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

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Case Reports

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Hepatic lymphoma presenting as liver abscess causing diagnostic dilemma: A case series

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SUMMARY

Hepatic lymphoma, including both primary and secondary involvement, can mimic liver abscesses due to overlapping clinical and radiological features. This case series presents four patients initially treated for liver abscesses based on symptoms of fever, abdominal pain, elevated inflammatory markers, and imaging showing hypodense liver lesions with rim enhancement. However, poor response to antibiotics prompted further evaluation. Biopsy and immunohistochemistry ultimately confirmed secondary hepatic lymphoma. These cases highlight the need to consider hepatic lymphoma in atypical or unresponsive liver abscess presentations. Early biopsy and histopathological analysis are essential for accurate diagnosis and timely initiation of appropriate lymphoma-directed therapy.

INTRODUCTION

Hepatic lymphoma is an uncommon cancer; it can be difficult to diagnose because of its vague symptoms. It can manifest as secondary hepatic lymphoma, in which the liver is impacted as a component of systemic lymphoma, or as primary hepatic lymphoma (PHL), which is limited to the liver with minimal nodal involvement.[1] Hepatic lymphoma is sometimes misinterpreted as more prevalent illnesses such as liver abscesses because of its rarity and overlapping clinical and radiological features with other hepatic lesions. Fever, pain in the right upper quadrant, and abnormal liver function tests are common presentations of liver abscesses, which are usually caused by bacteria, parasites, or fungi. Hypodense lesions with rim enhancement are frequently seen in imaging tests. Clinicians frequently start empirical antibiotic therapy and percutaneous drainage when confronted with such imaging findings. Alternative diagnoses should be considered if the clinical response is suboptimal. Radiological investigations play a crucial role in the initial evaluation of hepatic lesions. Abdominal ultrasonography (USG) often demonstrates hypoechoic lesions in the liver; however, these findings are nonspecific and may be observed in a broad spectrum of hepatic pathologies. Such lesions may reflect either benign or malignant hepatic conditions, including hepatic lymphoma, metastatic disease, pyogenic or amoebic abscesses, focal fatty changes, and hepatocellular carcinoma. In such cases, contrast-enhanced computed tomography (CECT) typically shows hypodense lesions with variable enhancement, often resembling liver abscesses. Magnetic resonance imaging (MRI) with the diffusion-weighted imaging (DWI) and hepatobiliary contrast agents can provide additional clues, with lymphoma often showing restricted diffusion and homogenous enhancement in later phases. Fluorodeoxyglucose positron emission tomography (FDG-PET/CT) is particularly useful in identifying systemic involvement, aiding in differentiation from isolated infections.[2]

This case series describes four patients who were initially diagnosed and treated as liver abscesses but were later found to have hepatic lymphoma. By presenting these cases, we aim to highlight the importance of maintaining a high index of suspicion in patients with atypical presentations or poor response to standard treatment, to avoid delays in appropriate management. A summary of the cases is presented in Table I.

CASE PRESENTATION

Case 1:

A 40-year-old male with newly diagnosed HIV infection presented with fever and epigastric pain for 3 months, associated with abdominal distension and jaundice. Laboratory tests showed leukocytosis with predominant neutrophils, elevated total bilirubin at 101.9 µmol/L (reference range: 3.4-20.5 µmol/L), ALT 87 U/L (0-55 U/L), and low inflammatory markers. Ultrasound (USG) revealed multiple hypoechoic lesions in the liver and splenic, with mild biliary dilatation, suggestive of metastatic disease. Contrast-enhanced CT (CECT) showed multiple hepatic and splenic masses; differentials included opportunistic infection in this immunocompromised patient. The patient was initially started on broad-spectrum antibiotics and antifungal. However, there was minimal clinical and laboratory improvement. A liver biopsy subsequently showed diffuse infiltration by large atypical lymphoid cells with high mitotic activity. Immunohistochemistry demonstrated diffuse CD20 and CD79a positivity, with CD10 and focal BCL6

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expression, consistent with diffuse large B-cell lymphoma (DLBCL), germinal center B-cell phenotype. Staging PET/CT demonstrated hepatomegaly with multiple hypermetabolic lesions in the liver and spleen (Figure 1).

Case 2:
A 21-year-old male with a history of immune thrombocytopenia in remission presented with lethargy, intermittent fever, loss of appetite and a 20 kg weight loss over 4 months. Full blood count was normal. However, total bilirubin was elevated at 49 µmol/L (3.4-20.5 µmol/L), ESR was 93 ml/hr (<15 mm/hr), C-reactive protein (CRP) 33.28 mg/dL (<0.3 mg/dL) and procalcitonin 0.39 ng/mL (<0.05 ng/mL). Abdominal ultrasound revealed multiple liver and splenic abscesses with several intra-abdominal lymph nodes; the largest lesion measured 2.3 x 4.0 cm in the spleen and 1.2 x 1.3 cm in the liver. CT abdomen and pelvis showed hepatosplenomegaly with multiple ill-defined lesions. He was initially treated with antibiotics, followed by empirical therapy for extrapulmonary tuberculosis. However, due to persistent fever and similar findings on post-treatment CT imaging, a liver biopsy was performed. Histology revealed granulomatous nodules containing scattered neoplastic cells with features of Reed-Sternberg and Hodgkin cells. The background revealed a mixed inflammatory infiltrate rich in eosinophils, reactive T lymphocytes, and histiocytes. Immunohistochemistry showed the neoplastic cells were positive for CD30 and PAX5, and negative for CD15, CD20, CD3, SMA, and CD34. These findings are consistent with classical Hodgkin lymphoma, likely of the mixed cellularity subtype.

Case 3:
A 65-year-old female with past medical history of type II diabetes mellitus, hypertension, and ischemic heart disease presented with prolonged fever, loss of appetite, and weight loss for 2 months. Initial blood test showed normal leukocyte count and liver enzyme level but elevated CRP at 20.8 mg/dL (<0.3 mg/dL). Blood culture on admission was positive for Salmonella non-typhi. In view of persistent fever during hospitalization, a CT scan was performed, revealing multiple ill-defined hypodense liver lesions (largest measuring 3cm x 3cm), likely representing liver abscess, along with intra-abdominal lymphadenopathy. Intravenous antibiotics were continued until a follow-up ultrasound revealed multiple ill-defined, partially liquefied hypoechoic liver collections at segment II, III, VI, and VII. Attempted pigtail drainage of the liver abscess yielded only approximately 3cc of cloudy fluid. A subsequent ultrasound performed three weeks after treatment showed no significant change in the liver lesions, with increasing size of segment III lesion and the appearance of new splenic lesions. Due to persistent fever and unresolved liver collections, a liver biopsy was performed. The liver biopsy showed diffuse infiltration by malignant lymphoid cells with enlarged pleomorphic nuclei, prominent nucleoli, occasional mitoses, and extensive necrosis, with no residual liver tissue. Immunohistochemistry was positive for CD20, BCL6, MUM1, and BCL2, negative for CD3, CD10, and CKAE1/AE3, with a high Ki-67 index of 80–90%, consistent with diffuse large B-cell lymphoma, activated B-cell subtype. Staging PET/CT revealed multiple hypermetabolic liver lesions (SUVmax: 21.2) along with hypermetabolic cervical, supraclavicular, axillary, and abdominopelvic lymph nodes (Figure 2).

Case 4:
A 38-year-old female with underlying paroxysmal supraventricular tachycardia was admitted for recurrent right parapneumonic effusion over the course of one month. Her full blood count and liver function test were normal, but CRP was elevated at 12 mg/dL (< 0.3 mg/dL). Pleural fluid drainage revealed an exudative picture, and pleuroscopy findings were unremarkable. Baseline abdominal ultrasound performed to investigate persistent fever showed hepatosplenomegaly with partially liquefied liver and splenic abscesses. Contrast-enhanced CT of the abdomen confirmed abscesses in segment V of the liver and the spleen, with surrounding inflammatory changes. She was treated empirically for disseminated tuberculosis but opted for early discharge. Approximately one month later, she re-presented with respiratory distress and required intubation. Repeated ultrasound showed unchanged liver and splenic lesion. Thus, a biopsy was performed and reported as diffuse large B-cell lymphoma, activated B-cell subtype. Unfortunately, the patient succumbed to secondary bacterial infection prior to the initiation of chemotherapy.

Table I: Typical Imaging Features of Liver Abscess and Hepatic Lymphoma Across Different Modalities

Imaging technique	Liver Abscess	Hepatic Lymphoma
CT	Typically appears hypodense with rim enhancement due to necrosis and inflammatory exudates. Gas bubbles may be present, especially in pyogenic abscesses caused by Klebsiella pneumoniae. Perilesional oedema and surrounding inflammatory changes are common.	Appears as a hypodense lesion, which may be solitary or multiple. They are often well-defined but lacks the classical rim-enhancement seen in abscesses. Necrosis, cavitation, and perilesional oedema are generally absent.
MRI	Demonstrates central necrosis, restricted diffusion on diffusion-weighted imaging (DWI), and perilesional oedema.	Lesions typically show homogeneous signal intensity, mild restricted diffusion, and absence of necrosis. The lack of perilesional inflammatory changes helps distinguish them from abscesses.
PET/CT	May exhibit mild-to-moderate FDG uptake	Shows intense FDG avidity due to the high metabolic activity of lymphoma.

Table II: Patient Demographic, Laboratory Findings, and Imaging Results

Clinical Data	Patient No.				Ref Range
	1	2	3	4	
Age, year	40	21	65	37	N/A
Sex	Male	Male	Female	Female	N/A
Comorbidities	RVD	ITP	DM/HPT//IHD	Paroxysmal SVT	N/A
Presentations Symptoms:					
Fever	+	+	+	+	N/A
Night sweats	-	+	+	+	N/A
LOA/LOW	+	+	+	+	N/A
Laboratory Findings:					
TWBC ($\times 10^9$/L)	14.3	4	9.3	10.5	4-10
LDH (U/L)	872	163	437	436	< 220
CRP (mg/dL)	1.05	33.28	20.81	7.93	< 0.3
PCT (ng/mL)	NA	0.39	0.21	0.26	< 0.05
CT Imaging Findings:	Multiple hypoechoic liver and splenic lesions	Multiple ill-defined non-enhancing hypodensities in liver. Multiple ill-defined non-enhancing hypodensities seen scattered throughout the spleen (largest 2.0 × 1.6 × 2.0 cm at inferior pole)	Multiple ill-defined hypodense liver lesion (largest 3cm x 3cm) suggestive of liver abscess with intraabdominal lymphadenopathy	Segment V liver and splenic abscesses with surrounding inflammatory changes	N/A
PET/CT	Hepatomegaly with multiple hypermetabolic liver and splenic lesions.	Not done	Multiple hypermetabolic liver lesion (SUVmax: 21.2) with multiple hypermetabolic cervical, supraclavicular, axillary, and abdominopelvic nodes	Not done	N/A
Initial diagnosis	Liver abscess	TB liver/spleen	Liver abscess	Disseminated TB	N/A
Definitive diagnosis	DLBCL, GCB subtype	Hodgkin Lymphoma, mixed cellularity subtype	DLBCL, ABC subtype	DLBCL, ABC subtype	N/A
Duration to diagnosis	10 days	30 days	39 days	32 days	N/A
Ann-Arbor Stage	IV	IV	IV	IV	N/A
Management	R-CHOP	ABVD	R-CHOP	NA	N/A
Outcome	CR	CR	CR	Deceased	N/A

Legend:
RVD: Retroviral Disease; ITP: Immune Thrombocytopenic Purpura; DM: Diabetes Mellitus; HPT: Hypertension; IHD: ischemic heart disease; SVT: Supraventricular Tachycardia; LOA: loss of appetite; LOW: loss of weight; TWBC: total white blood cells; LDH: Lactate Dehydrogenase; CRP: C-reactive protein; PCT: Procalcitonin; PET/CT: Positron Emission Tomography/Computed Tomography; TB: Tuberculosis; DLBCL: Diffuse Large B-cell Lymphoma; R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone; ABVD: Adriamycin (doxorubicin), Bleomycin, Vinblastine, and Dacarbazine; CR: complete remission; N/A: not available
GCB: germinal centre B-cell
ABC: activated B-cell

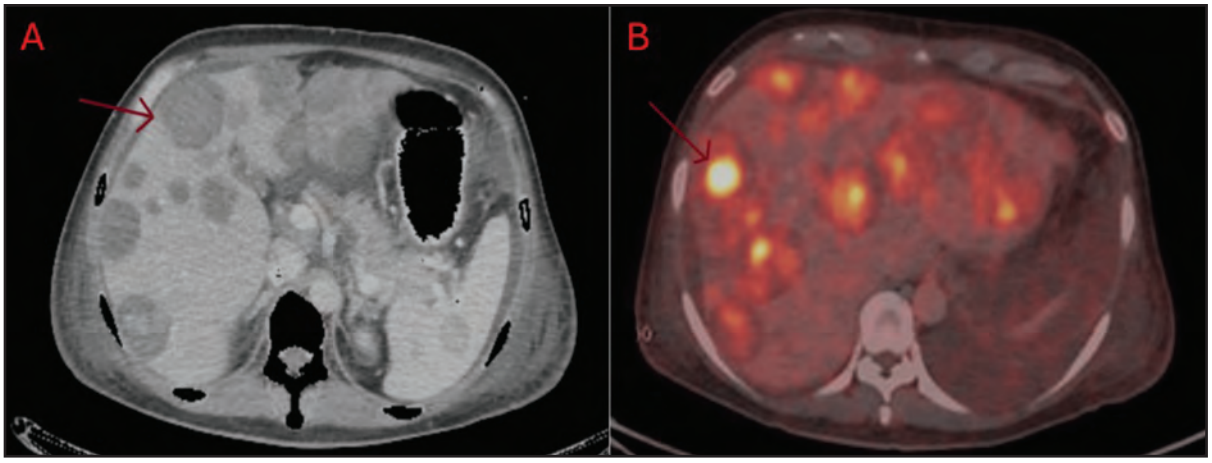

Fig. 1: Imaging Finding for Case 1: (A) Transaxial CT image showing multiple hypodense lesions in the liver (red arrow); (B) Corresponding PET/CT fusion image demonstrating diffusely increased FDG uptake in the liver (red arrow)

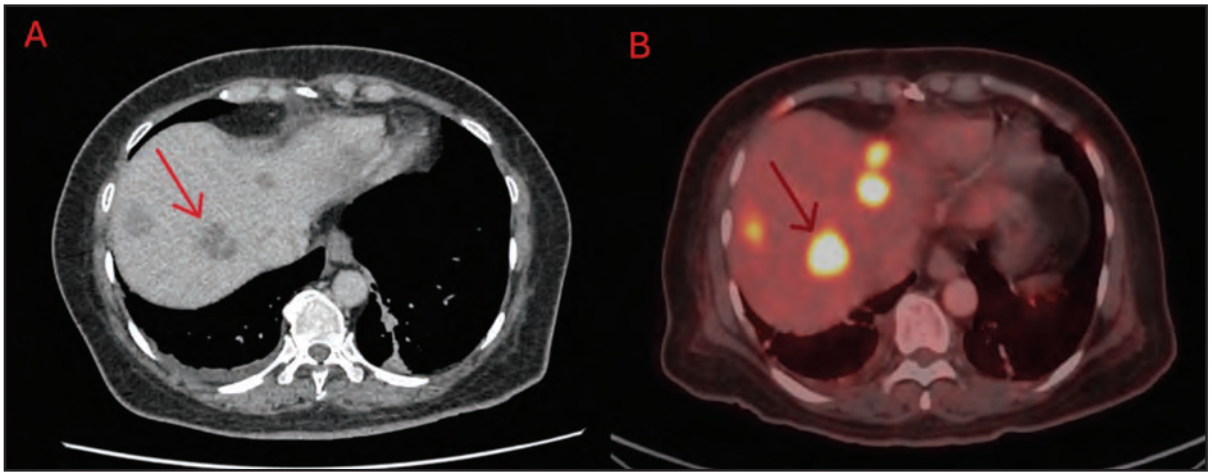

Fig. 2: Imaging Finding for Case 3: (A) Transaxial CT image showing multiple hypodense lesions in the liver (red arrow); (B) Corresponding PET/CT fusion image demonstrating diffusely increased FDG uptake in the liver (red arrow)

DISCUSSION

Hepatic lymphoma has been diagnosed in individuals aged 8 to 78 years (mean age: 48 years) and predominantly affects males.[1] This case series underscores the diagnostic dilemmas, radiological pitfalls, and critical role of histopathological confirmation in distinguishing hepatic lymphoma from infectious and inflammatory hepatic lesions. The clinical manifestations of hepatic lymphoma include right upper abdomen pain (43%), weight loss (35%), and fever (22%), and it has been associated with hepatitis B, hepatitis C, and human immunodeficiency virus.[3] In contrast, liver abscesses typically present with high fever, leukocytosis, right upper quadrant tenderness, and elevated inflammatory markers (CRP, ESR, procalcitonin).[4] These overlapping systemic inflammatory responses make symptom-based differentiation unreliable.

Xin Wei Yang et al. from China reported nine patients who were initially misdiagnosed with α-fetoprotein-negative hepatocellular carcinoma prior to pathological evaluation. The average delay from symptom onset to final diagnosis was 26.8 days (range: 14-47 days).[5] In our case series, all four patients were initially suspected of having liver abscesses based on presenting symptoms and imaging findings. They were empirically treated with broad-spectrum antibiotics or anti-tuberculosis medications, according to the working diagnosis. However, persistent symptoms despite adequate antibiotic therapy raised suspicion of an alternative aetiology. This underscores the importance of considering hepatic lymphoma in cases of liver abscess with poor clinical and radiological response.

Primary hepatic lymphoma (PHL) is extremely uncommon, as a healthy liver typically possesses a minimal interstitial component, with lymphocytes confined primarily to the portal region. As a result, liver lesions classified as lymphoma are more frequently observed as secondary extranodal infiltrations, as shown in the cases reported here. PHL was documented in only 6 cases (0.41%) in a study of 1,467 extranodal lymphoma cases conducted by Freeman et al.[6] Laboratory abnormalities associated with hepatic lymphoma include anaemia, neutropenia, hypercalcaemia and variably elevated levels of lactate dehydrogenase (LDH), serum alkaline phosphatase, β-microglobulin and aminotransferase activities.

Radiological examination is essential in the diagnosis of hepatic lesions. Secondary hepatic lymphoma is typically associated with nodal disease. Conversely, diagnosing primary hepatic lymphoma can be challenging, as it frequently mimics hepatocellular carcinoma or liver metastases from adenocarcinoma.[2] Imaging characteristics of hepatic lymphoma include a low-density mass on non-contrast CT, a slightly or internally enhanced mass on contrast-enhanced CT, and a homogeneously low-echo mass on ultrasonography. MRI can be particularly helpful in supporting the diagnosis of a lymphoma, when no morphological features of cirrhosis are evident in the surrounding liver parenchyma, when the tumour markers are negative, and when the hepatic lesion demonstrates iso-intensity with spleen parenchyma in both T1- and T2-weighted images.[2] FDG-PET may exhibit markedly diffuse hepatic tracer uptake, which can serve as the initial indicator of significant hepatic involvement.[7] In Cases 1 and 3, PET/CT revealed hypermetabolic hepatic and nodal involvement, prompting a diagnostic revision from infection to lymphoma. This underscores the diagnostic utility of PET/CT in cases where conventional imaging proves inconclusive. A study by Jia Chen et al. concluded that PET/CT demonstrates moderate sensitivity but low specificity for diagnosing lymphoma in patients with fever of unknown origin and lymphadenopathy.[8] However, due to limited resources, PET/CT imaging is not widely available at government hospitals. A summary of the radiological findings is presented in Table II.

Extended courses of antibiotic treatment should be avoided. Given the diagnostic ambiguity of hepatic lesions with overlapping imaging features, liver biopsy remains the gold standard for diagnosis. In our cases, image-guided core needle biopsies (CT- or US-guided) confirmed hepatic lymphoma through histopathology and immunohistochemistry (IHC). Once the diagnosis of lymphoma is established, the management strategy shifts significantly from treating infectious diseases to administering systemic chemotherapy. Diffuse large B-cell lymphoma is treated with the R-CHOP regimen, which includes rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) or more intensive regimens are used for patients with Hodgkin's lymphoma, depending on risk stratification.[9]

In all four cases, there were therapeutic delays prior to the accurate diagnosis of lymphoma. A liver biopsy should be considered in cases not responding to standard treatment. Delayed biopsy may lead to prolonged hospitalization, unnecessary procedures, and potential adverse outcomes. A multidisciplinary approach is essential; collaboration among radiologists, infectious disease physicians, and haematologists is critical for timely diagnosis and prevention of mismanagement.

CONCLUSION

Hepatic lymphoma masquerading as a liver abscess is an uncommon yet clinically significant presentation that poses both diagnostic and therapeutic challenges. This case series underscores the importance of maintaining a high index of suspicion for lymphoma in patients with atypical liver abscesses, particularly those unresponsive to standard antimicrobial therapy. Early integration of advanced imaging and histopathological evaluation is essential for accurate diagnosis and timely initiation of appropriate treatment. Further studies are warranted to better characterize this rare entity and to optimize management strategies aimed at improving patient outcomes.

DECLARATION

It is hereby acknowledged that consent for publication has been obtained from the patients or their caregiver.

CONFLICTS OF INTEREST

None.

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CASE REPORT

Role of carbon dioxide angiogram in endovascular abdominal aortic aneurysm repair (EVAR): A case series

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SUMMARY

Iodinated contrast media has been widely used as the main contrast agent since the early 1920's. However, recently carbon dioxide (CO_2) has emerged as an alternative media to iodine due to its special characteristics of non-nephrotoxic and non-allergenic properties. This study reports one of the earliest Malaysian experiences using CO_2 angiography as the primary intraoperative imaging modality during Endovascular Abdominal Aortic Aneurysm Repair (EVAR). This retrospective case series was conducted at Institut Jantung Negara (IJN) as the national tertiary cardiothoracic and vascular center. We analyzed six patients who underwent EVAR using CO_2 as the primary contrast agent between February and May 2021. Data collected included demographics, aneurysm morphology, renal function, operative details, complications, and postoperative outcomes. Six patients underwent EVAR, five elective and one emergency. All patients underwent operations with successful deployment of the device without intraoperative complications, conversion to open surgery or CO_2 related complications . Postoperatively, renal function was stable in five patients with one demonstrating a slight decline in renal function (eGFR 40 to 35) but not requiring dialysis. Completion angiogram using minimal iodine contrast used to confirm stent placement with no endoleaks. Follow up CT scans showed satisfactory graft positioning without evidence of endoleaks. Owing to special characteristics of CO2 it provides good clinical benefit especially in those with underlying CKD and iodine allergy. It is a feasible and safe alternative imaging modality for EVAR. This aims to increase familiarity among surgeons with the use of CO2 angiography in EVAR and other relevant vascular procedures.

INTRODUCTION

Iodinated contrast media (ICM) has been the basic foundation in vascular imaging as early as the 1920's, widely accepted for the last 100 years. Nevertheless, in recent years, Carbon Dioxide (CO_2) appeared as a new alternative due to its natural characteristics of non-toxicity, low cost, rapid tissue clearance, and wide availability.[1]

CO_2 angiography is distinctly beneficial for patients with iodine contrast allergies or those at high risk of iodinated contrast-induced nephropathy (CIN).[1]

In patients with abdominal aortic aneurysm (AAA) undergoing endovascular repair with chronic kidney disease or in acute renal failure, CO_2 angiography offers an opportunity to alleviate renal injury and potential requirement for dialysis[2] as these patient groups undergoing EVAR with renal failure experience significantly increased postoperative mortality and morbidity.[3]

This case series represents the first Malaysian experience in managing EVAR using CO_2 angiography as the primary intraoperative imaging modality, undertaken during the initial implementation phase at our centre. These could serve as the foundation of subsequent larger studies. The patient's background, pre-existing conditions, interventions and outcomes are discussed below.

METHODOLOGY

This is a retrospective case series conducted at Institut Jantung Negara (IJN) Kuala Lumpur, a national tertiary centre for cardiothoracic and vascular surgery.

The series includes all consecutive patients undergoing EVAR for AAA using CO_2 as a primary contrast agent between February 2021 till May 2021. No patients were excluded. Data were obtained from electronic medical records and operative notes. These include demographic background, morphology of the disease, preoperative and postoperative renal function, operative time, intraoperative complications, postoperative outcome and length of stay are presented in Table I.

PROCEDURAL PROTOCOL

In this case series, all patients underwent EVAR under general anaesthesia by an experienced consultant vascular surgeon, irrespective of their renal function status. Preoperatively, computed tomography was performed to confirm the diagnosis of AAA and precisely measure the aneurysm size and determine the suitability of either EVAR or open surgical repair. During admission, routine blood investigations were taken, including a preoperative renal profile, and were evaluated by the anaesthetist before surgery.

In our centre, the standard protocol for EVAR using CO_2 angiography begins with bilateral femoral arteries access using an initial 6Fr sheath. Following arterial puncture, three ProstyleTM 6Fr closure devices (Abbott Vascular) are

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Table I: Patient characteristics, procedural details, and postoperative outcomes

Case No, Gender/ Age	Comorbidities	Diagnosis	Procedure (Urgency)	Duration of Operation (Hours)	Post Op RP	Post Op RP	CO_2 related morbidity	Length Of Stay Post Operation (days)
1. Male/72	Ex-smoker/	Infrarenal AAA HTN/ HPLD	EVAR + CO2 Angiogram (Elective)	2.9	Urea 7.9/ Creatinine 151, eGFR >60	Urea 7.6/ Creatinine 142, eGFR >60	No	3
2. Male/59	Ex-smoker/ HTN/ HPLD	Infrarenal AAA + Occluded left CIA	EVAR + CO2 Angiogram + Femoral-Femoral	2.58	Urea 3.9/ Creatinine 117, eGFR 55	Urea 5.0/ Creatinine 117, eGFR 55	No	2
3. Male/63	Hypertension/ HPLD/ CKD	Infrarenal AAA	EVAR + CO2 CO2 Angiogram (Elective)	2.17	Urea 7.4/ Creatinine 155, eGFR 39	Urea 3.7, Creatinine 120, eGFR 53	No	7
4. Male/61	Smoker/HPLD	Infrarenal Saccular AAA	EVAR + CO2 Angiogram (Emergency)	2.8	Urea 4.2, Creatinine 77, eGFR >60	Urea 5.2, Creatinine 79, eGFR >60	No	3
5. Male/70	HTN/CKD	Infrarenal AAA	EVAR + CO2 Angiogram (Elective)	2.37	Urea 8.7, Creatinine 147, eGFR 40	Urea 8.8, Creatinine 166, eGFR 35	No	4
6. Female/64	HTN/HPLD	Infrarenal AAA with angulated neck	EVAR + CO2 Angiogram + Femoral-Femoral Bypass (Elective)	3.85	Urea 5.4, Creatinine 79, eGFR >60	Urea 5.3, Creatinine 61 eGFR	No	4

CKD: Chronic Kidney Disease; HPLD: Hyperlipidemia; HTN: Hypertension; EVAR: Endovascular Aneurysm Repair; CO2: Carbon dioxide; AAA: Abdominal Aortic Aneurysm

deployed on each side for pre-closure purposes. After deployment of Prostyle device, sequential iliac pre-dilatations are performed and gradually increasing the sheath size to accommodate larger delivery system required for the specific EVAR device.

Following vascular access, the CO_2 was delivered via a special Angiodroid machine (Angiodroid SRL, San Lazzaro di Savena, Italy). The sheaths are connected to CO_2 tubing via a three-way stopcock to the Angiodroid, ensuring concurrent delivery of CO_2 to both sides (Figure 1). This method allows overall visualisation of the arterial system, ensuring good-quality imaging and precisely assisting during the procedure. Injection parameters were :

- Volume approximately 80±20mL
- Maximum pressure of 700±50 mmHg.
- Injection timing : automated as per Angiodroid settings.

This Angiodroid machine helps to accurately administer CO_2 according to the volume, pressure, and timing of injection, as well as minimize radiation exposure.[1] Patient positioning was adjusted at slight lateral tilting or Trendelenburg position if necessary to optimise vessel visualisation.

RESULTS

Six patients underwent EVAR with CO_2 during the study period. Five underwent elective procedures and one was performed under the emergency list. The aneurysm mainly arose from infrarenal and one of them had a complex angulated neck. All surgeries went uneventfully, and grafts were deployed successfully without evidence of endoleak, and none required conversion to open surgical repair. At the end of the operation, completion runs were made by using iodinated-contrast media as an adjunct to confirm the stent placement and check for extravasation of contrast (Figure 2). The operation durations range from 2.17 to 3.85 hours in total. Postoperatively renal profiles were measured again immediately after 1-2 days. Out of six patients only one demonstrated a slight decline in renal function (eGFR 40 to 35) but not requiring dialysis. However, these observations require proper case-control or analytical study to determine the effect of CO_2 towards renal profile in detail. No CO_2-related complications arose during Intensive Care Unit (ICU) or ward stay, and their total length of stay postoperative period ranged from 2-7 days. Follow-up care CT scans were repeated and confirmed device placement and no evidence of endoleak in all cases (Figure 3).

DISCUSSION

AAA is characterized by an enlargement of abdominal aorta diameter by 3.0cm or more. The localized dilation of the aorta begins below the diaphragm and is classified based on their specific locations: supra-renal, pararenal or infrarenal arteries.[4] This must not be left untreated especially in large AAAs as rupture carries a mortality rate up to 80%.[4]

The increasing practice of EVAR in modern management of AAA, by introduction of endovascular stent into the vascular lumen to exclude aneurysm brings significant reduction in perioperative mortality when compared to open surgical repair by three-fold.[5] Advantages include smaller incisions, reduced risk of rupture and bleeding, and decreased renal hypoperfusion and surgical trauma.[3] This procedure is a minimally invasive surgery where a small incision is made percutaneously to introduce artificial stent and deployed within the aorta, reducing the risks of rupture and bleeding and thus favoured over open repair. At present, in those with pre-existing renal injury, surgeons preferred open repair compared to EVAR due to concerns use of iodinated-contrast media may result in dialysis postoperatively. Nonetheless,

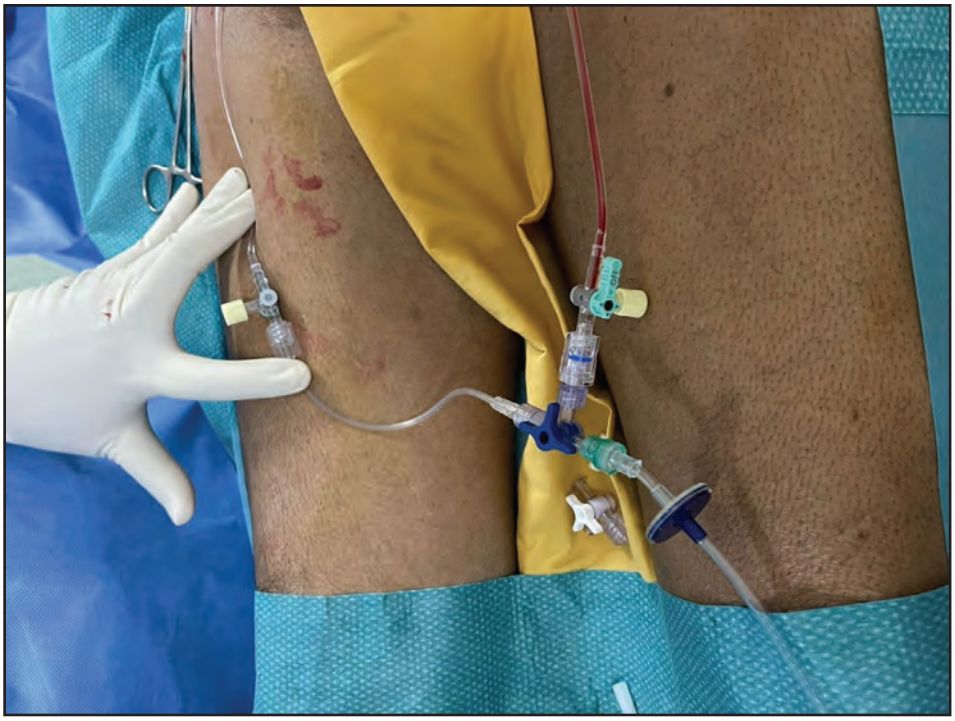

Fig. 1: Both femoral arteries cannulated with 6Fr sheaths, with CO_2 delivery tubing connected via a three-way stopcock

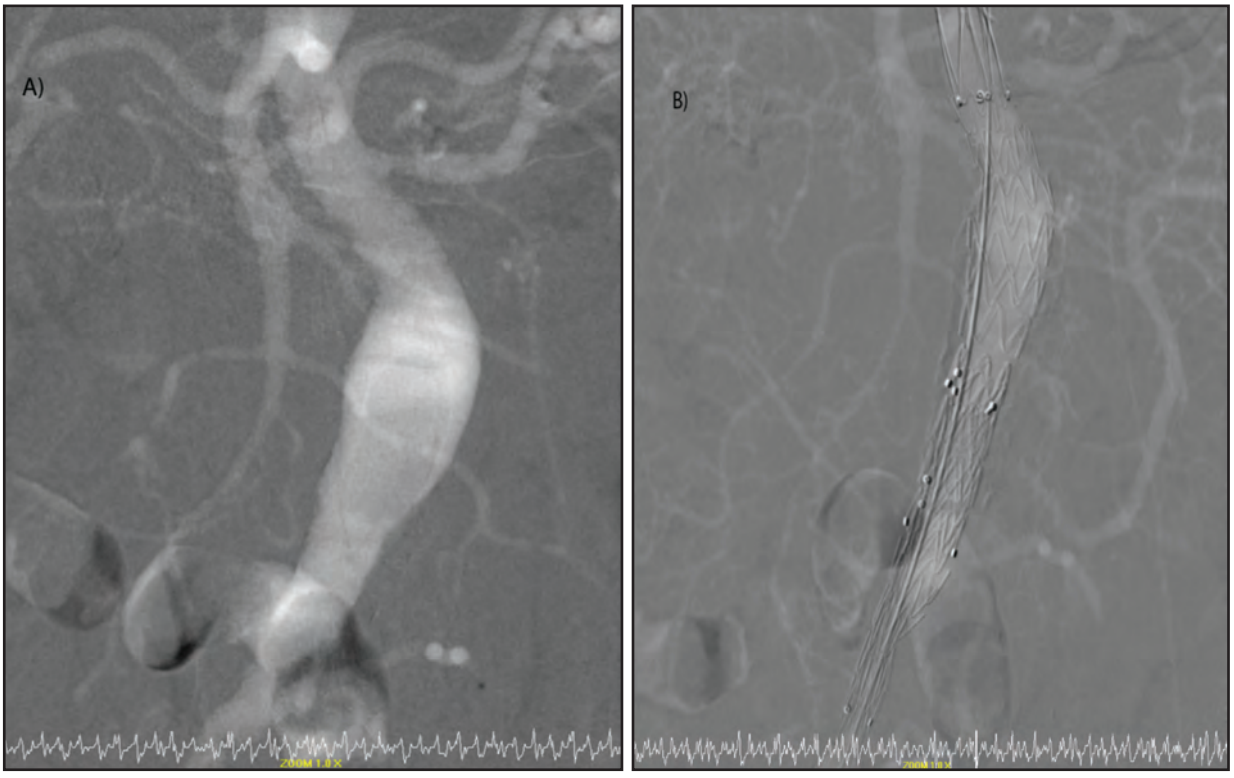

Fig. 2: A) Carbon dioxide (CO_2) digital subtraction angiography (DSA) showing an infrarenal abdominal aortic aneurysm (white arrow) prior to stent placement. B) Post stent deployment, CO_2 contrast completion run shows filling of abdominal aorta without evidence of endoleak.

severe pre-existing renal dysfunction in both open repair and EVAR is associated with poor outcomes regarding mortality and cardiovascular events.[6]

CO_2 angiography has recently gained attention as an alternative due to its safety, being a naturally existing inert substance, and its non-nephrotoxic and non-allergenic properties, especially in patients at risk of CIN. It has been

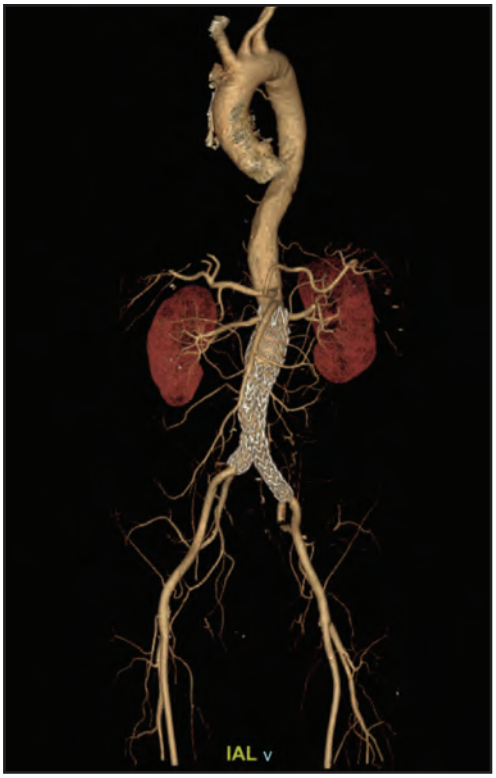

Fig. 3: Showed CT Aortogram of one of the patient with infrarenal AAA, post-EVAR.
No evidence to suggest Endoleak.

proven to be safe for vascular imaging in those with renal impairment requiring precise imaging and therapy.[7] The CO_2 can be used alone or in combination with ICM so that the regular dose of iodine is minimized, especially in procedures requiring large amounts of contrast volumes. It acts as a negative contrast agent due to its low-density properties as well as its ability to absorb X-rays to a minimal degree compared to surrounding blood vessels. The notable buoyancy of CO_2 allows it to float in the blood and visualize visceral arteries.[1,8] It accumulates in the anterior part of the vessels (useful in visualizing the superior mesenteric and celiac arteries) but does so poorly in posteriorly located vessels, as the CO_2 in the anterior portion does not displace blood at the lower part. It also provides better visualization in small vessels (less than 10 mm in diameter), promising good imaging quality, but it is less effective in larger vessels due to incomplete displacement of blood in the lower (posterior) part of the vessel, which can lead to poor visualization.[1,9] CO_2 is highly soluble - about 28 times more than oxygen and 54 times more than nitrogen allows its safe administration into arteries below the diaphragm and veins in the absence of gas embolism. It can be temporarily trapped in the right atrium and typically dissolves within 45 seconds if minimal, but takes longer to dissolve in larger volumes.[8]

From a practical standpoint, the CO_2 peculiar physical aspects such as ultra-low viscosity and immiscibility with blood allow for augmented imaging precision in certain applications. Furthermore, CO_2 toxicity is of minimal concern as it can be administered repetitively, indirectly enhancing accuracy during imaging and device deployment. They are widely available and less expensive, making them economically efficient compared to ICM.[1]

The CO_2 has several limitations and occasionally presents with rare, but severe side effects such as vapor air lock and air embolism. It is also less suitable to be used in procedures above the diaphragmatic region due to the risk of neurotoxicity. Patients may experience milder symptoms such as nausea, vomiting, abdominal discomfort and leg cramps (especially when CO_2 contrast is injected in peripheral vascular procedures). One of the important downsides of CO_2 angiography is that it may produce lower imaging quality in certain conditions. Due to its buoyancy properties, it does not adequately fill the posterior aspect of the blood vessels, as well as larger vascular diameters, and hence results in incomplete visualisation.

Our case series demonstrates that using CO_2 angiography as the main intraoperative agent allowed successful EVAR device deployment in all six cases without intraoperative complications, conversion to open surgery or significant postoperative renal dysfunction. Only one patient experienced a mild decline in eGFR not requiring dialysis. Adjunctive ICM use was minimal during completion runs, supporting the role of CO_2 in minimising iodine exposure. This is small, retrospective, single-centre series limits the generalisability of the results. No control group was included, hence no direct statistical comparison to standard ICM-based EVAR made.

Our primary goal objective is not to draw any statistical comparisons, instead we aim to show feasibility, technical aspects and outcomes to guide future clinical practice. As the leading vascular centre in Malaysia, we seized the opportunity to become the pioneer user of CO_2 angiography as the primary contrast agent in EVAR surgery. Previous studies often restricted CO_2 use specifically to cases associated with CIN and its contraindications, but our approach in these studies focuses on its application to a broader patient spectrum. This provides flexibility and productivity without being limited by usual criteria.

CONCLUSION

Due to the exceptional and unique properties of CO_2, it offers numerous advantages, as mentioned earlier. The use of CO_2 as an alternative contrast medium should be considered in modern EVAR, while ICM can still be used in minimal volumes as an adjunct. We aim to increase familiarity among surgeons with CO_2 angiography, not only in EVAR but also in various other relevant procedures, particularly for interventions below the diaphragm. Not only does it reduce the incidence of CIN, but it is also cost-effective and reduces resource utilization.

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Orbital rhabdomyosarcoma presenting as optic nerve glioma in a child

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SUMMARY

Orbital rhabdomyosarcoma is the most common primary malignant orbital tumour in children. It typically presents with rapidly progressing unilateral proptosis and may resemble other orbital conditions, making timely and accurate diagnosis essential. We present a case of a 5-year-old girl with progressive left eye proptosis over two weeks. Visual acuity and optic nerve function were initially preserved. Magnetic resonance imaging (MRI) revealed a lobulated mass encasing the left optic nerve, initially diagnosed as optic nerve glioma. Chemotherapy was initiated to address the optic nerve glioma, and the patient responded well after four cycles. However, one month later, the proptosis recurred with rapid progression, and her vision declined from 6/15 to finger counting. Fine needle aspiration biopsy (FNA) was inconclusive. An incisional biopsy performed three months later confirmed rhabdomyosarcoma. Due to the aggressive course, the patient underwent left orbital exenteration and completed chemotherapy. Eight months later, she presented with systemic symptoms. Imaging revealed a residual orbital mass, suggesting recurrence. As the family declined radiotherapy, second-line chemotherapy was initiated. Unfortunately, the patient passed away before completing treatment.

INTRODUCTION

Rhabdomyosarcoma is a soft-tissue sarcoma originating from mesenchymal cells that differentiate to form skeletal muscle.[1] Consequently, it can present in various parts of the body, resulting in complex and diverse needs for its clinical management. Approximately 40% of rhabdomyosarcoma cases occur in the head and neck region,[2] underscoring the importance of this area, concerning the disease's impact on patients and the challenges faced in treatment. The prevalence of rhabdomyosarcoma, along with the associated treatment difficulties, significantly influences paediatric oncology.

In this case report, we present a rare case of orbital rhabdomyosarcoma that was initially interpreted as an optic nerve glioma, making diagnosis and treatment particularly challenging. Empirical chemotherapy, started based on the initial impression, led to significant tumour shrinkage at first but was followed by an aggressive rebound. This ultimately required left orbital exenteration due to the rapid progression of the disease.

