing. Additionally, she had experienced abdominal distention for a month prior to this. Initially, her parents sought medical attention from a private ophthalmologist for her eye complaints, who then referred them to our centre.

Upon examination, her best corrected visual acuity (BCVA) was 6/45 in the right eye and 6/15 in the left eye. There was no relative afferent pupillary defect. Examination of the right eye showed periorbital ecchymosis with generalised conjunctival chemosis and subconjunctival haemorrhage, while the left eye appeared normal. Fundus examinations of both eyes revealed generalised optic disc swelling, dilated and tortuous veins, multiple yellowish retinal deposits on the fovea, and multiple retinal haemorrhages (Figs. 1a and 1b). No signs of neovascularisation or retinal ischaemia were observed. Optical coherence tomography (OCT) shows retinal deposits overlying the fovea in both eyes (Figs. 2a and 2b).

Laboratory tests revealed hyperleukocytosis, a total white blood cell count of 670 × 10^9/L (4.5–11.0 × 10^9), anaemia with haemoglobin level of 7.3 g/dL (12.0-16.0 g/dL), and thrombocytosis with platelet count of 930 × 10^9 (150-400 x 10^9/L). A full blood picture indicated the presence of blast cells, suggestive of CML in the late chronic or early accelerated phase. A contrast-enhanced computed tomography (CECT) scan of the brain was normal. However, CECT of the neck, thorax, and abdomen revealed gross hepatosplenomegaly, peribroncho-vascular nodules, ground-glass opacities in the basal segments of the left lower lobe, and small hilar nodes, indicating a possibility of

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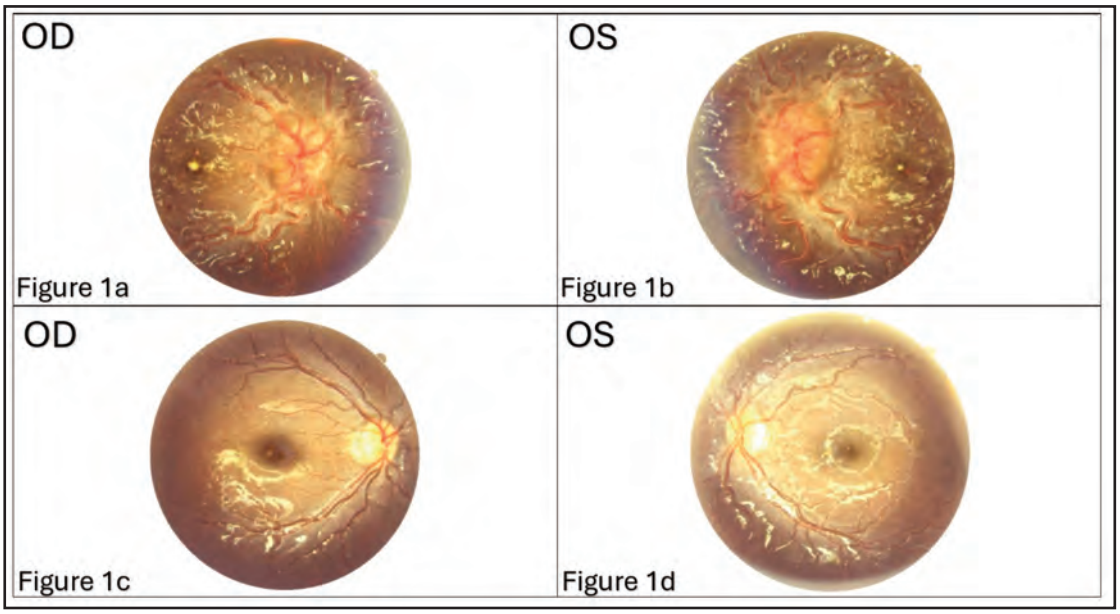

Fig. 1: 1a and 1b show both eyes' optic disc swelling with dilated and tortuous vessels and multiple retinal haemorrhages with leukaemic retinal deposits before treatment, and 1c and 1d show resolution of optic disc swelling and resolution of both eyes' dilated and tortuous vessels 6 months after treatment.

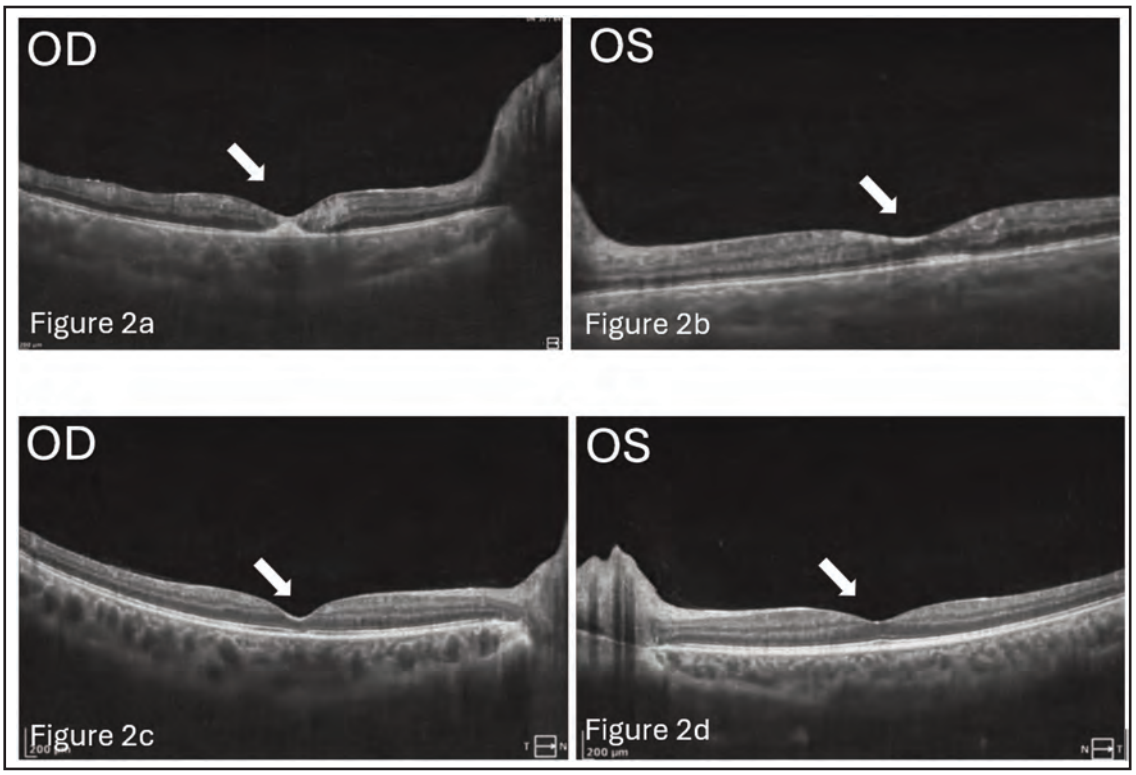

Fig. 2: Pre-treatment OCT shows leukaemic retinal deposits overlying the fovea in both eyes (Figure 2a and Figure 2b), and post-treatment OCT shows reduction of the leukaemic infiltrate in both eyes (Figure 2c and Figure 2d).

haematogenous malignancy with lymphangitic carcinomatosis. A paediatrician was consulted, and the child was diagnosed with hyperleukocytosis and anaemia secondary to CML. A bone marrow aspiration trephine biopsy was later performed, confirming the diagnosis of chronic myeloid leukaemia in the chronic phase.

The patient was started on a chemotherapy regimen that included intravenous Cytarabine 200mg/m^2 of her total body surface area for one week, followed by oral Imatinib 400mg daily and oral Hydroxyurea 1g daily. During her ophthalmology follow-up one month later, the subconjunctival haemorrhage had subsided, and her BCVA

improved to 6/36 for the right eye and 6/10 for the left eye. Fundus examination showed resolution of retinal haemorrhages, reduced tortuosity of vessels, and a less swollen but pale optic disc. There were retinal deposits in both foveae, more prominently in the right eye, which contributed to her poorer visual acuity in that eye. Her total white blood cell count improved to 5.8×10^9/L.

After seven months on Imatinib, the child became refractory to treatment, as evidenced by an increasing trend in total white blood cell counts. This necessitated a change from Imatinib 400mg daily to Nilotinib 200mg twice daily. Despite this change, the child's visual acuity continued to improve, reaching 6/12 for the right eye and 6/7.5 for the left eye. Fundus examination showed improvement in optic disc swelling, retinal vessel tortuosity, and a decrease in the retinal deposits (Figs. 1c and 1d). The OCT of the macula also revealed a reduction in retinal deposits, which contributed to improved visual acuity (Figs. 2c and 2d).

DISCUSSION

CML is a rare but significant haematological malignancy in the paediatric population, accounting for only 2-3% of childhood leukaemia.[5] Understanding the ocular manifestations of leukaemia is crucial, as the eye provides a clear window to observe the disease's effects on nerves and blood vessels. In 3.6% of cases, ocular symptoms can even be the first indication of leukaemia.[6] Ocular complications arise from direct infiltration of structures like the orbit, iris, choroid, and optic nerve or vascular abnormalities in the retina. Signs of leukaemic retinopathy can vary. It can present as multiple preretinal and intraretinal haemorrhages, Roth's spot, cotton wool spots, exudates, retinal venous tortuosity, perivascular sheathing, and neovascularisation.[7]

Ocular manifestations as the initial presentation in CML, although uncommon, can serve as a critical diagnostic clue. In the present case, an 11-year-old girl presented with sudden-onset unilateral periorbital ecchymosis with subconjunctival haemorrhages and blurred vision, with ophthalmic examination revealing optic disc swelling, dilated tortuous vessels, multiple retinal haemorrhages, and multiple retinal deposits later identified as secondary to hyperleukocytosis from underlying CML in the chronic phase. Retinal deposits are aggregates of malignant white blood cells (blasts or mature myeloid cells in the case of CML) that infiltrate the retinal layers, particularly the perivascular areas or subretinal space.[1,8] On OCT, these infiltrates appear as hyperreflective lesions. The concurrence of ocular signs, hepatosplenomegaly, and abnormal blood counts reinforced the systemic nature of her disease.

Paediatric CML is rare compared to adult CML and accounts for approximately 2-3% of cases of newly diagnosed paediatric leukaemia. According to the United States-based Surveillance, Epidemiology, and End Results cancer registry, the age-adjusted incidence rate from 2010 to 2014 was 1.4 per 1,000,000 for the 0-14 years age group and 2.1 per 1,000,000 for those aged 0-19 years.[5] Subconjunctival haemorrhage, although uncommon, can sometimes be an initial clinical sign of an underlying haematologic disorder, including CML.[1,4,8] This case emphasises the importance of thorough evaluation and consideration of haematologic malignancies in paediatric patients with unusual bleeding episodes.

CML is characterised by the uncontrolled proliferation of myeloid cells. It is typically marked by the presence of the Philadelphia chromosome (Ph chromosome), resulting from a translocation between chromosomes 9 and 22 [t(9;22)(q34;q11)].[2] While CML is more commonly diagnosed in adults, it can rarely occur in children, comprising less than 3% of paediatric leukaemia.[5] The diagnosis of CML in paediatric patients requires a high index of suspicion and a comprehensive diagnostic workup. Clinical manifestations can be diverse and often non-specific. Systemic signs may include fatigue, malaise, pallor, unexplained weight loss, easy bruising, recurrent infections, abdominal distension due to hepatosplenomegaly, and, in some cases, splenic infarction.[5] Spontaneous bleeding episodes, such as subconjunctival haemorrhage, may also be an early clue to an underlying haematological disorder.[1]

Ocular presentations, although less common, can be the initial manifestation of CML and include blurred vision, floaters, periorbital ecchymosis, optic disc swelling, retinal haemorrhages, Roth's spots, venous tortuosity, and leukaemic retinal infiltrates. These findings often reflect underlying hyperleukocytosis and leukostasis, which can compromise retinal and optic nerve perfusion.[1,7] Laboratory investigations, including complete blood count with peripheral blood smear, bone marrow aspiration, biopsy, and cytogenetic analysis, are essential for accurate diagnosis and risk stratification.

Management of paediatric CML often involves a combination of tyrosine kinase inhibitors (TKIs), such as Imatinib, Dasatinib, or Nilotinib, and occasionally stem cell transplantation in high-risk cases.[5] Despite the initial favourable response to Imatinib, the patient later became refractory, as evidenced by a rising white blood cell count. The transition to Nilotinib, a second-generation TKI, was a critical therapeutic pivot. Studies indicate that Nilotinib and Dasatinib are effective in paediatric patients resistant to Imatinib, with improved molecular response rates.[5] Visual improvement paralleled systemic haematologic remission. OCT demonstrated a reduction in retinal deposits and resolution of optic disc swelling, which correlated with BCVA improvement to 6/12 in the right eye. Nevertheless, persistent subfoveal deposits in the right eye explained the incomplete recovery, consistent with reported cases of residual structural damage post-infiltration.[8]

Given the rarity of paediatric CML and its diverse clinical presentations, collaboration among paediatric haematologists, oncologists, and other specialists is crucial for timely diagnosis and optimal management. Additionally, long-term follow-up is necessary to monitor treatment response, disease progression, and potential late effects of therapy in this population.

CONCLUSIONS

A child presenting with eye redness and poor vision should not be taken lightly. A holistic approach and thorough examination are paramount to a correct diagnosis. Co-management with a paediatrician is important to deliver the optimum treatment care. Timely identification of leukostasis retinopathy associated with CML is essential, and prompt initiation of treatment can potentially save lives and preserve vision.

REFERENCES

1. Yassin MA, Ata F, Mohamed SF, Alkhateeb A, Naeem U, Al-Qatami AI, et al. Ophthalmologic manifestations as the initial presentation of chronic myeloid leukemia: a review. Surv Ophthalmol 2022; 67(2): 530-43.
2. Kang ZJ, Liu YF, Xu LZ, Long ZJ, Huang D, Yang Y, et al. The Philadelphia chromosome in leukemogenesis. Chin J Cancer 2016; 35(1): 48.
3. Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Perspectives pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood 2016; 127(4): 392-9.
4. Lim J, Kim I, Sagong M. Leukostasis retinopathy as the first sign of chronic myeloid leukaemia with severe hyperleukocytosis: two case reports. Korean J Ophthalmol 2023; 37(3): 266-9.
5. Pushpam D, Bakhshi S. Paediatric chronic myeloid leukaemia: is it really a different disease? Indian J Med Res 2019; 149(5): 600-9.
6. Chaudhuri T, Roy S, Roy P. Ischaemic optic neuropathy induced sudden blindness as an initial presentation of acute lymphoblastic leukemia. Indian J Med Paediatr Oncol 2013; 34(4): 335-6.
7. Awuah A, Asiedu K, Adanusa M, Ntodie M, Acquah E, Kyei S. A case of leukemic retinopathy mimicking common ischemic retinopathies. Clin Case Rep 2016; 4(2): 133-7.
8. Pflugrath AE, Brar VS. Bilateral optic nerve and retinal infiltration as an initial site of relapse in a child with t-cell acute lymphoblastic leukemia. Am J Ophthalmol Case Rep 2020; 18: 100695.

Are we overlooking the bigger picture? The role of primary care in managing vision loss among the elderly

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SUMMARY

Vision loss in elderly patients presents significant diagnostic challenges in primary care, where early recognition and accurate diagnosis are essential to prevent irreversible complications. This case highlights the critical role of primary care physicians (PCPs) in early evaluation and timely diagnosis of vision loss in elderly patients. A 73-year-old man presented with progressive visual impairment, which was eventually diagnosed as bitemporal hemianopia due to a pituitary macroadenoma compressing the optic chiasm. Furthermore, this case illustrates the essential contribution of PCPs in coordinating multidisciplinary care, addressing the complex medical and psychosocial challenges faced by patients and their families, and ensuring holistic management to enhance both clinical outcomes and quality of life.

INTRODUCTION

Vision problems in the elderly significantly impact quality of life and often exacerbate other health issues. As the global population ages, the prevalence of conditions like cataracts, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy continues to rise, leading to functional disabilities, dependency, and increased risks of falls, social isolation, and mental health issues such as depression and anxiety.[1]

Less common but equally critical is chiasmal syndrome, characterized by bitemporal hemianopia due to optic chiasm compression, often caused by sellar or suprasellar masses like pituitary adenomas. Timely recognition is crucial, as delayed diagnosis can result in irreversible vision loss and broader systemic complications.[2]

PCPs, often the first point of contact, play a pivotal role in early recognition through thorough assessments, including visual acuity and field testing. However, such evaluations are underutilized, with vision loss frequently misattributed to aging or refractive errors, leading to delayed referrals and worsened outcomes.[3]

This case report underscores the importance of structured primary care evaluations, highlights a proposed flowchart for managing vision loss in elderly patients, and advocates for multidisciplinary collaboration to optimize outcomes and improve quality of life.

CASE PRESENTATION

The patient, a 73-year-old man, presented with progressive blurring of vision over one year, accompanied by peripheral field loss. There were no associated headaches, nausea, or constitutional symptoms. However, he reported fatigue and mild lethargy, which were initially attributed to aging and comorbid conditions. His medical history included dyslipidaemia, ischemic heart disease with coronary artery bypass grafting in 2013, and lymphocutaneous sporotrichosis. He was under treatment for mild hiatal hernia and benign prostatic hyperplasia.

At the time of presentation to the primary care clinic, his visual acuity (VA) was recorded as 6/6 in the right eye and 6/12 in the left eye. Due to these relatively preserved VA findings, his case was managed conservatively with advice on routine follow-up. However, no visual field assessment, such as confrontation testing or grid tests, was performed at the initial consultation.

The patient continued to experience worsening visual symptoms and returned to the clinic six months later, now complaining of bilateral eye discomfort and persistent fatigue. Referral to ophthalmology was made for suspected bilateral glaucoma. By this point, his VA had significantly deteriorated to 6/60 in the right eye and 6/24 in the left eye.

Further investigations revealed optic disc pallor on fundoscopy, with a vertical cup-to-disc ratio of 0.8 in the right eye and 0.7 in the left, indicative of optic nerve atrophy. Humphrey Visual Field analysis demonstrated bitemporal hemianopia, and optical coherence tomography showed thinning of the retinal nerve fibre layer, consistent with chronic chiasmal compression.

Contrast-enhanced computed tomography (CECT) of the brain in Figure 1 showed a well-defined extra-axial lesion in the pituitary fossa extending to the suprasellar region, measuring 2.8 cm x 3.0 cm x 3.2 cm (AP x W x CC). The lesion exhibited hypodensity, suggestive of necrosis, with no calcification. The optic chiasm was not visualized, likely due to compression, and the mass abutted the anterior, posterior, and middle cerebral arteries, all of which remained patent. Contrast-enhanced MRI in Figure 1 confirmed a sellar mass with suprasellar extension and optic chiasm compression, consistent with a pituitary macroadenoma.

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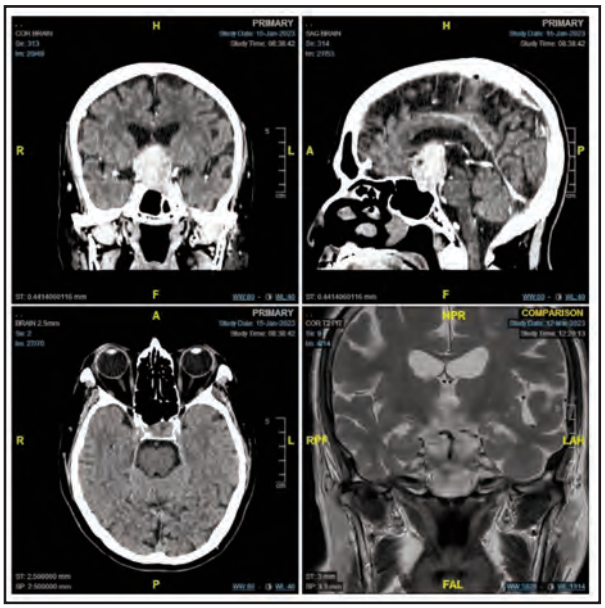

Fig. 1: Initial CT brain and MRI images of well-defined extra-axial lesion in the pituitary fossa extending to the suprasellar region

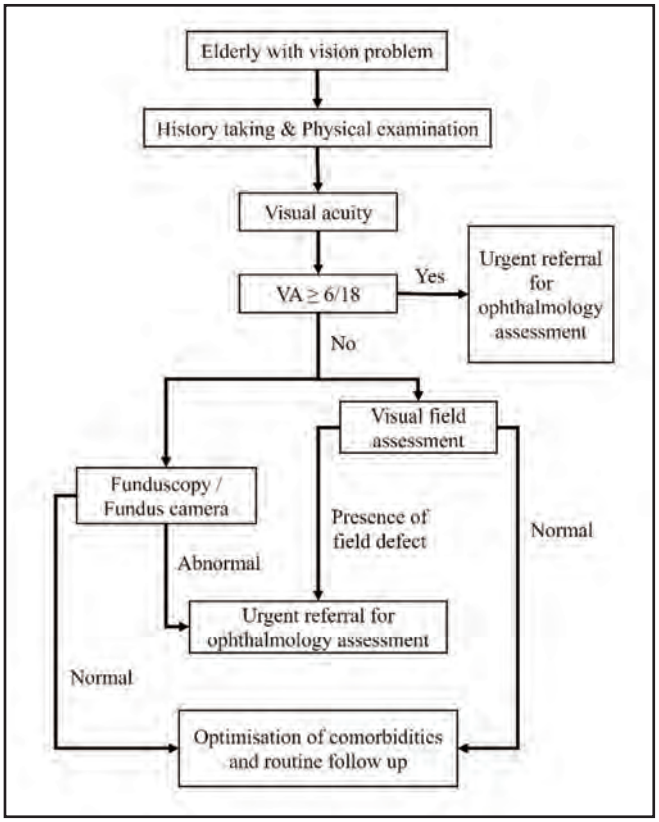

Fig. 2: Recommendation for primary care management of visual loss in the elderly

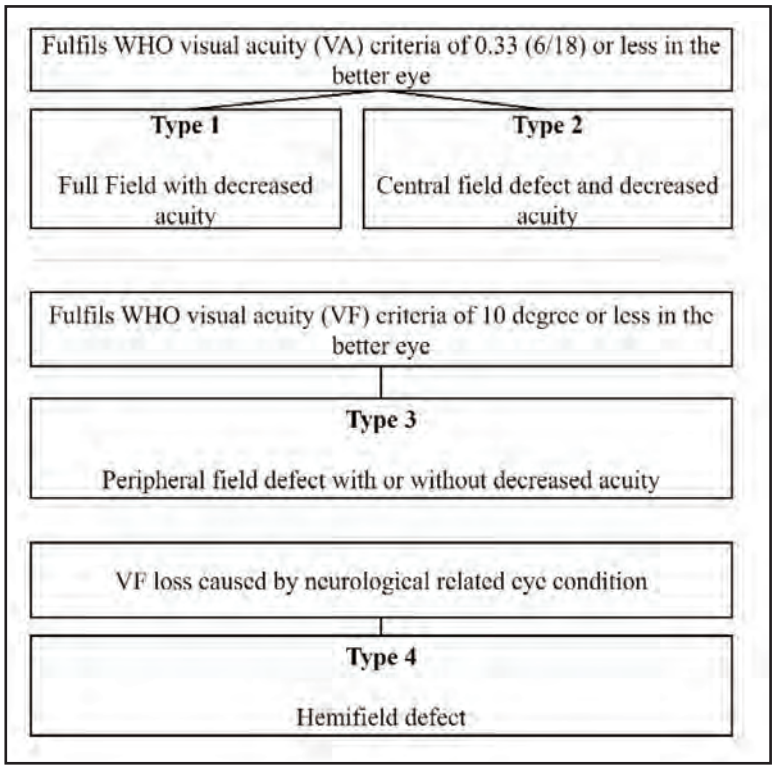

Fig. 3: Flow chart to classify types of visual loss in older adults according to WHO criteria as illustrated by Boey et al. (2022)[5]

The patient underwent transsphenoidal resection of the pituitary macroadenoma. Postoperative imaging demonstrated partial tumour resection, with residual changes attributed to postoperative effects. Histopathology confirmed a non-functioning pituitary adenoma.

Postoperative blood tests revealed evidence of hypopituitarism, including persistently low serum cortisol levels (105 nmol/L) and free thyroxine (FT4) levels at the lower end of normal (10.5pmol/L). These findings indicated ongoing hormonal insufficiencies, consistent with the effects of partial tumour resection and pre-existing pituitary dysfunction. Endocrinology recommended hydrocortisone supplementation to address adrenal insufficiency and levothyroxine therapy for hypothyroidism, with ongoing monitoring to ensure adequate hormonal replacement and symptom resolution.

The primary care physician coordinated multidisciplinary follow-ups, closely monitored symptoms like fatigue and signs of adrenal insufficiency, collaborated with endocrinologists on medication adjustments, and educated the patient and family on managing this chronic condition. This holistic, patient-centred approach significantly enhanced the patient's quality of life.

DISCUSSION

Vision loss in elderly, especially bitemporal hemianopia, profoundly impacts functional independence, increases fall risk, and diminishes quality of life. This discussion explores the unique challenges faced by PCPs, the complexity of care coordination, and the broader implications of multidisciplinary management.

1. Role of PCPs in Early Recognition of Vision Loss in the Elderly

In this case, the patient's progressive vision loss was initially attributed to common conditions such as refractive errors or cataracts, resulting in delayed recognition of the underlying pathology. However, this approach missed critical early signs, such as bitemporal field loss and optic nerve pallor, which could have been identified through a thorough history, confrontation testing, and fundoscopy.

The presence of comorbidities such as dyslipidaemia, ischemic heart disease, and benign prostatic hyperplasia may have further complicated the diagnostic process. These conditions, along with age-related changes, can obscure or mimic symptoms of serious ophthalmological or neurological pathologies. For example, fatigue attributed to aging or comorbid conditions in this patient may have been an early indication of underlying hypopituitarism, which was only identified after advanced imaging and endocrine evaluations. This highlights the need for PCPs to maintain a high index of suspicion when vision complaints are accompanied by systemic symptoms, even if seemingly nonspecific.

Distinguishing between age-related vision deterioration and pathological vision loss remains a significant challenge, especially in primary care settings with limited access to advanced diagnostic tools such as optical coherence tomography (OCT) or automated visual field analysers.[4] The

absence of these tools necessitates reliance on meticulous clinical assessments, including structured approaches to history taking, physical examination, and targeted use of available resources. To improve outcomes and reduce diagnostic delays, PCPs should adopt a systematic approach, such as the one proposed in Figure 2.

Figure 3 illustrates a structured flow chart designed to assist primary care providers in classifying types of visual loss among older adults who either meet the World Health Organization (WHO) criteria for low vision (visual acuity worse than 6/18) or present with hemifield visual defects.5

2. Challenges in Geriatric Populations

Elderly patients often present with overlapping symptoms, such as fatigue or headaches, that can obscure the primary pathology.[1] For instance, optic nerve atrophy in this case could have been mistaken for advanced glaucoma, delaying the correct diagnosis. Additionally, the risks associated with invasive interventions like transsphenoidal surgery are heightened in this population due to multiple comorbidities.[6]

PCPs play a critical role in preoperative optimisation and liaising with specialists to balance risks and benefits. Clear communication and shared decision-making are essential for minimizing complications and addressing patient and caregiver concerns.[7]

3. Coordination of Multidisciplinary Care

Managing chiasmal syndrome necessitates input from ophthalmology, endocrinology, neurosurgery, and radiology.[2] The PCP is the central coordinator, ensuring seamless communication and follow-up across these specialties. In this case, ophthalmology confirmed bitemporal hemianopia, endocrinology managed hypopituitarism, and neurosurgery performed tumour resection.

Psychosocial support is equally critical. The PCP provided reassurance, helped the patient and family adapt to vision loss, and connected them with community resources. This comprehensive approach enhances clinical outcomes and alleviates caregiver burden and emotional stress.[7]

4. Implications for Long-Term Management.

The PCP's role extends into long-term care, encompassing regular monitoring for tumor recurrence, visual function assessment, and endocrine stability. Vision rehabilitation, including occupational therapy and low-vision aids, may be necessary to maintain independence and improve quality of life.[7]

Additionally, addressing mental health concerns remains important. Encouraging participation in support groups or self-management programs can mitigate feelings of isolation, while professional mental health care may be warranted for more severe cases. Documenting these interventions ensures continuity and reimbursement where applicable.[8]

5. Broader Implications for Primary Care

This case exemplifies the vital role of PCPs in bridging the gap between initial presentation and specialist care. A structured, evidence-based approach enhances diagnostic accuracy, particularly in resource-limited settings where access to specialists may be delayed. Moreover, ongoing medical education and access to decision-support tools are essential for PCPs to recognize rare systemic presentations, ensuring timely interventions and optimal outcomesClick or tap here to enter text.[3]

In Malaysia's ageing population, optometrists serve as crucial allies in primary care by performing structured eye assessments that help detect early signs of visual impairment, including subtle field loss or optic disc changes. A study at Primary Eye Clinic (PEC) Universiti Kebangsaan Malaysia (UKM) reported a 16% prevalence of visual impairment among older adults, with cataracts and refractive errors as leading causes.[9] Embedding optometrists in multidisciplinary teams improves timely triage and reduces unnecessary referrals, allowing PCPs to focus on systemic illnesses while ensuring that elderly patients with visual symptoms receive appropriate and early intervention.

