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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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CONTENTS Page

Case Reports

CONTENTS Page

Acute upper limb ischaemia complication of thrombosed arteriovenous fistula

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SUMMARY

Thrombosed arteriovenous fistula is usually uncomplicated and adherent to the wall. Thrombosed vascular access causing acute limb ischaemia is rare, with only 16 cases reported in the literature. Varying treatment modalities such as percutaneous catheter-directed thrombolysis, aspiration, embolectomy, segmental aneurysm resection and ligation have been described in the literature for acute limb ischemia secondary to thrombosed fistula. The surgical approach aims to restore vascular patency, arterial stenosis and recurrence of acute limb ischaemia. This case series describes three cases of acute limb ischaemia due to a thrombosed fistula with a embolectomy via arterialized vein graft and ligation of the fistula at juxta-anastomosis. The clinical management and learning experience are shared within the report. This case report would timely contribute to the growing literature on thrombosed vascular access associated with acute limb ischaemia.

INTRODUCTION

Acute limb ischaemia (ALI) is a surgical emergency requiring urgent intervention. Upper limb ALI is commonly due to cardiac embolism and steal syndrome following vascular access creation. With the increasing global incidence of end-stage renal failure (ESRF) patients and advancement in medical care, multiple venous access creation prevails to be a necessary measure following aneurysmal degeneration and thrombosis of vascular access.[1] Chronic thrombosis of vascular access routinely does not require routine intervention unless associated with other complications. ALI is an infrequent complication of thrombosed vascular access, which occurs following multiple cannulations, fistula massage, dislodged free-floating thrombus and retrograde propagation to the arterial anastomosis. There are only 16 reported cases, with digital ischaemia being the most typical presentation.[2-4] We presented three cases of upper limb ALI secondary to a thrombus involving a brachial fistula. These cases would contribute to the growing literature on thrombosed vascular access associated with ALI with an alternative surgical approach.

CASE PRESENTATION

Case 1

A 66-year-old man presented following 24-hour symptoms of the right hand and distal forearm coldness and pain. He had a right brachiocephalic fistula (BCF) created 7 years ago, which failed to mature. Right brachio-basilic fistula was followed by transposition 6 years ago and was functional for 3 years. He was on regular dialysis via the right cuffed catheter.

There was an aneurysmal venous limb, and no thrill felt. His fingers, thenar and hypothenar eminence appear cyanosed (Figure 1a). He had a weak grip test and intact sensation, and prolonged capillary refill time was observed.

Computed tomography angiography (CTA) upper limb shows a thrombosed right BCF. Patent brachial artery down to a proximal third of radial and ulnar artery on delayed images. Faint opacification is seen distal to it due to heavy calcification.

We performed embolectomy in this case series via venotomy adjacent to juxta-anastomosis and ligation of venous limb. He had a stormy recovery requiring intensive care unit care, most likely due to reperfusion injury. His upper limb had a poor recovery, and the patient was counseled for above elbow amputation, which he refused. He passed away at home 1 month later.

Case 2

A 68-year-old woman presented with acute onset of right-hand pain and coldness while undergoing regular haemodialysis in our facility. She had multiple failed venous access and was dialysing using the right BCF, which was created 8 years ago and used for 6 years. She was on regular dialysis via right cuffed catheter when she complained of sudden pain and coldness 2 hours through her dialysis. Her dialysis was stopped due to worsening symptoms, and she was referred immediately to the surgical team.

Her fingers were cold with delayed capillary filling. Fingers appear cyanosed with peripheral capillary oxygen saturation ranging from 60 to 80% (Figure 1b). She had no muscle weakness; however, there was numbness over her fingers. The thrombosed arteriovenous fistula (AVF) had a pseudoaneurysm with no palpable thrill.

CTA shows thrombosed right BCF with non-opacification in the distal brachial artery measuring 2.7 cm in length with circumferential calcification of the right radial and ulnar arteries. Faint opacification is seen in the radial and ulnar

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Table I: Perioperative Outcome

	Case 1	Case 2	Case 3
Pre-op CK	7685 U/L	31 U/L	679 U/L
Thrombus	A short segment from the radial artery and distal brachial artery	Short segment thrombus at the distal brachial artery segment	6cm long thrombus from distal brachial and ulnar
Post embolectomy Backflow:			
Brachial	Good	Good	Good
Radial	Poor	Minimal	
Ulnar	Poor	Minimal	Good
Intra-op Finding	Unable to pass beyond 10cm from bifurcation likely due to heavy calcification	-	Unable to locate the radial artery due to collaterals formation
Post-op Pulse:			
Brachial	2+	2+	2+
Radial	Absent	2+	Absent
Ulnar	Absent	1+	Absent
Post-op HDS:			
Brachial	Biphasic	Biphasic	Biphasic
Radial	Absent	Biphasic	Biphasic
Ulnar	Absent	Monophasic	Biphasic
CRT Post-op	No Improvement	Improved	No improvement
Post-op CK	Improved	Improved	Improved
Compartment syndrome	No	No	No

Creatinine Kinase (normal range 26-192 U/L)

arteries with normal opacification of the right axillary and subclavian artery.

Following embolectomy, patient discharged well with no motor or neurological deficit 1 year following surgery.

Case 3

A 76-year-old woman, ESRF since 2007, complained of left-hand pain and coldness. She presented to the emergency department 24 hours following her symptoms. She had a left radio-cephalic fistula created 12 years ago, which lasted for 8 years, and left BCF 4 years ago, which thrombosed 3 years later. She has been on dialysis via right radiocephalic fistula since then.

On examination, her left hand was perishing cold with mottling of fingers, thenar and hypothenar eminence up to the mid-forearm. There was evidence of aneurysmal degeneration over the cubital fossa and pseudoaneurysm at the forearm with no palpable thrill (Figure 1c). She complained of pain during passive movement and could move her fingers but could not perform a grip test.

Given Rutherford IIb, she was advised for urgent embolectomy with a possible need for below-elbow amputation. However, she refused surgery then; hence, we proceeded with an imaging investigation and intravenous heparin infusion.

Duplex ultrasound showed thrombosis of the left brachial artery arising from BCF (at its bifurcation) extending distally with no flow to the radial and ulnar arteries.

The patient refused surgery as amputation was the primary concern. She was pharmacologically treated with intravenous heparin infusion and adequate analgesia. She revised her decision after 48 hours as there was no improvement, and an embolectomy was attempted to salvage her limb. Risk of ischaemic reperfusion injury, compartment syndrome and amputation was explained.

Postoperatively, no pulse was palpable; however, the radial and the ulnar signal were biphasic. The hand remained cold, and motor function remained the same. Two days after the embolectomy, she developed acute coronary syndrome during haemodialysis, which gradually deteriorated and succumbed.

All patients had creatinine kinase (CK) taken pre-operatively. An echocardiogram for all three patients did not show any evidence of cardiac thrombus. Computed tomography angiography of upper limb was done for Cases 1 and 2 (Figure 2).

Upon clinical diagnosis of acute limb ischaemia, heparin loading (80 unit/kg) and infusion (18unit/kg) were initiated. Lazy-S-incision was made with a proximal longitudinal incision along the medial border of the biceps, curve at cubital fossa skin fold to join medial border of brachioradialis distally, to expose distal brachial artery, bifurcation, and juxta-anastomosis. Brachial artery proximal to AVF anastomosis, radial, ulnar artery, and juxta-anastomosis were encircled with a vessel loop and vascular clamp (Figure 3).

Bolus heparin (40 unit/kg) was given before venotomy over the juxta-anastomosis, approximately 1 cm away from the anastomotic junction. Embolectomy of the brachial, radial and ulnar arteries was performed with assisted manipulation of Fogarty catheter Size 2 and 3. Heparin saline was flushed into the radial and ulnar arteries. Adjacent to venotomy, a non-absorbable suture was used to ligate close to the

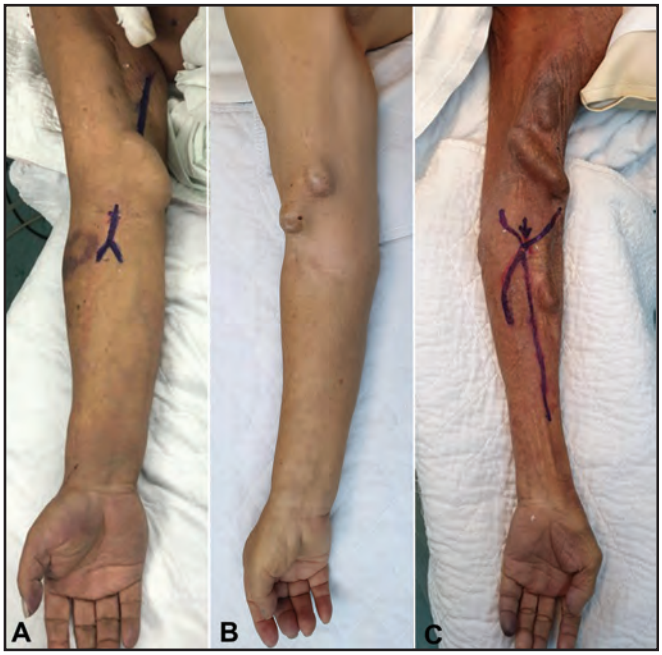

Fig. 1: Described cases of acute limb ischaemia. Brachio-cephalic fistula (BCF) failed to mature, brachio-basilic fistula transposition with evidence of aneurysmal vein (A), BCF with pseudoaneurysm at the site of needling (B), RCF with forearm pseudoaneurysm and BCF with an aneurysmal vein

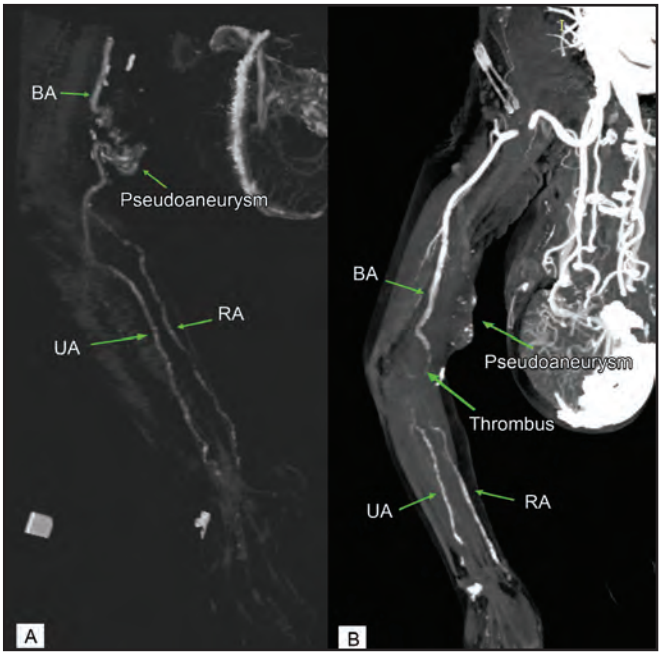

Fig. 2: CTA Images showing thrombosed right BCF. Patent brachial artery down to a proximal third of radius ulnar artery on delayed images. Faint opacification was seen distal to it due to heavy calcification (A), thrombosed right BCF with non-opacification in distal brachial artery measuring 2.7cm in length (B)

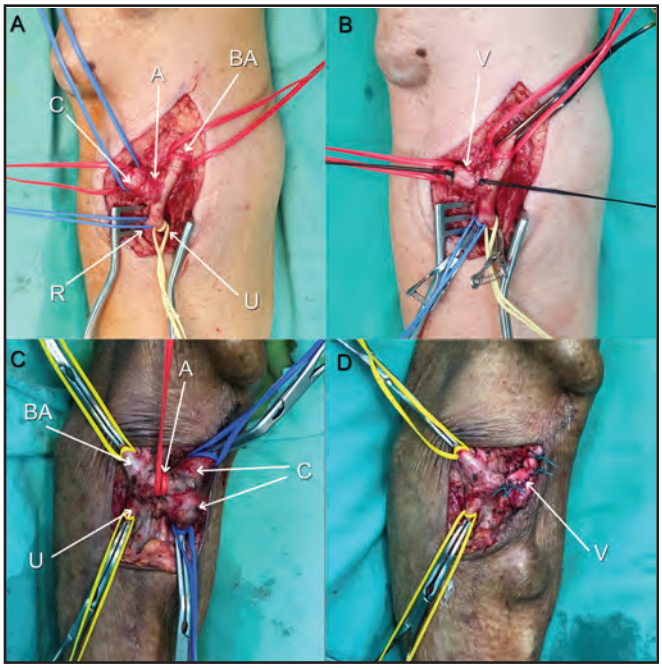

Fig. 3: Exposed vessel at cubital fossa, including arteriovenous anastomosis and juxta-anastomosis. Pre and post embolectomy images and site of venotomy at juxta-anastomosis. Case 2 (A, B) and Case 3 (C, D). BA: brachial artery; U: ulnar artery; R: radial artery; C: cephalic vein; A: anastomosis; V: venotomy

anastomotic junction. In our setting, we used coated polyester (Ethibond Excel) or Silk 1 to ligate approximately 2 mm from the anastomotic junction (Figure 3).

Refer to Table I for perioperative outcome findings.

DISCUSSION

Acute upper limb ischaemia is commonly associated with steal syndrome following vascular access creation and cardiac emboli. ALI associated with thrombosed AVF is under-reported, with the postulated hypothesis being it is due to significant aneurysmal venous degeneration causing distal arterial emboli. In ESRF patients with multiple comorbidities, a degenerative atherosclerotic vessel with collaterals and aneurysmal degeneration are common.[1,4]

Based on the PubMed literature search, 11 publications were related to our described cases, with 14 cases of ALI in thrombosed native fistula and 2 cases in polytetrafluoroethylene grafts.[2-4] All cases are thrombosed brachial fistula except two, from radial cephalic fistula. Most fistula were spontaneous ALI except in three cases following fistula massage and one after multiple cannulations.[3,5,6]

ALI is a surgical emergency requiring urgent intervention. Early intervention is of paramount importance than imaging investigation, as irreversible tissue damage may result in amputation. However, in early presentation and ambiguous scenarios, imaging investigation is warranted.

Multiple treatment patterns have been observed from the literature for the management of thrombosed AVF-causing ALI. Measures such as percutaneous catheter-directed thrombolysis, aspiration, embolectomy, segmental aneurysm

resection, and ligation have been described.[7] Catheter-directed thrombolysis has the benefit of being a less invasive procedure and is an ideal choice for distal limb ischaemia. However, there has been a concern about significant haemorrhage associated with thrombolysis. We opted for a surgical approach in our case series as we have no available intervention radiology services at our centre, and through this measure, we were able to intervene in the source of an embolus from a thrombosed fistula.

Elective ligation of the fistula is proven beneficial in high flow steal syndrome, heart failure and post-renal transplant patients.[8] Thrombosed fistula does not typically cause complications that require ligation. Jasinski et al. described a case of ALI following AVF ligation. The learning point from this case is ligation leaving a long stump is a precursor for thrombus and shower embolus. Ligation of the fistula should ideally be 2 mm from the anastomosis.[9]

Surgical embolectomy is the ideal intervention option as it is approachable at the extremity, and the lumen patency can be restored immediately. Embolectomy approach through the arterialised vein graft leaves the native artery undisturbed from potential stenosis. Also, following ligation of the fistula, potential recurrent limb ischaemia is preventable as the cause of such cases is from a thrombosed venous limb.

CK should be sent in a delayed presentation as a guide for intervention. High CK has a high predictor of compartment syndrome, ischaemic reperfusion injury and amputation.[10] As in our case, two patients who presented 24 hours following the onset of symptoms with high CK and distal vessel calcification contributed to poor outcomes despite surgical intervention.

CONCLUSION

Thrombosed AVF is usually uncomplicated and adherent to the wall. However, there is a high risk of thrombus dislodgement and embolism is largely underestimated. Early presentation and intervention are vital for good surgical outcome.

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DECLARATION

Funding not applicable.

CONFLICTS OF INTEREST

On behalf of all authors, the corresponding author states no conflict of interest.

ETHICAL APPROVAL

This manuscript is in line with local ethics protocol.

CONSENT TO PARTICIPATE

Patient and next of kin participation is entirely voluntary for this case report.

CONSENT FOR PUBLICATION

Written consent was obtained from the patient and next of kin for publication of their clinical details along with accompanying images.

CONTRIBUTORS

JM was involved in clinical care, conceptualisation and drafting of the manuscript. MTY and RH were involved in clinical care, revision of the manuscript for intellectual content and approval of the manuscript. YTT and TP are involved for the important intellectual content of the manuscript. All the authors read and approved the final manuscript.

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Ceftazidime-induced neurotoxicity in a peritoneal dialysis patient

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SUMMARY

Cephalosporins are commonly used broad-spectrum antibiotics in clinical practice. However, neurotoxicity is an underrecognized side effect of this antibiotic group, especially cefepime and ceftriaxone, owing to their special pharmacokinetic profile. It can manifest as encephalopathy, seizures and myoclonus, which may share a similar presentation as other acute pathology. The risk of neurotoxicity is higher among elderly and renal failure patients. This case involved a lady in her 60's with end-stage kidney disease on automated peritoneal dialysis and major depressive disorder, who developed acute psychosis and myoclonic seizures during the treatment for peritoneal catheter exit site infection using high-dose ceftazidime. Symptoms resolved after discontinuation of ceftazidime and use of antipsychotics and antiepileptics. Patient was discharged well, with normal neurology and mental status. This case illustrated the difficulty of distinguishing treatment-induced neurotoxicity from other concomitant acute medical illnesses and the possible deterioration of preexisting psychiatric illness. Thus, clinicians must be aware of appropriate antibiotic dosage and able to identify the predisposing factors of neurotoxicity. Although cephalosporin-induced neurotoxicity is mostly self-limiting following discontinuation of the antibiotic, severe cases may need additional supportive measures.

INTRODUCTION

Cephalosporins are among the commonest prescribed antibiotics in clinical practice owing to the broad spectrum of coverage. Hypersensitivity reactions are most commonly reported with the use of cephalosporins, ranging from mild cutaneous reactions to severe anaphylaxis, followed by acute interstitial nephritits and *Clostridium difficile* infection.[1] In fact, cephalosporins can also potentially cause encephalopathy, seizure and myoclonus due to their pharmacokinetic properties. Literature reported that neurological adverse effects are most evident with cefepime, followed by ceftriaxone, ceftazidime, cefotaxime, and cefazolin, in descending order.[2] A study reported a prevalence rate of 15% for cefepime-induced neuropathy among critically ill patients in the intensive care unit (ICU).[3] However, the true prevalence rate of cephalosporin-induced neurotoxicity was masked by underrecognition of the problem due to concomitant medical illness and underreporting due to a lack of objective laboratory diagnosis.

Here, we present a case of a 64-year-lady with psychiatric illness and end-stage kidney disease (ESKD) on automated peritoneal dialysis (APD) who developed encephalopathy and myoclonic seizures while being treated with high dose ceftazidime for *Pseudomonas aeruginosa* catheter site infection.

CASE PRESENTATION

This is a 64-year-old Malay woman, with a background history of diabetes mellitus type II, hypertension, dyslipidemia, ischaemic heart disease and anuric ESKD on APD. She also had major depressive disorder (MDD), which was stable on medications under psychiatric follow-up. She was recently admitted to nephrology ward in another hospital, being treated for local peritoneal dialysis catheter exit site infection. Swab culture yielded *Pseudomonas aeruginosa*. She was planned for outpatient treatment of oral Ciprofloxacin 250 mg twice daily and intravenous (IV) Ceftazidime 2 g on alternate days. On day 6 of treatment, after the third dose of IV Ceftazidime, she became aggressive and started to have auditory and visual hallucinations. Family members also noticed paroxysmal abnormal jerking movements of her limbs. She did not have a fever or abdominal pain since being discharged from the nephrology unit. APD was uneventful at home. She was brought to our hospital on day 8 of outpatient treatment. The last IV ceftazidime was administered on the day of admission before being admitted. Her body weight was estimated to be 60 kg. On presentation, she was afebrile. Her blood pressure and heart rate were 155/84 mmHg and 103 beats per minute, respectively. She was not tachypneic and saturated well on room air. She was disorientated, and Glasgow Coma Scale was 10 (GCS E4V1M5). Cardiovascular and respiratory system examinations were normal. Neurological examination of the limbs and cranial nerves were unremarkable, and there was no abnormal movement noted. There was no sign of acute peritonitis. Exit site was clean and dry.

Full blood count showed a normal total white cell count 8.0 x 10^3/µL, neutrophils 4.69 x 10^3/µL. The urea was 11.6 mmol/L, sodium was 146 mmol/L, potassium was 4.1 mmol/L, and creatinine was 975µmol/L. Serum albumin was 28 g/L, and her liver enzymes were normal. Corrected serum calcium was 2.20mmol/L. Magnesium level was 0.9 mmol/L, and phosphate level was 2.26 mmol/L. C-reactive protein was 7.15 mg/L, which was mildly raised. Blood glucose ranged

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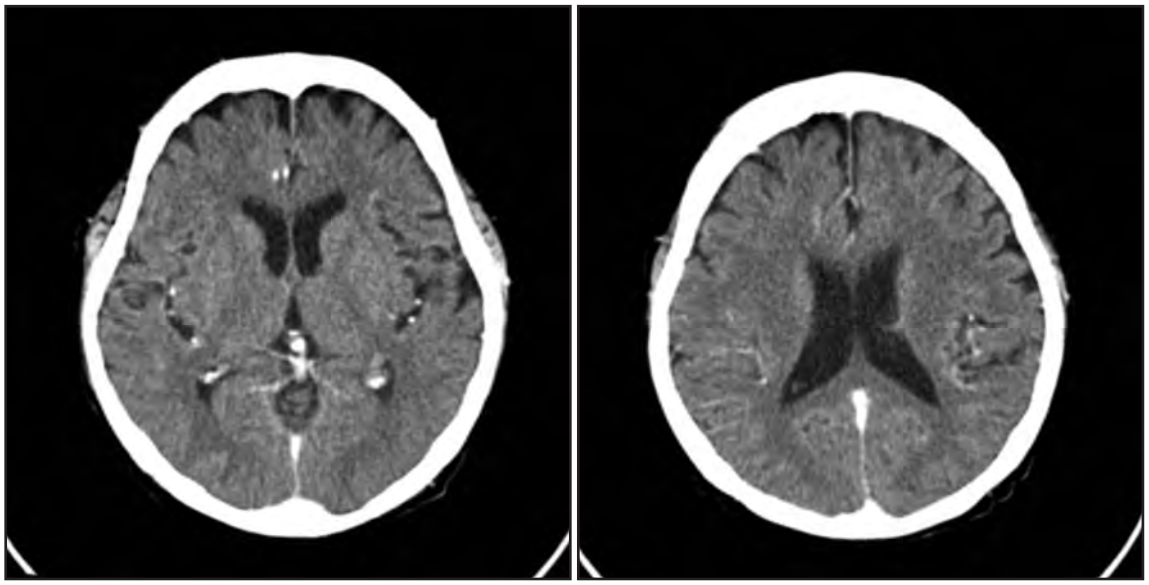

Fig. 1: Contrast-enhanced computed tomography of the patient's brain on day 1 of admission

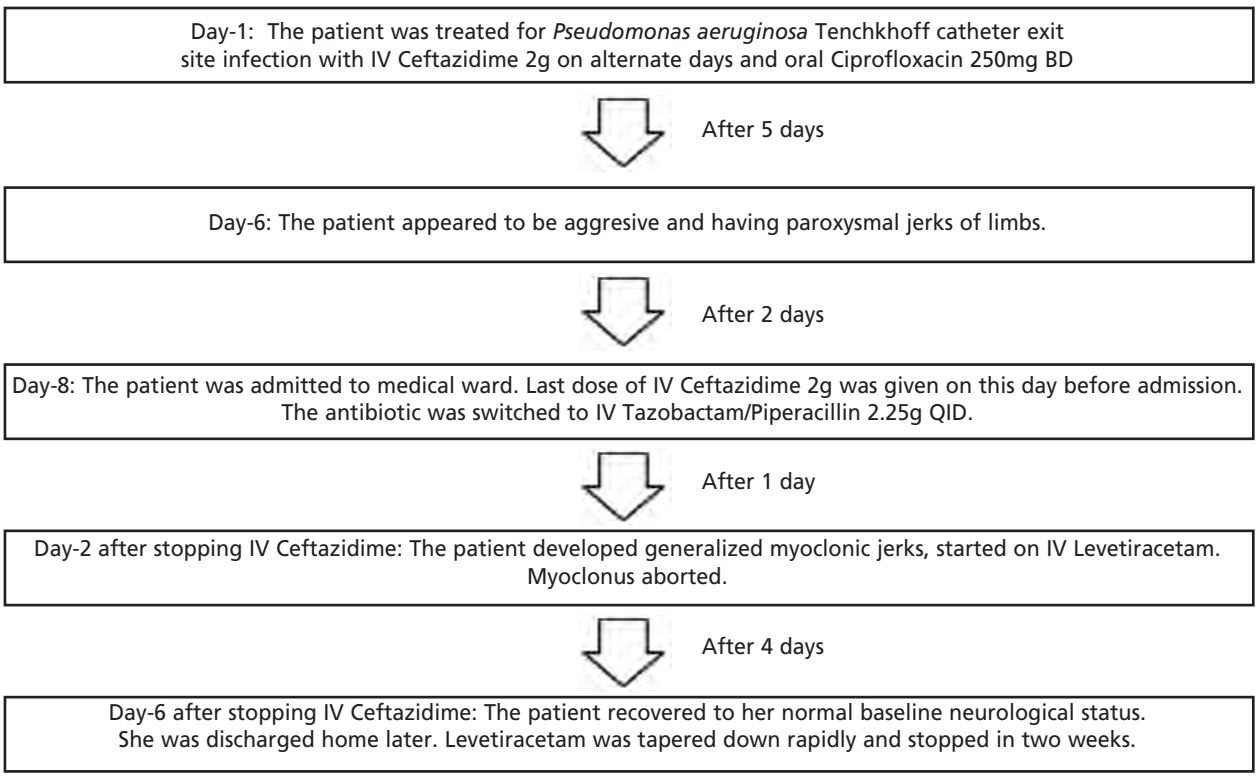

Fig. 2: Timeline of the patient's presentation

from 6.8-9.9mmol/L. Chest X-ray was unremarkable. Contrast-enhanced computed tomography (CT) of the brain showed only age-related cerebral atrophy, without any significant abnormality (Figure 1). Lumbar puncture was done. Cerebrospinal fluid (CSF) analysis showed only mildly elevated protein 0.67 g/L, but the other parameters are not suggestive of acute infection. Blood and CSF cultures were negative.

In ward, IV ceftazidime was changed to IV piperacillin/tazobactam for empirical treatment of sepsis. Oral ciprofloxacin was continued. Oral fluconazole was given as fungal prophylaxis. Gentamicin cream 0.1% was given as topical antibiotic. She was intermittently aggressive and had incoherent speech. Haloperidol was started to control her positive behaviours. On second day of admission, she developed myoclonic jerks of all limbs and face in ward and was treated with intravenous levetiracetam. Repeated CT imaging of the brain was unremarkable. Blood culture and CSF culture showed no bacterial growth. Subsequently, the patient still appeared lethargic but gradually improved to her baseline mental state on day 6 of admission. Electroencephalogram (EEG) was not done in time due to the complete neurological recovery. Intravenous antibiotics were continued for another 2 weeks for the treatment of exit site infection. Levetiracetam dose was tapered down and discontinued over 2 weeks. She was discharged well without any neurological deficit (Figure 2).

DISCUSSION

The mechanism of cephalosporins-induced neurotoxicity involves the inhibition of gamma-aminobutyric acid (GABA) binding to its receptors, leading to the hyperexcitability of neurons. Other mechanisms, like induction of endotoxins and facilitation of excitatory neurons, especially N-methyl-D-aspartate (NMDA) receptors, were also proposed.[4] Ceftazidime is not metabolised in the body, and up to 90 percent is excreted unchanged in the urine via the kidneys by glomerular filtration.[5] Therefore, neurotoxicity is common in elderly and renal impairment due to a longer half-life of the drug. Patients with underlying cerebral disease are at an even higher risk of developing neurotoxicity.[6] Clinical presentations of ceftazidime-induced neurotoxicity are heterogenous. A review of 12 cases of ceftazidime-induced neurotoxicity in patients with a mean age of 65 years and variable degree of renal insufficiency by Chow et al showed that the most frequent symptoms were confusion, myoclonus and generalised seizure, with incidence rates of 91%, 50% and 8%, respectively.[7] This case report highlighted the fact that this patient had an acute infection, ESKD and underlying psychiatric illness made the diagnosis of cephalosporin-induced neurotoxicity difficult as there were many other more common differential diagnoses, including uremia, electrolyte imbalance, major depressive disorder with psychosis, acute meningoencephalitis and septic encephalopathy. However, the blood and imaging results were not indicative of any of these factors. In this case, the diagnosis of ceftazidime neurotoxicity was made by exclusion of other common causes, and based on the temporal association of the development of encephalopathy and myoclonus after starting ceftazidime, and the resolution following discontinuation of cephalosporins. EEG is also useful to support the diagnosis in this case, though the findings are not specific.[6,7]

In peritoneal dialysis patients with exit site infection, intraperitoneal (IP) route of antibiotic would be a preferable choice.[8] Combination of ciprofloxacin and ceftazidime is given in patients with slow-resolving or recurrent Pseudomonas aeruginosa exit-site infection.[8] Intermittent dosing of IP ceftazidime (1000–1500 mg/day) may be given as day-dwell in patients on APD.[9] Alternate day dosing of IV ceftazidime of 2 g in this patient may lead to high peak dose on administration, which might have predisposed her to higher risk of neurotoxicity, in addition of age factor, evidence of old cerebral infarct and ESKD. A pharmacokinetic study suggested intravenous administration of 15 mg/kg ceftazidime in APD patients every 24 hours can be used to treat systemic or intraperitoneal infections, but data on the pharmacokinetic profile after repeated administration still lacks.[10] It is not common to monitor blood cephalosporin levels, thus careful monitoring for clinical manifestations of cephalosporin-induced neurotoxicity among these vulnerable groups of patients is very important. The typical time of onset of neurotoxicity ranges from two to ten days of initiation of the cephalosporin. It resolves 2–7 days following discontinuation. Discontinuation of cephalosporins and supportive care are usually sufficient.[6,7] Intermittent hemodialysis was described as a treatment for cephalosporin-induced neurotoxicity, owing to the dialyzability of cephalosporin.

CONCLUSION

Clinicians must be aware and able to identify high-risk patients and recognise the clinical manifestations of cephalosporin-induced neurotoxicity. The dosage of antibiotics has to be adjusted according to individual renal functions, body weight and clinical indications. Supportive care and withdrawal of cephalosporins are the mainstay of the treatments, but specific measures i.e. antiepileptics, antipsychotics or sedations are sometimes needed depending on the disease severity.

ETHICAL ISSUES

Written consent to publish this case report was taken from the patient. This case report has obtained approval from the National Medical Research Register (NMRR), Ministry of Health Malaysia: NMRR-21-1429-60929

DECLARATIONS OF INTEREST

None

DISCLOSURE

Financial support: none

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The rare case of synchronous multiple primary malignancies of invasive ductal carcinoma and diffuse large B-cell lymphoma in a single patient: A diagnostic conundrum

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SUMMARY

Synchronous multiple primary malignancies (SMPMs) denote the discovery of a second primary cancer within 6 months detection of a first primary cancer. Herein, we illustrate a rare case of SMPMs in a 62-year-old lady who had initially been diagnosed with primary breast invasive ductal carcinoma. A left mastectomy with axillary clearance was performed following a biopsy of a left breast lesion revealing an extensive high nuclear-grade ductal carcinoma in situ. Unfortunately, she presented to us with new complaints 2 months later with right lymphadenopathy and constitutional symptoms for a month. Excisional biopsy of a right cervical node was confirmative of a diffuse large B-cell lymphoma. She responded well to Rituximab–Cyclophosphamide–Doxorubicin–Vincristine–Prednisone (R-CHOP) regime for one cycle, followed by R-CHP regime for five cycles regimen. The presence of dual primary malignancies within 6 months fulfilled the diagnosis of SMPM in our patient. The clinical quandary in such cases may influence the diagnostic approach and treatment options. Hence a thorough clinical assessment and histopathological staging of both malignancies, as well as interdisciplinary team discussions, are essential.

INTRODUCTION

Multiple primary malignancies (MPMs) were initially described in 1889 by Billroth and reported in 1932 by Warren and Gates.[1] MPMs are defined as the presence of two or more distinct histological malignancies in the same person. Based on the time of diagnosis, MPMs can be further divided into two categories; synchronous multiple primary malignancies (SMPMs) are when the second primary cancer is diagnosed within 6 months, while metachronous multiple primary malignancies (MMPMs) are whenever the second primary cancer is diagnosed after 6 months detection of the first primary cancer. In order to establish the diagnosis, these two malignancies should not be due to tumour recurrence, metastasis, or local spread.[2]

SMPMs combination of a solid and haematological cancers are uncommon. For example, the simultaneous occurrence of a primary breast cancer and lymphoid tissue malignancy has rarely been reported in the literature,[3] though breast cancer is the most commonly diagnosed malignancy following treatment for Hodgkin's lymphoma.[4] Herein, we report a rare case of SMPMs involving an elderly women diagnosed with diffuse large B-cell lymphoma (DLBCL) who had been diagnosed with primary breast invasive ductal carcinoma 2 months prior. We aimed to highlight the diagnostic dilemma and therapeutic approach in our case, as well as provide a comprehensive discussion on the prevalence, risk factors and management approach in MPMs to promote awareness among clinicians on this unusual clinical condition.

CASE PRESENTATION

This is a case of a 62-year-old lady who presented with prolonged intermittent fever associated with cough, lethargy, marked loss of appetite and weight of nearly 8 kg for over a month with no night sweat. Her hypertension and dyslipidaemia were well controlled on medications, and she was on sulfasalazine prescription only for the past 18 years for rheumatoid arthritis. She neither smoked nor was she an alcoholic, however had a strong family history of lung cancer in her immediate family. Despite the completion of two courses of oral antibiotics, her symptoms persisted. Physical examinations were unremarkable.

