Occult intravascular large B-cell lymphoma presenting as postoperative thrombotic microangiopathy: a case report

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Case presentation

In August 2017, a 59-year-old male with good past health was admitted via the emergency department with a 4-day history of abdominal distension and epigastric pain. He had passed no stool for 2 days. Physical examination revealed epigastric tenderness and an empty rectum. Abdominal X-ray showed intestinal obstruction and erect chest X-ray showed no free gas under the diaphragm. Blood tests on admission revealed a normal complete blood count and acute renal failure (Table). The patient was started on intravenous (IV) fluid and IV amoxicillin and clavulanate. Urgent computed tomography (CT) abdomen and pelvis with contrast showed acute appendicitis with perforation and dilated small bowel without an obvious transition point. Emergency laparotomy revealed appendiceal diverticulitis with walled-off localised abscess formation around the appendix. The base of the appendix was healthy. Microscopic examination of the appendix showed dense mixed inflammatory cell infiltration in periappendiceal fat and serositis, with no evidence of malignancy, thrombosis or ischaemia.

Three days postoperatively, the patient developed fever and hypotension and was given IV piperacillin and tazobactam. There was no organomegaly, lymphadenopathy or skin lesions on physical examination. He became dull looking but there was no focal neurological deficit. Septic workups with blood and urine were negative. Sputum culture showed *Enterobacter cloacae*, resistant to amoxicillin and clavulanate. Widal test, Weil–Felix test, human immunodeficiency virus serology and tests for viral hepatitis were all negative. A second abdomen CT showed no gross infective foci and only a few subcentimetre lymph nodes. Plain brain CT showed no focal intracranial lesions. Blood tests showed a leukoerythroblastic blood picture and no circulating abnormal cells, and acute hepatic and renal failure with markedly elevated lactate dehydrogenase level (Table). Fever did not abate despite IV piperacillin and tazobactam, IV meropenem and IV anidulafungin were prescribed for support. In the second week postoperatively, blood tests showed progressive anaemia and thrombocytopenia with microangiopathic haemolytic anaemia (MAHA) and a leukoerythroblastic blood picture (Table and Fig a). Ferritin and triglyceride levels were markedly elevated.

Bone marrow biopsy was subsequently performed and revealed many abnormal pleomorphic large cells and haemophagocytosis (Fig). In view of the fever of unknown origin, cytopenia, hypertriglyceridaemia, markedly elevated ferritin and haemophagocytosis in the bone marrow, a diagnosis was reached of haemophagocytic lymphohistiocytosis (HLH) and dexamethasone 15 mg daily orally and IV immunoglobulin started. Trephine biopsy showed prominent infiltration of pleomorphic large cells in focal linear profiling and intrasinusoidal clusters. With immunohistochemistry, the large cells were shown to be positive for the markers cluster of differentiation (CD20) [Fig e], CD30, CD5, and negative for activin receptor-like kinase 1 and cyclin D1. Epstein-Barr virus–encoded small RNA in situ hybridisation was negative. A diagnosis was made of intravascular large B-cell lymphoma (IVLBCL).

The ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity, antigen and autoantibody assays were performed. There was severe reduction in ADAMTS13 activity to 5% with ADAMTS13 antigen level moderately reduced to 215 ng/mL (reference range: 430-970) and autoantibody level at 2.5 units/mL (negative: <15). This confirmed ADAMTS13 deficiency and functional defect compatible with the picture of malignancy-associated thrombotic thrombocytopenic purpura (TTP). The patient was prescribed immunochemotherapy with rituximab (recombinant anti-CD20), cyclophosphamide, vincristine and prednisolone, and rasburicase for prophylaxis of tumour lysis syndrome. Hydroxydaunorubicin was added in the second