6. Importance of a Holistic and Patient-Centered Approach

Beyond the diagnostic phase, PCPs play a pivotal role in managing the broader physical, psychosocial, and functional needs of elderly patients. Vision loss profoundly impacts activities of daily living (ADLs) such as managing medications, preparing meals, and maintaining personal hygiene. It also increases the risk of falls and related injuries, such as hip fractures.[7]

In this case, the PCP not only managed the patient's comorbidities, including ischemic heart disease and hypothyroidism, but also addressed the emotional impact of vision loss. The sudden transition from normal to impaired vision can be devastating, often resembling a grieving process. This places patients at risk for depression or adjustment disorders. Monitoring these psychological responses and providing timely intervention, such as counselling or referrals for mental health support, are integral to holistic care.

Educating the patient and family about the condition and its management fosters trust and ensures adherence to follow-up plans. This patient-centred approach improves engagement and overall quality of life.

CONCLUSION

Structured and timely evaluations in primary care are vital for elderly patients with vision loss. Early recognition of red flags, like bitemporal hemianopia, prevents delays in diagnosing serious conditions such as chiasmal syndrome. PCP plays a pivotal role in initiating investigations, coordinating multidisciplinary care, and addressing medical and psychosocial needs, ensuring better outcomes and quality of life.

DECLARATIONS:

There are no conflicts of interest among the authors regarding this case report. The patient and his family

members have provided written consent for the publication of this report and its accompanying images.

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REFERENCES

1. Kopp W. Aging and "Age-Related" Diseases - What Is the Relation? Aging Dis 2024; 16(3): 1316-46.
2. Beebe JD, Lee MS, McClelland C. Chiasmal and Retrochiasmal Disorders. Int Ophthalmol Clin 2019; 59(3): 59-81.
3. Al Nahdi AT, Alobaid AA, Alajmi AK, Al Majed AS, Alkhars AA, Alsayyar MA, et al. Assessment, types, and etiologies of vision loss in primary care settings. Int J Community Med Public Health 2021; 8(11): 5505-9.
4. Cunningham J. Recognizing age-related macular degeneration in primary care. JAAPA 2017; 30(3): 18-22.
5. Boey D, Fitzmaurice K, Tse T, Chan ML, Carey LM. Classifying Types of Visual Loss Linked With Function to Inform Referral to Vision Rehabilitation for Older Adults in Singapore. Gerontol Geriatr Med. 2022; 8: 23337214221130652.
6. Baquero GA, Rich MW. Perioperative care in older adults. J Geriatr Cardiol 2015;12(5): 465-9.
7. Wolvaardt E, Shukla K. Primary eye health care: the foundation for universal access to eye health. Community Eye Health 2021; 34(113): 65-66.
8. Bakri SJ, Amoaku WMK, Altman D, Quéré S, Quilantan J, Carpenter-Conlin J, et al. The MOSAIC Study: A Mixed-Methods Study of the Clinical, Emotional, and Financial Burden of Geographic Atrophy Among Patients and Caregivers in the US. Clin Ophthalmol 2024; 18: 2357-68.
9. Mohd Harimi A, Anis Humaira' A, Norliza M, Zainora M, Nur Syafiqah S, Qiu T. Profile of Visual Impairment in Older Adult Patients Attending Primary Eye Care Optometry Clinic: A Retrospective Study. Med Health 2022; 17(1): 122-32.

CASE REPORT

Miller fisher syndrome and Lyme disease: An exceptional case

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SUMMARY

Miller Fisher syndrome (MFS), a rare variant of Guillain-Barré syndrome, and Lyme disease (LD), a tick-borne illness caused by Borrelia burgdorferi, are distinct entities. Both can trigger immune-mediated neurological complications. However, their coexistence is exceedingly rare, with only one case previously reported. Here, we describe a 17-year-old boy with concurrent seropositivity for Borrelia burgdorferi IgM and anti-GQ1b IgM and IgG antibodies, supporting the co-occurrence of LD and MFS. He presented with bilateral ptosis and binocular diplopia following a riverside picnic one week prior, along with headaches, nausea, and lower extremity paraesthesia. Neurological examination revealed gait ataxia and areflexia, but brain imaging: CT and MRI, was unremarkable. Lumbar puncture showed elevated cerebrospinal fluid protein. The patient was treated with a five-day course of intravenous immunoglobulin and two weeks of oral doxycycline. He responded well to therapy and achieved complete neurological recovery within one month. This case illustrates the rare coexistence of MFS and LD, highlighting the diagnostic complexities and demonstrating the efficacy of timely immunoglobulin and antibiotic therapy.

INTRODUCTION

Miller Fisher syndrome (MFS) is an immune-mediated neuropathy characterised by ophthalmoplegia, ataxia, and areflexia. With an annual prevalence of one to two per million, MFS is more frequently reported in Asia, accounting for 15-25% of GBS cases, compared to approximately 5% in Western countries.[1] While MFS is commonly triggered by infections, particularly Campylobacter jejuni and Haemophilus influenzae, the potential role of Borrelia burgdorferi, the causative agent of Lyme disease (LD), in triggering post-infectious MFS-related neuropathies is less established. Although neurological complications of LD and MFS have been individually documented, serological co-occurrence remains exceedingly rare, with only one previous case reported.[2] Here, we describe an exceptional case of MFS in a teenager with confirmed Borrelia burgdorferi IgM and anti-GQ1b IgM seropositivity, suggesting a recently acquired Borrelia infection alongside concurrent immune-mediated neuropathy.

CASE PRESENTATION

A 17-year-old boy with no known comorbidities presented with a four-day history of bilateral ptosis and binocular diplopia, accompanied by fever, headache, nausea, and paraesthesia over the lower extremities. Upon further questioning, he reported attending a riverside picnic one week prior to the symptom onset. However, he was unaware of any tick bites during the outing.

His vision was 6/18 in both eyes, improving to 6/9 with a pinhole test. Ocular examination showed partial ptosis in both eyes, sparing the visual axis, complete ophthalmoplegia (Fig. 1) and tonic dilated pupils with diminished light reflex (Fig. 2A). The anterior segment and fundus examinations were unremarkable. Neurological examination revealed areflexia and gait ataxia.

Brain computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and spine were unremarkable. Lumbar puncture revealed elevated levels of CSF protein. Infective serology testing confirmed Borrelia burgdorferi IgM positivity. Immunoserology testing for anti-GQ1b IgM, IgG, and anti-GT1a IgG antibodies was also positive. A diagnosis of MFS and LD was established. The patient received a five-day treatment with intravenous immunoglobulin (IVIG) and a two-week course of oral doxycycline 200mg once daily. A complete recovery was observed within one month, as evidenced by improved light reflexes (Figure 2B), resolution of bilateral ptosis and external ophthalmoplegia (Figure 3). At three-month follow-up, the patient remained asymptomatic.

DISCUSSION

MFS is an antibody-mediated neurological disorder with anti-GQ1b ganglioside antibodies, detected in up to 80% of cases. These autoantibodies selectively target ganglioside-rich regions in the brainstem and peripheral nerves, leading to demyelination and axonal injury. The resulting neuropathy typically manifests as the classic triad of ophthalmoplegia, ataxia and areflexia.[1] Our patient presented with this hallmark triad, along with systemic symptoms including fever, headache, nausea, and limb paraesthesia, prompting a thorough neurological evaluation. The simultaneous detection of Borrelia burgdorferi IgM, anti-GQ1b IgM, IgG, and anti-GT1a IgG antibodies strongly supports a diagnosis of MFS potentially triggered by a recent LD infection.

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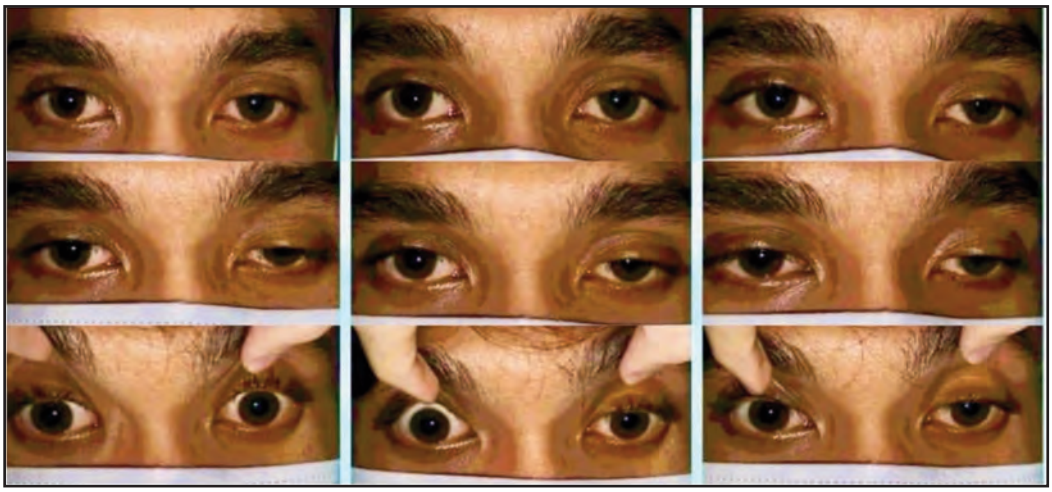

Fig. 1: Partial ptosis with "frozen eye" appearance in both eyes at presentation

Fig. 2: Pupillary examination at presentation (A) shows bilateral tonic dilated pupils, with improved light reflexes at one-month follow-up following immunoglobulin therapy (B).

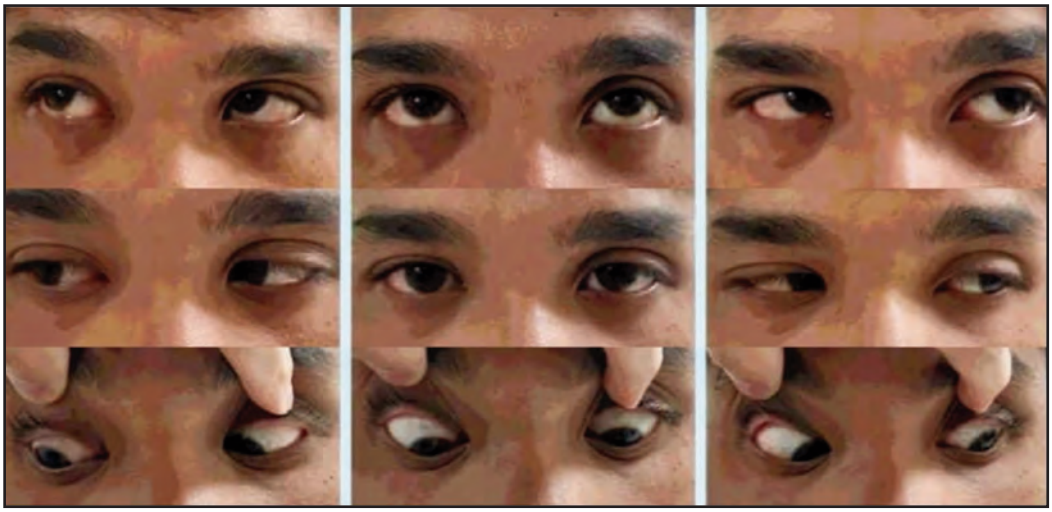

Fig. 3: Complete recovery of ptosis and ophthalmoplegia during one-month follow-up.

There are scarce reports describing cases of GBS and MFS associated with LD to suggest that Borrelia burgdorferi infection may trigger immune-mediated neuropathic complications. One comparable case involved an MFS patient without a known history of tick bites, who tested positive for Borrelia burgdorferi IgM in the CSF and seropositive for anti-GQ1b antibodies.[2] Notably, this patient showed neurological improvement by day four following treatment with IVIG and ceftriaxone,[2] contrasting with the more prolonged recovery observed in our case. Other documented cases include LD-associated GBS in a pregnant woman who presented with painful, asymmetric polyradiculopathy six weeks after a tick bite,[3] and MFS in an adult with a history of LD during adolescence.[4] Interestingly, previous cases occurred in individuals in their mid-20s to 30s.[2-4] In contrast, our case represents the youngest patient described to date, suggesting that Borrelia burgdorferi may trigger MFS across a broader age range than previously recognised.

While Borrelia burgdorferi is not known to induce ganglioside antibodies directly, infections may serve as nonspecific immune triggers in genetically predisposed individuals.[2-4] An essential diagnostic consideration in our case is the potential for a false-positive Borrelia burgdorferi IgM result, which may occur due to cross-reactivity with other infections or autoimmune processes. The lack of CSF analysis for anti-Borrelia antibodies and confirmatory Western blot and IgG seroconversion also introduces diagnostic uncertainty. However, the absence of other antecedent infections strengthens the hypothesis that LD contributed to immune activation in our patient, leading to MFS. Although classic LD features such as erythema migrans or joint pain were absent, the limb paraesthesia suggestive of radiculopathy, and the recent outdoor exposure raises suspicion for LD infection.[1]

Diagnostic evaluation plays a crucial role in confirming MFS while ruling out other neurological conditions.[1] CSF analysis in our patient revealed elevated protein levels, consistent with previously reported cases of albuminocytologic dissociation.[4] However, it is important to note that normal CSF protein levels do not exclude MFS, especially in the early stages due to the CSF test timing and individual variations.[1] Additionally, neuroimaging (CT and MRI) is mandatory in all cases presenting with neurological deficits to exclude inflammatory or infective processes in the brain or space-occupying lesions.[1,3] In this case, the diagnosis of MFS was confirmed through characteristic clinical findings and positive serology, with otherwise normal imaging studies.

The patient's favourable response to IVIG and doxycycline therapy underscores the importance of prompt diagnosis and treatment in both MFS and LD. While the management of MFS is primarily supportive, IVIG remains a cornerstone of treatment.[6] Given that MFS is an autoimmune disorder targeting gangliosides, early IVIG administration is critical, as it modulates the immune system, neutralises pathogenic antibodies, and minimizes further nerve damage.[3,6] MFS generally has a good prognosis and outcome, but prompt IVIG therapy shortens illness duration, promotes early recovery, and prevents lasting neurological complications.[6] The addition of doxycycline, the first line treatment of LD, effectively addressed the active infection, preventing potential long-term sequelae.[5] Though often costly, serological testing is essential for accurate and confirmatory diagnosis, especially in patients with atypical or overlapping symptoms in complex neurological diseases.

CONCLUSION

This case highlights the rare coexistence of MFS and LD, underscoring diagnostic and management challenges. Early treatment with immunoglobulin and antibiotic therapy is crucial for optimal recovery and improved neurological outcomes.

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DECLARATIONS

Consent was obtained from the patient prior to publication. There is no conflict of interest related to this study. This study was made without any financial support. This manuscript has been read and approved by the named authors.

REFERENCES

1. Noioso CM, Bevilacqua L, Acerra GM, Della Valle P, Serio M, Vinciguerra C, et al. Miller Fisher syndrome: an updated narrative review. Front Neurol 2023; 14: 1250774.
2. Pan D, Lee S, Gabra NI, Mathew J. Miller Fisher Syndrome and Neuroborreliosis: A Clinical Conundrum. Chest 2017; 152(4): A362.
3. Wakerley BR, Yuki N. Mimics and chameleons in Guillain-Barré and Miller Fisher syndromes. Pract Neurol 2015; 15(2): 90-9.
4. Ghani MR, Yousaf MIK, Van Bussum K, Shi P, Cordoves Feria RM, Brown M. Miller Fisher syndrome presenting without areflexia, ophthalmoplegia, and albuminocytological dissociation: A case report. Cureus 2022; 14(3): e23371.
5. Lantos PM, Rumbaugh J, Bockenstedt LK, Falck-Ytter YT, Aguero-Rosenfeld ME, Auwaerter PG, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis, and treatment of Lyme disease. Arthritis Care Res (Hoboken) 2021; 73(1): 1-9.
6. Mori M, Kuwabara S, Fukutake T, Hattori T. Intravenous immunoglobulin therapy for Miller Fisher syndrome. Neurology 2007; 68(14): 1144-6.

A devastating infectious sclerokeratitis after pterygium surgery: A case report

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SUMMARY

Pterygium excision is a common procedure with generally good outcomes, but infectious complications, although rare, can lead to severe visual impairment if not promptly managed. We report a case of a 71-year-old man who developed bacterial keratitis with dense stromal infiltrate, central corneal melt, and hypopyon following left eye pterygium excision with conjunctival autograft. Corneal scraping yielded Streptococcus pneumoniae. Despite aggressive treatment with antibiotics and antifungals, the condition worsened, requiring a large-diameter penetrating keratoplasty due to progressive corneal thinning and extension to the adjacent sclera. This case underscores the rare but serious risk of infectious sclerokeratitis after pterygium surgery, highlighting the importance of early diagnosis and prompt antimicrobial therapy. It also emphasises the need for careful preoperative assessment, meticulous intraoperative measures, and diligent post-operative follow-up if a good visual outcome is to be attained.

INTRODUCTION

Pterygium is a degenerative benign ocular surface disorder with a wing-shaped fibrovascular conjunctival growth that encroaches onto the cornea over time.[1] Symptoms of pterygium include foreign body sensation, persistent eye redness, and lacrimation. In advanced cases, it may cause visual disturbance due to astigmatism and obscuration of the optical axis by pterygium tissue.[1] The current gold standard treatment for clinically significant pterygium is excision with conjunctival autograft, demonstrating a low recurrence rate.[2] Although generally effective, this procedure is not without risks. We report a severe case of bacterial keratitis following pterygium excision with conjunctival autograft, which progressed to sclerokeratitis necessitating a large-diameter penetrating keratoplasty (PK).

CASE PRESENTATION

A 71-year-old man with no known comorbidities presented with left eye pain, redness, and reduced vision ten days after an uneventful pterygium excision with conjunctival autograft. No intraoperative adjuvants were used. Post-operatively, the patient was prescribed topical chloramphenicol 0.5% every four hours and dexamethasone 0.1% every two hours, in accordance with our centre's routine post-pterygium surgery protocol to control inflammation and reduce recurrence risk. The patient was compliant with the prescribed regimen; however, the medications ran out three days prior to presentation. There was no ocular trauma or foreign body exposure following the surgery.

His best corrected visual acuity (BCVA) was 6/18 in the right eye and counting fingers (CF) in the left eye. Initial examination of the left eye showed mildly swollen eyelids with meibomian gland capping. The conjunctiva was diffusely injected and chemotic, with a large corneal epithelial defect measuring 8 mm x 8 mm, dense stromal infiltrate, and central corneal melt, along with a 1.2 mm hypopyon obscuring the view of the fundus. B-scan ultrasonography revealed no evidence of loculation in the left eye. Anterior and posterior segment examinations of the right eye were otherwise unremarkable. His blood sugar profile was normal, and no further investigations for other immunosuppressive conditions were conducted.

Given the patient's presentation, a mixed infection was suspected, so he was started empirically with hourly topical Gentamicin 0.9%, Ceftazidime 0.5%, Amphotericin B 0.15%, and Fluconazole 0.2%, along with oral Doxycycline 100 mg once a day and Vitamin C 1 g/day. Corneal scraping was done prior to initiation of antimicrobial treatment. The Gram stain returned as no detectable organism; however, culture and sensitivity yielded Streptococcus pneumoniae from the cultured sample. Topical Ceftazidime was subsequently changed to topical Vancomycin based on the culture and sensitivity, which came back after five days of empirical antimicrobial therapy. Despite treatment, the left eye condition progressively worsened to total corneal ulcer, with an increasing hypopyon level, scleral abscess formation (Fig. 1), the development of peripheral anterior synechiae, and a subsequent rise in the intraocular pressure (IOP) requiring three types of IOP-lowering agents.

After 12 days of unsuccessful treatment, the patient was subjected to left penetrating keratoplasty (PK). The surgery was done on day 23 after his pterygium excision. Corneal tissue obtained from the surgery was sent for Gram stain, culture, and sensitivity. During post-PK review day 1, left eye conjunctival chemosis and injection reduced. The cornea appeared mildly hazy with a central epithelial defect (Fig. 2). Posterior synechiae were noted from 3 to 5 o'clock, and a cataractous lens was noted. No organism was isolated from

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Table I: Summary of post-pterygium sclerokeratitis cases reported over the last decade

Author, Year	Case	Technique	Latency period (after pterygium surgery)	Pathogen	Treatment
Fidelix et al., 2016[10]	51/Female **ANA positive	Bare sclera	2-3 months	No growth of organism	• Oral steroid • Immunosuppressive (Azathioprine, Cyclophosphamide) • Rituximab
Soleimani et al., 2019[4]	56/Female DM	AMT	27 days	Streptococcus Pseudomonas	• Topical antibiotics (Ceftazidime, Vancomycin) • Scleral patch graft and PKP
	62/Male No comorbidities	Conjunctival graft	32 days	No growth	• Topical antibiotics (Cefazolin, organism Amikacin) • AMT
	60/Male No comorbidities	AMT	35 days	Streptococcus	• Topical antibiotics (Cefazolin, Amikacin) • PKP
	62/Female No comorbidities	Conjunctival graft	32 days	Fusarium	• Topical antifungal (voriconazole) • PKP
Teoh et al., 2023[8]	75/Male No comorbidities	-	10 days	Pseudomonas aeruginosa	• Topical antibiotic (Gentamicin, Ceftazidime) • Topical NSAID • Systemic antibiotic (Ciprofloxacin)
Lee et al., 2007[9]	72/Female No comorbidities	-	6 months	MRSA	• Topical antibiotics (Ciprofloxacin, Vancomycin) • Systemic antibiotics (Amikacin, Ceftazidime) • Scleral patch graft and sliding conjunctival flap

ANA, anti-nuclear antibody; DM, diabetes mellitus; AMT, amniotic membrane transplantation; MRSA, Methicillin-resistant Staphylococcus aureus; PKP, penetrating keratoplasty; NSAID, non-steroidal anti-inflammatory drug

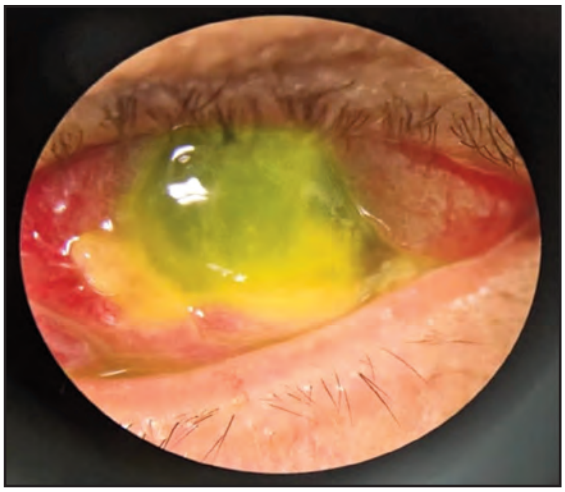

Fig. 1: Slit lamp examination of the left eye showed a total corneal ulcer with corneal melt and scleral abscess, along with diffuse conjunctival injection and chemosis.

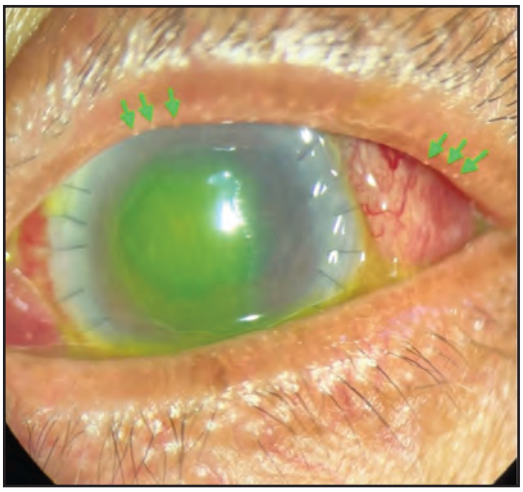

Fig. 2: Day-1 post-right penetrating keratoplasty showing reduced conjunctival injection and chemosis. The cornea is mildly hazy, with a central epithelial defect. The green arrows highlight clogged meibomian glands, suggestive of pre-existing meibomitis.

the sample. Topical antibiotics were maintained and tapered off gradually, while topical antifungal agents were discontinued early as there was no evidence of fungal growth. At his most recent follow-up, six months post-PK, his vision was hand movements with persistent left corneal button oedema. He was then counselled for a second left eye PK, but he was still undecided.

DISCUSSION

Pterygium excision with conjunctival autograft is a commonly performed procedure that remains the preferred technique to reduce the recurrence of pterygium.[1,2] Other reported complications include scleral ulceration, necrotising scleritis, perforation, iridocyclitis, cataract, and glaucoma.[3-5] Although rare, infectious scleritis and infectious keratitis,

collectively known as sclerokeratitis, are serious potential post-surgery complications.[3-5] The major risks for infectious sclerokeratitis include excessive intraoperative scraping, cauterisation, and adjunctive treatment with beta-irradiation and mitomycin C (MMC).[4] Additionally, a persistent corneal epithelial defect, chronic avascular zones at the pterygium site, and steroid-induced scleral ischemia also predispose to infection by the ocular surface flora.[4]

The development of infectious sclerokeratitis in our patient was likely multifactorial, with meibomitis (Fig. 2) as a pre-existing ocular surface disease and advanced age being a key contributor.[6,7] Older patients are more prone to tear film instability, dry eye, and age-related immune decline, all of which increase their susceptibility to infection.[6,7] Although no adjuvants were used, the intensive use of strong topical steroids post-operatively in our patient likely impaired immune defence and delayed corneal epithelial healing. This contributed to elevated proteolytic enzyme activity and corneal thinning, further compromising ocular integrity, particularly in the presence of meibomitis, which led to poor recovery and worsening of the infection. Similar post-pterygium sclerokeratitis cases published over the past decade are summarised in Table I.

A multifaceted approach is essential to prevent infective sclerokeratitis following pterygium excision. Pre-operative assessment should address any ocular surface diseases (OSD) such as dry eye, blepharitis, and meibomitis, which increase the risk of post-operative infection.[6] Intraoperatively, meticulous techniques, including complete pterygium tissue excision, appropriately sized conjunctival autograft with minimal tenons, and full coverage of the bare sclera, are paramount to minimise epithelial defects and complications.[5] Post-operative care should include the prompt commencement of broad-spectrum antibiotics and careful use of topical steroids, particularly in elderly patients, to prevent delayed healing and secondary infections.[7] Adjunctive amniotic membrane transplantation (AMT) provide anti-inflammatory and wound-healing benefits, potentially enhancing corneal recovery.[1] Alternatively, non-steroidal anti-inflammatory drugs (NSAIDs) may help control inflammation without the risks associated with steroids.[1]

Currently, there are no established guidelines or standardised risk stratification tools for managing infectious sclerokeratitis following pterygium surgery. Treating infectious keratitis itself is challenging, given the variability in individual immune responses. Clinical judgement remains essential, and clear communication between the consultant and the patient is critical, particularly in cases that are refractory to medical therapy. Urgent PK may be required to reduce the microbial load by removing the infected tissue, thereby helping to control the infection and potentially shorten the recovery period.[3,4] In this case, a large-diameter PK was preferred, as it ensured the complete removal of infected and necrotic tissue, preventing posterior scleral extension and eliminating the need for evisceration. A comprehensive perioperative approach and regular follow-up remain essential for early detection of infection, delayed epithelial defects, or severe inflammation following pterygium surgery.

CONCLUSION

Infectious sclerokeratitis is a rare but sight-threatening complication following pterygium surgery. Preventive measures, including thorough preoperative assessment to identify OSD or MGD, meticulous surgical techniques, and the judicious use of postoperative corticosteroids, are crucial in minimising the risk of infection and associated complications. Early recognition and prompt, targeted intervention remain essential to preserving visual outcomes in affected patients.

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DECLARATIONS

Consent was obtained from the patient prior to publication. There is no conflict of interest related to this study. This study was made without any financial support. This manuscript has been read and approved by the named authors.

REFERENCES

1. Shahraki T, Arabi A, Feizi S. Pterygium: an update on pathophysiology, clinical features, and management. Ther Adv Ophthalmol 2021; 13: 25158414211020152.
2. Kocamis O, Bilgec M. Evaluation of the recurrence rate for pterygium treated with conjunctival autograft. Graefes Arch Clin Exp Ophthalmol 2014; 252(5): 817-20.
3. Tittler EH, Nguyen P, Rue KS, Vasconcelos-Santos DV, Song JC, Irvine JA, et al. Early surgical debridement in the management of infectious scleritis after pterygium excision. J Ophthalmic Inflamm Infect 2012; 2(2): 81-7.
4. Soleimani M, Tabatabaei SA, Mehrpour M, Salabati M, Mahmoudzadeh R. Infectious keratitis after pterygium surgery. Eye (Lond) 2020; 34(5): 986-8.
5. Kodavoor SK, Preethi V, Dandapani R. Profile of complications in pterygium surgery - A retrospective analysis. Indian J Ophthalmol 2021; 69(7): 1697-701.
6. Kitazawa K, Inotmata T, Shih K, Hughes JWB, Bozza N, Tomioka Y, et al. Impact of aging on the pathophysiology of dry eye disease: A systematic review and meta-analysis. Ocul Surf 2022; 25: 108-18.
7. Lewis ED, Wu D, Meydani SN. Age-associated alterations in immune function and inflammation. Prog Neuropsychopharmacol Biol Psychiatry 2022; 118: 110576.
8. Teoh RJ, Lai YP, Rohanah A. Infectious surgically induced necrotising scleritis presenting 10 years post-pterygium excision: a case report. Malays J Ophthalmol 2023;5(1): 1-8.
9. Lee JE, Oum BS, Choi HY, Lee JS. Methicillin-resistant Staphylococcus aureus sclerokeratitis after pterygium excision. Cornea 2007; 26(6): 744-6.
10. Fidelix TS, Vieira LA, Trevisani VF. Management of necrotizing scleritis after pterygium surgery with rituximab. Arq Bras Oftalmol 2016; 79: 339-41.