Routine blood tests were equivocal with no derangement in full blood count parameter (white blood cell 4.85 × 10^3/uL, haemoglobin 12 g/dL, platelet 199 × 10^3/uL). Viral infective screening for human immunodeficiency virus (HIV), hepatitis B and hepatitis C, as well as acid-fast bacilli screening, were all negative. C-reactive protein (CRP) was raised (44.9 mg/L) but blood culture and sensitivity revealed no growth and she was afebrile in ward. However, lactate dehydrogenase (LDH) (2150 U/L), erythrocyte sedimentation rate (40 mm/Hr), and Ca-125 (2714.8 U/ml) were significantly elevated. Screening with abdominal ultrasound showed multiple nodular

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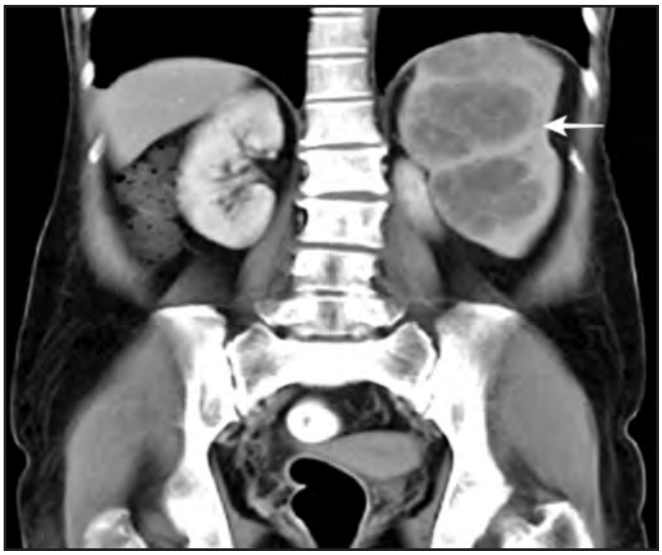

Fig. 1: Contrast-enhanced CT thorax, abdomen, and pelvis image. Multiple hypodense splenic lesions of varying sizes, with the largest measuring 5.4 cm × 6.8 cm

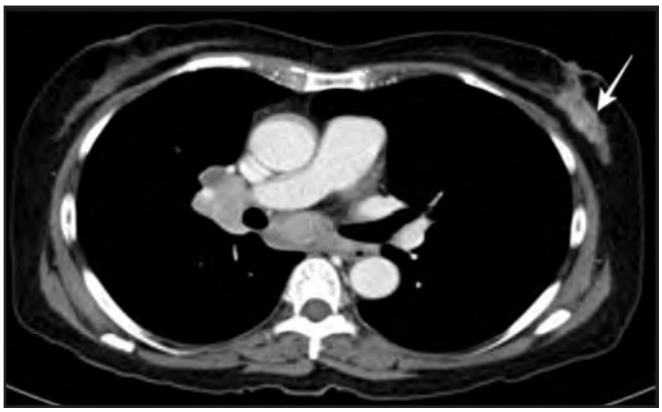

Fig. 2: CT scan image. An ill-defined enhancing lesion at the outer quadrant of the left breast

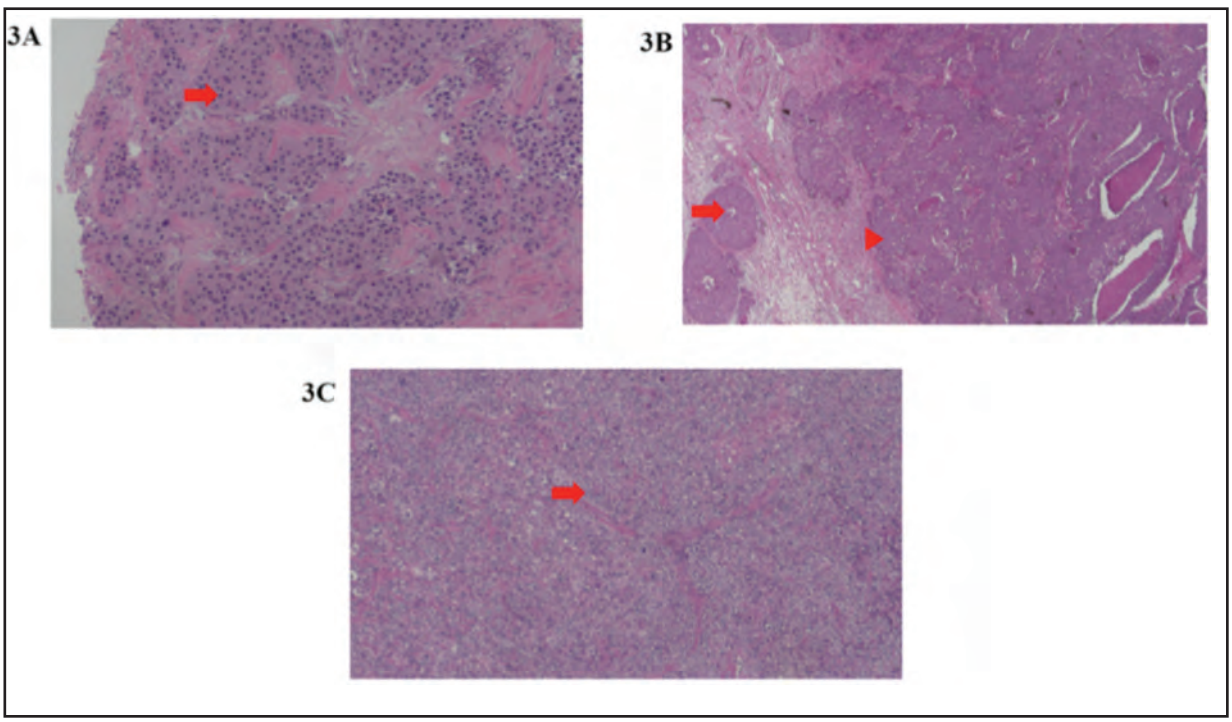

Fig. 3: Histopathological images. (A) Tru-cut biopsy of the breast showed extensive DCIS, composed of malignant cells with moderate to marked nuclear atypia filling the ducts (red arrow) with preserved myoepithelial lining (Haematoxylin & Eosin (H&E), 10×). (B) The mastectomy resection revealed multifocal invasive ductal carcinoma (read arrow head) in the background of extensive DCIS of moderate to high nuclear grade (red arrow) with central comedonecrosis and microcalcification (H&E, 4×). (C) Biopsy of the right lymph node showed diffuse and large malignant lymphoid cells (red arrow) with predominantly atypical centroblasts (H&E, 4×)

hypoechoic lesions within the spleen, with the largest measuring 5.8 cm × 4.4 cm. Differential diagnoses at that point include splenic abscess or a primary splenic tumour (lymphoma) or a splenic metastasis. She was empirically treated for splenic abscess with intravenous ceftriaxone. Subsequent contrast-enhanced computed tomography of the thorax, abdomen and pelvis confirmed the presence of multiple ill-defined splenic nodules that were detected on ultrasound. The largest nodule measures 5.4 cm × 6.8 cm (Figure 1). The lesions appeared heterogeneous with enhancing septae with no calcification. There was also an inadvertent finding of an ill-defined enhancing lesion at the outer quadrant of the left breast measuring 1.3 cm × 2.9 cm × 1.8 cm (Figure 2) with multiple mediastinal adenopathies

in the prevascular space, right para-trachea, pre-trachea, sub-carina and right hilar, as well as evidence of bilateral pulmonary lymphatic infiltration. The largest lymph node was noted at the subcarinal, measuring 2.3 cm × 4.6 cm × 5.9 cm. Mammography was performed showing suspicious pleomorphic clusters of microcalcification at the center outer quadrant of the left breast (BIRADS 5) and an ultrasound-guided tru-cut biopsy showed extensive high nuclear grade ductal carcinoma in-situ (DCIS) (Figure 3) with comedonecrosis and dystrophic calcification (Figure 3A).

Various subspecialties were referred for multidisciplinary discussion, including infectious disease, haematology, respiratory, cardiothoracic, oncology, surgical and radiology. Due to lymphoma suspicion, the patient was advised to undergo an imaging-guided spleen nodule biopsy at another equipped tertiary facility, but she declined due to complication concerns. She was treated as advanced breast cancer with splenic lesion to rule out lymphoma or metastasis and mediastinal adenopathy. Consultation with oncologist is suggested for wide local excision/mastectomy.

A left mastectomy with axillary clearance was performed within 3 weeks with histopathological results revealing extensive DCIS of moderate to high nuclear grade with central comedonecrosis and microcalcification (Figure 3B). Only 1 out of 17 axillary lymph node was identified with evidence of metastasis. Hence, a diagnosis of multifocal invasive carcinoma of no special type with Nottingham's Histologic Score 7 (Grade 2) was made based on histopathological evidence, indicating malignancy with moderate differentiation. Based on tumour node metastasis staging system, a stage pT1b (>3) pN1a (AJCC 8th Edition) was given. Immunohistochemical analysis demonstrated the absence of oestrogen and progesterone receptors and the presence of HER2. Intravenous antibiotic was completed for 2 weeks, and she was discharged well a week post-operation.

Uncertainty of multiple mediastinal adenopathies and splenic lesion origin have hindered the commencement of adjuvant chemotherapy for breast cancer, as it could aggravate cytopenia if lymphoma was the underlying cause. Hence, endobronchial ultrasound biopsies were performed. However, the results were inconclusive, with only scanty blood seen. Eight weeks after mastectomy, she was admitted while awaiting consultation with the cardiothoracic team with complaints of right neck swelling, intermittent fever, and weight loss. On examination, a right cervical node was palpable measuring 2 cm × 3 cm. A tissue biopsy taken revealed diffuse and large malignant lymphoid cells with predominantly atypical centroblasts (Figure 3C) (homogenous CD20+, CD10+ (70%) and BCL6+ (90%)). There were numerous apoptotic bodies and tangible body macrophages, and the presence of proliferation index (Ki67) was 75% highly suggestive of a DLBCL. Following consultation with oncology, she was scheduled to receive doxorubicin and cyclophosphamide as adjuvant chemotherapy for breast cancer, which is also indirectly used to treat lymphoma.

Hence, the patient was then referred to a tertiary centre for lymphoma treatment with Rituximab–Cyclophosphamide–Doxorubicin–Vincristine–Prednisone (R-CHOP) regime. In between treatments, repeated computed tomography scans after the third cycle of chemotherapy showed a significant reduction in the size of cervical, mediastinal, and hilar nodes with smaller splenic lesions, indicating treatment response. Fluorodeoxyglucose-Positron emission tomography (FDG-PET) scan performed 8 weeks following the completion of chemotherapy showed no evidence of local, regional nodal or systemic metastasis. She has been keeping well since and is on regular monitoring.

DISCUSSION

The incidence of MPMs is rare but their prevalence has been increasing. According to Warren and Gates criteria, each tumour must be histopathologically confirmed, and distinct from each other, and the probability of one metastasising to another must be ruled out.[1] Guidelines issued by the International Agency for Research on Cancer (IARC) in 2004 suggested SMPMs could be used when the second primary cancer is detected within 6 months, whilst the term MMPMs are used whenever the second primary cancer is detected after 6 months from the first primary cancer being diagnosed.[2] The synchronous type is less common, accounting for about 30% of all MPMs.[5]

In a study by Lv et al.[6], it was observed that among 161 MPMs patients, 98 patients (60.9%) were male and the median age in the synchronous cancer group was 64 years old. In addition, adenocarcinomas (55.1%) and squamous cell carcinomas (23.1%) were the most commonly reported types of pathology, while sarcomas (1.3%) and haematological malignancies (6.4%) were among the least reported. The digestive (48.7%), urogenital (21.8%) and respiratory (15.4%) systems were the three leading systems in the synchronous tumour group. In contrast, our patient is a lady with primary tumours of the breast and haematological origin.

The exact pathophysiology of MPMs remains largely unknown.[5] Common risk factors may include inherited cancer predisposition, cancer-promoting aspects of lifestyle, hormonal and environmental factors, treatment for previous primary cancer and increased surveillance among cancer survivors.[5] Additionally, people with rheumatoid arthritis, such as our patient, were also found to have an increased risk of lung cancer and lymphoma than the overall population.[7] It was hypothesised that a long-term immunologic stimulation may increase the risk of malignant transformation of immune system cells (which may lead to clonal selection and predispose CD5+ B cells to malignant transformation), reduce the number of T-suppressor lymphocytes (including those directed against the pro-oncogenic Epstein–Barr virus) and inhibit the natural killer cell activity in the blood, synovial fluid, tissue and lymph, thus increasing the risk of lymphoma.[3] Although immune dysregulation is a feature of both malignancies and autoimmune diseases, the precise mechanisms underlying this susceptibility remain uncertain.

Woo et al.[8] found that the prevalence of synchronous breast cancer with non-Hodgkin's lymphoma (NHL) or a DLBCL was only at 29.7%. This indicates that the co-occurrence of breast malignancy and DLBCL is rare,[7] even though breast cancer may be diagnosed following treatment of Hodgkin's

lymphoma.[4] Our patient initially presented with constitutional symptoms, raised LDH, ESR and Ca-125, with significant imaging findings on the breast, spleen and mediastinal. It was possible that both breast cancer and lymphoma were present at the time, however, due to a lack of histopathological evidence to suggest lymphoma at the time, the diagnosis of breast cancer was established first. It was not until she presented again 2 months later with a right cervical lymphadenopathy, made an excisional biopsy possible to confirm the diagnosis of DLBCL. This was a point of a diagnostic quandary for us as an excisional biopsy to the mediastinal region and spleen was difficult to perform[9] when she first presented. Furthermore, obtaining a tissue biopsy from a difficult location requires invasive procedure and speciality that are not typically offered by many institutions.[10]

The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F- FDG PET/CT) is a new imaging modality that can distinguish between benign and malignant cells based on their higher uptake by tissues with increased glycolysis. PET scans, when combined with minimally invasive procedures in interventional radiology, can be useful in identifying additional primary malignancies. The clinician should strive to obtain histological diagnosis under such circumstances as misinterpretation of PET scan will be catastrophic as it might steer the direction of care towards palliation. Other modalities of molecular cytogenetics study such as fluorescence in-situ hybridisation (FISH) and the presence of BCL6 gene are highly associated with lymphoma. From a diagnostic standpoint, early detection and confirmation of such tumours are critical to determining the best treatment option for patients.

There is no universal protocol for treating synchronous multiple cancers. SMPMs treatment decisions should be individually tailored with a multidisciplinary approach. Consensus on therapeutic strategies should be adequately communicated to patients to ensure transparency and understanding. Our case had undergone a mastectomy following the diagnosis of DCIS, followed by chemotherapy after the diagnosis of DLBCL was established later. Prognostic factors for each type of tumour play an important role when deciding on treatment strategies. The possibility of a curative approach, the palliative situation, the degree of metastasis for each tumour, and the complications anticipated from anticancer therapy are significant points to consider when making clinical decisions.[2]

CONCLUSION

Despite the rarity, the incidence of MPMs appears to be on the rise. Therefore, physicians should be vigilant about the possibility of patients being at risk for new and separate cancers. MPMs may pose as diagnostic and therapeutic dilemmas. Hence, a thorough clinical and pathological staging of both malignancies, as well as interdisciplinary team discussions are required to determine the best management plan for the patients. Future research is warranted, particularly in the treatment of patients with synchronous or metachronous multiple primary cancers.

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Foetal pelvic and left lower extremity lymphatic malformation

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SUMMARY

We report a case of foetal pelvic and lower limb lymphatic malformation that resulted in a fatal complication. At 31 weeks 4 days, an antenatal ultrasound revealed an isolated left lower limb swelling with no other abnormalities, which was possibly a haemangioma. At 38 weeks, a baby boy weighing 4.59 kg was delivered via elective caesarean section. Postnatal magnetic resonance imaging at 2 months revealed features consistent with a lymphatic malformation with both micro and macro-cystic components involving the pelvis, left thigh and left lower limb. He was planning for sirolimus therapy but was not executed due to his parents' indecision. Soon after, he developed an acute deterioration due to an intra-lymphatic bleed, which resulted in bowel ischaemia and perforation, which resulted in metabolic acidosis, renal failure and death.

INTRODUCTION

Vascular anomalies are classified as vascular tumours which include proliferative changes of endothelial cells (EC) and vascular malformations, which are structural vascular abnormalities without EC proliferation. Lymphatic malformation is one of the vascular malformations, and it is a congenital lymphatic dysplasia. It can be categorised as macrocystic, microcystic and mixed type.[1] After venous malformations, lymphatic malformations are the most common type of vascular. They are commonly found in the neck (70–80%) or in the axillary region (20%) and are hardly seen in the pelvis or extremities.[2] Approximately half of these lesions are discovered at birth and up to 90% become visible by the age of 2 years.[3] There have been few reports of neonatal lower limb lymphatic malformation that were diagnosed in the antenatal period and had various outcomes including termination of pregnancy, resolution after sclerotherapy or surgical resection.[4] We present a case of newborn with pelvic and left lower limb lymphatic malformation that resulted in a lethal complication.

CASE PRESENTATION

Madam S, the mother of Baby A is a 31-years-old, chemotherapy staff nurse and this is her third pregnancy. Her previous two pregnancies took place seven and three years ago. Both babies were born at full term via spontaneous vertex deliveries. They are currently in good health. There was no family history of congenital anomalies. Both parents had no prior medical illness. Early booking was done at 11 weeks and 1 day period of amenorrhoea (POA). A viable foetus was seen on transabdominal sonography (TAS). The crown rump length was 49.8 mm and the revised expected date of delivery corresponded with her last menstrual period. As for her antenatal history, Madam S was treated for vulvovaginal candidiasis with Clotrimazole pessary at 12 weeks POA. She also had iron deficiency anaemia which was treated with oral haematinics and parenteral iron at 33 weeks POA. Madam S has also admitted at 27 weeks POA for premature contraction and received dexamethasone in ward. During admission, her TAS revealed no abnormalities. At 29 weeks POA, Madam S developed herpes zoster and was treated successfully with oral Acyclovir.

Madam S was admitted for contraction pain and reduced foetal movement at 31 weeks and 4 days POA. Her vital signs were stable and her physical examination in the hospital was unremarkable. However, her TAS revealed that the foetus had left lower limb swelling. She was referred to the maternal-foetal medicine (MFM) specialist for confirmation of scan findings. Upon review by the MFM specialist, the left lower limb swelling was thought to possibly be a left lower limb haemangioma. Subsequent TAS showed that the foetus was growing, and there was no sign of hydrops. The parents were counselled regarding the potential outcome. Due to the foetal left lower limb swelling, Madam S underwent an elective lower segment caesarean section at 38 weeks POA. Baby A was born with a good Apgar score. The birth weight was 4.59 kg, the height was 55 cm and the head circumference was 36 cm.

Baby A was admitted shortly after birth for transient tachypnoea of newborn and left lower limb swelling. He did not have any syndromic features and his cardiorespiratory examination was normal. His left lower limb was enlarged from the groin to ankle with normal overlying skin (Figure 1). The swelling had the same soft consistency as the opposite side. He could move his left lower limb. There were no other birthmarks or skin abnormalities. Ultrasound of the left lower limb showed a low-flow vascular anomaly that may be a congenital haemangioma. On his second day of life, he was discharged with an outpatient magnetic resonance imaging (MRI) appointment.

MRI at 2 months old (Figure 2) showed multilobulated cystic lesions seen in the pelvis, deep intermuscular left gluteal, left

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Fig. 1: Photography of Baby A demonstrating the left lower limb swelling

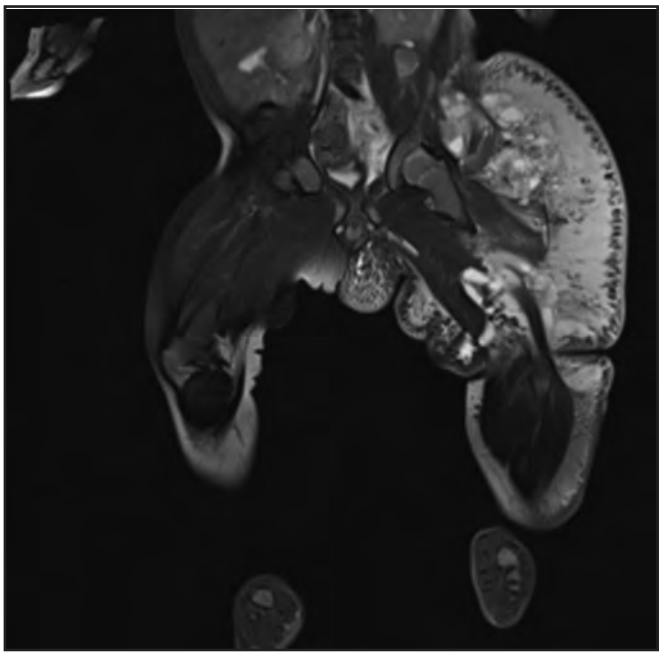

Fig. 2: MRI of pelvis and lower limbs of Baby A.

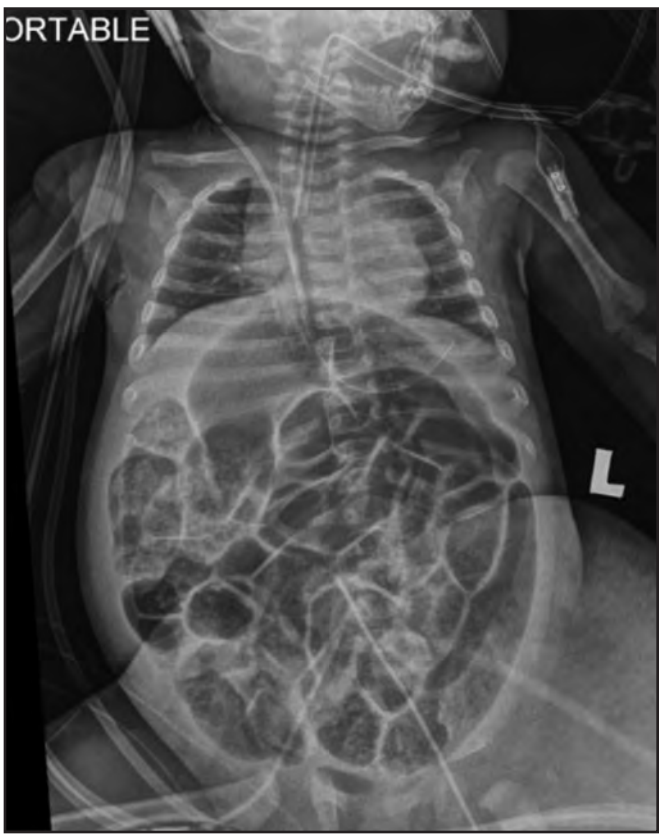

Fig. 3: Plain radiograph of Baby A when he deteriorated

thigh and deep subcutaneous layer of the lateral aspect of the left knee. The largest cystic component in the pelvis and thigh measures 1.2 cm and 1.8 cm, respectively. These cysts show peripheral rim enhancement post gadolinium. The overlying subcutaneous layer of the left thigh and distal left lower limb is thickened with a mass-like appearance, with no significant enhancement post gadolinium. It may represent the microcystic component. Overall, the MRI features suggest a lymphatic malformation with both micro and macro-cystic components affecting the pelvis, left thigh and left lower limb. Following consultation with the paediatric surgeon, it was planned to begin with Sirolimus for 6 months, followed by sclerotherapy if Sirolimus was futile. His parents needed more time to think about the treatment because they were not sure about it.

The day following the MRI, Baby A developed fever and did not urinate for 12 hours. He could still breastfeed normally and had normal bowel movement. Following morning, Baby A developed abdominal distension and became more lethargic with laboured breathing. He was rushed to emergency unit for resuscitation. He had poor perfusion. His abdomen was grossly distended and firm on palpation. Additionally, the left lower limb had increased swelling. Blood investigation revealed the metabolic acidosis and hypoglycaemia, along with a haemoglobin level of 7.1 g/dL. Plain radiograph of the abdomen showed dilated small and large bowels with a loss of polygonal shape. There was no bowel wall thickening or intramural gas (Figure 3). An ultrasound of the abdomen and left lower limb showed free fluid with echogenic debris seen predominantly in the perihepatic, subhepatic and perisplenic regions, raising the

Table I: Difference between congenital haemangioma and lymphatic malformation in ultrasound

	Vascular tumors: Congenital haemangioma	Vascular malformation: Lymphatic malformation
Sonogram	Heterogeneous subcutaneous mass Might contain a large visible vessel	Macrocystic component appears as multiple cystic formations of variable sizes with liquid content separated by thin hyperechogenic septa, compressible with ultrasound probe Microcystic component appears as solid formations with scattered cysts
Colour Doppler	Very high vascular density	Slow flow lesion Vascular signals are generally absent

suspicion of a perforated hollow viscus. Baby A required multiple inotropic supports and renal replacement therapy. Due to his declining condition, he was ineligible for exploratory laparotomy. Baby A deteriorated and succumbed to death the following day. An intra-lymphatic bleed that led to intestinal ischaemia and perforation was considered to be his cause of death.

DISCUSSION

We present a rare case of foetal lymphatic malformation that originated from the pelvic region to the left lower limb. Lymphatic malformations are benign masses containing fluid-filled channels or spaces that may be caused by abnormal lymphatic system development. They are rare, not cancerous and there is no known risk of malignant transformation. The prevalence of lymphatic malformations in the general population is estimated to be around 1:4000 live births.[5] Most are discovered at birth or during antenatal period, but they are rarely found in pelvic and extremities.[2,6]

The exact aetiology of lymphatic malformations is unknown. Lymphatic malformation is caused by abnormalities in the development of the lymphatic vascular system during embryonic growth.[5] Vascular endothelial growth factor (VEGF)-C and VEGF receptor type3 (VEGFR3), PIK3CA mutations have been detected in the lymphatic EC of the lymphatic malformation.[1,7] Madam S has worked as a staff nurse at a haematology day-care facility for the past three years and handled chemotherapy medications daily while she was pregnant. Study showed that the risk of congenital anomalies of the eye was significantly higher among the babies of nurses working in oncology unit. The risk of other congenital anomalies including circulatory system was also increased but they were limited by small number of cases and were not statistically significant.[8]

In this case, the swelling of the lower limb was discovered at 31 weeks POA, but it was initially thought to be a haemangioma. Ultrasound can be a useful imaging technique to differentiate between haemangioma and lymphatic malformation, as shown in Table I. However, there is a limitation if the lesion was extensive and deep-seated. Also, it is not always possible to come to a diagnosis with colour doppler alone. Therefore, MRI will be needed in certain situations.[9] Lymphangiomas detected in the second and early third trimesters had a worse prognosis as they have a stronger association with karyotypic abnormalities. Those detected in the middle to late third trimester however, have a decent prognosis.[4] Foetal karyotyping and antenatal foetal MRI were not done in this case due to a lack of resources. These tests can be offered to antenatal mothers since a normal karyotype and the lack of hydrops imply a good prognosis.[4] No complications from the vascular malformation, such as skin oedema, hydrops fetalis or polyhydramnios, were found during Baby A's subsequent TAS. TAS was essential to continuously monitor the development of the lesion and the emergence of complications. It is also essential for parental counseling and planning the mode of delivery. Termination of pregnancy was reported in other studies[4] but it was not permitted locally without proper indication.

Although cystic lymphangiomas are associated with genetic disorders such as Noonan syndrome, Turner syndrome, and Down syndrome, Baby A appeared normal without any syndromic features.[6] The baby's enlarged limb had the same soft consistency as his other normal limbs. It was incompressible, similar to venous malformations.[2] Features of macrocystic malformations include 1–3 large cystic lesions[1] with rim and septal enhancement[2] which are seen in this case. Cysts less than 2 cm, however, are classified as microcytic type.[2] The largest cyst, in this case, was only 1.8 cm. Besides that, the left thigh and distal left lower limb had a mass-like appearance at the subcutaneous layer with no significant enhancement post gadolinium which may indicate a microcystic component. This led to the conclusion that Baby A had a mixed kind of lymphatic malformation with a predominance of the microcystic type.

Sirolimus was offered as treatment in this case. Sirolimus is a mammalian target of rapaymycin (mTOR) inhibitor which is one of the most promising drugs for treating various vascular anomalies including lymphatic malformations.[1] However, Sirolimus should be administered at modest doses, after considering the risks and benefits, due to the high rate of adverse events, such as infections, blood or lymphatic problems, neutropenia, interstitial pneumonitis, or sirolimus hypersensitivity syndrome.[7] The risk of side effects made Baby A's parents unsure about starting Sirolimus. The lymphatic malformation complication led to Baby A's death. The clinical findings and imaging were suggestive of an intra-lymphatic bleed that led to bowel ischaemia and perforation. A foetal lymphangioma diagnosed during the prenatal period has a poor prognosis, with a mortality rate ranging from 50 to 100%. Because of this, all three reported cases of foetal abdominal lymphangioma that spread to an extremity resulted in the termination of the pregnancy.[10]

As primary care practitioners are often the first point of contact for antenatal mothers, it is critical that we detect

subtle findings on routine TAS and do not overlook measurements of all parameters and their correspondence to gestational age. Picking up a swelling could indicate fatal congenital malformations, necessitating immediate referral to the maternal foetal medicine specialist. Early detection may allow for better planning on the continuation of pregnancy, further evaluations as well as aid parental counseling and anticipation of the pregnancy. It was fortunate that Baby A was delivered via an elective caesarean section, avoiding the risk of birth trauma. Nonetheless, things did not turn out well because the lymphatic malformation eventually led to his death.

CONCLUSION

Foetal lymphatic malformation can be detected early during prenatal ultrasound and suspicious swellings should warrant urgent referral. If lymphatic malformation is detected early, treatment and delivery options, as well as the pregnancy's outcome, can all be planned for. Future cases of lymphatic malformations should be reported, and risk factors and causes for their occurrence may be researched. A multidisciplinary approach for cases of lymphatic malformation is preferred for the best perinatal outcome, including a comprehensive antenatal assessment and parental counseling with primary care practitioners, maternal foetal medicine specialists, neonatologists, and paediatric surgeons.

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DECLARATIONS

The authors declare they have no conflict of interest.

INFORMED CONSENT

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

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Post-COVID-19 febrile infection-related epilepsy syndrome in a child successfully treated with a multimodal approach

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SUMMARY

Post-infectious inflammatory syndrome following COVID-19 infection has been increasingly reported affecting multiple organs. Neurological presentations such as encephalopathy and seizures are common. Recently, during the surge of Omicron variant cases, we recorded a high prevalence of febrile seizure cases all over the country. Most febrile seizures are benign; however, a small proportion that progress into refractory epilepsy syndrome and require intensive care management. We report a 2-year-old child with refractory status epilepticus following COVID-19 infection, who was diagnosed and treated as febrile infection-related epilepsy syndrome (FIRES). A multimodal approach was adopted, using immunotherapy tocilizumab and ketogenic diet. The child currently has good seizure control but requires neurorehabilitation to improve ambulation, behaviour and cognition. This case highlights the importance of quick recognition of FIRES and its successful multimodal management that included tocilizumab.

INTRODUCTION

Neurological manifestations in relation to coronavirus disease 2019 (COVID-19) infections among the paediatric population have garnered much interest, with multinational studies reporting a prevalence of 22–44%.[1,2] Status epilepticus and encephalopathy were reported, but febrile infection-related epilepsy syndrome (FIRES) was rarely reported in adults and there was a single case report in a child with multisystem inflammatory syndrome in children (MIS-C).[3,4] FIRES is an epileptic encephalopathy of unknown aetiology affecting previously healthy children following a febrile illness. It has been defined under the subcategory of new-onset refractory status epilepticus (NORSE) and is similar to previous nomenclatures including acute encephalitis with refractory, repetitive partial seizures (AERRPS), or devastating epileptic encephalopathy in school-aged children (DESC).[5]

CASE PRESENTATION

A previously well and developmentally normal 2-year-old male initially tested positive by home self-test kit for COVID-19 and presented with fever and mild upper respiratory symptoms. He did not require hospital admission and was under home surveillance. On day 11 of illness, he presented with febrile seizures, requiring admission for 2 days and was discharged well, with no neurological deficits. Later on day 16 of illness, he presented again to a regional hospital with febrile status epilepticus lasting for 50 minutes. It was characterized by generalized tonic-clonic seizures with uprolling of eyeballs that were aborted with intravenous diazepam and phenytoin. He required intubation and ventilation for airway and cerebral protection for 72 hours and infusion of intravenous midazolam of 3 microgram/kg/minute. Following extubation, he remained encephalopathic with GCS 12-13/15. Unfortunately a few hours later, he developed recurrent refractory seizures that required multiple anti-seizure medications, including loading of phenytoin (30 mg/kg), phenobarbitone (40 mg/kg), levetiracetam (40 mg/kg) and infusion of midazolam 1 microgram/kg/minute. A regional hospital's first electroencephalogram (EEG) captured characteristic shifting ictal foci with an encephalopathic background seen in FIRES (Figure 1). He was transferred to our centre for further management on day 22 of COVID-19 infection.

Initial laboratory investigations during the presentation showed a total white cell count of 9.9×10^9/L, haemoglobin 13.6 g/dL, and platelet 184×10^9/L. The liver function test and renal profile were normal. Inflammatory markers such as C-reactive protein were normal (1 mg/L), and erythrocyte sedimentation rate was slightly elevated (18 mm/hr). His COVID-19 spike protein total antibody was positive 25.60 U/ml (normal <0.80 U/ml). His blood culture was negative. Cerebrospinal fluid findings did not suggest infection (no cells, glucose ratio 0.78%, total protein 0.2 g/L, and culture was negative). He did not fulfil the World Health Organization (WHO) case definition for MIS-C. His initial brain computed tomography and magnetic resonance imaging (MRI) were normal on days 16 and 20 of illness. The echocardiogram showed normal coronary arteries without any depression in ejection fraction.

In our centre, he was on continuous EEG monitoring which showed multiple episodes of a shifting pattern of focal electrographic and clinical seizures up to 30 times/hour (Figure 2). His clinical seizures were characterized by subtle blank stares, uprolling of eyeballs and twitching of upper limbs. He was given a single dose of intravenous tocilizumab (12 mg/kg) on day 22 of illness, as he was still febrile. He was readmitted to the paediatric intensive care unit (PICU) for cerebral protection on day 24 of illness and was commenced on therapeutic hypothermia to maintain a temperature

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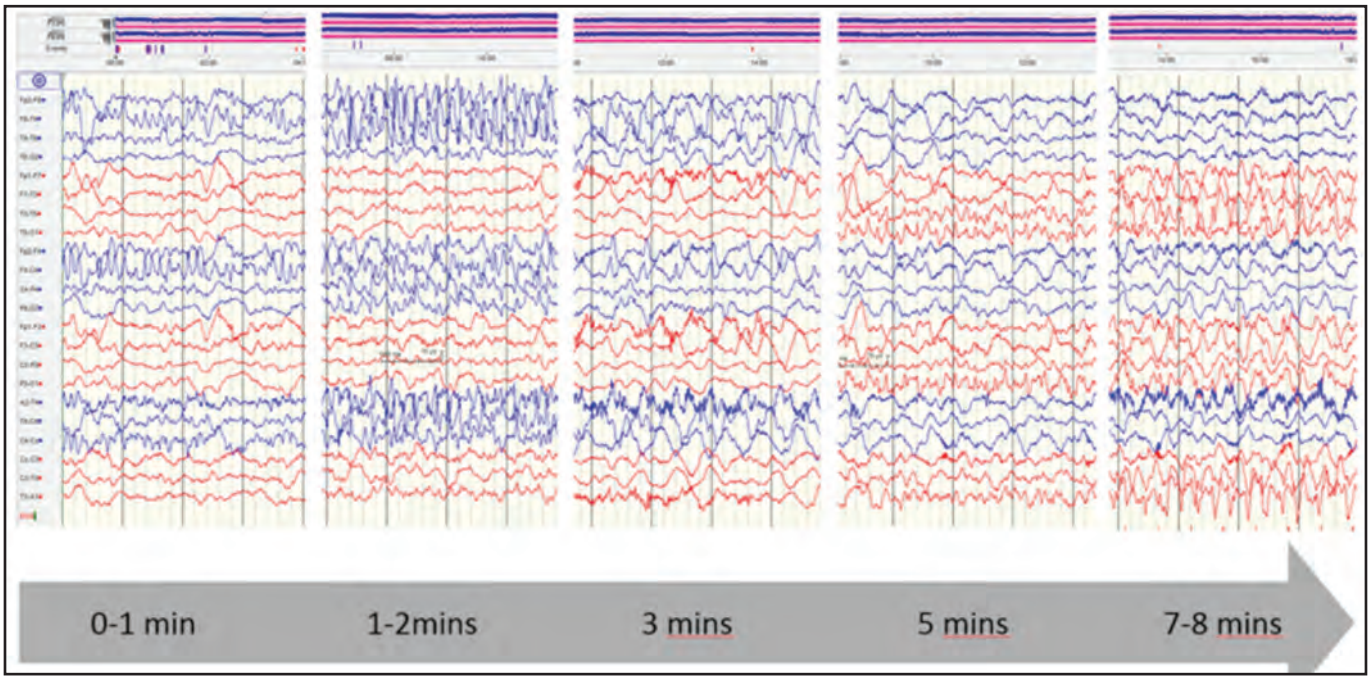

Fig. 1: A snapshots of first EEG captured a shifting pattern of electrographic seizures from right hemisphere to the left that lasted just over 8 minutes which is typically seen in a patient with FIRES

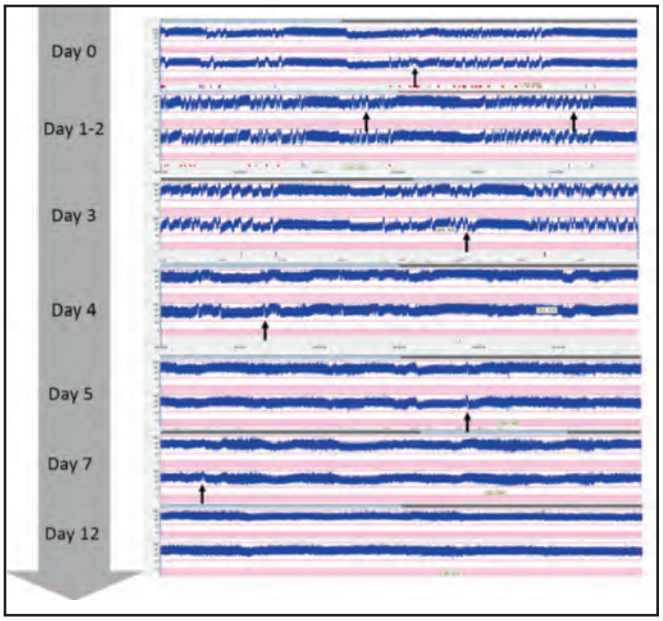

Fig. 2: A series of prolonged amplitude-integrated EEG (aEEG) monitoring in our centre. Cappings (arrows) on the aEEG represent electrographic seizures. As the days progressed, the number of capping had reduced notably from day 3 post tocilizumab and no further electrographic seizures seen by day 12 post tocilizumab

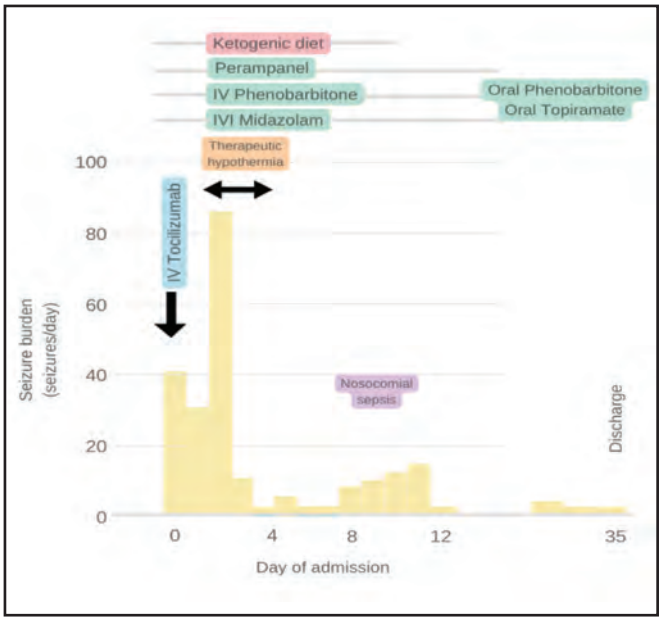

Fig. 3: The course of his illness during the hospital admission showing seizure burden following various treatments using a multi-modal approach

between 32 and 34°C for 72 hours. At this time, he was also started on ketogenic diet orally which subsequently had to be stopped due to feeding intolerance and diarrhoea (Figure 3). He required multiple antiseizure medications, namely midazolam infusion (titrated up to 3 µg/kg/min), a supratherapeutic dose of intravenous phenobarbitone (drug level: 223.10–401.34 umol/L range), and oral perampanel (loading dose 8 mg and maintenance dose 2 mg daily). His PICU stay of 2 weeks was complicated with nosocomial sepsis (Delftia acidovorans bacteremia), bicytopenia and acute kidney injury, which resolved over time. However, he became seizure free for 4 days on day 12 post-tocilizumab

administration. Following that, antiseizure medications, namely oral phenobarbitone and topiramate, were adjusted prior to discharge, when he only had brief daily seizures. His modified Rankin scale was 3; he was able to walk with assistance and had some fine facial and upper limb dyskinesia. During the outpatient clinic review at 3 weeks, 2 months and 4 months after discharge, he still has short brief seizures and remains nonverbal, had some aggressive behaviour and sleep disturbance. Repeat EEG showed mild background slowing, with no epileptiform discharges.