CASE PRESENTATION

A 5-year-old female with no known comorbidities presented with painless, progressive left eye proptosis that developed over a two-week period. She had no complaints of reduced vision, no history of ocular trauma, and exhibited no systemic symptoms. On ocular examination, there was left eye nonaxial proptosis with inferonasal displacement of the globe and almost complete ptosis of the upper eyelid. Hertel's exophthalmometry measurements revealed an anterior projection of the left eye at 13 mm compared to 9 mm for the right eye, exceeding the normal difference of 2 mm between both eyes. There was mild decreased ocular motility in the left eye during abduction and elevation. Visual acuity was 6/15 bilaterally, with intact other optic nerve function. Both anterior segment findings were unremarkable. Fundoscopic examination of the right eye was normal. However, the left eye showed a hyperaemic optic disc with blurred margins.

Magnetic resonance imaging (MRI) revealed a large lobulated mass occupying the left intraconal space and encasing the optic nerve. The mass was hyperintense on T2-weighted and FLAIR sequences, measuring 2.9cm x 2.5cm x 2.6cm (AP x W x CC) (Figure 2).

Given the patient's preserved vision but cosmetically disfiguring proptosis, treatment was initiated with four cycles of intravenous (IV) chemotherapy. The regimen included IV carboplatin (400 mg/m²), etoposide (100 mg/m²), daunorubicin (300 mg/m²), vincristine (1.5 mg/m²), actinomycin D (1.5 mg/m²), and cyclophosphamide (60–120 mg/m²/day), based on an initial working diagnosis of presumed optic nerve glioma. The patient demonstrated a favourable early response to the treatment (Figure 1).

Unfortunately, five months after completing the fourth cycle of chemotherapy, her left eye proptosis worsened rapidly. This led to a decline in vision from 6/15 to finger counting, along with a positive relative afferent pupillary defect (Figure 3A) in the left eye. She developed total ophthalmoplegia of her left eye, resulting in an almost "frozen" eye. Fine needle aspiration biopsy (FNA) was performed but yielded only adipose tissue. Due to the aggressive nature of the disease, a decision was made to perform a left orbital eye exenteration.

Histopathological analysis of the incisional biopsy revealed features consistent with spindle-cell rhabdomyosarcoma. The specimen showed sheets of malignant cells arranged in long sweeping fascicles and herringbone patterns, with areas of

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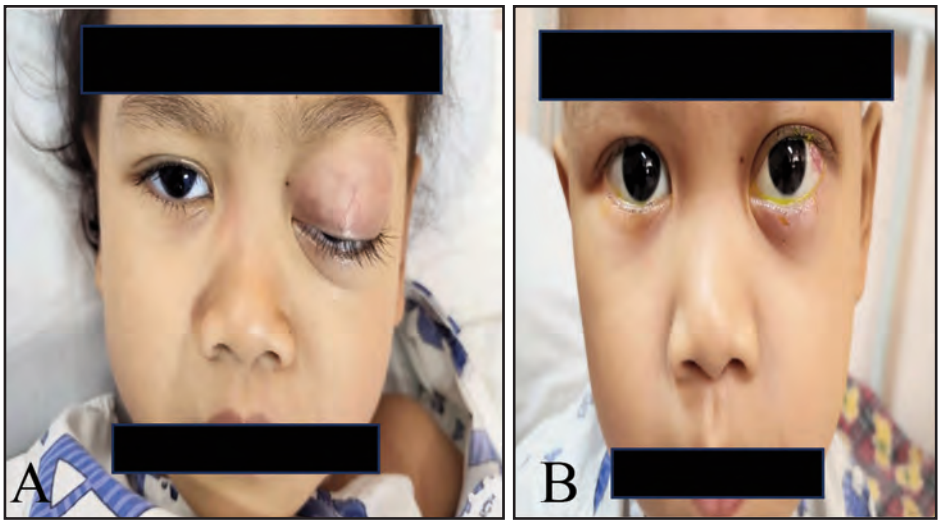

Fig. 1: Pictures before and after empirical chemotherapy (A) Left eye nonaxial proptosis with inferonasal displacement of the globe and almost complete ptosis of the upper eyelid. (B) Restored left eye position following completion of chemotherapy

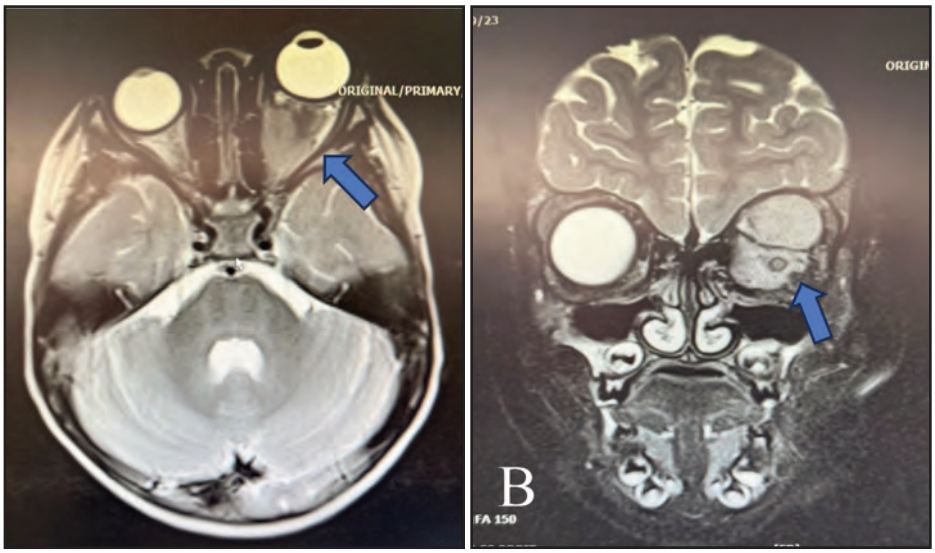

Fig. 2: MRI of the patient's brain and orbit. (A) T2-weighted axial MRI showing a lobulated mass encasing the optic nerve in left retrobulbar region. (B) T2-weighted coronal MRI showed the mass occupying the whole orbit space.

Fig. 3: (A) Left proptosis worsening 5 months after completed four cycles of chemotherapy. (B) Left orbital exenteration. (C) Post left orbital exenteration.

geographic necrosis. The tumor cells were oval to spindle-shaped, with elongated, vesicular nuclei, supporting the diagnosis.

The patient's condition initially improved within three months following left orbital exenteration, although a postoperative infection at the surgical site required one week of treatment. However, eight months later, the patient represented with constitutional symptoms. A repeat MRI revealed a residual orbital mass, suggestive of tumour recurrence. Due to parental refusal of radiation therapy, she was started on second-line chemotherapy. Unfortunately, she passed away three years after the initial diagnosis, before completing the second-line treatment.

DISCUSSION

Orbital rhabdomyosarcoma (RMS) is the most common primary orbital malignancy in children, typically affecting those between 5 and 10 years of age,[3] which aligns with our patient's presentation. Despite its well-established clinical and radiological features, RMS can occasionally present atypically, making diagnostic and therapeutic challenges. In our case, a 5-year-old girl presented with intraconal rhabdomyosarcoma that was initially diagnosed as an optic nerve glioma, illustrating the diagnostic difficulty of such atypical presentations.

Rhabdomyosarcoma most frequently originates in the extraconal space, typically within the superonasal quadrant of the orbit.[1,4] In contrast, our patient had an intraconal mass encasing the optic nerve which is a much rarer anatomical location. This intraconal origin altered the clinical impression and likely contributed to the initial radiologic diagnosis of optic nerve glioma. Anatomically, intraconal RMS may remain clinically silent longer due to deeper positioning, which could delay the onset of visible signs like eyelid swelling or significant globe displacement. Therefore, this case emphasizes the importance of considering RMS in atypical orbital locations, especially in children presenting with rapidly progressive proptosis.

As with most orbital tumours, histopathological confirmation is essential for an accurate diagnosis. In our case, the initial FNA was inconclusive and only yielded adipose tissue. This is a known limitation of FNA in rhabdomyosarcoma, as the sample is often too small to evaluate the tumour's structure properly. An incisional biopsy performed three months later confirmed the diagnosis of spindle-cell rhabdomyosarcoma, a subtype generally associated with a more favourable prognosis.[5] The delay in getting the right diagnosis probably gave the tumour time to grow, which shows how important it is to get a proper tissue sample early, especially when the diagnosis is uncertain.

Standard treatment for orbital RMS includes multi-agent chemotherapy, radiotherapy, and, when necessary, surgical excision.[6] According to the Intergroup Rhabdomyosarcoma Study (IRSG) protocols, orbital RMS is typically classified as Group III (gross residual disease after biopsy only) and falls into an intermediate-risk category when not resected fully. For intermediate-risk patients, the standard chemotherapy regimen is VAC (vincristine, actinomycin D, cyclophosphamide).

The patient was initially treated with a combination of carboplatin, etoposide, daunorubicin, vincristine, actinomycin D, and cyclophosphamide. Although this regimen may appear more intensive than standard first line treatment, it can be justified by the advanced local disease, the initial diagnostic uncertainty, and the tumor's location encasing the optic nerve.

The tumour initially responded well, however, it recurred aggressively five months later. Given the rapid progression and vision loss, orbital exenteration was required. Exenteration is generally reserved for recurrent or refractory cases and is associated with increased morbidity, both physically and psychologically.[6] Radiotherapy is usually considered when surgery cannot completely remove the tumour or in recurrence cases.[7] However, the patient's parents declined this modality despite evidence of tumour recurrence in repeated MRI.

The International Classification of Rhabdomyosarcoma categorizes tumours into botryoid, embryonal, alveolar, and spindle/sclerosing subtypes. Spindle-cell RMS typically has a favourable prognosis, particularly in children, with reported overall survival as high as 87.5%.[8]

However, our patient experienced rapid progression and recurrence, suggesting a more aggressive clinical course despite the histologic subtype. Certain molecular variants particularly those involving TFCP2 gene fusions are now known to be highly aggressive, with poor response to standard chemotherapy and early metastasis.[10] Zhao et al. (2015) described a series of spindle-cell/sclerosing RMS cases that exhibited high rates of recurrence and poor outcomes.[10] Similarly, Kumar et al. (2014) observed a disease-free survival rate of just 62.5%, despite an overall survival rate of 87.5% in their paediatric cohort.[11]

According to the Intergroup Rhabdomyosarcoma Study (IRS-IV), patients who began treatment promptly had a 10-year overall survival rate of up to 87%, and event-free survival of 77%, particularly when chemotherapy was combined with timely local therapy such as radiotherapy.[7]

Our case reflects this trend. The patient initially responded well to treatment, however, she experienced early relapse and, unfortunately, passed away within three years of diagnosis. She was unable to complete second-line chemotherapy and did not receive radiotherapy, as it was declined by her parents. This highlights the variability in clinical behaviour of spindle-cell RMS and suggests that early molecular profiling may help identify high risk cases and guide more personalized treatment strategies

CONCLUSIONS

This case highlights the challenges in diagnosing and managing orbital rhabdomyosarcoma, especially when it presents in an unusual location and mimics other conditions like optic nerve glioma. Although spindle-cell

rhabdomyosarcoma usually has a good prognosis in children, our patient experienced rapid progression and poor outcome. This shows that even favourable subtypes can behave aggressively. It also highlights the importance of performing an early incisional biopsy to ensure accurate diagnosis through adequate tissue sampling. Prompt treatment and considering molecular testing early may help guide better, more personalised care in similar cases.

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DECLARATION

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

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Vein of Galen malformation in neonate: A lesson learned

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SUMMARY

Vein of Galen Malformation (VGM) is a rare arteriovenous anomaly that presents a unique clinical challenge, particularly due to its association with heart failure and hydrocephalus. We report a case of a full-term male neonate diagnosed antenatally with the choroidal form of VGM, confirmed through pre- and postnatal magnetic resonance imaging. Arrangements were made for delivery at a tertiary centre with a multidisciplinary team, including an interventional radiologist; however, due to logistical constraints, this could not be accomplished. Clinical deterioration ensued on day 4 of life, marked by worsening heart failure necessitating aggressive ventilatory and hemodynamic support. The patient's condition progressed to severe pulmonary hypertension, multiorgan impairment, and disseminated intravascular coagulation (DIVC), resulting in a Bicêtre score of 1, signifying poor prognosis and high risk for endovascular intervention. The patient passed away on day 28 of life. This case adds to the limited literature on VGM management in Malaysia by illustrating the challenges of managing such a complex condition in resource-limited settings. It underscores the importance of coordinated delivery planning and timely referral to specialised centres with endovascular specialties.

INTRODUCTION

Vein of Galen malformation (VGM) is a severe and rare congenital intracranial anomaly characterized by arteriovenous fistulas between various arterial feeders and the median prosencephalic vein of Markowski.[1] The prevalence of VGM has increased over the past decade, with an estimated incidence of 1:58,100 live births.[2] Typically presenting in neonates with high-output heart failure and severe cardiopulmonary distress, VGM is often complicated by pulmonary hypertension, neurological, hepatic, and renal dysfunction. Historically, neurosurgical management yielded poor outcomes with a mortality rate around 90%. However, the advent of endovascular techniques has markedly improved prognosis, reducing mortality to approximately 50%.[3] This case report illustrated the critical role of prenatal diagnosis, the challenges of postnatal management, and the impact of timely delivery and treatment on outcomes.

CASE PRESENTATION

A full-term infant was admitted to the Neonatal Intensive Care Unit (NICU) at birth due to respiratory distress requiring support. The infant, delivered via caesarean section to a 40-year-old primigravida mother who is Human Immunodeficiency Virus (HIV) positive and on Highly Active Antiretroviral Therapy (HAART) with a low CD4 count, was conceived through in vitro fertilization using an ovum donor. Prenatal assessments revealed a Vein of Galen aneurysm, with associated dilated internal jugular veins, right atrial enlargement, and cardiomegaly, confirmed by foetal magnetic resonance imaging (MRI) (Figure 1). Despite recommendations for delivery at a tertiary centre due to potential postnatal complications, logistical challenges led to delivery at a secondary hospital.

At birth, the infant had Apgar Score of 7 at 1 minute and 9 at 5 minutes. Physical examination showed a weight of 2000g (<3rd centile), a length of 45 cm (10th centile), and a head circumference of 40cm (>97th centile), with a thrill palpable over his anterior fontanelle. Other anomalies include low-set ears, microtia, a receding chin, and a left preauricular tag, and signs of heart failure were present (hyperactive precordium, displaced apex beat, grade 4 ejection systolic murmur, and hepatomegaly extending 4 cm below the right costal margin).

Chest radiograph revealed cardiomegaly and plethoric lung fields (Figure 2). An echocardiogram identified pulmonary hypertension with dilated right heart chambers, a dilated superior vena cava (SVC) with reversed flow, increased blood flow through the aortic arch, and a small patent ductus arteriosus (PDA) with a right to left shunt. Postnatal MRI of the brain showed the choroidal variant of a vascular malformation, with multiple enlarged arterial branches originating from the posterior cerebral artery and bilateral posterior communicating arteries supplying a dilated prosencephalic vein of Markowski resulting in obstructive hydrocephalus (Figure 3a, 3b and 3c).

Upon NICU admission, the infant was started on non-invasive respiratory support and anti-heart failure medications, including intravenous Furosemide and oral Spironolactone. The initial Bicêtre score of 21 indicated a stable condition. However, on day 4, the infant's condition rapidly deteriorated, showing signs of cardiac decompensation further complicated by severe pulmonary hypertension, necessitating invasive mechanical ventilation and inhaled nitric oxide (iNO). Multiple inotropes including dopamine, dobutamine, and noradrenaline were initiated for cardiovascular support. The Bicêtre score dropped to 8,

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Table I: Bicêtre Score at Presentation and at Clinical Deterioration

Points	Clinical status	Points	Birth	Day 4	Final
Cardiac function	Normal	5	√		
	Overload, no medical treatment	4			
	Failure, stable with medical treatment	3			
	Failure, not stable with medical treatment	2			
	Ventilation necessary	1		√	
	Resistant to medical therapy	0			√
Respiratory function	Normal	5	√		
	Tachypnoea, finishes bottle	4			
	Tachypnoea, does not finish bottle	3			
	Assisted ventilation, normal saturation FiO2 <25%	2			
	Assisted ventilation, normal saturation FiO2 >25%	1		√	
	Assisted ventilation, desaturation	0			√
Cerebral function	Normal	5	√		
	Subclinical, isolated EEG abnormalities	4		√	
	Nonconvulsive intermittent neurologic signs	3			
	Isolated convulsion	2			
	Seizures	1			√
	Permanent neurological signs	0			
Renal function	Normal	3	√		
	Transient anuria	2			
	Unstable diuresis with treatment	1		√	
	Anuria	0			√
Hepatic function	No hepatomegaly, normal hepatic function	3	√		
	Hepatomegaly, normal hepatic function	2			
	Moderate or transient hepatic insufficiency	1		√	
	Abnormal coagulation, elevated enzymes	0			√
Total scores			21	8	1

reflecting significant clinical deterioration which rendered the infant too unstable for transfer to a centre with endovascular intervention capabilities.

In addition to developing clinical seizures, the patient experienced progressive multiorgan dysfunction. Renal function significantly declined (urea 5.9 mmol/L, creatinine 279 µmol/L), resulting in anuria and severe oedema. Liver function was also severely compromised, as evidenced by elevated transaminase levels (AST 934 U/L, ALT 834 U/L) and unconjugated hyperbilirubinemia (total bilirubin 766 µmol/L). Other laboratory workup showed (PT 67 sec, APTT >180 sec, INR 5.35) suggestive of disseminated intravascular coagulopathy (DIVC) refractory to cycles of fresh frozen plasma, cryoprecipitate, platelet transfusions, and vitamin K therapy. A reassessment revealed a Bicêtre score of 1, indicating a high risk for interventional embolization, leading to a decision for conservative management. Despite all efforts, the infant ultimately succumbed on day 28 of life (Table I).

DISCUSSION

VGM is the most common type of arteriovenous malformation in neonates and infants. Although endovascular embolization has improved outcomes, the complexity of VGM cases continues to present significant mortality risks.[2] The exact aetiology of VGM remains unclear but it is believed to stem from abnormal embryonic vessels development in the prosencephalon.[1] Although the exact genetic basis of VGM remains incompletely understood, emerging evidence suggests involvement of mutations in genes regulating vascular development and angiogenesis, including chromatin-modifying genes and those within the Ephrin signalling pathway.[4] Facial dysmorphism is not a typical feature of VGM; however, its presence in our patient raises the possibility of an underlying syndromic diagnosis. Unfortunately, due to resource constraints, further genetic evaluation could not be pursued. This underscores the pressing need to improve access to genomic diagnostics, especially in patients presenting with atypical or syndromic features. Meanwhile, maternal HIV infection and in utero exposure to HAART have been associated with a modest increase in congenital anomalies, though current evidence does not indicate an increased risk of intracranial arteriovenous malformations such as VGM in exposed infants.[5]

VGM is anatomically classified into choroidal and mural types. The choroidal type (Type 1) is the most common and severe, characterised by multiple feeding arteries entering the prosencephalic vein of Markowski, leading to high-output failure. Conversely, the mural type (Type 2) involves fewer arterial feeders, resulting in greater outflow resistance and less severe cardiac failure, with symptoms emerging later in infancy.[6] Although maternal HIV infection and in utero exposure to HAART have been associated with a mild increase in congenital malformations generally, studies have not demonstrated an elevated risk of intracranial arteriovenous anomalies such as VGM in exposed infants.

Prenatal diagnosis of VGM is typically achieved through colour Doppler ultrasonography during the third trimester. However, foetal MRI provides a more detailed evaluation of VGM's size and location, offering superior diagnostic clarity.[7] Early detection facilitates planning for delivery at a tertiary

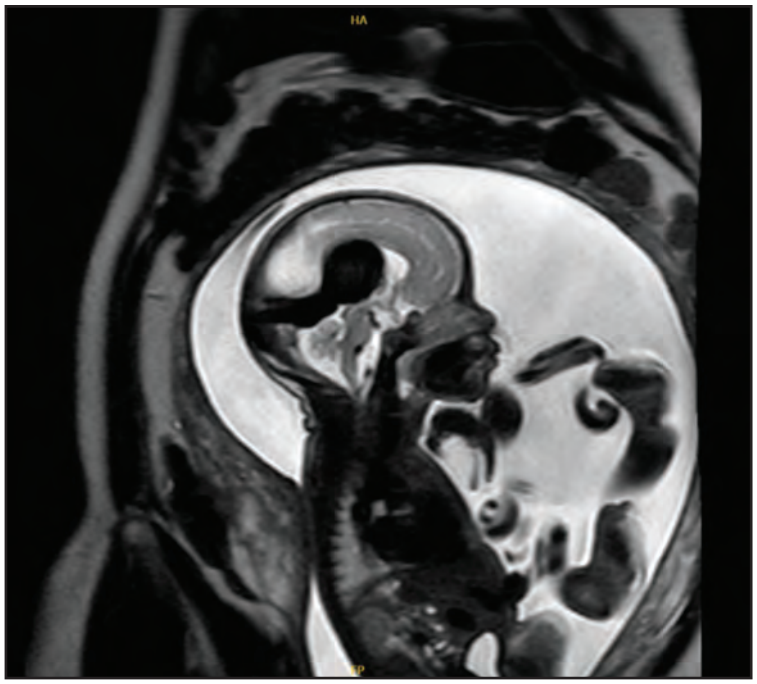

Fig. 1: Maternal T2-weighted magnetic resonance at 32 weeks of gestation showing a Vein of Galen malformation in the foetus, characterized by a dilated flow void structure in the posterior midline

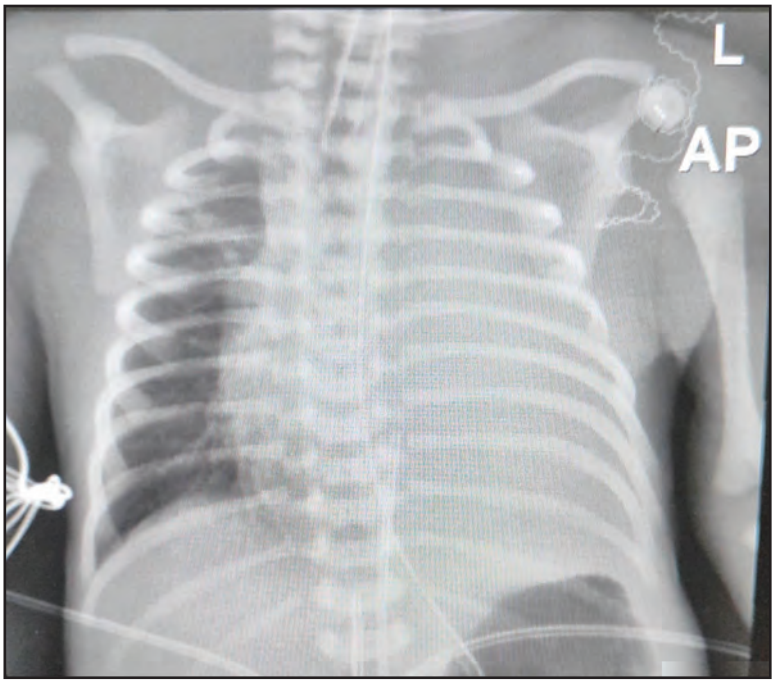

Fig. 2: Chest X-ray of the neonate showing cardiomegaly with an enlarged cardiac silhouette and pulmonary vascular congestion

centre equipped with a multidisciplinary team. In our case, logistical constraints led to delivery at a secondary hospital, adversely affecting the outcome. The high-flow nature of the choroidal type placed immense strain on the infant's heart exacerbated haemodynamic instability. The cerebral arteriovenous shunt diverted significant cardiac output from systemic circulation, leading to myocardial ischaemia, lactic acidosis and multiorgan failure despite aggressive interventions.[8] The inability to transfer the patient for further intervention highlights the critical need for delivery at a facility with the appropriate capabilities and expertise.

The timing and method of endovascular embolization depend on the clinical presentation, with the Bicêtre score

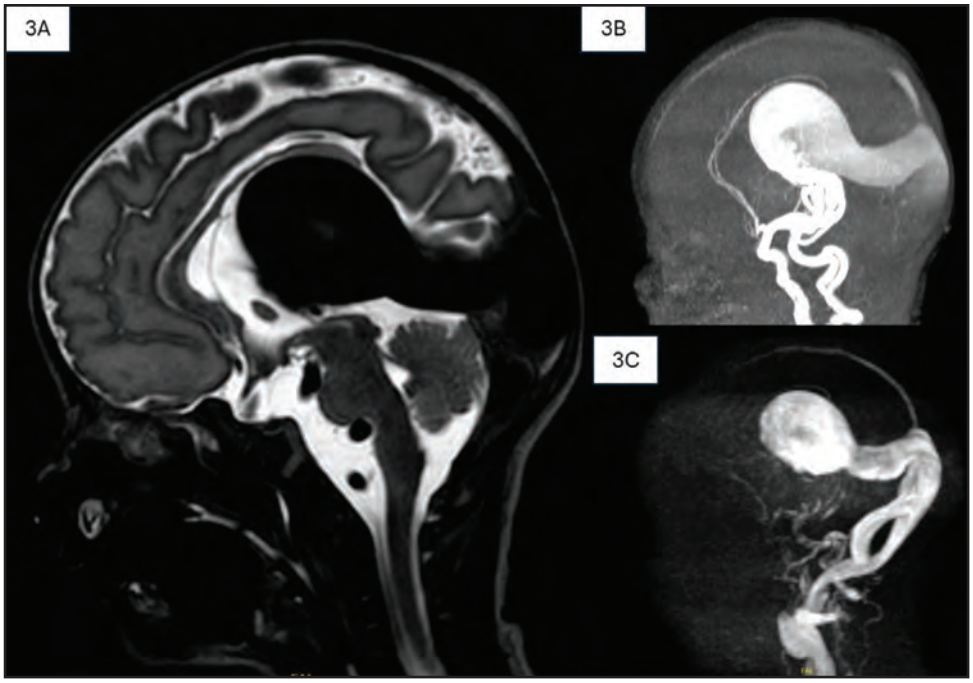

Fig. 3: A) Sagittal T2-weighted magnetic resonance image showing a choroidal-type Vein of Galen Malformation with dilated prosencaphalic vein of Markowski and persistent falcine draining sinus. B) Sagittal T2-weighted magnetic resonance angiography image showing enlarged branches of the anterior and posterior cerebral arteries coalescing to the dilated recipient vein. C) Sagittal T2-weighted magnetic resonance angiography image showing a Vein of Galen aneurysmal malformation in continuity with the dilated straight sinus, torcula herophili, and transverse sinus

guiding treatment decisions. Scores <8 suggest conservative management, scores between 8 and 12 warrant emergency intervention, and scores >12 allow for delayed treatment after 5 months, permitting the infant to grow and better tolerate the procedure.[9] Our patient's rapid clinical deterioration highlights the importance of monitoring Bicêtre score fluctuations, which affect risk stratification and intervention timing, particularly in centres lacking endovascular expertise. Recent reviews suggest that aggressive cardiac management and early neuro-endovascular intervention can achieve high survival rates with low morbidity, even with a Bicêtre score below 8.[2] Consequently, many referral centres have adopted a more nuanced approach, moving beyond rigid score cutoffs to make individualized care decisions based on evolving clinical circumstances.

Managing heart failure in VGM remains challenging, particularly due to the complexities involved in choosing the appropriate timing for intervention. Medical management primarily focuses on stabilizing the patient to allow for sufficient growth before considering more invasive procedures. This stabilization involves early cardiovascular interventions aimed at enhancing systemic output by reducing both systemic and pulmonary vascular resistance while improving myocardial function. Diuretics, such as furosemide, should be administered shortly after birth to manage fluid overload and reduce the workload on the heart.[10] Prostaglandin E1 is recommended to maintain adequate systemic circulation by promoting right-to-left ductal shunting, which is crucial in sustaining oxygen delivery. Inodilators, including milrinone and levosimendan, are also used to improve cardiac output by providing inotropic support while simultaneously dilating blood vessels.[11] Low doses of catecholamines like dopamine and noradrenaline are added to further support cardiac function.[9] Although previous guidelines advocated for the use of milrinone in combination with inhaled nitric oxice (iNO) for treating VGM-related pulmonary hypertension, recent evidence advises against relying solely on iNO. The potential ineffectiveness of iNO and its risk of exacerbating pulmonary oedema make it less favourable option.[9,11] Therefore, treatment strategies now focus on a more comprehensive approach, incorporating various pharmacological agents to optimize patient outcomes.

CONCLUSION

Despite advancements in endovascular embolization improving VGM prognosis, the condition remains associated with significant mortality. A multidisciplinary approach in intensive care, combined with early diagnosis, is crucial for optimizing outcomes. Ideally, intrauterine transfer or early postnatal transfer to a specialised centre with endovascular capabilities is essential. This case highlights the critical importance of prenatal diagnosis and meticulous planning for the delivery and care of neonates with VGM.

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COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CASE REPORT

A case of possible autoimmune encephalitis with complex neuropsychiatric presentation

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INTRODUCTION

Autoimmune encephalitis (AE) challenges diagnostic boundaries as it often presents with a myriad of symptoms that range from subtle cognitive impairments to overt psychiatric manifestations. This report aims to shed light on AE that first presented with depressive phenomenology in an elderly male wherein neurological assessment revealed preserved memory with occasional cognitive slowing, leading to a provisional diagnosis of Agitated Depressive Stupor. Upon discovering fluctuating levels of consciousness and focal clonic seizures, we describe the diagnostic journey, clinical course and subsequent therapeutic interventions in a steroid-responsive possible seronegative AE. As we delve into the complexities of this case study, we hope to contribute to the growing body of knowledge surrounding this enigmatic form of encephalitis whilst emphasising the importance of early recognition, accurate diagnosis and targeted management for improved patient outcomes. Through a comprehensive examination of this case report, we seek to enhance our understanding of the complexities surrounding AE, fostering awareness and considering future clinical approaches in the ever-evolving landscape of neuropsychiatry.

CASE PRESENTATION

An 86-year old White Caucasian male was reported to be feeling distressed and having episodes of 'disorientation' following difficulties with the use of his credit card while on a cruise ship from the Middle East to Australia. While initially expressing anxiousness without overt sadness, he later manifested with symptoms of agitation, pacing about and having sleep disturbances. There were no associated physical symptoms such as fever, vomiting or feeling imbalanced. There was no reported history of trauma to the head and there was no slurring or limb weakness. He was taken to a hospital in Bangkok and computed tomography (CT) brain imaging was unremarkable. He was subsequently allowed to return to the ship with the recommendation to rule out potential organicity if there was no clinical improvement. He unfortunately did not improve and was deemed unfit to continue his cruise journey and thus disembarked in Penang. On being admitted into a private specialist hospital, he was noted to exhibit reduced alertness (possibly following an earlier administration of a low-dose neuroleptic quetiapine for his agitation) but there were no fluctuating levels of consciousness. There was near complete psychomotor inhibition and impaired reaction to external stimuli by way of reduced responsiveness, but with consciousness retained and he would then return to the unresponsive state if undisturbed. Some grimacing with negativism was observed, as well as protective actions to prevent his hand from dropping on his face, but there was an absence of posturing, rigidity or waxy flexibility. There was no observation of any self-talking or suspicious behaviour and he instead exhibited a lack of mobility and speech.

There was no notable past history except for a recent shift towards a less talkative demeanour and increased fatiguability over two months prior to him being seen here and approximately a month after that, he exhibited an obsession with organising tasks in a meticulous and orderly manner. This behaviour escalated about eight days prior to admission when he was already on the cruise ship whilst demonstrating the similar preoccupations. There was no preceding history of memory loss or a decrease in his ability to execute activities of daily living (ADL). Premorbidly, he was described by his wife as a talkative and jovial person. He had retired as a banker years ago and there were no financial or family issues. They have two daughters. He was active in playing golf three times a week and was a social drinker. A thorough mental state examination could not be conducted at first contact due to his perceived stuporose state.

During his admission, he began to exhibit brief periods of increased verbalisation followed by a return to his persistently negative and depressed demeanour. A sense of impending doom emerged, accompanied by heightened agitation, especially in response to phone calls from his concerned daughters. Although he denied harbouring negative thoughts, he displayed restlessness and continuous murmuring. He refused feed during the initial part of the admission and his physical condition deteriorated, leading to unsteadiness and a notable decrease in confidence to mobilise. Initially, his fears displayed both nihilistic and paranoid elements. While the nihilistic thoughts diminished over time, the paranoid ideation persisted. Surprisingly, he attributed his condition at the time to his wife. His daughter later confirmed that he had shown a loss of interest in activities he once enjoyed, dating back as far as a year before the episode. No manic symptoms were reported.

Neurological assessment revealed relatively normal memory function although his responses were noticeably slowed.

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There were no signs of neck stiffness or features suggestive of extrapyramidal system involvement. Muscle strength was generally good although occasional twitching over certain muscles was suggestive of myokymia. Deep tendon reflexes were within the normal range and no nuchal pain was elicited during neck flexion. Tests for Babinski and Hoffmann reflexes were negative and his electroencephalogram (EEG) was reported as normal. A provisional diagnosis of Agitated Depression with Stupor was considered. During the initial four days of admission, antidepressant therapy with vortioxetine was initiated and his level of consciousness appeared to remain normal. However, on the fifth day, he began experiencing fluctuations in awareness and consciousness. He was found wandering around the ward and unable to recall his actions or behaviour afterwards. Around the same time, he experienced several episodes of focal seizures, characterised predominantly by the semiology of clonic seizures involving both lower limbs in the form of characteristic rhythmic twitching that lasted only a few seconds.

Given the progression of his symptoms, an antinuclear antibody (ANA) test for autoimmune encephalitis (AE) was conducted. The results were positive for ANA via immunofluorescence assay (IFA) and indirect immunofluorescence assay (IIFA), with anti-titin antibodies at borderline levels - all other tested antibodies were negative. AE, in particular anti-leucine-rich-glioma-inactivated 1 (LGI1) antibody disease, was considered a potential diagnosis and to err on the side of caution, he was then transferred to a neurological facility after interdepartmental liaison discussions.

Magnetic resonance imaging (MRI) brain revealed T2-weighted and FLAIR hyperintensity in the bilateral anterior cingulate gyrus. The EEG was normal. A lumbar puncture (LP) showed elevated protein levels (559.9 mg/L) without any white blood cells, with normal glucose levels, and no organisms identified. Levels of Vitamin B12, folate, electrolytes, thyroid function and anti-thyroglobulin antibodies were all within normal limits. Tumour markers, including prostate specific antigen (PSA), were also normal. Paraneoplastic screening was negative except for a borderline positive result for anti-titin antibodies (anti-Ri, -Yo, -Hu, -Recoverin, -SOX1, -AMPAR 1&2, -CASPR 2, LGI1, -DPPX 6, -GABA-B and -NMDAR). A CT scan of the thorax, abdomen and pelvis showed no evidence of malignancy.

Given his subacute symptom onset of less than three months, new neuropsychiatric (agitation, insomnia, reduced alertness, psychomotor inhibition, paranoia and later confusion) and neurological (delayed development of focal clonic seizures) findings along with MRI findings of encephalitis (hyperintensities in anterior cingulate gyri bilaterally) and a reasonable exclusion of alternative causes, a working diagnosis of possible AE was made and a treatment protocol mapped out. Probable or definite AE could not be considered due to the absence of epileptic or slow-wave activity on EEG, cerebrospinal fluid (CSF) pleocytosis and evidence of typical limbic encephalitis on MRI, namely in the form of medial temporal involvement.

He was initially treated with intravenous ceftriaxone 2g twice daily and intravenous acyclovir 500mg every 8 hours for one week, along with intravenous methylprednisolone 500mg twice daily for five days. He responded well to the low dose of the intravenous steroid, becoming noticeably more cheerful and eventually regaining full consciousness and cognitive functions. His mood returned to normal state and his seizures were well-controlled with levetiracetam, titrated up to 1g twice daily. He was eventually discharged after a total admission period of 29 days. A follow-up call to his daughter eight months later reported that he was doing well - independent in all ADL and ambulating with the aid of a Zimmer frame. Three months after that, he was said to have grown stronger although he had not yet resumed playing golf. At the most recent communication, three years after the initial episode, he was reported to be doing extremely well and had returned to his baseline physical condition. There were no neuropsychiatric sequelae and he had coped well with the COVID-19 pandemic, although he remained understandably cautious about socialising. He was later diagnosed with malignant melanoma following the pandemic - he accepted the diagnosis, underwent treatment and eventually made a full recovery.

DISCUSSION

AE presents a formidable diagnostic challenge, particularly when psychiatric-like symptoms dominate the clinical picture and paint a scenario suggestive of a mood disorder with accompanying disturbances in volition and/or movement abnormalities. This case of a male in his mid-80s highlights the critical importance of being vigilant in clinical practice and adopting a multidisciplinary approach to diagnose AE promptly, especially in its early stages. The broad spectrum of clinical presentations associated with AE, spanning from psychiatric symptoms to cognitive and neurological impairments, necessitates a comprehensive and nuanced diagnostic approach.[2] The initial psychiatric presentation of AE often leads to misdiagnosis and treatment delay, as observed in this patient who exhibited symptoms of anxiety, agitation and depression without overt neurological signs.[3]

Early and comprehensive autoantibody testing plays a crucial role in the diagnostic process for AE. In this particular patient, detecting positive ANA and borderline anti-titin antibodies heightened our suspicion of possible AE.[4] Moreover, specific autoantibodies such as anti-LGI1 play a pivotal role in confirming the diagnosis, facilitating the transition from a presumed primary psychiatric disorder to a diagnosis of AE - however, this did not seem to be the case in our patient. Diagnostic tools and neuroimaging, despite being indispensable, often need to be more conclusive in the early stages of AE. Advanced imaging modalities and EEG can furnish supportive evidence for the diagnosis, albeit with limitations.[3] In our case study, initial EEG and imaging studies yielded non-specific results, complicating the diagnostic trajectory. Nonetheless, the persistence of symptoms despite standard psychiatric interventions warranted further investigation, ultimately culminating in the diagnosis of possible AE.

The brain imaging findings in our patient favours AE, although MRI features of autoimmune encephalitis can overlap significantly with viral encephalitis. However, certain features can help differentiate the two.[5] In autoimmune encephalitis, the location of the lesions are bilateral and symmetrical predominantly in the limbic system commonly mesial temporal lobe including the hippocampus, amygdala, hypothalamus, cingulate gyrus and limbic cortex with rare or minimal diffusion restriction or enhancement. In contrast, the lesions in viral encephalitis are unilateral single lobe, asymmetrical lesions involving the limbic system. Lobar involvement in the inferior frontal significantly favours viral or infectious encephalitis.[6,7]

We favour a diagnosis of AE over viral encephalitis in this patient, although there are overlapping clinical features including seizures and altered cognition. The patient did not exhibit fever or vomiting, which are predominant clinical features in infectious or viral encephalitis.[7] In contrast, psychosis and seizures are more commonly associated with autoimmune encephalitis (AE) compared to viral encephalitis, aligning with this patient's presentation. Additionally, the presence of myokymia, a manifestation linked to peripheral nerve hyperexcitability has been reported in AE but not in viral encephalitis.[3] MRI of the brain demonstrated symmetrical bilateral anterior cingulate gyrus hyperintensities on T2/FLAIR sequences without enhancement or diffusion restriction, findings more suggestive of AE than viral encephalitis. Notably, leptomeningeal enhancement, observed in up to 38.5% of infectious encephalitis cases, was absent.[7] CSF cultures did not reveal any microorganisms, although viral PCR testing was not performed. Based on the diagnostic criteria proposed by Graus et al. (2016), the patient meets the definition of possible autoimmune encephalitis, fulfilling the criteria of subacute onset (less than three months), new focal central nervous system findings (lower limb clonic seizures), MRI evidence of encephalitis (bilateral anterior cingulate gyrus hyperintensities albeit not in the medial temporal lobes required for a definitive AE diagnosis), and reasonable exclusion of alternative causes.[1]

The limitations of this case report include the absence of CSF samples for Real-Time quantitative Polymerase Chain Reaction (RT-qPCR) viral panel testing and viral culture. In addition, the available autoimmune encephalitis panel was limited and CSF studies for oligoclonal bands and IgG index were not performed. These constraints preclude a definitive diagnosis, allowing for only a classification of 'possible' autoimmune encephalitis.

A multidisciplinary approach, encompassing collaboration among neurologists, psychiatrists and immunologists, emerges as a paramount path in navigating the diagnostic conundrum posed by AE.[8] Early integration of these specialities facilitates a comprehensive evaluation and expedites treatment initiation, thereby averting the harmful consequences of diagnostic delay. Prompt initiation of immunotherapy, including corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis, proves to be the cornerstone in the treatment paradigm of AE.[9] Early intervention facilitates symptom resolution and portends favourable long-term outcomes, underscoring the imperative importance of expeditious diagnosis and treatment initiation.

CONCLUSION

This case study epitomises the critical importance of considering AE it in the differential diagnosis of new-onset psychiatric disorders. Undoubtedly, it can prove challenging to routinely screen those without any prior psychiatric history but since most functional illnesses begin before the ages of 45-50 years, a high index of suspicion is recommended if acute and atypical psychiatric presentations occur in those older than that range and would thereby warrant a full organic work-up. By amalgamating insights from contemporary literature and embracing a comprehensive multidisciplinary approach, clinicians can enhance diagnostic accuracy, expedite treatment initiation and thereby optimise patient outcomes.

DECLARATION

The authors certify that they have obtained the patient's and families' consent. The patient understands that neither his name nor initials will be published and due efforts will be made to protect his identity; however, complete anonymity cannot be guaranteed.

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Pseudohyponatraemia in a patient with human immunodeficiency virus infection and plasma cell disorder

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SUMMARY

A 59-year-old man was admitted and treated for smear positive pulmonary tuberculosis. His co-morbidities were human immunodeficiency virus infection, schizophrenia and right otitis externa. He was initially thought to have persistent severe hyponatraemia, which was resistant to various therapeutic measures, including intravenous normal saline infusion, fluid restriction and even hypertonic saline correction. To complicate matters further, his blood electrolytes samples frequently showed technical errors in the analysers and could not be reported due to hyperviscosity state of the specimen. The presence of pseudohyponatraemia was subsequently confirmed based on normal measured serum osmolality, as well as normonatraemia seen on his venous blood gas analysis results. Investigations of pseudohyponatraemia led to discovery of a plasma cell dyscrasia, the possible diagnosis of which included Waldenström macroglobulinemia or IgM multiple myeloma. The patient eventually refused bone marrow aspiration and trephine biopsy for further evaluation. A high index of suspicion is required to differentiate pseudohyponatraemia from true hyponatraemia, to avoid misdiagnosis and mismanagement. When such circumstance is suspected, particularly in the setting of hyperproteinaemia or hyperlipidaemia, an analyser which utilises direct ion-selective electrodes, such as a blood gas machine, often reports normal sodium concentration and thus confirms pseudohyponatraemia.

INTRODUCTION

Hyponatraemia is a common electrolyte abnormality encountered in daily clinical practice, the presence of which at hospital admission has been associated with greater all-cause mortality and longer hospital stay.[1] Nonetheless, it is important to distinguish pseudohyponatraemia from true hyponatraemia as overzealous correction of the former can lead to adverse outcomes.