CASE REPORT

Paediatric jejunal diverticulum masquerading as severe constipation with intestinal obstruction: A rare primary care encounter

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SUMMARY

Paediatric jejunal diverticulum is rare. It is characterised by the presence of sac-like outpouchings of the small bowel wall. Although mostly asymptomatic, it is called diverticular disease when it becomes symptomatic and causes gastrointestinal (GI) bleeding, abdominal pain, and bowel obstruction. We describe a young boy who initially presented to primary care with the complaints of chronic colicky abdominal pain and constipation refractory to medical therapy. As his abdominal distension worsened and radiological findings remained inconclusive, he was referred to a tertiary centre for an emergency laparotomy. A segment of jejunal narrowing was found adjacent to a diverticulum, causing partial bowel obstruction. After segmental jejunal resection, he made an uneventful recovery and was discharged well. Histopathology confirmed a true diverticulum. This case highlights the need for clinicians, especially in primary care settings, to hold a high index of suspicion to consider the diagnosis of small bowel diverticular disease when patients of the paediatric age group presented with constipation with atypical features.

INTRODUCTION

Jejunal diverticulum (JD) is a rare entity. Historically, it has a reported incidence of 2% in small bowel contrast studies and 0.7% in autopsies.[1,2] Diverticulum can be classified as true and false. In the paediatric population, JDs are sometimes true diverticula that are congenital and involve the herniation of all layers of the gastrointestinal (GI) tract, forming a sac-like outpouching over the small bowel.[1] Contrastingly, a false diverticulum is acquired and more common among adults, in which a weakness in the muscularis propria layer allows the protrusion of mucosa and submucosa outward through the small bowel wall.[1,2] JDs are usually an incidental finding during surgery or radiological investigation done to assess other pathologies.[1-3]

JDs are mostly asymptomatic.[2,3] However, when symptomatic, JDs can present with a wide spectrum of clinical features, from minor complaints like colicky abdominal pain and constipation, to life-threatening complications including diverticulitis, perforation and bowel obstruction.[1-6] These potential sequelae can be fatal and often require urgent surgical intervention.[3-6]

JDs are exceedingly rare and tend to affect the elderly more.[1-5] Only a handful of paediatric JDs have been described worldwide.[3,6] Due to its exceeding rarity, the pathophysiology of paediatric JDs is not thoroughly understood.[2-4] This presents a diagnostic challenge, especially to primary care providers in resource-limited centres without radiological or surgical capacity. Therefore, treating clinicians must recognise alarming clinical features and consider early referral to tertiary centres for escalation of care in a timely manner. This case illustrates a rare encounter of a child with JD, who initially presented to primary care with constipation that was refractory to medical treatment, followed by intestinal obstruction and eventually required surgical resection.

CASE PRESENTATION

A 3-year-old boy was brought to primary care by his mother with complaints of colicky abdominal pain for 4 weeks. It was associated with worsening abdominal distension, constipation, and reduced flatus. Otherwise, the child remained well with no vomiting or other clinical features suggestive of infection or malignancy. He experienced similar symptoms two months ago, which resolved spontaneously within two days. He had previously had multiple visits to the local clinics and emergency department with similar complaints, but was discharged with laxatives. Otherwise, the child was born full term with no known antenatal complications or medical illness. Serial abdominal examination demonstrated a mildly distended abdomen but was otherwise unremarkable. He was discharged with syrup lactulose and glycerine enema.

The patient's symptoms worsened despite medical therapy. Besides the persistent constipation, the child developed postprandial vomiting with poor oral intake and worsening abdominal distension. He exhibited severe distress during episodes of abdominal colic, which was subsequently relieved after bowel opening. Otherwise, he was haemodynamically stable with good hydration status. Repeated abdominal

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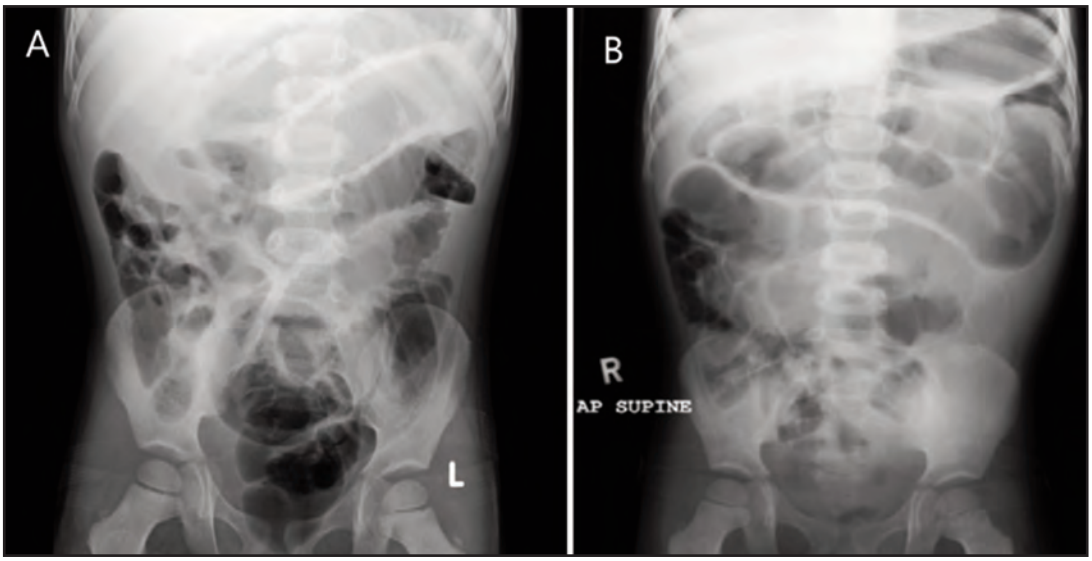

Fig. 1: Images of 2 abdominal plain films as the patient's abdominal pain worsens. Image (A) is the abdominal X-ray done in a local health clinic to show dilated bowels with faecal matters and image (B) was done before surgery to show dilated small bowels.

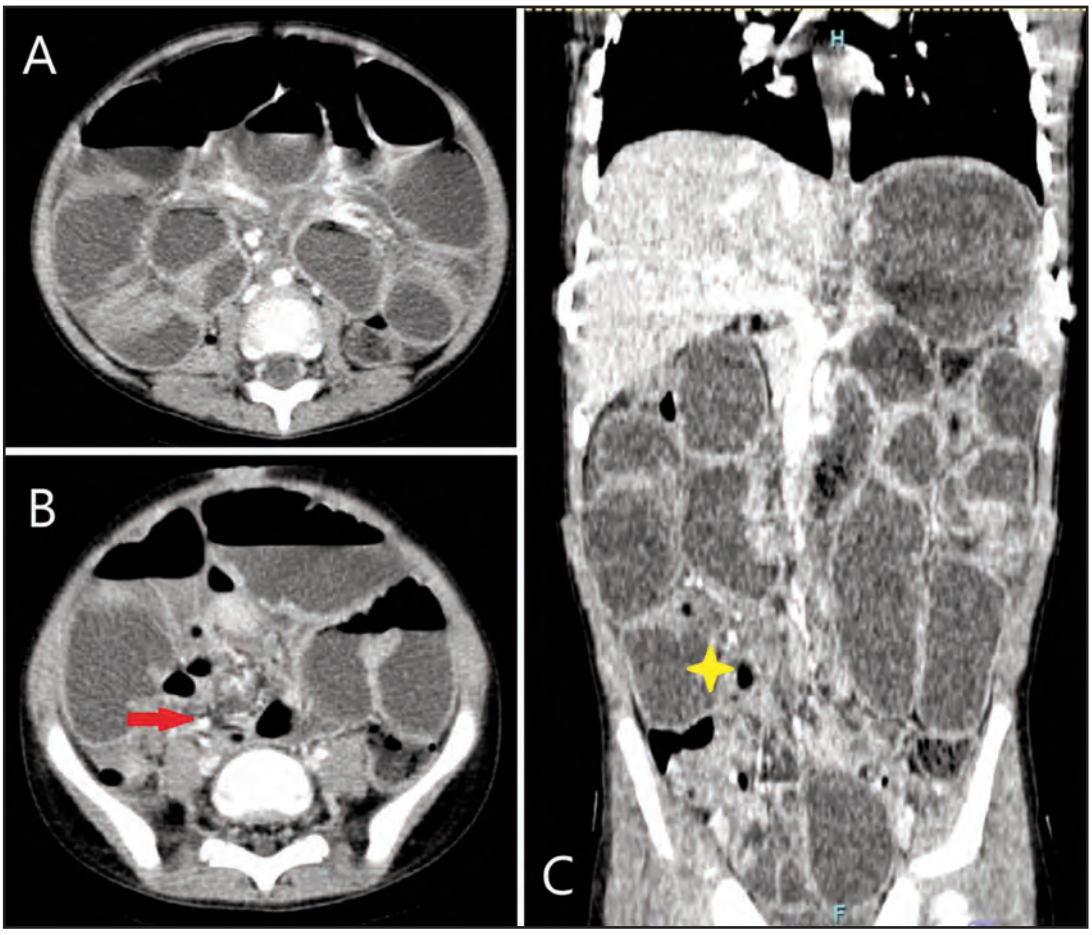

Fig. 2: Images of pre-operative contrast CT of abdomen and pelvis of the child. Images (A) and (B) are the axial CT view, showing dilated small bowels. In image (B), the transition point of the small bowel is seen at the right side of the pelvis, with surrounding mesenteric lymphadenopathy as shown with the red arrow. The anatomical landmark of the transition zone was further confirmed, as shown with a yellow star, in the coronal CT plane in image (C).

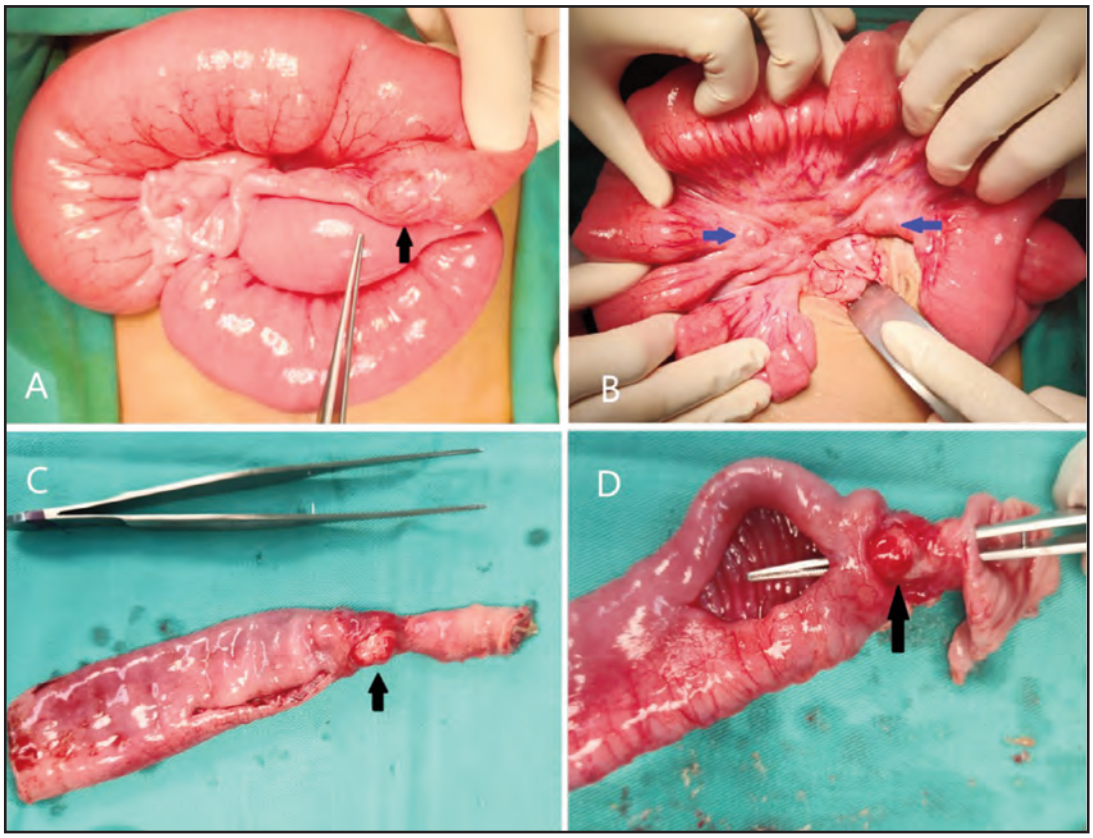

Fig. 3: The intraoperative images of a jejunal mass. Image (A) shows the mass of size 1.0cmx1.5cm as marked with a black arrow, at the antimesenteric border of the jejunum with a collapsed small bowel segment distal to it. Enlarged mesenteric lymph nodes can be seen as marked with blue arrows in image (B). Images (C) and (D) show the specimen of segmental jejunal resection, including the mass. It appears round, contracted, causing circumferential stenosis of the bowel adjacent to it, causing partial obstruction. The calibre of the jejunal lumen was so narrowed that it allowed only the passage of the tips of the forceps, as shown in image (D).

assessment did not find evidence of peritonism. Bowel sounds were normal. Plain abdominal radiograph showed dilated bowels with impacted stool. Due to multiple visits and constipation despite medical therapy, the diagnosis of bowel obstruction secondary to faecaloma was made, and the child was referred to a tertiary centre for specialised care.

During the admission, the child passed out only a small amount of stool despite regular sodium phosphate enema and rectal washout. Moreover, he had worsening colicky abdominal pain and distension. Abdominal ultrasound (USG) showed dilated bowels but was inconclusive. Contrasted computed tomography (CT) showed dilated small bowels with a transition zone at the right iliac fossa, surrounded by adjacent mesenteric lymphadenopathies. No normal appendix was visualised. Large bowels were normal with no faecaloma. No bowel diverticulum was noted on CT. At this point, the mother also recalled that the child had an episode of blunt injury to his abdomen one month ago. Considering the atypical clinical trajectory and radiological suspicion, the differential diagnoses at this point were small bowel obstruction secondary to possible delayed bowel injury, perforated appendicitis, or a duplication cyst. A decision was made for emergent laparotomy. Intraoperatively, an oval-shaped mass with the size of 1cm x 1.5cm was seen at the segment of distal jejunum, midway between the duodenojejunal (DJ) flexure and the ileocecal valve (ICV), at the antimesenteric border. It appeared contracted, causing circumferential narrowing of the adjacent jejunum and serving as a transition zone of the obstruction (Figure 3). The small bowel proximal to the constricting point was grossly dilated and distally collapsed. There was surrounding mesenteric lymphadenopathy. Otherwise, the bowels appeared viable. No adhesion, tumour or Meckel's diverticulum was identified. The diseased segment was resected, and primary anastomosis of the jejunum was performed.

The histopathological assessment of the diseased jejunal segment revealed the outpouching of all the layers through the bowel wall, which is consistent with the presence of a true diverticulum. There was no ectopic tissue seen within its lumen. No features suggestive of chronic inflammation or perforation were noted.

Post-operatively, the child made a swift recovery. He tolerated oral feeding without abdominal pain and distension and was discharged from the ward within 1 week. There was no evidence of wound complications or intra-abdominal collection upon 1-month follow-up. His constipation resolved and he was able to have bowel motion daily.

DISCUSSION

Paediatric jejunal diverticulum (JD) is rare and is characterised by the presence of sac-like protrusions or pouches (diverticula) in the jejunum in children.[1-4,6] It can be acquired or congenital. The congenital diverticula are true diverticulum, which is composed of all layers of the intestinal wall, distinguishing them from the false diverticulum. The formation of congenital diverticulum stems from developmental anomalies during foetal growth.[1,3,4]

The most important barriers to diagnosing this case at primary care are the non-specific clinical features combined with the rarity of paediatric JD. Notably, constipation is a ubiquitous complaint among the paediatric population. It would be difficult to attribute constipation, a common paediatric ailment, to the sequelae of a JD in a primary care setting. Constipation in children is commonly seen with a reported prevalence of varying degrees.[8] The prevalence of constipation or functional constipation in children varies according to different research, ranging from 1.1% to 31.4%.[8,9] Additionally, children with constipation also often present with abdominal colic which is typically non-specific and poorly localised.9 Additionally, frequently changing history from caretakers can be misleading for clinicians to detect alarming features of this patient.

Besides that, the aetiology of paediatric JD is also not well understood.[1-3,6] Moreover, due to the non-specific features of diverticular disease, it presents a diagnostic challenge to primary care providers with a reported prevalence of diagnosis of 0.1% of primary care consultations.[7] Certain genetic syndromes such as Marfan's syndrome, cystic fibrosis and other genetic disorders, may predispose children of younger age to develop diverticular disease. So, in such a group of children presenting with non-specific abdominal symptoms, primary care doctors should consider JD as a differential diagnosis, despite its rare prevalence.

Notably, the current management algorithm of diverticular disease is largely based on the understanding of the pathophysiology of colonic disease in adults.[5] This is because it is more common in adults, especially among the elderly. The adult diverticular disease is acquired and caused by the formation of false diverticula in the large bowel.[5] Due to increased intraluminal pressure and abnormal intestinal motility, a weakness or defect in the muscularis propria occurs, allowing the herniation of mucosa and submucosa outward through the bowel wall.[5] The stretch of the layers contributes to the structural weakness of the bowel wall and chronic thinning of the surrounding vessel wall, making it prone to complications like perforation and bleeding.[5]

However, such pathophysiology does not apply in diagnosing and managing paediatric JDs. Many cases remain asymptomatic and are discovered incidentally during imaging or surgical procedures for unrelated conditions. When symptomatic, they tend to present with non-specific features like vomiting, bloating, altered bowel habits and abdominal colic. It can mimic other GI disorders like constipation, perforated appendicitis, and Crohn's disease. However, paediatric JDs can also cause potentially fatal complications like GI bleeding, perforation and obstruction, which warrants urgent surgical intervention.[6] Some paediatric JDs can also present with diverticulitis, sepsis and peritonitis.[3,6]

Another important barrier of diagnosis in this case is also the lack of advanced radiological assessment modality in primary care. Generally, many diagnoses of paediatric diseases are often made clinically with minimal radiological assessment to reduce the unnecessary exposure to radiation risk for children. However, the diagnosis of paediatric JD often involves a combination of clinical suspicion supported by radiological assessment. This includes imaging techniques like CT scans which carries radiation risk, GI contrast study that may induce contrast allergy and intraoperative bowel examination which is invasive.[1,2] Moreover, very few JDs can be diagnosed with CT due to the difficulty in delineating it from the bowel loops.[2] While GI contrast study and advanced endoscopic techniques like video capsule endoscopy can be useful, it would be inappropriate and unsafe in this patient due to the development of bowel obstruction. Most importantly, all these are not available in resource-limited settings or in local clinics.

Management of paediatric JDs depends on the severity of the condition and the presence of complications.[1-4,6] Surgical resection is not needed if they are asymptomatic and an incidental finding. However, in the development of complications, surgical intervention is necessary. The most common surgical approach is segmental resection of the affected portion of the small bowel, followed by primary anastomosis to restore intestinal continuity. Laparoscopic surgery is increasingly favoured due to its minimally invasive nature and faster recovery times. While the minimally invasive technique is favourable, it is more suitable in elective cases of paediatric JDs. It was not performed in this patient because the laparoscopic port insertion and manoeuvre may injure the already dilated bowels. They also take up a larger space within the intraabdominal cavity, which can reduce the viewability of laparoscopic surgery. Overall, long-term follow-up is recommended to monitor of complications after surgery.

In this case, the initial differential diagnosis of a duplication cyst was nullified after histopathological confirmation of the presence of a true diverticulum. The possibility of Meckel's diverticulum was briefly considered. Meckel's diverticulum is a true diverticulum that is a remnant of an incompletely obliterated vitelline duct and has a completely different aetiology than a true JD.[10] Notably, this diverticulum was found in the jejunum, which is not typical of Meckel's diverticulum, which is located two feet from the ICV.10 It has no ectopic mucosa within. It is also round, short and contracted, distinguishing it from the typical appearance of a Meckel's diverticulum that is often two inches long.[10]

Some debates remain that histopathology surprisingly showed no evidence of chronic inflammation. Intraoperative specimens showed a contracted diverticulum, causing the luminal stenosis of the jejunal segment and causing obstruction. This is likely the sequelae of chronic inflammation of the JD, causing contracture and scarring of the surrounding tissue. We postulate that even as the chronic

inflammation over the JD has subsided, over time, the healing process has caused the gradual and ongoing contracture and lumen stenosis. This gives rise to the recurrent and insidious onset to the child's constipation and abdominal distension.

In summary, paediatric JD is a rare but potentially significant condition that requires a high index of suspicion for diagnosis. Its nonspecific symptoms and potential for severe complications underscore the importance of prompt and accurate diagnostic evaluation. Advances in imaging and surgical techniques have improved outcomes for affected children, but further research is needed to better understand the condition's pathogenesis and optimal management strategies. Early recognition and appropriate intervention are critical in ensuring favourable outcomes and minimising morbidity in this rare paediatric disorder.

Recognition of alarming features

The alarming features of abdominal distension should prompt primary care physicians to consider differential diagnoses, beyond functional constipation. As illustrated in the case above, there are instances in which the attending health care professionals may have missed the alarming features of constipation during the initial clinical evaluation, leading to the child recurrently failing pharmacological treatment and multiple visits with no clear diagnosis. Health care professionals, especially those at primary care settings are the patients' first contact to the healthcare system. They must be aware and capable of identifying alarming features based on thorough history taking and physical examination. This would help to improve patients' prognosis by prompting an early referral to the tertiary centre for escalation of therapy and further investigation.

CONCLUSION

We have encountered a rare case of paediatric jejunal diverticulum which presented initially as constipation and progressed to develop intestinal obstruction. Although constipation is commonly seen in children, recognition of alarming clinical signs and symptoms based on thorough history taking and physical examination in primary care settings is crucial, to ensure early and appropriate referral to tertiary centres is made in a timely manner.

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DECLARATIONS

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REFERENCES

1. Geroulakos G. Surgical problems of jejunal diverticulosis. Ann R Coll Surg Engl 1987; 69(6): 266-8.
2. Fintelmann F, Levine MS, Rubesin SE. Jejunal diverticulosis: findings on CT in 28 patients. AJR Am J Roentgenol 2008; 190(5): 1286-90.
3. Sayed L, Mann C, Ihedioha U, Ratliff D. Jejunal diverticulitis in a child. J Surg Case Rep 2012; 2012(8): 9.
4. Luitel P, Shrestha BM, Adhikari S, Kandel BP, Lakhey PJ. Incidental finding of jejunal diverticula during laparotomy for suspected adhesive small bowel obstruction: A case report. Int J Surg Case Rep 2021; 85: 106268.
5. Tursi A, Papagrigoriadis S. Review article: the current and evolving treatment of colonic diverticular disease. Aliment Pharmacol Ther 2009; 30(6): 532-46.
6. Cofini M, Quadrozzi F, Cofini G. A perforated jejunal diverticulum in childhood. J Case Rep 2014; 4: 481-3.
7. Wensaas KA, Hungin AP. Diverticular disease in the primary care setting. In: Journal of Clinical Gastroenterology. J Clin Gastroenterol 2016; 50 Suppl 1: S86-8.
8. Vriesman MH, Koppen IJN, Camilleri M, Di Lorenzo C, Benninga MA. Management of functional constipation in children and adults. Nat Rev Gastroenterol Hepatol 2020; 17(1): 21-39.
9. Tran DL, Sintusek P. Functional constipation in children: What physicians should know. World J Gastroenterol 2023; 29(8): 1261-88.
10. Hansen CC, Soreide K. Systematic review of epidemiology, presentation, and management of Meckel's diverticulum in the 21st century. Medicine (Baltimore) 2018; 97(35): e12154.

Thrombotic thrombocytopenia purpura in HIV patient: A rare case in Malaysia

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SUMMARY

HIV-associated thrombotic thrombocytopenic purpura (TTP) presents unique diagnostic and therapeutic challenges, as its clinical features may overlap with other complications like disseminated intravascular coagulation (DIC), and haemolytic uremic syndrome (HUS). This case report describes a 25-year-old male patient with TTP implicated by HIV. Laboratory findings revealed severe thrombocytopenia and fragmented red blood cells on peripheral blood smear, leading to a diagnosis of TTP. Notably, the patient's HIV viral load was found to be poorly controlled, contributing to the development of TTP. This report emphasises the importance of considering TTP in HIV-positive patients presenting with thrombocytopenia.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening blood disorder due to deficiency of ADAMTS13, which can lead to widespread microvascular thrombi, resulting in multiorgan failure, like the brain and kidney.[1-3] Most of the TTP cases are acquired, where there are autoantibodies against ADAMTS13.[1] It can be idiopathic or associated with autoimmune diseases, pregnancy, drugs or infection like HIV.[1] HIV infection is believed to directly trigger thrombotic thrombocytopenic purpura (TTP), likely by affecting vascular endothelial cells, leading to their dysfunction, localised thrombin formation, and depletion of ADAMTS13.[4] Although TTP is a very rare disease, a study in South Africa found that people with HIV are 15 to 40 times more likely to develop TTP compared to those without HIV, and over 80% of TTP cases in South Africa are found to be HIV-related.[4] TTP tends to occur more frequently in individuals with HIV who have advanced disease, low CD4+ T cell levels, and other coexisting opportunistic infections, with relatively high mortality.[2] Although the availability of antiretroviral therapy (ART) was expected to reduce the occurrence of HIV-associated TTP, current evidence indicates that HIV remains a significant contributor to secondary TTP2.

CASE PRESENTATION

A 25-year-old man initially complained of chronic cough for six months, associated with fevers and constitutional symptoms. On examination, he appeared emaciated and cachectic. Physical findings were unremarkable. The fourth-generation HIV test was reported positive, accompanied by a low CD4 count of 39 cells/mm3 and HIV viral load of 1075251 copies/ml. The tuberculosis workup was negative, and no positive respiratory culture was reported. Chest X-ray showed a clear lung field. He was treated empirically with antimicrobial therapy (Amoxicillin and Clavulanic acid), followed by anti-retroviral therapy consisting of PO tenofovir disoproxil fumarate/emtricitabine (300 mg /200 mg) 1 tablet daily and PO Efavirenz 600mg daily, alongside co-trimoxazole as primary prophylaxis of pneumocystis pneumonia.

One month after discharge, he presented with generalised tonic-clonic seizures for one day, associated with fevers. Upon arrival to the emergency department, he appeared tachypneic and delirious, with a Glasgow Coma Scale (GCS) score of E4V4M5. He was haemodynamically unstable, with blood pressure (BP) of 111/68mmHg, heart rate (HR) of 156bpm, respiratory rate (RR) of 24 per minute, and temperature of 40°C. The physical examination was unremarkable, with absent neurological deficits. Laboratory results depicted pancytopenia, acute kidney injury (AKI), transaminitis, and coagulopathy (Table I). A computer tomography (CT) scan of the brain showed no abnormalities. Lumbar puncture was not performed in the setting of haematological abnormalities. He was empirically started on intravenous ceftriaxone 2g twice daily and intravenous acyclovir 500 mg TDS, treating as presumed meningoencephalitis. Convulsions were controlled with a few antiepileptic agents, like intravenous levetiracetam, on top of phenytoin and phenobarbitone because of status epilepticus. He was subsequently intubated and ventilated for cerebral and airway protection.

Urgent peripheral blood smear demonstrated the presence of schistocytes, indicative of microangiopathic haemolytic anaemia (MAHA) (Table I). In the context of convulsions, fevers, severe thrombocytopenia, AKI, and MAHA, TTP was suspected. Fresh Frozen Plasma Transfusion (FFP) was given promptly. An urgent haematology consult was undertaken and plasma exchange with transfusion support was planned. However, the patient succumbed to his illness before plasma exchange could be initiated. The ADAMTS13 result (the test needs to be outsourced and not offered in our hospital), subsequently confirmed TTP. (Table I)

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Table I: Relevant investigation during the hospitalisation

Investigation	Normal Range	Pre-admission (First follow-up in clinic)	Day 1 (of admission)	Day 2 (of admission)
Hb, g/L	13-17	7.8	5.8	5.6
MCV (fl)	83-101	73	65	63
White Cell Count, 109/L	4-10	5.1	0.2	0.1
Platelet ,109/L	150-410	170	23	30
Reticulocyte Count, %	0.5-2.1		0.1	
Urea, mmol/L	3.1-8.2	2.4	19.8	17.8
Serum creatinine, mmol/L	62-115	64	264	238
Total bilirubin, umol/L	<21	7.3	9.6	10.6
Albumin, g/L	31-48	38	34	25
ALT, U/L	10-49	17	61	50
AST, U/L	<34	-	239	257
LDH, U/L	120-246	-	-	1422
pH	7.35-7.45	-	7.25	6.98
HCO3, mmol/L	18-23	-	11.4	8.9
Serum lactate, mmol/L	0.5-2.0	-	3.7	11.2
INR	0.82-1.03	-	1.45	1.81
APT, seconds	22-31	-	42.7	45.3
PT, seconds	9.4-11	-	14.6	17.9
CRP, mg/L	<10	-	93.4	140
Fibrinogen, g/L	1.85-4.27		2.85	-
Serum Ferritin, pmol/ml	48-708			3471.2
Triglycerides, mmol/l	<1.7			2.38
Sputum MTB C+S		No Growth		
Sputum AFB		Negative		
Serum parvovirus IgM			Negative	
Serum Cryptococcal Antigen			Negative	
Serum Toxoplasma IgM and IgG			Non-reactive	
G6PD			Normal	
Blood culture			Nil growth	
Blood fungal culture			Nil growth	
Full blood picture			presence of spherocytes and fragmented cells, suggestive of haemolysis	
ADAMTS13			Activity – 35% (40-130) Inhibitor – 22.5U/ml (Positive : >15U/ml) Inhibitor is positive at 22.5u/ml.	