DISCUSSION

Our case highlights a rare and difficult-to-manage FIRES following COVID-19 infection. The pathogenesis of FIRES is currently unknown, while neurological manifestations in COVID-19 infections that can develop during acute COVID-19 infection or after its recovery or arise in the course of a MIS-C are largely hypotheses.[6] It has been postulated that the relationship between febrile illness and status epilepticus suggests deleterious effects of inflammation and autoimmunity on the onset and progression of seizures.[5] In our case, the biphasic clinical course suggests the possibility of post-infectious inflammation induced by COVID-19 triggering an autoimmune phenomena. Previous literature reported no specific biomarker, but selective upregulation of CSF proinflammatory cytokines particularly IL-6, macrophage migration inhibitory factor (MIF) and chemokines such as CXCL10, IL-8 are the hallmark of FIRES, providing strong evidence for the involvement of innate inflammation in the pathogenesis.[5] Unfortunately, we could not perform these CSF biomarkers in this patient due to limited resources. His other investigations, including neuroimaging and metabolic studies, were normal, as commonly described in previously reported cases of FIRES.[7]

As the postulation of innate immune system dysfunction is the contributing aetiology, the role of immunotherapy blocking proinflammatory cytokines, such as interleukin-1b and interleukin-6, has been explored. A previous case report had shown that the combination of tocilizumab and ketogenic diet was temporally associated with resolution of uncontrolled seizures in anakinra-refractory FIRES.[8] Similarly, in another cohort, refractory status epilepticus was terminated after 1–2 doses of tocilizumab in six adult patients with a median interval of three days from the initiation. However, two patients experienced severe adverse events related to infection during the tocilizumab therapy.[9] Ketogenic diet also has been reported to be helpful in FIRES. A large multicentre case series reported cessation of seizures within 2 days of starting the ketogenic diet in one of the patients.[7] Peng et al. observed seven patients who achieved cessation of status epilepticus within an average of 5 days after a ketogenic diet initiation.[10] Despite reported success with immunotherapy and ketogenic diet in controlling refractory seizures, the outcome of FIRES is universally poor, with most survivors developing learning disabilities, cognitive impairment and chronic refractory epilepsy.[7]

CONCLUSION

Any presentation of new-onset refractory status epilepticus following COVID-19 infection in otherwise previously healthy children should prompt the diagnosis of FIRES and necessary investigations, including ideally checking for pre treatment CSF biomarkers if possible. A multimodal approach, including tocilizumab administration and commencement of ketogenic diet, could lead to early seizure cessation and hopefully better long-term neurological outcomes.

ETHICS STATEMENT

Written consent has been obtained from the parent for publication purposes. This case report has obtained an exemption for ethical approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-22-01335-BYT (IIR) dated 28th June 2022).

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

MAA and HM drafted the manuscript with inputs from all other authors. SM, ARM and TBK reviewed the manuscript and finalized the submitted version.

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Appendicitis masking a perforated urinary bladder due to polyembolokoilamania

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SUMMARY

Right iliac fossa (RIF) pain is the most common presentation in acute appendicitis (AA). There are several varying differentials to the symptom due to the anatomical proximity of the appendix to other structures, including the urinary tract. Polyembolokoilamania refers to the act of inserting foreign bodies (FB) into bodily orifices, often times leading to disastrous effects. This behaviour is almost never willingly shared during presentation due to its paraphiliac nature. We report a case of a teenage male who presented with classic symptoms and signs of AA, underwent an open appendicectomy; only to find a perforated urinary bladder (UB) due to FB insertion via the urethra.

INTRODUCTION

The inflamed appendix is the most common surgical cause of an acute virgin abdomen,[1] with its presentation and management well documented in surgical textbooks. With proper history taking, examination, as well as basic biomarkers, the diagnosis of an acute appendicitis (AA) can be made. Scoring systems and imaging assistance are occasionally used in tandem to aid in diagnosis.[2] The most common symptom of an AA is sudden lower abdominal pain, later localising to the right iliac fossa (RIF). There are multiple differentials to this presentation. A urinary bladder (UB) perforation is rarely considered to be a differential of sudden lower abdominal pain. In this case report, an open appendicectomy was performed in our centre for a teenage male patient who presented with symptoms typical of AA—revealing instead a perforated UB due to foreign body (FB) insertion.

CASE PRESENTATION

A 12-year-old male with a paediatric history of nephrotic syndrome in complete remission presented to the emergency department with sudden non-radiating RIF pain and vomiting of 1-day duration. He was otherwise afebrile with no genitourinary or other gastrointestinal symptoms. There was a history of several episodes of dysuria for the past 2 months but had resolved spontaneously and was not prevailing during the current presentation. On social history taking, it was noted that the patient's parents were recently divorced.

During the general examination, the patient was found to be dry, normotensive but tachycardic and afebrile. His abdominal examination revealed a tender, guarded McBurney's point with positive rebound tenderness and elicitable Rovsing's sign. Bowel sounds were normal otherwise. Other systemic examinations, including genitalia and hernial orifices revealed normal findings. Patient's erect abdominal X-ray was unremarkable. Blood tests indicated marked leucocytosis (25.27×10^9/L) with raised serum lactate (3.35 mmol/L). Renal and liver function tests were normal. Urinalysis was positive for protein (2+), leucocyte (1+) and nitrite (1+). qSOFA score was 0.

In view of the presentation of a young, fit patient in sepsis with a brief history of tender and guarded RIF, a provisional diagnosis of perforated appendicitis was made, and the parents were counseled for consent to proceed with an open appendicectomy. On entering the peritoneum through the Lanz incision, 200cc of turbid yellow fluid was found in the pelvic cavity. Despite that, the appendix was only mildly inflamed. Appendicectomy was performed without difficulty. No Meckel's diverticulum was found; however, slough was noted covering the small bowel in several places. Further exploration was arduous due to the small Lanz incision thus, conversion to midline laparotomy was made after intraoperative counseling with his parents by a surgical specialist.

On further exploration via the midline incision, the sigmoid colon was seen adherent to the fundus of the UB. Careful dissection revealed protrusion of a thin white plastic tube through the UB wall into the peritoneal cavity (Figure 1). It was then realised that the appendix was inflamed due to uroperitoneum caused by UB perforation. Methylene blue solution was infused retrogradely into the UB via a Foley's catheter, and the solution trickled out from the UB into the peritoneum through the lumen of the plastic tube, confirming a communication (Figure 2). The tube was removed prudently, later measured to be 7.2cm × 0.3cm (Figure 3). The perforation site at the UB was repaired with double-layer absorbable suture. Rest of bowels were thoroughly examined and found to be viable. A surgical drain was placed, and the abdomen was closed with no difficulties.

Evaluation was done later in ward by a psychiatrist who exposed a telling history by the mother that she had once caught her son inserting a marble into his urethra. The patient's act was reprimanded by her, and she thought the issue had resolved, thus it was not brought into light

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previously. The patient was soon informed of the details of intraoperative findings, and when queried, he immediately denied any act of urethral self-insertion. After a further dialogue, the patient admitted to inserting a cotton bud stick into his urethra 2 months ago and was unable to retrieve it but was not keen to reveal his intention for the behaviour.

Operative recovery went smoothly, and the surgical drain was removed. The patient was discharged with a urinary catheter. Histopathology of the appendix showed periappendicitis. Cultures of his urine sample were reported as mixed growth of multiple organisms, whereas his peritoneal fluid had no bacterial growth on culture. CT cystogram was performed 2 weeks post-operatively, showing no leakage. The urinary catheter was subsequently removed. On psychiatric follow-up, the patient was found to be depressed due to his parents' separation. He recuperated well and is reportedly in good spirits post counseling and therapy. There were no long-term complications concerning the bladder repair upon follow-up after a year.

DISCUSSION

Correctly diagnosing a sudden painful RIF for possible AA has always been considered a challenge to the surgical fraternity. Differentials of the symptom include gastrointestinal, urological, gynaecological, vascular and musculoskeletal pathologies. Surgeons have routinely relied on clinical history, physical examination findings and basic laboratory investigations for diagnosing an AA. Based on these parameters, various scoring systems were developed for diagnostic aid, yet there is insufficient evidence to support their use.[3] Few surgeons rely on them due to their low specificity.[2] The advent and emergence of radiological imaging, on the other hand, have proven to be a useful tool in the management of AA.[2] Imaging assistance is recommended in cases with indeterminate diagnosis—particularly in young or pregnant patients or those with atypical presentations.[3] An ultrasound is preferred for females (high preponderance of gynaecological disease), gravidae, or children; whilst a CT scan is advocated for the elderly.[3] Additional assessment by gynaecologists is also often requested for female patients of reproductive age with equivocal findings for the possibility of tubo-ovarian or uterine pathology.[2]

Treatment strategies for AA mainly involve an operative intervention, constituting either an open or laparoscopic approach. The laparoscopic method has always been favoured over open appendicectomy wherever not contraindicated and when technically feasible. It has been proven to have lower complication rates, reduced post-operative pain and shorter recovery and hospital stay.[3] Non-operative management of AA has been explored via primary antibiotic treatment, although it is not without controversy due to failure rates and the need for subsequent appendicectomy.[2]

Urinary tract infection (UTI) is also a well-known differential diagnosis for acute RIF. The patient will also classically present with dysuria, frequent voiding, incomplete voiding, haematuria and suprapubic tenderness. The upper urinary tract is involved in more severe cases, mainly in the form of pyelonephritis, whereby patients will be more ill and have back or loin pain in addition to symptoms of a lower UTI. UTIs are routinely diagnosed with the presence of an abnormal urinalysis, namely pyuria. Nevertheless, abnormal urinalysis is not a rare occurrence in patients with AA, with Scott et al.[4], Puskar et al.[5] and Kretchmar and McDonald[6] reporting incidences of 53%, 48% and 19%, respectively. The relation of pyuria with AA is due to the varying anatomical deviations of the inflamed appendix and its close proximity to the urinary tract, causing symptoms that mimic a UTI.[7] Thus, UTI is a probable diagnosis in an acute RIF with the presence of pyuria—nevertheless, it does not rule out an AA.

A rare differential diagnosis of the acute RIF is a perforated UB due to urethral FB insertion. The act of FB insertion into bodily orifices is termed as polyembolokoilamania. Most patients with polyembolokoilamania have some form of psychiatric abnormality.[8] Various cases of urethral self-insertion have been reported worldwide, but the true incidence is unknown since patients typically do not present themselves—unless a complication arises. The two methods of FB introduction into the UB are transurethral and trans-bladder. The transurethral approach was mainly self-inflicted, whereas all trans-bladder approach were iatrogenic.[9] Symptoms of FB in the UB are closely related to those of a UTI due to the FB being a bacterial harbour, irritating the bladder wall and later leading to cystitis and urinary stasis.

In this particular case, a prior imaging was not requested due to the typical history and examination findings resembling a perforated appendicitis in an otherwise young, healthy and fit male. It is difficult for practitioners to uncover acts of polyembolokoilamania in patients who present in an acute setting of abdominal pain since they will unlikely be forthcoming on this habit and possibly consider it unrelated or taboo. Obtaining such history voluntarily is implausible given that the act is done for either erotic stimulation, sexual curiosity or due to psychological problems.[10] The rarity of this confounding diagnosis is therefore proven to be a diagnostic challenge and makes it a story worth telling.

CONCLUSION

Presence of FB in the UB can manifest symptoms similar to that of an AA, albeit an unlikely diagnosis. Careful history taking, especially in ambiguous presentations of sudden RIF pain might reveal further information which could justify additional investigations prior to operation at the discretion of the practitioner. Routine usage of imaging assistance in all cases of acute RIF in conjunction with clinical findings will assist greatly in pre-operative management.

ACKNOWLEDGEMENT

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CONSENT

Written informed consent for photographs and publication was obtained from the patient's guardian (patient was a minor).

CONFLICT OF INTERESTS

The authors have no conflicts of interests to declare.

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CASE REPORT

Cystic hepatic metastases: A rare mimic of liver abscesses

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SUMMARY

Cystic hepatic metastases (CHM) in patients with colorectal cancer are rare but important to recognize. In patients presenting with sepsis, differentiating superinfection of CHM from liver abscesses becomes challenging. Our patient presented with fevers, abdominal discomfort and an ultrasound showed cystic liver lesions, with the largest lesion measuring 11.8 cm in size. With a clinical picture of sepsis, the lesions were thought to be due to liver abscesses. Despite percutaneous drainage and antibiotics, her septic parameters worsened. A computed tomography (CT) performed showed a circumferential bowel mass in the hepatic flexure, later confirmed as transverse colon carcinoma. In the setting of extrahepatic malignancy, CHM is an important differential diagnosis in patients found to have cystic liver lesions. Imaging of the liver may be helpful as hepatic metastases have a higher degree of septations on ultrasound, and rim enhancement on CT only occurs during the arterial phase, whereas rim enhancement persists throughout the arterial and portal venous phase in liver abscesses.

INTRODUCTION

Colorectal cancer is the third most common cancer contributing 10% of all cancers worldwide. Although colorectal cancer screening programmes have been available, 70% of patients present with stage III or IV disease: lung and liver metastases being most common.[1] Cystic hepatic metastases (CHM) from colon cancer however remain rare and can be difficult to differentiate from liver abscesses when a patient presents with sepsis. Herein, we present a case of cystic liver lesions, with the largest measuring 11.8 cm, highlighting the lessons learned from this case.

CASE PRESENTATION

A 66-year-old obese lady was admitted to the hospital with fevers, right-sided abdominal discomfort and loss of appetite. Two weeks prior, she presented with similar symptoms to a different center, and was diagnosed to have liver abscesses on computed tomography (CT); the largest lesion measuring 9.5 cm in size. There was also a short segment of bowel wall thickening at the hepatic flexure with large peri-colonic lymphadenopathy. She unfortunately self-discharged home against medical advice. During this admission, her blood investigations showed an elevated white cell count 25.2 (reference range 4.1–11.4 × 10^9/L), C-reactive protein of 149.3 (reference range <5 mg/L) and procalcitonin of 4.57 (range 0.5–2.0 ng/mL:systemic infection is possible but other conditions may also induce significant procalcitonin rises; 2–10 ng/mL: systemic infection is likely; ≥10 ng/mL: high likelihood of severe bacterial sepsis or septic shock). Her alkaline phosphatase level was elevated 439 (reference range 35–104 U/L), but all other liver enzymes remained normal. An ultrasound abdomen was performed, confirming uncomplicated cholelithiasis and comparing with previous imaging, the lesions have enlarged with liquefied components, the largest measuring 11.8 cm × 5.5 cm in segment VI of the liver (Figure 1). A percutaneous pigtail drain was inserted into the segment VI liver lesion, draining non-purulent serosanguineous fluid.

Despite the continuation of antibiotics and percutaneous drainage, the patient's septic parameters worsened, and hence contrast-enhanced CT was performed (Figure 2). This showed a slight improvement of the segment VI collection, however a circumferential bowel mass over the hepatic flexure was seen, causing luminal narrowing with proximal bowel dilatation. Her serum carcinoembryonic antigen (CEA) was raised at 13.2 (reference range <5 ng/mL).

Due to impending large bowel obstruction, a multidisciplinary discussion with the family was held, and we proceeded to a laparotomy. Her laparotomy findings confirmed a constricting tumour in the proximal transverse colon with liver and omental metastasis. A palliative loop ileostomy was performed. Immunohistochemical studies of the omental and peritoneal nodules biopsied were positive for CEA, but negative for cytokeratin 7 and 20, consistent with a colorectal cancer origin. Unfortunately, the patient continued to deteriorate clinically and passed away a few days after surgery due to overwhelming sepsis and multiorgan failure.

DISCUSSION

Cystic lesions in the liver are commonly found on imaging. The cause of these ranges from clinically insignificant benign lesions to potentially life-threatening and malignant lesions. There have been various classifications of cystic liver lesions and are mainly divided into infective (parasitic and non-parasitic) and non-infective causes (benign, pre-malignant, malignant and traumatic). Pre-malignant and malignant causes include biliary cystadenoma, intraductal papillary neoplasm of the bile duct, Caroli disease, bile duct hamartomas, biliary cystadenocarcinoma, cystic hepatocellular carcinoma, undifferentiated embryonal sarcoma and CHM.[2]

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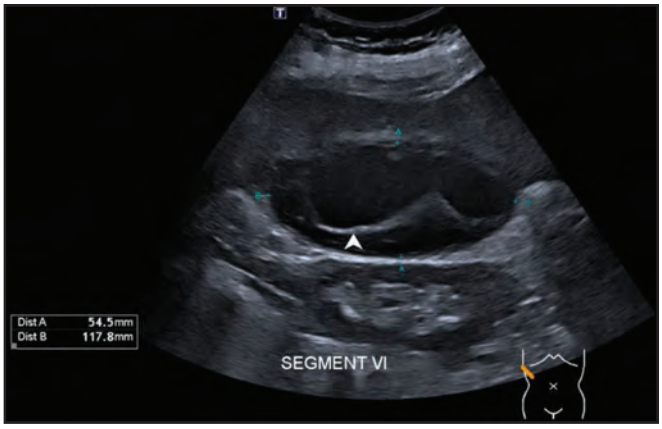

Fig. 2: Ultrasound scan showing a 11.8 cm × 5.5 cm cystic liver lesion with septation (white solid arrowhead)

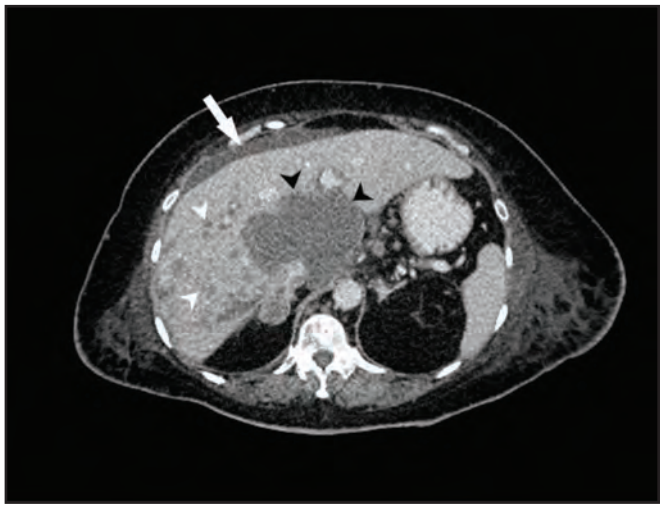

Fig. 2: CT image showing multiple cystic lesions in the liver (white solid arrowhead) with the largest in the caudate lobe (black solid arrowhead). Ascites present (white arrow). Note the heterogenous ill-defined borders of the largest cystic lesion with no rim enhancement

CHM from colon cancer is rare and only a few cases have been reported in the literature. In a study done in Japan, only 6 out of 325 cases were reported to be CHM in a span of 11 years.[3] Kidney, prostate, ovary/testis, squamous cell lung cancer, gastrointestinal stromal tumour, sarcoma, and neuroendocrine tumours have been previously described to be primary sources.[2]

The development of CHM is poorly understood. Theories include i) acceleration of tumour growth, outstripping its blood supply leading to central necrosis and haemorrhage or ii) accumulation of mucinous and serous fluid produced by mucinous adenocarcinoma as seen in patients with colorectal, ovarian and pancreatic cancer.[4,5] Pathological specimens from the case series in Japan confirmed necrotic changes with clots within cystic cavities.[3]

In a patient with sepsis, differentiating CHM from liver abscesses becomes challenging. Imaging the liver may be helpful in distinguishing the two. Hepatic metastases have a higher degree of septations on ultrasound and heterogenous ill-defined borders with arterial rim enhancement on CT corresponding to tumour viability at the periphery. Liver abscesses however have persisting rim enhancement throughout arterial and portal venous phases.[6,7] Our patient indeed had septations on ultrasound but no rim enhancement on arterial or portal venous phase on CT.

Aspiration of fluid from the lesions is usually not encouraged for diagnosis of CHM. However, if superinfection of metastatic liver lesions is suspected, a percutaneous needle aspiration or drainage is required. Our patient was initially thought to have liver abscesses based on her CT report and hence a percutaneous drain was inserted. Fluid analysis was reported to be serosanguineous in appearance, showed no atypical cells and the culture was negative, confirming a non-infective cause.

Management of metastatic colorectal cancer includes liver resection. The median survival post resection in patients with CHM was 57 months based on a small case series of six patients.[3] Our patient however was too unwell for a major surgery and hence a palliative loop ileostomy was performed

CONCLUSION

There are two major learning points in this case presented. The first is clinician awareness of CHM especially in a patient with underlying malignancy. A multidisciplinary team discussion involving radiologists, physicians and surgeons early in the admission would have given a better perspective on the course of management. These would include reviewing her previous CT images performed in the centre prior to admission, potentially identifying the more sinister cause of bowel thickening and avoiding a percutaneous drain insertion.

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DECLARATIONS

Consent was taken from next of kin of the patient. The authors declare no competing interests with respect to the authorship and publication of this article.

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Intrathoracic oesophageal perforation: A case series

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SUMMARY

Intrathoracic oesophageal perforation is a surgical emergency which is associated with high morbidity and mortality rates. Early diagnosis and appropriate intervention are imperative to reduce the morbidity and mortality. However, the rarity of this condition and its nonspecific presentation led to diagnostic and treatment delay. The management depends on the cause of perforation, the integrity of oesophagus, location of perforation and the time between perforation and presentation to hospital. Here, we discuss on two patients with oesophageal perforation, from clinical presentation and establishing diagnosis to prompt surgical management and outcome.

INTRODUCTION

Intrathoracic oesophageal perforation is a potentially life-threatening condition. Early diagnosis and appropriate intervention are imperative to reduce morbidity and mortality. The management depends on the cause of perforation, the integrity of the oesophagus, the location of perforation and the time between perforation and presentations to hospital. Here, we discuss on two patients with oesophageal perforation, from clinical presentation and establishing diagnosis to prompt surgical management and outcome.

CASE PRESENTATION

Case 1

A 55-year-old man presented to emergency department at 3.30 am with complaints of pain upon swallowing and shortness of breath after accidentally ingested chicken bone. On examination, he was clutching his chest in pain. He was tachycardic and tachypneic with no episode of hypotension or fever. His blood investigation was unremarkable. The initial neck x-ray did not show a foreign body in the neck and, there was no sign of pneumo or hydrothorax on the chest x-ray image. He was reviewed by ear-nose-throat (ENT) specialist and underwent examination under direct laryngeal and rigid esophagoscopy. A foreign body was seen at the posterior wall of the oesophagus 18 cm from upper incisor. The foreign body could not be removed because it was progressively moving into distal oesophagus. He developed respiratory distress immediately after being extubated in the operation theatre. Urgent computed tomography (CT) Thorax was performed and showed left hydropneumothorax causing mediastinal shift with ipsilateral lung collapse. Left chest tube was inserted and drained 600 ml of haemoserous fluid and the patient was reintubated. After 20 hours of rigid esophagoscopy, decision was made for exploration. He underwent emergency oesophagogastroduodenoscopy (OGDS) and exploration which showed perforated oesophagus at 33 cm from the incisor and a bone was seen in the stomach. Left video assistant thoracoscopy surgery (VATS) was performed immediately which showed perforation at left lateral wall of the lower oesophagus (Figure 1). Necrotic tissue was debrided followed by primary closure with interrupted 4.0 polydioxanone suture, approximating both mucosal and muscular layers. Post operation recovery was uneventful and contrast study showed no leak at repair site.

Case 2

A 48-year-old heroin chaser, presented to emergency department with severe epigastric pain and shortness of breath for 3 days. He had epigastric pain for 1 months associated with vomiting. On examination, he was found septic and tachypnoeic. His abdomen was tender over the epigastric region with no peritonitic sign. There was reduced air entry bibasally, more prominent on the right hemithorax. His chest x-ray showed pneumomediastinum and consolidation at the right lower zone. Computerized tomography (CT) abdomen and thorax showed extensive pneumomediastinum predominantly at the lower oesophageal region with bilateral hydropneumothorax and minimal pneumoperitoneum at the epigastric region. In view of clinical history and suspicious clinical findings, epigastric pain is more a sign in peptic ulcer pathology and less common sign of oesophageal perforation and while pneumomediastinum is major sign of oesophageal perforation, an urgent OGDS was performed and a perforation at lower oesophagus 35 cm from the incisor was seen. Right thoracotomy was performed immediately, revealing 1 cm perforation at the lower oesophagus and stage 2 empyema thoracis (Figure 2). Oesophageal perforation site was repaired primarily with interrupted 4.0 polydioxanone suture and right lung decortication was done. He had a stormy post operative recovery due to sepsis which required intensive care for more than a week. OGDS performed 1 week after surgery revealed healing with no defect seen at the repair site. Chest drain was removed after the OGDS.

DISCUSSION

Intrathoracic oesophageal perforation is a surgical emergency which is associated with high morbidity and mortality rates.[1,6] About 10 15% mortality reported when therapy is initiated within 24 hours of perforation and 40 60% when treatment is delayed. There are several contributing factors lead to rapid deterioration in cases of intrathoracic oesophageal perforation compared with

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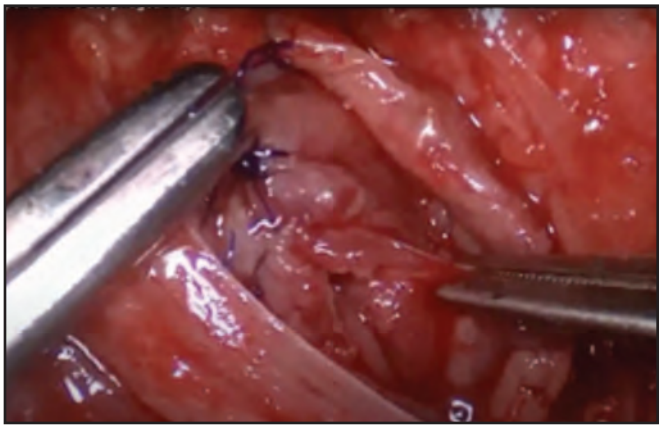

Fig. 1: Perforation at left lateral of lower oesophageal

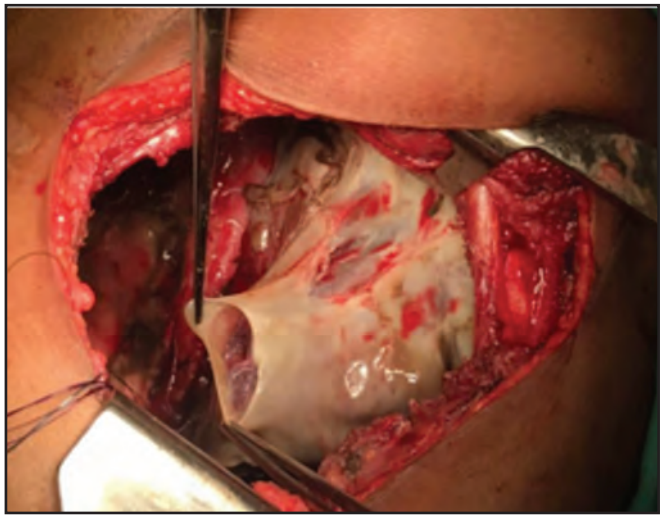

Fig. 2: Grade 2 lung empyema (Fibrinous cortex seen over the right lung)

cervical oesophageal perforation;[6, 7]

1) Anatomy of oesophagus; the mid oesophagus lies next to the right pleura while the te lower oesophagus lies next the left pleura. Once a perforation occurs, saliva, retained gastric contents or bile acid may enter directly to the respective pleural cavities and mediastinum.
2) Content of collection, gastric juice and bile acid which trigger a cytokine-mediated fluid sequestration leading to extensive inflammatory reaction and tissue destruction to pleural and mediastinum.
3) Contamination from oesophageal perforation allows bacteria access into the mediastinum and pleura cavity resulting lung empyema, mediastinitis and sepsis.

In both of our cases, patients deteriorated rapidly and progressed into sepsis. In case 1, patient developed respiratory distress immediately after rigid esophagoscopy while case 2, patient presented with sepsis and respiratory distress 3 days after complaining of epigastric pain which was a sign of oesophageal perforation.

The aetiology of oesophageal perforation is spontaneous (Boerhave syndrome), traumatic, iatrogenic or foreign bodies. In the era of advanced endoscopic therapies, iatrogenic perforation is the leading cause of oesophageal perforation which accounts for 70% of oesophageal perforation. Diagnostic OGDS reported a 0.03% risk of oesophageal perforation, and the risk increases when therapeutic procedure is performed endoscopically.

A total of 80% of patients presented with either chest or epigastric pain depending on perforation site. Epigastric pain can be misleading symptom with possibility of a perforated gastric ulcer.[1,2,6] Other symptoms are vomiting, haematemesis, dysphagia, tachypnea, cough and fever.[1,2] History of instrumentation or foreign body ingestion followed by the above symptoms should raise suspicion of oesophageal perforation.

In case 1, the clinical presentation was straightforward as it occurred directly after rigid oesophagoscopy. For case 2, the clinical presentation can be misleading with perforated gastric ulcer. However, the presence of pneumomediastinum and consolidation of right lung on chest x-ray had prompted us to re-evaluate the diagnosis. CT thorax and abdomen demonstrated extensive pneumomediastinum at lower oesophagus surrounded with fluid collection suggestive of oesophageal perforation. An urgent OGDS confirmed the diagnosis of oesophageal perforation.

The appropriate management of oesophageal perforation is controversial.[1-6] Early diagnosis within 24 hours of the incident is vital for good outcomes. Primary repair remains the preferred surgical treatment method in thoracic perforation. A successful outcome requires debridement of all necrotic tissue, vertical oesophagomyotomy to expose damaged mucosa, relief of distal obstruction in the case of strictures, two-layer tension-free closure and copious irrigation and drainage of the contaminated area.[6,7,8] A VATS approach has been successfully implemented, but further studies are needed to clarify its role in primary repair in comparison with conventional thoracotomy.[8] An on table OGDS is helpful to identify the site of perforation and guide the repair. If primary repair is not possible due to underlying oesophageal pathology, an oesophageal exclusion and oesophagectomy with delayed or immediate reconstruction can be considered. Oesophagectomy has the advantage of eliminating the source of infection and inflammation entirely, and restoring gastrointestinal continuity.[7,8] In the case of unstable patient intraoperatively, a drain can be inserted into the perforation as a controlled fistula and a feeding jejunostomy for post op nutrition. Patient can be brought in for definitive surgery later when he is hemodynamically stable.

Both of our patients underwent surgical primary repair and decortication successfully once diagnosis was established. Compared to case 1, case 2 had a stormy recovery owing to late presentation thus higher morbidity. However, both recovered eventually.

CONCLUSION

The rarity of this condition and its nonspecific presentations lead to diagnostic and treatment delay. Prompt identification of perforation, resuscitation, and timely surgical intervention are keys to successful outcomes.

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COMPETING INTERESTS

The authors declare no competing interests.

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CASE REPORT

Severe crescentic lupus nephritis treated with plasma exchange and modified dose of immunosuppressive therapy

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SUMMARY

Lupus nephritis (LN) is one of the major life-threatening systemic organ involvements in systemic lupus erythematosus. The prognosis and outcome of LN vary depending on its clinical presentation and histopathological classification. Crescentic LN occurs commonly in severe diffuse proliferative LN, often manifests as acute kidney injury requiring intensive immunosuppressive therapy and probable need for renal replacement therapy (RRT) and this is associated with poor renal outcome. We report a case of severe crescentic LN in a young girl who needed RRT while on the induction phase of immunosuppressive therapy with our modified induction regime and managed to discontinue after 5 months with significant kidney recovery.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterised by inflammation of different systemic organs with immunologic abnormalities. The natural course of the disease varies from mild mucocutaneous and musculoskeletal manifestation to life-threatening kidney, hematologic and central nervous system involvement – leading to fulminant organ failure and death. Early disease recognition, with judicious therapy and prompt treatment of complications, may improve the prognosis and outcome.

Lupus nephritis (LN) is one of the renal manifestations in SLE, and its presentation can be varying from asymptomatic microscopic haematuria and proteinuria to nephrotic or nephritic syndrome or a combination of both. Crescentic LN is the most severe manifestation of LN, presenting as rapidly progressive glomerulonephritis (RPGN) with hypertension, acute kidney injury and oliguria. The standard acute management of crescentic LN includes high-dose corticosteroids, induction therapy with immunosuppressive agent and probable need of renal replacement therapy (RRT) if indicated. The outcome of crescentic LN is usually poor, resulting in end-stage renal disease requiring long-term RRT.

CASE PRESENTATION

A 16-year-old girl presented with an 1-month history of bilateral lower limbs swelling, associated with facial puffiness, dyspnoea and reduced urine output for 1 week prior to presentation. Other systematic review was not significant and no other symptoms to suggest connective tissue disorder. She has no known medical illness and no significant family history of autoimmune diseases. Upon arrival at the hospital, she had four episodes of seizures and she regained consciousness in between episodes. Initial assessment revealed a young girl with anasarca, however, no stigmata of connective tissue disorder. She appeared pink, not in respiratory distress, and her blood pressure was 189/101mmHg on presentation. Her neurological examination was unremarkable. She was anuric on presentation despite on optimal dose of diuretics. She was stabilised with anti-seizure medication and antihypertensive. Immediate brain computed tomography (CT) was suggestive of posterior reversible encephalopathy syndrome (PRES), which was later confirmed by a brain magnetic resonance imaging, and no evidence of cerebral lupus.

Her blood investigations revealed acute kidney injury with a serum urea of 38 mmol/L and creatinine of 895 µmol/L with an estimated glomerular filtration rate (eGFR) of 5.1 ml/min/1.73 m^2 on presentation. There was hyperkalaemia with a serum potassium of 6.8 mmol/L, and metabolic acidosis with a pH of 7.22 and bicarbonate of 14.4 mmol/L. Her full blood count showed a normocytic normochromic anaemia with haemoglobin 8.8 g/L, total white cell count 7.2 × 10^9/L and platelet count 291 × 10^9/L. There was no evidence of haemolysis in peripheral blood film and coomb's test was negative. Her serum albumin was 14 g/L. Other laboratory investigations include urinalysis of protein 3+ and blood 3+ and urine protein: creatinine index (PCI) of 0.53 g/mmol creatinine. An ultrasound of kidney ureter bladder with renal doppler showed normal kidney size bilaterally with no evidence of renal vein thrombosis. Her workup for autoimmune disease revealed a positive antinuclear antibody with titre of 1:1280, positive double-stranded DNA, and low complement C3/C4 level of 24/5 mg/dL, respectively. Her screening for hepatitis B, C and HIV was non-reactive.