TABLE. Laboratory findings of the patient during the episode

	On admission	PO day 0	1st week PO	2nd week PO	After 2nd cycle of R-CHOP	Reference range
Complete blood count and peripheral blood smear						
Hb, g/dL	15.6	13.4	11.8	9.0	8.6	13.4-17.2
WBC count, $\times 10^9$/L	4.8	2.4	36.86	8.98	3.2	3.9-10.7
ANC, $\times 10^9$/L	3.4	1.6	29.86	7.81	2.11	2.1-7.8
Platelet count, $\times 10^9$/L	311	323	196	40	459	152-358
Reticulocytes, %	-	-	-	17.9	3.49	<2
nRBC/100 WBC	Nil	Nil	Nil	27	Nil	N/A
Blood smear review	-	-	Leukoerythroblastic blood picture, no abnormal cells	2+ schistocytes	No schistocytes	N/A
Biochemistry results						
Sodium, mmol/L	127	131	139	138	130	136-145
Potassium, mmol/L	5.2	4.9	3.8	4.2	4.7	3.5-4.5
Urea, mmol/L	18.1	24.8	30.1	31.3	8.3	3.0-9.2
Creatinine, μmol/L	541	541	458	251	75	64-111
Bilirubin, μmol/L	18	9	60	36	11	3-21
ALT, U/L	21	18	616	203	31	<61
ALP, U/L	94	53	281	247	221	53-128
Ammonia, μmol/L	-	-	189	66	-	18-72
LDH, U/L	-	450	3237	2861	435	125-220
Calcium, mmol/L	-	2.15	2.28	2.15	2.52	2.1-2.65
Phosphate, mmol/L	-	2.27	2.25	1.4	1.57	0.74-1.52
Ferritin, pmol/L	-	-	-	>89 600	-	49-615
Triglyceride, mmol/L	-	-	-	3.69	-	<1.7
Clotting profile						
PT, s	12.1	13.0	15.1	16.0	12.6	10.5-13.0
APTT, s	30.7	29.3	25.5	28.5	27.6	22.8-31.7

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; Hb = haemoglobin; LDH = lactate dehydrogenase; N/A = not applicable; nRBC = nucleated red blood cell; PO = postoperative; PT = prothrombin time; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; WBC = white blood cell

cycle of immunochemotherapy (R-CHOP, ie, a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) after which blood counts and liver and renal function test results markedly improved (Table). The patient was in complete remission after six cycles of R-CHOP. Nonetheless he died of inoperable squamous cell carcinoma of oesophagus 3 years after the diagnosis of lymphoma.

Discussion

Intravascular large B-cell lymphoma is a rare subtype of extranodal large B-cell lymphoma characterised by selective growth of neoplastic cells inside the lumina of small- and medium-sized vessels, often with an aggressive clinical course. There are two major patterns of clinical presentation: the classic form with neurocutaneous involvement and the haemophagocytic syndrome–associated form with multiorgan failure, hepatosplenomegaly, and pancytopenia. Diagnosis of IVLBCL is challenging due to its variable presentation. Imaging may be negative due to the lack of detectable tumour masses.

The initial presentation of this patient was atypical, with appendiceal diverticulitis and perforation. Review of the appendix specimen confirmed the absence of lymphoma involvement. There was no hepatosplenomegaly. The abrupt onset of anaemia and thrombocytopenia with MAHA raised the possibility of postoperative TTP. Patients with postoperative TTP characteristically have a normal complete blood count prior to surgery, but subsequently show MAHA with thrombocytopenia