Table II: Studies of patients with HIV associated TTP

Studies	Sample Size	Results
Muriel Meiring et al.[4]	40 patients	- Only 50% of TTP with HIV infected patients presented with autoantibodies to ADAMTS13. - HIV-positive persons who were not on combination antiretroviral therapy treatment (cART) seemed to have slightly lower ADAMTS13 levels than those who were on cART, although the levels were still in the normal range. - HIV-positive persons who were not on cART also presented with high amounts of autoantibodies against ADAMTS13.
Karen Gunther et al.5	20 patients	- 6 (30%) patients had activity of ADAMTS13 within the normal range. - Of the patients with reduced activity, 8 showed no evidence of an inhibitor.
Masoet et al.[8]	52 cases (41 is HIV infected)	- 90.2% of HIV-infected patients with TTP only received plasma infusion with good clinical response.
Novitzky, N. et al.[9]	44 patients (21 is HIV infected)	- HIV infected patients responded to FFP faster than HIV negative patients, and none of them required apheresis.

DISCUSSION

We described a case of TTP complicating HIV. Of note, TTP is rare, with a rate of nearly 0.0001% per year.[2] TTP is suspected in the presence of fever, thrombocytopenia, MAHA, neurological symptoms, and renal involvement.[3] A peripheral blood smear may reveal schistocytes, which are fragmented red blood cells, further supporting the diagnosis.[3] To confirm TTP, the ADAMTS13 activity assay is conducted, confirming the deficiency of the ADAMTS13 enzyme.[3] A Level of ADAMTS13 less than 10 IU/dL usually indicates severe TTP.[3] Additionally, testing for ADAMTS13 inhibitors can identify the presence of autoantibodies against this enzyme.[3] Of note, people living with HIV (PLHIV) were 40 times more likely to acquire TTP compared to those who had no HIV.[2] There are literatures reported that amongst the PLHIV afflicted with TTP, the ADAMTS13 level can be within near normal range with the presence of ADAMTS13 inhibitor (Refer to Table II).[4,5] On the contrary, our patient has fulfilled the pentad of TTP, ADAMTS13 level was not severely deficient, and there was presence of ADAMTS13 inhibitor.

It is crucial to exclude other opportunistic infections in this case. The patient had a negative tuberculosis workup prior to the current admission. Investigations on this admission, including serum parvovirus serology, serum cryptococcal antigen, serum toxoplasmosis serology, blood cultures, and blood fungal cultures, were all unremarkable. However, a lumbar puncture could not be performed due to severe thrombocytopenia, limiting our ability to rule out meningitis. Opportunistic infections remain a possible trigger for TTP, but based on the available investigations, no positive cultures were identified. Hemophagocytic syndrome was also considered as part of the differential diagnosis. The patient had an H Score of 164 (excluding bone marrow aspiration), indicating a 40-54% probability of hemophagocytic syndrome. However, the clinical presentation was consistent with the classical pentad, which was more suggestive of TTP.

Given the clinical context, we believe the TTP in this patient is related to HIV infection. Several mechanisms have been suggested for how HIV contributes to the development of TTP. It is proposed that endothelial dysfunction directly implicated by HIV can be the major driver of microvascular disease, resulting in inappropriate activation of the immune system and hypercoagulopathy.[3] Interestingly, underlying endotheliitis is present in both ART-naïve and ART-virally suppressed PLHIV3. On the other hand, HIV may directly induce chronic inflammation, promoting an autoimmune response against ADAMTS13 enzyme.[3] Its deficiency undermines the cleavage of vWF, leaving the hyperadhesive vWF unfolded in the micro-vessels and forming platelet thrombi.[3] Additionally, opportunistic infections (including cytomegalovirus, Hepatitis C, Kaposi sarcoma, Mycobacterium tuberculosis, etc) could provoke an immune response that affects both the endothelium and the coagulation system, thereby contributing to the development of TTP.[3] Another secondary trigger for HIV-related TTP is that HIV-associated complement activation poses a threat by developing immunothrombosis and mediating loss of endothelial cell integrity.[3]

There is a clinical overlap among TTP, Haemolytic Uremic Syndrome (HUS), and disseminated intravascular coagulation (DIC). In our case, the diagnosis is in favour of TTP, supported by low ADAMST13 and the presence of its inhibitor. Low ADAMTS13 activity and the presence of autoantibodies against ADAMTS13 further support a diagnosis of TTP. Conversely, DIC typically presents with a bleeding tendency and does not commonly exhibit neurological manifestations. It is less likely DIC in this patient as the initial INR was less than 1.5 and the fibrinogen level is not low. Both conditions may share similarities including anaemia and thrombocytopenia. However, rapid-onset DIC causes prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), low fibrinogen levels, and elevated D-dimer.[6] Importantly, the ADAMTS13 level in DIVC is unaffected. HUS was unlikely because there was no severe renal dysfunction and absence of diarrhoea from history. Louw et al., study demonstrated that there was only 1 patient in their study who had severe renal dysfunction.[2]

Considered as a medical emergency, TTP requires immediate intervention to halt its progress and prevent death. A valuable clinical tool called the PLASMIC Score is useful to predict the likelihood of TTP and guide further management, whilst awaiting ADAMTS13 results.[3] Each criterion in the score is assigned 1 point, and in our patient's case, the PLASMIC score was 6, strongly suggestive of TTP. The sensitivity and specificity of PLASMIC score of ≥ 6 are 85% and 89%, respectively.[7] A PLASMIC score < 6 is less sensitive to exclude TTP and the need for therapeutic plasma exchange.[7]

The mainstay treatment for TTP is plasma exchange, with the primary aim to remove autoantibodies against ADAMTS13 and replenish functional ADAMTS13.[3] Infusion of FFP alone at a dose of 30 ml/kg/day may be helpful to dilute ultra-large VWF and supply ADAMTS13.[2] There are also several studies have demonstrated that fresh frozen plasma, when used alone, can effectively treat TTP without the need for plasma exchange (Refer to Table II).[8,9] In contrast, for this patient, he did not respond to Fresh Frozen Plasma transfusion alone. Other treatment modalities include corticosteroids and rituximab, an anti-CD20 monoclonal antibody, which helps suppress the production of autoantibodies3. However, rituximab is usually used for refractory and immune/idiopathic TTP rather than secondary TTP, which is likely to be in this patient.[1] Additionally, Caplacizumab has been approved for the treatment of immune-mediated TTP (iTTP). It is an anti-VWF nanobody that prevents VWF-mediated platelet aggregation.[3] Despite its clinical use, studies on Caplacizumab are still limited[3], and to the best of our knowledge, we are not aware of any study for PLHIV. Overall, engagement in a multidisciplinary team including neurologist, haematologist, intensivist, infectious diseases physician, and pathologist limits adverse events and improves outcomes.

CONCLUSIONS

Despite significant advancements in therapy, HIV-associated TTP continues to pose a diagnostic challenge. It is of paramount importance to maintain a high index of suspicion for TTP. Early recognition and prompt treatment can be lifesaving and significantly reduce mortality rates. Further research is necessary to optimise treatment protocols for this specific subset of patients.

REFERENCES

1. Scully M, Rayment R, Clark A, Westwood JP, Cranfield T, Gooding R, et al. A British Society for Haematology Guideline: Diagnosis and management of thrombotic thrombocytopenic purpura and thrombotic microangiopathies. Br J Haematol 2023; 203(4): 546-63.
2. Louw S, Gounden R, Mayne ES. Thrombotic thrombocytopenic purpura (TTP)-like syndrome in the HIV era. Thromb J 2018; 16: 35.
3. Louw S, Jacobson BF, Wiggill TM, Chapanduka Z, Sarah Mayne E. HIV-associated thrombotic thrombocytopenic purpura (HIV-TTP): A practical guide and review of the literature. HIV Med 2022; 23(10): 1033-40.
4. Meiring M, Webb M, Goedhals D, Louw V. HIV-associated thrombotic thrombocytopenic purpura – What we know so far. Eur Oncol Haematol 2012; 8: 89-91.
5. Gunther K, Garizio D, Nesara P. ADAMTS13 activity and the presence of acquired inhibitors in human immunodeficiency virus-related thrombotic thrombocytopenic purpura. Transfusion 2007; 47: 1710-6.
6. Costello RA, Leslie SW, Nehring SM. Disseminated intravascular coagulation. StatPearls. 2024.
7. Paydary K, Banwell E, Tong J, Chen Y, Cuker A. Diagnostic accuracy of the PLASMIC score in patients with suspected thrombotic thrombocytopenic purpura. A systematic review and meta-analysis. Transfusion 2020; 60: 2047-57.
8. Masoet A, Bassa F, Chothia MY. HIV-associated thrombotic thrombocytopaenic purpura. A retrospective cohort study during the anti-retroviral therapy era. J Clin Apher 2019; 34: 399-406.
9. Novitzky N, Thomson J, Abrahams L. Thrombotic thrombocytopenic purpura in patients with retroviral infection is highly responsive to plasma infusion therapy. Br J Haematol 2005; 128: 373-9.

Hybrid treatment strategies for persistent sciatic artery aneurysm: A clinical case report

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SUMMARY

The persistent sciatic artery is a rare congenital anomaly often complicated by aneurysmal degeneration and chronic limb-threatening ischemia, leading to potential limb loss. A 73-year-old man presented with left fifth toe discolouration and rest pain. Imaging revealed a 15mm thrombosed persistent sciatic artery aneurysm and a hypoplastic superficial femoral artery. A hybrid approach combining endovascular embolisation and surgical bypass was performed, resulting in complete aneurysm thrombosis and restored perfusion. Hybrid strategies, balancing durability and reduced invasiveness, are increasingly favoured for managing persistent sciatic artery aneurysms. This case underscores the importance of early diagnosis, tailored treatment, and multidisciplinary care for optimal outcomes.

INTRODUCTION

The persistent sciatic artery (PSA) is a rare congenital vascular anomaly, with an estimated prevalence of 0.025% to 0.04% in the general population. First described by Green in 1832, PSA arises from the incomplete regression of the embryonic sciatic artery, which typically diminishes during foetal development.[1] Despite its rarity, PSA carries significant clinical implications, including aneurysmal degeneration and chronic limb-threatening ischemia (CLTI). Open surgical repair, while effective, requires extensive exposure and prolonged recovery, whereas endovascular approaches face challenges in achieving stable aneurysm exclusion and managing complex anatomy. This report presents a case of PSA aneurysm with CLTI, highlighting the value of early detection and a combined open-endovascular hybrid strategy to optimise anatomical repair, minimise complications, and address both structural and ischemic sequelae.

CASE PRESENTATION

A 73-year-old man presented with a four-month history of progressive discoloration and rest pain of the left fifth toe. Clinical examination revealed gangrene of the toe, consistent with CLTI (Figure 1a). Pulses were palpable in the left lower limb, except for the absent dorsalis pedis pulse, with a toe pressure of 20mmHg. The patient was a former smoker with no significant comorbidities.

Computed tomography angiography (CTA) revealed a 15mm partially thrombosed PSA aneurysm (Figure 1b). Imaging also showed a hypoplastic superficial femoral artery (SFA) that tapered off before reaching the popliteal artery (Figure 1c). Diagnostic angiography confirmed the PSA as the dominant blood supply to the left lower limb, with inadequate perfusion from the SFA.

A hybrid treatment approach of aneurysm embolisation and bypass to restore distal circulation was pursued. The procedure began with retrograde access to the below-knee popliteal artery using a 5Fr sheath. A 0.035" Glidewire (Terumo Cooperation) and a 5Fr straight catheter (IMAGER™ II, Boston Scientific) were advanced to the proximal PSA. The sheath was then exchanged for a 6Fr straight sheath (Fortress Introducer Sheath, Biotronik), and endovascular embolisation was performed using two 16mm Amplatzer Vascular Plugs (AVP II; St. Jude Medical, St. Paul, MN) deployed proximal and distal to the aneurysm (Figure 2b & 2c).

Following embolisation, a left common femoral artery (CFA) to below-knee popliteal artery bypass was performed using an ipsilateral reversed saphenous vein graft (RSVG). Completion angiography confirmed successful aneurysm exclusion and graft patency with distal perfusion to lower limb. The gangrenous fifth toe was disarticulated.

Postoperatively, the patient recovered well, with palpable posterior tibial pulse and wound healing (Figure 3a). The patient was discharged on dual antiplatelet therapy (tablet Cardiprin 100 mg daily and tablet Clopidogrel 75 mg daily). Follow-up duplex ultrasound and six-month CT angiography demonstrated complete aneurysm thrombosis, a patent RSVG, and restored limb perfusion (Figure 3c).

DISCUSSION

The persistent sciatic artery is a rare embryological remnant of the primitive sciatic artery, which typically regresses during foetal development. In cases where the SFA fails to develop adequately, the PSA persists, often coexisting with a hypoplastic SFA. Anatomically, the PSA originates from the internal iliac artery, traverses the greater sciatic foramen, and courses posteriorly in the thigh to connect with the popliteal artery.[1,2]

PSA is prone to aneurysmal degeneration, occurring in 15% to 44% of cases. This is attributed to its vulnerable anatomical location, which subjects it to repeated trauma and compression near the greater and lesser trochanters.

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Table I: Ahn-Mihn Classification of Persistent Sciatic Artery

Class	Superficial Femoral Artery	Persistent Sciatic Artery	Aneurysm	Pillet-Gauffre Classification
Class I	Complete	Complete	-	Type I, Va
Class Ia[a]			+	
Class II	Complete	Incomplete	-	Type III, IV
Class II[a]			+	
Class III	Incomplete	Complete	-	Type IIa, IIb, Vb
Class III[a]			+	
Class IV	Incomplete	Incomplete	-	None
Class IV[a]			+	

[a] "a" indicates accompanying persistent sciatic artery aneurysm.

Additionally, congenital deficiencies in the arterial wall's elastic tissue may contribute to structural weakness, accelerating aneurysm formation and atherosclerotic changes.[3] The pathophysiology of CLTI in PSA aneurysms typically stems from thromboembolic events originating from mural thrombus within the aneurysm or mechanical compression of collateral vessels by the aneurysmal sac.[4]

The most widely used classification system for PSA is the Pillet-Gauffre system, which categorizes PSA based on the developmental status of the PSA and SFA.[5] In 2016, Ahn et al. enhanced this system by incorporating aneurysm presence as an additional criterion, providing a more comprehensive framework for diagnosis and treatment planning (Table I).[4]

CTA is prioritised over duplex ultrasound for diagnosing PSA aneurysms, offering high-resolution 3D visualisation of deep anatomic structures to assess morphology, thrombus burden, and complications like rupture. While duplex avoids radiation, its limited depth resolution hinders accurate evaluation, making CTA critical for urgent intervention and surgical planning in complex cases.

The management of PSA aneurysms involves three primary treatment modalities: open surgery, endovascular therapy, and hybrid approaches. Each modality has its indications, advantages, and limitations, and the choice of treatment depends on the patient's clinical presentation, anatomical considerations, and overall risk profile.

Open surgical repair remains a cornerstone in managing complex PSA aneurysms, particularly those with extensive thrombosis or anatomical distortion. The procedure typically involves resection of the aneurysmal segment followed by bypass using autologous veins or synthetic grafts. While open surgery offers durable revascularisation, it carries risks such as wound infections, sciatic nerve injury, and graft failure, particularly in patients with poor distal runoff.6 Despite these challenges, open repair remains indispensable in anatomically complex scenarios where endovascular techniques are contraindicated or technically unfeasible.

Endovascular therapy has emerged as a minimally invasive alternative for managing PSA aneurysms, particularly in high-risk patients unsuitable for open surgery. This approach primarily involves two techniques: embolisation using coils or vascular plugs to exclude the aneurysm and stent-graft placement to reconstruct the arterial lumen. Embolisation is particularly effective for saccular aneurysms with narrow necks, while stent grafts are favoured for fusiform aneurysms with adequate proximal and distal landing zones. The advantages of endovascular treatment include reduced perioperative risks, shorter hospital stays, and faster recovery times. However, limitations such as incomplete exclusion in thrombus-laden or tortuous aneurysms can lead to endoleaks or stent migration.[3,4,7-9] Additionally, in incomplete PSA variants with insufficient collateral circulation, standalone endovascular therapy may fail to address ischemia, often requiring adjunctive bypass procedures.

Hybrid procedures, which combine open surgical bypass with endovascular aneurysm exclusion, have gained traction as a balanced strategy for addressing both limb ischemia and aneurysm-related risks. This approach typically involves performing a femoral-popliteal bypass to restore perfusion, followed by endovascular embolisation to exclude the aneurysm. By leveraging the durability of surgical bypass while reducing the invasiveness of open aneurysm resection, hybrid techniques offer a compelling solution for complex cases. Recent case studies highlight the efficacy of hybrid approaches, with reports of 100% technical success and low recurrence rates. For instance, a 2023 report described a 75-year-old patient with a thrombus-containing PSA aneurysm who underwent left femoral-popliteal bypass using a synthetic graft and subsequent endovascular plug embolisation, achieving complete aneurysm exclusion and resolution of ischemic symptoms at one-month follow-up.[7] Similarly, a 69-year-old male with CLTI underwent below-knee femoropopliteal bypass and Amplatzer plug occlusion, resulting in restored perfusion and technical success.[9]

The hybrid approach balances costs and outcomes: open repair avoids endovascular device expenses but risks costly complications like infections, while hybrid strategies reduce recovery time and reoperations, offsetting initial costs. Hybrid methods require advanced imaging, hybrid suites, and multidisciplinary teams, feasible only in tertiary centres, yet minimise morbidity such as nerve injury from open dissection. Though logistics demand team coordination, hybrid therapy optimises outcomes in settings with sufficient resources, whereas open repair remains pragmatic in resource-limited areas despite higher complication risks.

Our patient presented with a thrombosed Class IIIa PSA aneurysm according to the Ahn-Minh classification, complicated by CLTI. The hybrid approach, which combined endovascular embolisation with surgical bypass, was chosen to ensure both aneurysm exclusion and limb

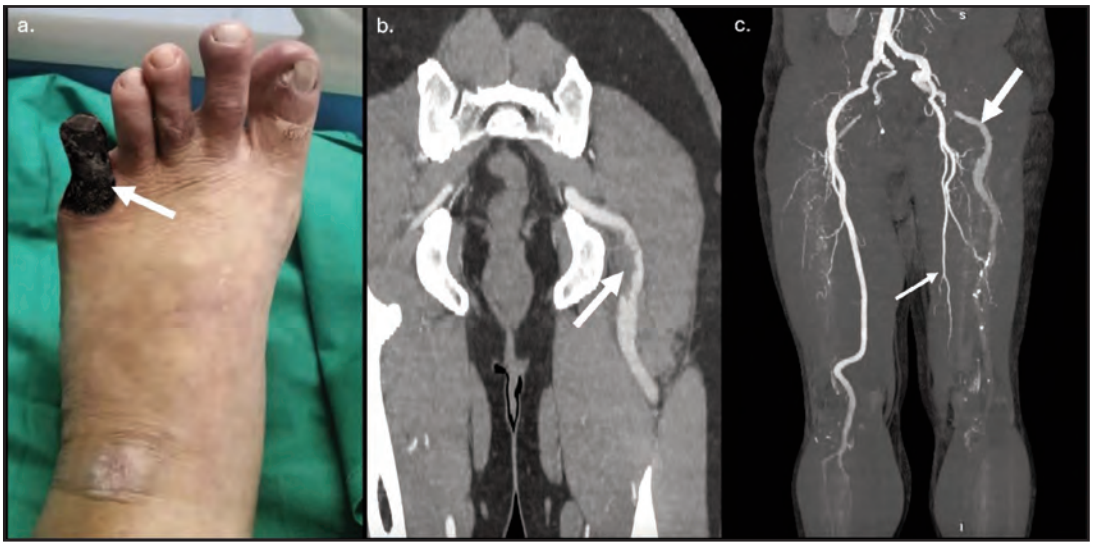

Fig. 1: (a) A 73-year-old man with a four-month history of progressive dry gangrene in the left fifth toe (white arrow). (b) Computed tomography angiography (CTA) revealed a 15-mm partially thrombosed PSA aneurysm (white arrow). (c) Reconstructed CTA showed a concurrent PSA aneurysm (large white arrow) with a hypoplastic superficial femoral artery (small white arrow)

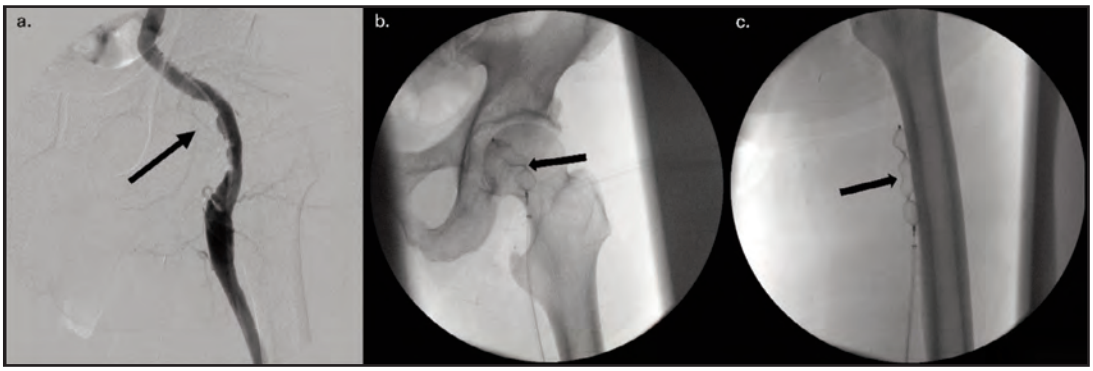

Fig. 2: (a) Intraoperative angiogram revealed thrombosed PSA aneurysm (black arrow). (b) and (c) Successful deployment of two 16mm Amplatzer Vascular Plugs (black arrows) proximal and distal to the aneurysm

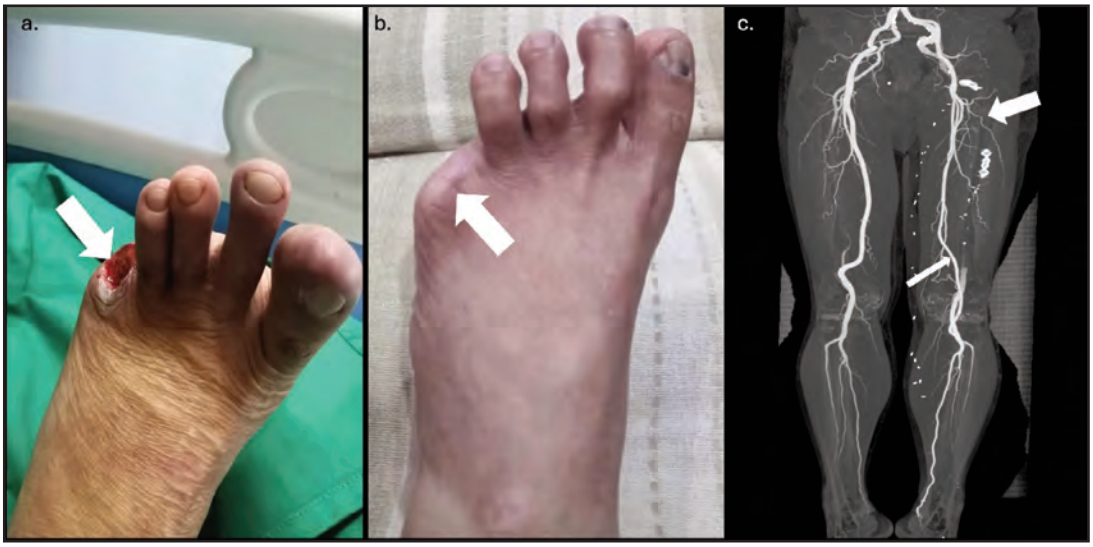

Fig. 3: (a) and (b) Photograph showing good wound healing (white arrows) following left fifth toe disarticulation. (c) Six-month CTA demonstrated complete PSA aneurysm thrombosis (large white arrow), a patent RSVG (small white arrow), and restored limb perfusion

revascularisation. This strategy aligns with recent trends favouring hybrid techniques for their balance of durability and reduced invasiveness. Retrograde access to the below-knee popliteal artery was chosen due to the failure of antegrade access through the ipsilateral common femoral artery, caused by the tortuous nature of the aneurysmal persistent sciatic artery, which hindered access to the aneurysmal sac, and to accommodate higher-profile access for the procedure. Therapeutic embolisation of PSA aneurysms has been reported in multiple cases, with most utilising intravascular coils. However, Amplatzer plugs, self-expanding nitinol mesh devices, had been chosen as it offer several advantages, including precise delivery, the ability to occlude large-diameter vessels, and reduced scatter on follow-up imaging.[10] Compared to coils, which can be challenging to place accurately and may require multiple units, Amplatzer plugs achieve equivalent efficacy with shorter procedure times.

Hybrid repair of PSA aneurysms combines risks from open and endovascular techniques, requiring surveillance addressing both complications while balancing cost and radiation exposure. Clinical follow-up at 1, 6, 12 months, and annually includes monitoring for claudication, rest pain, or acute ischemia, paired with ankle-brachial index (ABI) and toe pressure measurements to track perfusion. Imaging combines CTA (1 month, 6 months, annually) to verify aneurysm exclusion and bypass patency, and duplex ultrasound (3, 6, 12 months, annually) to assess graft velocity and detect recurrence. Early identification of bypass stenosis permits prompt percutaneous intervention, preserving graft function and improving outcomes.

CONCLUSION

Hybrid approaches, combining open bypass with endovascular exclusion, are increasingly favoured for managing PSA aneurysms complicated by CLTI. These strategies balance durability and reduced invasiveness, offering tailored solutions for complex cases. While open surgery remains essential for anatomical challenges, endovascular techniques benefit high-risk patients. Standardised protocols, guided by anatomic classification and individualised assessment, will further optimise outcomes for this rare yet high-stakes condition.

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DECLARATION

The authors have no conflict of interest to disclose.

REFERENCES

1. Green PH. On a new variety of the femoral artery: with observations. Lancet 1832; 17(442): 730-1.
2. Mandell VS, Jaques PF, Delany DJ, Oberheu V. Persistent sciatic artery: clinical, embryologic, and angiographic features. AJR Am J Roentgenol 1985; 144(2): 245-9.
3. Fukuda H, Onitsuka S, Yoshida S, Hirata Y, Hiromatsu S, Tanaka H. Endovascular stent-graft repair of a persistent sciatic artery aneurysm. Ann Vasc Dis 2017; 10(3): 246-9.
4. Ahn S, Min SK, Min SI, Ha J, Jung IM, Kim SJ, et al. Treatment strategy for persistent sciatic artery and novel classification reflecting anatomic status. Eur J Vasc Endovasc Surg 2016; 52(3): 360-9.
5. Gauffre S, Lasjaunias P, Zerah M. Artère ischiatique: à propos d'un cas, revue de la littérature et essai de systématisation. Surg Radiol Anat 1994; 16: 105-9.
6. Morisaki K, Yamaoka T, Iwasa K, Kuma S, Okazaki J. Persistent sciatic artery aneurysm with limb ischemia: a report of two cases. Ann Vasc Dis 2017; 10(1): 44-7.
7. Cvetic V, Miletic M, Lukic B, Nestorovic D, Kostic O, Sladojevic M, et al. Successful hybrid approach treatment of a large persistent sciatic artery aneurysm—a case report. Medicina (Kaunas) 2023 ; 59(7): 1328.
8. Birck LS, Damazzini R, Nunes WP, Lombard TF, Longhi JA. Endovascular repair of bilateral sciatic artery aneurysm with Covera® self-expandable covered stents—case report. J Vasc Bras 2023; 22: e20220064.
9. de Boer M, Joseph S, Shiraev T, Boyle R, Dubenec S. Hybrid repair of a persistent sciatic artery aneurysm. Vasc Endovascular Surg 2022; 56(8): 779-83.
10. Lee A, Hohmann SE, Shutze WP. Effectiveness of exclusion of a persistent sciatic artery aneurysm with an Amplatzer™ plug. Proc (Bayl Univ Med Cent) 2015; 28(2): 210-2.

The hidden danger of proton pump inhibitor: A case of hypomagnesemia

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SUMMARY

Hypomagnesemia has increasingly been reported as a side effect of prolonged use of proton pump inhibitors (PPI) over the years. It is a potentially serious but often under recognised complication. We present a case of a 75-year-old man who presented with bilateral upper and lower limb numbness. Laboratory evaluation revealed hypomagnesemia, hypokalaemia and hypocalcaemia, which was ultimately attributed to long-term use of a proton pump inhibitor. After discontinuation of the PPI, magnesium levels normalised, and the patient's symptoms resolved. There was also a clear causal relationship found between PPI rechallenge and recurrent hypomagnesemia throughout time. This case highlights the importance of recognising hypomagnesemia as a clinically significant side effect of long-term PPI usage. Dosage and duration of PPI should be reviewed regularly to assess the need for continuation to prevent unfavourable side effects.