With a clinical diagnosis of crescentic LN, she was given a 3-day course of intravenous (IV) methylprednisolone 250 mg daily, followed by a maintenance of 50 mg (1 mg/kg) daily. Renal biopsy was performed and showed three cores of renal

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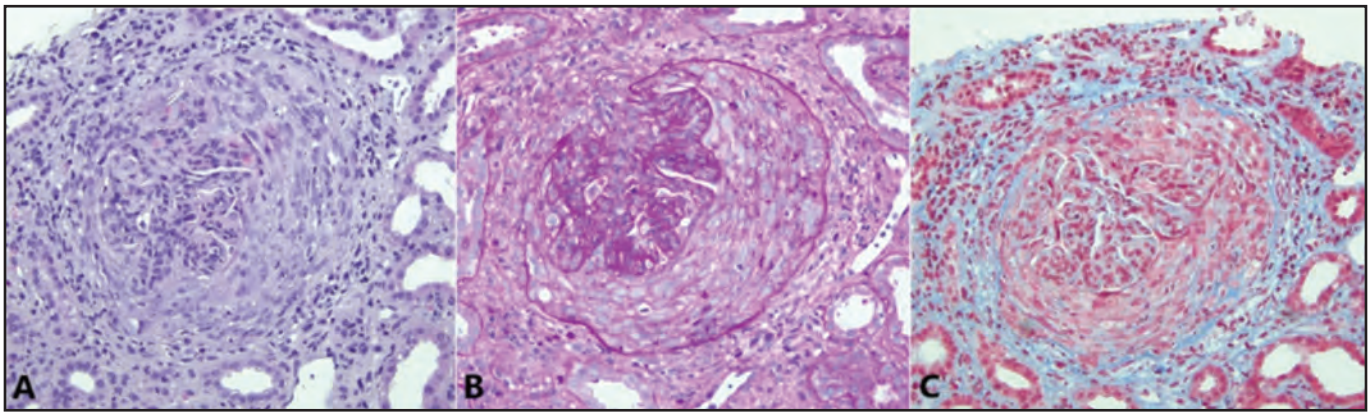

Fig. 1: Cellular crescent with endocapillary and mesangial hypercellularity in haematoxylin and eosin (H&E) stain (A), periodic acid-Schiff reaction (B) and Masson's trichrome stain (C)

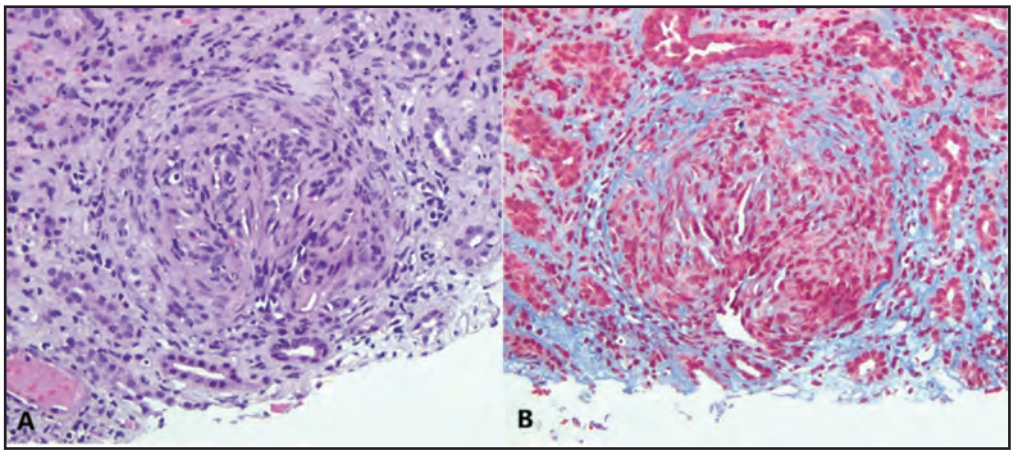

Fig. 2: Fibrocellular crescent in H&E stain (A) and Masson's trichrome stain (B)

cortical tissue comprising of a total of 35 glomeruli. There was a widespread crescents with 50% cellular crescents (Figure 1) and 50% fibrocellular crescents (Figure 2) seen. Eight glomeruli showed segmental sclerosis with adhesions and most of the glomeruli displayed endocapillary and mesangial hypercellularity with karyorrhexis and thickening of basal membrane with double contouring and subendothelial deposit. Pseudothrombi were seen in a few glomeruli. Presence of acute tubular injury with moderate infiltration of neutrophils, lymphocytes, plasma cells and scattered eosinophils within interstitium with 45% tubular atrophy and interstitial fibrosis. An interlobular artery showed evidence of vasculitis with fibrinoid necrosis. The immunofluorescence (IF) study revealed a full-house immunocomplex deposition with 3+ granular positivity for C3, C4, IgM and IgA and 1+ granular positivity for IgG at the mesangium and capillary loops.

The diagnosis of crescentic LN was established, and she was treated with six cycles of plasma exchange. In the ward, her platelet counts dropped further to the lowest reading of 57 × 10^9/L with no other cause to explain. Hence, she was treated as immune-mediated thrombocytopenic purpura and started on intravenous immunoglobulin (IVIg) for 5 days followed by a modified induction therapy regime with 2 weekly intravenous cyclophosphamide. Initial dose of 300 mg IV cyclophosphomide was given fortnightly for first 2 months followed by 250 mg fortnightly for another 4 months concurrent with a tapering dose of oral prednisolone 5 mg fortnightly until 25 mg (0.5 mg/kg) daily then tapered further by 5 mg monthly to maintain at 10 mg daily dose. She remained anuric throughout the admission and was initiated on haemodialysis then later converted to peritoneal dialysis, a month after. She was doing well with her continuous ambulatory peritoneal dialysis (CAPD), and her urine output and renal profiles improved significantly at 3 months of induction therapy. The need for her CAPD able to taper down slowly from daily to 3 days per week, and subsequently discontinued at 4 months of induction therapy with a serum creatinine of 161.2 µmol/L and eGFR of 40 ml/min/1.73m^2. Table I summarises her disease progress with treatment. She was planned for a total 6 months of 2-weekly intravenous cyclophosphamide followed by a maintenance therapy with mycophenolate mofetil (MMF) with regular follow-up in nephrology clinic.

Table I: Clinical course of the disease with treatment

Duration from presentation (Weeks)	Treatment			RRT	Creatinine µmol/L	UPCI g/mmol	Albumin g/L
	Corticosteroids	Cyc	Others				
1	IV MP 250 mg OD for 3 days then IV MP 50 mg OD for 6 cycles (total 12 days)	-	PLEX EOD				
		HD	895.5	0.53	14		
2	IV MP 50 mg OD	-		HD	455.3		31
3	Pred 50 mg OD	-	IVIg OD for 5 days	HD	428.9		29
4	Pred 50 mg OD	-	-	HD	525.0		26
5	Pred 45 mg OD	300 mg	-	HD	688.0		30
7	Pred 40 mg OD	300 mg	-	HD/PD	563.5		32
9	Pred 35 mg OD	300 mg	-	PD	453.1	0.54	29
11	Pred 30 mg OD	300 mg	-	PD	290.3	0.25	32
13	Pred 25 mg OD	250 mg	-	PD	289.1	0.29	29
15	Pred 25 mg OD	250 mg	-	dPD	339.0	0.13	35
17	Pred 20 mg OD	250 mg	-	dPD	245.3	0.25	31
19	Pred 20 mg OD	250 mg	-	dPD	195.5	0.66	30
21	Pred 15 mg OD	250 mg	-	Stopped	185.5	0.81	29
23	Pred 15 mg OD	250 mg	-	-	161.2	0.83	29

Cyc = cyclophosphamide, RRT = renal replacement therapy, UPCI = urine protein: creatinine ratio, IV = intravenous, MP = methylprednisolone, OD = daily, PLEX = plasma exchange, EOD = every other day, HD = haemodialysis, Pred = prednisolone, IVIg = intravenous immunoglobulin, PD = peritoneal dialysis, dPD = decremental peritoneal dialysis 3 days per week

DISCUSSION

Globally, the prevalence of SLE varies widely in different geographical regions, depending on the ethnicity, environmental exposures, and socio-economic status of the population. Its prevalence is low in the White population, with only 29 cases per 100,000 population in Malta of Europe, as compared to the Black population, which can be as high as 7,700 cases per 100,000 population in Senegal of Africa region.[1] A 38% of SLE has renal involvement with LN as the initial presentation, with higher overall morbidity and mortality as compared to those without renal involvement. In Malaysia, the estimated prevalence of SLE is 43 cases per 100,000 population, predominantly in the Chinese ethnic group.[2] The incidence of LN is higher in Malaysia as compared to global data, affecting 74% of SLE patients.[2]

LN can be classified into six classes based on its histopathological findings in the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for LN. Class I (minimal mesangial) and class II (mesangial proliferative) are considered as non-proliferative LN, whereas class III (focal proliferative and sclerosing) and class IV (diffuse proliferative and sclerosing) are considered as proliferative LN which require aggressive immunosuppressive therapy. Class V (membranous) LN commonly manifests as nephrotic syndrome and class VI (advanced sclerosis) LN is end-stage LN with a terminal prognosis. The natural course of LN is characterised by intervals of active disease and remission. Recurrent relapses of LN especially proliferative LN (class III and IV ISN/RPS) lead to cumulative insults to the kidneys, leading to progression to chronic renal failure and end-stage renal disease. Class V (ISN/RPS) LN has lower risk of renal failure; however, recurrent nephrotic syndrome can increase the risk of cardiovascular events. Thus, properly tailored immunosuppressive therapy is important to maintain disease remission and prevent progression to renal failure.

Crescentic LN has been observed in more than 50% of biopsy-proven RPGN, and around 10% of biopsy-proven LN with higher prevalence (21.7%) in class IV (ISN/RPS) LN.[3] It is one of the most challenging causes of RPGN as it is associated with poor treatment response and high risk of progression to end-stage renal failure especially in those with high serum creatinine upon presentation. Our case presented with acute onset and short disease duration of renal failure with a serum creatinine of 895 µmol/L requiring RRT, and her renal biopsy showed class IV (ISN/RPS) LN with widespread cellular and fibrocellular crescents, with high activity and chronicity indices and 45% of chronic tubule-interstitial damage. These characteristics indicate a poor prognosis and low renal survival rate.

The recommended induction therapy of proliferative LN according to Kidney Disease Improving Global Outcomes (KDIGO) in 2021 includes the use of intravenous methylprednisolone of 250–500 mg daily for 3 days, followed by oral prednisolone of 0.6–1 mg/kg daily to taper to less than 7.5 mg daily by the end of 3 months, with the addition of another immunosuppressive agent which is either intravenous cyclophosphamide 500 mg 2 weekly for total six doses (Euro Lupus Nephritis Trial Protocol) or oral MMF 2–3 g daily for 6 months (Aspreva Lupus Management Study).[4] National Institute of Health (NIH) protocol on the other hand uses high dose intravenous cyclophosphamide of 0.5–1 g/m^2 monthly for 6 months. In our centre, the induction therapy for proliferative LN consists of a lower dose of corticosteroids with intravenous methylprednisolone 250 mg daily for 3 days followed by oral prednisolone 0.5 mg/kg daily with a tapering dose of 5 mg per month to maintain at 10 mg daily. The intravenous cyclophosphamide protocol for induction therapy is 400–500 mg/dose 2 weekly for four doses in 2 months followed by 10–12 mg/kg/dose monthly for 4 months which is a combination of Euro Lupus Nephritis Trial Protocol and NIH protocol. Our treatment protocol utilises an overall

lower dose of immunosuppressive therapy with a lower risk of infection but is able to achieve a comparable long-term renal outcome as compared to world data.[5]

Our present case was treated with plasma exchange for six cycles followed by IVIg for 5 days which are not stated in any standard guidelines for the treatment of crescentic LN. She was then given an induction therapy with a lower dose of intravenous methylprednisolone followed by a standard dose of tapering oral prednisolone. The intravenous cyclophosphamide given was a modified regime of 2 weekly doses of 250–300 mg for a total of 6 months which is a much lower dose as compared to the standard treatment recommended by KDIGO in 2021. She was able to recover and discontinue her RRT after 4 months of treatment without any complications with infection.

CONCLUSION

Our treatment protocol utilise an overall lower dose of immunosuppressive therapy and adjunctive therapy of plasma exchange with lower risk of infection but able to achieve a comparable long-term renal outcome as compared to world data.[5]

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CASE REPORT

Collateral damage of COVID-19: Late presentation of cerebrovascular accident

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SUMMARY

Coronavirus disease 2019 (COVID-19) is associated with an increased risk of death due to the sequelae of inflammation and thrombosis. Patients infected with COVID-19 are at risk of ischemic stroke due to the effects of inflammatory cytokine storm, platelet activation, endothelial dysfunction and prolonged stasis. We report a case of severe COVID-19 infection who developed acute ischemic stroke during the course of his illness. The patient did not carry any traditional risk of stroke or thromboembolic event and was vaccinated. He tested positive for COVID-19 infection, but due to respiratory distress, he was intubated and ventilated. On the 11th day in intensive care unit, he was noted to be hemiplegic with poor neurological recovery. Despite being on treatment dose enoxaparin, his computed tomography confirmed a lacunar infarct in his brain and bilateral pulmonary embolisms. Twenty-five days later, he remained well and was discharged home with dabigatran and atorvastatin.

INTRODUCTION

In December 2019, Wuhan, China, reported viral pneumonia called SARS-CoV-2, a recently identified betacoronavirus of suspected zoonotic origin. It was later confirmed and named coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO). The clinical spectrum of this infection is variable, ranging from being asymptomatic to having a critical illness characterised by acute respiratory distress syndrome, resulting in hypoxic respiratory failure. COVID-19 is associated with significantly higher morbidity and mortality in the elderly and patients with co-morbidities.[1]

COVID-19 is associated with an increased risk of acute stroke, similar to other respiratory infections, which had been reported to be between 3.2 to 7.8-fold higher.[2] A systematic literature review was conducted in April 2020 which showed that the proportion of COVID-19 patients with acute ischemic stroke was estimated to be 4.9%.[3] This increased risk of ischemic stroke is due to the effects of inflammatory cytokine storm, platelet activation, endothelial dysfunction and prolonged stasis.[2,3] We report a case of COVID-19 complicated with acute ischemic stroke and pulmonary embolism in a previously well man.

CASE PRESENTATION

A 65-year-old man who completed his vaccination presented with fevers, cough, anosmia and shortness of breath. He had no underlying co-morbidities or risk factors for thrombosis. On examination, he was febrile with a temperature of 38.3ºC, a pulse rate of 110 beats per minute and normal blood pressure of 130/80 mmHg. He was in respiratory distress, tachypnoeic, with a respiratory rate of 26 breaths per minute and oxygen saturation of 81 under room air. Other pertinent findings include bilateral crackles on auscultation of the chest. Due to the increased work of breathing and poor oxygenation, he was intubated and ventilated.

Polymerase chain reaction (PCR) for SARS-CoV-2 was positive. An arterial blood gas (ABG) was performed, indicating type 2 respiratory failure. His chest radiograph (CXR) confirmed changes in COVID-19 pneumonia (Figure 1). An electrocardiogram (ECG) showed sinus tachycardia with no acute ischemic changes. Other blood test results include a normal haemoglobin 13.7 g/dL, normal white cell count of 6.8 × 10^9/L, mild thrombocytosis 567 × 10^9/L, and normal lymphocyte count of 1.15 × 10^9/L. He had mildly raised serum creatinine 127 µmol/L. His liver enzymes were normal. C-reactive protein (CRP) was slightly raised to 20.8 mg/L, D-dimer 322 ng/mL and a normal ferritin 400 mcg/L. A carotid Doppler ultrasound was performed, which was normal and had no haemodynamic repercussions. Antiphospholipid tests were negative.

Thus, our impression was of severe COVID-19 pneumonia category five. He was transferred to the intensive care unit (ICU) for ongoing care. Initial management includes intravenous methylprednisolone 140 mg and later dexamethasone 20 mg daily on a tapering dose. In addition, subcutaneous enoxaparin 60 mg twice daily was commenced for deep vein thrombosis (DVT) prophylaxis.

Whilst weaning off mechanical ventilation on day 11, his Glasgow Coma Scale (GCS)remained poor, and he was noted not to move his right side. Neurological examination confirmed right hemiplegia. Babinski's sign was negative, and his deep tendon reflexes were normal. A computed tomography (CT) scan of the head showed hypodensity over the left corona radiata (Figure 2). We also performed high-resolution CT (HRCT) and CT pulmonary angiogram (CTPA) of the lungs, which showed bilateral lower lobe pulmonary

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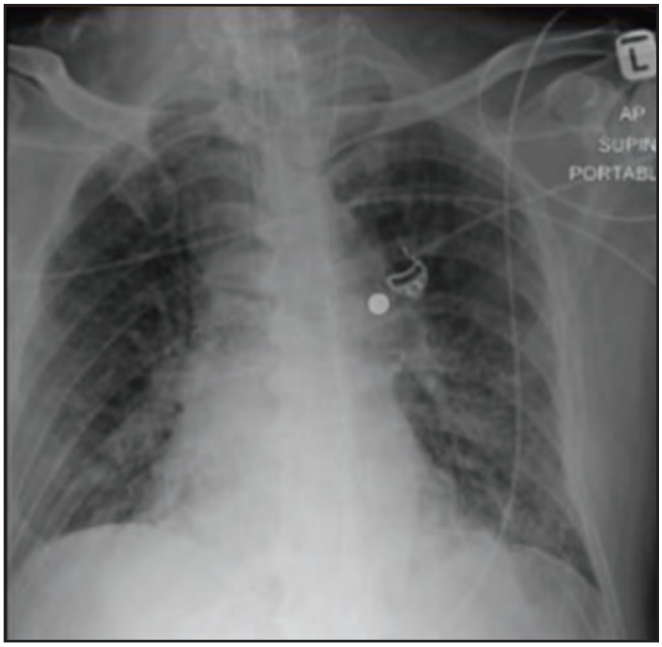

Fig. 1: Chest x-ray showed presence of ground-glass opacities in both lung

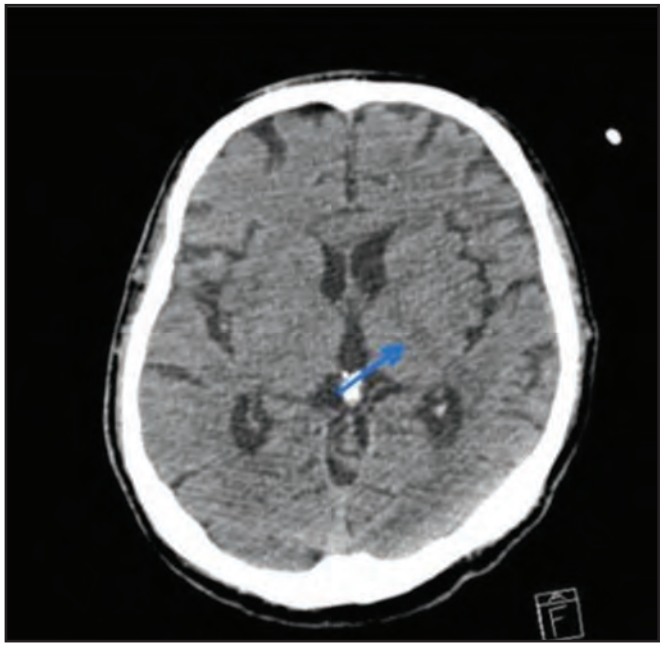

Fig. 2: A computed tomography (CT) scan of the head showed hypodensity over the left corona radiata

embolisms and organising pneumonia. During his ICU stay, his ECG on cardiac monitoring showed normal sinus rhythm.

He was later extubated and made a good recovery 3 weeks after extubation, not requiring further oxygen supplementation. His left hemiplegia improved; muscle power grade 4 over 5. His National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) were 5 and 3, respectively. He has been discharged home on dabigatran 15 mg and atorvastatin 40 mg. He had ongoing follow up with the physiotherapist and stroke rehabilitation team.

DISCUSSION

This case describes a confirmed case of COVID-19 infection complicated with acute ischaemic stroke and pulmonary embolism. The thrombotic events involving multiple organs in a patient with no known cardiovascular risk factors concomitant with COVID-19 infection are under-reported. The underlying pathological causes of brain ischemia and stroke in patients with COVID-19 include thrombosis, embolism and systemic hypoperfusion.

Thrombosis is caused by a cytokine storm and activation of the innate immune system, whereas embolic events are caused by pre-existing or new-onset cardiac arrhythmias. Patients with COVID-19 are found to have elevated levels of both interleukin-6 (IL-6) and CRP. IL-6 perpetuates the hypercoagulable state associated with COVID-19 through induction of tissue factor expression in mononuclear cells, triggering acute endothelial cell activation, activation of acute phase response resulting in enhanced fibrinogen production by hepatocytes and platelet hyperactivation and aggregation.[4] A thromboembolic storm can occur in patients with severe thrombosis. Clinical manifestations include right-sided cardiac overload due to pulmonary embolism or severe microvascular thrombosis like livedo racemosa or ischemia of the kidneys, muscle and liver. These will further increase the mortality risk of the patient.

Ischaemic stroke has been classified into different etiologic subgroups. These include cardioembolic, atherosclerotic, lacunar, other specific causes (dissections, vasculitis, specific genetic disorders, others) and strokes of unknown causes.[5] Revascularisation and the prevention of subsequent neuronal injury are the fundamental goals of advanced stroke treatment. Early intervention is essential in the reduction of morbidity and mortality. Predictors of premature mortality include advanced age, pre-stroke functionality, coronary artery disease and diabetes.[6] In an observational study, patients with neurological complications were found to have severe COVID-19 infection; up to 6% of patients had an acute ischemic stroke compared to 1% of patients with non-severe COVID-19 infection.[7]

Our case was challenging as the patient's presentation was noted while under sedation, and it was difficult to assess the patient's full neurological function, including GCS, power and sensation. In addition, the clinical detection of stroke could have been delayed due to deep sedation during mechanical ventilation. CT or MRI of the brain can be performed to aid the diagnosis in an intubated patient. However, rapid prehospital screening such as the Cincinnati Pre-Hospital Stroke Scale (CPSS) or Face, Arm, Speech, Time (FAST) score for prehospital screening is useful because any diagnosis is provisional until confirmed through investigation.[8]

CONCLUSION

A patient with no known cardiovascular risk factors for whom COVID-19 infection appeared to be an independent risk factor for developing acute ischaemic stroke due to the hypercoagulability state. Therefore, it is crucial to identify patients at higher risk of developing the thromboembolic disease by using the Cincinnati Pre-Hospital Stroke Scale (CPSS) or Face, Arm, Speech, Time (FAST) score as pre-admission assessment and start therapeutic dose of anticoagulation to reduce the risk of mortality and morbidity in those patients with high risk.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare no competing interests with respect to the authorship and publication of this article.

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Leech infestation causing haematuria

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SUMMARY

Leech infestation in the urinary bladder is a rare cause of haematuria and acute lower abdominal pain. In this case report, we discuss a 63-years old Malay man who presented with acute urinary retention for 1 day associated with lower abdominal pain. Subsequently, upon insertion of urinary catheter in the emergency department frank haematuria was noted. Images showed tubular structures within the urinary bladder. Based on strong clinical suspicion, cystoscopy was done, and diagnosis was confirmed.

INTRODUCTION

In Malaysia, leech is a common occurrence in paddy fields, agriculture and fishing industries. Leech - of the subclass Hirudinea, phylum Annelida has about 650 species of segmented worms. They are characterised by a small sucker which contains the mouth at the anterior end, and a large sucker at the posterior end.[1] They can range from a minute size to 20 cm in length and are known to grow to three times their size. These leeches are usually found in fresh water and land.[1]

There have been many cases of leech bites and leech infestations in Asia, Africa and the Mediterranean.3 These leeches can also enter human orifices such as vagina, urethra, rectum and eyes causing bleeding in these areas.[3] The bleeding is due to the secretion of hirudin, an anticoagulant by the leech.[2]

Salt, vinegar and alcohol can be used to remove external leeches. Leeches in the urinary bladder can be removed via cystoscopy, suprapubic approach or hypertonic saline irrigation.[2,4] However, studies have shown that removal by cystoscopy is the preferred approach as it is quick with less bleeding and discomfort to the patient.[4]

CASE PRESENTATION

A 63-years-old Malay fisherman presented with acute urinary retention for one day associated with lower abdominal pain. Prior to this presentation, the patient gives a history of having a leech bite him at the penile meatus while setting up his fishing net early in the morning. He managed to remove that leech and throw it away. However, he was unable to confirm if any other leech went into the meatus.

On presentation to the Emergency Department (ED), Foley's catheter was inserted, and frank haematuria noted. Initial bedside ultrasound in the ED showed moving tubular structures within the urinary bladder with blood clots (Figure 1).

Formal ultrasound in the Radiology Department revealed a large blood clot. We followed through with a CT urogram which showed a hyperdense elongated tubular structure at the anterosuperior aspect of the urinary bladder and a haematoma (Figures 2).

Since admission to ED, the patient had continuous haematuria leading to a drop in haemoglobin levels and low blood pressure due to volume loss. His haemoglobin level was between 9 and 10g/dL, and blood pressure reading was between 80 and 90/48-57 mmHg. Initial treatment given in Hospital Seri Manjung included bladder irrigation, fluid resuscitation and packed cell transfusion.

Case was discussed with the urologist from tertiary hospital. In view of copious amount of haematuria and blood clots within the urinary bladder, further 4-phase Renal computed tomography (CT)was ordered by Urology to rule out the possibility of transitional cell carcinoma. The 4-phase renal CT revealed an increasing size of haematoma with a persistent non-enhancing elongated tubular hyperdense structure within the urinary bladder.

The case was transferred to the Urology Department in tertiary hospital for further management. A cysto-endoscopy and clot evacuation and cysto-diathermy were done. Intraoperatively noted blood clots and a leech. The leech measured 16 cm in length (Figure 3). Multiple bite marks were seen in the bladder wall. The leech was removed using forceps, and clot evacuation was done.

Post-procedure, the patient was admitted to ICU for postoperative urosepsis requiring ionotrope support. Patient showed good recovery with good urine output and clear urine postoperatively. Foley's catheter was removed on day 5 of surgery, after which the patient was able to pass urine on his own.

DISCUSSION

As simple as it may sound, leech infestations can be quite detrimental and life-threatening. Leech infestation within the urinary bladder can cause haematuria leading to blood loss and severe anaemia requiring packed cell and fresh frozen plasma replacement.[4,5] Leech bite can cause prolonged haemorrhage due to presence of histamine like vasodilators in the leech saliva, hirudin (a potent antithrombin), hyaluronidase, and calin (a platelet aggregation inhibitor). Besides that, people are usually unaware of the leech bite as it is painless due to the existence of local anaesthetics secreted by the leech.[4,5]

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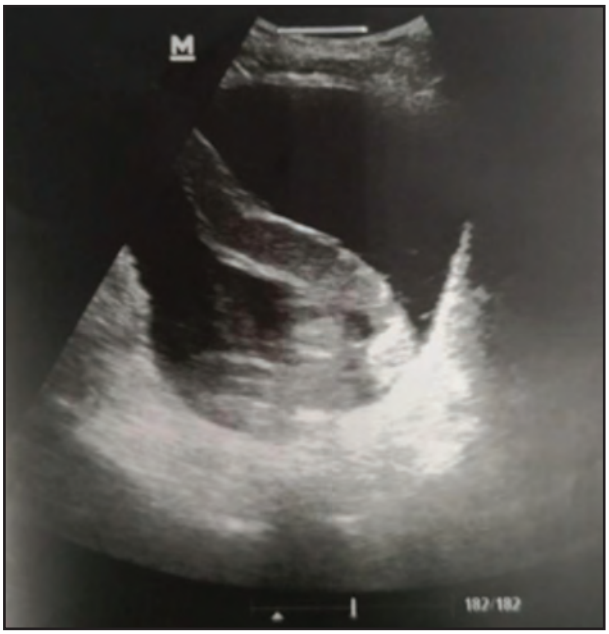

Fig. 1: Ultrasound images tubular structure within the urinary bladder likely of leech

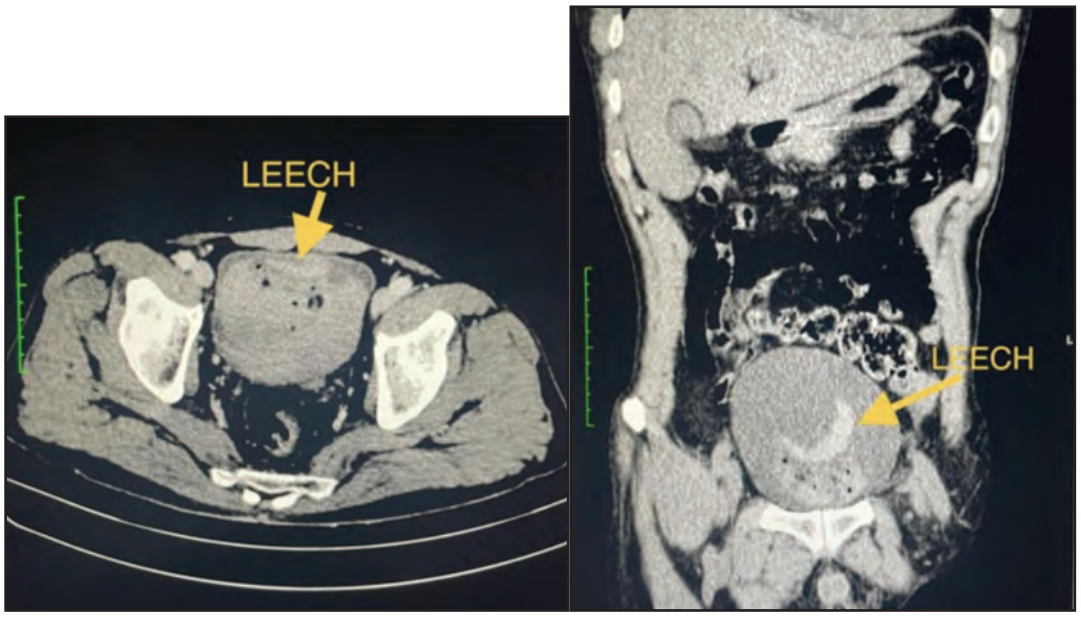

Fig. 2: CT images. Axial and coronal images from contrasted CT abdomen show tubular structures within the urinary bladder with blood clots suggestive of leech

Other sites of infestation include rectum. A case report of acute severe gastrointestinal bleeding following leech infestation highlights complications of leech infestation into the rectum requiring colonoscopy and endotherapy to arrest the bleeding.[6] A single case report of excessive intractable haemorrhage resulting from multiple leech bites which caused disseminated intravascular coagulation required fresh frozen plasma and erythrocyte suspension replacement.[5]

Few reported cases of nasal leech infestation presented with unilateral epistaxis and airway obstruction. These cases were treated with 10% lidocaine nasal spray and the leech subsequently removed via nasal endoscopy.[7,8]

Ocular leech infestation can present with subconjunctival haemorrhage. The leech was found over the bulbar conjunctiva near the limbus. These patients usually present with foreign body sensations. Treatment includes 4% xylocaine and 2% pilocarpine drops which results in the leech releasing its suction and dropping off.[9]

Other complications that can arise are remnant foreign bodies (suckers of the leech) embedded in the tissues at the bite site10 which requires surgical removal. These retained foreign besides can be a source of continuous bleeding or infection.

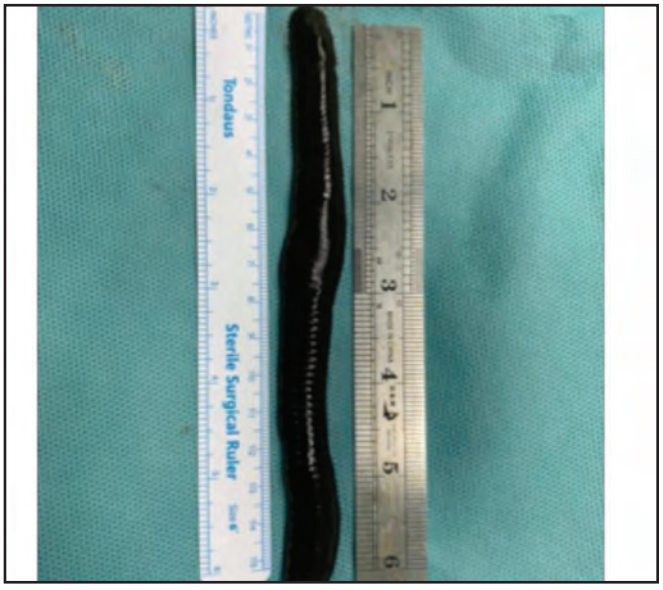

Fig. 3: Leech is removed via cystoscopy

This case is interesting since the main presenting complaint was unable to micturate and lower abdominal pain rather than haematuria. Leech infestation was later diagnosed correlating clinical and imaging findings. This patient experienced a large amount of blood loss requiring packed cell replacement. The leech was finally removed via cystoscopy. The patient made a full recovery with no obvious chronic complications at the time of writing.

Given the typical demography, the patient being a fisherman in a rural region, and clinical findings of haematuria with volume loss, and blood clots and foreign body within the urinary bladder; a leech infestation needs to be the main consideration. Early referral to tertiary centre and swift treatment are of utmost necessity to ensure patient survival. This patient successfully made a full recovery with no obvious chronic complications at the time of writing.

CONCLUSION

Leech infestation is a common occurrence in rural areas, though uncommon in cities. Haematuria is the most common presentation, however other presentations like urinary retention, as with this case, and a strong clinical history warrant a high index of suspicion. Adequate imaging and prompt treatment is needed for proper patient management.

CONFLICT OF INTEREST

There is no conflict of interest.

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CASE REPORT

Caecal endometriosis mimicking caecal tumour

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SUMMARY

Extra-pelvic endometriosis is a rare entity that presents extreme challenge to clinicians. Caecal endometriosis may pose a diagnostic dilemma preoperatively as it simulates various numbers of gastrointestinal pathologies with nonspecific manifestation. Even though endometriosis is a benign disease, invasion to the bowel can cause significant morbidity and mortality. Rectosigmoid junction is the most commonly affected bowel in extra-pelvic endometriosis while right sided colon involvement is rare. We report a case of a 29-year-old pregnant woman with incidental findings of caecal mass during lower segment caesarean section (LSCS) for foetal distress. The diagnosis of caecal endometriosis was made postoperatively by histopathological result of resected right colon. Distinguishing the diagnosis of the bowel endometriosis with colorectal cancer may be challenging, and this case emphasises the need to consider intestinal endometriosis in females at a reproductive age presenting with gastrointestinal symptoms and intestinal mass.

INTRODUCTION

Endometriosis is a benign gynaecological disease defined as the presence of endometrial tissue outside the uterine cavity, predominantly in the pelvic compartment. It is an oestrogen-dependent chronic inflammatory condition affecting women in the reproductive period with peak age in between 25 and 35 years. Up to 10% of the women reported to have endometriosis. The most frequent location of endometriosis is the ovary, pouch of Douglas and the uterosacral ligaments.[1] Bowel is the most commonly affected extra-pelvic location (3 to 12%), with majority in the rectosigmoid colon (50 to 90%). However, right sided colon involvement as depicted in this case report is a rare event with only 2 to 5% reported case.[1] With non-specific clinical manifestations and its rarity, distinguishing caecal endometriosis from other pathologies can be extremely difficult. In fact, only few similar cases have been reported to our knowledge.

CASE PRESENTATION

A 29-year-old woman at 31 weeks period of gestation presented with a sudden onset of continuous abdominal pain for one day. She denied any bowel symptom and significant past medical history. On physical examination, she was found to have a 30-weeks' gravid uterus and tenderness at right iliac fossa. After assessment by obstetric team, LSCS was decided for suspected abruptio placenta. During the operation, no abruptio placenta was found but there was localised pus collection at the right paracolic gutter with inflamed hard caecal mass. Several enlarged lymph nodes were also present along ileocolic vessels. Surgical team was summoned, and right hemicolectomy with ileocolic anastomosis was performed.

Histological findings revealed extensive decidualisation, involving the serosa, muscularis propria and submucosa, sparing the colonic mucosa, consistent with caecal endometriosis. This decidualised stroma was also infiltrated by mixed inflammatory infiltrates forming focal microabscess. Resected surgical margins were clear. She had uneventful recovery postoperatively and was well at one month post operation.