Pseudohyponatraemia is a laboratory artefact whereby sodium concentration of a given volume of serum is reduced when measured by indirect ion-selective electrodes (ISE) due to involvement of a preanalytical dilution step. This condition typically happens in the setting of marked hyperlipidaemia (hypertriglyceridaemia or hypercholesterolaemia) as well as hyperproteinaemia (paraproteinaemia, hypergammaglobulinaemia or intravenous immunoglobulin administration).[2]

We report a patient who initially manifested apparent resistant hyponatraemia, but was later found to have pseudohyponatraemia secondary to hyperproteinaemia due to a plasma cell disorder, two weeks after hospitalisation.

CASE PRESENTATION

A 59-year-old homeless man, who was a chronic smoker and had a history of intravenous heroin use more than three decades ago, presented to emergency department with a one-week history of intermittent fever, associated with cough productive of yellowish sputum mixed with blood streaks. He also experienced weight loss over the past two weeks but was unable to quantify it. Auscultation of the lungs revealed coarse crepitations over the left mid zone. His chest radiograph showed reticulonodular shadowing at the right upper zone as well as left upper and mid zones. He was admitted with a provisional diagnosis of community-acquired pneumonia, highly suspicious of pulmonary tuberculosis. Two days after admission, his sputum direct smear was tested positive for acid fast bacilli, for which he was treated with three tablets daily of a four-drug fixed-dose combination of antituberculosis therapy and pyridoxine 10 mg daily. Besides pulmonary tuberculosis, he was also diagnosed to have human immunodeficiency virus (HIV) infection, schizophrenia, and right otitis externa, all of which were managed by respective teams.

His initial laboratory investigations are shown in Table I. Plain computed tomography (CT) of brain was normal. Lumbar puncture was not performed due to patient's and family's refusal. In view of the finding of severe hyponatraemia (< 100 mmol/L) and hypokalaemia (1.8 mmol/L), he received 1.5 to 2.5 litres of intravenous normal saline with potassium supplementation every day during his first three days of hospitalisation. Workup of hyponatraemia showed normal measured serum osmolality, urine osmolality, urine sodium, serum cortisol and thyroid function. As the sodium levels did not seem to normalise with hydration, he was placed on fluid restriction due to a concern of possible syndrome of inappropriate antidiuretic hormone secretion (SIADH). Rapid sodium correction with hypertonic saline was also performed on one occasion. However, subsequent monitoring of his sodium levels turned out to be difficult due to either undetectable sodium levels (measured by indirect ISE) or repeated rejection of blood electrolytes samples by the chemical pathology laboratory (Table II). Further clarification from the laboratory revealed that his

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Table I: Initial blood investigations during admission

Investigations	Reference range	Values
Hb (g/L)	130 - 170	49
WBC (10^9/L)	4.0 - 10.0	5.8
Platelet (10^9/L)	150 - 410	479
Sodium (mmol/L)	136 - 145	<100
Potassium (mmol/L)	3.5 - 5.1	1.8
Chloride (mmol/L)	98 - 107	<50
Urea (mmol/L)	3.0 - 9.2	6.3
Creatinine (µmol/L)	64 - 104	81
Total Protein (g/L)	64 - 83	94
Albumin (g/L)	34 - 48	21
Globulin (g/L)	-	73
Total Bilirubin (µmol/L)	3.4 - 20.5	6.2
ALT (U/L)	0 - 55	7
AST (U/L)		43
ALP (U/L)	40 - 150	110
Corrected calcium (mmol/L)	2.10 - 2.55	2.78
Phosphate (mmol/L)	0.74 - 1.52	0.92
Magnesium (mmol/L)	0.66 - 1.07	0.83
CK (U/L)		<11
LDH (U/L)		965
CRP (mg/L)	< 5	179.5
ESR (mm/hr)	0.00 - 14.00	2
Morning cortisol (nmol/L)	-	369.2
TSH (mIU/L)	0.35 - 4.94	0.527
free T4 (pmol/L)	9.01 - 19.05	9.41
Triglycerides (mmol/L)	< 1.7	0.4
Total cholesterol (mmol/L)	< 5.2	1.5
HDL-Cholesterol (mmol/L)	> 1.0	0.5
LDL-Cholesterol (mmol/L)	-	0.9
HIV-	Positive	
HBsAg	-	Non-reactive
Hepatitis C antibody	-	Reactive
RPR	-	Non-reactive

Hb haemoglobin, WBC white blood cell, ALT alanine transaminase, AST aspartate aminotransferase, ALP alkaline phosphatase, CK creatine kinase, LDH lactate dehydrogenase, CRP C-reactive protein, ESR erythrocyte sedimentation rate, TSH thyroid-stimulating hormone, T4 thyroxine, HIV human immunodeficiency virus, HBsAg hepatitis B surface antigen, RPR rapid plasma regain

blood samples were too "viscous" to be analysed. The patient was otherwise alert and well-orientated despite being delusional with auditory hallucination.

Meanwhile, several venous blood gas analyses during this admission demonstrated mostly normal sodium levels (measured by direct ISE), ranging between 133 mmol/L and 145 mmol/L (Table II). The presence of normal sodium concentration, analysed using a blood gas analyser which measures sodium in serum water phase, as well as a normal serum osmolality confirmed that the low sodium levels reported by the laboratory were in fact pseudohyponatraemia, the possible cause of which in this patient was hyperproteinaemia (Table I). Further assessment for causes of hyperproteinaemia was carried out. The patient was subsequently discharged to a shelter home after sputum smear conversion and continued directly observed therapy (DOT) of antituberculosis treatment at chest clinic. He also received antiretroviral (ARV) therapy from the infectious diseases team and risperidone 1 mg every night by the psychiatry team.

One month after discharge, he was reviewed in haematology clinic. His peripheral blood film showed rouleaux formation. Free light chain kappa/lambda ratio was normal (1.336, normal range: 0.310 – 1.560) but serum immunoglobulin M (IgM) and beta-2 microglobulin were both elevated (32 g/L, normal range: 0.22 – 2.40, and 7.34 mg/L, normal range: 1.09 – 2.53, respectively). Additionally, serum protein electrophoresis and immunofixation showed oligoclonal bands with prominent IgM kappa paraproteinemia of 44.3 g/L near beta zone. The working haematological diagnosis was Waldenström macroglobulinemia or IgM multiple myeloma. Despite counselling on the risk of disease progression and potential complications of hyperviscosity, the patient refused bone marrow aspiration and trephine biopsy for further evaluation.

DISCUSSION

We report a case of pseudohyponatraemia secondary to markedly elevated IgM in the setting of a plasma cell dyscrasia. Our patient was found to have hyponatraemia during his admission for smear positive pulmonary tuberculosis and HIV infection. Common aetiologies which could underlie such presentation include dehydration, adrenal insufficiency, thyroid insufficiency or SIADH.[3] All these conditions exhibit low measured serum osmolality,

Table II: Serial serum sodium concentration monitoring during admission and the corresponding fluid management

Investigations	20.11.22	21.11.22	22.11.22	24.11.22	25.11.22	26.11.22	27.11.22	1.12.22	3.12.22	4.12.22	5.12.22	7.12.22	8.12.22	10.12.22	11.12.22
Laboratory sodium (mmol/L)	129	127	120	Rejected	<100	124	<100	119	Rejected	Rejected	-	Rejected	<100	-	<100
VBG sodium (mmol/L)								133	134	144	145	133		143	139
Serum osmolality (mOsm/kg)	300					291		300							
Urine osmolality (mOsm/kg)	631					529		352							
Urine sodium (mmol/L)	80					120		109							
Fluid management	1.5-2.5 L 0.9% NS/day		ROF 800 cc/day		3% saline correction	1.5-2 L 0.9% NS/day						1 L 0.9% NS/day		Liberal oral fluid intake	

VBG venous blood gas, NS normal saline, ROF restriction of fluid

which is not the case in our patient whereby the measured serum osmolality was normal. Besides, neither intravenous fluid therapy nor fluid restriction normalised his sodium levels. Furthermore, normal serum cortisol and thyroid function excluded adrenal and thyroid insufficiencies. The huge discrepancy between laboratory-measured sodium levels (indirect ISE method) and those measured by the blood gas machine (direct ISE method) subsequently alerted the treating team to the possibility of pseudohyponatraemia.

Water constitutes approximately 93% of a normal individual's serum. Sodium is only found in the serum water phase. In patients who have marked hyperlipidaemia or hyperproteinaemia, serum water fraction reduces significantly. Consequently, the sodium concentration per litre of serum (not serum water) becomes artifactually low. Among the two ISE methods (direct ISE and indirect ISE) used for measurement of serum electrolytes, indirect ISE is prone to give rise to pseudohyponatraemia in the setting of marked hyperlipidaemia or hyperproteinaemia because it involves a preanalytical dilution step. In our case, our laboratory used an indirect ISE method to measure serum sodium, thus resulted in spuriously low sodium concentrations. Meanwhile, the sodium concentration in the serum water phase is unaffected by changes in water percentage. Therefore, blood gas machine analysers, which uses a direct ISE method and does not have a predilution step, directly measures sodium concentration in the serum water phase and reported mostly normal sodium levels in our patient.[2]

Differentiating pseudohyponatraemia from true hyponatraemia is imperative to avoid unnecessary treatment with intravenous isotonic or hypertonic saline which may lead to iatrogenic hypernatraemia. When hyponatraemia occurs in the presence of hyperproteinaemia or hyperlipidaemia, suspicion of pseudohyponatraemia should arise. A repeat sodium concentration measurement by an analyser which utilises direct ISE method, for instance a point-of-care device or a blood gas analyser, should be performed. Of note, direct ISE method is also available in chemistry analysers. However, due to the higher cost, most laboratories measure electrolytes using indirect ISE method. If the repeat sodium concentration, measured by direct ISE method, is normal, then pseudohyponatraemia is confirmed. On the other hand, if a blood gas analyser is unavailable, pseudohyponatraemia can also be confirmed by a normal serum osmolality together with a high concentration of proteins or lipids. This is because true hyponatraemia, such as that seen in adrenal insufficiency or SIADH, is associated with low serum osmolality.[2]

Cases of pseudohyponatraemia have been described in patients with HIV infection and are attributed to hypergammaglobulinaemia.[4] Our patient has concomitant HIV infection and a plasma cell disorder (Waldenström macroglobulinemia or IgM multiple myeloma). HIV-infected individuals are known to have higher risks for plasma cell disorders, ranging from polyclonal hypergammaglobulinaemia, monoclonal gammopathy to multiple myeloma. Antigen stimulation and immunodeficiency are two possible mechanisms which contribute to this observation. Treatment of plasma cell disorders in HIV-infected patients is similar to that in general population.[5] In our case, since Waldenström macroglobulinemia and IgM multiple myeloma are two distinct entities with different prognoses and treatment plans, a bone marrow aspiration and trephine biopsy is essential in confirming the diagnosis and thereby guiding further management. However, it was not performed due to our patient's refusal.

CONCLUSION

Pseudohyponatraemia should be suspected when hyponatraemia occurs alongside normal measured serum osmolality, particularly in the setting of hyperproteinaemia and hyperlipidaemia. Recognition of this laboratory abnormality prevents misdiagnosis and thence inappropriate patient management.

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DECLARATIONS

Written consent from the patient's carer has been obtained prior to the publication of this case report. Both authors declare no conflict of interest.

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A case of ocular syphilis in a patient with unilateral progressive loss of vision

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SUMMARY

Ocular syphilis is a rare manifestation of systemic infection by Treponema pallidum, capable of affecting multiple ocular structures and causing irreversible vision loss if not promptly treated. We report a case of progressive bilateral visual impairment caused by ocular syphilis. A 49-year-old woman presented with progressively worsening blurry vision in both eyes over one month. There was no history of oral or genital ulcers, joint pain, tuberculosis contact, or high-risk sexual behaviour. Visual acuity was counting fingers in the right eye and 6/36 in the left. Relative afferent pupillary defect (RAPD) was noted in the right eye. Fundus examination revealed a swollen optic disc in both eyes. The right eye showed superonasal retinitis, retinal hemorrhages, vitritis, and signs of vasculitis. The left eye had no retinitis, vasculitis or hemorrhage. Syphilis serology was positive with an elevated erythrocyte sedimentation rate (ESR). Brain imaging revealed incidental finding of a cystic sellar lesion. Fundus fluorescein angiography showed areas of non-perfusion in the right superonasal retina. The patient received intravenous penicillin G 4 million units every 4 hours for 14 days and underwent sectoral laser photocoagulation in the right eye. Visual acuity improved to 2/60 in the right eye and 6/12 in the left. This case highlights the importance of early recognition and prompt treatment of ocular syphilis to prevent long-term vision loss, as severe or uncommon presentations may be associated with poorer outcomes.

INTRODUCTION

Syphilis caused by treponema pallidum (TP) remains a major global health problem. According to CDC, in national overview of STI in 2023, 209,253 cases of syphilis all stages including congenital syphilis were reported which is the greatest number of cases reported since 1950 and an increase of 1.0% since 2022.[1] Ocular syphilis is an uncommon but important complication of syphilis. Untreated ocular syphilis may lead to permanent vision loss.[2]

Ocular involvement can occur at any stage of syphilis in both HIV-positive and HIV-negative individuals. Eye involvement may be asymptomatic or present as an anterior, intermediate or posterior uveitis, a retinal vasculitis, retinitis, optic neuritis or scleritis.[3] Most cases of ocular syphilis present as uveitis, and the visual acuity depends on structures involved.[4]

As ocular syphilis can affect most structures in the eye and is known as The Great Masquerade, this makes diagnosis challenging. Thus, a high index of clinical suspicion is required to identify *Treponema pallidum* as the causative agent.

CASE PRESENTATION

A 49-year-old woman with no prior known medical illnesses presented with progressively worsening unilateral blurry vision for one month. She reported no associated symptoms such as eye redness or ocular pain. There was no relevant family history, no known contact with tuberculosis patients, and no joint pain, oral or genital ulcers. She denied any high-risk behaviours. She had been married for 23 years and has three children. Her husband also denied any high-risk behaviours or history of promiscuity.

On general examination, she appeared healthy, conscious, and well-oriented to time, place, and person. There were no skin lesions noted. Neurological examination, including other cranial nerves, was unremarkable. Respiratory and cardiovascular examinations were normal. No lymphadenopathy or hepatosplenomegaly was elicited.

Ocular examination revealed a visual acuity of counting fingers in the right eye and 6/36 in the left eye. Positive RAPD was noted in the right eye, along with reduced light brightness and red desaturation. Ishihara colour vision testing revealed 0/21 in the right eye and 10/21 in the left eye. The anterior segments of both eyes were normal. Anterior vitreous cells were present bilaterally, suggesting intraocular inflammation.

Fundus examination of the right eye revealed a swollen optic disc with obscuration of the major vessels. There was a patch of retinitis with surrounding retinal haemorrhage located superonasally, approximately 3-disc diameters in size, along with vitritis. The retinal vessels were slightly tortuous, with evidence of vasculitis and sclerosed vessels in the superonasal quadrant. There was no macular star (Figure 1a). Fundus examination of the left eye showed a swollen optic disc with vessel obscuration, although no vitritis, retinitis, or vasculitis was seen. The vessels were slightly tortuous, and the macular reflex appeared dull (Figure 1b). Intraocular pressure was within normal range in both eyes.

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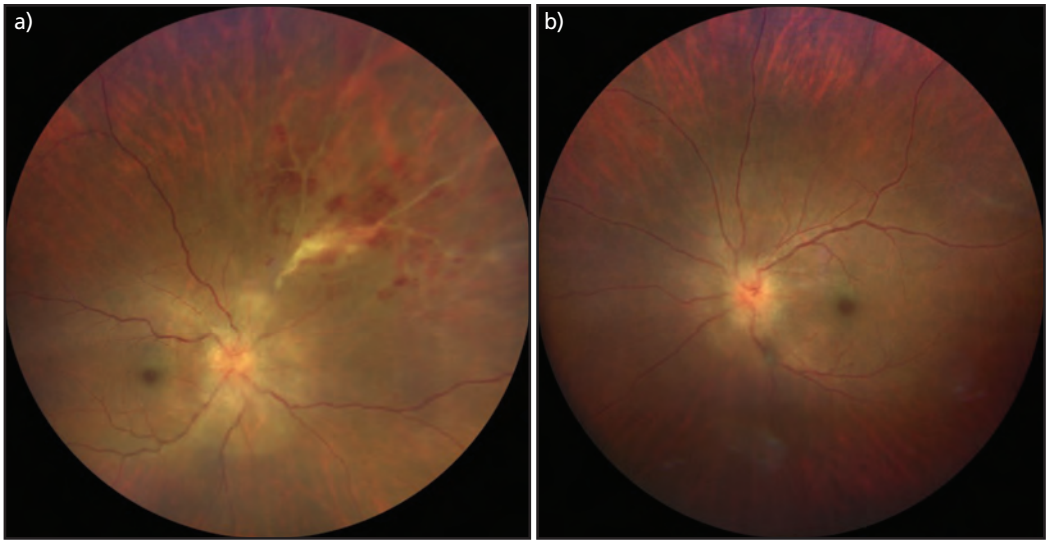

Fig. 1: a) Right eye fundus showed swollen optic disc and presence of retinitis at superonasal area surrounded by retinal haemorrhage with vasculitis and sclerosed vessels
b) Left eye fundus showed swollen optic disc with no retinitis or vasculitis

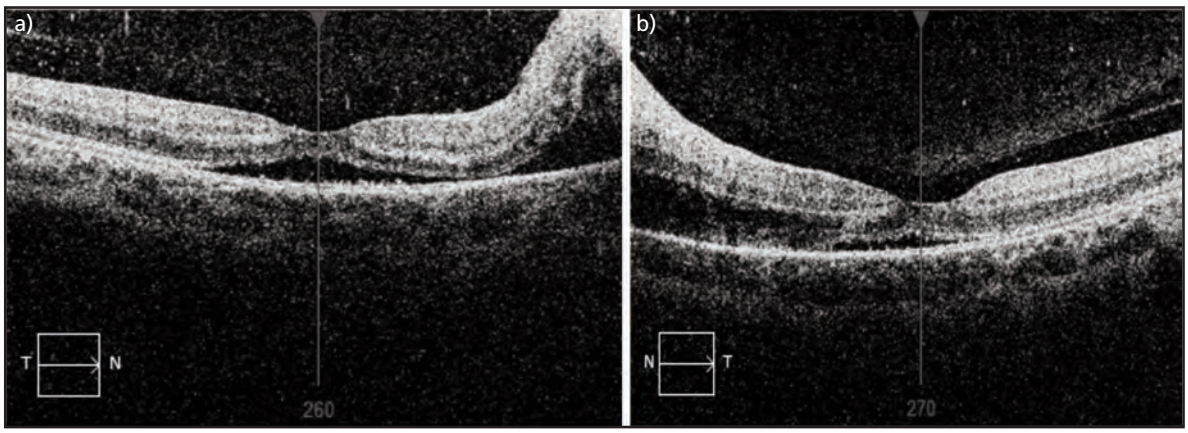

Fig. 2: Optical coherence tomography of the macula showed presence of peripapillary subretinal fluid with irregular protrusion of RPE in both eyes

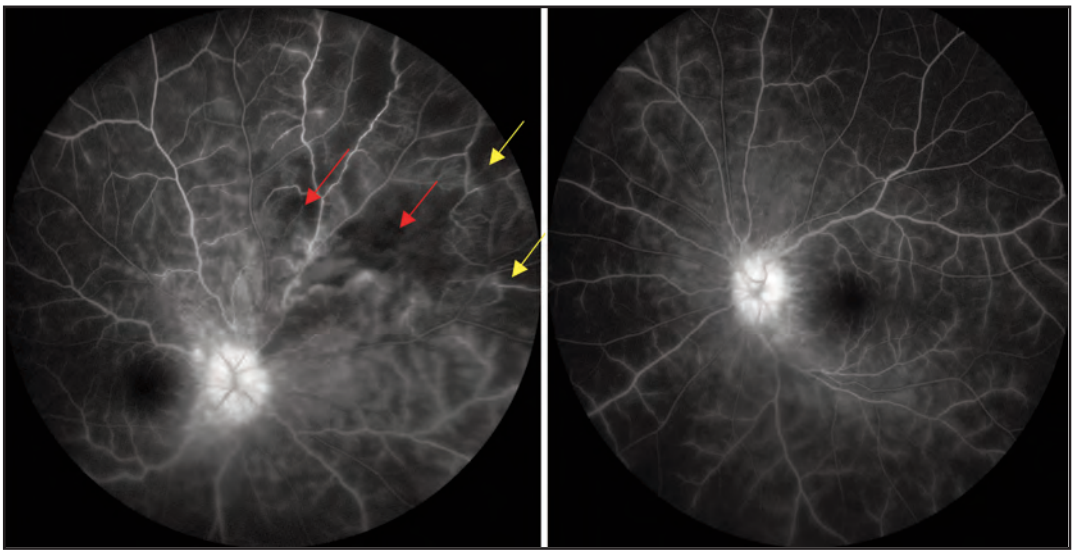

Fig. 3: FFA demonstrated masking from the haemorrhage retinitis (red arrow) with small areas of non-perfusion (yellow arrow) distal to it over superonasal quadrant of the right eye eye without leakage. FFA of the left eye was normal

Laboratory investigations revealed reactive syphilis serology, with an ESL titre of 219 and a rapid plasma reagin titre of 1:32, indicating active syphilitic infection. The ESR was elevated at 81 mm/h. Screening tests for HIV and hepatitis were non-reactive. A contrast-enhanced CT scan of the brain showed incidental finding of cystic sellar lesion thus she was referred to neurosurgical team. Optical coherence tomography (OCT) macula of the right eye showed presence of peripapillary subretinal fluid extending subfoveally with irregular protrusions of the retinal pigment epithelium (RPE) at macula and hyper reflective dots in the vitrous. Whereas for the left eye showed peripapillary fluid extending towards macula with subfoveal fluid and irregular protrusions of the RPE. (Figure 2). FFA showed masking from the haemorrhage retinitis with small areas of non-perfusion distal to it over superonasal quadrant of the right eye, however there was no dye leakage that indicate retinal neovascularization (Figure 3).

The patient was treated with IV Crystalline Penicillin G at a dose of 4 megaunits every 4 hours for a total duration of two weeks. In addition, sectoral laser photocoagulation was performed over the superonasal quadrant of the right eye. Upon completion of treatment, her vision showed only slight improvement, with visual acuity improving to 2/60 in the right eye and 6/12 in the left eye. The patient was discharged after completing her treatment course.

DISCUSSION

Syphilis is a systemic, bacterial infection caused by the spirochete Treponema pallidum. Due to its many protean clinical manifestations, it has been named the "great imitator and mimicker." Syphilis remains a contemporary plague that continues to afflict millions of people worldwide.[5] Most cases are sexually transmitted, but it also can be acquired congenitally. It can be recognized both in immunocompetent and immunocompromised individuals.

Ocular syphilis presents with varied phenotypes, including anterior uveitis, interstitial keratitis, scleritis, intermediate uveitis, posterior uveitis such as retinitis, chorioretinitis, and retinal vasculitis, as well as the distinctive acute syphilitic posterior placoid chorioretinitis. Optic nerve involvement may manifest as optic neuritis, papillitis, or optic peri neuritis, while panuveitis is also common. A study from Mohd Fadzil et al and Yang et al found that panuveitis is the most common presentation.[4,6] Other rarer presentations of ocular syphilis, such as stromal keratitis, iridocyclitis, necrotizing retinitis, optic atrophy, and retinal vasculitis, are only found in patients that have long-standing tertiary syphilis.[7]

As for our patient, she presented with right posterior uveitis with optic nerve involvement, while the left eye demonstrated isolated optic nerve involvement. The diagnosis was confirmed by reactive syphilis serology. Other than that, we also need to rule out other causes such as sarcoidosis, tuberculosis and other viral retinitis. A CT scan of the brain was performed and revealed a cystic lesion in the sellar region. To further evaluate the nature of this lesion and to rule out the possibility of a syphilitic cerebral gumma, an MRI of the brain was conducted. The MRI findings of empty sella made a syphilitic gumma appear unlikely.

It is important to note that ocular syphilis is a recognized variant of neurosyphilis and may present with similar features. The diagnosis of neurosyphilis remains a challenge due to the lack of any existing definitive standardized testing. It is, therefore, based on a combination of history, clinical findings, serological testing, and cerebrospinal fluid (CSF) analysis results. Although a definitive diagnosis of neurosyphilis requires CSF examination, it has been argued that this may not be essential if the results will not alter the management plan, as the CDC recommends the same treatment regimen for both ocular syphilis and neurosyphilis. In our case, the patient declined lumbar puncture.

Our patient was treated with IV Crystalline Penicillin G of 4 million units every 4 hours for 2 weeks duration as recommended by CDC. For treatment of ocular syphilis and neurosyphilis, the CDC recommends 18– 24 million units of IV penicillin for 10–14 days, with limited data to support IV ceftriaxone 1–2 grams for 10–14 days as an alternative therapy for a penicillin allergy.[8] The patient was also treated with sectoral laser pan-retinal photocoagulation due to the presence of capillary non-perfusion area without evidence of leakage on FFA. Some articles suggested that combination of laser pan retinal photocoagulation (PRP) and intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is an effective treatment for occlusive retinal vasculitis with neovascularization.[9,10]

Ocular syphilis is a treatable condition, and visual prognosis is generally favourable with appropriate antibiotic therapy, particularly when initiated before significant loss of visual acuity occurs.[11] In our patient, however, visual recovery was limited, predominantly in the right eye. This poor outcome may be explained by several factors highlighted by Zhang et al, who reported that delayed initiation of treatment (>12 weeks after onset of uveitis), prolonged ocular symptoms (>28 days), presence of macular oedema or chronic optic neuropathy, HIV co-infection, and poor baseline visual acuity are associated with worse visual prognosis.[12] At follow-up, Ishihara colour vision testing demonstrated minimal improvement, with OCT macula showing resolution of peripapillary sub foveal fluid. Nevertheless, temporal pallor of the right optic disc was noted, indicating optic atrophy.

CONCLUSION

Syphilis may go undetected without a high index of clinical suspicion due to its nonspecific presentations. All patients with vision loss and ocular inflammation should have syphilis testing as a part of their infectious disease workup. Early diagnosis and prompt treatment after onset of symptoms may contribute to a more favourable prognosis for ocular syphilis.

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When a simple surgery become a disaster: Right hepatic artery injury during laparoscopic cholecystectomy

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SUMMARY

Laparoscopic cholecystectomy (LC) is a standard surgical procedure for gallbladder removal, but complications such as vascular injuries can occur , transforming what should be a simple procedure into a potential disaster. This case report describes a 60-year-old woman with cholelithiasis who underwent LC under direct supervision of a digestive surgeon. During the procedure, while dissecting the fatty tissue between the gallbladder and duodenum, due to excessive fat and unclear structures, the surgeon inadvertently partially transected the right hepatic artery (RHA), mistaking it for the cystic artery due to an anatomical variation known as Moynihan's hump. The injury caused ischemia in the right lobe of the liver. Immediate laparoscopic repair of the RHA was performed using Prolene 7-0 sutures, with successful restoration of blood flow and recovery of liver color. Postoperatively, the patient's liver function normalized within a few days, and she was discharged on day six without complications. Follow-up imaging confirmed smooth blood flow in the RHA and no signs of liver damage. This case highlights the importance of recognizing vascular anomalies like Moynihan's hump during LC to prevent complications. It also demonstrates that laparoscopic repair of RHA injuries is feasible with skilled techniques, offering a minimally invasive solution for such complications.

INTRODUCTION

Laparoscopic cholecystectomy (LC) is a common surgical procedure but major surgery, possible risks, and some complications may accompany it.[1] Therefore mandatory for the surgeon to be familiar with all techniques, including vascular variations in the extrahepatic biliary structure. A possible concern is that intraoperative bleeding due to vascular injury is usually seen with individual bile duct injuries, but can also occur as an isolated vascular injury. Such injuries can occur due to improper surgery as well as variations in blood vessels such as Moynihan's Hump.[2,3] The Moynihan's hump or caterpillar hump arrangement is characterized by a convoluted right hepatic artery (RHA). Its running proximal and/or parallel to the cystic duct and inclines to a little brief cystic artery (CA).[4]

Laparoscopic cholecystectomy, despite being the gold standard for gallbladder removal, is associated with a complication rate of 1.6%-5.3%, with biliary and vascular injuries being the most significant. Recent studies indicate that biliary injuries are more common with laparoscopic cholecystectomy than with open cholecystectomy, occurring in 0.3%-0.5% of laparoscopic procedures. Risk factors for these complications include severe gallbladder inflammation, gallbladder fossa adhesions, chronic cholecystitis, and variant biliary anatomy, which may obscure the critical view of safety. Anatomical variations such as Calot triangle adhesions and gallbladder wall thickening greater than 5 mm have been identified as independent risk factors for complications after laparoscopic cholecystectomy.[11]

Vascular injuries during laparoscopic cholecystectomy, particularly to the right hepatic artery (RHA), occur in 12%-61% of cases with bile duct injuries, representing a potentially life-threatening complication. A multicenter study reported that 80.4% of vascular and biliary injuries occurred in non-specialized centers, with only 27.9% of patients undergoing vascular repair as first treatment. The need for vascular reconstruction has been associated with higher mortality rates, emphasizing the importance of early recognition and appropriate management. Laparoscopic repair of vascular injuries has emerged as a viable option, with studies demonstrating that reconstruction of the RHA can prevent complications associated with right hepatic ischemia, such as liver abscess, bile tumor, and liver atrophy. Successful early arterial reconstruction (within 4 days) has been shown to allow recovery from hepatic ischemia without evidence of hepatic atrophy or necrosis during follow-up, highlighting the importance of prompt intervention and specialized care.[8,12]

CASE PRESENTATION

A 60-year-old woman came with complaints of recurrent pain in the right upper quadrant of the abdomen. The results of the preoperative ultrasound examination showed the presence of stones in the cystic sack so the patient was diagnosed with cholelithiasis. No contraindications to surgery were found in the routine preoperative examination. Subsequently, laparoscopic cholecystectomy was performed on the patient under direct supervision of a digestive surgeon, as part of a training program for laparoscopic cholecystectomy procedures.

The anatomic relationship between the cystic duct and the

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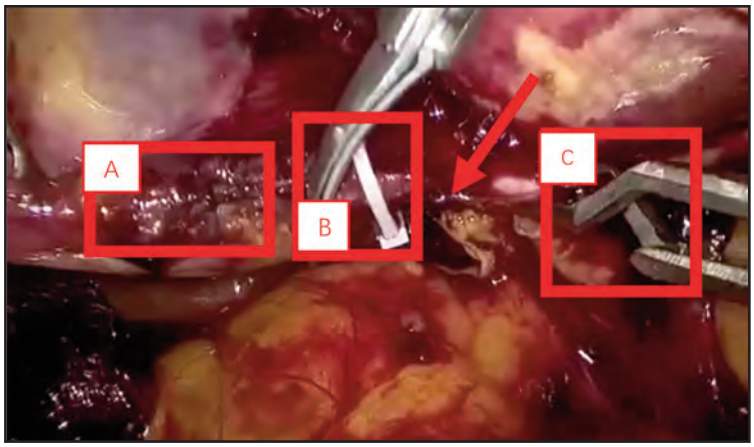

Fig. 1: The process of RHA anastomosis with the 7-0 Prolene suture (shown in the red arrow). In the figure, box A indicates the gallbladder, box B denotes the placement of a Hem-o-lok clip, and box C identifies the bulldog clamp.

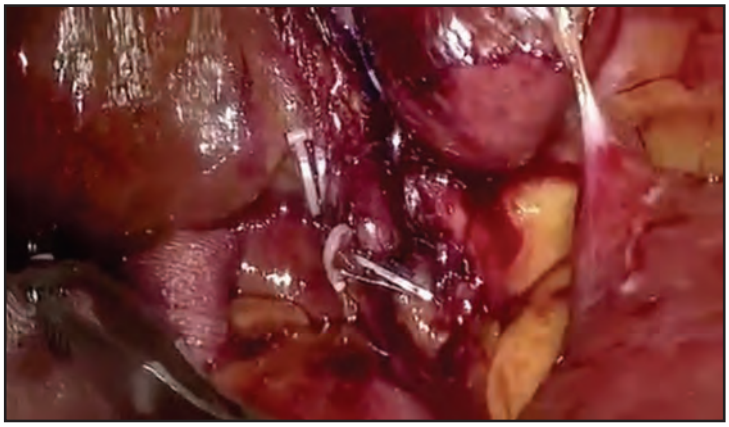

Fig. 2: The RHA end to end anastomosis is completed (shown in the red arrow)

common bile duct is unclear in this patient. During dissection of the fatty tissue between the gallbladder and duodenum, due to excessive fat and unclear structures, what was thought to be the cystic artery was actually the right hepatic artery (RHA) in Calot's triangle which was partially transected, mistaken for a cystic artery, moreover known as Moynihan's configuration The patient had a history of hypertension, which raised suspicion of high pressure, though pressure measurements were not performed during the procedure. The operator sees an RHA injury when there is still an ischemic line appears in the right lobe of the liver, similar to what typically occurs after portal vein branch ligation.. Therefore, laparoscopic RHA repair was performed immediately by supervising surgeon. Laparoscopic RHA repair started with the addition of 5 mm Trocar ports in the right upper and left upper quadrants. Then each end of the RHA is clamped with Bulldog and made a framework. The RHA was partially ruptured, then repaired by instrumentation prolene 7.0 suturing (Fig. 1 and 2). After opening the clamp on the RHA, the color of the right lobe recovered or was bright red. Cholecystectomy is continued, the visible cystic duct is clamped with a hemline as close as possible to the direction of the bladder. The proximal cystic duct is clamped with two metal clips and excised. The video scope is removed from the umbilical port and transferred to the epigastric port. Finally, the gallbladder was removed by pulling with forceps from the umbilical port, and the LC procedure was completed.

After performing repairing on RHA for 35 minutes on this patient, the color of the right lobe of the liver which was pale due to ischemia finally recovered to bright red. After surgery, the patient's serum transaminase level was slightly elevated but did not exceed three times the normal value, indicating mild hepatocellular injury without significant liver damage. Patients received symptomatic liver protective treatment with Stronger Neo-Minophagen C (SNMC) injections for 3 days. The patient was evaluated for 5 days without performing a follow-up CT scan for evaluation. The patient's liver function returns normally, and the patient can be discharged from the hospital on the fifth or sixth day postoperatively. Ultrasonography showed smooth blood flow in the RHA portal and showed no liver abscess or liver atrophy.

DISCUSSION

The vascular injury that occurs during laparoscopic cholecystectomy most commonly affects RHA. Despite excellent visualization of the gall bladder and surrounding structures during laparoscopy, sudden anatomical variations can be a cause of concern for surgeons. Since the routine use of laparoscopic technique, there has been an increase in the incidence of injuries to the structures adjacent to the gall bladder, commonly the common bile duct, cystic duct and vessels. The most common variations encountered in this region include Moynihan's hump. The convoluted course of the right hepatic artery, also known as Moynihan's hump or caterpillar hump, is an uncommon but critical irregularity that needs to be recognized to anticipate intraoperative vascular and biliary injuries during surgical procedures involving the liver and biliary organs.[5] According to Sangameswaran et al., the frequency of patients with a caterpillar hump or Moynihan's hump of the right hepatic artery is reported in the literature to range between 1% and 12.9%. The convoluted artery may pass dorsal or ventral to the common hepatic duct, with the dorsal course being more common. In both cases in this study, the convoluted right hepatic artery passed dorsal to the common hepatic duct. The hump may have a single or twofold loop, a double loop could be a commoner. Based on Sangameswaran et al's findings, one specimen exhibited a single loop formation while another specimen demonstrated a double loop configuration. The loop may be located outside or inside Calot's triangle. As reported in Sangameswaran's study, the single loop was found completely within Calot's triangle, while in the double loop case, the proximal loop lay outside Calot's triangle and the distal loop was located inside it. In a twofold loop bump, the cystic artery can emerge either from the proximal or distal loop, beginning from the last mentioned is more visit. In the present study, the cystic artery from double looped right hepatic arose from the distal loop. The cystic artery route emerging from the proximal loop is long and crosses over the convoluted right hepatic artery to reach the gall bladder whereas that emerging from a distal loop is exceptionally brief owing to the loop's nearness to the irritate bladder. The cystic course emerging from a single loop right hepatic course was long and the one emerging from the distal loop of twofold loop right hepatic was brief.[6]

According to the literature, right hepatic artery injury (RHA) accounts for 6.1-67% of the total incidence of biliary duct injury (BDI). Causes of RHA injury include anatomic abnormalities, pathological changes, artificial factors, technology, or even human error. If the surgeon is unfamiliar with or pays little attention to variations of the RHA, in cases of acute and chronic cholecystitis with unclear Calot's triangle anatomy, the RHA may be inadvertently spliced, mistaking it for a cystic artery.[7] In the case that describes the mechanism of transection of RHA in this patient, it occurs by mistaking RHA for a cystic artery. This excessive arterial pulsation was noted at the distal end of the RHA after the disconnection of electrocoagulation and makes the right lobe of the liver appear ischemic lines due to reduced blood supply to the right lobe of the liver.[8] The cystic artery passes through Calot's triangle and originates from a branch of the right hepatic artery (RHA). The bifurcation of the cystic artery divides into deep and superficial branches to the neck of the gallbladder. At the time of the LC procedure, the cystic artery tends to be hidden behind the gallbladder and is located slightly deeper and opposite the cystic duct. In one study, this type of variation was documented (73.3%) in 440 of 600 patients. Complicated deviations between the cystic arteries can increase the chance of injury during the LC procedure.[9] Therefore in this case the researcher attempted to explore several variations of cystic arteries, their complications, and management.

In the management of RHA injuries that occur during LC procedures, there is still much uncertainty and controversy in the existing studies. Several studies have shown that RHA ligase can cause pathological changes such as arterial ischemia, liver abscess, bile tumors, liver atrophy to anastomotic stenosis.[10] Li reported in his study that 3 out of 10 patients with RHA and BDI injuries had liver atrophy, liver abscess, and other manifestations. Other studies have suggested that the liver is double vascularized so that after RHA injury, a portion of the right lobe can receive collateral circulation from the uninjured left hepatic artery (LHA), to supply blood through the portal area and the perihepatic ligament. Therefore complex RHA repair is considered unnecessary. Yi Yu and Strasberg SM reported that only 10% of patients with RHA injury would develop a right hepatic infarct, and considered RHA too complex to repair because the effect was insignificant. Wu Bao's study suggested that the occurrence of complications after RHA injury may correlate with the location of the vascular injury or with bile duct injury as well. As in this case, vascular injury of the complicated junction site will impair the left-to-right blood supply, and the vascular plexus on the surface of the bile duct can lead to right hepatic ischemia and necrosis, or bile duct failure. This results in the appearance of a clear line of right hepatic ischemia in patients after RHA injury. Therefore, the blood flow of the injured RHA should be restored as soon as possible. To avoid the possibility of long-term complications, such as right hepatic ischemia.[10]

Based on the existing literature a few patients undergo reconstruction after switching to open surgery. Only one patient with an injury to the lateral wall of the RHA underwent laparoscopic-assisted reconstruction. The authors consider that laparoscopic magnification can display RHA and help assess surrounding tissue inflammation more clearly when compared to open surgery.[10] If the patient meets the indications for an end-to-end RHA anastomosis, RHA reconstruction can be completed with a laparoscope. Indeed, this requires a skilled vascular suture technique and a good work team. In this study, patients underwent repair of RHA transected with Prolene 7-0 sutures, the time to the separation of surrounding vessels and anastomoses was approximately 30 minutes. After the RHA blood flow is opened, the right half of the liver quickly recovers to a bright red, and the effect is fast and significant.

CONCLUSION

Laparoscopic RHA repair is feasible. Indeed, the number of cases in the study was small and the duration of follow-up was short. Therefore, meaningful long-term conclusions cannot

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Anaemia presenting as the sole symptom in a young woman: A case of malignant peripheral nerve sheath tumour of the small intestine

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SUMMARY

Malignant peripheral nerve sheath tumours (MPNSTs) with gastrointestinal involvement are uncommon. We report the case of a 22-year-old woman presenting with symptomatic anaemia requiring recurrent blood transfusions. Initial haematological evaluations revealed microcytic hypochromic anaemia. Both upper and lower endoscopies were normal, except for a positive rapid urease test result. However, computed tomography identified a tumour originating from the ileum and adherent to the urinary bladder, along with a mixed-density lesion in the right ovary. Following multidisciplinary team discussion, en-bloc resection of the ileal tumour and enucleation of the ovarian lesion, were performed. Histopathological analysis confirmed the ileal mass as an MPNST and the ovarian lesion as a benign cystic teratoma. This case highlights the rarity of ileal MPNSTs presenting with anaemia and emphasises the importance of complete surgical excision and vigilant follow-up owing to the potential for recurrence and metastasis.

INTRODUCTION

Malignant peripheral nerve sheath tumours (MPNSTs) are defined as neoplasms arising from peripheral nerves or exhibiting nerve sheath differentiation.[1] While most MPNSTs originate from major nerve trunks and are commonly located in the trunk, extremities, head, neck, or paravertebral regions, those arising from the nerves of the small intestine are exceedingly rare.[2] In this report, we present a case of ileal MPNSTs that manifested with anaemia as the primary symptom.

CASE PRESENTATION

A 22-year-old woman presented with a two-year history of progressive weakness, lethargy, anorexia, and weight loss. She also reported occasional episodes of epigastric discomfort and bloating but denied any haematemesis, melena, rectal bleeding, or other lower gastrointestinal symptoms. Her menstrual cycles were regular, and there was no family history of malignancy. The remainder of her systemic review was unremarkable.

On examination, the patient appeared alert but notably pale. She was afebrile, with a pulse rate of 80 beats per minute, blood pressure of 100/70 mmHg, and respiratory rate of 16 breaths per minute. Systemic examination revealed no palpable abdominal masses or other significant abnormalities.

Biochemical tests revealed a markedly low haemoglobin level of 4.4 g/dL, mild leucocytosis with a white blood cell count of 11.8×10^9/L, and an elevated platelet count of 870×10^9/L. Peripheral blood film and blood indices confirmed hypochromic microcytic anaemia. Results of renal profile, liver function tests, blood glucose levels, and coagulation profiles were all within normal limits. Chest radiography and electrocardiography findings were unremarkable. Oesophagogastroduodenoscopy (OGDS) showed no abnormalities, but the rapid urease test for Helicobacter pylori was positive. Similarly, colonoscopy findings were unremarkable.

She was admitted to medical ward for further assessment and blood transfusion because of the severity of her anaemia and transportation difficulties, as she lived far from the hospital. During her hospital stay, she developed a fever (38.8°C) and reported lower abdominal pain, although physical examination findings remained unremarkable. A computed tomography (CT) of the thorax, abdomen, and pelvis (Figure 1) revealed a left pelvic mass measuring 6.4 × 7.5 × 7.1 cm, originating from the small bowel and adherent to the dome of the urinary bladder. Additionally, the right ovary was found to be enlarged, with a complex mixed-density lesion measuring 4.4 × 3.3 × 2.1 cm. She was then referred to surgical team for management.