INTRODUCTION

Proton pump inhibitors are widely prescribed for the treatment and prevention of gastroesophageal reflux, peptic ulcer, gastritis and esophagitis. With rising PPI use, adverse effects like hypomagnesemia, organ damage, infections, and nutrient malabsorption are increasingly reported.[1] Although rare, proton pump inhibitor-induced hypomagnesemia (PPIH) is a clinically significant complication of prolonged PPI use. Hypomagnesemia can lead to neuromuscular complications, cardiac arrhythmia and other electrolyte disturbances. Withdrawal of PPI is the most effective approach to resolving hypomagnesemia in affected patients. Numerous studies have reported on the overutilisation of PPI worldwide. A local study by Far et al., demonstrated that 46% of patients were inappropriately prescribed PPI.[2] Through this case, we aim to emphasise the importance of recognising PPI-induced hypomagnesemia and the need for regular review of the indication of long-term PPI usage.

CASE PRESENTATION

A 75-year-old man presented with bilateral upper limb and lower limb numbness for one month. He also had intermittent muscle cramps over both calves for one week. He did not exhibit any body or limb weakness, imbalance, or unsteadiness. There was no history of fever, preceding respiratory or gastrointestinal illness, chest pain, palpitations, or seizures. Additionally, he did not experience arthralgia, rash, weight changes, cold intolerance or lethargy- features that might suggest connective tissue disease or hypothyroidism. His medical history includes ischemic heart disease, for which he underwent coronary artery bypass graft surgery (CABG) in 2014, along with well-controlled diabetes mellitus (HbA1c of 6.7%), hypertension, and dyslipidaemia. His medication includes T. Metformin 250mg BD, T. Bisoprolol 5mg OD, T. Perindopril 8mg OD, T. Amlodipine 10mg OD, T. Cardiprin 100mg OD, T. Isosorbide dinitrate 10mg TDS, T. Trimetazidine MR 35mg BD, T. Atorvastatin 40mg ON and sublingual glyceryl trinitrate as needed. Additionally, he had been on T. Omeprazole 40mg daily for the past ten years for gastroprotection, owing to his concurrent use of cardiprin. He was not on any diuretics. He had no history of alcoholism. He did not have family history of neuromuscular and connective tissue disorders.

On physical examination, he was alert and pink. Vital signs were stable, and no abnormalities were noted on cardiovascular and respiratory examination. Neurological examination revealed reduced pin-prick sensation over the bilateral hands and feet. Power and reflex were normal. Monofilament test was normal. Vibration and proprioception were preserved. Chvostek's sign was negative. A provisional diagnosis of bilateral symmetrical peripheral neuropathy, likely secondary to diabetic neuropathy, was made. Other differential diagnosis includes hypothyroidism, electrolyte or vitamin B12 deficiency. Laboratory investigations included serum magnesium, calcium, phosphate, vitamin B12, and thyroid function tests. However, serum sodium and potassium levels were not assessed initially. The results revealed hypomagnesemia (0.38mmol/L; reference range: 0.66-1.07mmol/L) and hypocalcemia (corrected calcium: 2.04mmol/L; reference range: 2.20-2.60mmol/L). Other blood investigations were normal. Calcium carbonate 1500mg tablets daily was prescribed and the patient was advised on a high magnesium diet. Serum magnesium and calcium, together with serum potassium, were repeated after two weeks. However, serum magnesium and calcium levels showed no improvement, and hypokalaemia was also present. (Table I). Further detailed history was taken to elucidate the cause. Medication reconciliation was notable for omeprazole. Given the patient's history of prolonged PPI use and the exclusion of other potential causes, such as diuretic use, gastrointestinal losses, a diagnosis of PPI-induced hypomagnesemia was made. Since the patient refused admission for intravenous magnesium infusion, he was counselled to discontinue omeprazole and to purchase oral magnesium supplements.

Magnesium levels normalised following a one-month discontinuation of omeprazole, without magnesium

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Table I: Blood investigation results

	08/12/23	15/01/24	15/02/24	08/04/24	10/07/24	17/07/24	26/08/24	12/09/24	21/10/24	Normal range
Magnesium	0.38	0.39	0.75	0.69	0.46	0.70	0.51	0.61	0.76	0.66-1.07 mmol/l
Corrected Calcium	2.04	1.92	2.40	2.33	2.24	2.34	2.25	2.30	2.18	2.20-2.60 mmol/l
Potassium	-	3.2	4.3	4.4	3.4	3.6	4.0	3.9	4.2	3.5-5.1 mmol/l

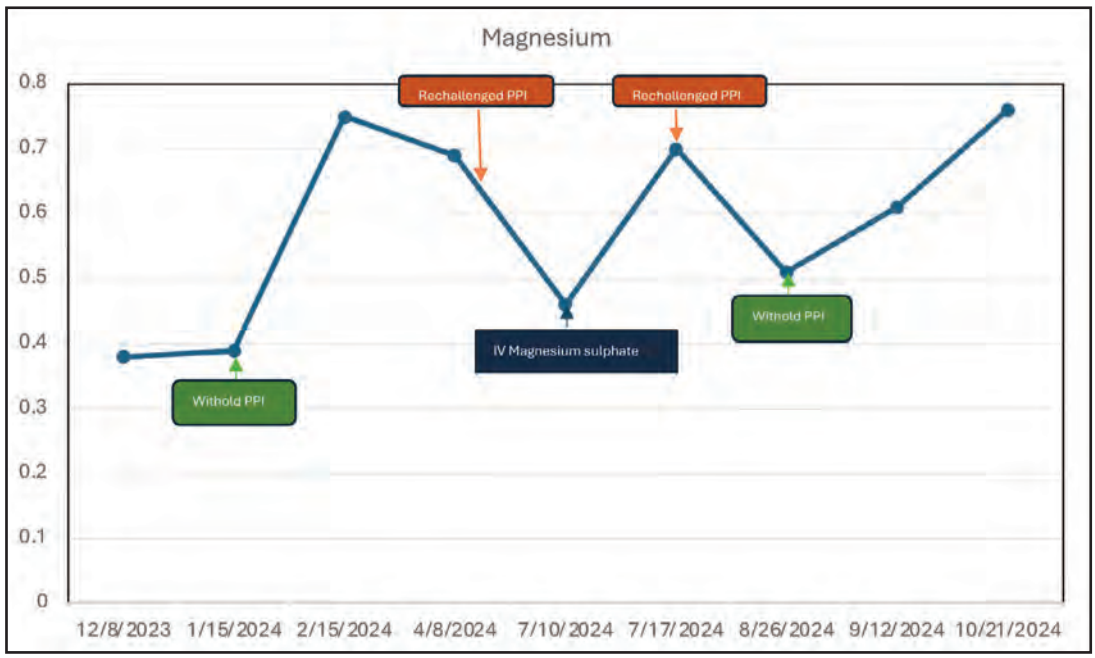

Fig. 1: Patient's serum magnesium levels

supplementation (as the patient did not purchase it), with normal serum magnesium recorded at 0.75mmol/L on 15/02/2024 and 0.69 mmol/L on 08/04/2024. (Table I and Figure 1). However, one month later, he was re-challenged with another type of proton pump inhibitor, T. pantoprazole 40mg OD, as he presented with gastroesophageal reflux disease symptoms. His magnesium level was only monitored after approximately two months of daily pantoprazole use, revealing a decline to 0.46 mmol/L. Around the same time, he experienced recurrent limb numbness. Electrocardiogram (ECG) findings revealed sinus bradycardia, Q wave in lead III and a VF, and T-wave inversions in V2-V4. He was referred immediately for hospital admission. In light of the elevated Troponin I levels, the cardiology team managed the case as non-ST elevation myocardial infarction (NSTEMI). He was corrected with intravenous magnesium sulphate during admission. The patient was started on dual anti-platelet therapy (DAPT), and pantoprazole was prescribed concurrently to reduce the gastrointestinal bleeding risk upon discharge from the hospital. His magnesium level was closely monitored during clinic visits. Serial monitoring revealed a decline in his magnesium levels from 0.87 to 0.51mmol/L within one month of resuming PPI therapy, prompting discontinuation of the medication. Following cessation of PPI, his magnesium levels rose progressively to 0.61 mmol/L after two weeks and reached 0.76 mmol/L over the following month, without magnesium supplementation. (Table I and Figure 1).

The normalisation of magnesium levels following proton pump inhibitor discontinuation, coupled with the recurrence of hypomagnesemia upon PPI resumption, underscores a strong causal relationship between PPI use and hypomagnesemia, regardless type of PPI.

DISCUSSION

Magnesium plays a crucial role in numerous functions in the body, such as bone development, neuromuscular function, signalling pathways, energy storage and transfer, stability of DNA and RNA, and cell proliferation.[3] Despite its importance, magnesium levels are not routinely monitored in patients, leading to its designation as the "forgotten electrolyte".[4] The body's magnesium levels are regulated through three main mechanisms: intestinal absorption, renal reabsorption and excretion, and exchange with the body's magnesium stores, primarily in the bones.[3]

Hypomagnesemia is particularly significant in clinical settings due to its potential to cause neuromuscular disturbances such as tetany, tremors, seizures, involuntary movements and as well as cardiac complications, including atrial and ventricular arrhythmias.[4,5] Other electrocardiogram changes include prolonged PR interval, widening of QRS complex and peaked or flattened T waves.[5] In such instances, it is crucial to perform an ECG to identify any potential cardiac complications, although this was not done in the present case during initial presentation.

Additionally, hypomagnesemia is often accompanied by hypocalcaemia and hypokalaemia, making it challenging to attribute specific clinical symptoms solely to low magnesium levels. It is postulated that magnesium deficiency impairs Na-K-ATPase and enhances renal potassium excretion, leading to hypokalaemia.[4] Various mechanisms have been proposed to explain hypocalcaemia in magnesium deficiency. One theory suggests it is due to reduced secretion of parathyroid hormone (PTH) or resistance to PTH.[5] Potassium or calcium depletion in these cases cannot be corrected until magnesium levels are restored.[4] The metabolic effects of magnesium may render hypocalcaemia and hypokalaemia refractory to treatment if there is concurrent hypomagnesemia.

Proton pump inhibitors are commonly prescribed for the treatment of gastroesophageal reflux disease, peptic ulcer disease, and for the prevention of gastric ulcers in patients requiring prolonged use of nonsteroidal anti-inflammatory drugs or corticosteroids. However, with the growing number of PPI use, the occurrence of adverse effects, including hypomagnesemia, increased risk of kidney, liver, and cardiovascular disease, dementia, susceptibility to respiratory and gastrointestinal infections, and impaired absorption of nutrients has been described consistently.[1] The association of hypomagnesemia and proton pump inhibitors was first described in 2006. Subsequently, several clinical studies were done to identify the association between PPI and hypomagnesemia. A meta-analysis by Srinutta et al., found that individuals who use PPIs are 1.83 times more likely to develop hypomagnesemia compared to those who do not use PPIs.[6] Nevertheless, the exact mechanism of PPI-induced hypomagnesemia remains unclear. The mechanism of proton pump inhibitor-induced hypomagnesemia is believed to be related to impaired intestinal absorption of magnesium, via alteration of intestinal mucosal pH and interference with transient receptor potential melastatin-6 (TRPM6)-mediated active absorption of magnesium.[7] Hypomagnesemia associated with PPI usage generally occurs after prolonged periods of use, usually more than six months.[8] There is also a dose-response correlation between proton pump inhibitor usage and hypomagnesemia. The odds of developing hypomagnesemia are more than twice as high for high-dose PPI users compared to low-dose users.[6] It is also independent of the type of PPI, as in this case, in which patient developed hypomagnesemia with either omeprazole or pantoprazole. In addition, concomitant diuretic usage increases the risk for PPI induced hypomagnesemia.[8]

Proton pump inhibitor is often co-prescribed in patients on dual antiplatelet therapy to reduce gastrointestinal bleeding risk. The concurrent use of DAPT and PPIs remains a topics of debate, with international guidelines offering varying recommendations on their concurrent use.[9] Therefore, PPI therapy should be individualised based on a patient's risk profile, with careful consideration of indication and treatment duration, for patients intolerant or contraindicated to PPIs, alternative gastroprotective agents such as H2-receptor antagonists or misoprostol may be considered, though these alternatives are less effective than PPIs for long-term management.[10]

The treatment of hypomagnesemia in patients depends on the degree of hypomagnesemia and the severity of symptoms. Oral magnesium is the preferred route of administration for patients with no or minimal symptoms. However, many patients are intolerant to oral magnesium due to side effects such as gastrointestinal discomfort and diarrhoea. Examples of oral magnesium include magnesium gluconate, magnesium oxide, magnesium carbonate, and magnesium gluconate. Intravenous magnesium repletion is the preferred route of administration in symptomatic hypomagnesemia. At the same time, the underlying cause should be corrected. Although magnesium levels transiently returned to normal after supplementation, recurrences were frequent in patients who continued on PPI. PPI withdrawal remains the gold standard to restore hypomagnesemia in PPI users.[7]

CONCLUSION

Clinicians should be aware of the potential for hypomagnesemia in patients on PPI, especially those on long-term PPI. Regular monitoring of serum magnesium levels may be warranted in these patients, especially if they exhibit symptoms suggestive of electrolyte imbalance. Additionally, regularly reviewing the indication for continued PPI use is also important to reduce the overuse of PPI. Educating and empowering prescribers and patients about the rationale for deprescribing is essential to ensure the success of this approach.

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CONFLICT OF INTEREST

None

REFERENCES

1. Yibirin M, De Oliveira D, Valera R, Plitt AE, Lutgen S. Adverse effects associated with Proton pump inhibitor use. Cureus 2021; 13(1): e12759.
2. Fah TR, Jun TY, Yan P, Yu CJ. Appropriateness of proton pump inhibitors prescription in patients admitted to a Malaysian tertiary hospital. Int J Public Health Res 2019; 9(1): 1043-50.
3. Fiorentini D, Cappadone C, Farruggia G, Prata C. Magnesium: biochemistry, nutrition, detection, and social impact of diseases linked to its deficiency. Nutrients 2021; 13(4): 1136.
4. Ahmed F, Mohammed A. Magnesium: The forgotten electrolyte-A review on hypomagnesemia. Med Sci (Basel) 2019; 7(4): 56.
5. Hansen BA, Bruserud O. Hypomagnesemia in critically ill patients. J Intensive Care. 2018; 6: 21.
6. Srinutta T, Chewcharat A, Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, et al. Proton pump inhibitors and hypomagnesemia: A meta-analysis of observational studies. Medicine (Baltimore) 2019; 98(44): e17788.
7. Gommers LMM, Hoenderop JGJ, de Baaij JHF. Mechanisms of proton pump inhibitor-induced hypomagnesemia. Acta Physiol (Oxf) 2022; 235(4): e13846.
8. Kieboom BC, Kiefte-de Jong JC, Eijgelsheim M, Franco OH, Kuipers EJ, Hofman A, et al. Proton pump inhibitors and hypomagnesemia in the general population: a population-based cohort study. Am J Kidney Dis 2015; 66(5): 775-82.

9. Saven H, Zhong L, McFarlane IM. Co-prescription of dual-antiplatelet therapy and Proton Pump Inhibitors: Current guidelines. Cureus 2022; 14(2): e21885.

10. Abrignani MG, Gatta L, Gabrielli D, Milazzo G, De Francesco V, De Luca L, et al. Gastroprotection in patients on antiplatelet and/or anticoagulant therapy: a position paper of National Association of Hospital Cardiologists (ANMCO) and the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO). Eur J Intern Med. 2021; 85: 1-13.

Acute compartment syndrome: A rare first manifestation of severe haemophilia A in neonate

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SUMMARY

Congenital haemophilia A, though often associated with iatrogenic bleeding, rarely presents with acute compartment syndrome. In a resource-limited rural facility, such a case poses a significant challenge to the managing team in terms of both diagnosis and treatment. This case report describes a term male infant of aboriginal ethnicity, born in a rural district hospital, who developed acute compartment syndrome in the left hand following a venepuncture. Emergency fasciotomy was performed on the dorsum of the left hand, which led to profuse bleeding. A packing and compression bandage was applied to control the bleeding, accompanied by multiple blood product transfusions. Family history revealed that the infant's maternal uncle had suffered from a bleeding disorder and succumbed to complications of the illness in his 30s, raising suspicion of congenital haemophilia. Later, factor VIII assay confirmed a 0% level, and factor VIII replacement therapy was promptly initiated. Homeostasis was achieved following factor replacement, and the fasciotomy wound healed well after three weeks. This case highlights the importance of early recognition and multidisciplinary management in resource-limited settings, as well as the need for timely factor replacement therapy to prevent life-threatening complications in neonates with undiagnosed congenital haemophilia A.

INTRODUCTION

Congenital haemophilia A is an X-linked recessive bleeding disorder caused by a deficiency of clotting factor VIII (FVIII), resulting from mutations in the F8 gene located on the long arm of the X chromosome (Xq28).[1] It typically presents in early childhood with spontaneous bleeding into joints and soft tissues but may also manifest during the neonatal period, particularly following traumatic delivery or iatrogenic interventions.[2] One of the rare but serious complications of haemophilia A is acute compartment syndrome (ACS), a surgical emergency caused by increased pressure within a closed muscle compartment, leading to compromised circulation and tissue viability. In neonates, ACS is extremely uncommon and often unanticipated in the absence of a known bleeding disorder.

This case report describes a neonate with previously undiagnosed severe haemophilia A who presented with life-threatening ACS in the postnatal period. It highlights the challenges of early recognition and the need for timely, multidisciplinary management of this rare complication, particularly in a resource-limited rural healthcare setting.

CASE PRESENTATION

A term male neonate, born via spontaneous vertex delivery to a nonconsanguineous couple, was admitted to the Neonatal Intensive Care Unit (NICU) at 24 hours of life for a massive haematoma involving the left hand. He was the sixth child of a 36-year-old mother of aboriginal ethnicity with an uneventful antenatal course and no significant medical history. The infant had a birth weight of 3.3 kg and cried spontaneously at birth. The immediate postnatal period was unremarkable. He received intramuscular vitamin K and the first dose of hepatitis B vaccine prior to transfer to the postnatal ward. At 13 hours of life, he developed jaundice and was diagnosed with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. A serum bilirubin sample was obtained via needle puncture from the dorsum of the left hand. Subsequently, the infant was nursed under phototherapy with his hands covered by mittens. The progressive swelling and discolouration of the left hand remained unnoticed until 10 hours later, when it was discovered during routine care, prompting an urgent referral to the NICU for further assessment and management.

Upon admission to the NICU, the infant's left hand was noted to be grossly swollen, bluish, and tense, with delayed capillary refill time and weak radial pulse volume – findings consistent with acute compartment syndrome (Figure 1). There was no evidence of bleeding or swelling at the site of the earlier intramuscular injection. The infant remained haemodynamically stable, and systemic examination was otherwise unremarkable. An emergency bedside fasciotomy was performed immediately as a limb-saving measure, even before blood parameter results were available. Unfortunately, the procedure was complicated by profuse bleeding from the incision site, necessitating two transfusions of fresh frozen plasma (FFP) and packed red blood cells, along with wound packing and compression. Empirical broad-spectrum antibiotic therapy was initiated, and intravenous tranexamic acid was administered in view of a presumptive diagnosis of haemophilia.

Subsequent investigations revealed a deranged coagulation profile (prothrombin time 15.8 seconds, INR 1.44, activated partial thromboplastin time >120 seconds) while haematological indices were within normal limits (total

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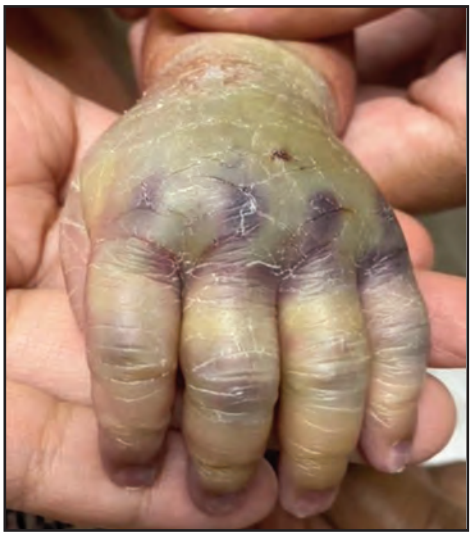

Fig. 1: Haematoma formed at the previous venepuncture site, resulting in compartment syndrome of the left hand

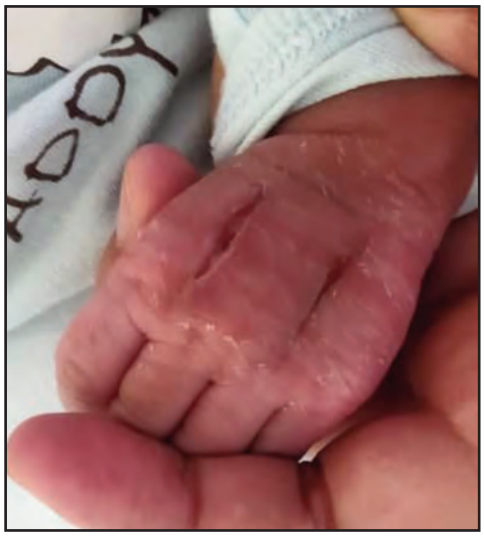

Fig. 2: Condition of left hand prior to discharge

white cell count 19.36 x 10^9/L, haemoglobin 20.3 g/dL and platelet count 202 x 10^9/L). A more detailed family history revealed that a maternal uncle had experienced frequent hospital visits for unexplained bruising and died in his 30s due to complications of the disease, raising suspicion of congenital haemophilia. An urgent coagulation factor assay subsequently confirmed the diagnosis of severe haemophilia A, with a factor VIII (FVIII) activity level of 0% and a factor IX (FIX) activity level of 49.6%.

High-dose intravenous FVIII replacement therapy (ALPHANATE®) was initiated. Despite a four-hour delay in starting treatment due to logistical delays in obtaining the factor concentrate (sourced from a tertiary facility located four hours away), the infant's haemostatic status improved significantly (prothrombin time 14.5 seconds, INR 1.32, activated partial thromboplastin time 62 seconds). FVIII activity increased to 22%, allowing gradual dose tapering guided by serial assays. The fasciotomy wound healed completely, with minimal scarring (Figure 2). The range of movement of the fingers and wrist joint were full, with immediate capillary refill time.

The infant was discharged on day 28 of life with a plan for weekly prophylactic intravenous ALPHANATE® therapy. Unfortunately, he developed a high-titre FVIII inhibitor after one month of therapy (FVIII inhibitor level 27.6 BU/mL), leading to discontinuation of FVIII replacement and a heightened risk of severe or life-threatening bleeding. As the infant resides approximately one hour from the nearest healthcare facility, a comprehensive multidisciplinary care plan was established. This included family and primary healthcare education, prepositioning of bypassing agent (recombinant factor VII) in the local pharmacy, and coordinated care planning involving emergency, medical, surgical, and dental teams in anticipation of potential catastrophic bleeding events.

DISCUSSION

Haemophilia A is an X-linked recessive disorder caused by a deficiency of factor VIII (FVIII), leading to impaired haemostasis.[1] While it most often presents between one and two years of age with joint bleeds, neonatal presentations such as intracranial haemorrhage after birth or iatrogenic bleeding are well described.[2] In rare instances, extensive intramuscular bleeding may precipitate ACS.[3]

ACS is defined as a critical elevation of interstitial pressure that leads to compromised microvascular blood flow and reduced tissue perfusion within a confined anatomical compartment.[3] It is recognised as a surgical emergency, as delayed diagnosis and intervention may result in irreversible tissue ischaemia and severe complications such as muscle necrosis, rhabdomyolysis, infection, limb amputation, or even death. The exact incidence is unknown; however, it is estimated to be approximately 3.1 per 100,000 adults. In the neonatal population, the incidence is not well established, with only a few cases reported. The most common causes include intrauterine compression, oligohydramnios, malpresentation at birth, birth trauma, arterial thrombosis and other perinatal factors such as sepsis and acquired coagulopathy.[4] Although rare, haemophilia has also been documented as an underlying cause in neonates.[5] Given this context, it is important to consider bleeding diatheses - most notably haemophilia A.

ACS is a clinical diagnosis. It warrants a prompt diagnosis as patient outcomes are dependent on immediate recognition and decompression. In situations where signs are equivocal, Doppler ultrasound or direct intracompartmental pressure measurements may be employed to confirm the diagnosis.[3] In our patient, the diagnosis of ACS was established on the basis of classical skin changes. With no immediate family history of bleeding disorders, no clinical evidence of active haemorrhage, and a progression of swelling over the preceding ten hours, an urgent fasciotomy was performed prior to confirmation of an underlying bleeding disorder.

Prompt decompression is critical in restoring function and preventing muscle necrosis, contractures, and long-term sequelae.

The role of fasciotomy in the management of ACS in patients with haemophilia remains a subject of debate, as the primary treatment focus is on achieving haemostasis. Current recommendations suggest that the initial step in suspected ACS among haemophilia patients is the prompt replacement of the deficient clotting factor, which may help alleviate rising compartment pressure.[3] However, the risk of irreversible tissue ischaemia remains high due to the narrow therapeutic window between symptom onset and permanent damage. Therefore, clinicians must carefully balance the risk of bleeding complications against the potential limb morbidity.

Blood product transfusion, particularly fresh frozen plasma or cryoprecipitate, and early administration of clotting factor replacement prior to fasciotomy may reduce the risk of significant intraoperative bleeding. However, in settings where clotting factor concentrates or blood products are unavailable, timely surgical intervention should not be delayed, as the risk of irreversible tissue ischaemia outweighs the risk of haemorrhage. The use of antifibrinolytics agents such as tranexamic acid may be considered as adjunct therapy. Antibiotic prophylaxis is also recommended, as persistent bleeding and open wounds pose a substantial risk of infection.[6] In this case, both tranexamic acid and prophylactic antibiotics were administered.

While fasciotomy can result in good functional recovery, the presence of an open wound necessitates high-dose and prolonged factor replacement therapy. Guidelines recommend maintaining the FVIII levels between 80-100% during the first 48 hours, and 30-60% between days 3 and 5 postoperatively.[6] These target levels were not achieved in our patient, with serial FVIII assays ranging between 2% and 22% despite high-dose therapy. Nevertheless, factor replacement was gradually titrated as haemostasis improved. With intensive and prolonged replacement therapy, the risk of inhibitor development is a major concern, as observed in this case. Inhibitors are reported to occur in approximately 30-35% of previously untreated children with severe haemophilia A, and are associated with increased morbidity, including joint deformities, life-threatening bleeds, and impaired quality of life for both patients and caregivers.[7] In the presence of FVIII inhibitor, the FVIII replacement therapy has to be discontinued to prevent further development of inhibitor. As the patient is still non-ambulating, the risk of active bleeding is still low, and no replacement therapy is mandated. However, in the case of future active bleeding, the usage of a bypass agent such as recombinant factor VII (rFVII) is recommended to bypass the common coagulation pathway that utilises factor VIII.[6] rFVII needs to be readily available in the nearby health facility to facilitate prompt treatment and eventually prevent catastrophic bleeds and further complications.

Optimal management of children with severe haemophilia with inhibitors requires a multidisciplinary approach, aiming to minimise bleeding complications and support long-term health and function.[8] Although this case was managed in a rural healthcare setting with limited resources, the multidisciplinary coordination between the surgeon, haematologist, emergency physician, pharmacist, public health team, and rehabilitation services ensured the patient received timely and appropriate care. Caregiver education is equally important to ensure adherence to therapy and long-term monitoring.

CONCLUSION

Severe congenital haemophilia A can present with life-threatening complications during the neonatal period, including the rare occurrence of ACS. In the case of unexplained ACS in neonate, haemophilia should be strongly suspected. Early recognition of ACS is critical, as delayed diagnosis may result in irreversible tissue damage and the need for surgical intervention. Prompt administration of clotting factor replacement remains the cornerstone of ACS management, with fasciotomy required in cases where haemostasis is not rapidly achieved. This case underscores the importance of high clinical suspicion, timely multidisciplinary intervention, and caregiver education, particularly in resource-limited settings. Specialised medications like the clotting factors also should be made more accessible especially to rural healthcare facilities.

REFERENCES

1. Tantawy AAG. Molecular genetics of hemophilia A: clinical perspectives. Egypt J Med Hum Genet 2010; 11(2): 105-14.
2. Dyson H. Neonatal haemophilia – a guide to recognition and management. Infant 2006; 2(4): 156-9.
3. Donaldson J, Goddard N. Compartment syndrome in patients with haemophilia. J Orthop 2015; 12(4): 237-41.
4. Shen AH, Tevlin R, Kwan MD, Ho OH, Fox PM. Neonatal compartment syndrome and compound presentation at birth. J Hand Surg Glob Online 2020; 2(3): 166-70.
5. Lassandro G, Amoruso A, Palladino V, Palmieri VV, Giordano P. The risk of venipuncture in newborn with severe hemophilia: Case report of a large elbow hemorrhage and literature review of compartment syndrome. Hematol Rep 2021; 13(2): 8967.
6. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 2020; 26 Suppl 6: 1-158.
7. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. Haemophilia 2003; 9(4): 418-35.
8. Bertamino M, Riccardi F, Banov L, Svahn J, Molinari AC. Hemophilia care in the pediatric age. J Clin Med 2017; 6(5): 54.