DISCUSSION

Since 1927, Sampson et al. theorised that endometriosis could result from retrograde deposition of endometrial remains during menstruation.[2] However, various theories have been proposed throughout the years, including the coelomic metaplasia of the peritoneum or the dissemination of endometrial particles through lymphatic and hematogenous pathways.[1] Nevertheless, the true pathogenesis of endometriosis remains unknown.

The common sites of endometriosis are the ovaries, cul-de-sac and uterosacral ligaments, while atypical nongynecological sites for the disease include the gastrointestinal tract, vermiform appendix, urinary tract and abdominal wall tissues, with additional reports on the pulmonary tract, lymphatic system, skin, musculoskeletal system and central nervous system.[2] These atypical sites pose significant challenge to ascertain the diagnosis.

It is noteworthy that the caecum is rarely involved, reported only 5% from of all intestinal endometriosis as the more common sites include the rectosigmoid, followed by small intestine and appendix. Clinically, caecal endometriosis can mimic several diseases such as Crohn's disease, appendicitis, diverticulitis and even colon cancer. Hence, distinguishing colonic endometriosis from other gastrointestinal pathologies can be arduous. It poses diagnostic dilemma to the clinician preoperatively as the clinical features of bowel endometriosis

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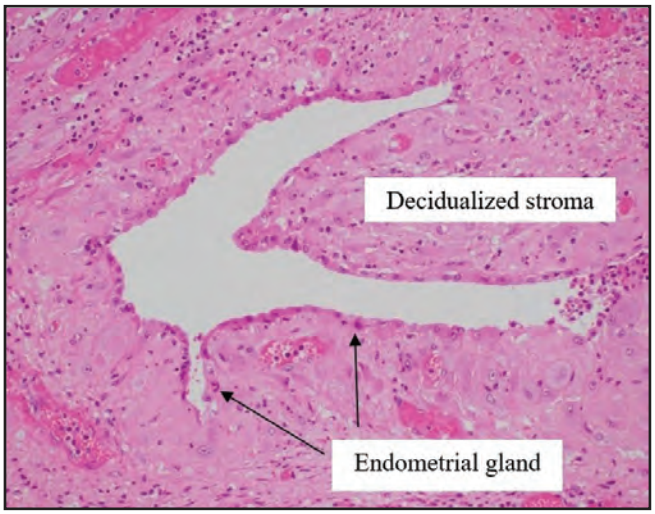

Fig. 1: Endometrial gland with surrounding decidualised stroma (20x)

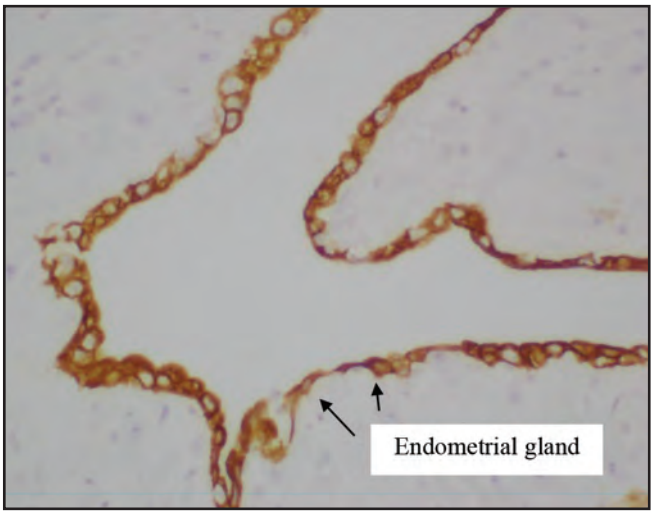

Fig. 2: CK7 highlights the endometrial gland (40x)

can be non-specific. These symptoms depend on disease localisation, size of nodule and depth of involvement of the bowel wall.[3] Thus, any cyclical pelvic symptoms should raise the suspicion of endometriosis.

Histologically, endometriosis with muscular infiltration was encountered in 71% of the cases and serosa infiltration in 9.6% of the cases. Penetration into the intestinal lumen is rare, reportedly found in 4.8% of cases.[3] Like a normal endometrial tissue, ectopic endometrial tissue in the caecum also underwent decidualisation in response to hormonal changes during gestation as depicted in the histological finding of our case (Figure 1). These endometrial stromal cells can invade through bowel wall causing inflammation. Immunohistochemical staining such as CK 7, is essential to confirm the lesion, is endometrial in origin.[3] The endometrioid glands are usually immunoreactive towards CK7 as portrayed by our patient (Figure 2).

Intestinal endometriosis is usually asymptomatic and most of the cases were found incidentally during surgery. Although no gold standard is universally accepted for the diagnosis of bowel endometriosis, magnetic resonance imaging (MRI) is one of the most used techniques with an 88% sensitivity and 98% specificity.[4]

Treatment is based on the clinical presentation of intestinal endometriosis. In case of endometriosis-related bowel obstruction, resection of the affected intestine is required, and 60 to 100% of patients reported an improvement after excision of deeply infiltrating lesions.[5] This is illustrated in our case, whereby patient made fully recovery after bowel resection. On the other hand, nonpenetrating lesion can be excised and followed by oestrogen suppression, or gonadotropin releasing hormone agonist (GnRHa).[1]

Surgery is still the treatment of choice to avoid neglecting malignant tumour and some complications such as perforation or bowel obstruction. Currently, there is no guidelines with high level of evidence existed specifying which lesions should be operated on, when this is indicated, and which standardised surgical technique is recommended. The preoperative differential diagnosis in this setting is almost impossible, resulting to the need for postoperative histological confirmation. Presentation as abdominal pain can be a clinical challenge due to absence of pathognomonic symptoms and can also masking as labour symptoms. Prompt and accurate clinical and radiological evaluation is necessary as complications of endometriosis such as bowel perforation and obstruction may require urgent surgical intervention. Ultrasound has limited role in diagnosing bowel-related mass. Adjunct axial imaging is also not possible due to hazard of radiation exposure to the foetus.

CONCLUSION

Our case demonstrates that despite its rarity, surgeons should aware that endometriosis may present as a colonic mass, and it should be considered in the differential diagnosis of females at fertile age presenting with abdominal mass.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the authorship, and/or publication of this article. The authors received no financial support for authorship, and/or publication of this article. Informed consent was obtained from the patient in this case report.

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Endobronchial solitary mixed squamous cell and glandular papilloma: A rare cause of left main bronchus obstruction

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SUMMARY

Papillomas of the respiratory tract are generally multiple and arise from the upper respiratory tract. Solitary pulmonary papillomas (SPP), especially of the mixed variety are rarely seen. Here, we report a case of 55-year-old woman who presented with left upper lobe collapse. Bronchoscopy showed an exophytic mass with an irregular polypoidal surface in the left main bronchus. Endobronchial biopsy confirmed mixed squamous cell and glandular papilloma, which was treated with the bronchoscopic resection using an electrocautery snare and cryoprobe.

INTRODUCTION

Solitary pulmonary papillomas (SPP) of the lower respiratory tract are rare benign neoplasms. They account for <0.5% of all lung tumours and ~7% of benign epithelial and mesenchymal lung tumours.[1] The precise aetiology of the respiratory papillomas remains unclear. The proven risk factors include human papilloma virus (HPV) infection and smoking.[2] Histologically, SPPs are classified as squamous cell papilloma, glandular papilloma and mixed squamous cell and glandular papilloma (MSCGP).[3] Amongst the three histologic subtypes of SPP, mixed papillomas are the rarest and constitute 15.8% of the cases.[4] Here, we report a case of MSGCP in a 55-year-old Indian woman who presented with a left main bronchus obstruction and was managed by bronchoscopic resection.

CASE PRESENTATION

A 55-year-old woman presented to the out-patient department with dyspnoea which gradually progressed from mMRC Grade 1 to mMRC Grade 3 over 1 month. She also had dry cough and low-grade fever for 5 days. She had no addictions and was on regular medication for hypothyroidism. On examination, breath sounds were diminished in left infra clavicular, mammary, supra scapular and upper inter scapular areas. A chest radiograph and computed tomography (CT) scan of the chest showed left upper lobe collapse. Diagnostic bronchoscopy performed under conscious sedation to ascertain the cause of collapse revealed an exophytic mass with an irregular polypoidal surface protruding from the left upper lobe bronchus and extending into the left main bronchus causing ~90% luminal occlusion (Figure 1A).

Endobronchial biopsy of the mass showed fibro-vascular papillary cores lined predominantly by glandular epithelia with foci of transitions into non-keratinising squamous epithelia. The glandular epithelium was composed of ciliated and non-ciliated pseudostratified columnar cells and a few mucous columnar cells. No nuclear atypia, stromal or vascular invasion was noted (Figure 2A, 2B, 2C). Immuno-histochemical analysis revealed squamous cells that were positive for p63 and cytokeratin 5/6 while the glandular epithelium was positive for CK7 (Figure 2D, 2E). A diagnosis of solitary mixed squamous cell and glandular papilloma was made.

Patient then underwent a whole-body positron emission tomography- computed tomography (PET-CT scan) which did not reveal any other focus of disease. The available treatment options were discussed with patient who then opted for endobronchial management of the benign tumour. The procedure was performed under general anaesthesia. Rigid bronchoscopic intubation was done and the tumour was excised using a combination of electrocautery snare and a 1.9 mm cryoprobe (Figure 1B). The base of tumour appeared to arise from the left secondary carina which was cauterised using a blunt tipped electrocautery probe to achieve haemostasis and prevent recurrence. The procedure was uneventful, and the patient was discharged on the next day. Histopathological examination confirmed the diagnosis of mixed squamous cell and glandular papilloma. On immunohistochemical analysis, both squamous and glandular epithelia were negative for p16 (Figure 2F).

Patient has been under regular follow up. Patient continues to remain symptom free 1-year post procedure. Surveillance bronchoscopy showed normal tracheo-bronchial tree with no recurrence of the tumour (Figure 1C).

DISCUSSION

Papillomas are rare benign lung tumours. They generally arise from the upper respiratory tract and are multiple in number. Solitary papillomas of the lower respiratory tract are

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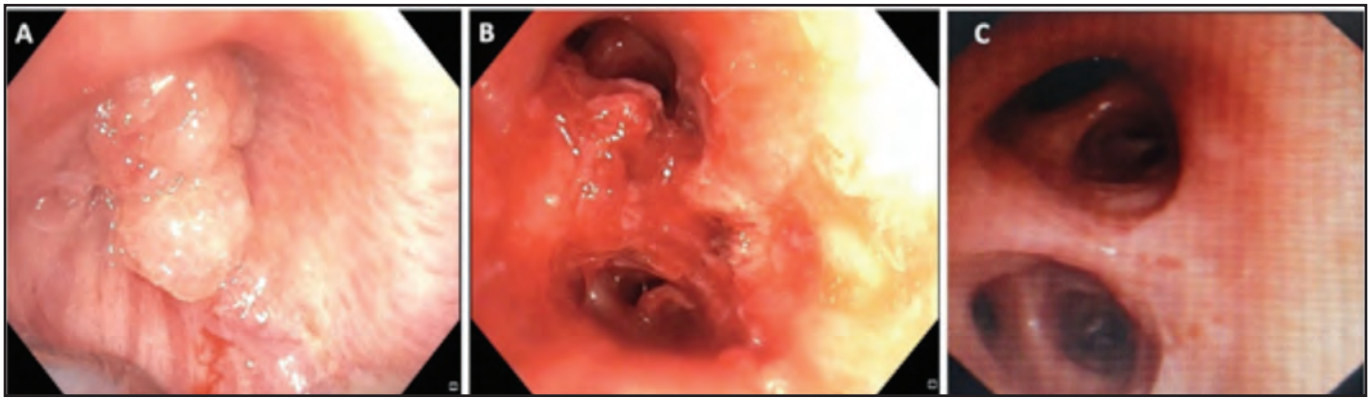

Fig. 1: A) Initial bronchoscopic image showing near complete occlusion of the left main bronchus with an exophytic mass having an irregular polypoidal surface; B) Image post endobronchial tumour removal showing patent segments of the left upper and lower lobes; C) Bronchoscopic surveillance image taken at 1-year follow up showing normal endobronchial anatomy with no residual disease

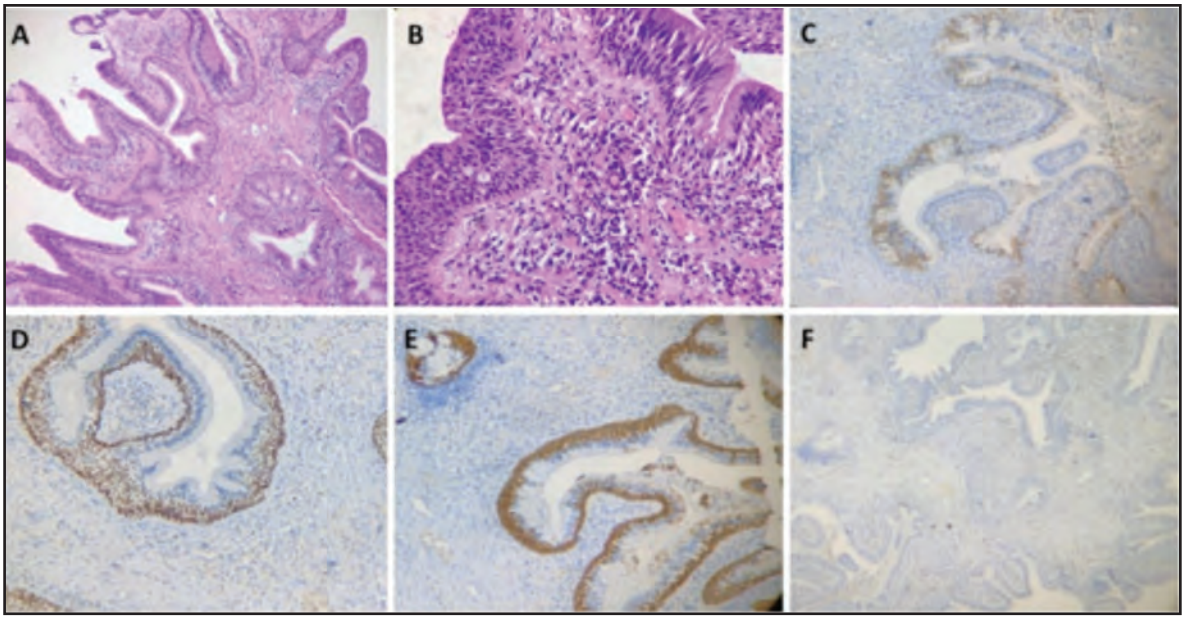

Fig. 2: A) Photomicrograph of the endobronchial biopsy showing papillary structures lined by epithelial cells without stromal invasion (haematoxylin and eosin stain, 10x); B) Tumour composed of squamous cells and ciliated columnar cells without nuclear atypia (haematoxylin and eosin stain, 40x); C) CK 7 positive columnar/glandular epithelium; D) p63 positive squamous epithelium and basal cells of glandular epithelium; E) CK 5/6 positive squamous epithelium and basal cells of glandular epithelium; F) Negative immunohistochemistry for p16

uncommon. The incidence of SPP is reported to be 3.95 cases/105 patients/yr. SSP's usually present in 3rd to 6th decade of life and affect men three times more commonly than women.[4] HPV infection, smoking and presence of an airway foreign body are the known risk factors for SPP.[2,5] Most common symptoms at presentation are cough, haemoptysis, dyspnoea, fever and wheezing. Histologically SPP are classified as squamous (65.35%), glandular (19.8%) or mixed squamous cell and glandular papillomas (15.8%). Malignant transformation is seen in squamous (10.8%) and mixed papillomas (25%).[4]

Mixed papillomas are the least common histologic type of SPP. They are generally seen from 3rd to 6th decade of life with the youngest case reported being 17 years old.[6] As compared to other papillomas, smoking history (78%) is more common in patients with MSCGP.[7] Patients with smoking history usually had a centrally located tumour.[8] MSCGP showed no predilection for any particular side of the lung and peripherally located papillomas were more common than central. Most of the previously reported cases of MSCGP are from the Korean and Japanese population.[9]

Our case is a middle-aged woman from India with a centrally located MSCGP. She had no prior history of smoking or passive cigarette smoke exposure. However, the patient had history of significant exposure to biomass fuel burning which she uses on a daily basis for household purposes. This biomass fuel exposure could have predisposed to development of the papilloma. Similar to cigarette smoke,

exposure to biomass fuel is a well-established risk factor for various respiratory diseases and malignancies in the developing world.[10] Association of airway papillomas with biomass fuel exposure is still unexplored.

There is no reported association between HPV and MSCGP.[9] Immunohistochemical analysis in our patient also showed that both squamous and glandular epithelia were negative for p16. Negative HPV status and common history of smoking in MSCGP may indicate an aetiological association with tobacco smoke. This is postulated as the most likely reason for higher malignant transformation (25%) in MSCGP as compared to other SPP. The higher risk of malignant transformation must be considered in deciding the treatment option for MSCGP. Conservative management may be justified in glandular papillomas but excision is to be preferred in squamous papillomas and MSCGP.

Results with both lung resection surgery and endoscopic removal of the lesion followed by close monitoring are encouraging. Lobectomy is the most commonly performed surgical procedure.[4,9] There are no randomised studies comparing surgery and bronchoscopic removal for management of solitary papillomas. Bronchoscopic approach can be offered to patients with purely endo-luminal lesions, and at centres with expertise in bronchoscopic removal of tumours. As the best treatment option remains unclear, it must be individualised to each patient after a through discussion with the patient regarding all the available options. Our patient wanted a less invasive procedure and hence chose to undergo bronchoscopic removal of the tumour. She has been under regular follow-up and surveillance bronchoscopy showed no recurrence after a period of 1 year.

CONCLUSION

Solitary papillomas of the lower respiratory tract are uncommon benign tumours of the tracheobronchial tree. A high index of suspicion is needed to diagnose these uncommon tumours. When they are purely endoluminal, a bronchoscopic resection of these tumours can be safely performed. Solitary papilloma is an uncommon cause of endobronchial tumour and must be considered as adifferential for benign endobronchial lesions. Biomass fuel exposure may be considered a risk factor forcentral papillomas, especially in the developing world.Selected cases of purely endobronchial tumours can bemanaged successfully with endobronchial resection.

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CASE REPORT

Recurrent medullary breast carcinoma with good response to chemotherapy. A case report and revisit of pathology

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SUMMARY

Medullary breast carcinoma (MBC) is an uncommon variant of invasive ductal carcinoma accounting for less than 5% of all the invasive breast carcinomas. Despite its aggressive histopathological features, it has a much better prognosis compared to triple negative breast cancers. Herein, we present a case of a 37-year-old women who presented with right breast lump and diagnosed with invasive breast cancer with medullary features after an elective lumpectomy and axillary dissection. Due to an unplanned pregnancy, planned adjuvant radiotherapy and chemotherapy were withheld after the primary surgery. Following the delivery of her child, she had a local recurrence with distant metastasis evidenced by clinical examination and computerized tomography (CT) scan. Despite the dismal situation, she had a good response to chemotherapy and subsequently underwent an elective mastectomy and repeated axillary dissection. The management and pathology of medullary breast cancer is discussed in this case report.

INTRODUCTION

Breast cancer is the commonest malignancy amongst females worldwide.[1] Among the subtypes of breast cancer, medullary breast carcinoma (MBC) is a rare variant of invasive ductal carcinoma and its reported incidence is fewer than 5% of all invasive breast cancers.[1] MBC is one of the invasive and malignant subtypes.[2] The five key histopathological features of typical MBC include syncytial growth pattern (>75%), without glandular and intraductal structures, diffuse lymphoplasmacytic infiltration in the stroma, moderate or marked nuclear pleomorphism and complete histological circumscription.[3] Recent World Health Organization (WHO) 2019 classification of breast carcinoma has re-categorised MBC as a subtype of invasive breast carcinoma-no special type (IBC-NST) with medullary pattern rather than a distinct morphological subtype of medullary carcinoma.[4] These tumours commonly occur in middle-aged women of 45 to 52 years.

Despite its aggressive histopathological appearance and malignant characteristics, MBC have a favourable prognosis if treated promptly. In this case report, we aim to revisit the histopathological diagnosis and create awareness of a patient diagnosed with recurrent metastatic MBC with good response to palliative chemotherapy.

CASE PRESENTATION

A 37-year-old woman presented to the breast surgery clinic with a right breast lump for 3 months. She was previously well with no significant past medical history or prior admissions. There was no history of oral contraceptive usage, no prior breast surgeries performed and no family history of breast cancer. Apart from a right breast lump, there were no skin changes over the overlying mass. Physical examination showed a firm mass with regular margin at upper inner quadrant, measuring 2 × 1 cm, well circumscribed and not fixed to skin or underlying muscle, no axillary lymph node palpable. Bilateral breast mammography and ultrasound revealed a right breast hypoechoic lesion at 2 o'clock which was radiologically classified as high-risk Breast Imaging-Reporting and Data System (BI-RADS) 4C. Ultrasound guided fine needle aspiration cytology (FNAC) from the lesion showed atypical cells with high suspicion of malignancy. Chest x-ray and ultrasound abdomen showed no evidence of lung and liver metastasis. The patient underwent an elective right parallelogram mastopexy lumpectomy and axillary node dissection. Post-surgery, recovery was uneventful and final histopathology results were consistent with MBC with clear margins (pT1c N0 M0). Arrangements for post-operative chemotherapy and radiotherapy to the breast after breast conserving surgery the during follow-up of 1 month post operation were unsuccessful as the patient had an unplanned pregnancy (Gravida 3 para 2 at 5 weeks of gestation) and unable to proceed for further adjuvant oncological treatments due to possible risks of chemotherapy induced foetal toxicity. The patient had an uneventful delivery and remained asymptomatic after her delivery. However routine health checks during the breast surgery clinic follow-up after the delivery of her baby a year later revealed a right breast lump. She was immediately investigated for recurrence of breast cancer. During this period, a repeated computerized tomography (CT) staging of thorax, abdomen pelvis revealed a suspicious right breast lesion (size measuring 5 × 4.8 cm) with extension to the anterior mediastinum and intrathoracic, bilateral pleural metastasis and multiple liver metastasis (Figure 1). A repeat biopsy of the right breast lump showed benign breast tissue. The case was discussed in the hospital's tumour board meeting and the consensus is to treat this as recurrent metastatic breast cancer despite the negative breast biopsy, for first line palliative chemotherapy with carboplatin and paclitaxel which she completed six cycles. Reassessment staging CT thorax, abdomen and pelvis revealed smaller

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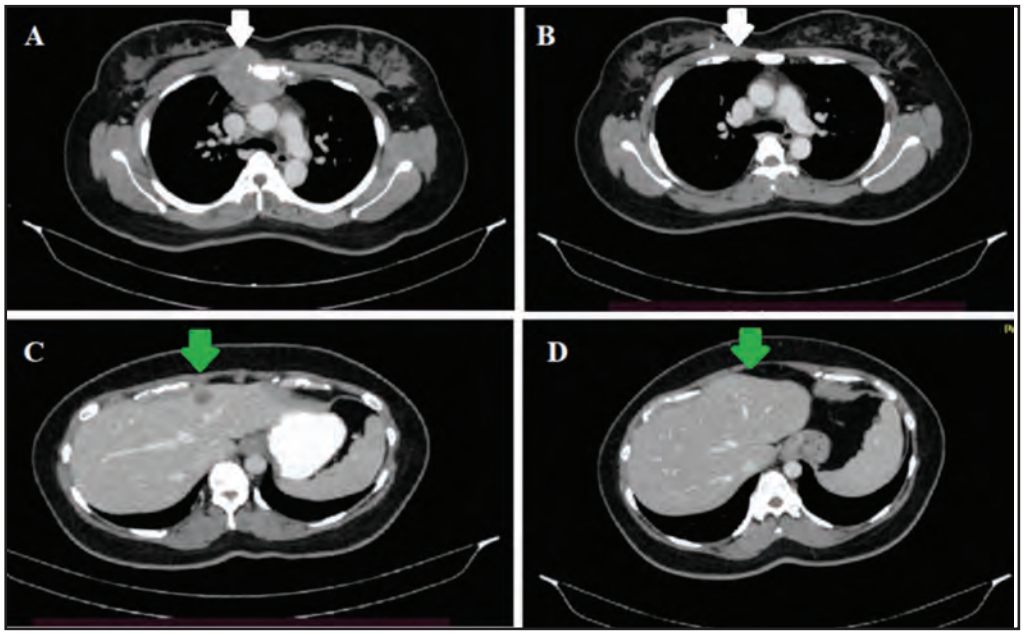

Fig. 1: Contrast enhanced CT thorax and abdomen showing pre- and post-chemotherapy with good response. Figure 1A showing pre-chemotherapy with right breast tumour with extension to the anterior mediastinum and intrathoracic, bilateral pleural metastasis which completely disappears after chemotherapy Figure 1B. Figure 1C which shows liver metastasis pre-chemotherapy (largest at segment II measuring 1.4 × 1.8 cm) which disappears after chemotherapy Figure 1D

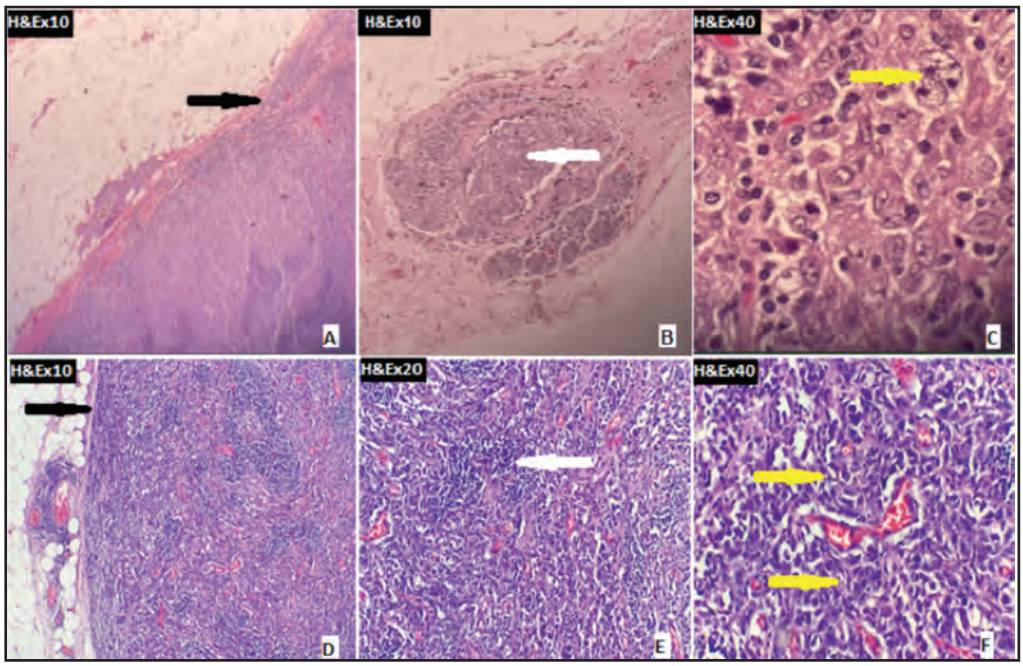

Fig. 2: A,B,C: First surgery right breast lumpectomy microscopic specimen. D,E,F: Second surgery right mastectomy microscopic specimen. A,B,D,E: Syncytial sheets of malignant epithelial cells with poor tubule formation accompanied by marked stromal tumour infiltrating lymphocytes (white arrow) and peripheral circumscription (black arrow). C,F. The tumour cells are large with moderately pleomorphic vesicular nuclei (yellow arrow), prominent nucleoli and moderate to abundant cytoplasm

right breast lesion (size measuring 2 × 1.5 cm) and right axillary lymphadenopathy with complete resolution of intrathoracic, pleural and liver metastasis (Figure 1). The patient underwent an elective right mastectomy and repeat axillary dissection. Post-operative recovery was uneventful, and the patient completed radiotherapy to right chest wall and supraclavicular fossa 40 Gy in 15 fractions for 3 weeks. During follow-up at 6 months post-surgery, the patient remains well with no signs and symptoms of disease recurrence.

First specimen of right breast lumpectomy measured around 85 × 40 × 40 mm, on serial cut sections revealed a tumour measuring 20 × 15 × 20 mm with irregular margin and had

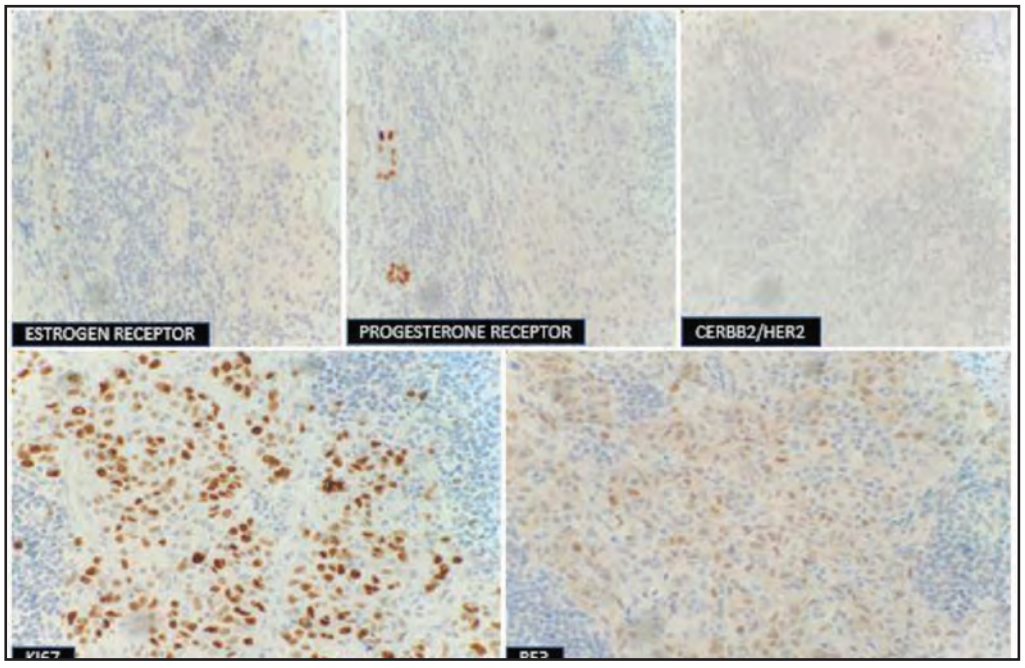

Fig. 3: IHC show negative for ER, PR and CerbB2/Her-2 and positive for Ki-67 (90%) and P53

a lobulated surface. Examinations revealed that the sections from the breast tissue exhibits malignant tumour infiltrates which are arranged in syncytial architecture. The tumour had a pushing border and was circumscribed (Figure 2A). There was also infiltration of lymphoplasmacytic cells within the collagenous stroma and lymphovascular invasion seen (Figure 2B). The tumour cells were pleomorphic with display of vesicular nuclei and prominent nucleoli with indistinct cytoplasmic border (Figure 2C). There were brisk mitoses seen with aberrant forms visualised. Histopathological impression, according to the Modified Bloom and Richardson criteria, was given as medullary carcinoma of breast grade III, with clear margins. All 16 axillary lymph nodes were free from metastasis. On immunohistochemistry study tumour cells were focally positive for CK 5/6 and CK7, negative for estrogen receptors (ER), progesterone receptors (PR), c-erb B2, CK20, p63 and LCA.

The patient underwent a second surgery of right mastectomy and repeated axillary dissection post chemotherapy due to recurrence and distant metastasis. The mastectomy specimen with nipple areola complex and skin were seen attached, measuring 175 × 165 × 50 mm, with well-healed scar seen at upper inner quadrant. Cut sections showed a circumscribed tumour with firm tan cut surface within the lower inner quadrant, measuring 20 × 20 × 15 mm. The histological examination showed similar features with the previous lumpectomy specimen - circumscribed tumour with pushing edges (Figure 2D) composed of malignant ductal epithelial cells arranged in interconnecting sheets, forming a syncytial network accompanied by marked stromal tumour infiltrating lymphocytes (Figure 2E). There was no overt tubule formation visualised. The tumour cells were large with moderately pleomorphic vesicular nuclei, small nucleoli and abundant cytoplasm (Figure 2F). The tumour size was 17 × 14 mm with clear resection margins. Tumour involvement was noted in 2 out of 4 axillary lymph nodes. The immunohistochemical study was positive for Pancytokeratin AE1/AE3, CK5/6 and p53 and negative for ER, PR and c-erb B2. Ki67 proliferative index was approximately 90% (Figure 3).

DISCUSSION

According to WHO, over 1.2 million women are diagnosed with breast cancer every year. Infiltrating ductal carcinoma is a broad entity which comprises tumours that exhibit one or more characteristics of specific types of breast cancers which includes tubular, papillary, medullary or mucinous differentiation.[2] MBC is rare and accounts for less than 5% of all invasive breast cancers.[1] Patients with MBC has an association with *BRCA* gene involvement. One study reported six cases of MBC (19%) among 32 *BRCA1*-associated breast cancers, compared to only one MBC (0.5%) among 200 patients without a family history of breast cancer.[5] This descriptive epidemiology study suggest that MBC is associated with germline mutations in the *BRCA1* gene. Due to the lack of facilities, the authors were not able to proceed with pre-test genetic counselling and germline *BRCA* testing.

Histopathological criteria to diagnose typical MBC include syncytial growth pattern of cells more than 75% of the tumour, well circumscription of microscopic mass, without glandular structures, diffuse lymphoplasmacytic infiltration and presence of marked nuclear pleomorphism with mitosis.[2-3] Sonographically, MBC often shows well circumscribed mass with hypoechoic structures which may mimic benign breast lesions such as fibroadenoma or phyllodes tumour. Thus, histopathologic evaluation is needed for definitive diagnosis. In our case, all the above features were present to clinch the diagnosis.

Compared to other types of breast cancer, triple negative breast cancer is highly invasive with limited treatment options, prone to recurrences, high metastatic potential and

has a poorer prognosis.[6] This is due to the lack of expression of ER, PR, and HER2 receptors making specific endocrine and targeted therapies ineffective. Therefore, chemotherapy has become the mainstay treatment for triple negative breast cancer. According to a report, the reported 5-year overall survival rate for metastatic triple negative breast cancers were 11% and for non-metastatic triple negative breast cancers were 81%.[7] MBC is a rare subtype of invasive ductal cancer and is frequently associated with triple negative breast cancer. However, triple negative MBC has a more favourable clinical outcome compared with the more common triple negative infiltrating ductal carcinoma, despite its aggressive histopathological features. Studies have reported that MBC had a longer 5- and 10-year survival in comparison to other triple negative subtype.[8] Due to the limited reports on MBC, a retrospective study reported a 5-year overall survival rate of 85% which is higher than other triple negative breast cancers.[9] It has been proposed that the presence of infiltration of lymphocytes and plasma cells assists in the suppression of MBC progression.[10] In our case, the patient had a local recurrence with distant metastasis which had good response to chemotherapy.

CONCLUSION

MBC is a rare subtype of infiltrating duct carcinoma which has high grade cytological features but has better prognosis as compared to invasive ductal carcinoma. Even in a metastatic setting, there is a possibility of good response with palliative chemotherapy. Careful histopathological evaluation and strict diagnosis criteria is necessary for definitive diagnosis and subsequent treatment.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of case report and accompanying images.

AVAILABILITY OF DATA AND MATERIALS

All data related to the outcome are included in the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interest.

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CASE REPORT

Multiple subcutaneous nodules and saccular abdominal aortic aneurysms as the presentations of primary antiphospholipid syndrome

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SUMMARY

Antiphospholipid syndrome (APS) is an acquired multisystem hypercoagulable disorder characterised by arterial and/or venous and/or microvascular thrombosis and/or pregnancy-related complications together with persistently elevated antiphospholipid antibodies (aPL). Here we describe a case of APS in a 46-year-old previously healthy man who presented with a 1-year history of intermittent high fever, multiple painful subcutaneous nodules over both lower limbs and worsening lower abdominal pain. Saccular aneurysms involving the left infrarenal aorta, aortic bifurcation and proximal right common iliac artery were reported in the computed tomography (CT) aortogram. He was initially treated as mycotic aneurysms with erythema nodosum with prolonged antibiotics, without any improvement. Physical examination at presentation revealed ill-defined, tender, purplish papules and nodules on his lower limbs. Investigations revealed normochromic normocytic anaemia (haemoglobin 10.1 g/dL), total white cell count 9.45 × 10^9/L, elevated erythrocyte sedimentation rate (111 mm/hr) and c-reactive protein (92.7 mg/L). Antinuclear antibodies and extensive microbiological studies were negative. Histopathological examination of the subcutaneous nodules showed small and medium vessel thrombosis without vasculitis, and negative direct immunofluorescence stain. Following that, he was found to have positive lupus anticoagulant and immunoglobulin G (IgG) anticardiolipin antibodies. The diagnosis of primary antiphospholipid syndrome was finally made, and warfarin was initiated. His subcutaneous nodules and abdominal aneurysms resolved completely within two months. Here we highlight the importance of skin biopsy in the diagnosis of APS. There should be a high index of suspicion for this rare condition as early diagnosis and treatment lead to better clinical outcomes and may avoid complications such as aneurysms.