The case was reviewed in a multidisciplinary team (MDT) meeting comprising a general surgeon, gynaecologist, and radiologist. Given the primary origin of the tumour in the small bowel, the team recommended an initial laparoscopic assessment of resectability, followed by a lower midline laparotomy for definitive surgical management.

During the laparoscopic assessment, minimal ascites was noted in the pelvis, with no evidence of peritoneal seedlings. The surface of the liver appeared smooth. The tumour (Figure 2) was identified as originating from the small bowel,

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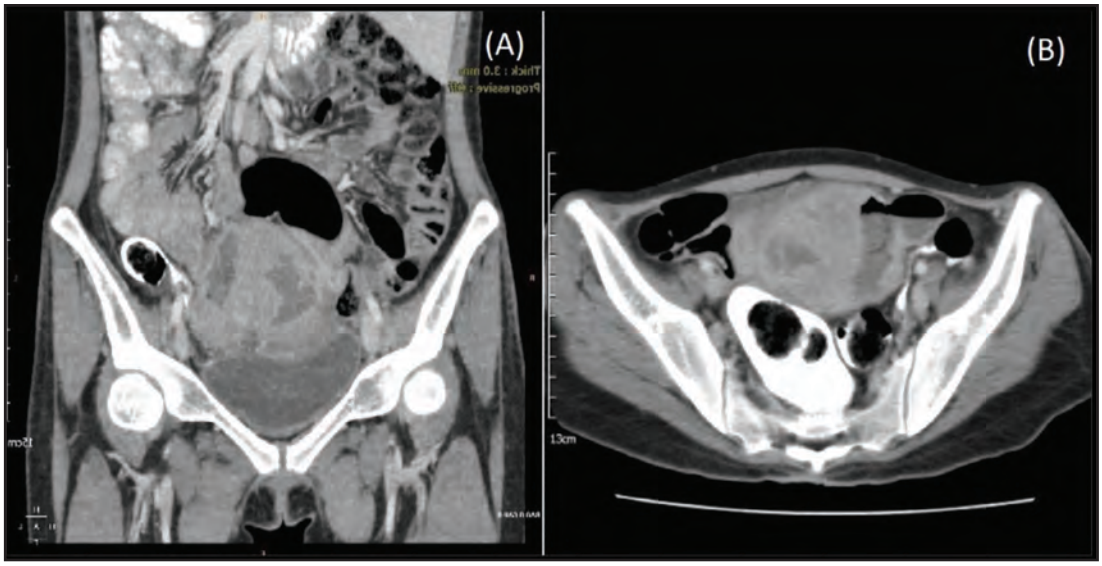

Fig. 1: CT scan of the abdomen and pelvis (A: coronal view; B: axial view) showing a pelvic enhancing tumour (blue arrow) arising from the small bowel and adherent to the dome of the urinary bladder

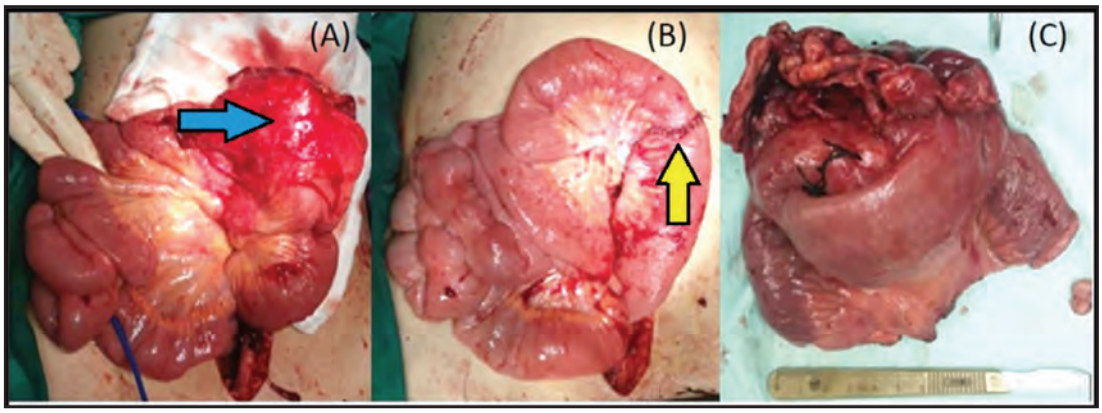

Fig. 2: A: Small bowel tumour (blue arrow) with multiple enlarged mesenteric lymph nodes; B: Primary anastomosis (yellow arrow) after en-bloc resection of the tumour; C: Resected specimen

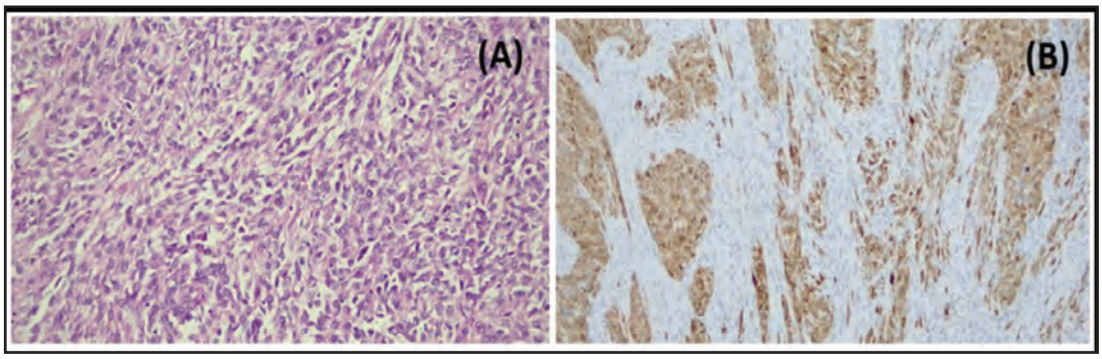

Fig. 3: A: Histopathological findings showed sheet and clumps of epithelioid tumour cells (Haematoxylin & Eosin stain); B: Positive S-100 in Immunohistochemical stain.

approximately 140 cm from the ileocecal junction, and was adherent to the dome of the urinary bladder. The greater omentum was also adherent to the tumour, and several enlarged mesenteric lymph nodes were observed adjacent to the mass. Because the tumour was operable conversion to laparotomy was performed and an en-bloc resection of the tumour was carried out, followed by primary end-to-end anastomosis of the bowel. Concurrently, the right ovarian lesion was successfully enucleated by the gynaecologist. There was no invasion of the ovary by the bowel tumour. The patient's postoperative recovery was uneventful. She passed stool and flatus by postoperative day 3 and was discharged on day 5 after tolerating oral intake well. She was doing well at her 3- and 6-month follow-up visits, with no bowel related symptoms.

Histopathological examination of the resected ileal tumour revealed a 23 cm segment of the ileum containing an annular, grey-white, fleshy mass measuring 4 cm in length and 2 cm in thickness. The tumour had narrowed the intestinal lumen to a diameter barely sufficient to admit a finger. Microscopically, the tumour consisted of sheets and clusters of epithelioid cells with clear cytoplasm, vesicular nuclei, and occasional spindle-shaped cells (Figure 3). Scattered osteoclast-like giant cells and areas of necrosis were present. The tumour infiltrated the full thickness of the ileal wall; however, mitotic figures were rare. All surgical margins were clear of malignancy, although five of the 14 resected lymph nodes showed metastatic involvement. The omentum was tumour-free. Immunohistochemistry showed that the epithelioid cells were strongly positive for S-100, with some spindle cells also staining positively, whereas the multinucleated giant cells were non-reactive. The tumour cells were negative for markers of lymphoma, gastrointestinal stromal tumour, leiomyosarcoma, germ cell tumour, and melanoma. The final diagnosis was a low-grade malignant peripheral nerve sheath tumour of the ileum (pT4N1). A histopathological examination of the right ovarian cyst confirmed that it was a benign cystic teratoma.

DISCUSSION

MPNSTs are exceedingly rare and rank as the sixth most common type of soft tissue sarcoma. Approximately 50% of the cases arise sporadically, whereas the remainder occur in individuals with neurofibromatosis type 1 (NF1).[1,2] In NF1-associated MPNST, tumours often develop through the malignant transformation of a plexiform neurofibroma or as a consequence of prior radiation exposure.[3,4] These tumours primarily affect adults aged 20 to 50 years, with a median age of 35. In this case, the patient was within the typical age range for MPNST but lacked the clinical features of NF1, suggesting a sporadic occurrence.

These tumours are most commonly found along the major nerve trunks, including those in the trunk, extremities, head, neck, and paravertebral regions. However, recent case reports have also documented MPNST in atypical locations, such as the liver, thyroid gland, skin, eighth cranial nerve, greater omentum, and small and large bowels.[3,4] MPNSTs originating from the small intestine are exceedingly rare. Most patients present with nonspecific symptoms, such as fatigue, weight loss, vomiting, abdominal pain, intestinal obstruction, or gastrointestinal bleeding.[4,5] In contrast, our patient presented atypically with anaemia, without overt signs of gastrointestinal disease. The anaemia was most likely due to slow, chronic bleeding from the tumour, which may explain the absence of obvious symptoms such as melena or haematochezia. The presence of hypochromic microcytic anaemia on the peripheral blood film further supports a chronic source of blood loss.

Diagnostic Role of Imaging and Histology

CT and magnetic resonance imaging (MRI) play important roles in the initial diagnosis and characterisation of tumours.[2,3,5] Key radiological features suggestive of MPNSTs include larger tumour size (>5 cm), infiltrative ill-defined margins, peritumoural oedema, intratumoural lobulation, bone destruction, and peripheral enhancement with a non-cystic or heterogeneous appearance on MRI. Morphologically, MPNSTs exhibit heterogeneity and often present as highly cellular spindle cell tumours arranged in fascicles. Immunohistochemical staining for S-100 protein is a key diagnostic marker for nerve sheath differentiation. The expression of additional markers, such as CD34 and Ki-67, can further assist in diagnosis. The presence of S-100 protein, along with elevated levels of p53 and Ki-67, provides valuable information for confirming the final diagnosis.[2,3,4]

Prognosis and Metastatic Potential

MPNSTs are associated with a high risk of local recurrence, with rates ranging from 40% to 60% within the first postoperative year. The lungs are the most common site of distant metastasis, while other metastatic locations include the liver, brain, bones, and adrenal glands. Factors associated with an increased risk of recurrence include the tumour's anatomic site, size (≥10 cm), and the adequacy of surgical margins.[6,7] The prognosis for MPNSTs of the small bowel tends to be poorer compared to other soft tissue sarcomas, although our understanding of this rare condition remains limited.[8,9]

Treatment Approach for MPNSTs of the Small Intestine (pT4N1)

The management of MPNSTs requires a multidisciplinary team (MDT) approach that integrates the expertise of surgeons, radiologists, and oncologists. Given the rarity of small intestinal MPNSTs, we applied oncological principles similar to those used for soft tissue sarcomas and gastrointestinal malignancies.

The primary treatment for MPNST with clinical pT4N1 status is surgical resection with wide negative margins (R0 resection) and regional lymphadenectomy. Complete surgical excision remains the cornerstone of treatment and the most significant predictor of survival.8,9 However, due to the high recurrence rate of MPNSTs, adjuvant therapy is often necessary even after R0 resection.

Adjuvant radiotherapy (RT) is often recommended to reduce local recurrence, particularly in cases of positive surgical margins or high-grade tumours.[10] Standard postoperative RT doses range from 50-66 Gy. However, its role in intra-abdominal MPNST remains uncertain due to potential toxicity to surrounding organs.[2] Given the patient's young

age, the achievement of clear surgical margins, and the lack of robust evidence supporting RT in this context, RT was not recommended.

While MPNSTs generally show a modest response to chemotherapy, adjuvant treatment may delay recurrence and improve survival, particularly in advanced or metastatic cases.[10] Because of the N1 status, which indicates a higher risk of systemic dissemination, doxorubicin, and ifosfamide combination chemotherapy was recommended. However, the patient declined adjuvant therapy.

Given the aggressive nature of MPNST, close posttreatment surveillance is essential. Given the limited data and lack of established guidelines for small-intestinal MPNSTs, our MDT recommended clinical assessments every 3–4 months, with abdominal and pelvic CT imaging every 6 months for 2 years, followed by annual surveillance for up to 5 years. Ideally, patients should be screened for NF1, because MPNSTs frequently arise in this genetic context, influencing prognosis and therapeutic decisions.

CONCLUSION

Our understanding of MPNSTs originating in the small bowel remains limited. Here, we present a rare case of MPNST arising from the ileum with an atypical presentation of anaemia. Accurate diagnosis and effective treatment require a multidisciplinary approach. Currently, no definitive treatment guidelines exist for small bowel MPNSTs. We recommend wide surgical excision as the primary treatment followed by vigilant monitoring for recurrence and metastasis. The efficacy of adjuvant RT and chemotherapy remains uncertain and warrants further investigation through clinical trials.

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DECLARATION

The authors declare no conflict of interest.

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Deadly cuddle of diffuse large B-cell lymphoma around the heart: A case report

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SUMMARY

Cardiac involvement in Non-Hodgkin Lymphoma is extremely rare. These rapidly growing high grade tumours are almost exclusively Diffuse Large B-cell lymphoma (DLBCL). This aggressive tumour is unusual among immunocompetent patients. This report describes the clinical case of a 70-year-old female who presented with cardiac tamponade in shock and heart failure symptoms. Investigations confirmed lesion within anterior and left pericardium with minimal mass effect onto the adjacent right lateral ventricle. This case highlights the importance of recognising uncommon presentations of PC-DLBCL. Definite diagnosis can be achieved through multimodality diagnostic imaging and/or pathological study.

INTRODUCTION

Cardiac involvement in Non-Hodgkin Lymphoma is extremely rare. Based on the 2015 WHO Classification of Tumours of the Heart and Pericardium, primary cardiac lymphoma (PCL) represents a minority 1-2% of all primary cardiac tumours.[1] About 80% of these rapidly growing high grade tumours are Diffuse Large B-cell lymphoma (DLBCL). The remaining 8.7-27.2% originate from disseminated lymphoma infiltrating the heart which occurs in advanced disease stage or diagnosed post mortem, with an incidence of 0.05%.[2] This rarity poses significant diagnostic challenges due to nonspecific cardiac symptoms and frequently under-recognised, complicating timely intervention and contributing to poor diagnostic outcomes.2 Right atrium is the most common location of PCL, with the tumour being intrapericardial during diagnosis.3 This aggressive tumour is unusual among immunocompetent patients.[3] Main presentation of PCL with cardiac tamponade only occurs in 20% of the cases.[4]

The authors report this remarkable clinical case due to its rare entity in the absence of immunodeficiency context.

CASE PRESENTATION

Case history and physical examination

A 70-year-old immunocompetent Malay lady with underlying hypertension and dyslipidemia presented to the emergency department of Hospital Taiping for sudden onset chest discomfort, shortness of breath and dizziness. Further history revealed she had a dry cough and was unable to lie flat for a week. She denies any palpitations, fever, loss of appetite or loss of weight. There is no family history of malignancy. She is a teetotaler and non-smoker. Premorbidly, she was an active housewife able to carry out daily activities without restriction, thus her patient performance status on the scale of Eastern Cooperative Oncology Group (ECOG) was zero.

On arrival, her blood pressure was 69/49, pulse rate of 94 , respiratory rate of 38 and oxygen saturation (SPO2) 88% under room air requiring face mask oxygen supplementation and immediately triaged to red zone. After 100 ml of fluid bolus over an hour, blood pressure picked up to 97/67. Physical examination revealed muffled heart sounds without murmur. Lung auscultation was clear and there were no signs of elevated jugular vein pressure, lymphadenopathies, organomegaly, or pedal edema. She was having cardiac tamponade clinically.

Investigation and Diagnosis

Her electrocardiogram was electrical alternans whereas chest X-ray showed water bottle sign of gross globular cardiomegaly. She was admitted to the CCU for pericardiocentesis. Urgent echocardiogram showed pericardial effusion at the measuring 2.09cm anteriorly and 1.76cm posteriorly with right ventricle diastolic collapse and distended inferior vena cava, besides discovery of an apical cardiac mass of size 5cm x 2cm. The ejection fraction was 65%, indicating preserved systolic function and suggesting that the clinical presentation was not due to cardiac failure.

Patient's full blood count, renal profile, thyroid function test, troponin I and tumour markers were within normal range. Troponin I remained within normal limits despite the presence of cardiac tamponade, as there was no evidence of myocardial ischemia. Her autoimmune antibody, Human Immunodeficiency Virus test and hepatitis panel were negative. For pericardial fluid analysis, the laboratory tests concluded as exudative effusion with lactate dehydrogenase level (LDH) of 797 U/L, negative cytology for malignant cells and negative smear for Acid Fast Bacilli. Her serum LDH was 480U/L.

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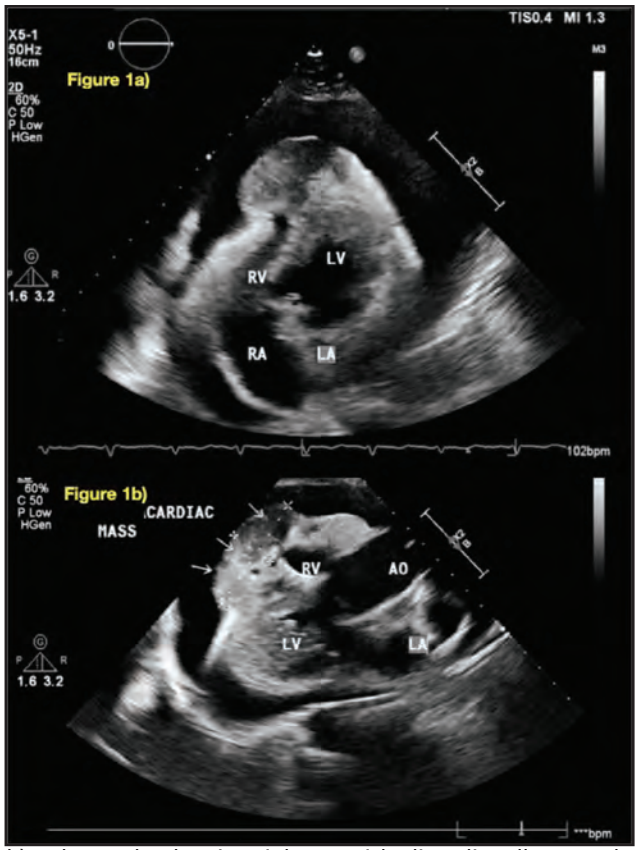

Fig. 1: 1a) and 1b): Echography showing right ventricle diastolic collapse and cardiac mass

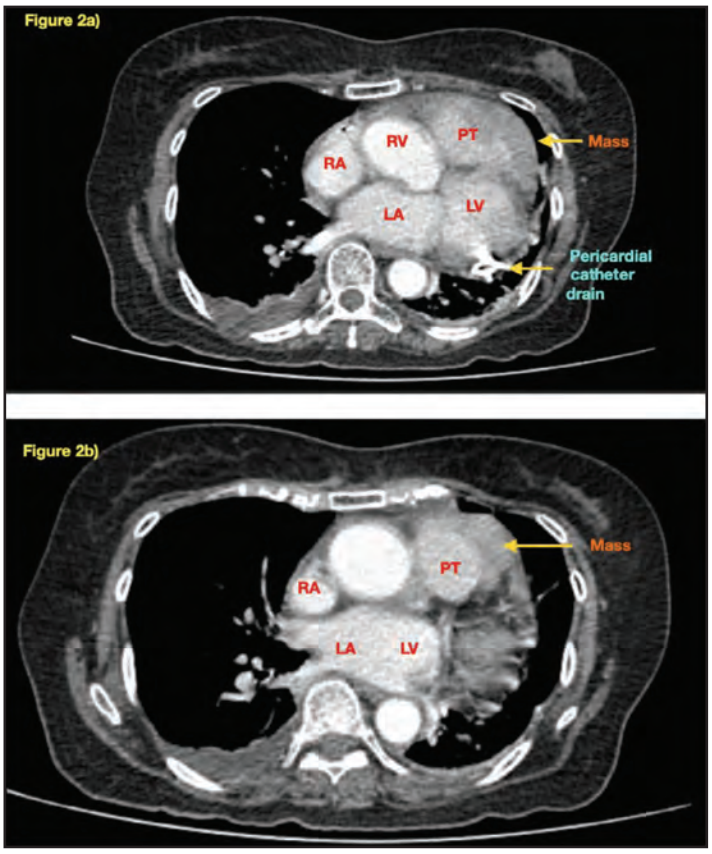

Fig. 2: 2a) and 2b) CECT scan showing cardiac mass (hyperdense crescentic lesion), pericardial catheter drain in situ surrounding pericardial effusion (RA = right atrium, LA= left atrium, RV= right ventricle, LV= left ventricle, PT= pulmonary trunk)

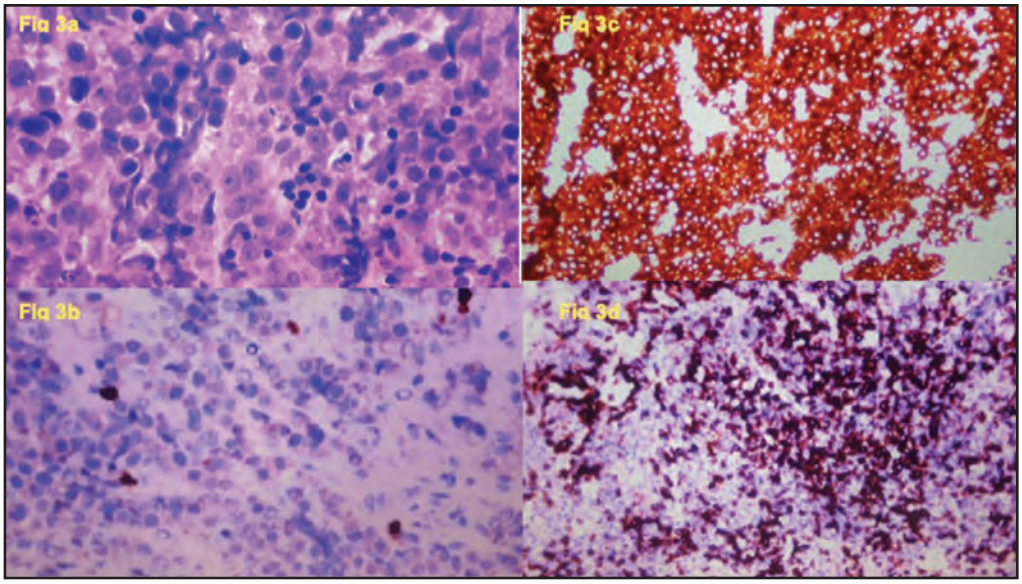

Fig. 3: Immunohistopathology alides from paricardial window biopsy
a) Hematoxylin & Eosin stain: ill defined tumour cells with nucleolar prominence. Moderate to high mitotic activity seen
b) Positive immunohistochemical staining for CD3
c) Positive immunohistochemical staining for CD9a
d) Positive immunohistochemical staining for CD20 Subsequently, the patient was referred to the Haematology team. Chemotheraphy was initiated with Rituximab, Cyclophosphamide, Etoposide, Vincristine, and Prednisolone (CEOP) after staging CT scan. She responded well with resolved pericardial effusion as per repeated echocardiogram post first cycle of R-CEOP

Management and Outcome

Pericardiocentesis drained a total of 1.5L of haemoserous fluid which relieved the patient's failure symptoms drastically and improved hemodynamically. Her blood pressure increased to 140/71 with a pulse rate of 100 post procedure. Pericardial drainage was discontinued after 2 days as there was no further fluid output. CECT showed a hyperdense crescentic lesion within anterior and left pericardium measuring 2.3x6.3x5.0 cm with minimal mass effect onto the adjacent right lateral ventricle; besides mediastinal lymphadenopathies over right lower paratracheal, subcarinal and paraaortic - largest measuring 1.5cm in short axis.

She was referred to the Cardiothoracic (CTC) team for biopsy and discharged well post biopsy. A biopsy via pericardial window over ventricle mass and pericardium presented tumour tissue formed by diffused patternless sheets of malignant medium to large lymphoid cells. The tumour cells possess ill-defined, scanty to moderate amounts of cytoplasm and exhibit hyperchromatic non-cleaved nuclei with nucleolar prominence. Moderate to high mitotic activity and focal tumour necrosis are observed. These cells also expressed bcl 2, CD20, CD79a, LAC and PAX5. 80% of the tumour cells stain positive for c-myc. Ki-67 proliferative index is 70-80%. Stains for ALK, CD3, CD10, CD19, CD21, CD23, CD30, CD56, CK AE1/AE2, Tdt and TTF1 show negative reactivity in the malignant cells.

Combination of her clinical and histopathological features concluded as high grade DLBCL, non-GCB type of intracardiac origin, Ann Arbour stage IVe, International Prognostic Index (IPI) score 3 or National Comprehensive Cancer Network (NCCN) -IPI score of 5. This put her into high-intermediate risk with 51% 5-year progression-free survival and 64% of 5-year overall-survival.

DISCUSSION

This case highlights the importance of recognising uncommon presentations of PC-DLBCL, especially life threatening complications as seen in this patient presenting with cardiac tamponade requiring urgent treatment. The differential diagnosis of a pericardial mass presenting with cardiac tamponade includes malignant metastases, primary cardiac angiosarcoma, and pericardial mesothelioma. Clinical presentation for PCL can be nonspecific, however both DLBCL and PCL are aggressive; with PCL particularly associated with poor outcomes.[5]

Definite diagnosis can be achieved through multimodality diagnostic imaging and/or pathological study (fluid cytology looking for presence of atypical lymphoid cells, immunohistochemistry, flow cytometry, or biopsy). In our case, early echocardiography was a non-invasive simple yet crucial diagnostic tool aiding in diagnosis and relieving the patient's cardiac tamponade in order to stabilise her condition. After that CECT scan confirmed intracardiac mass location - enabling the CTC team to localise the lesion percutaneously for tissue biopsy. Early recognition, accurate multimodal diagnostic imaging, and timely biopsy can significantly influence management decisions and improve patient outcomes. Complication of PC-DLBCL includes heart failure, angina, pericardial effusion, tumour embolisation, direct infiltration/compression of coronary arteries and electrical conduction system.[5,6] The latter manifests as

electrographic (ECG) abnormalities such as atrial arrhythmias and atrioventricular blocks, risking sudden cardiac death.[5]

First-line treatment for PCL is by R-CHOP chemotherapy regime.[4] Myocardial cell necrosis and infiltration by lymphoma cells which lack intercellular cohesion can predispose patients to angina, myocardial dysfunction, arrhythmias, thrombosis or myocardial rupture.[6] Hence, it requires multidisciplinary team monitoring from Cardiology and CTC throughout chemotherapy.

Overall response rate of PC-DLBCL to chemotherapy is 79%. It is reported complete remission of 59% in literature. Radiotherapy can be utilized for cardiac masses refractory to chemotherapy. For patients with coronary stenosis and/or haemodynamic compromise, surgical excision may be used as first line treatment. Despite advances in medicine, patients with PCL have grave prognosis with median survival of 7 months.[7] Although it has a high mortality rate, it can be cured with intense chemotherapy and post chemotherapy surveillance.

CONCLUSION

Isolated cardiac mass presenting as cardiac tamponade is rare in PC-DLBCL. Prompt diagnosis and coordinated multidisciplinary management involving cardiologists, haematologists, and cardiothoracic surgeons are crucial. Chemotherapy tailored by imaging and biopsy findings can achieve favorable outcomes even without surgical intervention, as demonstrated in this case.

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ETHICAL CLEARANCE

Ethical clearance has been obtained from NMRR Secretariat (NMRR ID-24-00408-M3) . Informed consent was obtained from patient/ patient's family members in line with COPE standards for his/her images and other clinical information to be reported in this journal. Due efforts are made to conceal their identity.

DECLARATIONS

The authors have no conflict of interest with respect to the case report.

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The wobbling titan: Acute post-infectious cerebellar ataxia

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SUMMARY

Acute post-infectious cerebellar ataxia (APCA) is a transient neurological disorder commonly observed in children following viral or bacterial infections. This case report describes a five-year-old girl presenting with sudden-onset unstable gait, without focal neurological deficits or systemic symptoms, after a recent febrile illness. Clinical examination revealed a wide-based ataxic gait and bilateral lower limb weakness. Investigations showed no evidence of infection or other neurological pathology. The patient was diagnosed with APCA and managed supportively, leading to complete resolution of symptoms. This case underscores the importance of considering APCA in children presenting with acute ataxia, particularly following recent infections, and highlights the need for thorough evaluation to exclude alternative aetiologies. Early recognition and appropriate management are crucial for favourable outcomes in patients with APCA.

INTRODUCTION

Cerebellar ataxia frequently caused by impairment of cortical signals from the cerebellum that manifest as incoordination in movement, gait abnormalities, changes in speech and eye abnormalities.[1] Acute cerebellar ataxia is known as sudden benign self-limited neurological complications that has temporary cerebellar dysfunction less than 72 hours of duration, in a previously healthy person.[2] It typically occurs in children less than 6 years old with an incidence of 1 in 100,000 to 500,000 and is commonly associated with post infectious autoimmune mechanism following infection from varicella zoster, Coxsackievirus, Echovirus, Enteroviruses, Epstein–Barr virus (EBV), Herpes simplex virus I, Measles virus, Mumps virus, Borrelia burgdorferi, and severe acute respiratory syndrome Coronavirus 2 (SARS–CoV–2).[4] However, the relative mechanism underlying the pathophysiology of cerebellum disruption is still unknown.4 Acute post-infectious cerebellar ataxia (APCA) is usually characterized by sudden ataxia following a period of illness and may present with other neurological sign and symptoms such as nystagmus, hypotonia, tremor or scanning of speech.[5] It is a diagnosis of exclusion after excluding other causes of ataxia with a thorough history that supports recent infection, clinical examination and biochemical tests. Imaging and lumbar puncture are not specific and can be deferred with watchful waiting under a close neurological follow-up.[4,6] Recovery varies from more than 2 weeks to months and complete recovery may take up to several months to years.[6]

CASE PRESENTATION

A five-year-old girl was first seen at the primary clinic during an acute presentation. She was brought in by her mother, who reported a complaint of unstable gait for the past two days. This episode was the first occurrence, and its sudden onset was noticed by the mother after the child woke up from sleep. The mother denied any worsening of the child's unstable gait. There were no speech abnormalities, dysphagia, headaches, gastrointestinal issues, or urinary/bowel incontinence reported. Additionally, there were no seizure episodes, traumas, fevers, or syncopal attacks. The child appeared to be active as usual with a normal appetite. The mother denied any clumsiness or recurrent falls prior to this incident. However, there was a history of fever with upper respiratory tract symptoms two weeks before the current presentation, lasting only five days. The child was treated symptomatically with paracetamol and subsequently recovered well.

Further history revealed that the child was born via emergency lower segment caesarean section (LSCS) due to failed induction at term, with a good birth weight. There was no prolonged admission following birth. However, the child had a history of meningitis at two months old, with no resulting neurological impairment, and she recovered well thereafter. She is immunocompetent, and her immunizations are up to date. There was initially noted to be a delay in speech until three years old; however, the child is now able to speak in four to five word sentences. Otherwise, gross motor, fine motor, and social skills are normal.

Returning to her current examination, she appeared well, with a normal colour, no respiratory distress, and no dysmorphic features. No saccadic abnormalities or meningeal signs were observed. During her gait examination, it was noted that the child had an unstable, wide-based ataxic gait. Vital signs were normal, and her height and weight were within the normal range. Examination of the throat, lungs, and cardiovascular systems revealed no abnormalities. Due to the child's lack of cooperation, cranial nerve and cerebellar examinations were not performed. However, no muscle atrophy was observed. Examination of the central nervous system in both the upper and lower limbs demonstrated a power of 4/5 in the upper limbs and proximal lower limbs and 3/5 in the distal lower limbs bilaterally. Both the upper and lower limbs had normal tone, reflexes, and sensation, with no fasciculations observed. The provisional diagnosis was acute cerebellar ataxia, and the child was referred to the emergency department for further evaluation.

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Upon admission, the child was afebrile, alert, and active. Her ataxia was observed to be gradually improving, and no new neurological symptoms developed during her hospital stay. Initial neurological assessment showed muscle strength graded at MRC 3–4/5; however, this was likely due to coordination difficulties from ataxia and limited cooperation during examination, leading to a false impression of muscle weakness. The child's progressive clinical improvement supported that the apparent weakness was functional and secondary to ataxia, rather than indicative of a primary neurological deficit. Throughout her admission, she demonstrated consistent neurological findings, including a wide-based ataxic gait without clonus or upper motor neuron signs. Power and tone were preserved, and no cranial nerve deficits were observed. Despite initial unsteadiness, she was able to climb onto the bed, walk with support, and eventually ambulate with minimal assistance. Her vital signs remained stable, and no signs of clinical deterioration were noted. Basic laboratory work-up including full blood count, renal and liver function tests, inflammatory markers (C-Reactive Protein, Erythrocyte Sedimentation Rate), and electrolytes were performed and yielded normal results. These findings helped rule out infective, inflammatory, or metabolic causes, further supporting a diagnosis of exclusion. In view of the reassuring progression, absence of red flags, and results indicating a ruling out or resolved infective process, neuroimaging was deemed unnecessary at that point.

The paediatric neurology team decided not to perform neuroimaging or lumbar puncture during the acute phase because of the clear signs of clinical improvement and the absence of any concerning features (such as altered consciousness, severe headache, focal deficits, or signs of increased intracranial pressure). She was diagnosed as Acute post infectious cerebellar ataxia (APCA) supported by the improvement of her motor exam over time reinforcing the likelihood of a pure cerebellar ataxia rather a concurrent motor pathology. She was managed conservatively with paracetamol and regular clinical monitoring. Physiotherapy was initiated during the admission and continued as outpatient post-discharge. A 4-day inpatient observation was sufficient to ensure symptom stabilization. The child achieved full recovery within two weeks of discharge. At the three-month follow-up, she remained clinically well with no residual ataxia. At the six-month consultation conducted via phone, the child was reported to be well with no residual impairment.

DISCUSSION

Acute post-infectious cerebellar ataxia (APCA) emerges as the primary consideration in children presenting with acute ataxia.[3] APCA may arise following viral or bacterial infections, or even post-vaccination, typically manifesting within days to weeks.[7] Notably, studies have demonstrated autoimmune reactivity targeting cerebellar Purkinje cells post-infection, shedding light on the underlying pathophysiology. However, the precise mechanisms driving cerebellar disturbance remain elusive.[4]

While cerebrospinal fluid (CSF) analysis has been investigated in cases of APCA, its diagnostic yield appears limited, with lumbar puncture generally warranted only in cases of suspected meningitis.[8] Life-threatening or surgical pathology as an etiology for acute ataxia in children is rare, but it is important to remain vigilant to avoid missing the diagnosis. Life-threatening etiologies of ataxia can be classified into four categories: strokes, neoplasms, infections and/or inflammations, and toxic ingestions.[9]

For instance, ataxia due to a brainstem lesion, cerebral hemorrhage, brain infarction, or posterior fossa tumors (such as medulloblastoma or cerebellar astrocytoma) is usually accompanied by warning neurological signs and symptoms such as progressive headache, vomiting, altered consciousness, papilledema, cranial nerve involvement, or long tract dysfunction. In this case, none of these worrisome signs and symptoms were present apart from the ataxia.[9]

Moreover, the presentation of ataxia was acute and non-progressive, and upon close observation, her condition was improving. These characteristics are highly suggestive of APCA and are unlikely to be associated with structural lesions, which usually cause a progressive or steadily worsening course of neurological deficits rather than spontaneous recovery. Therefore, a surgical mass lesion or cerebellar tumor was deemed clinically unlikely, eliminating the urgent need for neuroimaging. On the other hand, toxic ingestion and trauma were considered the least likely based on the history and normal systemic examinations.[9]

Furthermore, a thorough differential diagnosis of acute cerebellar ataxia is essential, encompassing conditions such as Guillain-Barré syndrome, acute cerebellitis, acute disseminated encephalomyelitis (ADEM), and labyrinthitis. It is crucial to distinguish APCA from acute cerebellitis, as the latter represents the most severe end of a continuous clinical spectrum originating from APCA.[9] In general, children with acute cerebellitis present with more severe symptoms such as vomiting, fever, altered mental status, other signs of meningeal irritation, or seizures, and appear more ill compared to those with APCA.[9] In such cases, neuroimaging such as brain MRI typically shows inflammatory changes and may require urgent intervention.

Opsoclonus-myoclonus syndrome (OMS) is another immune-mediated paraneoplastic encephalopathy that may be difficult to distinguish from APCA in the early stages. However, unlike APCA, OMS does not show rapid improvement and is usually accompanied by additional symptoms such as feeding difficulties, regression, sleep disturbances, rapid saccadic eye movements, and paroxysmal movements. Hence, if there is minimal improvement with paroxysmal limb or eye movements, it is essential to consider OMS.[9]

Immune-mediated forms such as acute disseminated encephalomyelitis (ADEM) are typically severe at onset and occur in the context of viral or post-viral infections. The most typical symptoms of ADEM include bilateral or unilateral pyramidal signs (60–95%), acute hemiplegia (76%), ataxia (18%–65%), and cranial nerve palsies.[9]

Guillain-Barré syndrome (GBS) is another immune-mediated condition that presents with symmetrical weakness and progressive ataxia. Younger children may present with

symptoms such as meningeal signs, leg pain, vomiting, and agitation, while neurological examination reveals reduced or absent muscle stretch reflexes. Additional symptoms such as oculomotor paresis may increase suspicion for the variant of GBS known as Miller-Fisher Syndrome (MFS).[9]

Labyrinthitis presents similarly to APCA but is distinguished by additional symptoms such as vertigo, more severe systemic illness, and prominent vomiting. While nystagmus can occur in both conditions, it is typically more pronounced and persistent in labyrinthitis. In contrast, in APCA, if nystagmus is present, it is usually mild and not a dominant feature.[9]

Distinguishing among these entities necessitates meticulous history-taking, physical examination, and further investigative workup.[10] Neuroimaging, such as brain MRI, was not performed in our case because APCA usually shows no abnormalities on MRI. However, severe forms, such as acute cerebellitis, can present with neurological and systemic symptoms along with cerebellar or meningeal inflammatory changes on MRI.[6]

APCA, particularly in children, is often a clinical diagnosis based on a history of rapid-onset ataxia following a prodromal viral illness, with exclusion of serious or life-threatening conditions.[7] Neuroimaging is typically not required unless symptoms are atypical or concerning.[7] In addition, the clinical decision to avoid neuroimaging was reinforced by ongoing improvement during observation, supporting a transient and functional disturbance rather than a structural lesion. This approach is supported by evidence from Nussinovitch et al., which recommends neuroimaging only in cases where there is no improvement in 1–2 weeks, and Segal et al., who concluded that observation is safe in typical APCA cases in young children with recent viral illness and no additional neurological findings.[2, 5] These evidence-based recommendations support the decision of the clinician to carefully monitor the patient in the hospital for any new neurological signs or deterioration.

The child showed significant clinical improvement, suggesting a transient dysfunction rather than a structural lesion, thus making imaging unnecessary. A conservative approach was adopted and continuously reassessed to avoid unnecessary sedation and imaging, provided the child's safety was not compromised. In this case, the absence of focal neurological signs, negative blood investigations for infection, and the patient's uneventful clinical course along with complete resolution of the ataxic gait after discharge support the diagnosis of acute post-infectious cerebellar ataxia (APCA), which typically requires only conservative symptomatic treatment and regular follow-up to ensure full recovery.[6]

Empirically, there is still a lack of strong evidence on the effectiveness of corticosteroids or IVIG as treatment for APCA.[1] Nonetheless, several case reports have noted marked improvement following treatment with corticosteroids or IVIG. These considerations may be discussed on a case-by-case basis in the absence of consensus protocols. Furthermore, some research has indicated that autoimmune cerebellar ataxia may be effectively treated with IVIG. Therefore, clinicians may consider steroids, antivirals, or IVIG in cases with persistent symptoms, signs of inflammation, or suspected immune-mediated pathology.[1]

While APCA stands as the leading cause of acute ataxia in children, its association with various infections underscores the importance of vigilance among clinicians. Nevertheless, before reassuring families and initiating supportive care, a thorough evaluation to rule out more ominous pathologies remains paramount.

CONCLUSION

In summary, acute post-infectious cerebellar ataxia (APCA) is a common cause of acute ataxia in children, often triggered by viral or bacterial infections. While the exact causes are not fully understood, autoimmune reactions targeting cerebellar cells post-infection are suspected.

Diagnosing APCA relies on thorough clinical evaluation and ruling out other possible causes. In our case, the absence of serious symptoms, coupled with negative test results and the child's swift recovery, supported the diagnosis of APCA.

Early recognition and proper management led to the child's complete recovery, emphasizing the importance of prompt diagnosis and follow-up for children with acute ataxia. Clinicians must remain vigilant for APCA in such cases, ensuring thorough evaluation before reassuring families and providing supportive care. Further research is needed to better understand APCA and improve treatment strategies.

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CASE REPORT

Acute suppurative thyroiditis complicated by Klebsiella infection: A case report

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SUMMARY

Thyroid gland is naturally resistant to infection due to its unique anatomy and physiology. Acute suppurative thyroiditis (AST) is therefore a rare occurrence on its own, making this reported case occurring without any predisposing factors even more unusual. We present a case of AST with Klebsiella pneumoniae thyroid abscess in an elderly non diabetic Malay gentleman. This abscess was complicated with Klebsiella infection and was surgically treated with a hemithyroidectomy.

INTRODUCTION

The thyroid gland is typically resistant to infection due to its well-developed capsule, high iodine and hydrogen peroxide content, and extensive vascular and lymphatic systems.[1,2] Early detection and treatment of any thyroid infection are crucial to prevent severe complications and long-term effects. Other than that, distinguishing acute suppurative thyroiditis from subacute thyroiditis is essential, as the two conditions require entirely different management approaches. It is also important to identify the predisposing risk factors and treat them accordingly to prevent recurrent infection.

CASE PRESENTATION

A 77-year-old Malay man with a history of benign prostatic hypertrophy presented to the Emergency Department with generalized lethargy, which led to a fall. Upon evaluation, the patient reported a sudden onset of painful swelling in the left anterior neck over the past 3 days which had gradually increased in size associated with hoarseness. He also experienced lethargy and reduced appetite but denied any dysphagia, odynophagia or aspiration symptoms. There were no restricted neck movement, stridor or shortness of breath. Additionally, he was non diabetic and showed no other symptoms of thyroid dysfunction, fever or constitutional symptoms. There was also no history of smoking or alcohol intake.

On examination, he appeared comfortable with stable vital signs and no signs of respiratory distress. Additionally, there were no signs indicative of chronic hyperthyroidism. A diffuse swelling measuring approximately 10 cm x 6 cm was noted on the left side of the neck, extending from midline to left lateral neck involving the sternocleidomastoid muscle. The swelling was tender and firm on palpation without overlying skin erythema or warmth. It was fixed, making it impossible to palpate beneath the mass. The trachea was slightly deviated to the right, and no other cervical lymph nodes were palpable. Hoarseness was also present and there was no restricted neck movement. Intraoral examination was normal while flexible nasopharyngolaryngoscopy showed left vocal cord palsy at paramedian position, partially compensated by the mobile right vocal cord. There was no pharyngeal wall medialization and no abnormalities seen at the pyriform sinus.