CASE REPORT

Nephrotic syndrome in a non-diabetic adult: A case for primary care vigilance

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SUMMARY

Nephrotic syndrome presents a diagnostic challenge in primary care due to its nonspecific symptoms, which may overlap with more common conditions such as heart failure or liver disease, and the need to exclude secondary causes. Additionally, as nephrotic syndrome is relatively uncommon in non-diabetic adults, diagnosis in this group is less straightforward. We present the case of a man who came to primary care with frothy urine, bilateral lower limb swelling and significant weight gain, without evidence of underlying heart or kidney disease. Laboratory findings suggested nephrotic syndrome, and he was referred to a nephrologist, where further evaluation, including a renal biopsy, determined the aetiology. This case provides valuable insight into real-world diagnostic challenges and management approaches in this uncommon but serious condition. It shows the importance of maintaining a high index of suspicion for nephrotic syndrome in adult patients with unexplained oedema and proteinuria by primary care doctors, and it emphasises the value of prompt specialist referral and multidisciplinary care to optimise patient outcomes.

INTRODUCTION

Nephrotic syndrome (NS) has an incidence of approximately three new cases per 100,000 adults annually.[1] Data on adult NS in Southeast Asia and Malaysia are still limited. Diagnosing NS in primary care can be particularly challenging due to the nonspecific early symptoms and the need to exclude secondary causes. Symptoms such as leg swelling and frothy urine are common in primary care and can be misinterpreted for other more common conditions like heart failure, liver disease or venous insufficiency. The key challenge is to look beyond common causes, consider NS early and order confirmatory tests promptly.

NS is characterised by proteinuria greater than 3.5g/24hr, hypoalbuminemia below 3g/dL, hyperlipidaemia and oedema. Timely diagnosis and management are essential to avoid complications.[2] The underlying causes of NS vary with age; in children under 16, minimal change disease (MCD) is the most common. However, in adults aged 15 to 65, a broader range of causes is seen. Primary glomerular diseases such as focal segmental glomerulosclerosis (FSGS), MCD, IgA nephropathy and, less frequently, membranous nephropathy (MN), are more common in adults.[2-4] Adults with NS also face additional challenges, as the disease spectrum is broader and influenced by demographic factors such as age, race and geography, encompassing both primary and secondary causes. This makes early kidney biopsy critical to accurately diagnose the condition and guide subsequent treatment, especially after excluding secondary causes.[5]

Clinical decisions made in primary care involved ordering initial investigations, managing symptoms, excluding secondary causes like infections or diabetes and referring the patient to nephrology for further evaluation and biopsy. This highlights the role of primary care doctors as the first line of detection, starting management and coordinating with specialists to ensure timely diagnosis and comprehensive care. This case report describes a 44-year-old man with symptoms suggestive of NS, demonstrating the diagnostic challenges and key clinical decisions in primary care.

CASE PRESENTATION

A 44-year-old man with underlying hyperlipidaemia (on Tab Simvastatin 40mg daily) presented to the primary health clinic with a chief complaint of progressive bilateral lower limb swelling. The swelling initially began around the ankles one month ago but gradually extended upward, becoming increasingly severe over time. Additionally, he reported persistent frothy urine for four months and an unintentional weight gain of 10 kilograms over the past seven months. His weight was 84 kg at presentation, with a BMI of 32.6kg/m². The patient expressed concern that the swelling had not resolved and was progressively worsening.

On general examination, the patient was alert and in no acute distress. Vital signs were within normal limits with a blood pressure of 122/81mmHg and a heart rate of 80 beats per minute. Physical examination revealed bilateral lower limb oedema extending up to the mid-shin. There was no facial swelling or oedema in other parts of the body. No signs of pleural effusion or ascites were observed. On cardiovascular examination, the apex beat was not displaced with no abnormal heart sounds such as S3, S4 or murmurs, which could be associated with complications of nephrotic syndrome. Respiratory examination was unremarkable. The absence of these additional signs helped further confirm the presence of NS without other systemic manifestations and may help rule out secondary causes such as heart failure, chronic liver disease or autoimmune disease.

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Table I: Investigations to exclude secondary causes of Nephrotic syndrome

Investigation	Result
Sodium	141
Potassium	4.3
Creatinine	103.6 µmol/L
Urea	3.5 mmol/L
eGFR	79 mL/min/1.73m^2
HbA1c	5.7%
HBsAG	Non-reactive
Anti HCV	Non-reactive
HIV Antigen/ Antibody	Non-reactive
TSH/Free T4	3.62 / 10.62
ANA	Positive but speckled 1:100
C3, C4	Negative

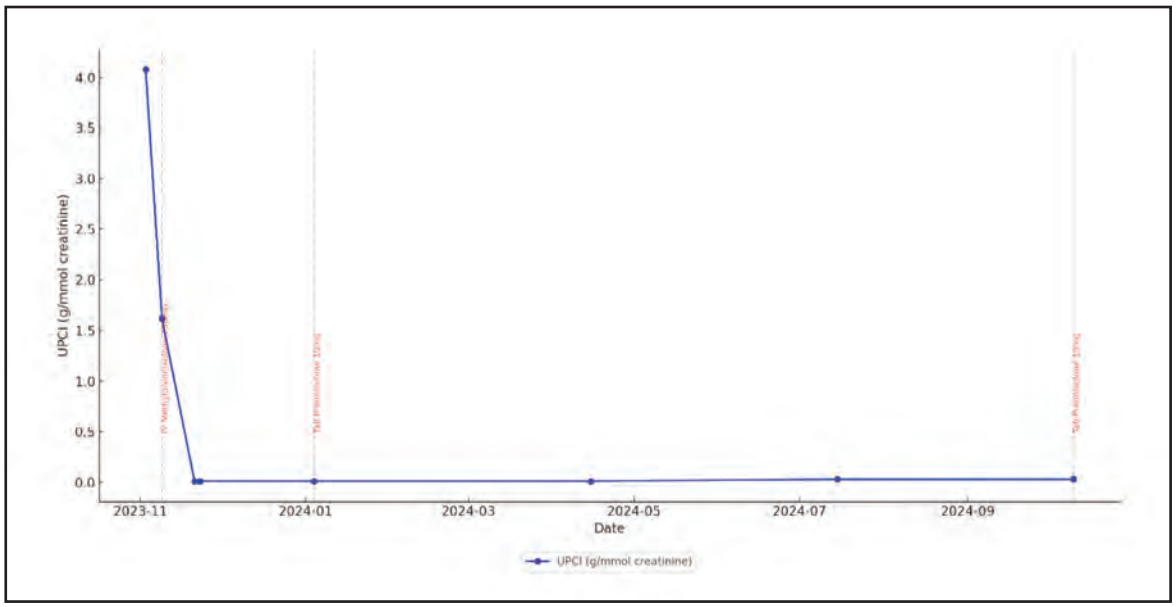

Fig. 1: Proteinuria trend with steroid treatment

Initial laboratory tests revealed proteinuria with a urine dipstick reading of 3+. The patient was also found to have an elevated urine protein-to-creatinine ratio of 4.08g/mmol, which corresponds to a 24-hour urine protein of 40g, hypoalbuminemia with an albumin level of 15g/L, and hyperlipidaemia, with total cholesterol and triglyceride levels of 16.26mmol/L and 7.79mmol/L, respectively. Liver enzymes were within normal range. These findings meet the criteria for NS. Secondary causes such as infections (hepatitis B, hepatitis C, and HIV), diabetes mellitus, thyroid dysfunction and autoimmune conditions like lupus nephritis were excluded through further laboratory testing (Table I).

The patient was initially prescribed tablet frusemide 40mg daily to reduce the oedema and scheduled for follow-up. As he was stable, outpatient management was deemed appropriate while waiting for the investigation results. He was advised to return earlier if symptoms worsened or new ones developed. However, a few days later, the patient returned earlier with worsening bilateral leg swelling now extending to the thighs and accompanied by tenderness. While thrombosis was suspected as a complication, the absence of typical symptoms of deep vein thrombosis (DVT), such as redness, warmth or pain on palpation along the veins, made DVT unlikely. This ruled out DVT as the cause and led to an urgent referral to a nephrologist and subsequent hospital admission for further evaluation.

While in the ward, a renal biopsy was performed to establish a diagnosis. The results showed mild mesangial proliferation without sclerotic changes. Immunofluorescence revealed only non-specific IgM staining, with all other markers being negative. A renal biopsy was considered necessary to identify the underlying cause of nephrotic syndrome. All key renal compartments were evaluated, but the possibility of missing FSGS due to sampling limitations was acknowledged. Although the biopsy findings were inconclusive and pointed toward MCD, the findings show the challenges in diagnosing NS, where even a renal biopsy may not fully determine the underlying cause.

The patient was initially treated with intravenous methylprednisolone and was maintained with oral prednisolone. He responded well to the treatment, showing a significant reduction in proteinuria and improving albumin levels with completely resolved oedema. Other treatments

included intravenous frusemide 80 mg once daily for 5 days, tablet simvastatin 40 mg once daily and tablet perindopril 2 mg once daily throughout the admission. The patient was discharged well from the nephrology ward after an 8-day admission, with resolution of lower limb swelling and pain. At discharge, his medications included prednisolone 30 mg once daily, frusemide 40 mg once daily, simvastatin 40 mg at night and perindopril 2 mg once daily. He was also advised to restrict fluid intake to 800 mL per day.

The patient's condition relapsed after a few months, and a repeat biopsy was recommended to confirm the findings. However, the patient declined the biopsy and preferred to continue with corticosteroid therapy, which was increased briefly during the relapse. Currently, the patient is doing well and continues regular follow-up care with both the primary care and nephrology teams (Figure 1).

DISCUSSION

NS has an annual incidence of approximately 3 per 100,000 adults.[1] In non-diabetic adults, primary glomerular diseases such as FSGS, MN and MCD are the prominent causes.[2] Secondary causes include Diabetes mellitus, infections, malignancies and autoimmune disorders, requiring comprehensive evaluation.

NS in non-diabetic adults is a complex condition with notable diagnostic and management challenges for primary care doctors. While specialist care is often needed, primary care doctors are key in early recognition, coordinating care and long-term management. This 44-year-old man case highlights these complexities, from initial suspicion to comprehensive evaluation and collaborative care.

Clinical Challenges in Diagnosis

NS often presents with generalised and subtle symptoms like peripheral oedema and frothy urine, as seen in this case. These symptoms overlap with other conditions frequently encountered in primary care, such as heart failure, liver disease or venous insufficiency. Recognising NS requires a high index of suspicion, especially in patients presenting with unexplained oedema and proteinuria. Early urinalysis and serum albumin tests help detect NS. In this case, 3+ proteinuria on dipstick, low albumin (15g/L) and high cholesterol (16.26mmol/L) were all suggestive of NS. These tests, readily available in primary care allow primary care doctors to initiate timely referrals for specialised care.[6]

While laboratory tests can suggest NS, they cannot identify the underlying cause. Renal biopsy remains the gold standard for diagnosis, as demonstrated in this case.[1,3,5] Renal biopsy is generally indicated in adults with NS as it plays a crucial role in differentiating between primary and secondary causes of NS and helps guide treatment decisions.[3,5,6] The benefits of early biopsy include better risk stratification, specific therapies and improved outcomes through early intervention. However, it is important to note that renal biopsy may not be easily accessible in all district settings in Malaysia, where limited resources and specialised personnel can delay diagnosis and treatment.[7]

Biopsy findings can be inconclusive, as FSGS may not be apparent in cases where the lesion is focal, requiring a much larger biopsy sample. When the biopsy is not definitive, the clinicians need to correlate histological results with clinical and laboratory data in order to ascertain the likely cause of the disease and its course of treatment.

Based on the biopsy findings showing mild mesangial proliferation without sclerotic changes, non-specific IgM staining on immunofluorescence and the excellent response to corticosteroid therapy, the most likely underlying cause in this patient is MCD. IgA nephropathy and membranous nephropathy was less likely due to the absence of immune complex deposits, and although FSGS can be missed on biopsy, the clinical presentation and response to treatment further support MCD as the probable diagnosis in this case.

Clinical Challenges in Management

The management of NS begins in primary care as they play an important role in managing care with symptom control and referral to nephrologist.6 In this case, diuretic therapy with frusemide was appropriately started to manage oedema. Primary care doctors should also address cardiovascular risk factors, considering the hyperlipidaemia and hypercoagulability linked to NS8. Patients with NS are also at higher risk of thromboembolic events, infections and progression to chronic kidney disease (CKD),[3,8,9] of which this patient did not suffer from these complications.

Long-term management focuses on maintaining remission, preventing relapses and managing complications. This includes using additional medications like ACE inhibitors or ARBs to reduce proteinuria, diuretics for oedema and statins to manage hyperlipidemia.[3] Monitoring kidney function and protein levels is essential, along with addressing side effects of steroids such as osteoporosis and weight gain. Regular follow-ups are important to monitor patients' condition, adjust treatment and prevent disease progression.

The cornerstone of NS treatment is immunosuppressive therapy, primarily corticosteroids.[3] In this case, the patient received methylprednisolone followed by oral prednisolone, demonstrating a standard therapeutic approach, with the patient initially responded well. However, the patient later experienced a relapse and declined a second biopsy. In this context, a prudent approach would involve reinitiating corticosteroids to achieve remission. Subsequently, introducing a steroid-sparing agent and calcineurin inhibitor like cyclosporin could be considered to maintain remission and prevent further relapses.[3]

The unpredictable course of NS requires an individualised treatment plan. Although this patient responded well to corticosteroids, some patients progress to CKD or end-stage renal disease. Primary care is essential for ongoing care, managing comorbidities, encouraging lifestyle changes and

supporting the patient's psychological health. Primary care doctors should educate patients on medication adherence, dietary changes (like low-sodium and protein-adjusted diets) and the need for regular follow-up.[1,3] These measures not only enhance clinical outcomes but also encourage patients to take an active role in their own care.

CONCLUSION

This case highlights the crucial role of primary care doctors in recognising and managing nephrotic syndrome (NS) in non-diabetic adults. It underscores the challenges posed by nonspecific symptoms and the importance of renal biopsy to establish a diagnosis. In situations where biopsy findings are inconclusive, clinicians should integrate clinical findings, laboratory data and imaging to guide treatment. Empirical treatment with close monitoring may be considered when clinical suspicion is high. Multidisciplinary collaboration is key to optimising outcomes, especially when access to specialised care is limited. This case also emphasises the need for structured referral systems between primary care and the nephrology team to ensure effective follow-up to support long-term management and reduce complications in patients with NS.

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DECLARATION

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REFERENCES

1. Hull RP, Goldsmith DJ. Nephrotic syndrome in adults. BMJ 2008; 336(7654): 1185-9.
2. Reynolds SB, Lutz RW. Diagnosis and management of nephrotic syndrome in an adult patient: A case report. Int J Case Rep Images 2016; 2016;8(7): 529-32.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021;100(4S): S1-S276.
4. National Renal Registry. 8th report of the Malaysian Registry of Renal Biopsy [Internet]. Kuala Lumpur: National Renal Registry; 2022 [cited 2025 May 27]. Available from: https://www.msn.org.my/nrr/8th-report-of-the-malaysian-registry-of-renal-biopsy-2022/
5. Canetta PA, Radhakrishnan J. The evidence-based approach to adult-onset idiopathic Nephrotic Syndrome. Front Pediatr 2015; 3: 78.
6. Baldwin MD. The primary care physician/nephrologist partnership in treating chronic kidney disease. Prim Care 2014; 41(4): 837-56.
7. Ramachandran R, Sulaiman S, Chauhan P, Ulasi I, Onu U, Villaneuva R, et al. Challenges in diagnosis and management of glomerular disease in resource-limited settings. Kidney Int Rep 2022; 7(10): 2141-9.
8. Kodner C. Diagnosis and Management of Nephrotic Syndrome in Adults. Am Fam Physician 2016; 93(6): 479-85.
9. de Seigneux S, Martin PY. Management of patients with nephrotic syndrome. Swiss Med Wkly 2009; 139(29-30): 416-22.

CASE REPORT

Acquired Methemoglobinemia in Adults. When and how to treat?

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SUMMARY

Acquired methemoglobinemia (MH) is a rare but potentially life-threatening condition in which exposure to certain medications, chemicals or toxins causes an excessive amount of methaemoglobin (metHb) to be present in the blood, resulting in reduced oxygen delivery to tissues. Dapsone and primaquine are often used for prophylaxis and treatment of Pneumocystis jirovecii pneumonia. Primaquine is also a common anti-malarial therapy. We report 3 cases of acquired MH recently encountered in our centre. The three patients had different pre-existing conditions, posed different diagnostic challenges, and received different treatment modalities, but fortunately, all had favourable outcomes. We aim to raise awareness among clinicians to consider acquired MH as a differential diagnosis of a patient with unexplained hypoxia and to re-visit the treatment approaches.

INTRODUCTION

MH develops when haemoglobin (Hb) is oxidised to contain iron in the ferric (Fe^{3+}) rather than the normal ferrous (Fe^{2+}) state.[1] Oxidised iron molecules are unable to bind and transport oxygen, leading to decreased oxygen delivery and eventual tissue hypoxia.[1] MH may be congenital or acquired.[1] Acquired MH is caused by exposure to substances that oxidise Hb either directly or indirectly, producing excess metHb that exceeds the body's capacity to convert the iron within Hb back to the Fe^{2+} state.[1] Individuals with congenital MH tend to be asymptomatic.[2] On the contrary, manifestations of acquired MH can be severe or even fatal.[2] Symptoms, which include cyanosis, pallor and fatigue, develop when metHb level reaches 1.5g/dL (approximately 10% total Hb).[3] Clinical severity is multifactorial and depends on the percentage of metHb.[1] We aim to discuss the pros and cons of each treatment option to guide clinicians in decision-making.

CASE PRESENTATION

Case 1

A 35-year-old woman with Systemic Lupus Erythematosus (SLE) and antiphospholipid syndrome presented with symptoms of an upper respiratory tract infection (URTI) of one week. Additionally, she complained of breathlessness and reduced effort tolerance. She received cyclophosphamide for active lupus nephritis, but due to inadequate response, this was replaced with rituximab. She was prescribed dapsone for prophylaxis against Pneumocystis jirovecii pneumonia as she had a hypersensitivity reaction to trimethoprim/sulfamethoxazole (Bactrim).

At the Emergency Department (ED), pulse oximetry recorded an oxygen saturation on room air of 83%, which increased to 95% with supplemental O_2 8L/min via face mask. She had mild tachypnoea with peripheral and central cyanosis. However, arterial blood gas (ABG) indicated good oxygenation with a partial pressure of oxygen (PaO_2) 194mmHg. Chest radiography (CXR) showed normal heart size and clear lung fields. In view of a preexisting diagnosis of concomitant APS, echocardiogram and computed tomography pulmonary angiogram (CTPA) were performed to exclude both pulmonary hypertension and pulmonary embolism (PE). Both tests were reported as normal. A diagnosis of MH was considered, and review of an earlier ABG result revealed a metHb level of 11.6%. This finding was initially missed, as not all ABG analysers measure metHb levels, and it was therefore not specifically sought.

Diaminodiphenyl sulfone (DDS) (Dapsone) was identified as the cause and was immediately stopped. The toxicologist advised administering intravenous Methylene Blue at a 1mg/kg dose, after excluding Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. MetHb level decreased to 1.9% after a single MB dose an hour later, with complete resolution of symptoms and cyanosis. She was discharged from the hospital the next day. A follow-up metHb level at two weeks showed a metHb of 0.6%.

Case 2

A 19-year-old international student with no prior health issues presented to the ED with five days of fever, myalgia, headache, vomiting and diarrhoea. She had a history of jungle trekking in Kashmir during a recent family vacation.

She was febrile with mild splenomegaly, but other vital signs were normal. Given her travel history, blood films for *malaria parasites* (BFMP) were performed, confirming a diagnosis of Plasmodium falciparum malaria. She was started on Artemether/Lumefantrine (Riamet) and a single dose of primaquine (after excluding G6PD deficiency) as per local treatment guidelines for malaria.

Three days later, oxygen saturation on room air recorded an oxygen desaturation to 85% but she remained clinically well. She was able to speak and ambulate fully without any breathlessness. MH secondary to primaquine was suspected and subsequently confirmed by ABG results of PaO_2 124mmHg with metHb level of 10.5%. As she was asymptomatic, Methylene Blue was not given. She was monitored and discharged from the hospital three days later when her metHb level reduced to 7.2%. Outpatient review 10

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Table I: Summary of patients' characteristics and management

Characteristic/Case	Case 1	Case 2	Case 3
Age (years)	35	19	32
Gender	Female	Female	Male
Race	Chinese	Indian	Malay
Primary Disease	SLE and APS with URTI	Malaria	Severe PJP in advanced RVD
Inciting Drug	Dapsone	Primaquine	Primaquine
Clinical severity (O2 requirement)	8L/min (FM)	None	15L/min (HFNC)
Hb level (g/L) on admission	8.0	10.0	12.0
Initial metHb level (%)	11.6	10.5	10.5
Treatment prescribed	MB	Supportive	ascorbic acid
Time to recovery	1 hour	10 days	7 days

Note: SLE-Systemic Lupus Erythematosus, PJP-Pneumocystis jirovecii pneumonia, APS-antiphospholipid syndrome, URTI-upper respiratory infection, RVD-Retroviral Disease, HFNC-High-flow nasal canula, FM-face mask, MB-Methylene Blue

Table II: Incidence of common drugs that cause methemoglobinemia

Medical Group	Common	Uncommon	Rarely
Analgesic-Antipyretic	Phenazopyridine Phenacetin		Acetaminophen Fentanyl
Anticonvulsant			Phenobarbital
Anti-Infective	Dapsone Primaquine	Sulphonamides	Chloroquine Nitrofurantoin
Local or Topical Anaesthetic (Topical)	Benzocaine Amethocaine Prilocaine	Lidocaine Cetacaine Tetracaine	
Vasodilator	Nitrates derivatives	Nitrates derivatives	
Miscellaneous		Methylene Blue Metochlopramide	

Source: Alanazi MQ[7]

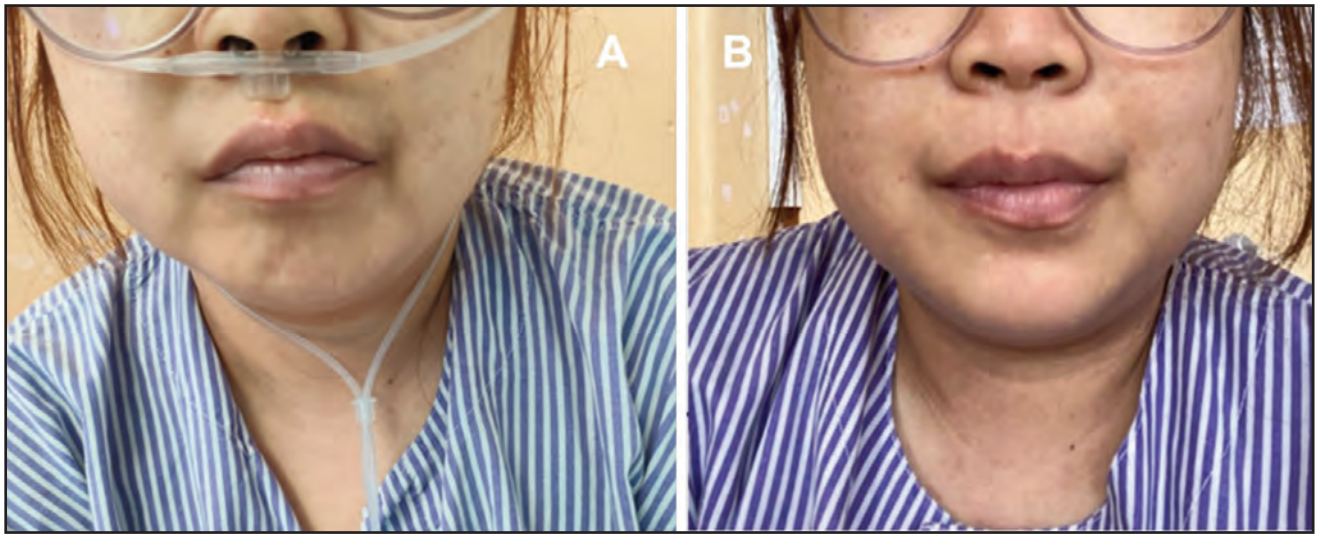

Fig. 1: Photos of patient in case 1 (Photo consented for publication purposes). Image on the left (A) showing pre-Methylene Blue, which patient having central cyanosis and required oxygen support, while image on the right (B) was post-Methylene Blue that cyanosis resolved and weaned off oxygen support.

days after discharge showed metHb had further decreased to 1.8%.

Case 3

A 32-year-old man with Retroviral Disease (RVD) but non-compliant to therapy, presented with fever, cough and exertional dyspnoea for two weeks. At ED, SaO2 at room air was 88% and improved to 97% on O_2 10L/min via face mask. CXR showed changes typical of Pneumocystis jirovecii pneumonia, and sputum examination later confirmed this diagnosis. He received trimethoprim/sulfamethoxazole and prednisolone as treatment for Pneumocystis jirovecii

pneumonia, but developed transaminitis. Hence, treatment was transitioned to second-line therapy of primaquine and clindamycin. Investigations for other opportunistic infections, including tuberculosis, were negative.

He had favourable clinical and radiologic responses to PJP treatment and was weaned off supplemental oxygen. Unfortunately, 10 days later, he developed tachypnoea and cyanosis. He had hypoxia requiring high-flow nasal cannula (HFNC) oxygen support. CTPA excluded PE. Having encountered two prior cases of unexplained hypoxia, the patient was checked for MH. Indeed, ABG showed PaO_2 on room air of 131mmHg and a metHb level of 10.5%. This patient developed acquired MH from primaquine, which was immediately discontinued.

He was prescribed high-dose oral vitamin C (1g TDS) for a week. Intravenous pentamidine replaced the combined therapy of primaquine and clindamycin. He gradually recovered and was discharged well. In retrospect, Methylene Blue should have been the treatment of choice in this patient, as Methylene Blue was clinically more severe in him compared to Case 1.

DISCUSSION

Literature search did not yield any known predisposition nor association of SLE, RVD and malaria with MH, except in the drugs used. SLE and RVD are immunocompromised states which place patients at increased risk of opportunistic infections. Bactrim, dapsone and primaquine are commonly prescribed as prophylaxis and treatment for Pneumocystis jirovecii pneumonia. A retrospective review of 138 patients with acquired MH by Ash-Bernal et al., revealed that the majority (42%) of cases were caused by dapsone.[4] This study reported that these patients, while on therapeutic doses of dapsone, had a mean metHb concentration of 7.6% but did not exhibit any effects.[4] Thus, the authors postulated that patients with chronic low-grade MH required a 'second-hit' event, most commonly anaemia, to further compromise oxygen tissue delivery and cause symptomatic hypoxia.[4]

The interval between time of exposure to the inciting drug and the onset of symptoms varied among our three cases - 8 months, 3 days and 10 days, respectively.

We suspect patient (Case 1) had asymptomatic chronic low-grade MH after initiation of dapsone. However, it was then aggravated by anaemia, which she required a blood transfusion from recurrent hemorrhoidal bleeds prior to the current admission.

Based on recommendations by Iolascon et al., no added treatment or oxygen supplementation is necessary for minimally symptomatic or asymptomatic patients.[3] Conversely, treatment should be initiated for symptomatic patients with a high metHb level of 10%-30%.[3] The recommended first-line treatment is intravenous MB.[3]

MB acts by accepting an electron from nicotinamide adenine dinucleotide phosphate (NADPH) to become leucomethylene blue. Leucomethylene blue acts to reduce ferric (3+) to the ferrous (2+) state, which binds oxygen in the erythrocytes. Significant reduction in metHb level is expected within an hour of MB,[3] as seen in Case 1, where the patient achieved a normal metHb level with the fastest recovery time among the three cases.

On the other hand, methylene blue may induce haemolytic anaemia in populations with G6PD deficiency.[3] G6PD, as the first enzyme in the hexose monophosphate shunt, is the sole source of NADPH in the erythrocyte, and methylene blue reduction to leucomethylene blue is a NADPH-dependent process.[5] Individuals with G6PD deficiency may not produce sufficient NADPH to reduce MB to LMB. Thus, methylene blue as an oxidant may induce haemolysis and paradoxically, worsen MH in a G6PD-deficient patient.[3]

Ascorbic acid is a natural water-soluble vitamin which reduces excessive oxidative stress. Whilst ascorbic acid can directly reduce metHb, the reaction rate is too slow to be effective when used alone, as it may take 24 hours or longer to lower the metHb level.[3] This explained the length of time (7 days) taken to normalise metHb level with high-dose oral ascorbic acid in Case 3. Intravenous ascorbic acid was not available in our centre. MB would be the preferred treatment according to Iolascon et al., recommendation.[3] Furthermore, there is no standardised dose for ascorbic acid used to treat MH.[3] Doses for adults are highly varied and range from 0.5g orally every 12 hours for 16 doses, to 6g to 30g intravenously given as a single dose or in divided doses.[6] Hence, ascorbic acid serves as an adjunct or alternative therapy when MB is not available.[3]

Although metHb levels in all three cases were similar, manifestations were more significant in Cases 1 and 3. It has been reported by Ludlow et al., that any pathology that impairs oxygen delivery, such as anaemia, congestive heart failure, chronic obstructive pulmonary disease, may worsen symptoms of MH.[1] Anaemia with Hb 8g/L reduced from a baseline of 11g/L was likely the precipitating cause in Case 1 and chest infection as the exacerbating factor in Case 3.