INTRODUCTION

Antiphospholipid syndrome (APS) is an acquired multisystem hypercoagulable disorder. This condition has variable clinical presentations, and a high index of suspicion is necessary to clinch the diagnosis. We describe a patient with primary APS who presented with subcutaneous nodules and abdominal aortic aneurysms which are unusual presentations of this condition.

CASE PRESENTATION

A 46-year-old Chinese man presented with recurrent painful subcutaneous nodules on his lower limbs for the past 1 year. He sought treatment at a private dermatology clinic 6 months ago. A skin punch biopsy of a left thigh nodule was reported as erythema nodosum. Direct immunofluorescence was negative. He was treated with a course of antibiotic.

A month later, he developed intermittent lower abdominal pain that gradually became persistent and was associated with fever. Upper and lower endoscopy were performed by a private gastroenterologist, and histopathological examination of the colon revealed mild non-specific proctitis. Subsequently, a computed tomography (CT) of the abdomen was performed as his symptoms persisted. CT abdomen revealed aortic aneurysm. A CT aortogram (Figure 1b) demonstrated saccular aneurysms involving the left infrarenal aorta, aortic bifurcation and proximal right common iliac artery. The proximal right common iliac artery aneurysm was associated with perivascular hematoma that caused significant compression and stenosis of the right common iliac artery. He was treated for mycotic aortic aneurysms with IV ceftriaxone 2 g daily for 10 days and underwent endovascular aneurysm repair (EVAR) with right internal iliac artery embolisation (Figure 1c). After surgery, he was commenced on IV amoxicillin/clavulanic acid 1.2 g thrice daily, which was then replaced by the oral route upon discharge.

He was readmitted a week later with fever and painful nodules over his lower limbs (Figure 1a) for 3 days. Further history revealed that he had intermittent oral ulcer that healed spontaneously without scarring for the past 3 months. He denied any joint pain, alopecia, eye symptoms, genital ulcers, headache, weight loss or night sweats. There was no recent history of travel or contact with patients with tuberculosis. Family history was negative for connective tissue disease or cardiovascular diseases. His past medical

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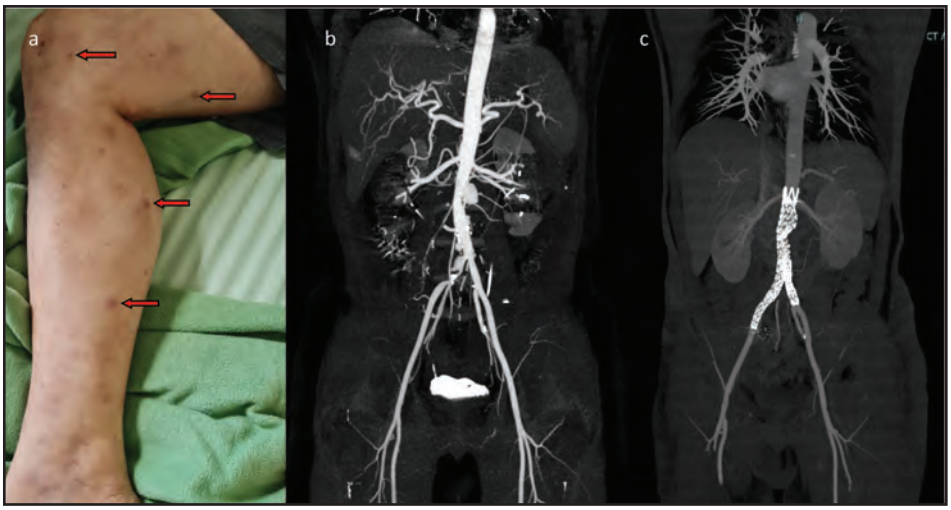

Fig. 1: a) Several discrete, violaceous, tender nodules over the right lower limb. Computed tomography (CT) images showed b) Pre-EVAR (endovascular repair of aortic aneurysm): saccular aneurysms at the left infrarenal aorta, aortic bifurcation, right common iliac artery c) Post-EVAR: EVAR stent *in situ*

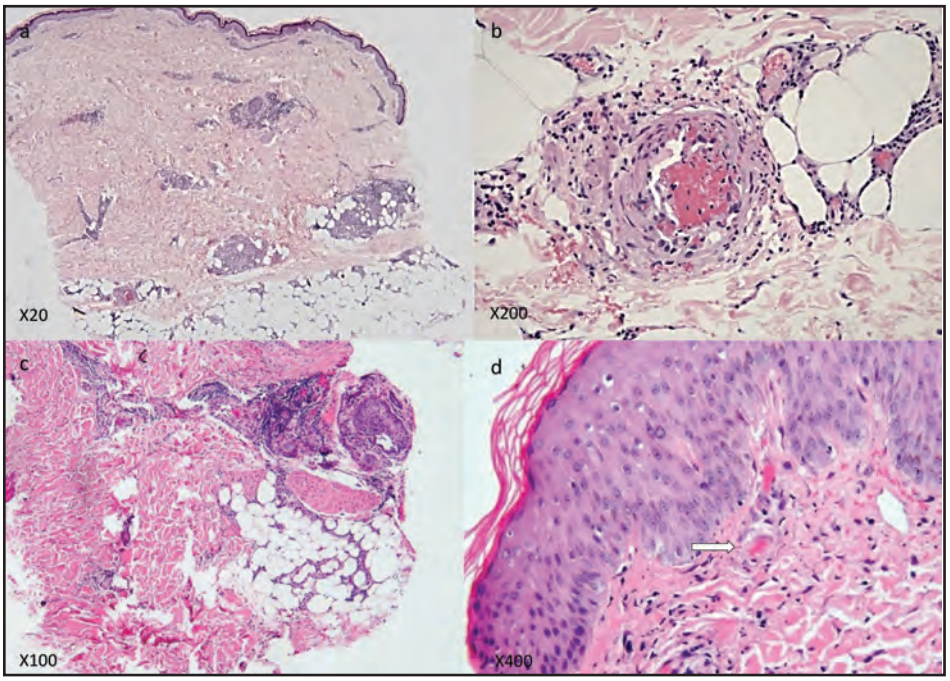

Fig. 2: Histopathological examination of skin biopsy performed at our centre (haematoxylin and eosin) showed a) infiltrates over periadnexal and perivascular areas with vessel thrombosis in the dermis and subcutaneous tissue; b) at higher magnification showed intraluminal fibrin thrombi with extravasated red blood cells and perivascular lymphocytic and histiocytic infiltrates. Histopathological examination of skin biopsy performed at a private centre one year before presenting to us (haematoxylin and eosin) showed c) panniculitis; d) at higher magnification showed vessel thrombosis in the deep dermis

history includes hypertension on oral amlodipine 5 mg daily. He was an active smoker and denied any intravenous or recreational drug use. Physical examination revealed several discrete, purplish, tender papules and nodules on his lower limbs. Examination of the cardiovascular, respiratory and neurological system were normal.

Several differentials were considered including infectious panniculitis, erythema induratum of Bazin, polyarteritis nodosa, Behcet's disease and vasculopathy.

Blood investigations showed normochromic normocytic anaemia (haemoglobin 10.1 g/dL), elevated alanine transaminase (ALT 74 U/L), erythrocyte sedimentation rate (ESR 111 mm/hr) and c-reactive protein (92.7 mg/L). Renal function was normal. Investigations for infective cause were negative for mycoplasma, leptospirosis, hepatitis B, hepatitis C, HIV, cytomegalovirus immunoglobulin M (IgM) and Epstein-Barr virus IgM. Blood cultures and QuantiFERON TB were also negative. Autoimmune screen including rheumatoid factor, antinuclear antibodies and

antineutrophil cytoplasmic antibodies were negative. Hypercoagulable screen was positive for lupus anticoagulant (LAC) and anticardiolipin (aCL) IgG but negative for aCL IgM and β2-glycoprotein I antibodies (anti-β2GPI). A repeated CT aortogram revealed that all previous aneurysms were thrombosed, and EVAR stent was *in situ*.

Histopathological examination of skin biopsy of the right posterior calf nodule showed small and medium vessel thrombosis in the mid-dermis and subcutaneous tissue with no vasculitis (Figure 2a and b). His initial biopsy performed a year ago at a private centre was re-examined with deeper sections which showed small vessel thrombosis with panniculitis in the subcutaneous tissue (Figure 2c and d), similar to our present biopsy. Tissue for bacterial culture, Mycobacterium tuberculosis culture and polymerase chain reaction (PCR), non-tuberculous mycobacterial culture and PCR, fungal culture and PCR were negative.

In view of the skin biopsy findings, positive LAC and aCL IgG and no underlying autoimmune disease, he was diagnosed with primary APS. He was commenced on warfarin and had complete resolution of subcutaneous nodules and abdominal pain. A repeat CT scan at 2 months after warfarin initiation showed resolution of abdominal aneurysms. He was planned to complete warfarin for at least 6 months and to repeat the antiphospholipid antibodies 6 months after discontinuing warfarin.

DISCUSSION

APS is a multisystem prothrombotic disorder with a definitive diagnosis based on fulfilling at least one clinical and one laboratory criteria in the updated Sapporo or Sydney criteria.[1] Clinical criteria include vascular thrombosis involving arterial, venous or small vessel in any tissue or organ; or pregnancy morbidity such as one or more unexplained deaths involving a morphologically normal foetus at or after 10 weeks of gestation, one or more premature birth of a morphologically normal infant before 34 weeks of gestation due to eclampsia or placental insufficiency or three of more unexplained consecutive spontaneous abortions before 10 weeks of gestation.[1] Laboratory criteria include presence of LAC, aCL IgG and/or IgM isotype in medium or high titre or anti-β2GPI IgG and/or IgM isotype in two or more occasions, at least 12 weeks apart. APS affects about 5 new cases per 100,000 persons per year with a prevalence of 20-50 cases per 100,000 persons per year.[1] The age groups most affected are the young and middle-aged with more females affected than males. The ratio of females to males are 1:3.5 for primary APS and 1:7 for secondary APS due to SLE.[1]

Primary APS is not associated with any underlying disease whereas secondary APS occurs in association with an underlying autoimmune disease, namely systemic lupus erythematosus. Presence of aPL in patients with systemic lupus erythematosus ranges from 10-30%. Besides, aPL may also be detected in association with infections, drugs and malignancy. However, the titres are usually low and transient and do not increase the risk of thrombosis or result in pregnancy morbidity. On the other hand, aPL may be present in about 1-5% of healthy individuals but are clinically asymptomatic.[1] Furthermore, the number of positive aPL determines the risk of thrombosis. The presence of a single aPL confers a lower risk of thrombosis or pregnancy morbidity compared to those with triple positivity. Of all the aPL, presence of LAC is strongly associated with APS.[2]

The key pathogenetic factor in APS is endothelial dysfunction. Antiphospholipid antibodies bind to membrane receptors in the endothelium which set off a cascade of events leading to thrombosis. β2GPI may be required in some cases for this process to occur. In APS, the synthesis of nitric oxide, which is important in vasodilation, is impaired. In addition, platelets and monocytes exhibit a prothrombotic phenotype in the presence of aPL. There is also dysregulation of vascular tone and activation of the complement cascade in the presence of aPL.[3]

The clinical manifestations of APS are variable ranging from cutaneous to visceral involvement. The most common clinical presentation is venous thrombosis. Cerebrovascular events are the most common manifestation of arterial thrombosis. Cutaneous signs may be the initial presenting signs and they are present in 4-55% of patients with APS.[4] The most common skin manifestation is livedo reticularis, followed by necrotic cutaneous ulcers, digital gangrene, subungual splinter haemorrhages, pseudovasculitic lesions, livedoid vasculopathy, atrophie blanche, Degos-like lesions and primary anetoderma.[4]

Subcutaneous papules and nodules as presentation of APS are rarely reported.[5,6] Ishikawa et al.[5] described four patients, two of whom had primary and secondary APS, respectively. These patients reported tender papule or nodule on the finger, sole and leg. Histopathological examination showed vessels with organised thrombi and surrounding neovascularisation. Farrant et al.[6] reported a patient with a history of deep venous thrombosis who had recurrent subcutaneous nodules which was complicated by hepatic vein thrombosis. Our patient also had recurrent subcutaneous nodules of his lower limbs for several months before diagnosis was made. As there are many differential diagnoses to consider for subcutaneous papules and nodules, a skin biopsy for histopathological examination is essential for definitive diagnosis.[5]

In general, abdominal aortic aneurysms (AAA) have a prevalence of about 2-12% and predominantly involve male gender above 65 years of age. These aneurysms are more commonly fusiform and infrarenal in origin.[7] Our patient although was young, had the traditional risk factors in developing aneurysm which included male gender, hypertension and being an active smoker. Interestingly he had saccular aneurysms at multiple sites of the aorta which suggested a different pathogenesis.

The pathogenesis of aneurysm formation includes immune-mediated processes leading to activation of matrix metalloproteinases (MMP) that degrade elastin in the aortic wall. The adaptive immune system is also involved.[8] Aneurysms have been reported as rare clinical manifestations of APS.[9] Studies have shown that the

Table I: Summary of published cases of primary antiphospholipid syndrome (APS) with aneurysms[9,10]

Age, Gender	Clinical manifestations	Arteries involved	aPL antibodies	Treatment
46, male (Current case)	***Persistent abdominal pain, recurrent subcutaneous nodules***	***Abdominal aorta (bifurcation, infrarenal), right common***	***LAC, IgG aCL***	***Warfarin***
34, female	Occlusion of small cerebral arteries	Carotid, middle cerebral artery	aPL	N/A
31, male	DVT, PE, migraine	Jejunal, pancreatic, superior mesenteric, renal	LAC, IgG aCL	Warfarin
20, male	PE	Pulmonary (saccular)	aCL	Coil embolisation, low dose heparin
38, female	Recurrent pregnancy loss	Splenic, hepatic, renal (saccular)	IgG aCL	N/A
42, female	Recurrent pregnancy loss, thrombocytopenia, haemolytic anaemia, stroke	Hepatic	LAC, IgG and IgM aCL	Warfarin
45, male	Kidney infarct, DVT, PE	Abdominal aorta (infrarenal) (saccular)	LAC, IgM and IgG aCL, anti-β2GPI, anti-phosphatidylserine	LMWH, warfarin, vascular surgery
51, female	Leg ischemia	Middle cerebral artery, abdominal aorta (infrarenal) (fusiform)	LAC	Heparin, warfarin
48, female	Recurrent pregnancy loss, recurrent DVT	Abdominal aorta (infrarenal)	LAC, IgG aCL, IgG anti-β2GPI	Heparin, aspirin, IVIg
67, male	Recurrent DVT, PE	Abdominal aorta	LAC	Warfarin
44, female	DVT, PE	Left main coronary	LAC, anti-β2GPI	Antiplatelet, anticoagulant
76, male	Stroke, idiopathic retinal vasculitis, aneurysms, neuroretinitis (IRVAN syndrome)	Retinal vessels	LAC, IgM and IgG aCL IgG and IgM anti-β2GPI, IgG and IgM anti-phosphatidylserine	warfarin
21, male	Superior vena cava syndrome	Coronary	N/A	Cardiac surgery
50, male	Multiple transient ischemic attack, amputation of toes bilaterally	Abdominal aorta	N/A	Vascular surgery
60, female	DVT, pregnancy loss	Abdominal aorta (fusiform)	LAC, IgG aCL, IgG anti- β2GPI	HCQ, aspirin
22, male	Pulsatile abdominal mass, migraine	Coeliac trunk, splenic, renal, superior mesenteric, right common iliac, external iliac (saccular)	LAC, IgG aCL	Aspirin, HCQ

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism; LAC, lupus anticoagulant; aCL, anticardiolipin; aPL, antiphospholipid antibodies; anti-β2GPI, anti-β2 glycoprotein I; LMWH, low molecular weight heparin; IVIg, intravenous immunoglobulin; HCQ, hydroxychloroquine; N/A, not available

prevalence of aPL in AAA is 13.5% which is almost similar to other immune-mediated diseases such as systemic lupus erythematosus, giant cell arteritis and early rheumatoid arthritis.[8] It has been postulated that APS and aneurysm share similar pathogenetic mechanisms which are immune-mediated. Pro-inflammatory T cells are present in the tissue and peripheral blood of patients with AAA. B cells are responsible to produce aPL that enhances MMP-9 activity and/or induce accelerated degradation of elastin with arterial wall remodelling. Both processes lead to AAA progression. In addition, patients with aPL and AAA also have raised inflammatory markers. Generally, presence of aPL in cardiovascular disease and immune-mediated diseases have been associated with poor outcome.[8] Cases of primary APS with aneurysms are summarised in Table I. Majority of them (87.5%) were younger than 65 years with equal gender proportion. The most common affected vessel was the aorta. Other affected arteries included the coronary, carotid, retinal, middle cerebral, pulmonary, splenic and hepatic arteries. Of those cases whereby the morphology of aneurysms was described, saccular aneurysm was more common compared to fusiform aneurysm. The most common aPL detected was LAC, followed by antiCL and anti-β2GPI.

The treatment of APS involves antithrombotic therapy[1] with warfarin which is initially bridged with unfractionated heparin or low-molecular weight heparin till therapeutic anticoagulation is achieved. Studies have demonstrated that risk of recurrence of unprovoked venous thromboembolism was higher in patients with aPL and increases further in those with the same positive aPL on both occasions.[2] Lifelong anticoagulation is then necessary. In patients with venous thrombosis, target INR is 2.0-3.0 whereas for those with arterial thrombosis and/or recurrent thrombosis, a higher target INR of 3.0-4.0 or combined treatment of low dose aspirin with warfarin with target INR of 2.0-3.0 have been suggested.[1,2] A study has showed that combination therapy of low dose aspirin with anticoagulation reduced thrombosis recurrence to 6.9% compared to 23.7% on anticoagulation and 37.2% on antiplatelet therapy alone. Besides that, there is also longer time to recurrence with combination therapy.[2]

In cases of APS with aneurysms, caution must be exercised regarding the use of antithrombotic agents due to the risk of aneurysmal rupture. Treatments that have been utilised in cases of APS with aneurysms include warfarin, antiplatelet therapy, vascular surgery, heparin, hydroxychloroquine, coil embolism and intravenous immunoglobulin.[9,10] Excision

should be considered for cases with large aneurysms that are at risk of rupture. For smaller aneurysms, endovascular repair can be considered.[10]

Behcet's disease (BD), which is a diagnosis of exclusion, is an important differential diagnosis to consider due to the presence of subcutaneous nodules and thrombosis. Both fusiform and saccular arterial aneurysm formations at abdominal aorta, thoracic aorta, pulmonary, femoral, popliteal, brachial, iliac, mesenteric and subclavian arteries have been described in BD. Our patient scored 2 in the revised International Criteria for Behcet's disease (ICBD) criteria 2014 with a short duration of oral aphthosis of 3 months. In addition, there was no vasculitis or neutrophilic vascular reaction on histopathological examination, which are important features of BD. Furthermore, treatment of BD involves mainly immunomodulatory agents. Our patient responded well to anticoagulation, with no further development of other features of BD thereby refuting this diagnosis.

CONCLUSION

We described a case of APS in a male patient who presented with multiple saccular arterial aneurysms and subcutaneous nodules. A skin biopsy is deemed imperative to reach the diagnosis. In cases where the patient did not improve with treatment, a re-examination of the biopsy sample or a repeat biopsy is warranted. There should be a high index of suspicion with the combinations of unusual clinical presentations of APS, as a few organ systems can be affected concurrently. Early diagnosis and treatment lead to better clinical outcome and may avoid complications such as aneurysms.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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Atrial septal defect: Massive pulmonary embolism mimic in point of care ultrasound

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SUMMARY

Massive pulmonary embolism (PE), which manifests as the obstructive shock is one of the most unforgiving medical emergencies. Due to the overriding concern of adverse outcomes associated with delayed treatment, the diagnosis is commonly made based on clinical symptoms and bedside point of care ultrasound (POCUS) assessment in order to enable the timely institution of life-saving reperfusion therapy. The presence of McConnell's sign portends the possibility of PE with high specificity. Notwithstanding, this eponymous sign is also fraught with limitations as some cardiopulmonary pathologies may also manifest such a sign. Therefore, recognition of its mimickers is vital to guide clinicians to a correct diagnosis which then translate to the right treatment for patients. Herein, we report a case of undiagnosed atrial septal defect masquerading as massive PE in a 27-year-old lady, who presented with shock with concomitant McConnell's sign during the puerperal period. It is hoped that this vignette serves to remind the clinicians that it is important to be able to expound the differentials of McConnell's sign as its presence is not pathognomonic of PE. Besides, the incorporation of point-of-care cardiac doppler ultrasound (POCDUS) in an emergency setting should be considered as part of the POCUS evolving continuum to augment its diagnostic accuracy.

INTRODUCTION

Massive pulmonary embolism (PE) arises due to catastrophic pulmonary vasculature occlusion culminating in obstructive shock. Fatality is inevitable if diagnosed late or missed as its definite thrombolytic treatment is a time-sensitive therapy. Hence, majority of the massive PE cases are diagnosed based on patients' clinical conditions and point of care ultrasound (POCUS) findings.[1] Among the sonographic features of massive PE, McConnell's signs is one of the most highly cited findings, in which if present concurrently with acute hypotension will create a heightened suspicion towards massive PE.[2,3] Herein, we describe a case of undiagnosed atrial septal defect (ASD) complicated by right heart failure, mimicking a massive PE by presenting with shock and McConnell's sign during POCUS evaluation. The final diagnosis was uncovered by a comprehensive transthoracic echocardiogram and a normal CT pulmonary angiogram (CTPA) subsequently.

CASE PRESENTATION

A 27-year-old lady, who was 13 days post-spontaneous vaginal delivery, presented to the health clinic with the chief complaint of dizziness for 1 day associated with presyncope. Otherwise, she denied episodes of palpitation, pleuritic chest pain, reduced effort tolerance or haemoptysis. At the presentation in the health clinic, her blood pressure measured 76/47 mmHg with a pulse rate of 89 bpm and peripheral oxygen saturation of 92%. Physical examination was unremarkable. She was immediately transferred to the Emergency Department (ED), Hospital Tengku Ampuan Rahim, for suspected acute PE.

Assessment in ED revealed a dehydrated patient with coated tongue and fluid resuscitation was commenced promptly. Physical examination was unremarkable except for signs pertaining to dehydration. Despite 1 litre of fluid resuscitation, she remained hypotensive with blood pressure ranging from 77/57 to 90/60 mmHg and she was subsequently started on intravenous noradrenaline infusion. The presence of type 1 respiratory failure warranted her to be given supplemental oxygen of 3 L/min. To note, she was not tachycardic throughout the observation. Electrocardiogram showed left axis deviation with right bundle bunch block. (Figure 1) On the other hand, POCUS evaluation pre-fluid resuscitation demonstrated dilated right atrium and ventricle with D-shaped ventricles and kissing inferior vena cava (IVC). A repeated POCUS was performed and showed an increment of IVC diameter to 1.7 cm with dilated right atrium and ventricle with McConnell's sign observed. In view of patient's prevailing history, haemodynamic instability with POCUS findings suggestive of massive PE, she was thrombolysed with intravenous (IV) tenecteplase 6000 IU followed by intravenous heparin infusion. Her D-dimer result later was 0.9 µg/ml, which was marginally raised.

The thrombolysis therapy was uneventful, and she was admitted to high dependency ward for close monitoring. CTPA was performed the following day and there was no CT evidence of PE. In addition, bilateral lower limb doppler ultrasound was also performed and similarly did not detect any evidence of deep vein thrombosis. In order to elucidate the aetiology of the abnormal POCUS findings, a comprehensive transthoracic echocardiogram was performed, which illustrated a large secundum ASD with the dilated right ventricle (Figure 2). Anticoagulation therapy was discontinued, and the final diagnosis was revised as

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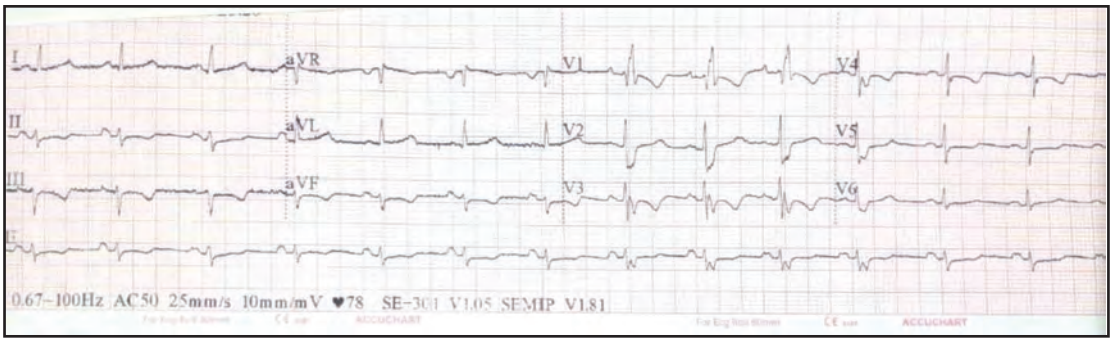

Fig. 1: ECG shows left axis deviation with right bundle brunch block. Widespread T Inversion seen from V1 to V4

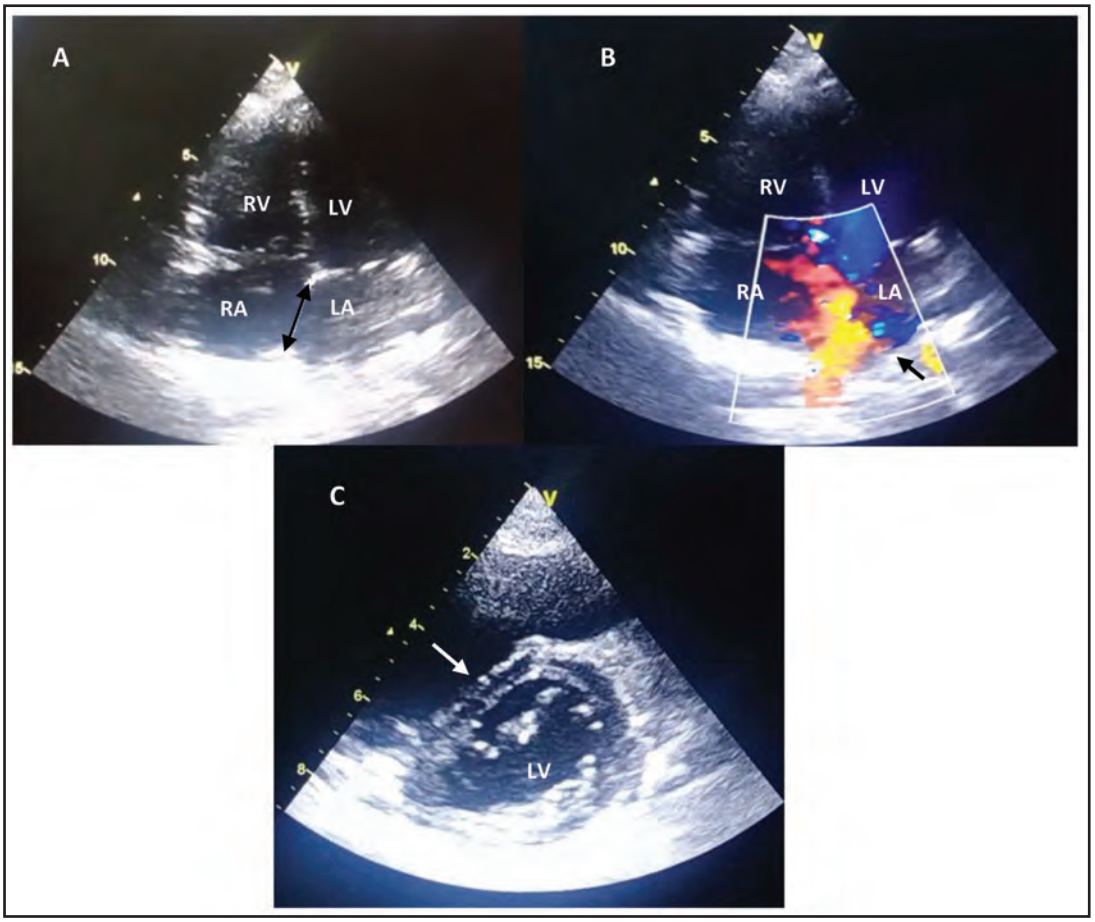

Fig. 2: Transthoracic echocardiogram. (A) ASD [double-headed arrow] with dilated RV and RA. (B) ASD with prominent left to right shunt on colour doppler USG [black arrow head] (C) Dilated LV with septal flattening. [white arrow head] ASD=atrial septal defect; LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle

symptomatic large secundum ASD. She was discharged home well and referred to another cardiology institution for further treatment. At the time of writing this report, she remained well and was scheduled for ASD repair.

DISCUSSION

Acute presentation with haemodynamic compromise and hypoxaemia often prompts the clinician to consider the diagnosis of massive PE. Though tachycardia was absent in this case, the abrupt symptoms onset during the puerperal period and the presence of right ventricular strained ECG patterns strengthened the suspicion PE. Bedside POCUS has been recommended as the initial test in evaluating such patients with suspected massive PE, characterised by haemodynamic instability to elicit signs of acute pulmonary hypertension or right ventricular dysfunction. In highly unstable patients, reperfusion therapy should be instituted if there is supporting evidence of PE based on POCUS findings. Final confirmation with CTPA would be performed once the patient has been stabilised.[1]

Acute PE has been known to be able to contribute to RV pressure overload and dysfunction, which could be detected by POCUS. Numerous echocardiographic features of PE have been enumerated in the European Society of Cardiology guidelines.[1] They are represented by RV dilation as well as measurements that could suggest right heart strain or dysfunction, such as disturbed RV ejection pattern (60-60 sign), abnormal Tricuspid Annular Plane Systolic Excursion (TAPSE) and McConnell's signs. The caveat is that any significant cardiac or pulmonary pathology could mimic such findings. In our case, the subject demonstrated RV dilation, septal flattening as well as McConnell's signs during POCUS.

McConnell's sign, depicted as right ventricular mid-free wall akinesia with apical preservation, was first described by McConnell et al in a seminal paper published in 1996. In the original report, this finding had a 77% sensitivity, 94% specificity, positive predictive value (PPV) of 71%, negative predictive value of 96% for the presence of PE in patients.[4] In recent years, Daley et al. who examined a cohort of 136 subjects with suspected PE, demonstrated that the McConnell's sign only had a sensitivity of 33% towards acute PE, whilst the specificity remains as high as 99%.[5] On the other hand, Vaid et al who retrospectively analysed 73 patients with McConnell's sign detected by echocardiogram, demonstrated that the PPV of this sign on acute PE was only 57%.[6] Considering all these, McConnell's sign should not be used in isolation when making a diagnosis of PE in patients, as well as directing the use of reperfusion treatment in unstable patient.

A myriad of published cases illustrating McConnell's sign as PE mimickers have been reported. Rafie et al described two cases with this eponymous sign attributed to right ventricular ischaemia caused by acute occlusion of right proximal coronary artery.[7] Walsh et al highlighted a case of pulmonary hypertension due to chronic obstructive pulmonary disease and systemic lupus erythematosus with similar finding.[8] To the best of our knowledge, our case represents the first case of undiagnosed ASD mimicking as massive PE which demonstrated McConnell's signs during ED presentation. Overall, these case vignettes serve to remind the clinicians to be cognizant of the McConnell's sign differential diagnoses, as a plethora of cardiopulmonary pathology with RV strain could demonstrate such eponymous sign.

In retrospect, the pre-syncopal attack in our case represents the first manifestation of severe ASD. Though it is unclear why she was devoid of heart failure symptoms during her recent pregnancy. Yet, it is crucial to consider the possibility of undiagnosed congenital septal defects when assessing individuals with such presentation. We postulate that the McConnell's sign observed in this case was probably due to the volume gradient from the shunt. The hypotensive episode was unlikely due to an obstructive shock caused by massive PE as there was no evidence of PE based on the CTPA findings and serial normal lactate level. Furthermore, the D-dimer value was only marginally raised and bilateral lower limb doppler was negative. Hence, it is reasonable to speculate that the hypotensive episode could be caused by a combination of hypovolemia with right ventricular failure as a result of untreated ASD.

Decision on the selection of ultrasound modes depends of the clinical disease suspected by the clinicians. In general, colour Doppler ultrasound would be considered only if there is a need to measure and visualising blood flow during POCUS evaluation. For example, it would be utilised when evaluating a subject with suspected deep vein thrombosis or even in a subject with suspected vascular injury.[9,10] Our case highlights that incorporation of cardiac Colour Doppler during POCUS (POCDUS) should be considered during critical setting, especially among subjects with evidence of structural cardiac abnormality during initial assessment, as it could assist in revealing the underlying abnormal shunt or valvular pathology. Nevertheless, adoption of POCDUS in critical settings remains to be elucidated in future studies to determine its diagnostic value when being applied within a limited time under emergency situations.

CONCLUSION

Acute PE is a life-threatening condition and yet treatable with prompt diagnosis and intervention. POCUS together with typical physical signs and symptoms have been typically employed to diagnose PE, especially when CTPA is not readily available or clinical circumstances hinder such an approach. Among the echocardiography signs observed in acute PE, McConnell's sign has long been established as a reliable sign with high specificity. However, there is always an exception as reported in this case and clinician should be aware that McConnell's sign is not equivalent to acute right heart strain from PE. It is crucial to contemplate other conditions and utilise other diagnostic tools to enhance diagnosis accuracy, which in this case is by using the colour doppler. In future, the use of POCDUS can be expounded upon and studied to evaluate its value in a high-strung emergency setting.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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Delayed haemoperitoneum post-paracentesis: Still an enigma

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SUMMARY

Paracentesis or colloquially known as abdominal tapping is a bedside clinical procedure commonly performed to aid in the diagnosis of the underlying cause as well as to relieve symptoms attributable to ascites. In practice, therapeutic paracentesis for symptomatic ascites remains as one of the commonest indications for this procedure, principally undertaken among patients with decompensated liver cirrhosis. Despite the inherent coagulation aberrations among the later, paracentesis-associated haemorrhagic complications remains scarce especially for non-large volume paracentesis (LVP). In this vignette, we describe an unusual case of non-LVP associated delayed haemoperitoneum which occurred in a middle-aged gentleman with co-existing advanced chronic kidney disease and newly diagnosed liver cirrhosis. This report serves to remind the clinicians to be vigilant about such complication among patients with concomitant liver cirrhosis and advanced renal disease.

INTRODUCTION

Paracentesis is a common clinical procedure routinely undertaken to obtain a peritoneal fluid sample or to drain symptomatic ascites for both diagnostic or therapeutic purposes.[1] It is generally regarded as a safe and simple procedure that can be performed bedside with little risk of major complications.[2,3] Nevertheless, there has been anecdotal evidence to suggest that such procedure carries a remote possibility of causing haemorrhagic complication, with delayed haemoperitoneum representing the rarest form of complications.[4,5] In this report, we describe a patient with co-existing advanced chronic kidney disease (CKD) and newly diagnosed liver cirrhosis who developed delayed haemoperitoneum following its inaugural diagnostic and therapeutic paracentesis. To the best of our knowledge, this is the first case of haemoperitoneum induced by non-large volume paracentesis with a delayed onset.

CASE PRESENTATION

A 54-year-old man with underlying advanced CKD, type 2 diabetes mellitus, hypertension and dyslipidaemia was referred to emergency department (ED) from nephrology daycare clinic for uraemia and fluid overload due to advanced CKD. He reported progressive abdominal swelling for 3 months which was associated with bilateral lower limb swelling and orthopnea. At the presentation in ED, his BP was 187/102 mmHg, and heart rate was 71 beats/minute with peripheral saturation of 99% under room air. Physical examination revealed bilateral lung crepitations and clinical findings in keeping with gross ascites. Laboratory results demonstrated significant renal function derangement with urea and creatinine levels of 49.5 mmol/L and 907 µmol/L, respectively. Subsequently, he was admitted to a medical ward for urgent haemodialysis (HD) and paracentesis.

At day 4 of admission, therapeutic and diagnostic paracentesis was performed in a single attempt at a right lower quadrant of the abdomen, which successfully drained 2.4 L of straw-coloured peritoneal fluid. Before the procedure, he had an international normalised ratio (INR) of 1.37 with aPTT and PT times of 42.6 seconds and 18.3 seconds, respectively. On the other hand, full blood count demonstrated haemoglobin (Hb) of 7.4g/dL and platelet of 128×10^9/L.