Both total white cell count and C-reactive protein (CRP) were raised at 18.9 10^9/L and 25 mg/l respectively and patient was started on intravenous amoxycillin-clavulanate 1.2g TDS. Sugar level was normal however thyroid function test showed hyperthyroidism where T4 was elevated at 20.78 pmol/L and thyroid stimulating hormone reduced at 0.342 mIU/L . Patient later underwent a contrast enhanced computed tomography (CT) scan of the neck which showed a well defined rounded hypodense lesion of HU 78, seen occupying the left thyroid lobe measuring 4.1x4.7x5.8cm with wall enhancement post contrast and focus calcification at the centre of the lesion. There was presence of significant surrounding perilesional fluid and streakiness at the superior aspect, with fluid tracking along the left carotid space, retropharyngeal space and left submandibular space. There was mass effect to the right onto adjacent hypopharynx, larynx, trachea and esophagus with minimal narrowing of the trachea at the region with narrowest diameter measuring 1.1cm. Left internal jugular vein was also partially compressed however still remain patent. These CT findings were suggestive of infected or hemorrhagic left thyroid nodule with mass effect and significant surrounding inflammatory changes.

Fine needle aspiration cytology (FNAC) of the neck swelling was done under aseptic technique and yielded approximately 45cc of purulent, hemoserous fluid. Cytological examination revealed a hemorrhagic cystic content with numerous inflammatory cells, predominantly neutrophils and lymphocytes. After 5 days of IV antibiotics , he was discharged home with oral antibiotics amoxicillin clavulonic acid but returned to Emergency Department with worsening neck swelling after 4 days at home. An ultrasound guided drainage was arranged and 40cc hemopurulent fluid was drained, however the swelling recurred within days and hence a left hemithyroidectomy was performed on day 4 of admission. Intraoperative findings showed there was presence of left thyroid cystic mass containing hemopurulent

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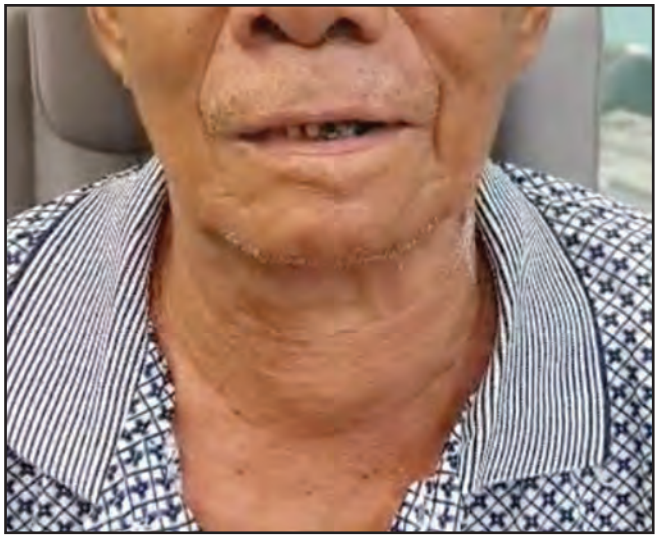

Fig. 1: Left neck swelling

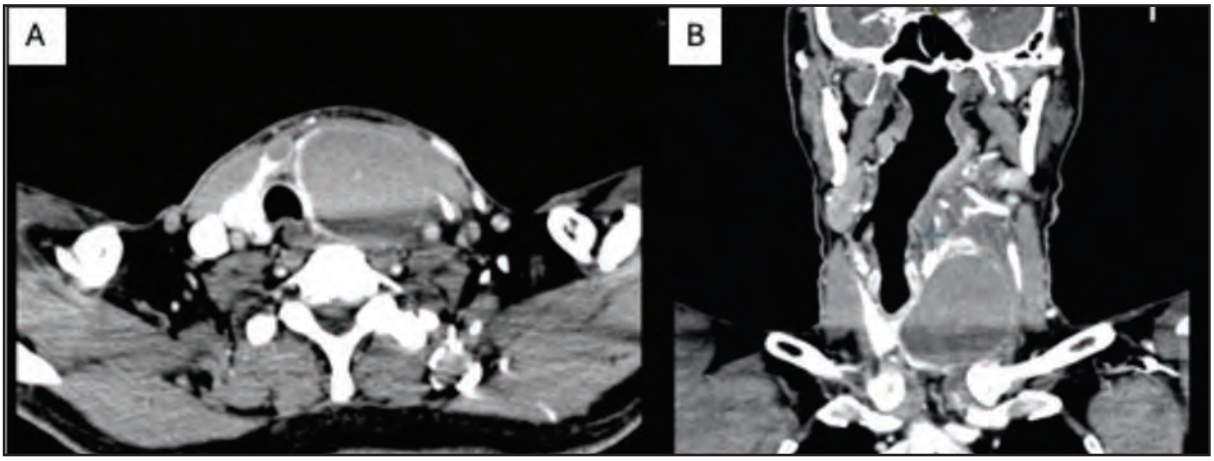

Fig. 2: CT scan (A : axial) and (B : coronal) images of left thyroid mass

fluid, strongly adhered to strap muscles and carotid sheath. The left recurrent laryngeal nerve was identified and preserved, while parathyroid gland were not identified. Histopathological examination showed predominantly neutrophilic abscesses with surrounding granulation tissue suggestive of acute suppurative thyroiditis. Culture and sensitivity came back as Klebsiella pneumoniae sensitive to amoxycillin clavulonic acid.

Post operatively, he recovered well, discharged home on day 4 and completed total course of 10 days of antibiotics. His thyroid function taken at 3 weeks post operative eventually normalised. There were no recurrent neck swelling however his left vocal cord palsy persisted. He required nasogastric tube feeding postoperatively. A swallowing assessment at two months showed no signs of aspiration, allowing him to resume oral feeding. A repeat CT scan in view of persistent vocal cord palsy was done after 3 months which showed no evidence of tumour recurrence. He was offered injection laryngoplasty which he was not keen and subsequently defaulted.

DISCUSSION

Acute suppurative thyroiditis (AST) leading to thyroid abscess, is exceptionally rare because the anatomy and physiology of the thyroid gland make it naturally resistant to infection. The well encapsulated gland with rich blood supply, extensive lymphatic drainage and high iodine concentration inhibiting bacterial proliferation all contribute to this1. In addition , thyroid gland's resistance to infection is also partly due to its continuous production of hydrogen peroxide (H_2O_2), which is essential for thyroid hormone synthesis and also possesses antimicrobial properties. H_2O_2 creates a locally oxidative environment that inhibits microbial growth, contributing to the gland's natural sterility.[2] In some cases of thyroid infection, there may be identifiable predisposing factors such as congenital anomalies like a thyroglossal duct or pyriform sinus fistula, disseminated infection via hematogenous or lymphatic spread or less commonly, trauma that breaches the thyroid capsule, such as biopsy, FNAC or a retained foreign body from prior surgery.[1,3] Nevertheless in many instances, the source of the thyroid infection is not clear and it may be

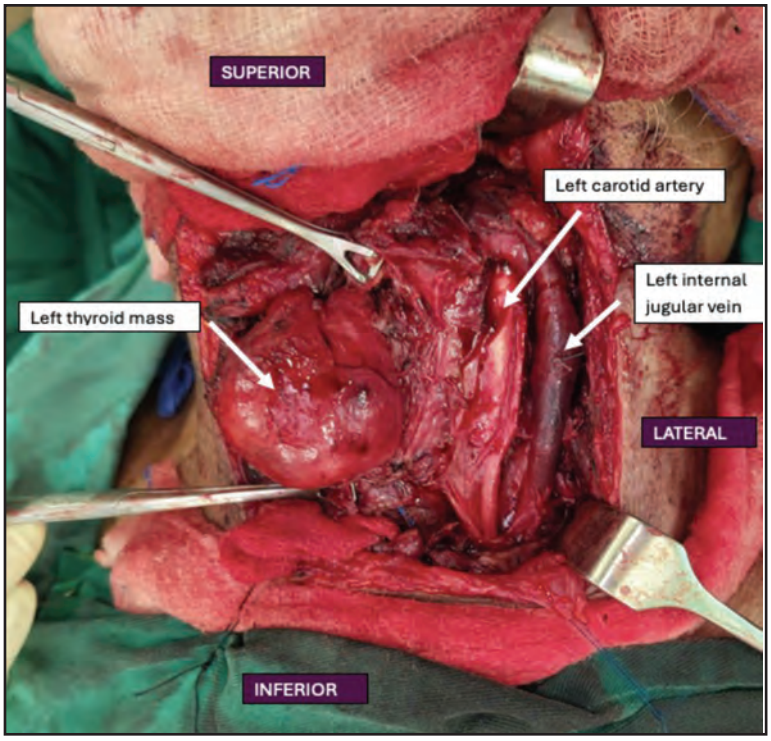

Fig. 3: Intraoperative image , left thyroid mass reflected medially

attributed to the overall immunosuppressive state of the patient e.g. poorly controlled diabetes or other immunosuppressive diseases e.g HIV, although this was not seen in our case.[4]

Mortality rate from AST reported in a systematic review by Lafontaine et al (2020) was said to be around 7.9%, where it is highest with fungal infection.[5] Common presenting symptoms and signs were neck pain, fever, dysphagia, raised white cell count or C-reactive protein with or without hyperthyroidism.[5] Another condition that can present in a similar fashion is subacute thyroiditis or also known as de Quervain's or granulomatous thyroiditis. It is important to differentiate these two as subacute thyroiditis is usually self-limiting and the treatment approach differ where anti-inflammatory and glucocorticoids are first line. In contrast, patients with AST typically present in a more severe, septic state with significantly elevated white cell counts and inflammatory markers. Unlike subacute thyroiditis, they do not respond to glucocorticoids.[5]

In immunocompetent patients, approximately 75% of AST cases are reportedly caused by bacteria, with gram positive organisms being the most common, followed by tuberculosis and fungal infections.[5] Organisms commonly found to be associated with thyroid infection are Staphylococci and Streptococci spp. This is followed by rarer cases of infection by Klebsiella pneumoniae like in our case here or Salmonella spp in other incidents.[6] Klebsiella pneumoniae is a gram negative, rod-shaped organism found as commensals in certain parts of the body like mouth, skin and GI tract where they do not cause any illnesses. In certain cases, these infections can progress to a severe form, with reports highlighting a rise in virulence that results in widespread abscesses. Frequently affected areas include the liver, kidneys, lungs, muscles, thyroid, cerebrospinal fluid and eyes.[7]

Imaging are helpful and some studies suggest that ultrasound is the best in looking at early abscess formation. However, CT is a better modality to delineate the anatomy, extension especially in cases involving deeper and retrosternal space and also pyriform sinus fistula if present.[5] In our case, CT was selected as the imaging modality due to the presence of a complication - vocal cord palsy -which raised concern for deeper extension of the underlying pathology. Needle aspiration is the most conclusive method to confirm AST.[5]

AST carry the risk of complications both from the disease itself and also its management. These include extension of the abscess to cause descending necrotising mediastinitis, pericarditis, deep neck abscesses leading to airway obstruction or dysphagia and also trachea or oesophageal involvement / fistula.[5,6] Some of the patients can also have recurrent laryngeal nerve palsy which will be elaborated later, or persistent thyroid dysfunction as a sequelae of AST.[5]

First line of managing AST is source control and this is moving away from surgical intervention towards less invasive method. Needle aspiration along with intensive antibiotic therapy has become the preferred minimally invasive intervention. However in certain cases like ours, there is still a need for the more conventional method like incision and drainage or hemithyroidectomy especially in very ill deteriorating patients or where there is presence of recurrent laryngeal nerve palsy. This is to alleviate pressure,

reduce the degree of injury with the aim to preserve the integrity of the nerve.[8]

Vocal cord palsy is much more commonly encountered in cases of thyroid malignancy rather than benign ones8. The pathogenesis of vocal cord palsy in benign cases is said to be mainly due to direct compression of the recurrent laryngeal nerve and/or its blood supply by the massive thyroid mass against cervical spine or trachea.[8,9] This can cause neuropraxia and surrounding inflammation leading to recurrent laryngeal nerve dysfunction.[9] Therefore, hemithyroidectomy is recommended for certain benign thyroid tumours associated with vocal cord palsy to alleviate compression and potentially restore nerve function. In our case, the decision to proceed with hemithyroidectomy instead of incision and drainage was made due to persistent vocal cord palsy and the lack of improvement despite two times aspiration, which heightened the suspicion of malignancy, apart from the other indication highlighted earlier.

Vocal cord palsy in benign cases is reported to resolve after thyroidectomy in approximately 89% of cases, some as early as day 3 post operative and others up to 12-18months.[8] However, this was not observed in our case. The reason for this is not clear, as the histopathological examination excluded malignancy and post op CT scan did not show any other abnormalities along the nerve course. The most likely explanation for the persistent vocal cord palsy is probably inflammation.

Following resolution of an acute infection, it is recommended to assess for presence of a pyriform sinus fistula using a barium swallow or contrast enhanced CT with the trumpet manoeuvre, along with microlaryngoscopy5. Evaluation for a pyriform sinus fistula is strongly recommended, particularly in the pediatric population as it is a congenital anomaly. Assessment is also advised in cases of recurrent thyroid abscesses and those affecting the left thyroid lobe, given the higher prevalence reported in previous studies—an observation thought to be linked to embryological development.[10] If present, this is then managed with fistula ablation or excision of fistula tract with or without hemithyroidectomy5. In our case, no fistula or other risk factors were identified. Patient showed good recovery at follow-up, except for the persistent vocal cord palsy, which he was not keen for intervention.

CONCLUSION

Though rare, thyroid abscess or AST poses a significant risk of complications and long-term effects if not identified and treated promptly. It can often be mistaken for subacute thyroiditis; therefore, in more severely ill and septic patients, the possibility of a thyroid abscess should always be considered.

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CASE REPORT

Acute angle closure glaucoma secondary to vitreous haemorrhage in neovascular age-related macular degeneration: A rare complication

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SUMMARY

Acute angle closure glaucoma (AACG) secondary to vitreous haemorrhage is a rare but devastating complication of neovascular age-related macular degeneration (AMD). We report a visually devastating case of AACG in a 60-year-old gentleman with multiple systemic comorbidities. He initially presented with a central scotoma in the left eye and was diagnosed with bilateral AMD with subretinal fibrosis in the left eye. After being lost to follow up, he returned with a new submacular haemorrhage in the right eye, for which intravitreal anti-vascular endothelial growth factor (VEGF) therapy was planned. However, before treatment initiation, he developed sudden painful vision loss, elevated intraocular pressure (IOP) and signs consistent with secondary AACG. Imaging confirmed a massive vitreous haemorrhage with no evidence of intraocular malignancy. Despite aggressive medical therapy, the patient's vision deteriorated rapidly to no light perception, necessitating cyclodiode laser treatment for pain control. This case illustrates the rare but serious complication of vitreous haemorrhage in neovascular AMD with associated risk factors emphasizing the importance of early recognition and intervention to prevent secondary AACG and permanent vision loss.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of severe visual impairment in the elderly.[1] It typically begins with the accumulation of drusen in the macula and may progress to advanced stages, characterized by either neovascular AMD or non-neovascular AMD. In neovascular AMD, abnormal vessel growth often leads to subretinal haemorrhage and other exudative complications. Although vitreous haemorrhage is a known consequence of neovascular AMD, secondary acute angle closure glaucoma (AACG) is an exceedingly rare complication.[2]

In such cases, extensive vitreous haemorrhage can cause forward displacement of the lens–iris diaphragm, resulting in occlusion of the anterior chamber angle and a rapid rise in intraocular pressure (IOP), ultimately precipitating AACG. This acute presentation represents an ophthalmic emergency requiring immediate intervention to prevent irreversible vision loss. Here we report a rare presentation of AACG secondary to vitreous haemorrhage in neovascular AMD, aiming to enhance clinical awareness of this uncommon complication by emphasising its underlying pathophysiology, associated risk factors and the necessity of prompt recognition to avoid diagnostic delay and irreversible vision loss.

CASE PRESENTATION

A 60-year-old gentleman with a history of intravenous drug use, alcohol consumption and multiple comorbidities including diabetes mellitus, hypertension, hyperlipidaemia, iron deficiency anaemia and hepatitis C presented with a three-month history of central scotoma in the left eye. He denied any metamorphopsia, eye pain or history of trauma. Examination revealed a best corrected visual acuity (BCVA) of 6/9 in the right eye and 6/36 in the left eye.

Fundus examination of both eyes revealed macular drusen and subretinal fibrosis in the left eye without retinal haemorrhage. Optical coherence tomography (OCT) showed drusen in both eyes without subretinal fluid, as well as retinal pigment epithelium (RPE) atrophy in the left eye. These findings were consistent with bilateral AMD, with advanced disease and subretinal fibrosis in the left eye. A one month follow up was advised for monitoring, however the patient did not attend the scheduled visit.

Three months later, the patient returned with complaints of bilateral eye metamorphopsia. Best-corrected visual acuity (BCVA) had declined to 6/24 in the right eye and remained at 6/36 in the left eye. Fundus examination of the right eye revealed a submacular haemorrhage approximately three disc diameters in size, located inferotemporally within the vascular arcade, along with extensive subretinal drusen. The right eye showed no signs of diabetic retinopathy, while the left eye demonstrated mild non-proliferative changes, with no other significant differences from previous findings (Figure 1). OCT demonstrated multiple haemorrhagic PED and subretinal fluid (SRF) in the right eye (Figure 2). The diagnosis of neovascular AMD was made clinically based on funduscopic and OCT findings, as FFA and ICG were not performed for this patient. A treatment plan was initiated,

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Table 1: Summary of published case report on acute angle closure in neovascular AMD/ PCV

Author (year)	Age (year)	Primary pathology	Mechanism of acute angle closure	VA & IOP (mmHg)	Risk factors	B-scan findings	Treatment (besides medication)	Final outcomes
Chen et al.[6] (2000) (case 1)	57	nAMD	Bullous haemorrhagic RD	HM, 67	DM, HPT, HPL, CVA	Massive subretinal hematoma, bullous haemorrhagic RD	-	Phthisical eye
Chen et al.[6] (2000) (case 2)	78	nAMD	Diffuse subretinal / choroidal haemorrhage	NPL, 50	Coronary artery disease (post CABG)	Haemorrhagic RD temporo-inferior	Sclerotomy and blood drainage and AC	Phthisical eye
Chen et al.[6] (2000) (case 3)	55	nAMD	Haemorrhagic RD	CF, 42	HPT, HPL, hyperglycaemia	Haemorrhagic RD temporo-inferior	reformation Sclerotomy and drainage	VA HM
Chen et al.[6] (2000) (case 4)	67	nAMD	Total haemorrhagic RD	Not documented, 70	DM, HPT, HEP C	Diffuse subretinal haemorrhage with total RD	Sclerotomy and AC reformation	Phthisical eye
Baskaran et al.[8] (2017) (case 1)	67	PCV	Annular haemorrhagic CD	NPL, 50	DM, HPT	Annular haemorrhagic CD with “kissing choroids”	CPC diode laser	Phthisical eye
Baskaran et al.[8] (2017) (case 2)	71	PCV	Annular haemorrhagic CD	NPL, 40	DM, HPT	Annular haemorrhagic CD with “kissing choroids”	CPC diode laser	Phthisical eye
Jersey et al.[4] (2020)	80	nAMD	VH	NPL, 74	Post IVT injection	VH, severe narrowing of anterior chamber angle	-	VA NPL

nAMD; neovascular age-related macular degeneration; PCV, polypoidal choroidal vasculopathy; DM, diabetes mellitus; HPT, hypertension; HEP C, hepatitis C; HPL, hyperlipidaemia; CVA, cerebrovascular accident; CABG, coronary artery bypass graft; AC, anterior chamber; RD, retinal detachment; VH, vitreous haemorrhage; VA, Visual acuity; CF, counting finger; HM, hand movement; NPL, non-perception to light; CPC, cyclophotocoagulation

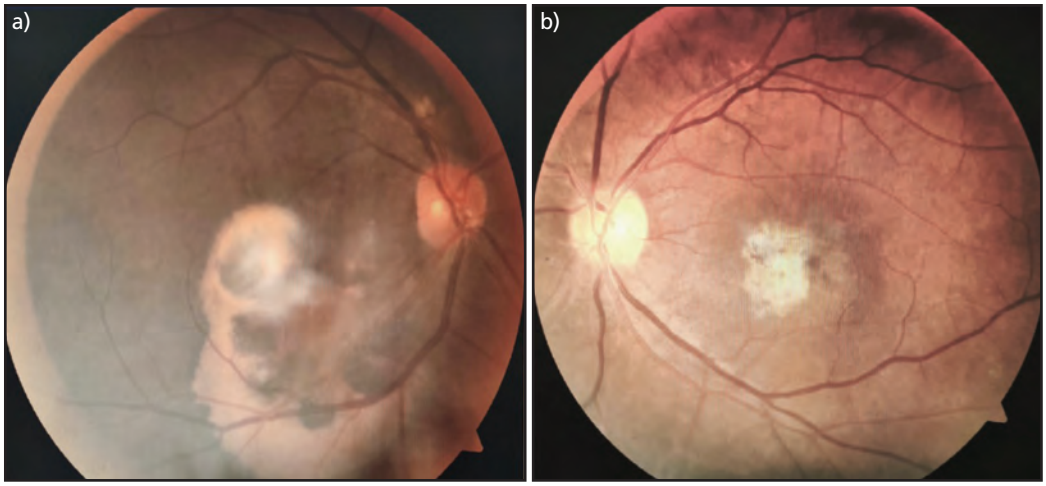

Fig. 1: a) Right eye fundus showed a submacular haemorrhage inferotemporally with extensive subretinal drusen
b) Left eye fundus showed macular subretinal fibrosis and dot haemorrhage at inferonasal area

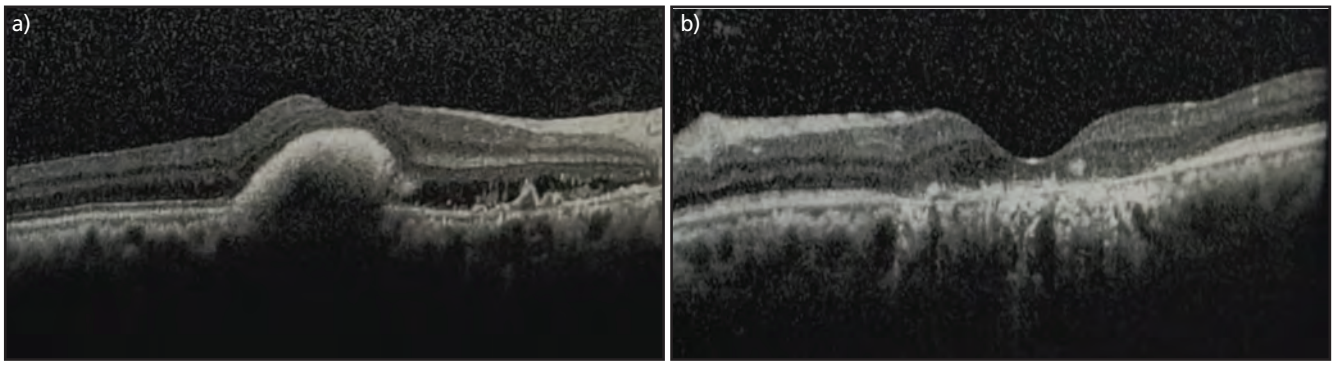

Fig. 2: a) Right eye OCT showed haemorrhagic PED, multiple drusen and SRF
b) Left eye OCT showed outer retinal layer atrophy

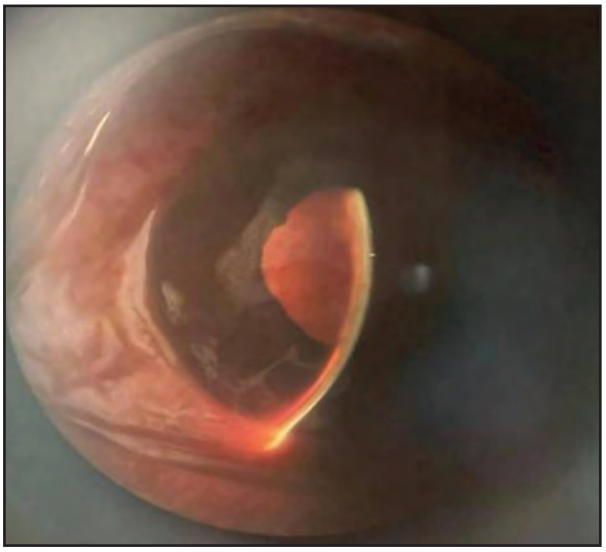

Fig. 3: Slit lamp photograph of the anterior segment of the right eye shows a flat anterior chamber with iridolenticular touch to the cornea

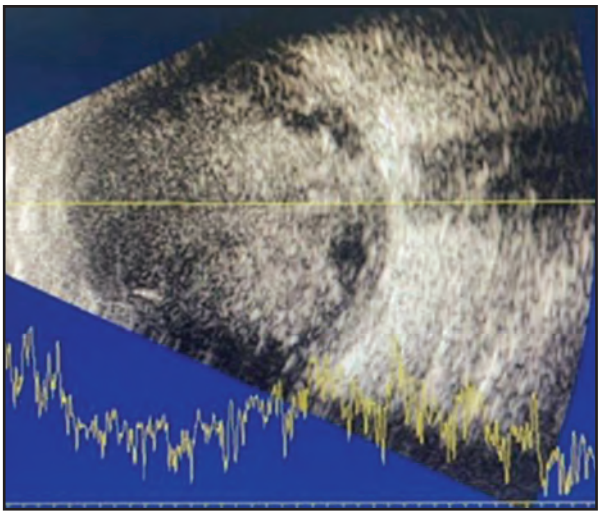

Fig. 4: B-scan ultrasound of the right eye shows dense, diffuse vitreous haemorrhage with no evidence of a retrolenticular mass

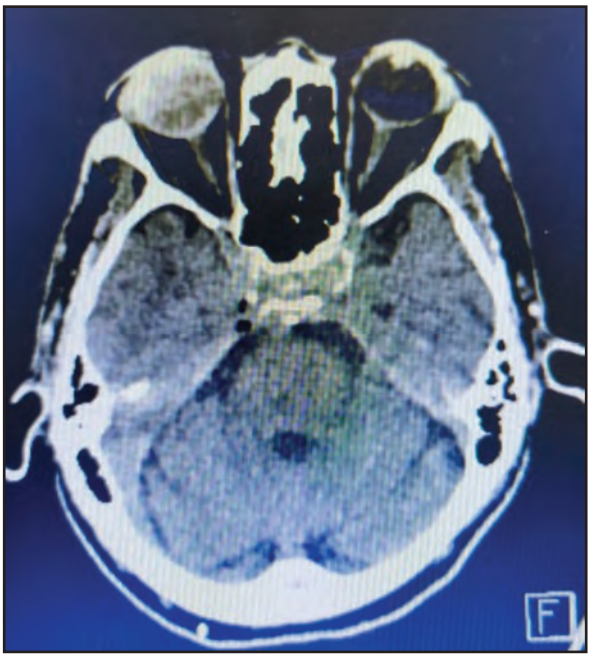

Fig. 5: CT scan of the orbit in the axial plane showed a diffuse heterogeneous hyperdensity within the vitreous chamber of the right eye, suggestive of vitreous haemorrhage

consisting of monthly intravitreal anti-vascular endothelial growth factor (VEGF) injections for the right eye over a three month period.

Two months later, the patient was scheduled for his first intravitreal injection. However, one week before the procedure, he developed a three day history of acute onset painful redness in the right eye, progressive visual loss, headache, nausea, and vomiting. He denied any recent ocular trauma or procedures performed outside the institution. On examination, BCVA was hand movement in the right eye and 6/36 in the left eye. A positive relative afferent pupillary defect (RAPD) was noted in the right eye. The cornea was edematous, the anterior chamber was shallow with endothelial touch and the pupil was mid-dilated, fixed and non-reactive (Figure 3). Fundus visualization in the right eye was obscured by a dense, reddish retrolental hue. The left fundus remained unchanged from previous examinations. IOP was markedly elevated at 50 mmHg in the right eye and 14 mmHg in the left eye. Gonioscopy evaluation demonstrated closed angles in the right eye and open angles in the left, with no signs of rubeosis iridis or peripheral anterior synechiae.

B-scan ultrasonography showed a large hyperechogenic shadow in the posterior chamber of the right eye suggestive of vitreous haemorrhage without evidence of an intraocular mass (Figure 4). CT imaging of the orbit ruled out intraocular malignancy (Figure 5). The patient was admitted for IOP control and managed with a combination of a single stat

dose of intravenous acetazolamide 500 mg, oral acetazolamide 250 mg four times daily, topical latanoprost 0.005% at night, topical timolol 0.25% twice daily, topical dorzolamide 2% three times daily, topical brimonidine 0.15% three times daily, topical dexamethasone 0.1% every four hours and oral glycerol syrup 30 mL three times daily during the ward stay. Oral celecoxib 200 mg twice daily and oral paracetamol 1 g four times daily were prescribed for pain control. Despite these interventions, the patient experienced persistent pain and high IOP, rapid progression to no light perception vision over the next day of admission and worsening corneal edema. As the patient's vision had declined to no light perception with no potential for recovery, surgical intervention was not indicated. Transscleral cyclodiode photocoagulation (TSCPC) was performed to control intraocular pressure and alleviate ocular pain, resulting in marked symptomatic improvement. However, the right eye subsequently progressed to phthisis on further follow-up. This case highlights the progression of neovascular AMD with secondary complications, AACG from vitreous haemorrhage causing in poor visual outcomes despite timely interventions.

DISCUSSION

Massive intraocular haemorrhage leading to AACG is a rare sequela of neovascular AMD and is often associated with at least one predisposing factor, such as oral anticoagulant use, blood dyscrasia, or systemic hypertension.[3] Although the exact mechanisms leading to vitreous haemorrhage in neovascular AMD remain unclear, breakthrough vitreous haemorrhage is reported more frequently in polypoidal choroidal vasculopathy than in exudative AMD.[4]

Previous studies have identified histologically that disciform scars with choroidal neovascularization in AMD as the primary source of haemorrhage in most cases.[3,5] When these abnormal vessels extend into fibrous scars, mechanical stress increases the risk of rupture, producing massive haemorrhages that penetrate all retinal layers and extend into the vitreous. The vitreous haemorrhage causes increased pressure in the posterior chamber, leading to forward displacement of the iris-lens diaphragm. This forward shift results in sufficient iris displacement to obstruct aqueous outflow in the anterior chamber, ultimately culminating in acute angle closure glaucoma.

Unlike suprachoroidal haemorrhage, which often occurs during hypotony, surgery or rarely from anticoagulation, bleeding in neovascular AMD typically follows mechanical disruption of choroidal neovascular membranes and often preceded by submacular haemorrhage.[3,5] Clinical observations support this mechanism. Chen et al., in their follow-up of two cases of neovascular AMD with submacular haemorrhage and a case with a disciform scar reported that severe eye pain and elevated intraocular pressure developed 2–4 weeks after the onset of rapidly progressive visual blurring and visual field defects.[6]

As demonstrated in this case, the patient had a documented submacular haemorrhage prior to the onset of vitreous haemorrhage, during which a course of three consecutive intravitreal injections was planned. This approach is consistent with current evidence indicating that anti-VEGF therapy either alone or in combination with pneumatic displacement using intravitreal tissue plasminogen activator (tPA) is generally preferred for medium-sized submacular haemorrhages.[7] Monotherapy was selected in this instance as it is less invasive, well-tolerated, and effective in suppressing choroidal neovascular membrane activity.[7]

Impaired local haemostasis is a recognized predisposing factor for massive intraocular haemorrhage in macular degeneration, particularly among patients taking anticoagulants such as warfarin or NSAIDs, or those with systemic conditions like diabetes mellitus.[3,6,8] In this case, the vitreous haemorrhage may have been influenced by the patient's systemic comorbidities particularly diabetes mellitus, anaemia and chronic hepatitis C which are associated with increased vascular fragility. Although the patient was not receiving anticoagulant therapy, microvascular compromise due to diabetes and systemic hypertension likely contributed to the haemorrhagic event. Additional systemic risk factors, such as advanced age and arteriolosclerosis, may further increase vascular fragility, rendering vessels more susceptible to mechanical shearing forces.[8] A summary of cases and associated risk factors reported in AACG secondary to neovascular AMD or related pathologies, such as polypoidal choroidal vasculopathy (PCV), is shown in Table I.

Management of AACG secondary to massive subretinal or vitreous haemorrhage remains a significant clinical challenge, often associated with poor outcomes. Medical therapy alone is frequently inadequate for controlling IOP and many cases reported in the literature have required enucleation or cyclodestructive procedures to relieve intractable pain.[5,6,8] In the present case, conservative treatment failed to control IOP, necessitating cyclophotocoagulation for pain management. Although timely surgical interventions such as sclerotomy, haemorrhage drainage or anterior chamber reformation may reduce IOP and provide symptomatic relief, these procedures rarely restore useful vision.[5,6,8] Importantly, the timing of surgical intervention appears to play a critical role in outcomes. Prolonged elevation of IOP can result in irreversible ischemic damage to intraocular tissues and lead to phthisis bulbi. In contrast, early intervention aimed at decompressing the globe and restoring IOP may help preserve ocular structure and alleviate pain, although visual recovery remains limited.[5] Therefore, in cases where IOP is refractory to medical management, prompt surgical consideration is essential not with the aim of restoring vision, but to prevent irreversible structural damage and improve patient comfort.

CONCLUSION

Acute angle closure glaucoma secondary to vitreous haemorrhage is a rare but vision threatening complication of neovascular AMD. This case highlights the importance of regular follow up, recognition of systemic and ocular risk factors and early intervention to mitigate pain and preserve ocular integrity even when visual recovery is limited.

ACKNOWLEDGEMENTS
None

DECLARATIONS
Written consent was obtained from the patient including the use of anonymized medical data and images for the publication of this case report, ensuring compliance with ethical standards.

CONFLICT OF INTEREST
None declared.

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CASE REPORT

Unveiling the mystery: Late detection of global developmental delay and hypotonia linked to ring chromosome 22

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SUMMARY

Ring chromosome 22 syndrome (r(22)) is a rare chromosomal disorder first described by Weleber et al. in 1968. Due to lack of clinical recognition and low suspicions, the syndrome is under-diagnosed, and its true incidence remains unknown. We present a case report of a patient diagnosed with r(22) syndrome, exhibiting features of global developmental delay (GDD), hypotonia and autism. The case, a three-year-old girl, presented with developmental delays in motor, cognitive, and language domains, accompanied by generalized hypotonia. Karyotyping revealed the presence of a ring chromosome 22 with deletion q13.3 (r(22q13)). The clinical manifestations, genetic findings, and management strategies of this rare syndrome were discussed in detail. This case report highlights the importance of early basic karyotyping in the investigations of a child with GDD, hypotonia and autism. This also underscores the importance of early recognition of GDD and hypotonia by primary care workers, leading to multidisciplinary intervention to improve developmental gains and quality of life for individuals with r(22) syndrome. The diagnosis of r(22) syndrome should be considered in all individuals with hypotonia of unknown aetiology with speech delay.

INTRODUCTION

Ring chromosome is a rare type of intra-chromosomal structural abnormality with an estimated occurrence of 1 in 50,000 newborns. There are two structural types, which are complete ring chromosome without the loss of genetic materials by telomere-telomere fusion or an incomplete ring.[1] There are various types of ring chromosomes identified but the most frequently seen were ring 13 (14%), X (12%), 22 (10%), 15 (9%), 14 (7%), and 18 (7%).[2] Ring chromosome is diagnosed via karyotype analysis. In clinical practice, most pediatric patients with ring chromosomes are detected through unexplained global developmental delay especially speech domain, growth retardation, hypotonia and intrauterine growth restrictions.[2] The clinical features vary depending on the phenotype and genomic anomalies include terminal deletions of 22q13 (89%), terminal deletions and interstitial duplication (9%), and interstitial deletions (2%).[3] Differential diagnosis for this includes Prader-Willi, Fragile X, velocardiofacial syndrome (deletion 22q13), Williams syndrome, autism spectrum disorders and cerebral palsy.[4] Patients with this syndrome warrant a referral to clinical geneticists for explanation on the variability of the phenotype, including the physical, developmental and behavioral aspects, the relationship between genotype and phenotype and the natural history of the syndrom.[4] In addition, the clinical geneticist can determine the indication for genetic testing of family members and the method of this investigation.[4]

This case report describes the clinical presentations of the child, investigations done prior to detection of abnormal karyotype and the management of the child with r22. This case also highlighted the importance of early detection by primary care during follow-up to improve the quality of life for the individual and optimization of the management.

CASE PRESENTATION

Our case was a three-year-old girl with GDD, hypotonia and autism. She was delivered to a 29-year-old woman via elective Lower Segment Caesarean Section (ELLSCS) at 38 weeks of gestation due to breech presentation. Her parents were not related, and it is not a consanguineous marriage. She was youngest out of three siblings and her two elder brothers were healthy. There was no family history of any syndrome or inherited diseases in the family. She had her routine follow-up at the health clinic as per schedule for immunizations and growth. Her height and weight were within normal range throughout the follow up in the health clinic except for her head circumference noted to be below -2SD in growth chart at the age of three months which over time, after nine months old the head circumference achieved normal size for age.

At the age of one-year-old, her development was noticed to be significantly delayed as compared to other children and her own siblings but was not addressed by the health clinic personnel during follow-up. Until she was one year and five months, she was finally referred to the Paediatric Clinic for further evaluation. At this presentation, her developmental age was six to nine months old where for gross motor, she was able to sit unsupported and crawl, but not able to pull to stand. For fine motor, she demonstrated inferior pincer grasp and pointing at distant object with index finger, however, not able to bang two cubes or hold pencils to scribble. She responded to her name; however, she was unable to

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Table I: Baseline investigations and results

Investigations	Results	Units	Range
Full blood count			
White cell count	14.7	109 / L	4.0 – 11.0
Haemoglobin	11.9	g/ dL	11.5 – 16.0
Hematocrit	39.7	%	35 – 47
Platelet	285	109/ L	150 – 400
Renal Profile			
Urea	4.0	mmol / L	1.8 – 6.0
Sodium	136	mmol / L	135 – 145
Potassium	4.7	mmol / L	3.5 – 5.0
Chloride	100	mmol / L	98 – 107
Creatinine	40	umol / L	31 - 52
Calcium	2.67	mmol / L	2.25 – 2.75
Magnesium	0.82	mmol / L	0.70 – 0.95
Phosphate	1.69	mmol / L	0.74 – 1.52
Liver Function Test			
Total Protein	74	g / L	56 – 75
Albumin	43	g / L	38 – 54
Globulin	31	g / L	20 – 39
Alkaline Phosphatase	253	U / L	<500
Aspartate Transaminase	42	U / L	5.0 – 34.0
Alanine Transaminase	30	U / L	5.9 – 37.0
Total Bilirubin	3.9	umol / L	5.1 – 20.5
Lactate	3.4	mmol / L	0.5 – 2.2
Ammonia	57	umol / L	18 - 72
Creatinine Kinase	118	U / L	34-204
Thyroid Function Test			
Thyroid stimulating hormone (TSH)	0.96	mIU / L	0.35 – 4.94
Free T4	11	pmol / L	9.00 – 19.00
IEM, blood	Non-significant changes of one or more acylcarnitines / amino acids		

understand "no" or "bye-bye". Speech domain was the most delayed, where she was able to do polysyllabic sound only with no meaningful word identified. On physical examination, she had a flat nasal bridge with no other features of dysmorphism. There was one naevus depigmentosus over her right posterior calf. She also had haemangioma over her right shoulder, which parents claimed had been reducing in size since birth. Generally, she had normal muscle mass with no fasciculation. Neurological examinations revealed hypotonia and hyperreflexia of all four limbs with no clonus and Babinski were down going.

A list of investigations (Table I) was carried out, and all results were normal. All the organ functions were normal with no clinical features of organ abnormality. Magnetic Resonance Imaging (MRI) was done at the age of one-year-eight-months old to rule out central cause, however, no focal brain lesions identified, but there was incidental finding of presence of fluid in mastoid air cells. This finding correlate with conductive hearing loss detected during hearing test due to bilateral middle ear effusion. Thus, she was also seen by the Ear, Nose and Throat (ENT) team and was planned for bilateral myringotomy and adenoidectomy.

Throughout her follow up at the Paediatric clinic, there was very slow progress in her development with no further improvement in her speech. At two-year-old, she was able to walk independently with a wide based gait, started to have neat pincer grip and mouthing. She was also able to understand simple instructions and "bye-bye", which corresponds to twelve-months milestones. However, there was no progression in speech and social domains. She was communicating with parents by pointing at objects of interest. As she grew up, she started to show some behavioural features of autism including poor eye contact, decreased socialization, stereotype movements, and inappropriate tantrums. Hence, an early intervention program was recommended and referral to occupational therapist, physiotherapist, and speech therapist were arranged to strengthen her muscle, improve her motor functions as well as communication skills.

In view of her poor progression in developmental milestones, especially in speech despite therapy and normal baseline investigation, basic karyotyping was sent at the age of two-year-eight-months old. Her karyotype result showed a ring at chromosome 22 in which breakage and reunion occurs at 22p13 and 22q13 (46, XX r (22) (p13q13)). The phenotype of this case was terminal deletion of 22p13q13. Given the possibility of inheritance in chromosomal anomalies, parental karyotyping is often considered to determine recurrence risk and genetic counselling needs. With regular therapies, at the age of three-year-old, she was able to walk independently with a wide-based gait, crawling upstairs but unable to run yet. For a fine motor, she was able to hold pencils with palmar grasps and made a tower of three cubes. In addition, she was able to point at toys when requested and obey simple commands. There was also an improvement in self-care, such as dressing and holding and drinking from a cup with little assistance. However, there was no improvement in speech. After a year of early intervention programme (EIP), there was no further developmental gains. Following diagnosis, a referral was made to the clinical geneticist to provide further genetic counselling.