We aim to raise awareness amongst clinicians to consider MH as a differential diagnosis for hypoxia, especially when SaO_2 and PaO_2 results in ABG are discrepant. The presence of central cyanosis clinically is probably the most important clue when considering MH. All patients prescribed medications commonly associated with MH should be monitored closely for such a potential complication. Strong oxidising drugs produce more MH than weak oxidising drugs (Table II).[7] These are not uncommon medications used in daily clinical practice, hence noteworthy to keep in mind.

In addition, quantifying metHb level aids in the assessment of disease severity to guide therapeutic decisions. Once MH is diagnosed, the offending drug must be withheld immediately. Subsequently, treatment choice will depend on the stratification of its severity.

CONCLUSION

This case series highlights the importance of early recognition of MH to reduce morbidity and prevent mortality. Outcomes

of all three patients were good, but time to recovery differed amongst them. The threshold for initiating therapy and the choice of treatment should be individualised. Although providing supportive care and administering intravenous ascorbic acid were effective in reducing metHb levels in our patients, early intervention with MB could potentially hasten their recovery, enabling earlier discharge from hospitals.

REFERENCES

1. Ludlow JT, Wilkerson RG, Nappe TM. Methemoglobinemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Aug 28. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537317/
2. Sahadevan M, Mahendran M, Govindan S, Viswanathan TT. Gasping on Oxygen: A case report on toxic hemoglobinemia. J Interdiscip Med 2021; 6(2): 112-5.
3. Iolascon A, Bianchi P, Andolfo I, Barcellini W, Fermo E, De Falco L, et al. Recommendations for diagnosis and treatment of methemoglobinemia. Am J Hematol 2021; 96(12): 1666-78.
4. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia, a retrospective series of 138 cases at 2 teaching hospitals 2004. Medicine (Baltimore) 83(5): 265-73.
5. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. Br J Haematol 1983; 54(1): 29-41.
6. Sahu KK, Dhibar DP, Gautam A, Kumar Y, Varma SC. Role of ascorbic acid in the treatment of methemoglobinemia. Turk J Emerg Med 2016; 16(3): 119-20.
7. Alanazi MQ. Drugs may be Induced Methemoglobinemia. J Hematol Thromboembolic Dis 2017; 06(01): 270.

CASE REPORT

Evaluation of the apogeotropic posterior canal benign paroxysmal positional vertigo: Case studies from a tertiary clinic perspective

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SUMMARY

Benign paroxysmal positional vertigo (BPPV) is a prevalent vestibular disorder characterised by intermittent vertiginous episodes due to dislodged otoconia predominantly affecting the posterior canal. Atypical variants like apogeotropic posterior canal BPPV (aPC-BPPV) present diagnostic challenges and are likely underreported, particularly in Malaysia. We present two cases of aPC-BPPV. The first involves a 57-year-old female with persistent vertigo, initially misdiagnosed as right anterior canal BPPV. Video head impulse testing (VHIT) revealed reduced VOR gain in the right posterior canal, and the Demi-Semont manoeuvre successfully resolved her symptoms. The second case is a 62-year-old female, also misdiagnosed with left anterior canal BPPV. VHIT confirmed left posterior canal involvement, and repeated Demi-Semont manoeuvres led to symptom resolution. These cases highlight the intricate diagnostic challenges associated with aPC-BPPV, especially in differentiating it from contralateral anterior canal BPPV. Conventional diagnostic methods may yield incorrect results, emphasising the importance of incorporating advanced tools like VHIT as an ancillary assessment for precise canal identification. Atypical nystagmus and persistent symptoms after standard treatment warrant re-evaluation, with unresolved anterior canal (AC-BPPV) cases referred to a tertiary centre, as they may represent aPC-BPPV. Effective management often requires repeated, canal-specific manoeuvres such as the Demi-Semont, which have shown greater success in relieving symptoms in aPC-BPPV cases. Accurate diagnosis and targeted treatment are crucial for managing atypical BPPV. Improved awareness and advanced diagnostic methods, such as VHIT, can enhance outcomes, especially in cases where atypical presentations are not well-documented.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a common vestibular disorder resulting from otoconia displacement in the semicircular canals, resulting in vertigo. The otoconial particles may either float (canalolithiasis) or adhere to the cupula (cupulolithiasis).[1] BPPV classification is based on oculomotor responses during changes in head positioning. The Dix-Hallpike manoeuvre evaluates vertical canal involvement while the supine head roll test assesses horizontal canal involvement. Nystagmus patterns help identify the affected semicircular canal.[2]

Nonetheless, clinical presentations may not always align with established diagnostic criteria. Although BPPV typically affects the anterior, posterior, and lateral canals, atypical variants such as apogeotropic posterior canal BPPV (aPC-BPPV) and others have been observed. aPC-BPPV is the most documented atypical variant but is infrequently reported in Malaysia, where common BPPV cases prevail.[2,3]

This article offers an in-depth description of our experiences with aPC-BPPV and provides a thorough review of relevant literature. To our knowledge, there are no published cases of aPC-BPPV in Malaysia. Through this, we aim to enhance diagnostic accuracy and treatment efficacy for such cases.

CASE PRESENTATION

Patient 1

A 57-year-old woman was under clinical observation for two years due to recurrent episodes of BPPV. She was diagnosed with bilateral mild to severe sensorineural hearing impairment approximately ten years prior. The initial evaluation revealed the presence of down-beating torsional nystagmus during the Dix-Hallpike manoeuvre towards the right, indicative of right anterior canal BPPV (AC-BPPV). The MRI of the brain was unremarkable. Consequently, a deep head hanging manoeuvre was executed. A week later, the patient returned with analogous complaints of recurrent vertigo. Upon re-evaluation using the Dix-Hallpike manoeuvre, a down-beating torsional nystagmus was again observed, corroborating the diagnosis of right-sided AC-BPPV. She was treated with the deep head hanging manoeuvre; however, her symptoms did not resolve. A repeated Dix-Hallpike manoeuvre indicated the presence of ageotropic nystagmus upon positioning to the right.

Following this, a video head impulse test (VHIT) was conducted to further assess the vestibulo-ocular reflex (VOR) function across all six semicircular canals, which disclosed a reduced VOR gain in the right posterior semicircular canal (Figure 1). In response to these findings, she was treated with the Demi-Semont manoeuvre. During her subsequent consultations, the patient exhibited persistent symptoms

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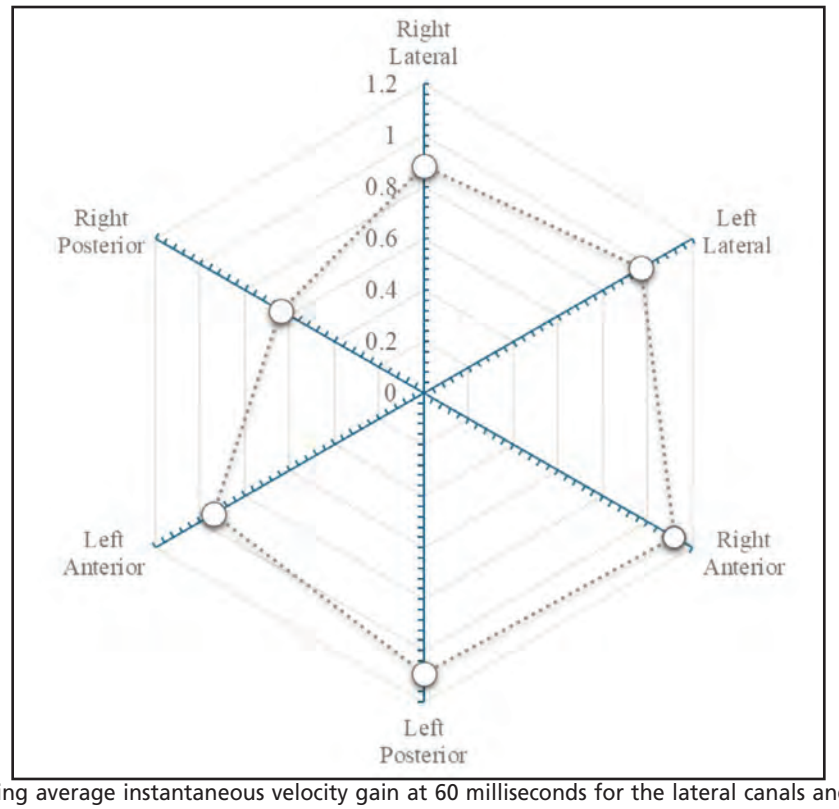

Fig. 1: VHIT results showing average instantaneous velocity gain at 60 milliseconds for the lateral canals and the velocity regression gain for the vertical semicircular canals (anterior & posterior) for Patient 1. There was a clinically significant reduction of VOR gain in the right posterior semicircular canal with VOR gain of 0.64 ± 0.25 as compared to the average VOR gain of other canals of 1.0 ± 0.11.

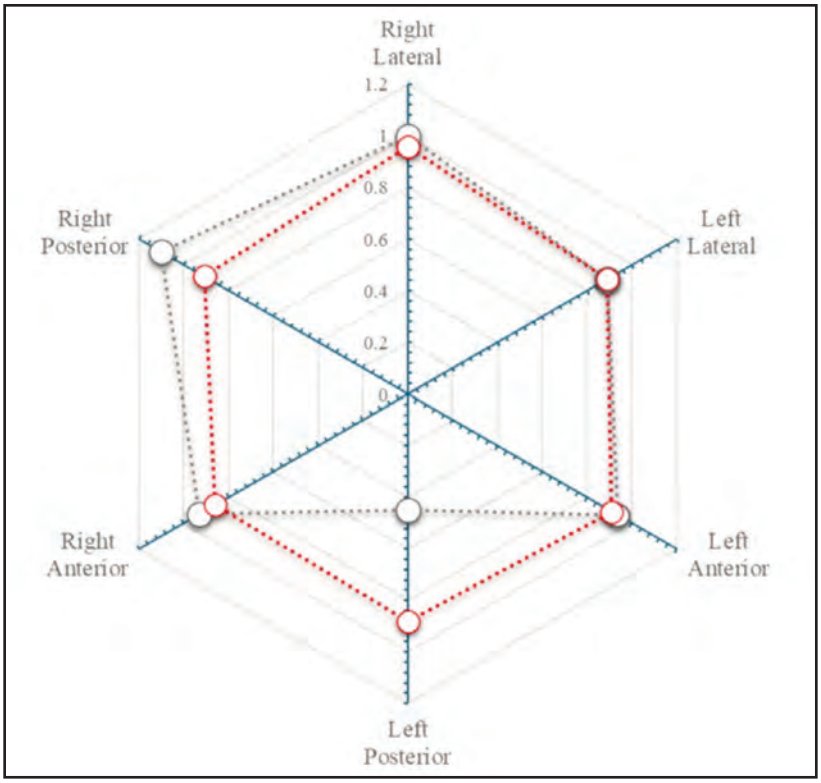

Fig. 2: VHIT results showing average instantaneous velocity gain at 60 milliseconds for the lateral canals and the velocity regression gain for the vertical semicircular canals (anterior & posterior) for Patient 2. The dotted red and grey-lined markers indicate the VOR gain of the first and second VHIT evaluations, respectively. The second evaluation showed a clinically significant reduction of VOR gain in the left posterior semicircular canal at 0.45±0.35.

despite adherence to a structured vestibular rehabilitation program. Nevertheless, she maintained an active lifestyle and reported a significant reduction in the incidence of dizziness.

Patient 2

A 62-year-old woman presented with a three-month history of episodic vertigo. The pertinent medical history included a prior diagnosis of acute labyrinthitis, which had been treated following an upper respiratory tract infection that occurred two months earlier. A baseline audiogram indicated a mild to moderate sensorineural hearing impairment in the right ear, alongside a profound sensorineural hearing loss in the left ear.

Initial assessment revealed a slight rotational down-beating nystagmus upon Dix-Hallpike manoeuvre to the left, indicating left anterior semicircular canal involvement. The results of the initial VHIT were deemed unremarkable (Figure 2). Subsequently, she underwent treatment involving the deep head hanging manoeuvre. Upon follow-up two weeks later, the patient reported ongoing episodes of persistent paroxysmal vertigo. The Dix-Hallpike manoeuvre performed towards the left indicated an up-beating torsional nystagmus. The Epley manoeuvre was executed as part of the treatment.

During her next appointment, she encountered another episode of positional vertigo, with the Dix-Hallpike manoeuvre exhibiting torsional up-beating nystagmus upon left positioning. A VHIT was conducted, which demonstrated a reduced VOR gain in the left posterior semicircular canal (Figure 2). She was then treated with the Demi-Semont manoeuvre. This episode persisted for approximately six weeks, during which each consultation necessitated the execution of the Demi-Semont manoeuvre as the assessment confirmed a diagnosis of left aPC-BPPV. Throughout this timeframe, a vestibular evoked myogenic potential (VEMP) test showed normal functionality of the saccule and inferior vestibular nerve in both auditory canals. Patient 2 reported symptomatic relief following each Demi-Semont manoeuvre and ultimately achieved symptom resolution after three treatment sessions. Furthermore, her brain MRI did not reveal any abnormalities that could be linked to her condition.

DISCUSSION

Posterior canal BPPV is the most common form of BPPV. In its cupulolithiasis variant, nystagmus is characterised as vertical, torsional, and up-beating, with a more prolonged but less intense presentation than in the canalithiasis variant. At the same time, patients with bilateral SNHL may have concurrent vestibular degeneration, affecting hair cells, nerves, or labyrinthine structures, leading to impaired balance, as seen in Patient 1.

aPC-BPPV is marked by nystagmus occurring in any head-hanging position (right, left Dix-Hallpike, or head-hanging).[4] This nystagmus has no latency, follows a crescendo-decrescendo course, lasts longer, and is less intense. It is primarily vertical-down-beating with a torsional component (clockwise for the right ear, anticlockwise for the left) and does not fatigue with repeated positioning.4 Reduced labyrinthine impedance (as in superior canal dehiscence) and otolithic membrane damage can facilitate otolith mobilisation and displacement, increasing the risk of aPC-BPPV.[5]

Canalith jam occurs due to endolymphatic flow blockage by otoconial particles, leading to a transient reduction in the vestibular-ocular reflex. The condition may arise due to innate semicircular canal stenosis or the formation of a plug by otoconial debris, with these theories interrelated as canal stenosis can increase the risk of debris jamming at the stenosed site.[6] This jamming alters intracanal hydrostatic pressure, causing persistent deflection of the cupula and spontaneous nystagmus with all head position changes.[6]

Diagnosing aPC-BPPV is challenging due to the difficulty in distinguishing it from contralateral AC-BPPV, as both conditions can be provoked by head-hanging positions (Dix-Hallpike test, straight head-hanging position). Differentiating these conditions is crucial as their treatments differ. The suspicion of atypical nystagmus should prompt further positional testing to determine the debris location within the canal. Helminski observed that in anterior canal BPPV, nystagmus typically has a slight or absent torsional component towards the affected ear, whereas the torsion is directed away from the involved ear in aPC-BPPV.[7]

aPC-BPPV can be treated with the Quick Liberatory Rotation manoeuvre. Other effective manoeuvres include the Demi-Semont and the 45-degree forced prolonged position technique.[8] These manoeuvres confirm the diagnosis of aPC-BPPV, as AC-BPPV does not respond favourably to these treatments. Vannucchi et al. reported a 68.7% success rate with these manoeuvres.[4] They also reported complete resolution in 5 of 11 patients (45%) with aPC-BPPV three days after a single Demi-Semont manoeuvre.[4] While the frequency of manoeuvres was not specified, repeated treatments are common in BPPV and likely applicable. In our case, symptoms are resolved after multiple Demi-Semont sessions.

VHIT may help to confirm the involved canal by detecting impairments in the vestibulo-ocular reflex (VOR) of the affected semicircular canal. Overall, VHIT sensitivity in identifying the affected semicircular canal was reported to be 72.9%. Castellucci et al. stated that VHIT differentiates aPC-BPPV from contralateral anterior canal BPPV in cases of positional downbeat nystagmus, thereby guiding appropriate corrective manoeuvres.[9] A reduction in VOR gain for the involved canal, which normalises upon symptom resolution, is seen on VHIT.[9] Follow-up post-treatment is crucial, as treatment response helps distinguish aPC-BPPV from the rarer AC-BPPV.

While referral to tertiary centres is ideal, aPC-BPPV can be diagnosed clinically without VHIT through careful history and positional testing. The Dix-Hallpike may show down-beating torsional nystagmus, with the torsional component beating away from the affected ear. Comparing both sides aids lateralisation. The Demi-Semont manoeuvre can assist in both diagnosis and treatment, especially in experienced hands. We recommend attempting it in patients with

persistent, prolonged, non-latent torsional down-beating nystagmus.

The cases exemplify the diagnostic and therapeutic complexities of aPC-BPPV, consistent with current literature. Both patients experienced persistent vertigo despite standard repositioning manoeuvres, necessitating the need for careful differentiation from atypical BPPV forms. The reduction in VOR gain in the implicated canals underscores the importance of using VHIT as an ancillary tool for accurate canal identification. In line with current recommendations, persistent and unresolved AC-BPPV cases should be reviewed or referred to a tertiary vertigo centre, as they may be aPC-BPPV, necessitating targeted management for better patient outcomes.

CONCLUSION

This research highlights the diagnostic and therapeutic challenges inherent in aPC-BPPV. Persistent or refractory AC-BPPV should be further investigated for possible canalith jam of the posterior semicircular canal. Accurate identification, facilitated by the VHIT is vital for effective intervention. The efficacy of specialised manoeuvres like the Demi-Semont highlights the significance of individualised approaches. These findings underscore the need for greater awareness and precise management to improve outcomes in atypical BPPV cases.

CONFLICT OF INTEREST

The author(s) declare no conflicts of interest regarding the research, authorship, and publication of this article.

REFERENCES

1. von Brevern M, Bertholon P, Brandt T, Fife T, Imai T, Nuti D, et al. Benign paroxysmal positional vertigo: Diagnostic criteria. J Vestib Res 2015; 25(3-4): 105-17.
2. Califano L, Mazzone S, Salafia F, Melillo MG, Manna G. Less common forms of posterior canal benign paroxysmal positional vertigo. Acta Otorhinolaryngol Ital 2021; 41(3): 255-62.
3. Richard W, Zainal H, Jamaluddin S, Rasheed s, Al-Hadeethi Y. Balance Disorders: A review of patients at a specialized vestibular clinic. IIUM Medical Journal Malaysia 2022; 21: 121-7.
4. Vannucchi P, Pecci R, Giannoni B, Di Giustino F, Santimone R, Mengucci A. Apogeotropic posterior semicircular canal benign paroxysmal positional vertigo: some clinical and therapeutic considerations. Audiol Res 2015; 5(1): 130.
5. Castellucci A, Malara P, Martellucci S, Delmonte S, Ghidini A. Fluctuating posterior canal function in benign paroxysmal positional vertigo depending on how and where otoconia are disposed. Otol Neurotol 2021; 42(2): e193-e8.
6. Martellucci S, Castellucci A, Malara P, Pagliuca G, Clemenzi V, Stolfa A, et al. Spontaneous jamming of horizontal semicircular canal combined with canalolithiasis of contralateral posterior semicircular canal. J Audiol Otol 2022; 26(1): 55-60.
7. Helminski JO. Peripheral downbeat positional nystagmus: Apogeotropic posterior canal or anterior canal BPPV. J Neurol Phys Ther 2019; 43 Suppl 2: S8-S13.8.
8. Vannucchi P, Pecci R, Giannoni B. Posterior semicircular canal benign paroxysmal positional vertigo presenting with torsional downbeating nystagmus: an apogeotropic variant. Int J Otolaryngol 2012; 2012: 413603.9.
9. Castellucci A, Malara P, Martellucci S, Botti C, Delmonte S, Quaglieri S, et al. Feasibility of Using the Video-Head Impulse Test to Detect the Involved Canal in Benign Paroxysmal Positional Vertigo Presenting With Positional Downbeat Nystagmus. Front Neurol 2020; 11: 578588.

CASE REPORT

Reconstruction using free fibular flap in surgical treatment of maxillary juvenile ossifying fibroma in children: A case report

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SUMMARY

Fibro-osseous lesions are rare benign tumours, with ossifying fibroma (OF) being the most common type in the head and neck region. Fibula free flap is the preferred choice for maxillo-mandibular defect reconstruction in paediatric patients, as it provides both bone and soft tissue components. We report a case of a 10-year-old girl presenting with a lump on the right cheek for the past six months. Surgical management of OF depends on clinical and radiological manifestations and typically involves enucleation, curettage, or resection. The aggressive nature and high recurrence rate make radical surgery the preferred therapy. Defects in the maxilla resulting from tumour removal can lead to serious functional and aesthetic deformities. Reconstruction using a free fibula flap in children with OF yields satisfying results with minimal postoperative morbidity while maintaining aesthetics and functionality over time. A multidisciplinary team is required in managing such complex cases to ensure a good outcome.

INTRODUCTION

Ossifying fibroma (OF) is the most common benign fibro-osseous lesion of the head and neck region, commonly affecting patients aged 20 to 40, though it is sometimes also found in children (juvenile ossifying fibroma/JOF). JOF is divided into trabecular type (juvenile trabecular ossifying fibroma/JTOF) and psammomatoid type (juvenile psammomatoid ossifying fibroma/JPOF). JTOF more frequently affects the maxilla and shows erosion and invasion into the surrounding structures, while JPOF mostly affects the sinonasal.[1]

Patients with OF usually present with a painless, slow-growing mass but might also be accompanied by pain or paraesthesia, face deformity or asymmetry, proptosis, sinus obstruction, teeth displacement, or intracranial complications. On the other hand, JOF tends to be painless while growing rapidly and causes destruction to adjacent structures.[1,2] Surgical management involves enucleation, curettage, or resection. Small lesions are treated conservatively with enucleation or curettage, while larger lesions require radical surgery and reconstruction. Mandibular OF are typically well-defined and can be surgically removed with ease, while maxillary OF are more challenging to treat due to possible expansion into the maxillary sinus.[1] Reconstructive surgery of the maxilla might be required to restore functionality and aesthetic following tumour removal, ensuring normal functions of the stomatognathic system, separating oral from sinonasal cavity, and restoring normal facial contours. Reconstruction using a fibula flap is an effective method of treating maxillo-mandibular defects in adult patients and is reported to have a high recovery rate with low postoperative morbidity in paediatric patients. Complications at 30 and 90 days following surgery were reported in less than 20% of patients, the most common being minor wound healing issues, such as cellulitis and wound dehiscence. The harvesting of fibula flaps does not cause any long-term orthopaedic complications, as previous studies reported paediatric patients with fibula flaps to have normal limb length and gait.[2] Considering the complexity of such cases, the involvement of a multidisciplinary team is required to ensure a good outcome. The objective of this study is to evaluate the benefits of fibula free flap in maxilla-mandibular reconstruction in children with oncological issues. The study aims to highlight the postoperative outcomes of the fibula-free flap, focusing on functional and aesthetic aspects.

CASE PRESENTATION

A 10-year-old girl complained of a growing lump on her left cheek for the past six months. The lump originated in her left upper jaw, on the gum of her first molar, after a tooth extraction. At the first presentation at the hospital, the lump was approximately the size of a baseball and was painless, but after a month grew into the size of a basketball, covering her oral cavity, causing difficulties in feeding and significant pain due to the mass pressing into surrounding structures. On physical examination, a mass was observed in the left maxillary region, 8x8x10 cm in size, firm and immobile, painless upon palpation, with no active bleeding.

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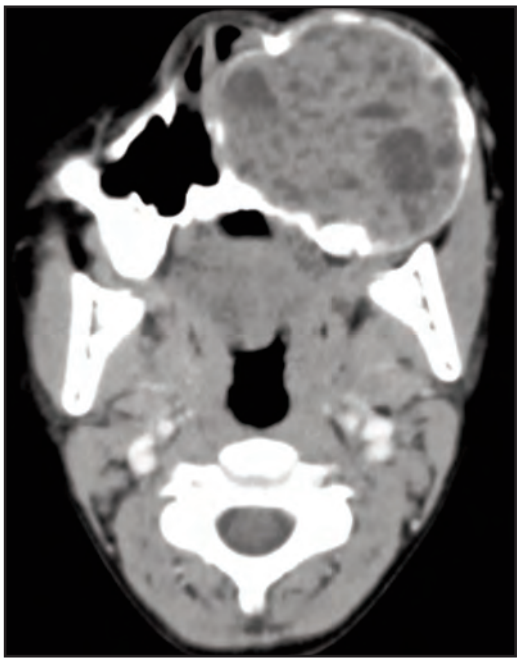

Fig. 1: Contrast CT scan of the head showing a mass arising from the left maxilla

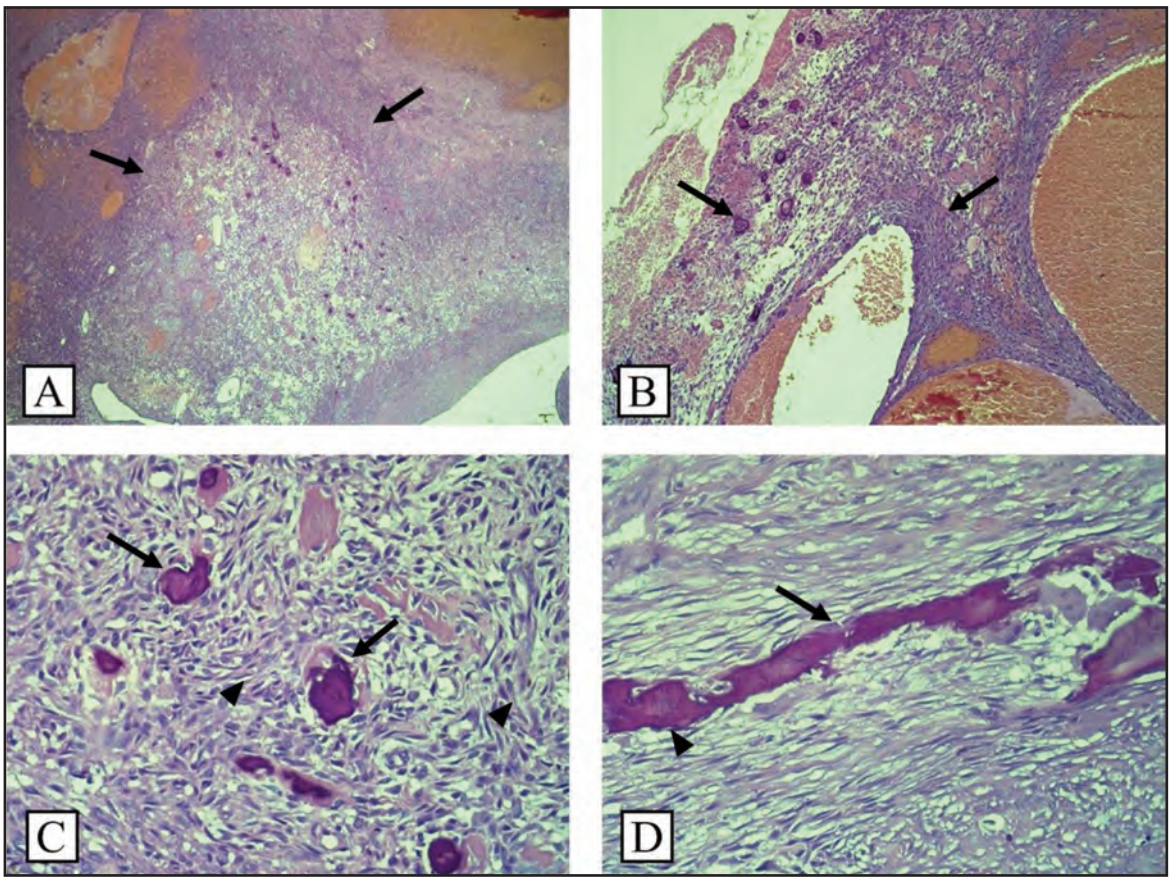

Fig. 2: Histopathology from surgical specimen stained with haematoxylin-eosin: (A), (B) fibro-osseous tumour mass (arrow) (4x, 10x); (C) ossification (arrow) between spindle cells (arrowhead) (10x); (D) bony trabeculae (arrow) with osteoblastic rimming (arrowhead) (40x)

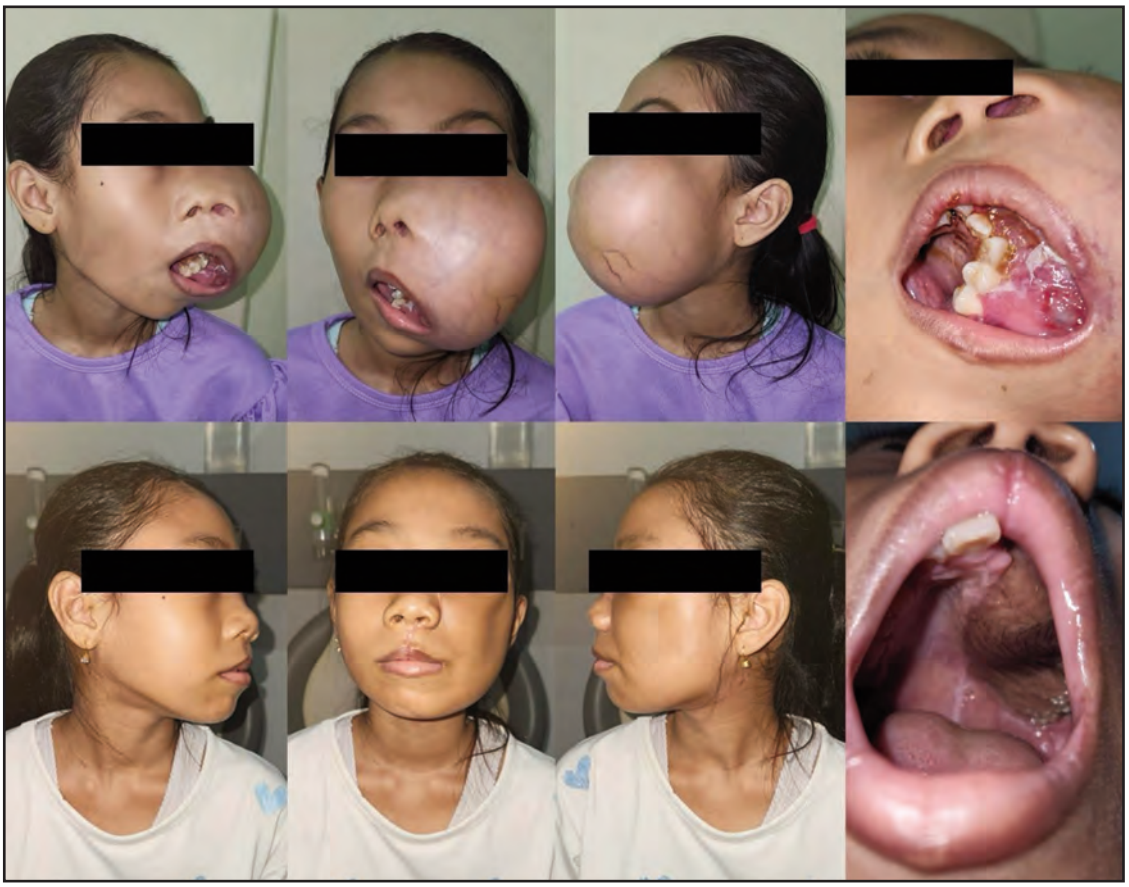

Fig. 3: Preoperative (upper row) and postoperative image of the patient on 2-month follow-up (lower row)

Examination of the intraoral cavity showed a mass on the left maxilla pressing centrifugally and covering 30% of the oropharynx.