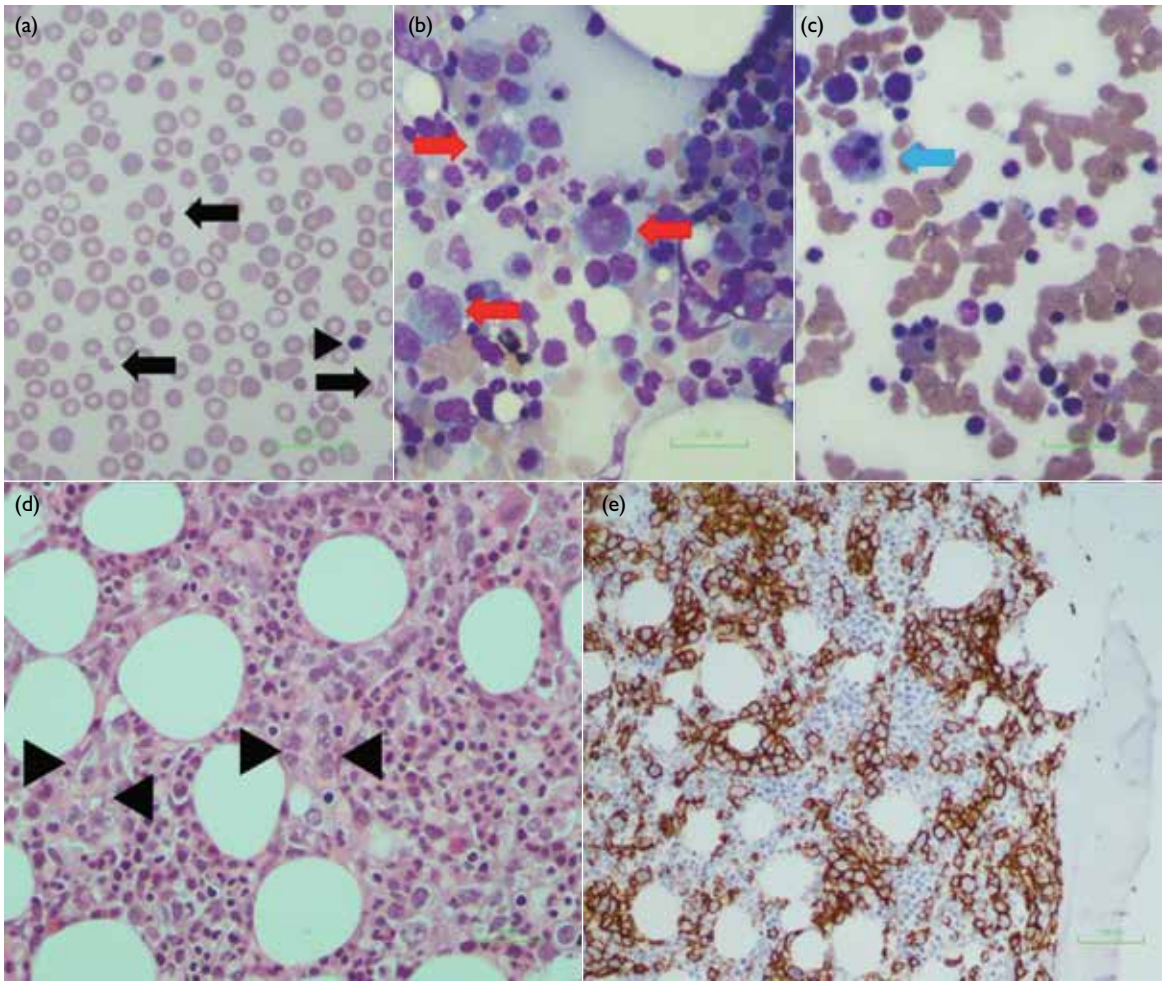

FIG. Peripheral blood and bone marrow aspirate, trephine biopsy and immunohistochemistry findings in the patient. Peripheral blood ([a], May-Grünwald stain ×200) shows microangiopathic haemolytic anaemia with many schistocytes (arrows), prominent polychromasia, and nucleated red blood cells (arrowhead). Bone marrow aspirate ([b] & [c], May-Grünwald stain ×400) shows many large pleomorphic lymphoid cells with irregular to grossly bizarre nuclear configuration, coarse chromatin, prominent nucleoli, and moderate to large amount of basophilic cytoplasm (arrows in [b]). Some haemophagocytic figures mostly engulfing erythroid precursors are evident (arrow in [c]). Trephine biopsy ([d], haematoxylin and eosin stain ×400) shows clusters of pleomorphic large cells with irregular and bizarre nuclear configuration, mildly condensed chromatin and prominent nucleoli are enclosed by the sinusoidal endothelial cells (arrowheads). Immunohistochemical staining ([e], ×200) for the marker cluster of differentiation 20 highlights the focal linear filing and intrasinusoidal clusters of large B-cells

about 5 to 9 days after surgery.[1] Fever, renal impairment, and neurological symptoms are variably present. Nonetheless the abundance of schistocytes and nucleated red cells in the blood film and acute liver failure did not support a diagnosis of postoperative TTP, warranting further investigations.

Neoplastic cells may cause endothelial damage and result in release of ultra-large von Willebrand factor multimers. Autoantibodies against ADAMTS13 may also play a role in pathogenesis, leading to platelet activation and thrombotic microangiopathy.[2] In our case, ADAMTS13 activity was markedly reduced at 5%, unusually low for malignancy-associated TTP (median ADAMTS13 activity: 50%).[3] Some secondary TTP cases have been reported with markedly reduced ADAMTS13 activity[4] but the significance is uncertain. The ADAMTS13 activity was also disproportionately lower than the antigen level, indicating a functional defect that may be seen in acquired TTP. Negative autoantibody against ADAMTS13 suggests against a diagnosis of idiopathic TTP. Distinguishing malignancy-associated TTP from idiopathic or postoperative TTP is important since therapeutic plasma exchange is effective in idiopathic or postoperative TTP but not in malignancy-associated TTP.

Although the anaemia and thrombocytopenia could be explained by the MAHA, hyperferritinaemia, hypertriglyceridaemia and haemophagocytosis in bone marrow were compatible with HLH. Of note, the current diagnostic criteria for HLH were originally proposed for diagnosis in paediatric patients.[5] Criteria cut-offs such as a ferritin level >500 ng/mL may not be applicable in adults where there are many other reasons for such a high level. Bone marrow biopsy is the preferred investigation in the diagnosis of HLH and IVLBCL. A high index of suspicion should be maintained since the peripheral blood may not show abnormalities specific to these diagnoses.

Author contributions

Concept or design: All authors.
Acquisition of data: All authors.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: WK Lam.
Critical revision of the manuscript for important intellectual content: WK Lam, ESK Ma, SF Yip.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki and has provided informed consent for all treatments and procedures, and consent for publication.

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