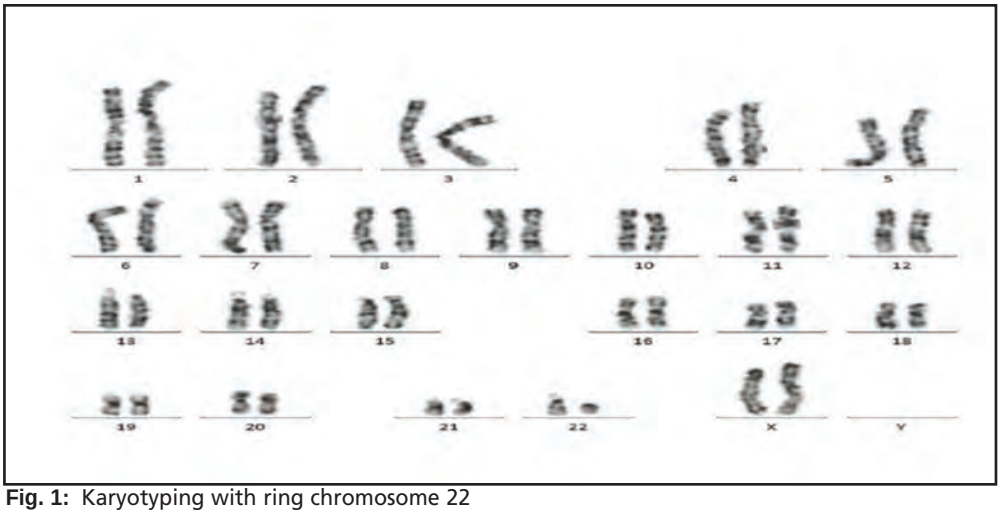

Fig. 1: Karyotyping with ring chromosome 22

DISCUSSION

Our case was a three-year-old girl, who presented with global developmental delay with severe speech impairment and hypotonia. The clinical manifestation or features of an individual with a ring chromosome varies depending on the chromosome involved and its phenotype. According to previous studies, the most seen features in r(22) include mental retardation, delayed motor development and hypotonia. Dysmorphic features such as epicanthic folds, microcephaly, hypertelorism, flat nasal bridge and high arch palate were also reported.[5] In this case, the only feature seen was a flat nasal bridge. Microcephaly was detected at a later age which subsequently became normal for her age.

As she grew up, she started to demonstrate autism features in terms of behaviours. Based on previous case reported, 75% of cases were diagnosed with autism, 9.4% as autism spectrum with wider variability in symptoms, skills and disability.[6] There were also cases reported with central nervous system abnormalities including dilatation of ventricles, cerebral atrophy, large cisterna magna and meningioma.[5] Other than that, mental and physical regression also reported with mood and anxiety disorder, chronic seizures requiring anticonvulsant as well as sensorimotor polyneuropathy.[5]

As for this case, she had routine follow up at a health clinic for development and immunization. Unfortunately, developmental abnormality and hypotonia were not identified earlier. The non-specific presentation, combining global developmental delay (GDD), hypotonia, with or without autism, leads to a broad range of differential diagnoses. Thus, it was important to recognize the problem early and proceeded with further investigations to identify the cause including basic karyotyping. As illustrated by this case, there was a delay in establishing the diagnosis which further delayed the intervention therapy. This was due to lack of recognition that chromosomal abnormality could be the cause for developmental delay and hypotonia with or without autism. To improve this, continuous education among primary care personnel should be provided, especially on how to identify and evaluate developmental delays that need early referral. A periodic clinical audit and communications strategies had been suggested as means to evaluate healthcare performance, reduced diagnostic error and to improve the quality of patient care.[7] A comprehensive developmental assessment by a trained primary care doctor should include a thorough review of development and growth. This process must be conducted closely together with specialist evaluations at the primary care centre and that early referral should be initiated as soon as when there is suspicion of developmental delay.

Early detection can play an important role in managing individuals with r(22) for a better quality of life. Since the main presentation was developmental delay, early intervention programs, intense occupational and physiotherapy as well as speech therapy will be beneficial to strengthen their muscles and improve their communication skills.[8] Early referral to physiotherapy, occupational therapy may give a major advantage for the child's development. Speech and language therapy were important as speech delay was usually the hallmark feature for r(22) syndrome. Many children may require ongoing and intensive speech-language therapy throughout their formative years.[9] The introduction of augmentative communication methods in the early stages of development can facilitate language utilization and alleviate frustration among a significant number of children undergoing speech-language therapy.[9] It was crucial to periodically reassess speech-language profiles as they can evolve over time, influencing the therapeutic approach needed for each child.[9] Similarly, to this case, she was in an early intervention program and on regular therapy with physiotherapy, occupational and speech therapy, but her speech progress was poor.

There were case reported that child with ring chromosome had concurrent recurring or persistent otitis media with or without effusion.[10] This case also was diagnosed with middle ear effusion (MEE) detected through hearing assessment and proven through her Magnetic Resonance Imaging (MRI) brain. She was planned for grommet insertion in view of persistent effusion despite pharmacological treatment. Speech delay is a hallmark feature of Phelan-McDermid syndrome (PMS), a genetic disorder most often caused by deletions or mutations affecting the SHANK3 gene on chromosome 22q13.3.[11] Marked impairment or even absence

of speech is reported in 50–88% of individuals with PMS, with up to 70% being non- or minimally verbal, and language impairment is consistently observed across diverse populations and genetic backgrounds.[12] Additional factors such as intellectual disability, hearing problems, and neurological issues can further influence communicative abilities.[13] In this case, her hearing improved following treatment of the middle ear effusion (MEE). Therefore, her speech delay is more likely attributable to underlying features of the chromosomal anomaly or possibly related to autism spectrum disorder.

The most important management for those with ring chromosomes was referral to genetics, especially for the parents. Geneticists can provide a thorough information and explanation to the parents to have more understanding about the r(22) syndrome.[4] The size of deletions will provide information on the number of medical comorbidities, gross motor skills, qualitative abnormalities in reciprocal social interactions, and qualitative abnormalities in communication. Larger deletions were associated with a higher likelihood of dysmorphic features and more severe medical comorbidity especially neurological symptoms, whereas smaller deletions were correlated with autism spectrum disorder, seizures, hypotonia, sleep disturbances, abnormal brain MRI, gastroesophageal reflux, and certain dysmorphic features.[10] Similarly, to our case, she was planned for fluorescence in situ hybridisation (FISH) to identify the genomic sequence. The clinical geneticist can determine the indication for genetic testing of family members. In this case, the clinical geneticist has not yet decided on parental karyotyping; however, it may be conducted in the future to determine inheritance.

CONCLUSION

The clinical features of ring chromosomes vary depending on the specific chromosome affected and its genotype. Diagnosing individuals with this condition was challenging due to the combination of non-specific symptoms, mimicking other disease or syndromes. However, the emphasis should be placed on early chromosomal analysis to detect any abnormalities, rather than solely focusing on the early detection of this specific anomaly. Early chromosomal analysis is to be considered in all cases of hypotonia and global developmental delay, even when dysmorphism is minimal and that baseline and IEM screening are unremarkable. To achieve that, the health care staff especially in primary care must have high level of suspicion and curiosity to detect the abnormalities. Proper counselling by a geneticist is recommended to provide further information and investigations needed. A long-term monitoring and follow up would be beneficial to monitor and detect any complication or other medical problems that may occur as the age increases.

ETHICS STATEMENT

Written informed consent was obtained from the minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable data included in this article.

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COMPETING INTEREST

The authors declare that they have no conflict of interest.

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CASE REPORT

Bilateral exudative retinal detachment in preeclampsia with HELLP syndrome: A case report and literature review

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SUMMARY

Preeclampsia (PE) and haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome are severe hypertensive disorders of pregnancy that can lead to significant systemic complications, including ocular manifestations such as bilateral exudative retinal detachment (ERD). ERD, though rare, can cause significant visual morbidity. Management primarily focuses on treating the underlying hypertensive disorder and controlling blood pressure, typically resulting in a favourable visual outcome. We present a case of bilateral ERD associated with severe PE and HELLP syndrome in a 37-year-old postpartum female. The patient presented with sudden, painless bilateral visual acuity reduction one day following an emergency caesarean section performed due to severe PE complicated by HELLP syndrome. Fundus examination revealed bilateral ERDs. The patient was managed conservatively with strict blood pressure control and optimization of her systemic condition. At one-month follow-up, her best-corrected visual acuity improved to 6/6 bilaterally. Despite the conservative management of ERD, this case emphasizes the crucial role of prompt recognition and control of severe hypertensive disorders of pregnancy in preserving visual function.

INTRODUCTION

Hypertensive disorders of pregnancy remain a leading cause of maternal and perinatal morbidity and mortality globally.[1] The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines PE as the development of hypertension (blood pressure ≥140/90 mmHg) after 20 weeks of gestation, accompanied by proteinuria or other signs of end-organ dysfunction.[1] A particularly severe complication of Preeclampsia (PE) is haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, a critical obstetric emergency.[1] While the primary focus of management is on mitigating maternal and fetal complications, the effects of these disorders can extend to various organ systems, including the eyes.

Exudative retinal detachment (ERD) is a recognized ocular complication of severe PE and HELLP syndrome, characterized by the accumulation of subretinal fluid between the neurosensory retina and the retinal pigment epithelium, without the presence of a retinal tear.[2] This fluid build-up is a result of vascular leakage and increased permeability, which are hallmarks of the systemic vasculopathy observed in hypertensive disorders.[2,3] Given the retina's highly vascular nature, it is particularly susceptible to these systemic vascular changes, potentially leading to vision-threatening complications. We report a case of bilateral ERD in the setting of severe PE complicated by HELLP syndrome, highlighting the importance of prompt recognition and systemic control in achieving visual recovery.

CASE PRESENTATION

A 37-year-old female, para 2, with a significant antenatal history of gestational diabetes mellitus and maternal obesity managed with dietary control, underwent an emergency caesarean section due to severe PE complicated by HELLP syndrome. Her blood pressure ranged from 123–156/70–96 mmHg throughout admission, with proteinuria of 2+. Blood investigations revealed haemoglobin of 10.5 g/dL, platelet count of 45 × 10^9/L, and aspartate aminotransferase of 68 U/L. The coagulation profile remained within normal limits.

One day post-operatively, the patient reported a sudden onset of painless, bilateral blurred vision, accompanied by visual field defects. Her best-corrected visual acuity (BCVA) was 6/30 in both eyes. There was no relative afferent pupillary defect (RAPD). Confrontation visual field testing revealed binasal field defect. Slit-lamp examination of the anterior segment was unremarkable. Dilated fundus examination revealed bilateral temporal ERDs with macular involvement (Fig.1). There was a shallow detachment from 7-11 o'clock in the right eye. The left fundus showed bullous retinal detachment from 1-7 o'clock, accompanied by a shallow diffuse detachment from 11-1 o'clock. No retinal tears or holes were identified.

The patient was managed conservatively with strict blood pressure control, optimization of her systemic condition, and close monitoring of her renal and hepatic function. At one-month follow-up, her BCVA improved to 6/6 bilaterally, with complete resolution of bilateral ERDs (Fig. 2). Her blood pressure and laboratory parameters, including liver enzymes and platelet count, had returned to normal ranges.

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Table I: Summary of published report on ERD complicating severe PE

Author, Year	Age/ Parity/ Gestational Age	Ocular Symptoms	Fundus Findings	Management	Visual Acquity		Recovery time (days)
					Initial	Final	
Zebbache, 2021[4]	25/ Primid 30 weeks POG	Vision loss after wake up from sleep	BE bullous serous detachment with macula involvement	Conservative	PL (BE)	6/6 (BE)	Few days
Benlghazi et al., 2023[6]	26/ Primid 39 weeks POG	Blurred vision, metamorphopsia	BE macular detachment	Conservative	6/7.5 (BE)	6/6 (BE)	30
Phang et al., 2022[5]	30/ Primid 32 weeks POG	Visual fog	BE multifocal serous detachment involving the posterior pole	Conservative	6/60 (BE)	6/6 (BE)	7
Khallouli et al., 2021[7]	32/ Multipara 33 weeks POG/	Blurred vision, metamorphopsia	BE bullous serous detachment with macula involvement	Oral Prednisolon 1.5 mg/kg/day for one week	3/60 (RE)	6/6 (BE)	60
Limon, 2020[8]	24/ - 35 weeks POG	Blurred vision	RE diffuse / LE focal serous detachment	Conservative	CF (RE) 6/9 (LE)	6/6 (BE)	60 (RE) 30 (LE)

Abbreviations: PL, light perception vision; CF, finger counting vision; BE, both eyes; RE, right eye; LE, left eye

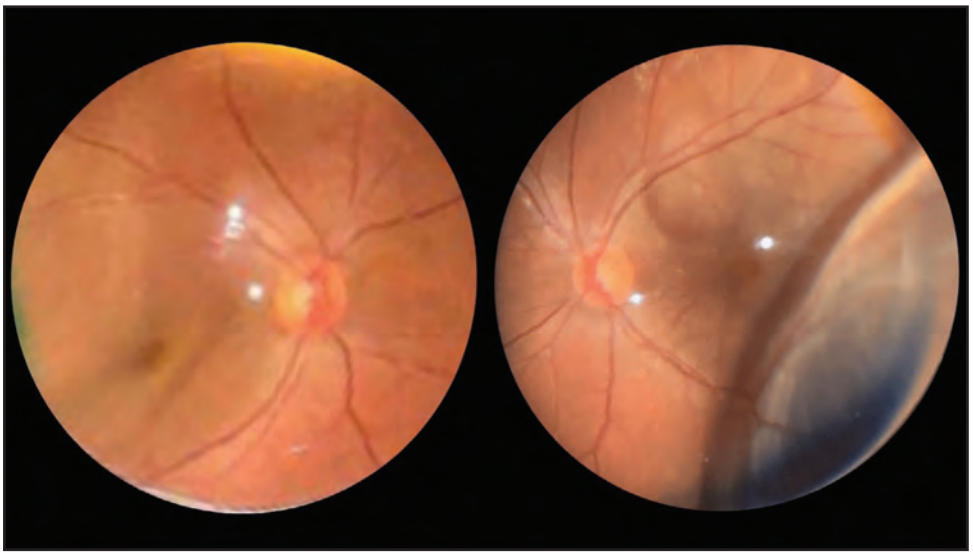

Fig. 1: Bilateral exudative retinal detachments with macular involvement at presentation

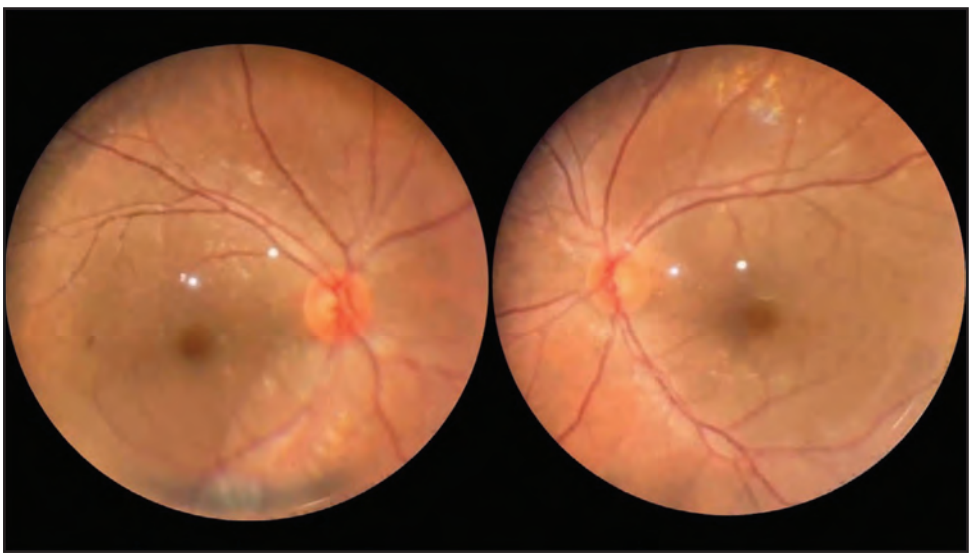

Fig. 2: Complete resolution of bilateral exudative retinal detachments at one-month follow-up

DISCUSSION

ERD is a rare but significant complication affecting 1-2% of severe PE cases and 0.9% of HELLP syndrome cases,[4] that occurs across a broad spectrum of obstetric patients, regardless of parity as illustrated in Table I.[4–8] The consistent finding of bilateral ERD across all cases underscores the systemic nature of the underlying vasculopathy. The abnormal placentation in PE and HELLP syndrome leads to increased systemic vascular resistance and vasospasm, contributing to choroidal ischemia and compromising the integrity of the RPE.[5,6] While HELLP syndrome predominantly occurs during the third trimester, it can manifest or worsen postpartum in up to 30% of cases.[9] Thus, the development of ERD in postpartum PE is a clinically recognized phenomenon. The postpartum presentation of our patient, occurring one day after childbirth, aligns with previous report.[7]

Presenting visual acuity in ERD varies significantly, from perception of light (PL) to near-normal vision.[4–8] Visual field defects are also variable, encompassing curtain defects, scotomas, hemianopia, and total field loss.[2] This is largely influenced by the extent of serous detachment. Diffuse, bullous ERD with macular involvement leads to poorer vision as seen in our case and previous reports,[4,6–8] while small, localized SRF collections in the posterior pole tend to cause visual distortion, such as metamorphopsia[5,7] with less pronounced visual acuity loss.[5,8]

Management of ERD in severe PE and HELLP syndrome is primarily conservative, focusing on strict blood pressure control and optimization of underlying systemic conditions.[2,8] This approach is based on the understanding that ERD in these conditions is a manifestation of systemic vascular changes, similar to hypertensive choroidopathy observed in malignant hypertension.[2,3] Although oral prednisolone has been considered,[7] clinical outcomes are generally comparable to those achieved with conservative management alone.[4–8] ERD secondary to hypertensive disease typically carries a favorable prognosis with good visual outcomes.[3–8] However, severe ERD can lead to geographic chorioretinal atrophy, a potential complication occurring in up to 8.5% of PE cases.[10]

The recovery time for visual acuity varied from a few days to months, with all patients ultimately achieving 6/6 bilaterally.[4–8] If ERDs do not resolve as expected, it is important to rule out other potential causes, such as infective or inflammatory diseases or retinal tears.[2]

This case report, along with the reviewed literature (Table I), emphasizes the importance of awareness among obstetricians, midwives and private practitioners regarding the ocular complications of severe or poorly controlled hypertensive diseases. Prompt recognition and control of severe hypertension are essential for preserving visual function in these high-risk patients. While the role of hypertensive vasculopathy in ERD is recognized, further studies are needed to elucidate additional factors that may contribute to its manifestation in PE and HELLP syndrome. Longitudinal studies exploring the long-term ocular health of these patients are also crucial.

CONCLUSION

This case serves as a reminder of the potential for vision-threatening complications such as ERD in severe hypertensive disorders of pregnancy, including the postpartum period. Even subtle visual disturbances such as metamorphopsia or slight blurry vision warrant a comprehensive ophthalmic examination in any pregnant or postpartum woman presenting with visual complaints. Early detection, prompt intervention, vigilant monitoring and collaborative management between obstetrics and ophthalmology are essential to ensure optimal visual outcomes.

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DECLARATIONS

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

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Refractory neurotrophic keratitis in a young adult: A case report on the role of multimodal therapies

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SUMMARY

Neurotrophic keratitis (NK) is a rare, degenerative corneal disease that presents significant treatment challenges. We present a case of a 20-year-old female with a history of recurrent herpetic stromal keratitis (HSK) who developed bilateral NK complicated by persistent epithelial defects (PED), superimposed infective keratitis and band keratopathy (BK). A 20-year-old female with history of recurrent herpetic stromal keratitis with recurrent corneal epithelial defect initially presented with left eye pain, redness, and photophobia. Best-corrected visual acuity (BCVA) was 6/6 in the right eye and 6/12 in the left with a central epithelial defect of 5.4×5.8 mm. Despite treatment for corneal epithelial defect, symptoms worsened bilaterally as she developed recurrent HSK with PED. The diagnosis of NK was diagnosed and treated with lubricants, bandage contact lens, temporary tarsorrhaphy, punctal plug and initiation of autologous serum eye drops. However, she developed superimposed mixed bacterial and fungal infective keratitis while on autologous serum eye drop, necessitated temporary cessation of serum drops and initiation of antimicrobial therapy. Following treatment, the infective keratitis resolved but epithelial defect was persistent. Insulin eye drops were initiated, yielding only partial improvement. Subsequently, the patient developed BK. EDTA chelation with basement membrane polishing was performed, leading to complete resolution of PED and BCVA improvement to 6/12 in both eyes. This case illustrates the complexity of NK management and highlights the value of a multimodal approach in achieving successful clinical outcomes.

INTRODUCTION

Neurotrophic keratitis (NK) is a rare, degenerative disease of the cornea resulting from impaired trigeminal innervation, leading to reduced or absent corneal sensation and poor epithelial healing. It affects fewer than 5 individuals per 10,000 population.[1] Common causes include herpetic keratitis, intracranial lesions, and neurosurgical trauma to the ophthalmic branch of the trigeminal nerve. Ocular risk factors such as chemical burns, corneal dystrophies, long-term topical medications, and anterior segment surgery, as well as systemic conditions like diabetes, leprosy, and multiple sclerosis, have also been implicated.[2]

Managing NK remains a significant clinical challenge. Conventional therapies include preservative-free artificial tears, tarsorrhaphy and use of therapeutic contact lenses.[4] More recent approaches explore topical agents such as autologous serum eye drops, which offer essential growth factors that support epithelial repair.[3,4,6]

Insulin eye drops have also shown promising results in persistent epithelial defects (PED) refractory to standard treatments.[5-7] In addition, band keratopathy (BK) which is a complication seen in longstanding ocular surface disease, can be effectively managed with ethylenediaminetetraacetic acid (EDTA) chelation and polishing, which improve both vision and comfort.[8-10]

This case report presents a challenging case of bilateral NK complicated by PED, superimposed infection, and BK, successfully treated using a multimodal approach. The case highlights the utility of combining established and novel therapies to achieve epithelial healing and visual rehabilitation.

CASE PRESENTATION

A 20-year-old female with underlying allergic rhinitis first presented to our clinic at the age of 15 with a 3-day history of bilateral eye redness, tearing, itching and blurred vision. The best-corrected visual acuity (BCVA) was 6/7.5 in the right eye (RE) and 6/6 in the left eye (LE). Both eyes demonstrated macropapillae with conjunctival injection, clear cornea, deep and quiet anterior chambers and clear lenses. Other ocular examinations were unremarkable. She was diagnosed with bilateral allergic conjunctivitis and commenced on topical olopatadine 0.1% twice daily (BD) in both eyes (BE).

In October 2022, three years later, she developed bilateral eye redness with discomfort. The BCVA was 6/12 in RE and 6/15 in LE. Examination revealed macropapillae, conjunctival injection, and central corneal epithelial defects without stromal infiltrates in both eyes. Corneal sensation was reduced bilaterally. A diagnosis of bilateral herpetic epithelial keratitis was made, and she was commenced on oral acyclovir 400 mg five times daily for 10 days, followed by a prophylactic dose of 400 mg twice daily for four months, along with topical moxifloxacin 0.5% 4-hourly, olopatadine

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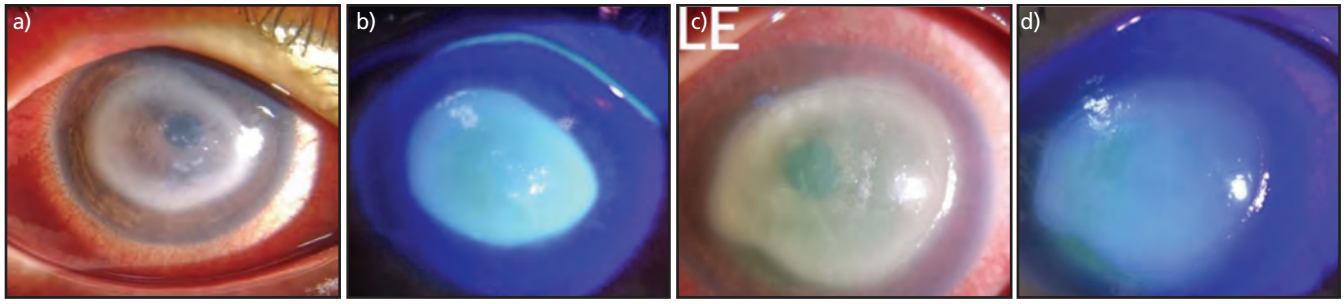

Fig. 1: Anterior segment photos at diagnosis: (A, B) right eye, (C, D) left eye, with diffuse illumination and fluorescein staining showing a ring of stromal infiltrate with oedematous cornea and large, central epithelial defect

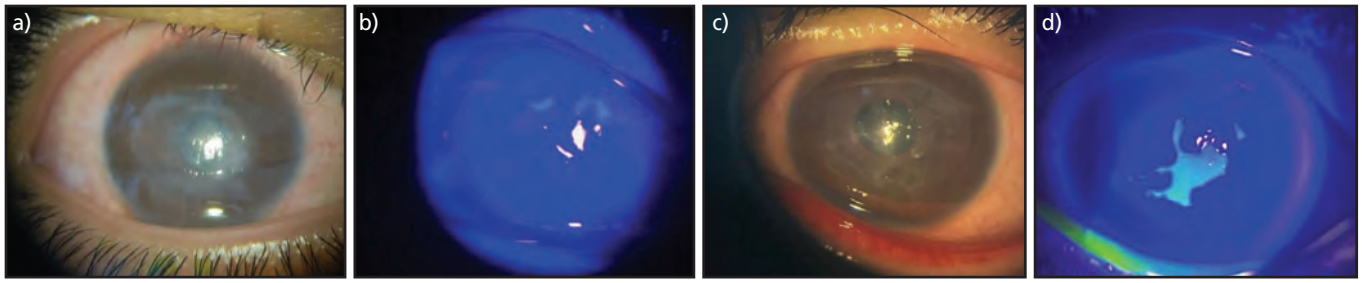

Fig. 2: Photos post-autologous serum therapy: (A, B) right eye, (C, D) left eye showing improvement of ring stromal infiltrate with persistent epithelial defect

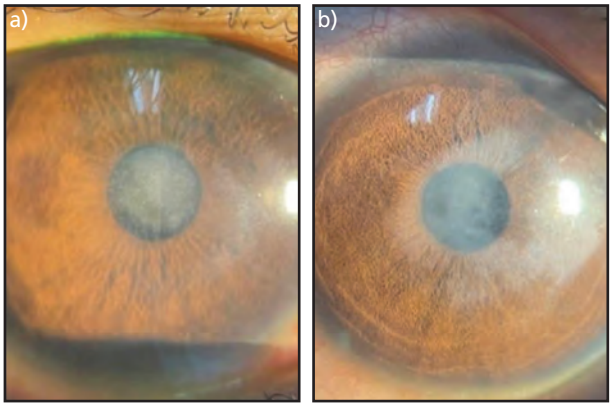

Fig. 3: Photos six-months post-EDTA chelation and polishing: (A) right eye, (B) left eye showing residual stromal fibrosis.

0.2% every morning and preservative-free artificial tears (ATPF) hourly in both eyes. The epithelial defects resolved, with improvement of BCVA in both eyes to 6/7.5, and she remained asymptomatic for one year.

On 30 November 2023, one year later, she presented with left eye redness, tearing, and reduced vision in the LE. BCVA was 6/6 in RE and 6/12 in LE. LE examination revealed a central epithelial defect (5.4 × 5.8 mm) without stromal infiltrate. Four days later, she developed tearing, pain, and reduced vision in RE. BCVA had decreased to 6/60 in RE and counting fingers in LE. Both eyes demonstrated conjunctival injection and central epithelial defects (RE: 8.2 × 6.8 mm; LE: 5.4 × 5.8 mm). The cornea showed central stromal ring infiltrates with associated corneal oedema and Descemet's folds. Fine keratic precipitates were present bilaterally with 1+ anterior chamber cells in both eyes. Corneal sensation was significantly reduced bilaterally (Figure 1).

She was diagnosed with bilateral herpetic keratouveitis and commenced on oral acyclovir 800 mg five times daily, topical prednisolone acetate 0.1% twice daily, topical moxifloxacin 0.5% five times daily, ATPF every two hours and oral vitamin C 1 g daily. Despite treatment, the epithelial defects remained large with poor healing. A diagnosis of bilateral neurotrophic keratitis (NK) secondary to herpetic keratitis with persistent epithelial defects (PED) was made.

Topical autologous serum eye drops were initiated every two hours in both eyes, and oral acyclovir was continued at a prophylactic dose of 400 mg twice daily. Topical corticosteroids were discontinued in view of impaired

epithelial healing. A temporary central tarsorrhaphy was performed in the left eye. After three days of autologous serum therapy, the ring infiltrates became less dense, corneal oedema reduced and there was slight improvement in the epithelial defects bilaterally. BCVA improved to 6/12 in RE; LE vision was not quantifiable due to the tarsorrhaphy.

At one-week review, she reported worsening vision in RE. Examination revealed a new central stromal infiltrate within the pre-existing ring infiltrate, accompanied by an endothelial plug and a streak hypopyon. BCVA decreased to counting fingers. Corneal scraping was performed for Gram stain, full examination and microscopic evaluation (FEME), and culture and sensitivity (C&S). Based on clinical judgment, a diagnosis of mixed bacterial and fungal keratitis was made. While awaiting laboratory results, intensive broad-spectrum antibacterial and antifungal therapy was initiated, including topical gentamicin 0.9%, ceftazidime 5%, and amphotericin B 0.15% hourly. Autologous serum was withheld in RE during active infection but continued in LE. Corneal scrapings revealed no organisms, and cultures were negative. As the endothelial plug worsened despite treatment, therapy was switched to topical vancomycin 2% and voriconazole 1% hourly, leading to resolution of stromal infiltrates, endothelial plug, and hypopyon. Autologous serum was resumed in RE after four weeks.

At six-week follow-up, tarsorrhaphy in LE was discontinued due to minimal improvement in the epithelial defect. Over several months, the epithelial defects gradually reduced in size, with symptomatic improvement. At six months, she was asymptomatic with improvement of BCVA to 6/7.5 in RE and 6/12 in LE; however, PED persisted in both eyes, more marked in LE (Figure 2).

Given the persistent PED, she was started on topical insulin eye drops 0.5 IU four times daily (QID) and punctal plugs were inserted bilaterally. Progress remained slow despite multimodal therapy. At one-year follow-up, she developed bilateral band keratopathy (BK). In view of PED and BK, EDTA chelation with basement membrane polishing using a diamond burr was performed under general anaesthesia, followed by application of bandage contact lenses (BCL).

Four days post-procedure, complete resolution of PED was achieved. At one month, she had minimal residual stromal scarring and BCVA of 6/12 in both eyes. At six months post-procedure, residual stromal fibrosis persisted, more pronounced in LE (Figure 3). She was prescribed scleral contact lenses, which improved BCVA to 6/7.5 in both eyes. She expressed great satisfaction as she could resume her studies and driving.

DISCUSSION

Neurotrophic keratitis (NK) is a rare, degenerative corneal disease with a reported prevalence of ≤5 per 10,000 individuals.[1] It results from impairment of trigeminal innervation to the cornea, leading to loss of corneal sensation, decreased tear production, and disruption of epithelial metabolism and wound healing.[2] The corneal nerves are essential for maintaining ocular surface integrity; their loss initiates a cascade of epithelial breakdown, stromal melting, and potential perforation.[2] The most common aetiologies of NK include herpetic keratitis, diabetes mellitus, chemical or surgical trauma, and neurosurgical procedures.[2] In our patient, the contributing factors were recurrent herpetic keratitis, which may impair epithelial regeneration.[4]

Clinical presentation depends on the disease stage, as classified by Mackie2: Stage 1 - punctate epithelial keratopathy, tear film instability, conjunctival staining, and early stromal changes. Stage 2 - persistent epithelial defects (PED) with stromal oedema and loose epithelial margins. Stage 3 - corneal ulceration, stromal melting, and perforation. Our patient initially presented with Stage 2 NK, progressing to Stage 3, complicated by mixed bacterial–fungal keratitis and later band keratopathy (BK).

Management of NK is challenging, aiming to promote epithelial healing, suppress inflammation, and prevent stromal loss.[4] Conventional therapies include preservative-free lubricants, therapeutic contact lenses, and tarsorrhaphy.[4] Biologic therapies such as autologous serum eye drops provide epithelial growth factors, neurotrophic factors and vitamins that support corneal healing by promoting proliferation, migration and maturation of corneal epithelial cells and reduction in stromal fibrosis,[3,4,6] but their use carries a risk of microbial contamination.[3,6] Our patient developed secondary infection while on autologous serum, which improved after cessation and targeted antimicrobial therapy. The preparation of the eye drops was done at the transfusion medicine laboratory at HPUSM according to the Standard Operation Procedure (SOP). The process included collection of blood from the patient, centrifugation and packaging of the separated 100% serum in sterile eye drop vials. The patient was instructed regarding transport, proper storage of the eye drops in freezer and its proper use to minimize risk of contamination similar to previous literature.[3,6]

Topical insulin eye drops, as used in our case, are a novel option for refractory PED. Insulin shares structural similarities with insulin-like growth factor-1 (IGF-1) and promotes keratinocyte migration and proliferation.[5,6] Recent studies have reported successful epithelial closure in PED of various aetiologies, including herpetic keratitis, with minimal adverse effects.[6,7] The advantages of insulin include readily availability, cost effectiveness, excellent tolerance and absence of unfavourable side effects with no effect of serum glucose levels.[5-7]

Our patient's late course was complicated by BK, a frequent sequela of chronic ocular surface inflammation.10 EDTA chelation is an established treatment for complete removal symptomatic BK, effectively removing calcium plaques and improving the ocular surface.[9,10] In this case, there was PED with loose epithelium and poor adherence to underlying basement membrane hence EDTA chelation was combined with basement membrane polishing using a diamond burr (DBP). DBP has shown a lower rate of recurrences compared to epithelial debridement alone. The smooth surface left after polishing allows new epithelial growth and stimulate reactive fibrosis and extracellular matrix proteins that may contribute to stronger epithelial adhesion.[8] We observed

complete removal of BK with complete epithelial closure within four days following the procedure with significant visual recovery in our case.

This case demonstrates that even in severe, chronic NK complicated by infection and BK, good anatomical and functional outcomes can be achieved with a multimodal, stepwise approach. Early diagnosis, careful monitoring, and timely integration of both conventional and novel therapies—such as autologous serum, topical insulin, tarsorrhaphy, punctal occlusion, and EDTA chelation—are critical for preserving vision and quality of life in affected patients.

CONCLUSION

Refractory neurotrophic keratitis poses significant therapeutic challenges. This case highlights that even in advanced, refractory neurotrophic keratitis complicated by persistent epithelial defects, secondary infection, and band keratopathy, vision can be preserved with a structured, multimodal approach. Combining conventional measures such as tarsorrhaphy and punctal occlusion with novel therapies like autologous serum and topical insulin eye drops, followed by EDTA chelation and basement membrane polishing, resulted in complete epithelial closure and significant visual recovery. Early recognition, close monitoring, and timely escalation of therapy in neurotrophic keratitis is crucial. Further studies are needed to validate the role of topical insulin and combined surgical–medical strategies in similar complex cases.

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Open ligation of a right portohepato venous shunt: A case report

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SUMMARY

Intrahepatic portosystemic venous shunts (IPSVS) are incidentally diagnosed and generally asymptomatic. Treatment is usually indicated if patient develop symptoms. We present a case report on a patient with symptomatic IPSVS and our surgical approach on the management of IPSVS. The highlight of this discussion is to demonstrate the benefits open surgical approach to treat IPSVS when IR facility is not available.

INTRODUCTION

Intrahepatic portosystemic venous shunt (IPSVS) are rare abnormal blood vessel connections of the intrahepatic vein with branches of the portal vein or inferior vena cava (IVC) (1). The shunts are described in five morphological types (2). A single large vessel of constant diameter connecting the right portal vein directly to the (IVC) is regarded as Type 1. Type 2 is a localised peripheral shunt with single or multiple communications found between peripheral branches of portal and hepatic veins in one hepatic segment. For Type 3, an aneurysmal connection is formed between the peripheral portal and hepatic veins. Type 4 is regarded as multiple communications between peripheral portal and hepatic veins diffusely in both lobes. Finally, Type 5 is described as patent ductus venosus. In this case report, we present a case of IPSVS type 3 treated via an open surgical ligation method.

CASE PRESENTATION

We have a 40-year-old Indian female with a background of dyslipidaemia, and chronic Hepatitis B, presented with right hypochondrium pain for two weeks. Patient's condition worsened four months later, developed cardiac failure symptoms, reduced effort tolerance, bilateral lower limb oedema, New York Heart Association (NYHA) Class II and sleep disturbance, West Haven Grade I. These symptoms have affected her work. Clinically, she was afebrile, with a blood pressure of 110/ 72 mmHg, heart rate of 80 bpm and examination showed mild right hypochondrium tenderness. There were bilateral lower limbs pedal oedema up to mid shin.

INVESTIGATIONS

Blood investigations showed total bilirubin level of 18 umol/L, Alkaline Phosphatase (ALP) 80 U/L, Alanine Amino Transferase (ALT) 55 U/L and Aspartate Amino Transferase (AST) 43 U/L. Serum ammonia was 40 umol/L. Other blood parameters such as full blood count, renal profile, coagulation profile and serum amylase were normal. Ultrasound of the hepatobiliary system showed a portal vein aneurysm. Contrasted Tomography (CT) multiphase imaging of the liver demonstrated a finding of fatty liver, and communication between the right anterior sectoral branch of portal vein and distal branch of middle hepatic vein (MHV) (Figure 1). Echocardiogram showed left ventricular ejection fraction of 65%, the size of all heart chambers normal, with mild mitral regurgitation. Oesophagogastroduodenoscopy (OGDS) were normal as well.

We have decided for an open ligation of the shunt instead of interventional radiographic approach due to financial reasons. The patient was explained regarding the procedure, risk and benefits followed by an informed consent.

TREATMENT

Intra-operative ultrasound color doppler flow was carried out to identify the fistulous communication of the middle hepatic vein and anterior sectoral branch of the right portal vein. The site of fistulous communication was marked with diathermy on the liver surface. The segment VII was dissected with Cavitron Ultrasonic Surgical Aspirator (CUSA) until the fistulous communication was identified (Figure 2). The fistula is subsequently ligated with Hem-o-lok clips and divided between ties and prolene 4/0 sutures reinforcement. Post ligation, ultrasound doppler pressure wave forms were absent over portal vein branches and hepatic vein tributaries confirmed dissociated system.

OUTCOME AND FOLLOW-UP

Patient recovered well post operation. There were no peri-operative complications. There was transient rise in ALT (379 U/L) and AST (415 U/L), however ALP, bilirubin, renal profile, full blood count, and coagulation profile remained normal. She was discharged well three days post surgery. Follow-up two months later, patient's symptoms markedly improved. Her ALT was 82 U/L, AST was 48 U/L, with normal ALP and bilirubin levels. A repeat CT assessment showed complete resolution of the fistula (Figure 3).

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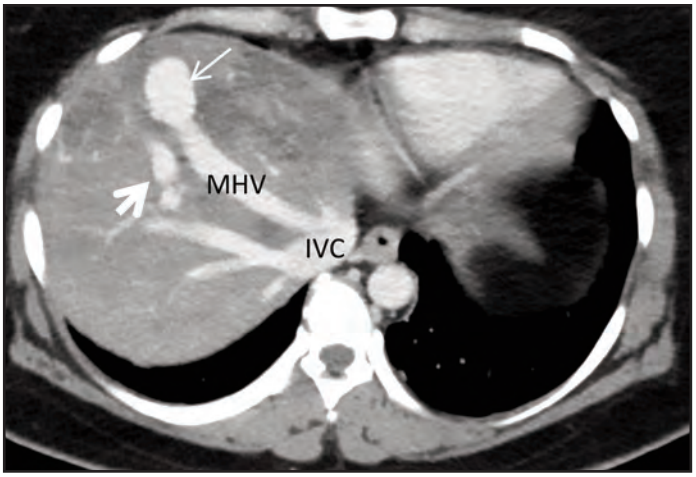

Fig. 1: CT Axial view. Presence of the shunt (thin arrow) connecting the MHV and the anterior sectoral branch of right portal vein (thick arrow). MHV - middle hepatic vein, IVC - inferior vena cava

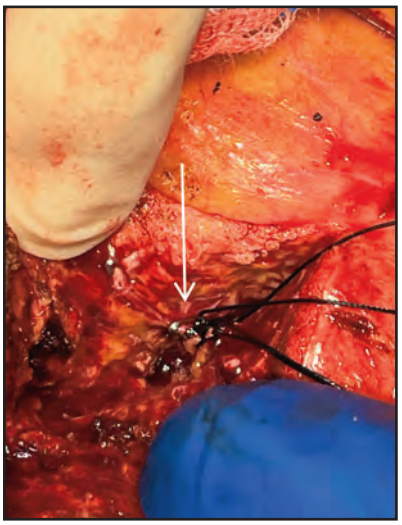

Fig. 2: Ligation of the IPSVS (arrow) using Hem-o-lok clips and Prolene 4/0 suture ties

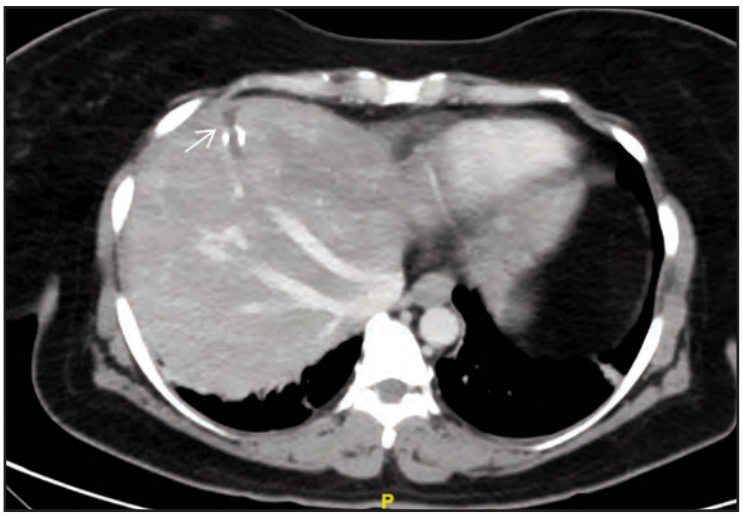

Fig. 3: Complete disconnection of the shunt (arrow) based on repeat CT assessment 2 months post-surgical ligation

DISCUSSION

Intrahepatic portosystemic venous shunt can either be congenital, acquired or iatrogenically formed for therapeutic purposes. At the present literature, it is still an extremely rare disease with an incidence of 1 in 30,000 to 1 in 50,000 for congenital, but still unknown for acquired.[3]

The pathophysiology of IPSVS centers on an abnormal vascular connection within the liver that diverts the blood from the portal vein to the systemic (hepatic) veins without passing through the intervening capillary (sinusoids) beds of the liver parenchyma. In acquired, theories have suggested the role of portal hypertension in cirrhotic liver that resulted with expansion of collateral circulation may cause the formation of a IPSVS which is usually located peripheral vessels of the liver, however in non-cirrhotic liver, it is still unknown, although there are theories in trauma-related which may have contributed from absorption of injured necrotic liver in combination with open inflow and drainage of adjacent vessels, creating a direct connection between the vessels, but are commonly reported as hepatic arterio-portal fistula.[4-6] For congenital IPSVS, it was thought to be persistence communication of cranial and caudal hepatic sinusoids formed by vitelline and umbilical veins.[7] Although this patient has chronic hepatitis B, she does not exhibit symptoms of portal hypertension and routine hepatobiliary system ultrasound, nor intraoperative examination of liver did not show any evidence of cirrhosis. The etiology of her condition is still not known, although suspecting it could possibly be congenital.