A CT scan showed a mass arising from the left maxilla suspected as an ameloblastoma, involving the 23, 24, 25, 26, 27, and 28 teeth, expanding to the left maxillary and ethmoidal sinus, nasal and orbital cavity, pressing onto medial and inferior rectus muscles causing left ocular proptosis, and destructing the left sphenoid wing, inferior orbital rim, maxillary and ethmoid sinus wall, and pterygoid plate. No intracranial involvement was observed. The lesion was accompanied by bilateral cervical lymphadenopathy, the largest being 1.2 cm in diameter. Biopsy of the lump showed ossifying fibroma.

After another month, the patient experienced a significant amount of bleeding from the lump and weight loss of eight kilograms. A treatment plan was devised together with a plastic and reconstructive surgery specialist to carry out a wide excision of the mass, followed by total maxillectomy and defect reconstruction using a free fibula flap. The total maxillectomy was performed using the anterior skin approach. The fibula free flap was anastomosed using end-to-end anastomosis between the donor peroneal artery and the recipient superior thyroid artery, and between the donor comitans vein and the recipient external jugular vein. The surgery was deemed a success, and the patient was instructed to return for postoperative follow-up.

On 2-month follow-up, the patient presented with good mastication and swallowing functions despite having no teeth on her left upper jaw and denied having any pain or difficulties with feeding, speaking, or walking. A skin paddle of the free fibula flap was observed to be the same colour as the donor with soft hairs. A left Weber-Ferguson incision scar and submandibular scar were in good condition.

DISCUSSION

Fibro-osseous lesions are rare benign tumours, with ossifying fibroma being the most common type in the head and neck region. JOF is a type of ossifying fibroma found in children, usually presenting as a aggressive, rapid-growing mass causing destruction to adjacent structures, and further classified into trabecular type (JTOF) and psammomatoid type (JPOF). JOF is most commonly found in the posterior mandible and very rarely arises from the maxilla.[1,2]

On a CT scan, JOF is characterised by a growing lesion with well-defined borders, is locally aggressive, and causes cortical destruction. The lesion might be radiolucent or radiopaque.[1] In our case, a CT scan showed an expansile lytic lesion with solid and cystic components arising from the left maxilla, causing cortical destruction without infiltration to the surrounding structures, a benign but aggressive lesion. On histopathology, JTOF is unencapsulated but has a well-defined border with a loose structure of hypercellularised stroma of spindle cells and osteoid structures in-between,

while JPOF is characterised by small uniform ossicles embedded in stroma of spindle and stellate cells.[3] In our patient, histopathology showed a fibro-osseous lesion, the fibrous component being proliferating fibroblasts with spindle cells, and ossifying component being cementum-like islands and osteoblastic rimming on bony trabeculae. No nuclear atypia or mitosis was found. Based on the results of anatomical pathology examination, specific classification between Juvenile Trabecular Ossifying Fibroma (JTOF) and Juvenile Psammomatous Ossifying Fibroma (JPOF) cannot always be determined in every case. Despite the presence of a large tumour, in some cases, the histological features distinguishing these two subtypes may not be sufficiently clear or adequately represented in the available tissue sample. However, based on the anatomical pathology findings, the histological features predominantly show ossicle or psammoma components rather than trabecular bone and its anastomosis. Therefore, the histological characteristics of this case are more consistent with Juvenile Psammomatous Ossifying Fibroma (JPOF).

Surgical management of OF depends on clinical and radiological manifestations. Titinichi5 proposed a management protocol in which curettage with peripheral ostectomy is the first-line choice of treatment, particularly for medium-to-large neoplasms of the maxilla and mandible, and those with well-defined borders on CT scan. Enucleation is reserved for small, well-defined lesions of the mandible. Resection with defect reconstruction is recommended for large, infiltrative lesions, particularly in the posterior maxilla; those with poorly defined borders and multilocular appearance on CT scan; or cases of recurrence. Resections should be done with a clear margin of not more than 5 mm.[3] In this patient, a wide excision was carried out considering the large size of the mass, its aggressive growth, and possibility of a recurrence, followed by a total maxillectomy and defect reconstruction using osteoseptocutaneous fibula free flap for maxillary framework and soft tissue palate.

Recurrence following conservative surgery (enucleation or curettage) is reported to be as high as 38.4%, compared to radical surgery (surgical resection) with a recurrence rate of 1.6%. Tumours with locally aggressive behaviour and ill-defined borders on CT have a higher recurrence rate compared to those with well-defined borders due to incomplete excision in the infiltrative borders.[4] In this patient, the wide maxillary defect was reconstructed using a free fibula flap, corresponding with studies by Carvalho et al.,[5] and Zhang et al.,[6] which reported complete excision as the main choice of treatment in OF with a high recovery rate and low recurrence rate. The studies also recommend defects caused by tumour removal to be reconstructed using free flap grafting.

A maxillary defect due to tumour removal or trauma might cause significant functional disruption and aesthetic deformity. The main objectives of reconstruction are to reduce deformity, restore function, particularly mastication and speaking, provide structural support for external facial reconstruction, and restore the external facial aesthetics. The free fibula flap was introduced by Hidalgo in 1989 and has been a widely used method of maxillofacial reconstruction.[6] Reconstruction in paediatric patients has been shown to provide satisfactory results with minimal postoperative morbidity.

The osteoseptocutaneous fibula free flap provides bone, muscle, and skin that can be utilised simultaneously in a defect reconstruction. It has good periosteal blood supply, facilitating multiple osteotomies and allowing the fibula to be moulded according to the desired maxillary contour, and allows the possibility of dental implants in the future. The free fibula flap is also superior for reconstruction with a large defect, providing adequate tissue while maintaining the "like with like" principle. The fibula itself is a non-weight-bearing bone and can be harvested up to 25 cm in length, leaving only the most proximal and distal parts to preserve the knee and ankle joints.[7] However, the fibula flap does come with certain limitations. Fibula free flap in oncology patients may have cause delays in starting adjuvant treatments, such as radiotherapy, due to the postoperative recovery period.[8] Paediatric patients undergoing the surgery will also require long-term monitoring to assess their growth, such as craniofacial growth and gait.[9]

Postoperative complications at 30 and 90 days following free flap surgery in paediatrics were reported in less than 20% of patients, consistent with other studies reporting minimal complications following free flap reconstruction in maxillofacial defects.[2] Slijepcevic et al.,[9] reported free flap failure incidence in only 1 out of 89 patients of paediatric maxillomandibular reconstruction with fibula free flaps, showing that reconstruction using free flaps can be utilised in paediatric patients with a high success rate and low risk of failure. The most common postoperative complications were wound healing issues, such as cellulitis and wound dehiscence.[2] On 2-month follow-up, our patient had good mastication and swallowing functions despite having no teeth on her left upper jaw and denied having any pain or difficulties with feeding, speaking, or walking. Long-term outcomes and complications are evaluated using questionnaires of patient satisfaction and quality of life. In our centre, we use a questionnaire that has been translated and validated into the Indonesian language.

Long-term complications related to craniofacial growth were reported in a quarter of patients and mostly occurred in patients younger than 10 years of age or with lateral or hemimandibular defects.[9] The satisfying result is also seen in the long-term outcome of osteoseptocutaneous fibula free flap for various extended mandible defects, both in the function and quality of life (QoL). The QoL showed satisfactory outcome in swallowing, speech, eating function, and also donor site morbidity. The neo-mandible also seems to be well-developed and symmetrical despite the lack of a growth point.[10] Dental rehabilitation may facilitate normal occlusal relationship and midface growth.[9] As of the writing of this article, our patient has been referred to a prosthodontist for a dental rehabilitation.

Management of patients with JOF is best carried out by a multidisciplinary group comprising head and neck surgeons, plastic surgeons, radiologists, anaesthesiologists, and nursing staff experienced in head and neck cancer reconstruction. Other professionals might be added into the team if deemed necessary.

CONCLUSION

JOF is a rare fibro-osseous lesion characterised by an aggressive nature and a high recurrence rate. Diagnosis should be based on a combination of clinical-pathological and radiological correlations. Management of JOF requires a balance between extensive lesion removal while preserving the surrounding anatomical structures. In paediatric oncological cases requiring maxilla-mandibular reconstruction, the free fibula flap offers significant benefits by providing a bony framework and replacing the soft tissue components such as the palate, gingiva, and buccal mucosa. This approach helps minimise long-term complications, including plate extrusion, infection, and growth disturbances in children. Multidisciplinary teamwork is important in managing these patients to ensure the best outcomes.

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DECLARATION

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REFERENCES

1. Titinchi F, Morkel J. Ossifying fibroma: analysis of treatment methods and recurrence patterns. J Oral Maxillofac Surg 2016; 74(12): 2409-19.
2. Mücke T, Hölzle F, Loeffelbein DJ, Ljubic A, Kesting M, Wolff KD, et al. Maxillary reconstruction using microvascular free flaps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 111(1): 51-7.
3. Titinchi F. Juvenile ossifying fibroma of the maxillofacial region: analysis of clinico-pathological features and management. Med Oral Patol Oral Cir Bucal 2021; 26(5): e590-7.
4. Chrcanovic BR, Gomez RS. Juvenile ossifying fibroma of the jaws and paranasal sinuses: a systematic review of the cases reported in the literature. Int J Oral Maxillofac Surg 2020; 49(1): 28-37.
5. Carvalho B, Pontes M, Garcia H, Linhares P, Vaz R. Ossifying fibromas of the craniofacial skeleton. In: Martinez EP, editors. Histopathology Reviews and Recent Advances. London: IntechOpen; 2012. 121-32
6. Zhang WB, Wang Y, Liu XJ, Mao C, Guo CB, Yu GY, et al. Reconstruction of maxillary defects with free fibula flap assisted by computer techniques. J Craniomaxillofac Surg 2015; 43(5): 630-6.
7. Kim D, Dreher M. The Fibula Free Flap in Maxillary Reconstruction. Atlas Oral Maxillofac Surg Clin North Am 2007; 15: 13-22.
8. Lee CW, Dupré S, Marlborough F, Ahmed OA, Ragbir M, Saleh DB, et al. Postoperative radiotherapy delay in head and neck cancer patients undergoing major resection and free flap reconstruction. J Plast Reconstr Aesthet Surg 2022; 75(7): 2084-9.
9. Slijepcevic AA, Wax MK, Hanasono M, Ducic Y, Petrisor D, Thomas CM, et al. Post-operative outcomes in pediatric patients following facial reconstruction with fibula free flaps. Laryngoscope 2023; 133(2): 302-6.
10. Atmodiwirjo P, Bangun K, Rachadian Ramadan M, Tania V, Djohan M, Ralena NA, et al. Does free fibular flap reconstruction affect the quality of life in pediatric patients with various extend of mandible defects? J Craniofac Surg 2024; 35(5): 1411-6.

A cyclic bleeding conundrum: A case of recurrent catamenial haemothorax

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SUMMARY

Catamenial haemothorax (CtH) is a rare manifestation of endometriosis and falls under one of the manifestations of thoracic endometriosis syndrome (TES). It is often difficult to diagnose in its initial presentation unless an accurate history of symptoms coincides with menstruation. We report a case of a nulliparous lady with a history of endometriosis who presented with a sudden onset of shortness of breath. She was initially treated as pneumonia, then presented with recurrent episodes of catamenial haemothorax. Diagnosis can be aided by computed tomography (CT) thorax, which can identify features of TES; however, the gold standard is direct visualisation with video-assisted thoracoscopic surgery (VATS) and histopathological evidence of endometrial cells in the thoracic cavity. CT Thorax revealed pleural nodules at the right hemidiaphragm, while biopsy of the pleural tissue via pleuroscopy was consistent with endometriosis. The intra-operative VATS findings included two litres of blood in the pleural cavity, as well as pleural nodules and fenestrations on the diaphragm. We discuss the difficulty in diagnosis during the initial stage, the possible pathophysiology of this condition and its treatment.

INTRODUCTION

Endometriosis is a benign gynaecological disorder defined as endometrial tissue that lies outside of the uterine cavity. It is estimated that it affects 6-10% of women in the reproductive age,[1] although the actual numbers may be higher, as many go undiagnosed. The most common site affected by endometriosis outside of the pelvic region is the thoracic cavity, which includes the lung parenchyma, diaphragm and pleura, with the right hemithorax being more affected. In the thoracic cavity, endometriosis can manifest as catamenial pneumothorax (73%) or haemothorax (14%), catamenial haemoptysis (7%) and/or pulmonary nodules (6%),[2] and falls under the umbrella term of Thoracic Endometriosis Syndrome (TES).[2-4]

CASE PRESENTATION

We present a case of a 40-year-old nulliparous woman with underlying endometriosis. She has had a chronic history of severe dysmenorrhea since her early teens, before seeking medical attention and eventually diagnosed with endometriosis in her late 20s. She underwent laparoscopic removal of endometrioma and laparoscopic cystectomy for bilateral ovarian cysts in 2009. She has been married for more than 15 years, however, she suffers from primary subfertility as a result of underlying endometriosis. Besides that, she also has a strong family history of breast cancer, leukaemia, and oral, cervical and uterine malignancy.

She initially presented with a sudden onset of breathlessness and right-sided chest pain and was treated for community-acquired pneumonia with a course of intravenous antibiotics and discharged home. However, her dyspnoea did not completely resolve, and she presented a week later with worsening shortness of breath. Chest x-ray showed she had a spontaneous right-sided pneumothorax and thus was managed with chest tube insertion. Once the pneumothorax resolved, the chest tube was removed, and she was discharged home. Outpatient contrast-enhanced computed tomography (CECT) Thorax was done to investigate the cause of spontaneous pneumothorax, and it showed two pleural-based nodules at the right hemidiaphragm. A radioconference was held, and it was noted that close correlation to menstruation history was needed.

The patient presented again with recurrent hydropneumothorax at intervals of 6 months, 3 months and 1 month before undergoing a pleuroscopy. Biopsy of the parietal pleura was consistent with endometriosis; other pleural fluid investigations were negative for malignancy and bacterial growth. She had another two episodes of recurrent haemothorax, which brings the total to seven incidences of catamenial pneumo- and haemothorax over a period of 18 months. Retrospectively, a detailed history was taken, and it was found that each episode had coincided within 1-2 days of her menstruation. Thus, she was diagnosed with recurrent catamenial haemothorax (CtH).

Upon elective admission, she was asymptomatic. However, physical examination revealed reduced breath sounds in the right basal zone, and the chest x-ray showed right pleural effusion. She underwent right video-assisted thoracoscopic surgery (VATS). Intra-operatively, there was 2L of blood in the pleural cavity with pleural nodules and fenestrations on the diaphragm, mainly at the tendinous part. Diaphragm fenestrations were resected using a stapler device, the pleural layer at the lower hemithorax was excised (pleurectomy), as well as pleural nodules, and pleurodesis was done.

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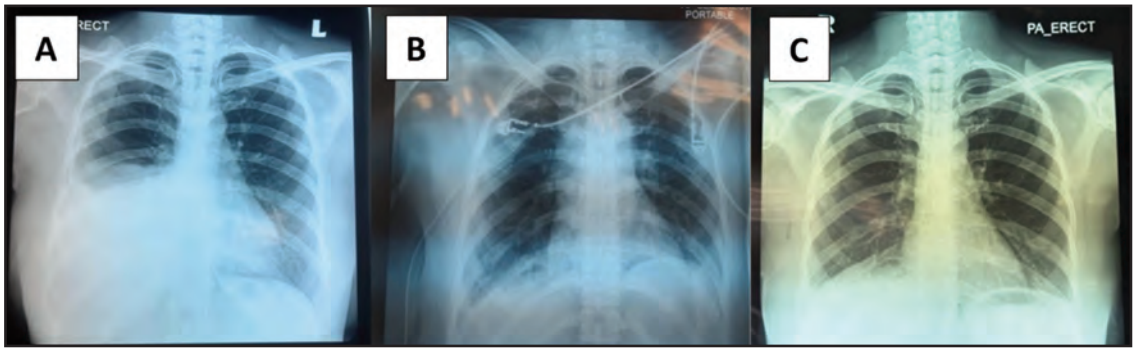

Fig. 1: (A) Pre-operative chest X-ray illustrating right-sided pleural effusion with a blunted right costophrenic angle. (B) Immediate postoperative chest X-ray with right chest drain in situ, showing resolved right haemothorax. (C) Post-operative Day 4 chest X-ray with resolved haemothorax and lungs well expanded following right chest drain removal

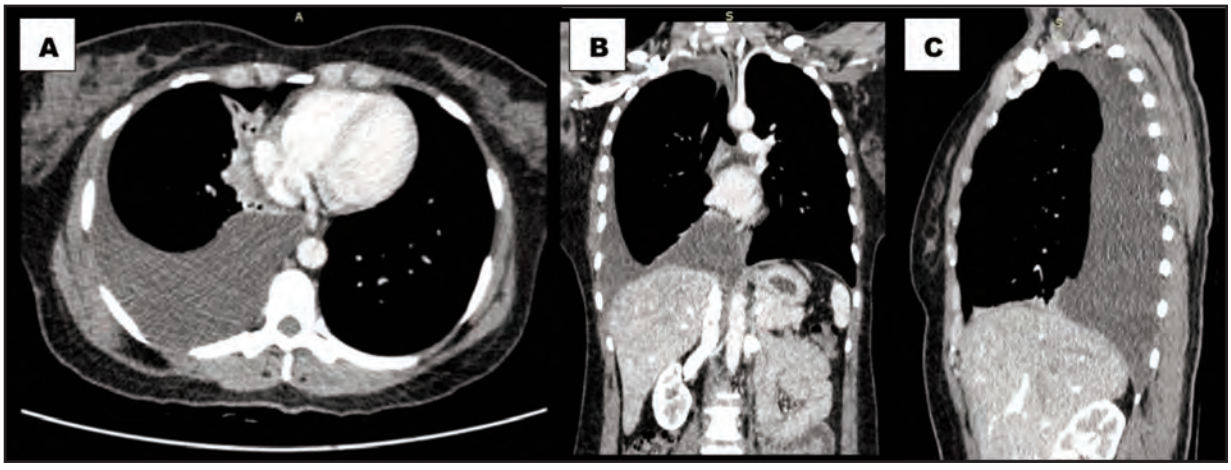

Fig. 2: Multi-density right pleural effusion on axial (A), coronal (B) and sagittal (C) cuts of CT Thorax, consistent with right haemothorax

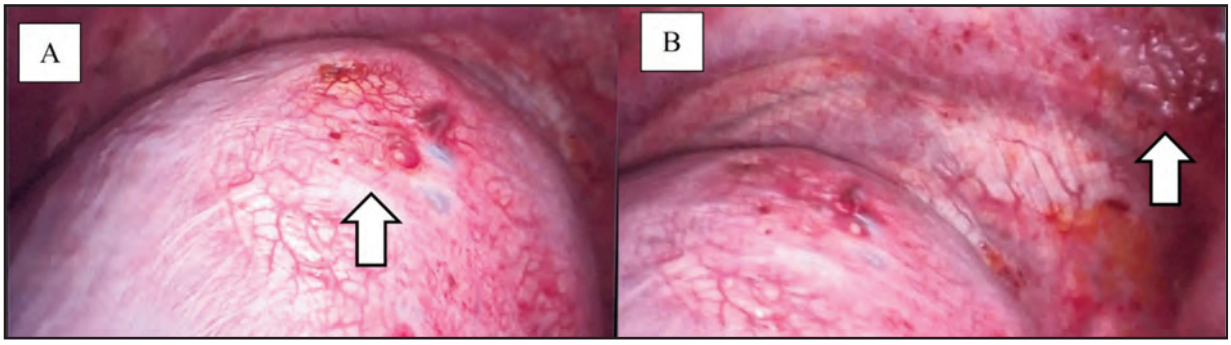

Fig. 3: Intraoperative images via video-assisted thoracoscopic surgery (VATS). (A) The arrow indicates fenestrations and nodules over the diaphragmatic surface. (B) The arrow points at multiple pleural nodules lining the pleural cavity

She recovered well in the post-operative period, the chest drain was removed on the fourth post-operative day, and she was discharged home well. Intraoperative biopsy of the pleural nodules was proven to be endometriosis. During the follow-up period, her symptoms had resolved, however, she complained of neuropathic pain. She was referred to the Gynaecology Team for hormonal treatment to manage endometriosis and the Acute Pain Service for pain optimisation.

DISCUSSION

Extra-pelvic manifestation of endometriosis is rare and is considered part of the disease progression of endometriosis, as it tends to develop after a chronic history of pelvic endometriosis, and in the later part of the reproductive age. As reported in literature,[2] the peak incidence age for endometriosis is 24 to 29 years old, while the peak incidence rate for TES is 30-34 years old. TES is difficult to diagnose, rarely during the initial presentation, as it is often missed. It

carries an interval of 8-19 months from the onset of symptoms to diagnosis and management.[5] This is quite similar to our index patient presented above, who has suffered with endometriosis since early teenage years and subsequently required surgery.

Signs and symptoms of CtH may be vague, as it can mimic a myriad of other respiratory disorders, such as infection or malignancy, and therefore is often missed in the initial stage. A high level of clinical suspicion is required to reach an accurate diagnosis. This can be achieved with thorough history-taking of symptoms that are directly linked with menstruation and/or have a close cyclical relation with menstruation. In terms of imaging, chest radiography is the first line, followed by subsequent CECT Thorax. They are both sensitive in detecting pneumo- or haemothorax, but are unable to pinpoint the underlying pathology.6 MRI, rarely done, can aid in detecting diaphragmatic lesions, but is also unable to accurately diagnose CtH. Other investigative tools include bronchoscopy or pleuroscopy, which can help obtain a biopsy in order to make a histopathological diagnosis, however, they can still be missed if lesions are located peripherally.[7] It must be noted that brush cytology may sometimes be more superior in acquiring sample for accurate diagnosis.[8] However, the gold standard for achieving a correct diagnosis of TES is via VATS, where the classical features of diaphragmatic and pleural lesions, as well as blebs, bullae and scarring, are directly visualised.[1] Our patient was initially thought to have a lung infection, then developed spontaneous pneumothorax with an unknown cause. However, after CECT revealed pleural nodules, there was clinical suspicion of endometriosis. This was later confirmed with a biopsy via pleuroscopy and reinforced during VATS.

The pathophysiology of TES is uncertain. Multiple theories have been proposed, but none can be solely attributed to the disease manifestation, therefore, it is likely that it is multi-factorial or multi-causal.[1] The most popular theory is the retrograde menstruation theory, which postulates that during menstruation, endometrial cells undergo migration through the fallopian tube and into the pelvis. There, these cells will then plaster themselves onto peritoneal surfaces. After chronic and repeated retrograde migration, endometrial cells migrate further into the right paracolic gutter and towards the right hemidiaphragm. Once there, they implant themselves onto the sub-diaphragmatic surface and subsequently migrate through congenital or acquired fenestrations in the diaphragm and enter the right pleural cavity. This theory explains why TES is more common on the right hemidiaphragm (85%), as the falciform and phreno-colic ligaments prevent migration flow to the left sub-diaphragm.[5] This is the most probable diagnosis for our patient, as evidenced by diaphragmatic fenestrations and the nature of right-sided dominance of disease.

Another theory to emerge hypothesises that mesothelial cells of the diaphragm undergo metaplasia due to external stimuli such as high oestrogen exposure and transforms into endometrial cells. This can also explain the rare cases of endometriosis found in men, following a high-dose oestrogen exposure. Besides retrograde menstruation flow, endometrial cells may disseminate via the lymphatics or haematogenous route. This theory can illustrate why bronchopulmonary lesions are bilateral, and how some rare cases of endometrial cells have been found in the brain and bone. Lastly, the prostaglandin theory accounts for rare cases of TES, where blebs and bullae are the only pathological lesions observed. During menstruation, prostaglandin F2-alpha levels increase, causing bronchoconstriction and vasoconstriction, which can then cause alveolar rupture and develop into catamenial pneumothorax or haemothorax.

The treatment for TES is with multi-modal and multi-disciplinary approach, where it can be divided into medical and surgical management, with gynaecology and thoracic disciplines. The first-line medications recommended are gonadotrophin-releasing hormone (GnRH) analogues. However, this can cause menopausal-like side effects and osteoporosis, and can fail in 50% of cases, especially when not coupled with surgery.[10] Other options are oral contraceptive medication and GnRH antagonists. Hormonal medications tend to be prescribed long-term due to the chronic and recurrent nature of the disease, even after surgery, in order to prevent recurrence.

VATS is the ideal surgical approach to manage TES manifestations, as it is both diagnostic and therapeutic.[1] It is also an option to be considered for those with recurrent refractory disease. Endometrial implantation on the diaphragm and pleura can be fulgurated with bipolar diathermy or excised with energy devices, while infiltrative or larger lesions can be resected with stapler devices, and larger defects repaired using synthetic mesh. Pleurodesis, either chemical or mechanical, can also be administered for pleural lesions as well as pleurectomy. However, there is insufficient evidence to prove that it reduces the rate of recurrenceI.9 Following surgery, these patients must be monitored with hormonal suppression therapy in order to reduce the risk of recurrence.[9]

CONCLUSION

CtH is a rare manifestation of endometriosis and is difficult to diagnose correctly. Initial symptoms may resemble common thoracic pathologies, however, there should be a high clinical suspicion in these patients who have a concurrent history of endometriosis, in order to reach a timely diagnosis and to prevent morbidity and mortality for women of childbearing age. VATS is the gold standard for diagnosis and can also be therapeutic. Although surgical pleurodesis has been found to be superior to hormonal suppression, a combined surgical and medical approach to the management of TES provides the best outcome and helps in preventing recurrence.

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DECLARATION

The authors would like to declare no conflict of interest.

REFERENCES

1. Nezhat C, Lindheim SR, Backhus L, Vu M, Vang N, Nezhat A, et al. Thoracic endometriosis syndrome: a review of diagnosis and management. JSLS 2019; 23(3): e2019.00029.
2. Joseph J, Sahn SA. Thoracic endometriosis syndrome: New observations from an analysis of 110 cases. Am J Med 1996; 100: 164-70.
3. Nezhat C, King LP, Paka C, Odegaard J, Beygui R. Bilateral thoracic endometriosis affecting lung and diaphragm. JSLS 2012; 16: 140-2.
4. Nezhat C, Main J, Paka C, Nezhat A, Beygui RE. Multidisciplinary treatment for thoracic and abdominpelvic endometriosis. JSLS 2014; 18(3): e2014.00312.
5. Channabasavaiah AD, Joseph JV. Thoracic endometriosis: revisiting the association between clinical presentation and thoracic pathology based on thoracoscopic findings in 110 patients. Medicine (Baltimore) 2010; 89: 183-8.
6. Fukuda S, Hirata T, Neriishi K, Nakazawa A, Takamura M, Izumi G, et al. Thoracic endometriosis syndrome: Comparison between catamenial pneumothorax or endometriosis-related pneumothorax and catamenial hemoptysis. Eur J Obstet Gynecol Reprod Biol 2018; 225: 118-23.
7. Kuo PH, Wang HC, Liaw YS, Kuo SH. Bronchoscopic and angiographic findings in tracheobronchial endometriosis. Thorax 1996; 51: 1060-1.
8. Tripp HF, Thomas LP, Obney JA. Current therapy of catamenial pneumothorax. Heart Surg Forum 1998; 1: 146-9.
9. Chetambath R, Kumar P, Nandini V, Chandran S, Chacko A. Catamenial haemothorax-A rare cause of pleural effusion. Lung India 2023; 40: 541-4.

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