Despite previous paracentesis and ultrafiltration during haemodialysis, the ascites had reaccumulated rapidly, and examination showed gross ascites with prominent fluid thrill. Therapeutic paracentesis was repeated on day 6 of admission; however, it drained haemoserous fluid, and the procedure was abandoned after draining 500 ml of haemoserous fluid due to concern of possible intraabdominal injury. Nevertheless, reevaluation with bedside ultrasound (USG) refuted this as it showed gross ascites and large pockets of ascites. Furthermore, the size of the branula used was only 16G. During observation, he remained well and did not exhibit signs of haemodynamic instability or peritonism. In retrospect, in order to mitigate the risk of bleeding, heparin-free HD had been prescribed since the day before the inaugural paracentesis.

Alarmingly, his haemoglobin dropped acutely from 7.0 g/dL to 5.6 g/dL within a span of 3 days after the second paracentesis which yielded haemoserous fluid. Consequentially, he was transfused with two pints of packed cells. An urgent Contrast Enhanced Computed Tomography (CT) of the Abdomen and Pelvis was performed following the precipitous drop in haemoglobin. The CT revealed complex ascites with features consistent with liver cirrhosis. There was no evidence to suggest active bleeding. To substantiate our suspicion of probable haemoperitoneum, USG-guided paracentesis was repeated at day 13 of admission, which

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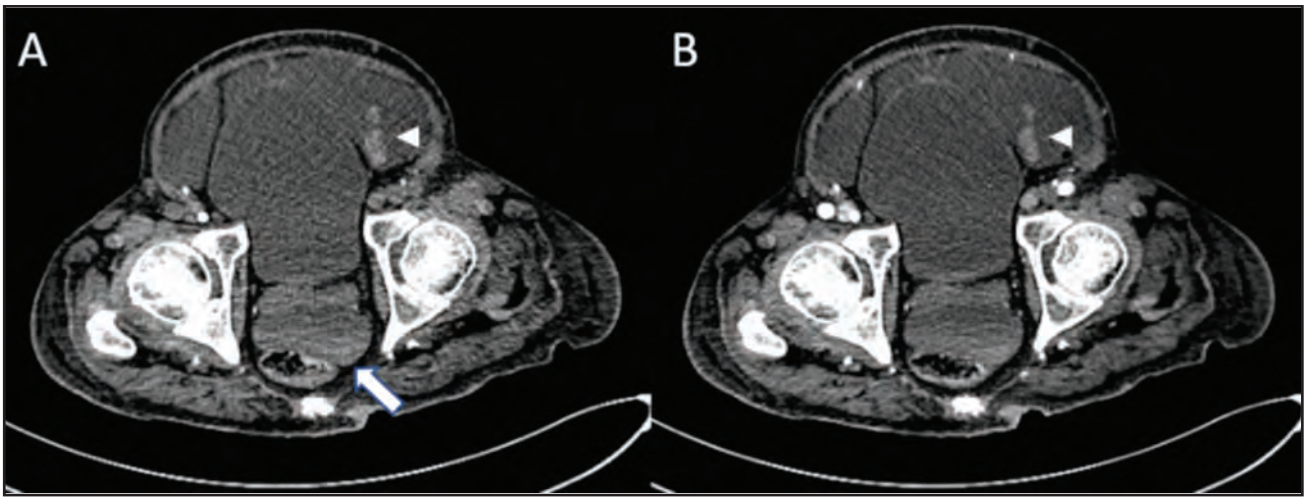

Fig. 1: Axial CT abdomen images in unenhanced (A) and arterial (B) phases at the level of the pelvis. These images demonstrate lobulated, non-enhancing hyperdensities at the left iliac fossa suggestive of blood clots (white arrowheads). Presence of hyperdense layering at the dependent region of vesicorectal pouch (white arrow) is suggestive of layering of blood products within the gross ascites. There was no evidence of active arterial bleed demonstrated in this study

drew bloody ascites and thus confirmed haemoperitoneum. In order to rule out intraabdominal bleeding, an emergent CT angiography (CTA) of the abdomen was performed, which did not show evidence of active bleeding, besides the presence of hyperintensities seen at the left iliac fossa suggestive of blood clots. In addition, there were no collateral intraabdominal varices seen (Figure 1).

In view of the findings of haemoperitoneum as well as the presence of liver cirrhosis, he was referred to the surgical team and hepatology team for co-management. To note, the Child-Pugh Score was B (8) with Model for End-Stage Liver Disease (MELD) score of 24 on admission. As screening for viral hepatitis B and C, and subsequently, autoimmune panel were all negative, the cause of the liver cirrhosis was believed to be due to metabolic associated fatty liver disease (MAFLD). During the multidisciplinary discussion, it was decided that the haemoperitoneum would be drained via percutaneous pigtail. On day 15 of admission, a peritoneal pigtail catheter was inserted under USG guidance over the largest pool area at a right lower quadrant, which drained bloody ascites fluid. A total of 15 L ascitic fluid was drained over 2 weeks, and human albumin replacement was given to prevent post-paracentesis hypotension. Later, the peritoneal fluid investigation and tumour markers ruled out suspicion of malignancy. A low serum-ascites albumin gradient (SAAG) of 0.8 g/dL, together with a low ascitic protein of 2.4 g/dL could suggest a renal predominant cause of the ascites. The pigtail catheter was removed on day 29 of admission, and he was discharged well the following day. At the time of writing, he remained well and had been undergoing regular haemodialysis. To note, there was no subsequent admission for symptomatic ascites in the last 3 months after discharge.

DISCUSSION

Paracentesis is the most common bedside procedure utilised by physicians in treating patients with ascites. This procedure is primarily carried out with the intent to relieve the symptoms of tense ascites or to ascertain the aetiology of the ascites, and both could be due to a multitude of pathologies.[1] Despite being predominantly performed among liver cirrhosis patients who commonly have abnormal coagulation parameters and thrombocytopaenia, the procedural complications are infrequently reported.[2] According to published literature, haemorrhagic complications related to paracentesis are extremely rare with an incidence rate of less than 1%.[2,3] Among the reported haemorrhagic complications were abdominal wall haematoma, pseudoaneurysm and haemoperitoneum, with later portending the worst survival outcomes.[4]

Delayed haemoperitoneum defined as onset of haemoperitoneum after 24 hours of paracentesis represents the rarest paracentesis-associated complications. As a rule of thumb, haemorrhagic transformation of peritoneal fluids on the following peritoneal tapping dictates a close monitoring for haemoperitoneum as it could be the precursor of an ongoing occult intraperitoneal bleed. In our case, the bloody ascitic fluid which clinched the diagnosis of haemoperitoneum happened 10 days after the first paracentesis in the absence of abdominal symptoms. In contrast, Arnold et al.[6] reported a case series of acute haemoperitoneum manifesting with shock and abdominal pain leading to the suspicion of such complications. The two extreme timeline variation for haemoperitoneum manifestation highlights both spectra of haemoperitoneum and underscores the perils of delayed onset haemoperitoneum which commonly lack overt symptoms till the late stage.

Several mechanisms have been theorised to explain the occurrence of delayed haemoperitoneum. The causal link has been commonly attributed to the abrupt splanchnic circulation decompression as a result of sudden shift in the intra-abdominal pressure after large-volume paracentesis

(LVP), defined as removal of more than 5 L of ascitic fluid. This would lead to a rise in the portosystemic blood flow via collaterals resulting in dilation and rupture of friable mesenteric varices.[6,7] Yet, our case did not corroborate with this theory as the inaugural peritoneal tapping only drained 2.4 L of ascitic fluid. In addition, the large pockets of ascites confirmed by ultrasound abate the likelihood of intra-abdominal organ or vessel puncture. This was further supported by the abdomen CTA findings, which did not identify any active bleeding organ or vessel. While the actual source of bleeding in our case remains an enigma, there is a common patient characteristic that coincides with several case reports. Co-existing liver cirrhosis and advanced renal disease elevate the risks of procedural-related bleeding complications in these reports.[4,8] To note, heparin-free haemodialysis had been prescribed prior to the inaugural paracentesis, which aims to mitigate the bleeding risk.

The diagnostic strategy to determine the aetiology of haemoperitoneum is contingent on the patient's haemodynamic status. In general, imaging in the forms of abdomen ultrasound or CT, and subsequently CTA if the former was negative, should be performed emergently following diagnostic paracentesis in order to exclude bleeding vessels or organ. In addition, it could also assist in planning the therapeutics subsequently after uncovering the cause of bleeding.[9] A multidisciplinary discussion should be made on the detection of haemoperitoneum, especially in the case of unstable patients. This is crucial because an exploratory laparotomy might be warranted to diagnose and to ligate the active bleeding vessels in the later. Yet, there is a possibility that the source of bleeding might not be identified during laparotomy. Under such circumstances, an unstable patient may decompensate further post-operation leading to hepatorenal syndrome or hepatic encephalopathy where liver transplantation might be required.[5,6] Considering all these, multidisciplinary evaluation is warranted and especially the risk and benefits of invasive approach must be carefully discussed with patients or the next-of-kin.

Due to the rarity of delayed haemoperitoneum post-paracentesis, most of the treatment approach is based of anecdotal evidence or expert opinion. Majority of the published cases ascribe the causes to intraabdominal variceal bleeding that are discovered via either abdominal CTA, exploratory laparotomy, transjugular intrahepatic portosystemic shunt or autopsy.[4-6,8] Therefore, all treatment strategies revolve around the ligation or embolisation of bleeding varices depending on the identification of the culprit varices. Haemoglobin and coagulopathy optimization, when necessary via judicious blood transfusion is also pivotal. In the case series published by Arnold et al, they identified sources of bleeding originated from either bleeding mesenteric varices, colon transversum varices, small bowel varices or variceal bleed at multiple sites. Furthermore, the fatality rate was 50% and the survivors (2/4) had been treated with variceal ligation or embolisation. It is noteworthy that 1 of the fatal cases succumbed due to disseminated intravascular coagulopathy (DIVC) within 1 week after the right hemicolectomy, which was performed to stop the colon transversum variceal bleeding.[6]

Clinicians should apprise themselves of the caveat of CTA examination in the detection of bleeding sites. According to a systematic review by Garcia-Blazquez, the overall sensitivity of CT angiography for detecting active acute gastrointestinal haemorrhage was 85.2 % (95 % CI 75.5 % to 91.5 %) influenced by the severity of bleeding.[10] In our case, we postulate that the source of bleeding most likely originated from venous bleeds, which are subtle and difficult to be detected via conventional CTA. This is supported by the absence of intraabdominal varix on the CT scan, as well as oesophageal or gastric varix during oesophagogastroduodenoscopy assessment done around the time of the incidence. Moreover, it is believed that the intraabdominal bleeding could have been stopped at the point of CT examination. This is evidenced by the Hb trend where the Hb stabilised following initial packed cells transfusion.

Lastly, exploratory laparotomy would be controversial due to the potential risk of hepatic decompensation or even a non-diagnostic surgical exploration as the bleeding could have ceased. Additionally, with a baseline coagulopathy and thrombocytopenia in cirrhotic patients coupled with a possibility of DIVC as alluded earlier, invasive procedures can be perilous. In light of this, a conservative approach was adopted in this case and the haemoperitoneum was drained via pigtail catheter inserted under ultrasound guidance in order to prevent abdominal compartment syndrome and peritonitis. The favourable 3 months survival at the time of writing provides evidence that conservative approach would be a viable treatment option in haemodynamically stable individuals with no active CT or clinical evidence of ongoing intraabdominal bleeding.

CONCLUSION

Delayed haemoperitoneum, a complication of paracentesis, is a substantial and challenging clinical problem, albeit its rarity. Patients with co-existing advanced renal disease and liver cirrhosis warrant active monitoring for such complication, as they could occur even in the event of non-large volume paracentesis. The management strategy should be contingent on patient's haemodynamic and premorbid status underpinned by multidisciplinary collaboration. A decisional balance would dictate either a conservative approach or high-risk exploratory laparotomy with the intent of ligating the bleeding varices if identifiable to be the best course of treatment.

ETHICAL APPROVAL

This case report has obtained approval from the National Medical Research Register (NMRR), Ministry of Health Malaysia: NMRR-23-00155-YPX

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Acute interstitial nephritis associated with cosmetic soft-tissue hyaluronic acid filler injections: Two case reports from Sarawak, Borneo

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SUMMARY

We report two cases of acute interstitial nephritis occurring in two women after having received cosmetic breast augmentation with breast filler injections. Both patients deteriorated rapidly developing acute kidney injury which required acute haemodialysis. They remained dialysis dependant but started to have renal recovery by week 7 and eventually were successfully weaned off dialysis. At 6 months post event, they remain dialysis free but continue to have chronic kidney disease with an eGFR 27 and 42 mL/min/1.73m2 respectively.

INTRODUCTION

Cosmetic soft tissue fillers have been used to augment the appearance of facial contours, breasts, buttocks and other areas. Adverse effects associated with these cosmetic fillers have been reported however acute interstitial nephritis (AIN) associated with soft tissue filler injections is uncommon. We report two cases of AIN associated with hyaluronic acid cosmetic breast filler injections done by the same unlicensed practitioner.

CASE PRESENTATION

Case 1

We describe a 41-year-old lady, with no known medical illness who underwent a cosmetic bilateral breast filler procedure by an unlicensed practitioner on 17th March 2022. She received 500 mls of hyaluronic acid gel breast filler, injected at multiple sites bilaterally. Thirty minutes after the procedure, she developed dizziness and shortness of breath, with pain over bilateral breasts up to the neck region and she returned to the unlicensed facility to seek treatment.

She was then sent to the Emergency and Trauma Department (ETD) 4 hours post procedure, where she was hypotensive (BP 75/35 mmHg) and tachycardic (HR 107/min). There was no rash, fever or joint pains. Her initial blood investigations revealed a total white cell count of 39 000 and creatinine of 89 µmol/L. She was empirically treated as anaphylactic shock and intramuscular adrenaline and intravenous hydrocortisone was administered. Subsequently her blood pressure normalised and hydrocortisone was stopped after 1 day. Interestingly her urine pregnancy test was noted to be falsely positive. She was confirmed not pregnant by negative transabdominal and transvaginal ultrasonography and negative serum beta-HCG.

Despite adequate fluid resuscitation and blood pressure optimisation, she became oliguric and her renal function rapidly deteriorated with creatinine increasing to 169 µmol/L and 331 µmol/L at 12 hours and 24 hours respectively post filler. She also developed refractory hyperkalemia (K 7.3 mmol/L) despite medical therapy and a decompensated metabolic acidosis with a blood pH of 7.038, and bicarbonate of 5 mmol/L. She was admitted to the intensive care unit (ICU) and underwent acute haemodialysis.

On day 2 of ICU admission, infective changes over the breast wounds were noted, and an ultrasound was done which showed collections bilaterally. An ultrasound guided aspiration was performed and 20 mls of pus was aspirated. The pus culture grew Pseudomonas aeruginosa spp and the patient was treated with appropriate antibiotics. Throughout her hospital stay, multiple aspirations and wound desloughing were carried out however due to persistent and severe infection, bilateral mastectomy needed to be performed at week 4 post filler. Intraoperatively it was noted that the infection had extended to the pectoralis major muscle bilaterally. Histopathological examination showed extensive fat necrosis with neutrophilic microabscesses and areas of haemorrhage, as well as a marked foreign body inflammatory reaction surrounding some amorphous material, postulated to be the breast filler substance used.

Another complication was noted about 2 weeks post filler procedure. The patient unexpectedly developed bilateral hearing loss. She was referred to the otorhinolaryngology (ENT) team and after assessment was deemed to have bilateral sensorineural hearing loss, postulated to be associated with the hyaluronic acid filler procedure. She was regularly assessed by the ENT team but despite all efforts this hearing loss persisted.

Throughout the admission, she needed multiple sessions of intermittent haemodialysis. Serum creatinine peaked at 1002 µmol/L at week 4 post filler (Graph 1) with her urine output at that time being 500 mls per day. Urinalysis showed leukocyturia and proteinuria, with urine protein:creatinine

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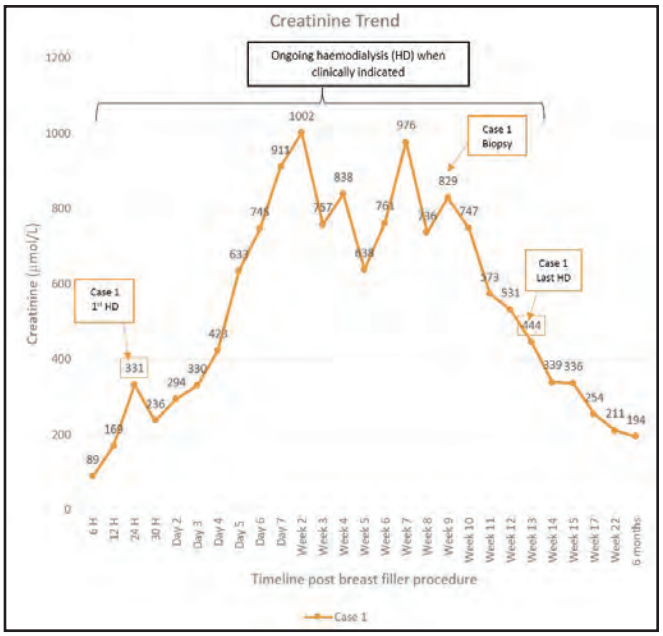
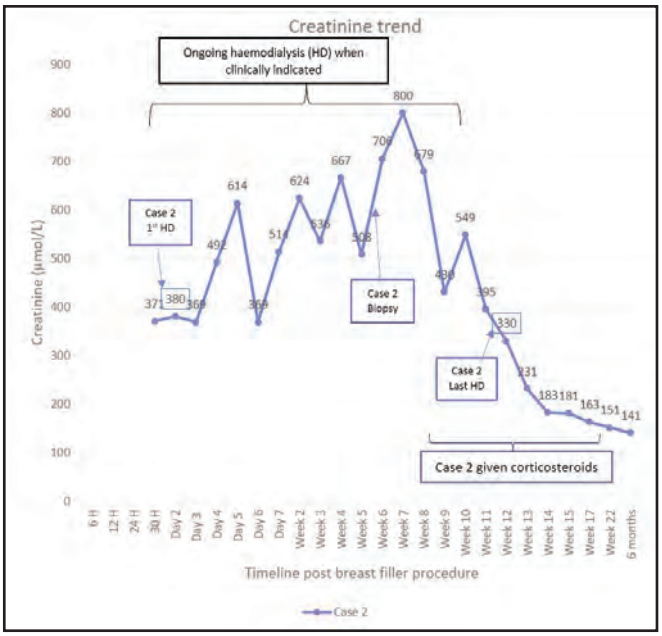
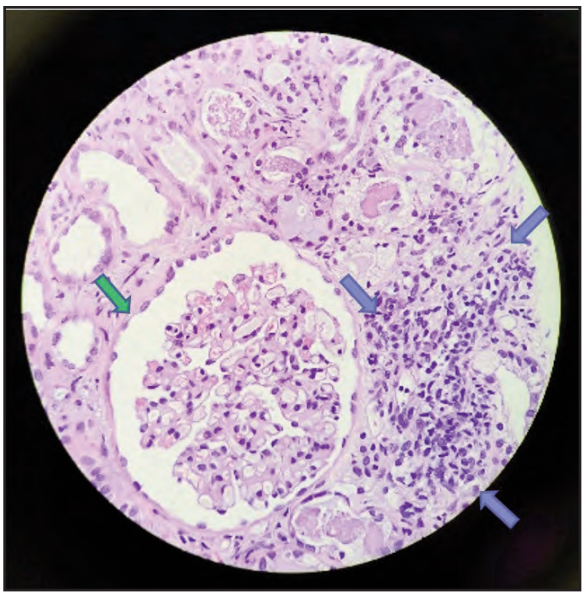


Graph 1: Creatinine trend of Case 1

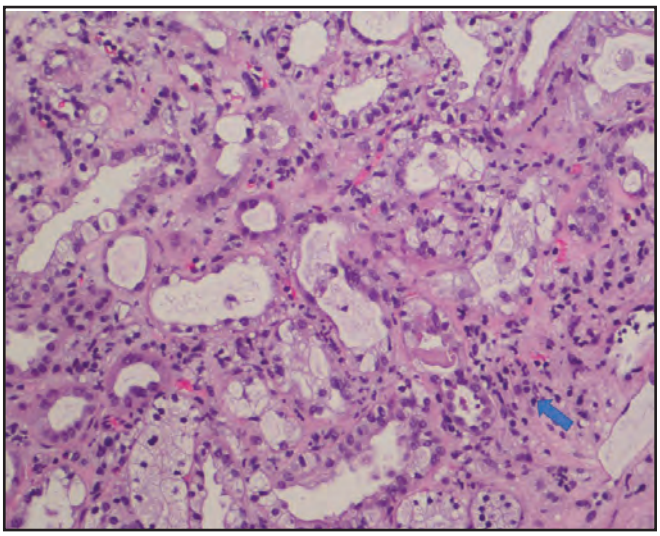


Graph 2: Creatinine trend of Case 2



Renal histopathology for Case 1

Fig. 1: Renal tubular granular cast with interstitial lymphocytic infiltrates depicting AIN (blue arrows). The glomerulus is normal (green arrow)
(H&E stain, magnifcation 400 x)

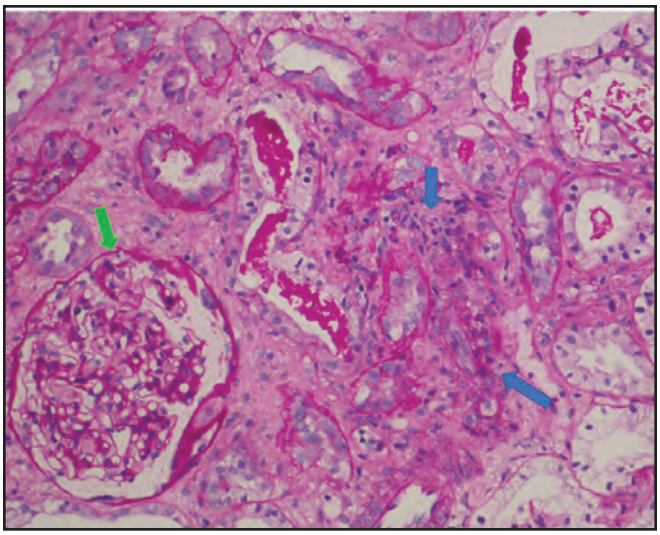


Renal histhopathology for Case 2

Fig. 2: Dilated tubules with desquamated epithelium and casts within the lumen. Interstitial oedema with mixed mononuclear and neutrophilic infiltrate (blue arrows), occasional eosinophils are seen depicting AIN changes
(H&E stain, magnification 200 x)

ratio of 166 mg/mmol. She had no evidence of a urinary tract infection. As she continued to require dialysis support, a renal biopsy was carried out 8 weeks after the initial breast filler procedure. It revealed acute tubular necrosis (ATN) and AIN with interstitial lymphocytic infiltrates (Figure 1). No steroids were given for her AIN due to the recent severe infection.

Her haemodialysis was gradually weaned down to once weekly and she was discharged after 2 months of hospital admission. She was successfully weaned off dialysis 3 months after filler injection and at last follow up at 6 months, her creatinine was 194 µmol/L, with an eGFR 27 mL/min/1.73m^2. Urinalysis is negative for proteinuria and hematuria. Her hearing however still remains impaired.



Renal histopathology for Case 2

Fig. 3: Tubules are separated by oedema and inflammatory infiltrate (blue arrows) depicting AIN changes No change to glomerulus (green arrow) is noted (PAS stain, magnification 200 x)

Case 2

A previously healthy 33-years-old lady also underwent the same cosmetic bilateral breast filler procedure the next day, at 4 pm on 18th March by the same unlicensed practitioner. She also received 500 mls of hyaluronic acid gel injected at multiple sites bilaterally. Post procedure, she experienced swelling and pain over bilateral breast until her neck region which worsened and 30 hours later, she presented to the ETD with shortness of breath.

At ETD, her blood pressure was 122/79 mmHg with normal oxygen saturation but she was tachycardic (122 beats/min) and tachypneic (33 breaths/min). No rash, fever or joint pains were noted. Her electrocardiogram showed sinus tachycardia but no other features of pulmonary embolism was demonstrated. Initial blood investigations, revealed severe decompensated metabolic acidosis with a pH of 6.948 and bicarbonate of 3.1 but no hypoxemia. Other parameters taken showed acute kidney injury (AKI) with a serum potassium of 7.5 mmol/L, urea 14.4 mmol/L, and creatinine of 371 µmol/L. Her calcium was 1.6 mmol/L, phosphate 4.48 mmol/L and sodium was 116 mmol/L. Her total white count was high at 39 200 but other blood investigations including liver function tests were normal. Of note, the patient also had persistent false positive urine pregnancy test, but confirmed not pregnant after repeated assessments by the obstetric and gynaecology team.

She was intubated and resuscitated with intravenous (IV) crystalloids and sodium bicarbonate therapy. However in view of persistent metabolic acidosis and anuria, acute haemodialysis was initiated and the patient was admitted to ICU. Lung fields on her initial chest radiograph were clear, however 3 days later, she developed bilateral pleural effusion which required chest tube drainage due to persistent hypoxia. Pleural fluid analysis was transudative in nature. She was successfully extubated on day 5 of admission.

The patient underwent breast ultrasonography which revealed features suggestive of right breast mastitis which was treated conservatively and improved with antibiotics.

Similar to the first patient, she also developed bilateral sensorineural hearing loss about 2 weeks after the filler procedure and was seen multiple times by the ENT team.

In view of persistent anuria and dependence on dialysis, a renal biopsy was done 5 weeks post filler procedure which revealed AIN with eosinophilic, mononuclear and neutrophilic mixed interstitial infiltrates (Figure 2). She was started on IV methylprednisolone 500 mg for 3 days at week 8 post filler, followed by oral prednisolone 1 mg/kg/day for her AIN, which was tapered over 14 weeks.

Her serum creatinine peaked at 800 µmol/L (Graph 2) at week 7 post filler and she required regular intermittent haemodialysis. After this however, her urine output started to improve and her hemodialysis was gradually weaned down to once a week and she was discharged after 2 months of stay in hospital.

Her urine output and renal function continued to improve and the dialysis was successfully stopped 3 months after the filler procedure. Six months post filler procedure, her creatinine tapered to 141 µmol/L with an eGFR of 42 mL/min/1.73m^2 and repeated urinalysis is negative for proteinuria and hematuria. Her hearing however did not recover and she continues to have bilateral sensorineural hearing loss. The relevant authorities were notified regarding both cases and the unlicensed practitioner.

DISCUSSION

Cosmetic enhancement with fillers are not without complications. These include infection, dislocation of the injected gel, early degradation of gel, firm breasts and nodules, and visible nodules.[1]

An article published in the CDC Mortality and Morbidity Weekly Report reported three cases of acute renal failure associated with cosmetic buttock soft-tissue filler injections in North Carolina in 2007.[2] Records indicated that the injections contained liquid silicone. Of the three reported cases, creatinine on presentation was 4.2 mg/dL (371 µmol/L), 4.0 mg/dL (353 µmol/L) and 11 mg/dL (972 µmol/L) respectively. The second and third patients had a renal biopsy done. The second case showed ATN with casts, and the third demonstrated AIN. These two patients who underwent a biopsy required haemodialysis that was successfully weaned off and eventually their renal function returned to normal. The article highlighted the dangers of receiving cosmetic injections from unlicensed practitioners.

AIN is a condition which is characterised by inflammatory infiltrate in the interstitium of the kidneys. AIN has been found most often as a result of drugs, but infection, systemic diseases and idiopathic forms have also been identified.[3-5] AIN is a common cause of acute kidney dysfunction but interestingly, articles have described only a minority of patients (<10-15%) presenting with the classical triad of fever, rash and eosinophilia,[3,6,7] however a proportion of the cases needed renal replacement therapy.[7]

The use of corticosteroids in AIN is still controversial as data is limited. A few studies have shown benefits with corticosteroid usage.[6,8] In the study by González et al, patients who were not given steroid therapy had significantly higher final serum creatinine level and significantly higher proportion of patients required chronic dialysis.[6] This study also found benefit with earlier steroid initiation. Prendecki et al found that steroid-treated patients had better eGFR at all time points post biopsy up to 2 years and fewer steroid-treated patients were dialysis dependant by 6 and 24 months.[8] Murithi et al demonstrated that longer duration of drug exposure and longer delay in starting steroid therapy was associated with poorer renal recovery.[9] Overall, studies have shown that earlier offending drug withdrawal and earlier steroid usage was associated with better renal outcomes.[4,6]

We describe two cases of AIN associated with bilateral hyaluronic acid breast filler procedure which most likely had systemic absorption and was excreted through the kidneys.

Both patients developed the same clinical course of pain and swelling at bilateral breasts up to the neck region. Both patients' serum creatinine levels rose to 330-370 mmol/L one day post filler injection and both needed emergent dialysis. Thereafter both patients remained dialysis dependent for about 3 months but were successfully weaned off dialysis eventually with partial renal recovery

Case 1 presented earlier with anaphylactic shock, but had more severe infection of the breast injection sites requiring surgical intervention and hence did not receive steroids for her AIN. This could explain the more marked ATN seen on her renal biopsy. The AIN changes were not as pronounced possibly because her renal biopsy was performed 3 weeks later than case 2. After stopping dialysis, Case 1's creatinine remained higher compared to Case 2 up until 6 months.

Case 2 had a more delayed presentation resulting in severe anuric AKI but her infection was not as severe and she received a course of steroids for her AIN. These measures may have potentially aided in more rapid renal recovery as compared to case 1. The AIN was postulated to be due to an immune related response secondary to the hyaluronic acid filler injection which likely had systemic absorption. It is uncertain if earlier use of steroids would have made any difference in the final outcome as both cases were very ill in the early stage and steroid use was not considered then.

CONCLUSION

To the best of our knowledge, these are the first two reported cases in Malaysia of AIN due to hyaluronic acid cosmetic breast filler injections resulting in severe dialysis requiring acute kidney injury, with eventual partial renal recovery. The public should be aware of potential adverse reactions with various cosmetic procedures and should be educated to seek treatment by licensed personnel.

Written informed consent was obtained from the patients for the publication of this case report and any accompanying images.

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Laugier-Hunziker syndrome in a young girl

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SUMMARY

Laugier-Hunziker syndrome (LHS) is a rare, acquired disorder characterised by circumscribed pigmented macules of the oral mucosa. This rare condition usually occurs on the lips and the acral glabrous skin (mainly fingers and toes). There have been a few instances where fingernail and toenail melanonychia coexist, but not in this patient. Since very similar mucocutaneous lesions are also seen in malignancy syndromes, LHS is an exclusion diagnosis. It occurs mainly in middle-aged individuals with a ratio of approximately of 2:1 between female to male. Nonetheless, cases among children and adolescents were also reported. We describe a case report of a young Malay girl who was incidentally found with multiple oral labial lesions while presented to the clinic with other concerns.

INTRODUCTION

Laugier-Hunziker syndrome (LHS) is often diagnosed by exclusion after ruling out all other potential causes of oral and labial hyperpigmentation, such as physiologic pigmentation and inherited lentiginosis-related disorders like Peutz-Jeghers syndrome (PJS). Drug-induced pigmentation, Addison's disease (AD) and other illnesses characterised by diffuse oral mucosal pigmentation must also be considered in the differential diagnosis.

The diagnosis of LHS is supported by the absence of systemic symptoms as well as by negative results from the relevant diagnostic test.

This syndrome typically affects women of middle-aged and primarily Caucasian origin.[2] Recognition of this syndrome is essential in middle-aged patients because the development of new areas of pigmentation, especially in mucosal surfaces, may be related to malignancy. Although mucosal melanomas are uncommon, they should always be considered when making a differential diagnosis among Caucasians. Among young patients, however, there have been reports of LHS cases3 including reports on familial cases of LHS.[1]

CASE PRESENTATION

A 12-year-old Malay girl was brought by her parents to a primary care clinic in Kuantan. The parents were concerned with her noticeable rapid growth for the last year which was concurrent with her attainment of menarche. She is the youngest of four siblings and at her current age, she is the tallest compared to her elder sisters. Anthropometry examination revealed both her weight and height for age were at the 90th centile and appropriately following the mid-parental height growth chart.

There was no history of malaise, fatigue, fainting episodes, weight loss, recurrent abdominal pain, intermittent vomiting, gastrointestinal bleeding, palpitation or shortness of breath. There was no relevant drug history. There was no history of gastroesophageal reflux disease and gastritis.

Parents were non-consanguineous. There was no history of diabetes mellitus, thyroid disease, intestinal polyposis or mucocutaneous pigmentary diseases in the family. Psychosocial screening using the HEADSSS approach revealed no significant problem, especially in the dietary, sexual and mental aspects.

Her dental history was unremarkable with the last visit to a dentist being three years ago.

Upon physical examination, she appeared relaxed and comfortable in a euthyroid state. Her vital signs include a temperature of 36.7°C, a blood pressure of 100/60 mm Hg, a heart rate of 82 beats/min and a respiration rate of 14 breaths/min. There were no dysmorphic facial features or neurocognitive stigmata. The further assessment noted the patient was in Tanner stage 2.

Examination of the oral mucosa revealed multiple melanotic macules with clearly defined borders on the lower and upper labial mucosal area as shown in Figure 1. There were no similar lesions over the vermilion border and the buccal mucosa on both sides. The other mucosal surfaces, such as the oropharynx, conjunctiva, oesophagus, anus, vulva and perineum were not affected. She has no skin and fingernail or toenail involvement.

Upon incidental discovery of the oral melanotic macules, the parents admitted that they had never realised about the presence of mucosa pigmentation. The lesions were asymptomatic and the related inquiries were negative. Nevertheless, they were concerned about the lesions' progression and underlying cause.

Complete blood cell count, serum electrolytes, liver function test and chest radiograph revealed no abnormality. Referrals to paediatrician and dermatologist were made and the following investigations; serum cortisol, TSH, FSH and LH, all within normal range, and abdominal ultrasound was unremarkable.

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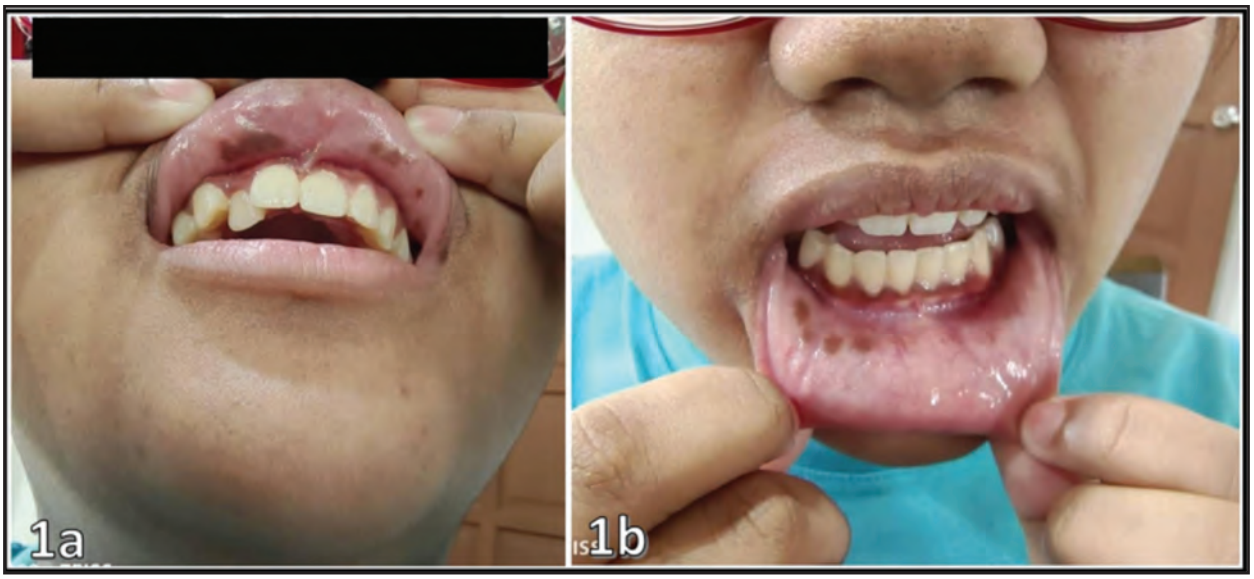

Fig. 1: (a) Hyperpigmented macules over upper labial mucosa and (b) lower labial mucosa

Given the pigmented macules on the upper and lower labial lip, no history of medication intake, and standard laboratory investigations, a diagnosis of LHS was made. The parents were reassured of the benign nature of the disorder and that treatment was unnecessary. Our patient and his parents did not have any cosmetic concerns. As such, no treatment was given. Further follow-up 6 months later noted no progression of the lesions with no psychosocial concern identified.