Most of the cases are asymptomatic which are diagnosed incidentally during routine imaging.[8] Symptoms of IPSVS are hepatic encephalopathy (50% of cases reported) which may sometimes be mistakenly diagnosed as having psychiatric disorder, hepatic dysfunction, cardiac dysfunction and renal dysfunction.[9] However, in children, hyperammonia was the common clinical manisfestation (85%), followed by jaundice (80%), cholestasis and or hypergalactosemia.[3]

Treatment is indicated in symptomatic patients.[5, 8-10] Our patient has developed symptoms relating to cardiac failure and hepatic encephalopathy and thus, a definitive treatment is indicated for her to prevent worsening of symptoms. Whereas for asymptomatic patient, studies have suggested to calculate the shunt ratio, which is calculated using the Doppler US, by dividing the blood flow volume at the shunt orifice by the total portal blood volume. The risk of symptomatic IPSVS increases proportionately with shunt ratio. If the shunt ratio exceeds 60%, treatment is indicated even if patient is asymptomatic.[7-9]

Majority IPSVS are reportedly treated via interventional radiological (IR) approach as this is the current widely adopted approach.[3-5,9] These shunts can be treated using embolisation principles. The choice of embolisation approach can either be embolic agents or embolic materials. Surgical approaches would be either surgical occlusion, ligation of the shunts, or hepatic resection.[5] Although, there have been reports of perioperative poor effectiveness, especially in cirrhotic liver patients. There was also observation study that have showed newly formed shunts at other locations.

Zhang et. al compared the efficacy and safety of surgical ligation versus endovascular embolisation for congenital extrahepatic portosystemic shunt (EPSVS).[11] Patients in both arms had significant clinical improvements with no recurrence after three years of follow-up. Serum ammonia returned to normal levels within six months. It had shown that both methods are equally effective, with intervention group showing shorter procedure time and less intraoperative blood loss, whereas in the surgical arm, ligation is feasible with safety and may avoid future recurrence.

A recent literature used the measurement of occluded portal pressure as guide to determine whether to perform staged or complete ligation of the shunt.[3] Using occluded portal pressure indicator of 26 cmH_2O, staged ligation is performed if the patient developed portal hypertension as evidence by portal pressure is > 26mmHg, and complete ligation is done if the portal pressure is < 26 cmH_2O. The importance of performing pre-operative occlusion portal pressure measurement is to evaluate the plasticity of the inthrahepatic portal vein. This helps to reduce the risk of post-operative portal hypertension, portal vein thrombosis and even mortality.

Our case reinforces that open surgical ligation can be performed safely with favourable outcomes, making it a valuable option in resource-limited centres.

CONCLUSION

IPSVS are incidentally diagnosed and are generally asymptomatic. Treatment is usually indicated for symptomatic patients and treatment is mostly via IR approach. However, a classical open surgical approach has shown beneficial symptomatic relief with no complication. This serves as a good alternative treatment to IR method when the expertise, cost & logistics are not feasible to perform.

ACKNOWLEDGEMENT

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DECLARATIONS

This case report has obtained an informed consent from the patient herself for permission to publish. There are no conflicts of interest to be declared.

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Classical Hodgkin Lymphoma presenting in late pregnancy: A case report

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SUMMARY

Hodgkin Lymphoma (HL) is the fourth most common type of malignancy in pregnancy which accounts for around 3.2% of all the cases. Diagnosis is generally delayed in pregnancy due to physiological changes in pregnancy mimicking constitutional symptoms of lymphoma, hence high index of suspicion is required to diagnose such antenatal women in time to optimize the overall outcome. We present a case of 22-year-old Primigravida at 35 weeks period of gestation who presented to emergency with complaints of neck swelling for 5 days without any constitutional symptoms. The diagnosis of Hodgkin lymphoma was confirmed by lymph node biopsy. Induction of labour was done at 37 weeks with the uneventful birth of a healthy baby. After delivery CECT was done and stage III Hodgkin lymphoma was confirmed and patient was given 6 cycles of chemotherapy. Lymphoma in pregnancy presents a complex clinical scenario that requires careful consideration of both maternal and fetal factors throughout pregnancy. A multidisciplinary approach involving obstetricians, haematologist /oncologist, and neonatologists is essential to optimize the care of these patients and ensure the best maternal and fetal outcomes.

INTRODUCTION

Diagnosis of cancer during pregnancy is traumatic to the patient, and her family, and poses a challenge to the treating team. Cancer is diagnosed in 0.1%-0.7% of pregnancies and is the second most common cause of maternal mortality after pregnancy-related complications.[1] In pregnancy, usually, the diagnosis is delayed as the constitutional symptoms may mimic physiological changes of pregnancy. Lymphoma is the fourth most common type of cancer in pregnancy with Hodgkin's lymphoma (HL) being more common than non-Hodgkin lymphoma (NHL).[2] Management of lymphoma during pregnancy should be a multidisciplinary approach maintaining a fine balance of potential harmful effects of diagnostic as well as therapeutic intervention on fetal development without a compromise on the treatment. Whether to give chemotherapy during the antenatal period or delay till delivery and the type of chemotherapy depends on the extent of the disease, histopathological type, severity of the disease, and period of gestation at presentation.

CASE PRESENTATION

A 22-year-old Primigravida 35 weeks period of gestation presented to emergency with complaints of sudden onset neck swelling since last 5 days. There was no history of any fever, night sweats, cough, sore throat, weight loss, loss of appetite, or easy fatigability. A fine needle aspiration cytology (FNAC) taken at the regional hospital before her referral was suggestive of lymphoproliferative disorder and the patient was referred for further management to our institute. The patient was booked and supervised for the index pregnancy at a regional hospital and her antenatal period was uneventful till date. There was no significant past medical, surgical, or family history to report. On admission, her vitals were stable with normal general physical examination and no obvious pallor. There was a diffuse, nontender neck swelling with enlarged lymph nodes bilaterally. The largest lymph node was around 3x 3cm. The neck swelling was not moving with swallowing. There was no lymphadenopathy in the axilla or groin. Obstetrical examination revealed uterus corresponded with 32 weeks with flanks full, cephalic presentation with regular fetal heart rate. Her haemoglobin was 10.4g/dl, TLC 11.34x10^3/dl, platelets 3.55 lac/dl, and ESR 99mm/hour. TSH was raised 13.85 micro-IU/dl with normal T3, T4 and anti-TPO antibodies. Her serum urea was urea 11mg/dl, creatinine 0.5mg/dl, SGOT/PT/ALP 41U/L, 55U/L, 509U/L, LDH 414.2U/L, viral markers were non-reactive and coagulation profile was normal. USG for fetal well-being done at 16 weeks and 35 weeks and were normal for gestational age. USG neck was done which revealed a heterogeneously hypoechoic lesion in the supraclavicular region of size 6.7 x 4 cm with internal vascularity. Multiple enlarged lymph nodes with heterogenous echotexture with loss of fatty hilum seen in the bilateral cervical region at multiple stations. The thyroid gland appeared normal. USG chest was normal. Cervical lymph node biopsy was taken. Histopathology (HPE) confirmed the diagnosis of classical Hodgkin lymphoma [Fig.1]. Immunohistochemistry (IHC) showed CD15 +, CD30+, MUM1-ve and PAX5 weak +ve , ALK1-ve, CD 45-ve, OCT2-ve, CD3-ve, and CD20-ve pattern [Fig 2]. By time HPE report came, she was already 37 weeks, and after discussion in the medical tumor board meeting a decision for elective induction of labour was taken. Labour was induced with intracervical foley's catheter and tablet misoprostol 25 microgram simultaneously. She required 4 doses of misoprostol 25 micgrogram 4 hours apart . The patient had

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a full-term vaginal delivery of a girl child with a birth weight of 2320 grams with no gross congenital malformations. Apgar Score of 8,10 at 1 and 5 minutes. The patient was observed for 24 hours and underwent contrast enhanced computed tomography (CECT) neck, chest, abdomen for the staging and echocardiography (EHCO) as pre-treatment evaluation. ECHO was suggestive of mild MR, mild TR with normal biventricular function with mild circumferential pericardial effusion seen. CECT Neck, chest, and abdomen revealed the presence of an ill-defined soft tissue density mass lesion arising from the mediastinum and extending into apical and anterior segments of RUL having postcontrast attenuation value of 105 HU and measuring 7x7x10.2cm. The mass lesion extends into the pre-paratracheal region with compression of the trachea at the lower trachea and carina level. The lesion was seen to cause encasement of the ascending aorta and its branches, SVC, brachiocephalic vein, subclavian vein on the right side, and bilateral common carotid, however, no intraluminal extension/thrombus was seen. Mass was seen to displace the brachiocephalic vein, left common carotid artery, and left subclavian artery laterally causing mediastinal widening. Multiple enlarged peripherally enhancing bilateral axillary lymph nodes were noted, the largest on the left side measuring 4.2 x 2.3 cm seen in axial, sagittal and coronal view [Image 1 (a), (b), (c)]. Multiple enlarged peripherally enhancing lymph nodes were noted in cervical lymph node stations bilateral II, III, IV, and bilateral supraclavicular. Mild splenomegaly noted (Ann Arbor staging -III). She was planned for six cycles of ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) regimen chemotherapy by the medical oncology team. The patient and family were explained about the disease in detail, the possible risks and benefits of chemotherapy. Effect of chemotherapy on future fertility was discussed and available options for fertility preservation were discussed. Possible adverse effects of breastfeeding on the baby were discussed and milk suppression was given after discussion. The patient was then started on chemotherapy with an ABVD regimen which she tolerated well. She received 6 cycles of chemotherapy and her follow-up positron emission tomography-computed tomography (PET-CT) showed complete remission of the disease. Both mother and baby are doing well and are under follow up.

DISCUSSION

Lymphomas are the fourth most common type of malignancy in pregnancy after melanoma, breast cancer and cervical cancer.[1] Hodgkin lymphoma (HL) is more common than Non Hodgkin lymphoma (NHL).[2] Reported incidence of HL in pregnancy is around 1/1000-1/6000 deliveries. Symptoms of HL includes the development of palpable lymph nodes or constitutional symptoms like weight loss, night sweats, palpitations, and fatigue. Diagnosis is usually delayed in pregnancy as physiological changes of pregnancy mimic constitutional symptoms of lymphoma. Sometimes the patient may remain asymptomatic for a long period as in our case where swelling in the neck developed suddenly causing discomfort in neck at 35 weeks that brought her for evaluation. There were no constitutional symptoms in our patient.

Histopathology confirmation is must for the diagnosis. Imaging studies usually CT or PET combined with CT are required to stage patients with lymphoma. These tests cause significant radiation exposure to babies and are not recommended during pregnancy.[3] Chest X-ray with abdominal shield and ultrasound for abdominal assessment can be done. MRI without gadolinium administration can be used whenever required. Iodine-based contrast agents are contra-indicated during all stages of pregnancy.[4] In our case our patient presented at 35 weeks of pregnancy and by the time her diagnosis of HL was confirmed by histopathology she was already 37 weeks with no aggressive or high risk features requiring emergency management, hence delivery followed staging CECT was planned after discussion in the tumor board.

Mainstay of treatment for HL is chemotherapy. However chemotherapy can adversely effect the growing fetus. Hence, most crucial aspect in the management of HL is to decide on timing of initiation of chemotherapy and timing of delivery. It is good to prolong pregnancy to avoid preterm birth where-ever possible.[5] Teratogenic effect of chemotherapy administered to mother depends on period of gestation at exposure, dose of drug and type of drug given. Chemotherapy if administered between 2-8 weeks of pregnancy increases risk of congenital malformations and should be avoided. Treatment after thirteen weeks is considered safe and without teratogenic effect bur can be associated with preterm delivery, fetal growth restriction and low birth weight babies.[6] Most commonly used regimen for treatment includes bleomycin, doxorubicin, vinblastine and vincristine. This regimen is known to be safe when administered after first trimester.[7] Accurate assessment of prognosis is must to direct appropriate treatment at early phase. Moshe Y et al discussed about management of HL according to pregnancy stage and disease stage. During first trimester, termination of pregnancy after discussion and informed consent can be considered as one of the option in case waiting for few weeks can put the life of mother in danger. Vinblastine therapy or steroids only therapy can be considered in women who wants to continue pregnancy but treatment in necessary and cannot be postponed. In second and third trimester, early stage and advanced stage disease is treated with ABVP regimen for 4-6 months and 6-8 months respectively. In patients who are receiving chemotherapy during antenatal period their delivery should be postponed for 2-3 weeks following treatment for the bone marrow to regains its function. Lymphoma with supradiaphragmatic involvement can be treated with radiotherapy during pregnancy with adequate abdominal protection. Targeted therapy with Rituximab, a first-generation anti-CD 20 monoclonal antibody is known to cross the placenta, hence avoided during pregnancy. Management of advanced disease, visceral involvement, sub-diaphragmatic disease or disease with rapid progress remains controversial. As it increased the risk of abortion and congenital malformations with alkylating agents or multi-agent regimens such as MOPP (mechlorethamine hydrochloride, oncovin, procarbazine hydrochloride) & MOP (mechlorethamine hydrochloride, procarbazine hydrochloride), these drugs are to be best avoided during pregnancy.

Sometimes treated cases of HL present with relapse during pregnancy. Depending upon the time of appearance of symptoms after initial regimen relapse can be described as early (post ABVP <6 months) or late (beyond 6 months, especially if exposed to 2-4 cycles of ABVP only). In early relapse cases termination of pregnancy and treatment with second line regimen, high dose therapy or ASCT (Autologous stem cell transplantation), platinum and gemcitabine-based therapy can be considered. For late relapse cases ABVP during pregnancy, delivery and HDT/ASCT and alternate therapy with platinum /gemcitabine can be tried.[8]

Clinical features and prognosis are comparable in pregnant and non-pregnant patients and long term survival rate in patients in both groups is same. However, disease with advanced stage is common in pregnant women. Patients who are on chemotherapy in the postpartum period should be discouraged from breastfeeding, as most chemotherapeutic drugs can be excreted into breast milk and may cause potential risk to the baby.

The gold standard and first-line treatment in HL is the ABVD regimen showing a cure rate of 90% and is found to have very low gonadotoxic potential.[9] Some studies show that the ABVD regimen was associated with a significant fall in both ovarian follicle and endometrium thickness at 6 month follow-up time but it was followed by recovery at 12 months in both ovaries. So generally many young patients receiving this regimen are not offered fertility counselling. But 15-20% of cases are refractory to ABVP regimen or relapse on treatment or in need of salvage therapies that are usually more gonadotoxic and onco-fertility counselling is a must in those cases.[10] Embryo preservation is the oldest method of fertility preservation. Now oocyte preservation, ovarian tissue cryopreservation and its transplantation in females are being increasingly used.

CONCLUSION

Hodgkin lymphoma in pregnancy presents a complex clinical scenario that requires careful consideration of both maternal and fetal factors throughout pregnancy. With appropriate management, including the use of chemotherapy regimens deemed safe for pregnancy and close monitoring of fetal well-being, favourable outcomes can be achieved for both the mother and the baby.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INFORMED CONSENT

Patient and her husband's consent was taken.

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Annexure 1: Summary of Cases of Hodgkin lymphoma diagnosed for the first time during pregnancy from 2009-2024

Authors	No. of cases	Age (years)	Parity	Trimester	Presenting symptoms	Type of HL	Stage	Treatment received	Treatment delivery	GA at (weeks)	Maternal Outcome	Fetal Outcome
Israel R et al.	01	26	NA	I	Persistent & Progressive Lymphadenopathy	MC	IIIA	NA	AVD (8)	10	CR	A
Iriyana N et al.	01	34	P2	II	Enlarge bilateral neck lymph node, supraclavicular, & Axillary lymph nodes	NS	IVA	II PP	ABVD (3.5)	PP: ABVD(6)	41 UN	CR
Chunag FL et al.	01	25	NA	I	Cough Unintentional weight loss Right supraclavicular 2cm lymph nodes	NS	IIIB	NA	ABVD	FT	CR	UN
Kasonkanji E et al.	01	26	NA	II	Painless progressive cervical lymphadenopathy	NA	NA	NA	ABVD(6)	FT	CR	UN
Cotteret C et al.	01	41	NA	III	Right supraclavicular adenopathy upto 3 cm	NA	IIA	III PP	Corticosteroids ABVD PP: ABVD	33	CR	PT
Delzotto J et al.	01	21	P0	II	Shortness of breath Facial swelling Lightheadedness Intermittent night sweats Syncopal event Enlarges the neck. Lymph node Swelling in the neck	NS	NA	II	Antenatal ABVD PP: ABVD + RT	28	CR	PT

NICU admission

Significant interaction between amoxicillin/clavulanate and warfarin: A case report highlighting international normalized ratio elevation and management strategies

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SUMMARY

This case report emphasizes a notable interaction between amoxicillin/clavulanate and warfarin, leading to a substantial elevation in INR values from a baseline of 1.4 to 7.9. The increase in INR highlights the influence of amoxicillin/clavulanate on the anticoagulant effects of warfarin, which is likely the result of its disruption of gut flora and vitamin K metabolism. After the transition to flucloxacillin, an INR reduction to 3.0 was noted, this fall in INR levels was consistent with the latest studies suggesting the reduced impact of flucloxacillin on INR. The stabilization of the patient's INR following the change in antibiotics suggests that flucloxacillin is comparatively safer for individuals on warfarin.

INTRODUCTION

Warfarin is an oral anticoagulant widely used for the prevention and treatment of thrombosis. Globally, warfarin is one of the most frequently used oral anticoagulants for long-term therapy[1] In 2022, an analysis across 12 European Union countries was done and it showed that Warfarin is still the primary oral anticoagulant in 20–40% of patients requiring long-term anticoagulation, particularly in patients with mechanical heart valve.[2] In the United Kingdom, approximately 1% of the general population and 8% of those over 80 years are prescribed warfarin.[3]

In Europe, guidelines from the European Society of Cardiology recommend its use in specific indications such as mechanical heart valves, while Direct Oral Anticoagulants (DOACs) are replacing warfarin in other settings.[4,5] Monitoring the International Normalised Ratio (INR) is crucial during warfarin therapy. The dosage is adjusted to maintain INR within the therapeutic range to avoid thrombotic or haemorrhagic complications.[4]

Antibiotics may interact with warfarin, leading to significant INR changes. Multiple reports document elevation of INR levels and/or haemorrhage associated with combined amoxicillin and warfarin use.[5,6] Amoxicillin is recognised for its effect on INR, whereas amoxicillin/clavulanate which is a combination beta-lactam/beta-lactamase inhibitor, has less comprehensive literature regarding its isolated impact on INR levels.

This case report seeks to investigate the effect of amoxicillin/clavulanate on INR in a patient undergoing warfarin therapy for thromboembolic event prophylaxis. This example highlights the importance of closely monitoring INR levels and adjusting warfarin dosages as needed when administering amoxicillin/clavulanate to ensure both patient safety and effective anticoagulation.

CASE PRESENTATION

A 93-year-old man presented to the emergency department after having a mechanical fall at home. He reported losing his balance while attempting to get into bed; there was no prodromal dizziness and he was alert and orientated on arrival. His medical history comprised pulmonary embolism (on long-term warfarin alternate day dosing of 1 & 2mg), Ischaemic heart disease, type 2 diabetes, osteoarthritis, age-related macular degeneration and cataracts.

During admission, he developed a productive cough and low-grade pyrexia. He was found to be SARS-CoV-2 positive on PCR. Inflammatory markers on admission showed leucocytosis and an elevated c-reactive protein (Neutrophils 8.2x 10^9/L, CRP - 280mg/L). Empirical oral amoxicillin/clavulanate with a dosage of 625 mg three times a day was initiated in accordance with local guidance for suspected bacterial pneumonia complicating COVID-19. Baseline International Normalised Ratio (INR) four days earlier was 1.4. After Day 1 of amoxicillin/clavulanate the INR rose to 5.7, peaking at 7.9 on Day 2 and reaching 7.5 on Day 3. Warfarin was withheld; no overt bleeding occurred and phytomenadione 1mg was administered to counter the elevated INR.

Potential contributors to the supra-therapeutic INR such as reduced dietary vitamin K intake was confirmed by reviewing each patent's dietary intake such as diet history and diet documentation but no significant changes in diet patterns were recorded due to the patient being on a diabetic hospital diet. To rule out hepatic dysfunction as a contributing factor, liver and renal functions were observed to be within the reference limits as indicated by stable liver enzymes levels (AST, ALT, Bilirubin). Finally, medication non-adherence was considered through self-reporting of patient's pill counts but none appeared contributory.

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Table I: Trend of INR Levels in response to amoxicillin/clavulanate and flucloxacillin treatment

Day	Drug Administered	INR Value	Interpretation
Baseline (4 days before)	None	2.0	Pre-treatment baseline INR value.
Day 1 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	5.5	Elevated INR following start of amoxicillin/clavulanate.
Day 2 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	7.9	Peak INR observed; concern for increased bleeding risk.
Day 3 of Amoxicillin/Clavulanate	amoxicillin/clavulanate	7.5	Slight decrease, received 1mg phytomenadione.
Day 1 after switch	flucloxacillin	6.6	Switched to flucloxacillin; INR begins to decline.
Day 3 after switch	flucloxacillin	3.0	INR significantly decreased, trending toward normalization.

Further, computed tomography of the thorax and abdomen revealed no intra-abdominal or intrathoracic source of sepsis. Persistent fever prompted re-examination, which demonstrated erythematous swelling of the right forearm consistent with cellulitis. Amoxicillin/clavulanate was discontinued and oral flucloxacillin 1000 mg every 6 hours was commenced.

Following the antibiotic switch the INR declined to 6.6 on Day 1 and to 3.0 on Day 3, with subsequent readings remaining within the therapeutic range. No INR-related complications were observed and warfarin therapy was resumed at the patient's usual dose once the INR stabilised.

DISCUSSION

The observed increase in INR from 1.4 to 7.9 within two days of initiating amoxicillin/clavulanate highlights a significant interaction between this antibiotic and warfarin. The increase in INR observed in our patient can be attributed to amoxicillin/clavulanate's effect on gut flora and vitamin K metabolism.[7] Although gut flora plays an important part in the conversion of vitamin K, liver enzymes have also been said to play an equally significant role in the metabolism of vitamin K. Patients with liver failures as a result of lack of liver enzyme excretion disrupts the metabolism of vitamin K in their bodies.[6]

Most penicillin-class antibiotics can boost warfarin's effects, thereby increasing the risk of bleeding, especially when administered intravenously.[10] This results in decreased vitamin K producing bacteria, which in turn leads to reduced amount of vitamin K absorbed, and thus manifests as vitamin K deficiency; the exception to this is dicloxacillin and nafcillin, which reduce the efficacy of warfarin by increasing warfarin's metabolism.[6,7]

After the switch from amoxicillin/clavulanate to flucloxacillin, a significant reduction in INR from 6.6 to 3.0 was observed over a period of three days.

1. Timeline of Antibiotic Initiation vs INR Rise
Written pharmacologic expectations suggest that transient antibiotic administration (such as amoxicillin/clavulanate) usually takes several doses to significantly inhibit gut flora and affect vitamin K levels. In your case, INR rose dramatically within 24 hours, after just the first few doses (INR 5.5 after <24 hours and 5 doses by Day 2; peaked at 7.9 by Day 2). This is earlier than typical but aligns with acute potentiation of warfarin metabolism or altered pharmacodynamics.

2. Resolution after Antibiotic Switch
The INR decline after switching from amoxicillin/clavulanate to flucloxacillin, without new antibiotic exposures, supports a direct drug–warfarin interaction rather than delayed drug-induced INR rise or COVID-only effects.

This data corroborates existing literature suggesting that Flucloxacillin exerts minimal impact on INR in contrast to amoxicillin/clavulanate. Mannheimer et al. (8) found that flucloxacillin exerted minimal effects on INR in warfarin users, consistent with our findings.8 In contrast, a case report from China states that β-lactam or β-lactamase inhibitors like amoxicillin/clavulanate and piperacillin or tazobactam generally produce a more substantial increase in INR. The clavulanate component in amoxicillin/clavulanate inhibits bacterial β-lactamases, further disrupting gut flora and leading to reduced vitamin K synthesis. Similarly, piperacillin or tazobactam have been associated with coagulopathy through a vitamin K-dependent mechanism. Thus, while flucloxacillin can alter INR levels due to microbiome disruption, its effect is typically less significant than that observed with other β-lactamase inhibitors.[9]

While COVID–19–associated coagulopathy may have contributed to baseline warfarin destabilization, the very sharp rise and rapid fall in INR aligning with antibiotic change favour a primary pharmacologic interaction, rather than a slower, more diffuse COVID-driven INR elevation. COVID-19 is known to induce a pro-inflammatory and pro-thrombotic state, frequently disrupting coagulation pathways, including elevated D-dimer, CRP, and derangements in INR control, even in the absence of interacting medications.[10] Several reports have shown that patients on warfarin may experience supratherapeutic INR levels during acute COVID-19 infection due to increased sensitivity or decreased clearance of the drug.[10] While this may have contributed to the observed INR rise, the sharp elevation shortly after starting amoxicillin/clavulanate and its subsequent decline following antibiotic withdrawal support a pharmacologic interaction as the primary driver.

This example highlights the necessity of careful INR monitoring when antibiotics are administered to individuals on warfarin. Amoxicillin/clavulanate and warfarin must be carefully managed to prevent any problems that could arise from high INR levels. Clinicians should anticipate potential INR fluctuations when commencing or modifying antibiotic treatment and adjust warfarin dosages accordingly to maintain therapeutic INR levels.

CONCLUSION

The normalization of the patient's INR following the alteration of antibiotics indicates that flucloxacillin is comparatively safer for individuals on warfarin. It is advised that clinicians modify INR monitoring protocols while initiating or adjusting antibiotic treatment in patients on warfarin. This is especially crucial with antibiotics that notably affect INR levels, such as amoxicillin/clavulanate. Consistent monitoring and prompt modification of warfarin dosage can avert problems associated with elevated INR and provide safe therapeutic treatment.

Further research is required to examine the comprehensive interactions between antibiotics and warfarin, especially those involving prolonged or intricate treatment protocols. Examining the mechanisms regulating these interactions and their clinical ramifications may yield better guidelines for managing INR and enhancing patient safety. Subsequent research should concentrate on evaluating the effects of different antibiotics on INR levels across diverse patient demographics to improve our comprehension and management of anticoagulant treatment.

CONFLICT OF INTEREST

None

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DECLARATION

We affirm that this work is original, and consent was obtained from the patient. There were not any conflict of interest by the authors.

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CASE REPORT

Racing heartbeats at high altitude: A case of relapsed hyperthyroidism on the Everest Base Camp trail

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SUMMARY

High-altitude environments impose significant physiological stress, particularly on individuals with pre-existing medical conditions. This case report describes a physically fit 36-year-old woman who experienced a relapse of hyperthyroidism on the eighth day of her ascent to Everest Base Camp at an altitude of 5,180 m. Upon returning to sea level, she presented to the emergency department with persistent palpitations and a 3-kg weight loss over twelve days. Thyroid function tests confirmed a relapse of hyperthyroidism. Her liver enzymes were elevated 12 days later, suggestive of hepatocellular injury.

Liver injury following high-altitude exposure is rare but may be attributed to hypoxic stress, oxidative damage, and metabolic strain. Hyperthyroidism increases the metabolic rate and oxygen demand, potentially increasing the liver's susceptibility to hypoxia-induced injury. In this case, the interplay between preexisting thyrotoxicosis, high-altitude hypoxia, oxidative stress, and rapid descent likely contributed to transient liver dysfunction. Additional risk factors, including cold exposure, inadequate caloric intake, and dehydration, may have further exacerbated hepatic stress.

The patient was treated with radioactive iodine therapy for definitive hyperthyroidism control along with supportive care. Her liver enzymes normalised within three months after the descent. This case emphasises the importance of pre-travel risk assessment for individuals with thyroid disorders planning high-altitude activities. Clinicians should acknowledge the potential for hepatic stress in patients with hyperthyroidism exposed to high altitudes and advise appropriate preventive measures. Further research is needed to explore the impact of high-altitude hypoxia on liver health, particularly in individuals with underlying metabolic conditions.

INTRODUCTION

High-altitude environments, typically defined as elevations above 2,500 meters, present significant physiological challenges due to reduced atmospheric pressure and oxygen availability. These conditions can cause various altitude-related illnesses, ranging from acute mountain sickness to severe conditions such as high-altitude cerebral oedema and high-altitude pulmonary oedema. While hepatic dysfunction at high altitudes is less commonly reported, hypoxic stress and hepatic ischemia may contribute to liver injury.

Individuals with preexisting medical conditions, such as hyperthyroidism, may be particularly vulnerable to these physiological stresses, although this aspect remains largely unexplored. Hyperthyroidism, characterised by excessive thyroid hormone production, accelerates metabolic processes and increases oxygen consumption, potentially exacerbating hypoxic stress at high altitudes.[1] This case report details a young woman with relapsed hyperthyroidism who developed liver injury after descending from the Everest Base Camp trail.

CASE PRESENTATION

Case History

A 36-year-old female with a known history of Graves' disease for the past five years had been managed with oral carbimazole (5 mg) daily. After maintaining euthyroid status for six months, her dose was tapered to three times per week before being discontinued in November 2023. Her last thyroid function test (TFT) seven weeks before the trek showed normal thyroid stimulating hormone (TSH; 2.87 mIU/L) and free thyroxine (T4; 9.8 pmol/L) levels. She had no prior history of liver disease, medication overuse, alcohol consumption, or smoking. Physically fit and active, she had previously summited two peaks above 4,000 meters over two consecutive years without complications.

On 10 September 2024, she embarked on a 12-day trek to the Everest Base Camp (5,364 m). Despite following a specified acclimatisation protocol, she experienced racing heartbeats, laboured breathing, and fatigue on the eighth day at an altitude of 5,180 m. Her symptoms were managed with rest, hydration, and meals. She had successfully reached the Everest Base Camp the following day and descended to Lukla (2,804 m) over three days. Throughout the trek, her blood oxygen levels, measured with a pulse oximeter, remained above 95% except for occasional dips (91%–94%) at altitudes above 5,000 meters. She had no muscle pain or other features suggestive of rhabdomyolysis.

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Twelve days after returning, she presented to the emergency department with persistent palpitations and noticeable weight loss. TFT confirmed a third relapse of hyperthyroidism, and she was started on 30 mg carbimazole, tapered to 15 mg within one week. Factors contributing to the relapse included young age (<40 years), a noticeable goitre, large thyroid volume, and high baseline free T_4 levels (≥40 pmol/L).

Clinical Findings

Her initial assessment revealed a pulse rate of 111 beats per minute, with normal blood pressure, respiratory rate, and electrocardiogram. Thyroid function tests showed a suppressed TSH level (<0.005 mIU/L) and an elevated free T4 concentration (58.7 pmol/L), consistent with relapsed hyperthyroidism and thyrotoxicosis. Liver function tests were initially within normal limits but demonstrated elevated aspartate aminotransferase (AST, 97 U/L) and alanine aminotransferase (ALT, 165 U/L) levels, 2.77 to 4.71 times above the upper normal limit, 12 days later, indicating hepatocellular injury. The ALT level subsequently peaked at 178 U/L. Both AST and ALT were normalised within three months after the descent. Her alkaline phosphatase, γ-glutamyl transferase, and bilirubin levels were within the normal range.

The viral serologies were negative for hepatitis A, B, C, and E. The autoimmune marker tests were negative for anti-nuclear, anti-smooth muscle, anti-mitochondrial, and anti-liver kidney microsome antibodies. Her immunoglobulin G level was within normal limits. Autoimmune hepatitis was excluded.

The abdominal ultrasound was unremarkable. The thyroid ultrasound scan in June 2023 showed a thyroid of normal size with no nodules, indicating a reduction from the mild enlargement seen in the 2019 scan (right lobe: 2.3 × 2.1 × 4.7 cm, left lobe: 2.4 × 1.7 × 5.5 cm, isthmus: 0.3 cm).

DISCUSSION

This case highlights the interplay between hyperthyroidism and high-altitude exposure in contributing to liver injury following a trek on the high-altitude Everest Base Camp trail. While various hypothetical mechanisms can be proposed, her hyperthyroidism status may have increased her vulnerability to hepatic stress. The timeline of liver injury induced by high-altitude exposure remains poorly understood. A metabolically active organ with high oxygen demand, the liver is vulnerable to hypoxic injury at high altitudes due to reduced oxygen availability. This patient experienced a hyperthyroidism relapse in a hypoxic and physically demanding environment after 9.5 months of successful remission. A previous systematic review suggests that patients with Graves' disease have a 50% relapse rate within 6–18 months after discontinuing antithyroid therapy.[2] Hyperthyroidism increases the metabolic rate and oxygen consumption, potentially increasing the liver's susceptibility to hypoxia and ischemic hepatopathy. In this case, a combination of these factors and high-altitude exposure likely contributed to liver injury.

Non-regulating oxidative stress plays a key role in hypoxic liver injury. Mitochondrial efficiency declines in low-oxygen environments, producing excessive reactive oxygen species (ROS) that damage cellular components. The thyrotoxicosis state may have acted synergistically with high-altitude hypoxia to cause liver injury. Elevations between 3,500 and 5,500 meters cause an approximately 25% reduction in maximal oxygen uptake, leading to high-altitude hypoxia. At such a high altitude, the expected resting oxygen saturation is around 82%–80%[3], and hepatic antioxidant defences are reduced, allowing greater ROS accumulation than the physiological level, leading to oxidative stress in hepatocytes.

While this patient's ascent followed established safety guidelines with appropriate acclimatisation protocols, her rapid 3-day descent did not provide sufficient time to adjust. Upon return to a normobaric, oxygen-rich environment, individuals previously adapted to hypobaric hypoxia may experience 'de-acclimatisation' phenomena, characterised by oxidative stress and inflammatory activation in tissues of vulnerable organs. This process has been conceptualised as a form of hypoxia-reoxygenation injury, where the richer oxygen environment acts as a pathophysiological insult. The insult acts as an analogue to toxicant exposure, causing a delayed and reversible pattern that aligns with transient hepatic stress rather than overt hepatocellular failure. Hypothetically, this rapid physiological transition can exacerbate physiological stress and increase the risk of cellular injury. Hypoxia-inducible factor 1 (HIF-1) plays a critical role in these scenarios. Experimental data from animal studies show that HIF-1 helps cells adapt to low oxygen levels by regulating physiological processes, such as oxygen delivery, energy metabolism, and inflammation, through ventilatory acclimation to hypoxia. It also helps to maintain oxygen homeostasis by promoting glycolysis, erythropoiesis, and angiogenesis.[4] However, prolonged or excessive HIF-1 activation under hypobaric hypoxia can disrupt cellular equilibrium, leading to oxidative stress, inflammation, and metabolic and structural damage in the liver. Changes in vascular dynamics and organ-specific blood flow regulation further aggravate these effects. The delicate physiological balance achieved at high altitudes is disrupted by rapid reoxygenation during descent. HIF-1 may remain active, perpetuating the damage initiated during hypoxia and amplifying oxidative stress and inflammatory responses.[5] It stimulates the release of proinflammatory mediators[6], leading to liver injury.

While mild, asymptomatic elevations in ALT and AST levels – defined as less than five times the upper limit of normal – are relatively common in primary care settings[7], such findings should not be dismissed. The appearance of transaminitis in these contexts follows an unpredictable trajectory, with a latency period ranging from days to weeks. For example, haematological de-acclimatisation from hypoxia is known to manifest within two weeks[8], suggesting that the effects of hepatocyte hypoxia-reoxygenation injury might follow a similar timeline. Although unmeasured factors could theoretically contribute to the observed liver enzyme elevation, this patient denied alcohol consumption, medication or herbal supplement use, and strenuous activity

during the post-travel period. She resumed her usual daily routine and rested considerably due to palpitations and fatigue. Hence, the liver transaminases elevation is most plausibly attributed to physiological responses of transient hepatic stress related to high-altitude exposure.

Additionally, the exacerbation of oxidative liver damage due to cold exposure at high altitudes (≤19°C), imbalanced energy intake/expenditure, glycogen depletion, and dehydration further highlight the multifaceted nature of altitude-induced liver injury. The body accelerates metabolic processes to generate internal heat, especially through non-shivering thermogenesis in the brown fat, liver, and muscles. This heightened metabolic activity elevates the production of ROS as a byproduct, contributing to oxidative stress.[9] Experimental data from animal studies show that exposure to acute or chronic cold ambient temperatures of around 4°C–10°C prompts metabolic and hepatic adaptations[10], underscoring how cold stress and high altitude can interact to impact liver health. Cold stress may also compromise the liver's antioxidant defences, as the enzymes and molecules responsible for neutralising ROS become overwhelmed. This imbalance between ROS production and antioxidant capacity can lead to oxidative stress in liver cells, triggering inflammation and potential cellular injury.

A disparity between energy expenditure caused by prolonged physical activity and energy intake from an unaccustomed Nepali diet is common. In this case, a 64-kg individual engaging in without load, self-selected speed or normal pace cross-country hiking with a metabolic equivalent of six for seven hours would burn approximately 2688 kcal. However, typical trekking foods – such as eggs (boiled, poached, scrambled, or omelettes), Tibetan bread (fried and sweetened), a handful of French fries, and vegetable fried rice or plain rice – provide significantly fewer calories. Although precise caloric measurement was not performed, the patient's meals were photo-documented during the trek. Using AI-based dietary analysis, the average daily caloric intake was estimated at approximately 2,000 kcal, compared with an energy expenditure of about 2,688 kcal based on activity level and environmental conditions. This modest calorie deficit, combined with inadequate intake of essential nutrients and a reduced appetite commonly experienced at high altitudes, may have contributed to metabolic stress and delayed transient liver enzyme elevation. Nevertheless, these estimates are inferential and based on photo-assisted dietary approximation rather than direct calorimetry. Dehydration, common in high-altitude environments and often compounded by poor hydration strategies due to cool and windy conditions, further exacerbates hepatic stress by reducing blood flow to the liver, thereby contributing to transaminitis development days later.

Treatment Plan

Given her third hyperthyroidism relapse and elevated liver enzymes, this patient was counselled for definitive treatment with radioactive iodine therapy (RAI). Since she exhibited no signs of thyroid storm or liver failure, she promptly underwent RAI, leading to symptom resolution. She was also given supportive care, including hydration, rest, and liver function monitoring. Her liver enzyme levels normalised within three months after the descent. Currently, she is on lifelong thyroid replacement therapy.

Implications for Clinical Practice

This case highlights several important considerations for attending medical practitioners managing patients with thyroid disorders planning to engage in high-altitude activities:

1. Pre-travel risk assessment: Patients with hyperthyroidism, even if well-controlled, should undergo a comprehensive pre-travel assessment before engaging in high-altitude activities. Monitoring their thyroid hormone levels 2–4 weeks before travel may help identify those at risk of relapse. They should also be counselled on strategies to manage potential relapse at high altitudes, including carrying an adequate supply of antithyroid medication for use if necessary.

2. Recognition, monitoring, and mitigation of relapsed hyperthyroidism at high altitudes: The prompt recognition of relapsed hyperthyroidism at high altitudes can be challenging because there is no reliable medical laboratory to guide diagnosis confirmation. The diagnosis relies primarily on the patient's ability to maintain a high index of suspicion and associate palpitations with a potential relapse of hyperthyroidism. The patient must distinguish between palpitations resulting from hyperthyroidism relapse and those induced by excessive exertion on a physically demanding, hilly trail. This patient was fortunate that liver injury resulting from relapsed hyperthyroidism manifested only at sea level. Had it occurred at a high altitude, medical evacuation by helicopter would have been the most appropriate and beneficial course of action.

CONCLUSION

This case highlights the link between hyperthyroidism relapse and increased susceptibility to hypoxic liver injury at high altitude. As this is a single case report, causal inference cannot be established. The proposed mechanisms are speculative and should be interpreted with caution. Nonetheless, the case contributes to existing knowledge by highlighting that even a well-managed thyroid condition does not eliminate the risks of high-altitude exposure. Awareness of relapse beyond six months post-treatment is crucial for effective risk mitigation. A thorough pre-travel assessment is essential, and clinicians should recognise the potential for hepatic stress in patients with hyperthyroidism at high altitude. Further research is needed to understand the effects of high-altitude hypoxia on liver health, particularly in those with metabolic conditions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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CASE REPORT

The Unseen Fragility: Challenges in Diagnosing Osteogenesis Imperfecta in Neonates

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SUMMARY

Unexplained multiple bone fractures in infant can indicate non-accidental injury, however metabolic bone disease or skeletal dysplasia should always be considered as a differential diagnosis. We report a case of a term baby delivered via spontaneous vertex delivery following induction of labour for intrauterine growth restriction. Third trimester sonography revealed multiple congenital anomalies namely Dandy-Walker variant, hypomineralization and short limbs. At birth he showed relative macrocephaly, a long trunk and rhizomelia. In the absence of bony fractures and blue sclerae, he was diagnosed with skeletal dysplasia and discharged home on day five of life. On day thirty of life, he returned with a closed fracture of right femur prompting further evaluation. Blue sclerae, and a skeletal survey indicated of multiple old fractures with Wormian bones, suggesting Osteogenesis Imperfecta Type III. In conclusion, suspecting and evaluating Osteogenesis Imperfecta in infant with skeletal anomalies in the absence of initial overt symptoms is challenging. Early recognition and management are crucial for optimizing outcomes and preventing long term complications.

INTRODUCTION

Unexplained multiple bone fractures in infants often raise suspicion of non-accidental injury, but metabolic bone diseases or skeletal dysplasia should also be considered. Conditions associated with increased bone fragility, such as osteogenesis imperfecta (OI), can be subtle and challenging to diagnose, especially in the absence of obvious fractures. A high index of suspicion is critical when clinical features of bone fragility are present, though the correct subtype diagnosis can be difficult to determine.

This case highlights the challenges in early recognition and diagnosis of bone fragility disorders, particularly when clinical signs may not fully manifest at birth.

CASE PRESENTATION

A term infant was delivered via spontaneous vertex delivery following induction of labour for intrauterine growth restriction. Third-trimester sonography identified multiple congenital anomalies, including a Dandy-Walker variant, skeletal hypomineralization, and limb shortening. Amniocentesis revealed a normal karyotype (46, XY). The mother's antenatal course was unremarkable, with no significant complications or medical history. There was also no family history of bone-related problems. The infant had good Apgar scores and did not require resuscitation at birth. His birth weight was 2.97kg (between the 10th to 50th centile), with a length of 47cm (at the 10th centile), and a head circumference of 34.5cm (at the 50th centile).

Clinically, the infant exhibited relative macrocephaly, a long trunk, and rhizomelia, with no other significant dysmorphic features. A chest radiograph performed at birth was reported to show normal bone density with no evidence of fracture. Formal brain ultrasonography on day four of life revealed bilateral choroid plexus cyst and prominent cisterna magna. In the absence of bony fractures or blue sclerae, further investigations for bone hypomineralization and a skeletal survey were not pursued, and a clinical diagnosis of skeletal dysplasia was made. The infant was discharged on the fifth day of life with a scheduled follow-up plan.