DISCUSSION

LHS is an uncommon condition with few reported cases. Previous research revealed a 2:1 overall female-to-male ratio, indicating a predominance of women. After carefully going over the information, a preference for women became evident. There were 76 patients in total, and 55 (72.37%) were women.[4] The illness typically affects people between the ages of 40 and 55, with a mean age of onset of 50 years, per study.[4,6] It can sporadically happen before puberty as in this patient.[6,7]

The oral lesion in LHS can be lenticular, circular, linear in shape, single or confluent, brown, black, or grey, with a smooth surface and clearly or vaguely defined edges. Similar lesions may also exist in other mucosal surfaces, such as the oropharynx, conjunctiva, oesophagus, anus, vulva and perineum, as well as the facial skin, belly and other places.[4] Up to 60% of instances can affect nails, but in this patient, there was no evidence of fingernail or toenail melanonychia.[1] By screening out other conditions that can also lead to high mucocutaneous pigmentation, LHS is diagnosed. The differential diagnosis should include PJS and AD.

PJS is an uncommon form of autosomal dominant genodermatosis that manifests as gastrointestinal polyposis and mucocutaneous pigmentation, a more significant risk for various cancer types. The diagnostic criteria for PJS include the presence of two or more histologically confirmed PJ polyps, any number of PJ polyps in individuals with a positive family history of PJS, or in an individual who also has characteristic mucocutaneous pigmentation. Hamartomatous polyps, commonly manifest when a person is still relatively young, are also a part of PJS. Polyps typically first emerge when a person is 11-years-old. However, PJS was ruled out during the diagnosis because there was no unfavourable family history. No colonoscopy examination was done in this patient.

AD commonly presents with mucocutaneous discolouration. The skin, mouth cavity, conjunctiva, and genitalia can all be impacted by pigmented lesions. Brown spots on the tongue, palate, buccal mucosa, gingiva and gingiva are still other early signs of AD; however, unlike LHS, these spots are more dispersed and involvement of the palmar creases and flexural sites on the face where they are more evident because they are subject to pressure and light. Systemic manifestations of AD include anorexia, lack of energy, nausea, vomiting, weight loss, stomach and muscle discomfort, and orthostatic hypotension. In addition, AD patients may also have anaemia, lymphocytosis, eosinophilia, hypercalcemia, hyperkalaemia, hyponatremia, hypoglycaemia and high ACTH levels. For this patient, except for the pigmentation of the oral cavity, she did not have any other related symptoms. The blood investigations were also normal, ruling out AD.

The other differential diagnosis of mucocutaneous pigmentation should consider rare genetic syndromes like McCune-Albright syndrome, LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retardation of growth, deafness), and LAMB (lentigines, atrial myxomas, mucocutaneous pigmentation). Again, except for hyperpigmentation, the patient has no symptoms of the syndromes above.

Up to now, no evidence supports that there is a malignant tendency associated with LHS. It seems that there is no

systemic abnormality or familial factor associated with the syndrome. Generally, pigmentary changes in individuals with LHS do not disappear naturally but slowly increase along with aging. There are, therefore, no justifications for LHS therapy other than aesthetic and psychological components. Successful removal of pigmented lesions using laser techniques was reported[8] and to prevent the lesions from reoccurring, it is advisable to avoid the sun.[9]

In adolescents especially female, psychosocial assessment is warranted during follow-up to identify stress and anxiety in relation to unreasonable worry about the cosmetic appearance of the oral lesion. Reassurance and parental empowerment with correct knowledge is the key.

CONCLUSION

When making a differential diagnosis for mucocutaneous pigmentation, primary care doctors should always consider Laugier-Hunziker syndrome (LHS), particularly if the patient has no systemic symptoms. Despite its low prevalence, a rapid clinical diagnosis will allow the exclusion of more severe pigment illnesses and avoid the need for an additional test, intrusive examinations, and treatments. Specific investigation to establish the diagnosis is still unknown, but a more significant challenge in primary care is in identifying the lesion and establishing the cause of hyperpigmentation. It's important to underline the importance of promptly detecting LHS in young patients as early detection and diagnosis in this group of patients may prevent the emergence of mental health issues such as stress and anxiety connected to the uncertainty of the condition. Although most pigmentation disorders are benign or nonspecific, some disorders of skin pigmentation present cosmetic or psychological challenges to the patient, necessitating evaluation and treatment. Proper diagnosis of these common skin conditions will allow the physician to facilitate appropriate skin treatment and reassure the patient.

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CONFLICT OF INTEREST

None to declare.

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CASE REPORT

Massive haemorrhagic pericardial effusion as the cardiac manifestation of Salmonella enteritidis infection in a severely immunocompromised patient

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SUMMARY

A 41-years-old gentleman was admitted for reduced effort tolerance with non-specific symptoms of weight loss and generalised body weakness. Chest X-ray (CXR) showed cardiomegaly. Echocardiography showed a large pericardial effusion with septation. Emergency pericardiocentesis was performed and pericardial fluid culture grew *Salmonella enteritidis (S. enteritidis)*. He tested positive for the retroviral disease, with a CD4 count of 10 cells/µL. Intravenous (IV) ceftriaxone was administered. A pericardial drain was inserted due to the rapid re-accumulation of pericardial fluid after the initial pericardiocentesis. He also had drainage of his left pleural effusion. He had a guidewire exchange of pericardial drain around 2 weeks after admission, with flushing performed whenever the flow was poor. A repeat echocardiogram showed early signs of constrictive pericarditis with residual pericardial effusion in which intra-pericardial fibrinolysis was considered. He was started on antiretroviral therapy (ART) and his condition remained stable. The pericardial drain was kept throughout his admission. Unfortunately, he developed severe sepsis and succumbed to it about a month post-admission.

INTRODUCTION

Acute pericarditis manifesting with massive haemorrhagic pericardial effusion is a potentially life-threatening condition that should be identified and treated early. Non-typhoidal *Salmonella* infection is a recognised but rare cause of pericarditis with pericardial effusion.

More than 200 serovars of *Salmonella* had been identified to have clinical implications in human.[1] The first case of non-typhoidal *Salmonella* pericarditis by *S. choleraesius* was reported in a 36-years-old woman in 1936. In 1961, seven other cases were reported infected by *S. typhimurium*, *S. parathyphi A*, *S. blegdam* and *S. Newport*. The majority of the cases involved children under 2 years of age.[2] In recent years, there have been reports of non-typhoidal *Salmonella* causing pericarditis with pericardial effusion, mainly in immunocompromised adult patients. We report a case of massive haemorrhagic pericardial effusion due to *S. enteritidis* pericarditis in a severely immunocompromised patient with an advanced retroviral disease.

CASE PRESENTATION

A 41-years-old man who was a non-smoker and non-alcohol drinker presented with unintentional weight loss of up to 8 kg, loss of appetite, lethargy, reduced effort tolerance, and unwell for 3 months. He was sexually active with multiple male partners.

He was admitted to a district hospital for symptomatic anaemia 1 week and was transfused with two pints of packed cells around 1 week before his current presentation.

However, his general condition did not improve after discharge, thus, he presented to our hospital, which is a tertiary referral hospital. His vital signs showed blood pressure of 120/72 mmHg, heart rate of 126 beats per minute, a temperature of 36.7°C and respiratory rate of 28 breaths per minute. On examination, he appeared cachectic-looking and had oral thrush and generalised macular rashes. Auscultation of his lung and heart revealed left lower zone crepitations with no audible murmur or pericardial rub.

Laboratory examinations showed pancytopenia with a white cell count of 2.77 x 103 µL predominantly neutrophil of 77%, haemoglobin of 7.9 g/dL, platelet of 40 x 103 µL and C-reactive protein (CRP) of 952 nmol/L. 12-lead electrocardiogram (ECG) showed ST-segment elevation at leads II, III, aVF and V2-V6 (Figure 1A). CXR showed cardiomegaly with a globular heart (Figure 1B). Bedside transthoracic echocardiogram (TTE) showed a massive pericardial effusion with septation, with the deepest pool of 4 cm (Figure 2A) and also left pleural effusion.

An emergency pericardiocentesis was performed and drained about 500 ml of haemorrhagic pericardial fluid. Pericardial fluid analysis showed a total protein of 63 g/L, lactate dehydrogenase (LDH) of 1,787 U/L and glucose level of <0.11 mmol/L. The ratio of pericardial fluid to serum protein and LDH were 0.84 and 3.64, respectively which indicate exudative pericardial effusion based on Light's criteria. His pericardial fluid grew *S. enteritidis*. Other investigations performed on the pericardial fluid such as cytology, acid-fast bacilli (AFB) and TB GeneXpert study were negative. His human immunodeficiency virus (HIV) and hepatitis B tests were positive. His CD4 cell count was 10 cells/µL.

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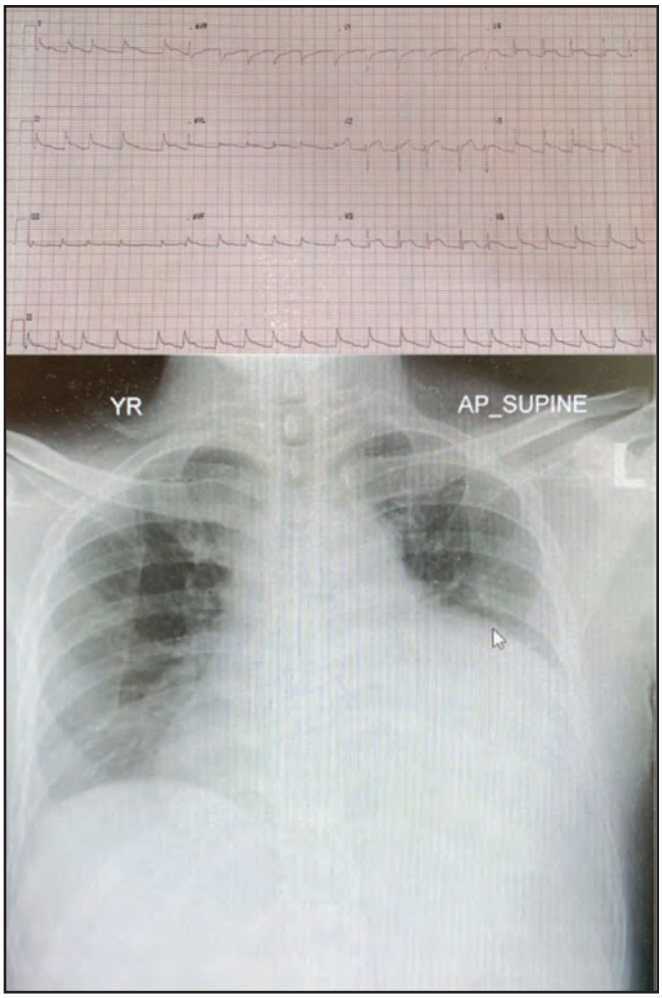

Fig. 1: (A) ECG showing ST-segment elevation at leads II, III, aVF, and V2-V6. (B) CXR showing cardiomegaly with a globular heart

He was given IV ceftriaxone for the treatment of S. enteritidis pericardial effusion. Pleural tapping on his left pleural effusion was performed on day 2 of admission, which drained out 500 ml of exudative haemoserous fluid. A pleural fluid study showed similar exudative features. There was no growth from the pleural fluid culture. Cultures taken from his blood, urine and stool were all negative. Around day 5 of admission, there was re-accumulation of both pericardial and left pleural effusion from repeated TTE. A second pericardiocentesis was performed and drained out 350 ml of haemorrhagic fluid which also grew *S. enteritidis*. In the same setting, a pericardial drain was inserted using a triple-lumen catheter in anticipation of rapid re-accumulation of pericardial fluid again. A pigtail catheter was also inserted for his left pleural effusion. Computed tomography (CT) scan thorax showed no pleuro-pericardial fistula, thus, the pleural pigtail catheter was removed 6 days later.

His pericardial catheter drained around 100-200ml of fluid daily for 1 week but subsequently reduced to less than 50 ml daily, prompting the cardiology team to perform a reassessment and guidewire exchange of his pericardial drain around 2 weeks post admission. He would undergo flushing of his pericardial drain as necessary when the drainage was poor. A repeated TTE was performed around 4 weeks post-admission and showed a reduction in pericardial effusion with evidence of organised effusion and shuddering of the septum, indicating early onset constrictive pericarditis (Figure 2B & C). Intra-pericardial fibrinolysis was planned but was postponed due to his persistently low platelet.

In addition to antibiotics, he was started on ART with oral tenofovir-emtricitabine and efavirenz on the 10th day of admission. IV antibiotics were changed from IV ceftriaxone to IV cefepime because of concerns about ceftriaxone-induced hyperbilirubinemia as his total and direct bilirubin level were increasing by four-fold from 30 µmol/L and 25 µmol/L to 114 µmol/L and 105 µmol/L respectively within 10 days of starting on IV ceftriaxone. As he remained clinically stable, the antibiotic was switched to oral trimethoprim-sulfamethoxazole for the continuation of treatment of his *Salmonella* infection. However, he developed severe sepsis on day 30 of admission with an episode of hypotension, hypoglycaemia and severe metabolic acidosis with haematochezia. IV antibiotics were then escalated to IV meropenem as he had a urine culture that grew extended-spectrum beta-lactamase *Proteus mirabilis*. He succumbed to death due to severe sepsis.

DISCUSSION

Massive haemorrhagic pericardial effusion due to non-typhoidal *Salmonella* pericarditis is a rare presentation. The occurrence of pericarditis can be due to the affinity of *S. enteritidis* to the pericardium. Patients who are immunocompromised were more likely to develop severe pericardial effusion with some presenting with cardiac tamponade.[3] Our patient had an advanced retroviral disease, which likely explains why he developed massive pericardial effusion.

The treatment modality for the pericardial effusion of such extent includes IV antibiotics and invasive procedures to drain the fluid.

Antibiotic treatment based on the culture and sensitivity report is the mainstay of non-typhoidal *Salmonella* pericarditis presenting with pericardial effusion. Those with less extensive pericardial effusion responded better with antibiotics treatment only.[2,4] The use of cephalosporin and quinolone group of antibiotics in the treatment of Salmonella pericardial effusion has been described.[5] Most antibiotics are administered through IV and orally. However, there has been a case report on the use of intra-pericardial antibiotics for the treatment of acute purulent pericarditis caused by *Staphylococcus aureus* infection.[6]

Needle pericardiocentesis is essential for diagnosis and offers symptomatic relief in the management of pericardial effusion. However, a high rate of fluid re-accumulation could happen, as seen in our patient, which calls for the consideration of other treatment modalities. Hence, an indwelling pericardial catheter was inserted to drain out the rapidly accumulating pericardial fluid to prevent the need for repeated needle pericardiocentesis. A study has shown that

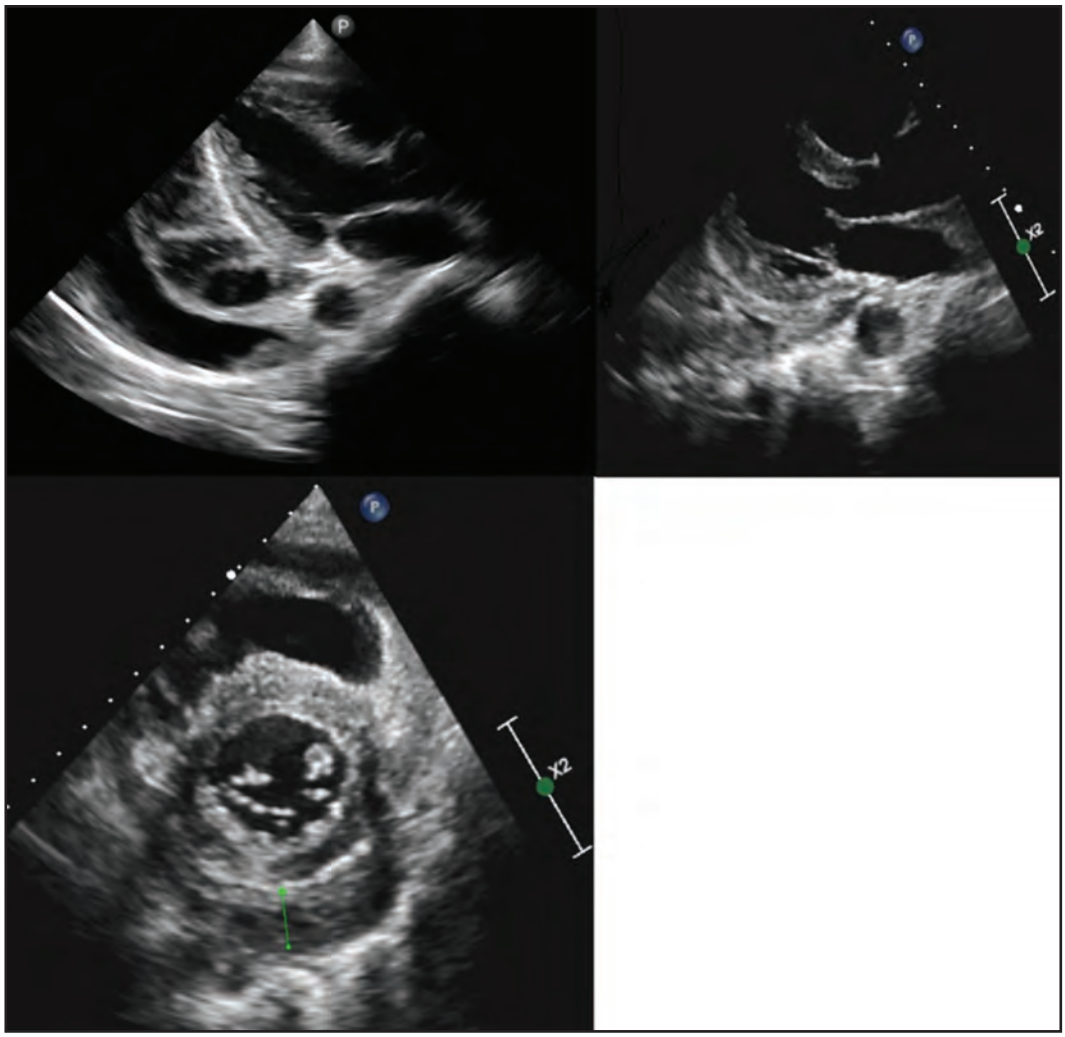

Fig. 2: (A) Parasternal long axis view showing septated pericardial fluid at the posterior pericardium (white arrow). Pleural effusion was also seen (dotted arrow). (B) Parasternal long axis view and (C) short axis view showing organised pericardial effusion

pericardial catheter placement is a safe alternative to needle pericardiocentesis without increasing the risk of arrhythmia.[7] Our patient experienced poor drainage from his pericardial catheter despite changing to a new catheter through guidewire exchange, likely due to the presence of septation in his pericardial fluid which was seen on TTE. There might be a role of intra-pericardial fibrinolysis in such a situation.

This could be considered in a setting without cardiothoracic service. There were surgical interventions such as pericardial window, pericardiotomy or pericardiectomy which could only be done by the cardiothoracic surgeons. However, there is no definite timing for each of these interventions.

Intrapericardial fibrinolysis in the treatment of exudative pericarditis is associated with lower morbidity compared to pericardiectomy and is less invasive.[8] There is still no definite answer regarding the best time to perform intra-pericardial fibrinolysis, which will have the best prognostic outcome. It could be either administered early when the initial echocardiogram showed evidence of septation or fibrin, or later to allow sufficient time for the antibiotic to take effect and when the evidence of constrictive pericarditis is more apparent.

Our patient seemed to improve with the treatment of IV antibiotics and pericardial drain, which has a 92% treatment success rate based on a case series of 12 adult patients.[9] However, given his severe immunocompromised state, there was always a risk of keeping the pericardial drain too long, in addition to flushing the catheter whenever the drainage was poor. This probably predisposed him to secondary bacterial infection, which could have resulted in him developing severe sepsis. However, all his repeated cultures at the time of his deterioration and demise were negative.

CONCLUSION

Non-typhoidal *Salmonella* pericarditis could present with massive haemorrhagic pericardial effusion in an immunocompromised host, as seen in our case report. It warrants a high index of clinical suspicion for early diagnosis and prompt treatment with IV antibiotics and pericardiocentesis with or without pericardial drain. It is

equally important to manage other risk factors such as patient's underlying immunocompromised state and pericardial catheter care which increase the patient's risk of secondary infection, resulting in poor clinical outcomes.

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CASE REPORT

A rare presentation of delayed bilateral vocal cord paralysis post radiation treatment

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SUMMARY

Bilateral vocal cord palsy is a life-threatening condition that can occur due to a plethora of causes. Radiotherapy associated vocal cord immobility is one of the rarest causes associated with this condition and has only been reported a handful of times. We present a case involving a 73-year-old man with a history of glottic carcinoma who had undergone radiotherapy 4 years ago. He presented to the emergency department with a 5-day history of shortness of breath, odynophagia, noisy breathing, low grade fever and sore throat. Further examination via bedside flexible nasopharyngolaryngoscopy (FNPLS) revealed no bulging of the lateral or posterior pharyngeal wall. However, his bilateral vocal cord abductors were immobile in a median position with an almost slit like opening. His epiglottis, arytenoids and bilateral false cords were oedematous with an obvious pooling of secretion at both pyriform fossae. There was no clinical or radiological evidence of tumour recurrence. He was diagnosed with bilateral vocal cord palsy with supraglottitis. An emergency tracheostomy and subsequent direct laryngoscopy were performed to secure his airway. Throughout his hospital stay, he also suffered from other conditions such as community acquired pneumonia, Forrest III ulcer at the pylorus, type 2 myocardial infarction and pulmonary embolism. He was successfully treated for those medical conditions and discharged after a period of 12 days. Radiotherapy induced bilateral vocal cord palsy is not a common finding and can be life threatening if left untreated. Knowledge regarding this condition will aid in diagnosing and treating patients early, producing a better outcome.

INTRODUCTION

Radiation therapy is one of the most effective and suitable therapies available for head and neck cancer. With early laryngeal cancer especially those in stage I and stage II being primarily a local disease, radiotherapy is the principal treatment modality to preserve the larynx. Only more advanced laryngeal cancers are treated via a combination of surgery and radiotherapy or chemotherapy. Radiotherapy itself comes with its fair share of complications and has many documented side effects, including mucositis, skin reactions, decreased salivary flow, soft tissue fibrosis, osteoradionecrosis and perichondritis. Most of the complications occur early but some may occur years after radiation therapy. Radiotherapy-induced peripheral nerve palsies have been reported although quite rarely, usually after a latent period of 1-5 years. There are two mechanisms that explain these injuries, with the first being radiation-induced scarring along the course of the recurrent laryngeal nerve, and the second being vascular insult with ischemia and obliteration of small capillaries leading to degenerative changes.

CASE PRESENTATION

A 73-year-old Chinese man with a previous history of laryngeal cancer treated with radiotherapy presented to the emergency department with the chief complaint of noisy breathing for the past 5 days, associated with sore throat, odynophagia, hoarseness, occasional low-grade fever, and shortness of breath. The emergency department team started the patient on nasal prong oxygen at 3l/minute and administered intravenous dexamethasone 8mg and nebulised adrenaline, before referring the patient to both the otorhinolaryngology, and anaesthetic team respectively.

Further history from the patient revealed that he had underlying diabetes mellitus and hypertension for more than 10 years with no proper follow-up, purchasing oral hypoglycaemic agents and anti-hypertensive medications from a private pharmacy. He was also previously diagnosed with glottic carcinoma (T1NoMo) in 2018 and was treated via radical 3D radiotherapy to the larynx amounting to 55 Grays in 20 fractions. He was under regular follow-up with the hospital until the covid pandemic struck. Prior to the pandemic, his findings during his follow-ups were unremarkable. He otherwise has no known allergies.

On examination, the patient had a full GCS with stridor, tachycardia and tachypnoea. There was a predominant breathiness quality in his voice. He was unable to complete sentences. His vital signs were, blood pressure:156/98 mmHg, pulse: 120 beats per minute, respiratory rate: 40 times per minute, temperature: 36.5 Celsius and oxygen saturation: 98% under nasal prong. Auscultation revealed equal air entry bilaterally with transmitted sounds. A chest radiograph was done, which revealed bilateral lower zone haziness. At the same time his white cell count was 27.2 (normal value: 4.0-10.0) and C-reactive protein was 84.33 (normal value: <5.00), suggestive of community acquired pneumonia (CAP), and he was administered intravenous ceftriaxone 2gm per day.

Bedside flexible nasopharyngolaryngoscopy (FNPLS) was done, and the summarised findings are as follows: epiglottis,

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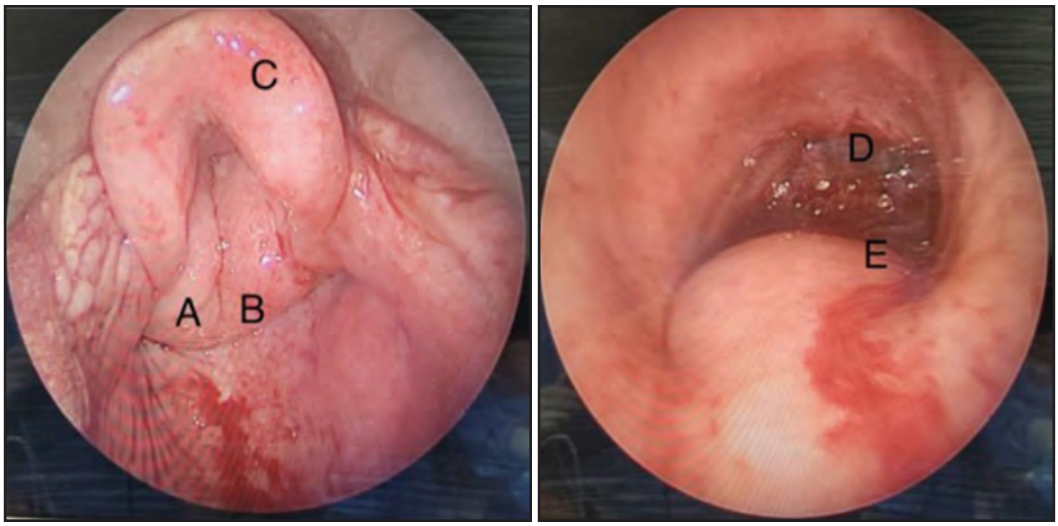

Fig. 1: The direct laryngoscopy findings intraoperatively; A: Left arytenoid, B: Right arytenoid, C: Epiglottis, D: Tracheostomy tube, E: Posterior tracheostomy wall

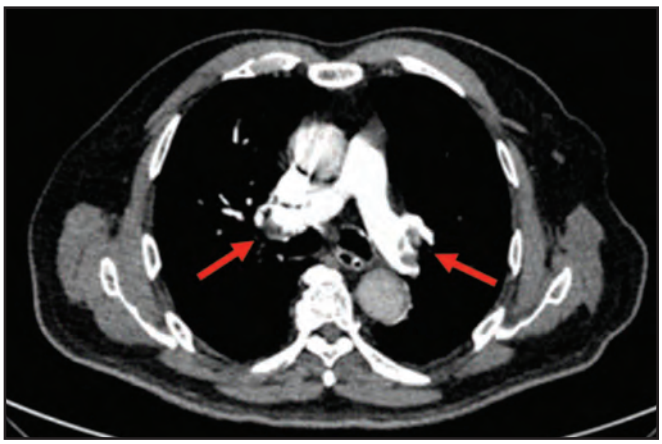

Fig. 2: CTPA showing filling defect in bilateral pulmonary arteries (indicated by red arrows)

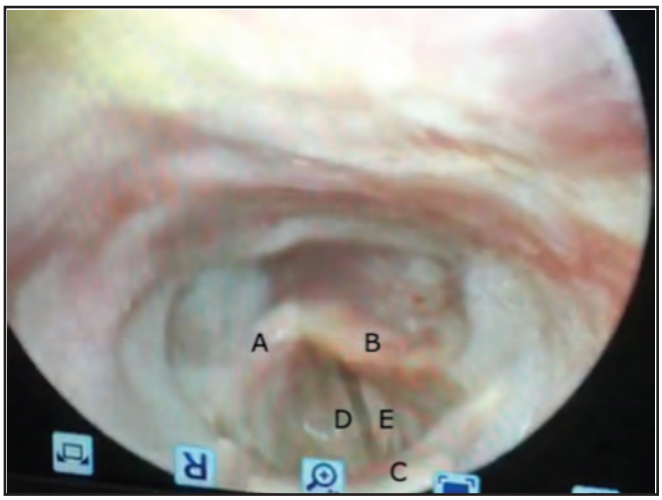

Fig. 3: Bilateral abductor palsy with slit like airway still seen during review of the patient; A: Right arytenoid, B: Left arytenoid, C: Epiglottis, D: Right vocal cord, E: Left vocal cord

arytenoids and bilateral false cords were oedematous; secretion pooling at both pyriform fossae; bilateral vocal cords abductor palsy; and vocal cords in median position with an almost slit like opening. There was no narrowing of the lateral or posterior pharyngeal wall, and no masses were noted. Our provisional diagnosis for the patient was bilateral vocal cord palsy secondary to radiotherapy with supraglottitis. The rest of his physical examination was unremarkable.

The patient was then immediately taken to the operation theatre whereby he was intubated via awake fibreoptic nasal intubation and given a STAT dose of IV cefuroxime 1.5gm. We then proceeded with an emergency tracheostomy to secure his airway, and a direct laryngoscopy examination under anaesthesia to look for any masses or lesions. Direct laryngoscopy findings were unremarkable, there was no clear mass on inspection of the laryngeal subsites, the visualised subglottis was normal until the carina, and cricoarytenoid joints were palpated with no evidence of fixation or subluxation. Post procedure, he was transferred to the intensive care unit (ICU). Despite being a popular treatment choice for the management of bilateral vocal cord palsy, posterior laser cordectomy was not offered for this patient due to his multiple comorbidities and underlying medical issues.

Post emergency tracheostomy, the patient had coffee ground secretion from his nasogastric tube. He was then diagnosed with a small Forrest III ulcer at the pylorus following an esophagogastroduodenoscopy (OGDS). Hence, he was started on a proton pump inhibitor, intravenous pantoprazole 40mg daily.

He was also diagnosed with type 2 myocardial infarction and pulmonary embolism over the next few days of his admission. His computed tomography pulmonary

angiogram (CTPA) showed filling defects involving bilateral main pulmonary arteries extending to their segmental and subsegmental branches. He was treated with a combination of clopidogrel and enoxaparin for his condition.

After 12 days of hospital admission, he was allowed to be discharged home. A bedside FNPLS showed that the supraglottitis had resolved however his vocal cord mobility remained the same, with bilateral true cords in median position with no abduction. He was also scheduled for an outpatient computed tomography (CT) brain to upper thorax to assess for any radiologic evidence of recurrence and to assess the course of both recurrent laryngeal nerves. The findings of the CT scan revealed no evidence of any recurrence at the larynx and the course of both the recurrent laryngeal nerves were not impinged by any lesion or mass. The findings in the brain revealed old multifocal infarcts but no evidence of any lesion. Two weeks post discharge his FNPLS findings remained unchanged.

DISCUSSION

The larynx is an important structure that is involved in phonation, respiration, and deglutition. It is innervated by two branches of the vagus nerve, which are the recurrent laryngeal nerve and the superior laryngeal nerve. The recurrent laryngeal nerve innervates four of the intrinsic laryngeal muscles: thyroarytenoid, posterior cricoarytenoid, lateral cricoarytenoid, and interarytenoid muscles. Injury to any one of these nerves may lead to vocal fold paresis or paralysis. The difference between the two is that vocal fold paresis implies various degrees of vocal fold hypomobility due to neurological injury or from weakness of the nerves, whereas vocal fold paralysis implies complete vocal fold immobility due to the neurological injury.[1] Since the vocal fold is crucial for survival, its impairment can cause complications such as dysphagia or aspiration. When bilateral vocal cords are paralysed, airway obstruction becomes the cause for concern.[2] When this happens, securing the airway via a tracheostomy or intubation is of utmost importance.

There are many different aetiologies of vocal fold paralysis. The most common causative factor is due to surgery, and data from previous studies demonstrate between 25 to 58% of cases are linked to surgery, notably thyroidectomy. Neoplasia is the second most common aetiology, ranging from 7 to 17% of cases.[2] A common cause of vocal fold paralysis which is avoidable is from intubation, which contributes between 2 to 18% of cases. Radiation induced neuropathies in head and neck cancer is a rare complication, contributing to only 1 to 9% of cases.[3] The time lag on the other hand can be up to 35 years, and the most commonly affected cranial nerves are the vagus, trigeminal, spinal accessory, oculomotor, abducens, optic, and hypoglossal.[4] Other causes include neuromuscular disease, viral infections such as coronavirus disease, autoimmune disease and toxicity.

We were able to rule out coronavirus as a potential cause because the patient's voice was normal prior to the event and his covid polymerase chain reaction (PCR) results were negative. As neuromuscular disease can also be one of the causes of bilateral vocal cord palsy, peripheral nerve conduction and an MRI brain would help to rule out neuromuscular causes. However, those tests were not performed as a full neurologic examination was carried out and no abnormalities were detected. At the same time the patient also did not complain of any neurologic symptoms. Another helpful examination would be the utilisation of a laryngeal electromyography (LEMG) unit, which records the electrical activity produced by the laryngeal muscles and gives specific information as to whether the nerve input into a particular muscle is normal or abnormal. This will allow us to differentiate whether the aetiology is due to neural injury or from cricoarytenoid joint ankylosis. We however do not possess an LEMG unit in our centre. Hence, despite the CT scan showing no abnormality over the region of the cricoarytenoid joint, there does remain a distinct possibility that this may be related to a neuromuscular disease.

A literature search associating radiotherapy and delayed vocal fold paralysis produced several results. In 1995, Stern et al reported three cases of vocal fold palsy 21 to-34 years after radiotherapy,[4] whereas Lin et al mentioned that six out of 19 subjects who developed radiation induced cranial nerve neuropathies suffered from recurrent laryngeal nerve palsy, with a latency period that extended up to 20 years.[5] Prepageran in 2005 also reported a case of bilateral vocal cord immobility 15 years after head and neck radiotherapy in a patient with laryngeal carcinoma.[6] In 2012, Jaruchinda et al reported a rate of 7.14% of vocal fold paralysis in a group of 70 people who underwent head and neck radiotherapy, with the time lag varying between 14 to 35 years.[7] A newer study in 2015 by Crawley and Sulica reported 10 cases of vocal fold paralysis causing dysphonia and dysphagia, with an onset of paralysis between 1 and 27 years after irradiation therapy.[8]

Unilateral vocal cord palsy is more commonly seen on the left side due to the longer course of the left recurrent laryngeal nerve. The paralysed vocal cord is unable to adduct and abduct, leading to glottic incompetence. Even though the contralateral unaffected vocal cord can abduct, it is usually insufficient to produce normal phonation oscillation bilaterally. Therefore, patients with unilateral vocal cord palsy often present with dysphonia such as hoarseness, vocal fatigue, weak or breathy voice and sometimes even cough or aspiration. Bilateral vocal cord palsy on the contrary presents with normal or near normal phonation with respiratory distress, spanning from mild stridor upon exertion to life threatening airway obstruction necessitating emergency tracheostomy.[9] Our patient presented with a life-threatening shortness of breath due to bilateral vocal fold immobility with superimposed infection (supraglottitis) 4 years after completion of radiotherapy to the larynx. Since he missed his follow-ups during the covid pandemic, it is difficult to determine if there was one vocal cord that had been affected before the other. At the same time, antibiotics were necessary not only to treat his pneumonia but also his supraglottitis. Unfortunately, during his hospital stint, he developed other acute life-threatening conditions such as community acquired pneumonia, Forrest III ulceration, type 2 myocardial infarction and pulmonary embolism. These conditions are usually associated with physiologic stress,

which was most probably triggered by his acute upper airway obstruction. However, despite suffering from various other medical problems throughout his stay, our focus in this case report is on the rare complication of delayed vocal fold paralysis following radiotherapy.

CONCLUSION

As radiotherapy can potentially cause laryngeal neuropathy years after treatment, patients who have undergone radiotherapy are encouraged to seek immediate consultation at their nearest otorhinolaryngologist if they notice any changes to their voice or experience any form of breathing difficulty. This is because although neuropathies secondary to radiation are relatively rare, they are usually permanent and can significantly affect patients' quality of life with minimal potential for spontaneous recovery. Therefore, as clinicians, it is crucial that these patients are followed up regularly on a lifelong basis so that we can identify, detect, and treat this condition early.

CONSENT

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

CONFLICT OF INTEREST

There was no conflict of interest.

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