On the day thirty of life, the infant was re-admitted with swelling and pain in the right thigh, without any preceding trauma. Re-evaluation revealed blue sclerae, though no other obvious bony deformities were noted. A skeletal survey demonstrated generalized osteopenia, old rib fracture (Figure 1), bowing of both femora with a fracture of the right femur (Figure 2), bowing of both humeri a distal right radius fracture with callus formation, and the presence of Wormian bones (Figure 3). Blood investigation showed a normal bone profile (calcium 2.7mmol/L, phosphate 2.12mmol/L and alkaline phosphatase 319IU) and a normal parathyroid hormone level of 3.31pmol/L (normal range: 1.59 – 7.24pmol/L), but a deficiency in Vitamin D at 20.8nmol/L (normal range: 75 – 100nmol/L). Based on clinical and radiographic findings, a diagnosis of osteogenesis imperfecta type III was established. The Orthopaedics team initiated non-surgical management, and the infant was supplemented with multivitamins. A repeat Vitamin D assessment at the age of 2 months showed normalisation of levels. He was also referred for genetic evaluation.

DISCUSSION

Osteogenesis imperfecta (OI) is a genetic disorder resulting from mutations affecting type I collagen synthesis, presenting as a rare skeletal dysplasia. It is characterized by decreased bone density, increased fragility, and a heightened risk of

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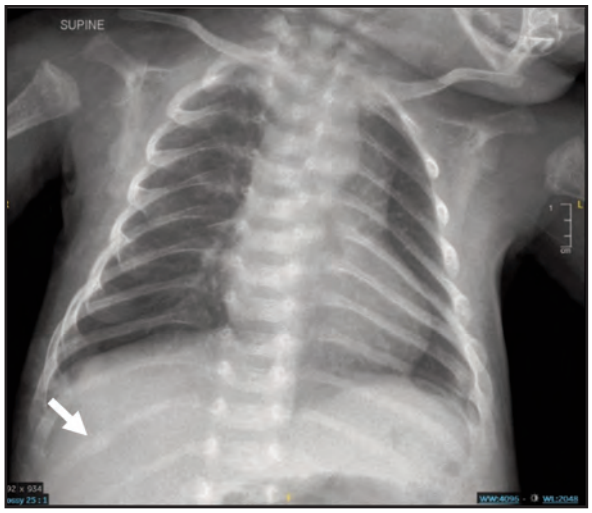

Fig. 1: Chest radiograph showing osteopenia and old rib fracture

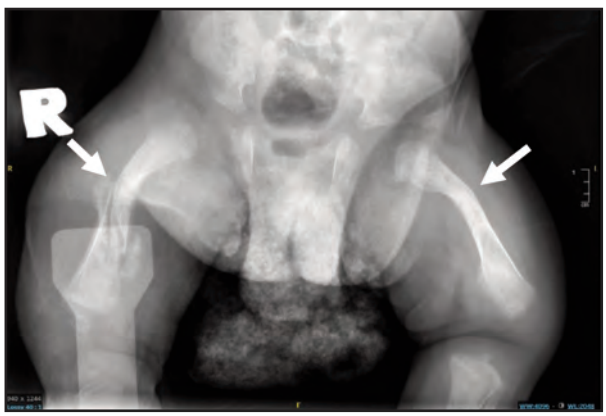

Fig. 2: Pelvic radiograph showing bowing of bilateral femur and fracture of right femur

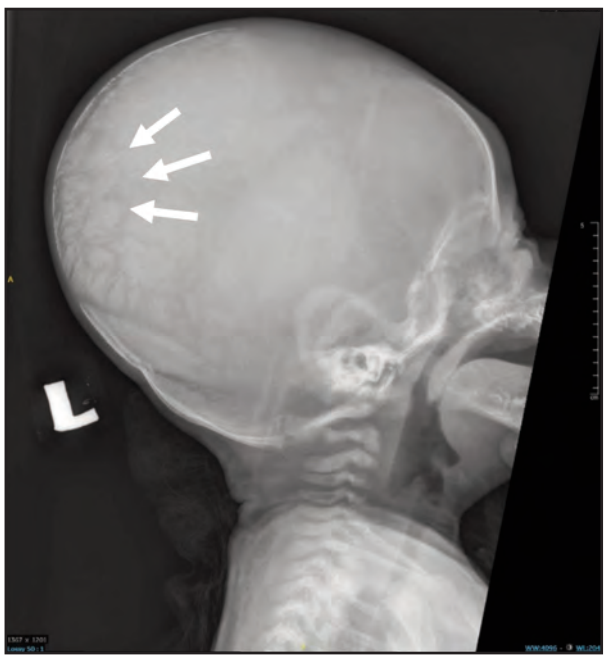

Fig. 3: Skull radiograph showing presence of Wormian bones

fractures.[1] The clinical spectrum of OI is highly variable, ranging from perinatal lethal forms marked by crumpled ribs, a fragile cranium, and multiple long bones fractures at birth, to milder forms that are either asymptomatic or present with subtle osteopenia and no skeletal deformities.[2]

Diagnosis of OI is primarily based on clinical and radiographic findings; however, on general examination, the absence of fractures and blue sclerae at birth makes recognising non-lethal forms of OI particularly challenging. Prenatal ultrasound can therefore be especially valuable in identifying non-lethal forms of OI, providing early insight into potential skeletal abnormalities, particularly when skeletal hypomineralization or limb shortening is detected.[3] In this case, however, these ultrasonographic findings, along with other suggestive features of OI were overlooked, resulting in a delay in diagnosis and management until the patient presented again one month later. This underscores the importance of not neglecting antenatal findings, even when classic features like fractures or blue sclerae are absent. Bone hypomineralization and limb shortening may be the earliest indicators of OI and ensuring close postnatal follow-up and early imaging in such cases can significantly improve patient outcomes by enabling timely diagnosis and intervention.[4]

Since the diagnosis of OI was not initially established, the patient was at risk of being misidentified as a victim of child abuse when presenting with multiple fractures. Differentiating OI from nonaccidental injury can be challenging, as OI is rare while child abuse is more common.[5] Features that helped to distinguish OI in our case include the presence of blue sclerae, Wormian bones on skull X-ray, and bone deformities. However, milder forms of OI, may not have these typical features, making diagnosis more difficult. Additionally, blue sclerae can be a normal finding in infants up to four months old, further complicating the distinction. While OI should always be considered in cases of unexplained fractures, it is also important to recognize that children with OI can still be victims of abuse. A careful and thorough assessment is essential to ensure the correct diagnosis and appropriate management.

The management of OI requires a multidisciplinary approach focused on fracture prevention, bone density improvement, and orthopaedic complications.[6] Bisphosphonates are commonly used to enhance bone strength and reduce fracture risk, while surgical interventions may be necessary to correct deformities and improve mobility.[7] In this case, the infant was managed conservatively, highlighting the importance of ongoing monitoring and early intervention to optimize long-term outcomes. Additionally, the patient had a low vitamin D level, a common finding in OI.[8] Vitamin D deficiency can worsen bone fragility and influence disease severity. Therefore, supplementation along with drug therapy and adequate calcium intake, is essential to support bone health and mitigate disease progression.

The discussion has emphasized the critical role of early detection and intervention in improving outcomes for neonates with OI. Through heightened awareness, serial imaging, and genetic testing, healthcare providers can identify the condition early, enabling timely management.

CONCLUSION

In conclusion, the early identification of OI is essential for optimizing outcomes. By recognizing prenatal signs, performing comprehensive post-natal assessments, and conducting serial imaging, healthcare providers can ensure timely diagnosis. Genetic testing further confirms the condition, allowing for early intervention that significantly reduces complications and improves long-term prognosis for affected infants.

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DECLARATIONS

The authors have no conflicts of interest to disclose.

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Primary large cell neuroendocrine carcinoma arising from the uterine corpus

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SUMMARY

Large cell neuroendocrine carcinoma (LCNEC) of the endometrium is a rare high-grade malignancy with an aggressive course, the definitive preoperative diagnosis is difficult due to non-characteristic radiological and pathological findings. We report a case of pure endometrial LCNEC in an 82-year-old woman who presented with an ill-defined solid tumour originating from the endometrium and extending through the myometrium with ovarian, fallopian tube and omentum metastases. The tumour was highly pleomorphic with a high nuclear/cytoplasmic ratio and large nuclei, highly cellular with solid sheets of large cells and interspersed areas of extensive necrosis. Tumour cells expressed CD56, synaptophysin, chromogranin A, p53 and p16. Ki67 was 80%. The disease progressed and the patient died two weeks after surgery. To facilitate differential diagnosis in high-grade undifferentiated endometrial tumours lacking typical morphological features of neuroendocrine tumours, LNEC should be considered and neuroendocrine markers should be added to the immunohistochemical panel.

INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) of the uterine corpus is a rare high-grade entity of with an aggressive progression. Neuroendocrine carcinoma (NEC) arising from the endometrium make up less than 1% of all uterine endometrial carcinomas with early hematogenous/lymphogenous metastasis and poor prognosis. Uterine LCNEC is particularly rare with limited data to case reports.[1]

CASE PRESENTATION

An 82-year-old woman presented with abdominal pain and ascites. After radiological imaging with detection of heterogeneous mass and ascites, she underwent surgery (Figure 1). The uterine corpus was completely filled with an ill-defined, white, solid tumour arising from the endometrium, infiltrating the wall and extending through the myometrium. The surfaces of the ovaries and fallopian tubes were covered with small white tumour nodules. The surface of the omentum majus was covered with small white nodules and the sectioned surface was covered with numerous white solid tumour nodules. Microscopically, the tumour was highly cellular with solid sheets of large cells and interspersed areas of extensive necrosis. The tumour cells were highly pleomorphic with relatively abundant eosinophilic cytoplasm, high nuclear/cytoplasmic ratio and large nuclei (Figure 2). There were numerous abnormal mitotic figures and cell apoptosis. The mitotic count of tumour cells was >10 per 2 mm^2. Immunohistochemically, tumour cells showed expression of p53 and p16. The proliferation index with Ki67 was 80%. Vimentin and CK8/18 were only focally positive. There was no staining for panCK, CK7, ER, PR, PAX8, WT1 and CD45. The surfaces of the ovaries and fallopian tubes were infiltrated by the tumour. Due to unclear differentiation and marked nuclear atypia, staining with neuroendocrine markers was performed. The tumor cells were strongly positive for CD56, synaptophysin and chromogranin. The diagnosis of large cell neuroendocrine carcinoma of the endometrium was established. According to the American Joint Committee on Cancer (AJCC) staging system and the International Federation of Obstetrics and Gynaecology (FIGO), the tumour stage was pT3a N2a M1, FIGO IIIA (tumour involving serosa or adnexa with macrometastases in para-aortic lymph nodes). The patient died two weeks after surgery.

DISCUSSION

NECs are categorised into well or poorly differentiated grades and further subdivided into small cell neuroendocrine carcinoma (SCNEC) or LCNEC. These types of tumours are mainly found in the lungs and less commonly in the gastrointestinal or genitourinary tract. The incidence of NEC and LCNEC in the female genital tract is low, with the uterine cervix being the most common site. LCNEC of the endometrium is extremely uncommon.[2]

No diagnostic criteria have been proposed for endometrial neuroendocrine carcinoma. According to the WHO classification for lung tumours, LCNECs are diagnosed based on large cell size exhibiting low nuclear/cytoplasmic ratio, >10 mitotic figures in 2 mm^2, and by showing both neuroendocrine histology and at least one immunohistochemically positive neuroendocrine marker (chromogranin, synaptophysin or CD56).[3] Our case fulfils these criteria.

Little is known about the molecular characteristics of endometrial NECs and how they differ from lung NECs and more common endometrial cancer histotypes. Howitt et al.

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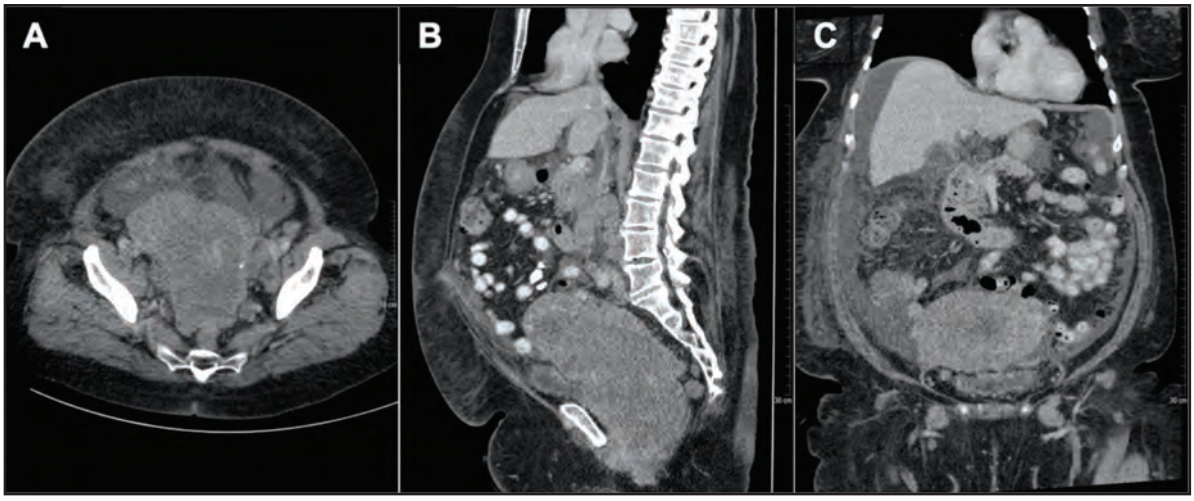

Fig. 1: Preoperative findings on computed tomography. (A) Axial reconstruction shows the giant mass lesion in the uterus with loss of normal architecture. (B) Sagittal reconstruction demonstrates the mass lesion with paraaortic lymph node metastasis and (C) coronal reconstruction shows the mass lesion in the uterus with bilateral inguinal lymph node metastasis and diffuse ascites

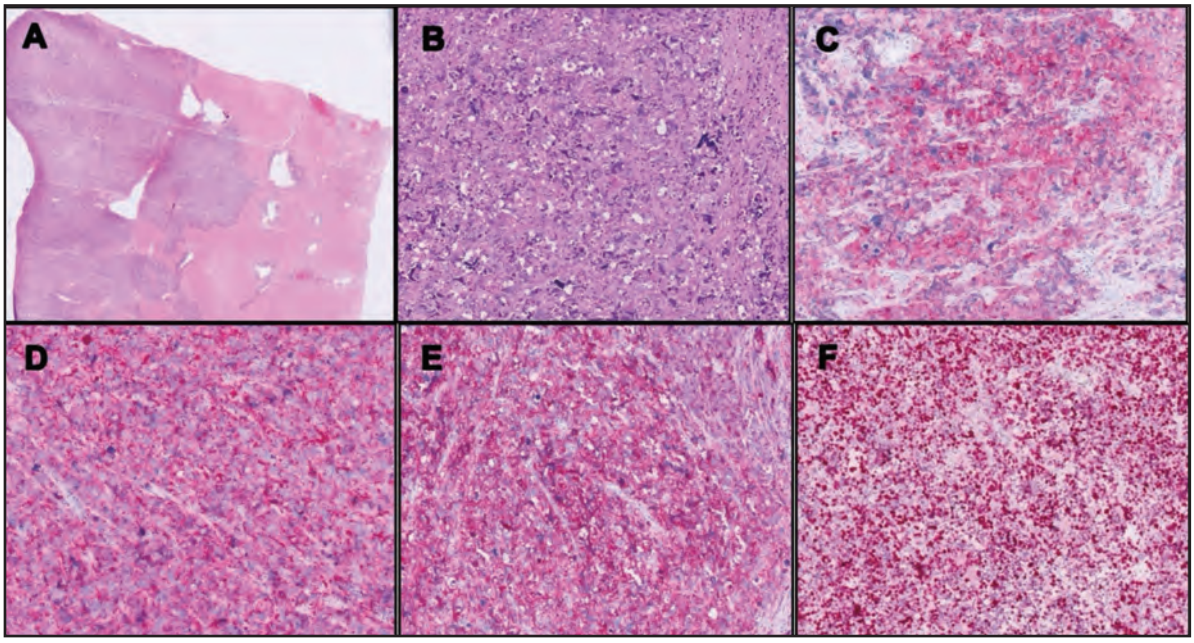

Fig. 2: Histology and immunohistochemistry. (A) Tumour with solid sheets of large cells and areas of extensive necrosis arising from the endometrium and extending through the myometrium. (B) The tumour cells are highly pleomorphic with a high nuclear/cytoplasmic ratio, large nucleoli and numerous mitotic figures and cell apoptosis. Immunohistochemically the tumour cells showed expression of (C) chromogranin A, (D) synaptophysin and (E) CD56. (F) The proliferation index with Ki67 was 80%

conducted a study to investigate the molecular changes in a series of 14 cases of pure NEC (including LCNEC and SCNEC) and mixed NEC with LCNEC or SCNEC components, along with endometrioid adenocarcinoma or carcinosarcoma, using a targeted next-generation sequencing panel known as 'Oncopanel'. The molecular analysis of the tumours identified four significant groups via the Cancer Genome Atlas: POLE mutated/ultramutated, microsatellite instability/hypermutated, TP53 mutated/high copy number or no specific molecular profile. It was discovered that half of the cases were either ultramutated or hypermutated. The different histological components of mixed carcinomas were sequenced separately. The molecular alterations between the two components were nearly identical, with the non-NEC component having a slightly increased tumour mutation burden. However, only carcinomas with pure SCNEC morphology exhibited a molecular profile that would be anticipated in typical pulmonary SCNEC (RB1 deletion and TP53 mutations). It has been recommended that immune checkpoint inhibition could be a viable treatment approach for microsatellite instability NEC. It is recommended that all endometrial NEC be tested for mismatch repair abnormalities through molecular or mismatch repair protein immunohistochemistry.[4] In our case, we performed

immunohistochemistry for MLH1, PMS2, MSH2, and MSH6 mismatch repair genes. This showed no loss of these markers, so no microsatelite deficiency was found by this immunohistochemistry.

The staging of endometrial cancer currently utilizes the FIGO system. The AJCC staging system aligns its tumour (T), lymph node (N) and metastasis (M) categories with the FIGO system. The NCCN guidelines for the management of uterine neoplasms use the 2018 FIGO staging criteria.[5] However, the 2023 update considers histological and molecular characteristics to generate sub-stages that are more accurately linked to prognosis and treatment options:

Stage I POLE mutated: POLE mutated endometrial cancer confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type.

Stage II p53 abnormal: p53 abnormal endometrial cancer confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type.[6] Management guidelines are expected to be updated soon.

However, there is limited data available to guide the management of uterine LCNEC, which is typically treated similarly to LNEC of the cervix. A multimodal approach involving surgery, chemotherapy, and radiotherapy is commonly used. LNEC of the uterus are managed initially with cytoreductive surgery. The standard surgical procedures consist of total hysterectomy and bilateral salpingo-oophorectomy. In cases with distant metastasis, lymph node dissection and omentectomy are also performed. Following surgery, there is presently no agreement on the optimal therapy. In the majority of cases, adjuvant chemotherapy comprising of platinum and etoposide, along with radiotherapy, are administered or planned. When LNEC is diagnosed on a preoperative curettage or endometrial biopsy, neoadjuvant therapy may be considered.[7]

CONCLUSION

LNEC of the endometrium is very rare, highly aggressive and difficult to diagnose. Prognosis is poor due to rapid progression and the absence of established therapy. The imaging findings lack specificity and no pathological criteria have been proposed. To facilitate the differential diagnosis of endometrial malignancies, especially in cases with unusual morphology and receptor negativity, it is necessary to assess neuroendocrine differentiation and perform appropriate immunohistochemical stains. However, in some high-grade undifferentiated tumours, as in our case, the morphological features are not typical of a neuroendocrine tumour and yet LNEC should be kept in mind and the neuroendocrine immunohistochemical markers should be added to the immunohistochemistry panel. Additional research is required to develop an effective therapy protocol.

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CASE REPORT

Liver metastatic colon cancer in adolescent: A case report

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SUMMARY

Colorectal cancer (CRC) is typically a disease of the elderly, but recent years have shown a rising trend in adolescents and young adults. Pediatric CRC is exceptionally rare, with an incidence of about 1–2 per million, and often presents at an advanced stage with complications such as obstruction or metastasis. We report the case of a 13-year-old female who developed colorectal cancer with synchronous liver metastasis. She initially presented with progressive abdominal pain and constipation, mimicking functional gastrointestinal disorders, which contributed to a delay in diagnosis. Imaging revealed a descending colon mass with liver involvement, and she underwent left hemicolectomy with permanent stoma formation. Histopathology confirmed moderately differentiated adenocarcinoma infiltrating the serosa, with intravascular invasion and metastasis in 10/10 mesocolon lymph nodes (pT3, pN2b). Postoperatively, she recovered well and later underwent liver metastasectomy, followed by surveillance colonoscopy at eight months. She is currently receiving chemotherapy with Capecitabine. This case illustrates the diagnostic challenges of CRC in young patients, where non-specific symptoms can lead to late-stage detection and poorer prognosis. The rarity of pediatric CRC, combined with limited access to genetic and molecular testing in resource-limited settings, further complicates management. Early recognition and timely intervention are essential to improve outcomes and guide long-term care strategies.

CASE PRESENTATION

A 13-year-old female presented to the Emergency Department with a one-week history of persistent abdominal bloating and pain. There was no associated nausea, vomiting, or fever. The patient reported no bowel movement for approximately one week, with the last passage of flatus occurring earlier on the day of admission. Oral intake remained adequate. Her baseline bowel habits included daily bowel movements 1-2 times per day; however, she recently experienced prolonged defecation time and a sensation of incomplete evacuation. The patient has no family history of hereditary polyposis syndromes or colorectal cancer.

On physical examination, the patient appeared weak with normal blood pressure, heart and respiratory rate, no fever and great oxygen saturation. Conjunctivae were non-anemic, and sclerae were non-icteric. Cardiopulmonary examination was unremarkable. Abdominal inspection revealed distension without visible peristalsis or masses. Bowel sounds were present at 9-10 per minute. Palpation was soft with no tenderness or guarding. Percussion elicited hypertympany. Extremities were warm with no peripheral edema.

A rectal exam showed a strong sphincter tone, collapsed rectal ampulla, no tenderness or mass, and small feces present without blood or mucus. Hirschsprung's disease (short segment) was suspected. Supporting tests included abdominal radiograph and blood work, which showed hemoglobin (Hb) 11.5 g/dL, white blood cell count (WBC) 8.8 $\times 10^9$/L, and platelet count (PLT) 278 $\times 10^9$/L. The patient was hospitalized, fasted, and managed with intravenous fluids (D5% ½ NS), omeprazole, nasogastric tube, urine catheter, rectal tube decompression, and twice-daily rectal washing. Colonoscopy was not performed. Contrast-enhanced abdominal Computed Tomography (CT) revealed colonic dilatation, an intraluminal tumor mass in the descending colon, and liver metastasis.

Intraoperatively an intraluminal tumor mass was identified in the descending colon, measuring 6 × 2 × 2 cm. A left hemicolectomy was performed over a length of 20 cm, and end colostomy was performed. There were multiple enlarged mesenteric lymph nodes. On postoperative day one, she had no nausea or vomiting, passed stool via colostomy, and started a clear fluid diet. Vital signs were stable, pain was mild (VAS 2/10), and the colostomy was viable. NGT output was 50 cc of clear yellow fluid. She was gradually advanced to oral feeding via nasogastric tube and tolerated a soft diet by postoperative day four. The patient was discharged on postoperative day five in good condition.

Histopathological examination revealed a moderately differentiated adenocarcinoma, not otherwise specified (NOS), with infiltration reaching the serosal layer. Both proximal and distal resection margins were free of carcinoma. Evidence of intravascular invasion was noted. Metastatic carcinoma cells were identified in all 10 of 10 mesocolon lymph nodes examined. The final pathological staging was pT3, pN2b. Further management included liver metastasectomy. Eight months after surgery, surveillance colonoscopy was performed. The patient is currently undergoing chemotherapy with Capecitabine. The patient remaining in good condition.

DISCUSSION

Colorectal cancer (CRC) in childhood and early adolescence is exceptionally rare, with an incidence of 1–2 per million, but it often presents at advanced stages with complications

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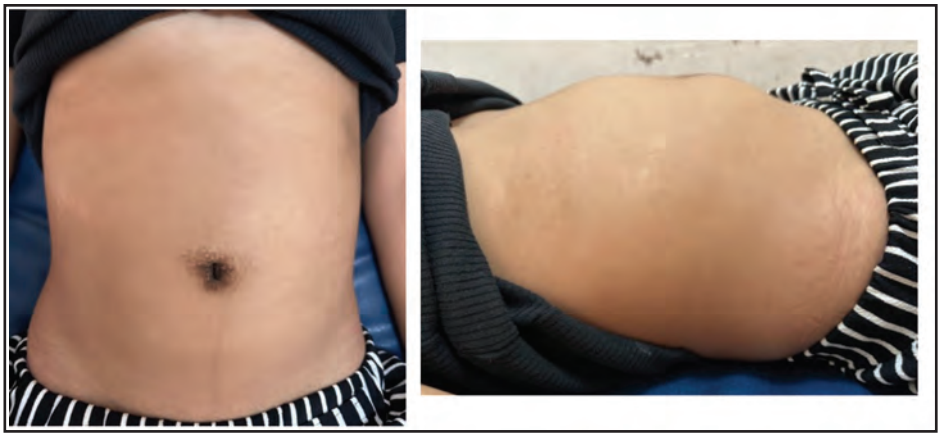

Fig. 1: Physical Examination Results

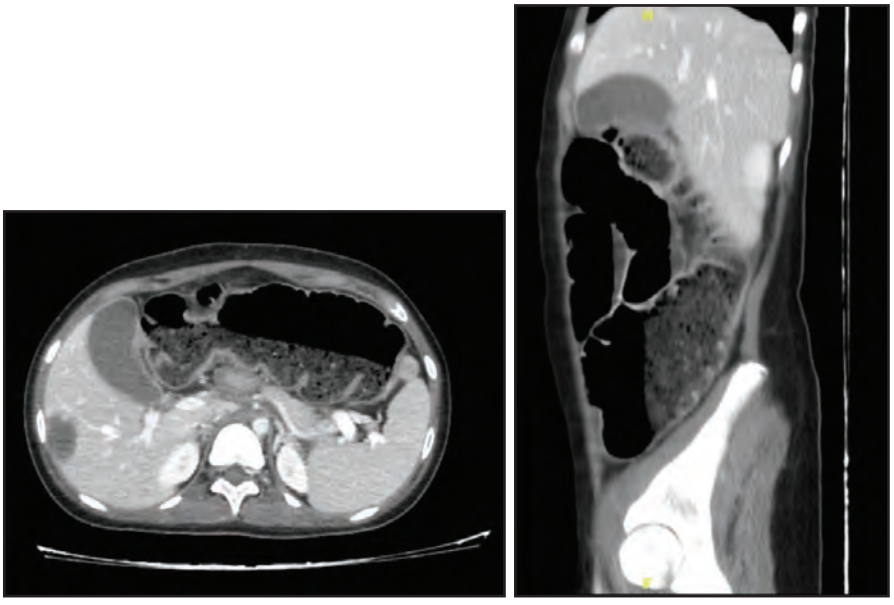

Fig. 2: Pre surgery Abdominal CT Scan with contrast showing the tumor has metastasized to the liver

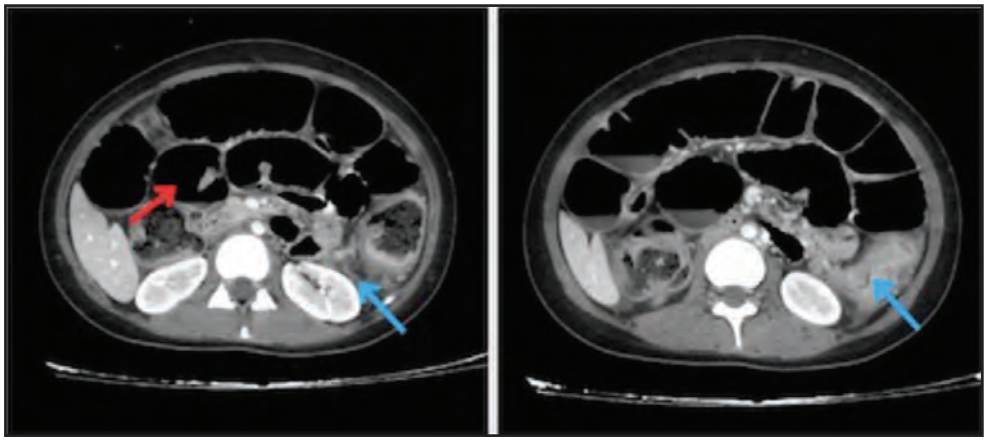

Fig. 3: Pre Surgery Abdominal CT Scan with contrast (Blue arrow: Descending colon tumor ; Red Arrow: Bowel dilatation from the proximal part of the liver)

such as obstruction.[1,2] While CRC typically affects individuals over 50, early-onset colorectal cancer (EOCRC) cases are increasing, raising concerns about genetic and environmental factors as well as delayed diagnosis. Nonspecific symptoms such as abdominal pain, bloating, and altered bowel habits often overlap with benign conditions, causing diagnostic delay and poorer prognosis compared with adults.[3] Although incidence rates in Southeast Asian countries such as Indonesia, Malaysia, and Thailand remain lower than in other Asian regions, they are steadily increasing due to lifestyle changes, urbanization, and limited screening access.[4]

Our patient presented with symptoms resembling functional constipation or Hirschsprung's disease, but imaging revealed a descending colon mass with synchronous liver metastasis, confirming malignant large-bowel obstruction. Pediatric CRCs are frequently aggressive, with histologies such as mucinous adenocarcinoma or signet-ring cell carcinoma and advanced stage at presentation, consistent with previous series of early-onset CRC.[5,6]

Intestinal obstruction in adolescents has a broad differential diagnosis, which includes congenital causes such as Hirschsprung's disease or malrotation, as well as acquired conditions like intussusception, adhesions, inflammatory bowel disease, and, rarely, malignancy.[2,3,6] In younger patients, colorectal carcinoma is seldom suspected because symptoms such as constipation or abdominal distension are more commonly attributed to benign disorders.[3] In this case, the patient initially had normal bowel habits followed by sudden cessation of defecation and progressive abdominal distension, a presentation that could mimic functional constipation or acute intestinal obstruction from other causes. However, the absence of prior surgery (excluding adhesions), the left-sided colonic dilatation on imaging, and the presence of a discrete mural mass favored a diagnosis of large-bowel obstruction secondary to malignancy. This emphasizes the importance of maintaining a high index of suspicion for colorectal cancer in adolescents presenting with abrupt-onset obstructive symptoms unresponsive to standard management.

Genetic predisposition contributes to EOCRC development, particularly in syndromes such as Lynch syndrome, caused by mutations in mismatch repair genes (MLH1, MSH2, MSH6, PMS2), and familial adenomatous polyposis (FAP) due to APC mutations.[1,7] However, most early-onset cases occur sporadically. Only about 11.9% of patients under 35 have a first-degree relative with CRC, though this increases the risk up to fourfold.[1,7] Beyond hereditary factors, modern dietary patterns high in processed foods, red meats, and sugars contribute carcinogenesis through obesity, chronic inflammation, and altered gut microbiota.[7,8] These findings emphasize that, in addition to genetic predisposition, modifiable lifestyle factors play an important role in the rising incidence of CRC among adolescents and young adults. Although this patient had no family history of CRC or polyposis syndromes, universal testing for mismatch repair deficiency is recommended in all CRC cases to detect Lynch syndrome, which is common in early-onset disease.8,9 Genetic evaluation has important implications for prognosis, therapy (e.g., immune checkpoint inhibitors in MSI-H tumors), and familial counseling.

The presence of synchronous liver metastasis at diagnosis indicates stage IV disease. In adults, resection of colorectal liver metastases combined with perioperative chemotherapy (FOLFOX-based regimens) improves survival.[7] Pediatric oncologists often extrapolate these regimens, with reports of successful use in adolescents with metastatic CRC.[3,7] In our patient, surgical resection (left hemicolectomy and liver metastasectomy) followed by Capecitabine-based chemotherapy resulted in favorable short-term outcomes, consistent with previous reports.[4,9]

Histopathological examination revealed moderately differentiated adenocarcinoma with serosal infiltration, intravascular invasion, and extensive nodal involvement (pT3, pN2b), reflecting aggressive tumor biology typical of pediatric CRC.[6,8] Although confirmatory genetic testing was not available in this setting, hereditary causes should be suspected at such a young age. The absence of molecular profiling limited consideration of targeted or immunotherapies despite their established role in MSI-H or dMMR tumors.[9,10]

Pediatric CRC poses unique challenges due to delayed diagnosis, absence of pediatric-specific guidelines, and limited access to molecular testing.[2,9] Management generally follows adult protocols, though differences in tumor biology, chemotherapy tolerance, and psychosocial aspects such as fertility and quality of life should be considered.[7,10] This case underscores the importance of early recognition of colorectal cancer in adolescents and the need for greater access to genetic and molecular diagnostics to improve management and outcomes.

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CASE REPORT

Endocervical adenocarcinoma in early pregnancy managed with neoadjuvant chemotherapy and delayed surgery: A case report

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SUMMARY

Endocervical adenocarcinoma during pregnancy is rare and poses significant diagnostic and management challenges. The optimal management approach remains uncertain due to the limited number of reported cases. Managing this condition during pregnancy requires a careful balance between effective oncologic treatment and preserving fetal health. We present the case of a 34-year-old woman, gravida 2 para 0+1, diagnosed with FIGO stage IIA1 HPV-associated endocervical adenocarcinoma at 12 weeks gestation. Following multidisciplinary discussion, neoadjuvant chemotherapy was initiated. She underwent a cesarean delivery at 35 weeks and 4 days of gestation, followed by radical hysterectomy, bilateral salpingectomy, ovarian transposition, and pelvic lymphadenectomy. Postoperative histopathology showed no lymphovascular invasion. The patient remains disease-free 14 months after treatment.

INTRODUCTION

Cervical cancer during pregnancy is a rare but serious condition that presents significant challenges in terms of diagnosis and management. It occurs in approximately 1.4 to 4.6 per 100,000 pregnancies, with adenocarcinoma representing about 10-20% of those cases.[1] The unique circumstance of a growing fetus adds complexity to the diagnostic process and treatment decisions. Endocervical adenocarcinoma, often linked to high-risk human papillomavirus (HPV) types 16 and 18, may be aggressive and require early identification and management. Whether pregnancy can accelerate the progression of cancer is still controversial. Some scholars have found that the levels of estrogen, progesterone, and human chorionic gonadotropin during pregnancy are positively correlated with HPV 16 and HPV 18 infection, which indirectly suggest that pregnancy may promote the progression of cervical cancer.[2] Some studies have shown that the lymphatic circulation and blood flow of the reproductive organs of pregnant women increases, the immunity of the body decreases in the early stage of pregnancy and cervical dilation after delivery, and other factors may accelerate the metastasis of tumours, thereby accelerating the development of cervical cancer.[3]

Currently, there is no standardized treatment protocol for cervical cancer in pregnancy. Most management decisions are based on expert consensus and multidisciplinary cancer case conferences, with existing guidelines primarily focused on squamous cell carcinoma.[4,5] Key factors influencing management include gestational age, tumour stage and histology, the presence or absence of metastases, and the patient's preferences regarding the continuation of pregnancy.

Herein, we present a case of FIGO stage IIA1 HPV-associated endocervical adenocarcinoma diagnosed during the first trimester. This report highlights the role of neoadjuvant chemotherapy (NACT) and coordinated surgical planning in achieving favorable maternal and fetal outcomes.

CASE PRESENTATION

A 34-year-old woman, gravida 2 para 0+1, presented to the gynecology clinic following an abnormal cervical cytology report suggestive of atypical glandular cells favoring neoplasia. She had previously missed her follow-up appointment and was found to be 6 weeks and 5 days pregnant during the clinic visit. Repeat cytology and HPV DNA testing confirmed adenocarcinoma in situ (AIS) and the presence of high-risk HPV types 16 and 18. Colposcopic examination revealed a suspicious cervical lesion. A biopsy was taken, and histology suggested AIS with the possibility of invasion.

At 12 weeks of gestation, a large loop excision of the transformation zone (LLETZ) was performed (Fig.1). Histopathological examination confirmed HPV-associated endocervical adenocarcinoma in the background of AIS. The radial margin was involved, and lymphovascular space invasion (LVSI) was present. The depth of stromal invasion measured 4.5 mm with an 8 mm lateral spread. An additional biopsy from the posterior fornix also indicated adenocarcinoma (Fig.1a).

Subsequent imaging including MRI of the pelvis and low-dose CT of the thorax showed no evidence of local or distant metastasis. The diagnosis was staged as FIGO stage IIA1 cervical adenocarcinoma. After detailed discussions involving gynecologic oncology, radiology, pathology, and maternal-fetal medicine, the patient and her family opted to continue with the pregnancy.

A management plan was formulated involving four cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel. Chemotherapy was administered during the second and third

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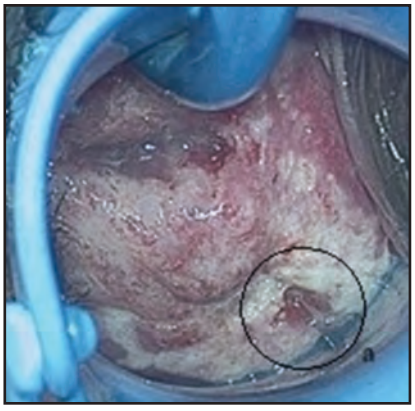

Fig. 1: Colposcopic image a 12 weeks gestation, prior to LLETZ
a: The biopsy site is located at the posterior vaginal fornix

trimesters, aiming to control tumor progression while allowing the pregnancy to continue to a viable gestational age. Fetal development was closely monitored, and no complications were reported during chemotherapy.

At 35 weeks and 4 days, she underwent an elective cesarean section. A healthy male infant weighing 2500 grams was delivered with Apgar scores of 8 and 9 at one and five minutes, respectively. Following delivery, the patient underwent a radical hysterectomy, bilateral salpingectomy, ovarian transposition, and pelvic lymphadenectomy. Histopathological analysis revealed a well-differentiated adenocarcinoma with a maximum depth of invasion of 3 mm and no evidence of lymphovascular space invasion. Surgical margins were clear, with the closest margin measuring 12 mm. No adjuvant therapy was deemed necessary.

Postoperatively, the patient had an uneventful recovery and was discharged after seven days. At the time of this report, 14 months postoperatively, she remains disease-free with no evidence of recurrence. She continues regular follow-up with gynecologic oncology and receiving psychosocial support for survivorship care.

DISCUSSION

Management of cervical cancer during pregnancy involves careful consideration of multiple factors including gestational age, cancer stage, histology, and patient preference. This case underscores the importance of early cervical screening and diagnostic follow-up. LLETZ was essential in confirming the diagnosis and guiding further management. Although cold knife conization is typically preferred for diagnosing and managing AIS or suspected invasive disease, adjustments are often necessary during pregnancy to reduce procedural risks. In this case, LLETZ was selected as a safer alternative due to its lower risk of hemorrhage and cervical incompetence, especially when performed during the first trimester. The procedure was completed at 12 weeks of gestation without complication, enabling definitive histological assessment while preserving pregnancy viability. This case supports growing evidence that, when clinically indicated and performed with careful technique, LLETZ can be a safe and effective diagnostic approach during early pregnancy in appropriately selected patients.[6]

Neoadjuvant chemotherapy (NACT) represents a viable treatment option for cervical cancer during pregnancy when preservation of gestation is prioritized. Administration of carboplatin and paclitaxel during the second and third trimesters has been shown to be relatively safe and effective in delaying tumour progression while allowing fetal maturity.[7] In this case, coordinated planning enabled both optimal oncologic control and timely caesarean delivery, followed by definitive surgical management.

Although fertility-sparing options such as interval trachelectomy or large conization may be considered in selected patients with early-stage disease (≤IB1), these were not suitable in this case. The patient had FIGO stage IIA1 adenocarcinoma with vaginal involvement and lymphovascular space invasion, which precluded conservative surgery. Current National Comprehensive Cancer Network (NCCN) and European Society of Gynaecological Oncology (ESGO) guidelines recommend radical hysterectomy with pelvic lymphadenectomy or concurrent chemoradiotherapy for this stage.[4,5] Radical surgery was therefore chosen to achieve complete tumour resection and staging while avoiding the long-term morbidity of pelvic radiation in a young patient.

These findings align with published reports supporting the feasibility of delaying definitive surgery until fetal maturity in carefully selected patients. For instance, Guo et al. described a 36-year-old woman diagnosed with stage IB3 cervical cancer at 13 weeks gestation who underwent NACT, followed by caesarean section and radical hysterectomy at 36 weeks, with favourable maternal and neonatal outcomes.[8] Similarly, Li et al. reported two cases of locally advanced cervical cancer managed with chemotherapy and delayed surgery, both resulting in live births and no recurrence during follow-up.[9] Collectively, these cases, including our own, underscore the potential of individualized, patient-centred treatment strategies in achieving favourable outcomes without compromising maternal or neonatal safety.

Long-term follow-up data from similar cases have also been reassuring. Children exposed to platinum-based chemotherapy during the second and third trimesters generally demonstrate normal physical growth and neurodevelopmental outcomes, with no significant increase in congenital anomalies. Nevertheless, ongoing pediatric follow-up remains important to monitor for potential late effects.

Ovarian transposition was considered appropriate given the patient's young age and the absence of ovarian metastasis. Studies suggest ovarian preservation may be oncologically safe in early-stage adenocarcinoma, though more evidence is required.10 Ultimately, the patient's values and preferences played a vital role in decision-making, supported by a multidisciplinary team.

According to current guidelines, including those from the NCCN and the ESGO, patients with stage IIA1 cervical cancer post-radical hysterectomy are generally recommended to receive adjuvant radiotherapy, particularly in the presence of risk factors such as lymphovascular space invasion (LVSI), deep stromal invasion, or close surgical margins.[4,5] However, in this case, adjuvant treatment was not administered due to favourable postoperative histopathological findings, including clear surgical margins, a maximum stromal invasion depth of only 3 mm, and absence of LVSI. This individualized approach highlights the importance of tailoring treatment to each patient's clinical and pathological profile. Although omission of adjuvant therapy diverged from standard protocols, the patient remains disease-free 14 months postoperatively. Continued close surveillance remains crucial, and this case contributes to growing discussions on de-escalation of therapy in selected patients with favourable prognostic features.

The main limitation of this report is its single-case nature, which restricts generalizability. However, detailed documentation of such rare cases remains valuable in guiding clinical decision-making and expanding available evidence on safe oncologic management during pregnancy.

Importantly, this case reinforces the principle that management of cervical cancer in pregnancy must be highly individualized. Factors such as gestational age at diagnosis, tumour staging, histopathological characteristics, and the patient's personal wishes all play critical roles in decision-making. The omission of adjuvant therapy, guided by favourable pathological findings, further supports the evolving discourse on treatment de-escalation in selected low-risk patients. As more cases are reported and long-term outcomes become clearer, collective experience will help refine future guidelines and better define optimal management strategies for cervical cancer in pregnancy.

CONCLUSION

Cervical cancer diagnosed during pregnancy can be safely managed through a multidisciplinary and individualized approach. Neoadjuvant chemotherapy during the second and third trimesters allowed fetal maturity without compromising oncologic outcomes, and timely definitive surgery achieved complete disease control.

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DECLARATION

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