Clinical Case Report

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A challenging case of intravascular large B-cell lymphoma presenting as pyrexia of unknown origin

A case report

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Abstract

Introduction: Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large cell lymphoma, characterized by the growth of neoplastic cells within the lumina of small blood vessels, without an obvious extravascular tumor mass or presence of circulating lymphoma cells in the peripheral blood.

Patient concern: A 68-year-old woman presented with fever of unknown origin and abdominal pain.

Diagnosis: Bone marrow aspiration showed abnormally large cells with increased hemophagocytic activity. Trephine biopsy showed moderate to large neoplastic cells with single and multiple prominent nucleoli sequestered in the blood vessel lumen. Immunohistochemistry was positive for CD20, PAX5, CD79a, MUM1, and BCL2 and showed a high proliferative fraction of 80% confirming the diagnosis of IVLBCL.

Interventions: The patient received six cycles of R-CHOP chemotherapy.

Outcomes: The patient has been in remission for nearly two years after completing the treatment.

Conclusion: Clinical recognition of IVLBCL remains a challenge. Standard staging and therapeutic approaches need to be addressed to further elucidate the characterization and management of this rare disease.

Abbreviations: AFP = α-fetoprotein; CA = cancer antigen; CEA = carcinoembryonic antigen; CT = computer tomography; FDG = 18F-fluorodeoxyglucose; IVLBCL = intravascular large B-cell lymphoma; PET CT = positron emission tomography/CT; R-CHOP = rituximab-cyclophosphamide-doxorubicin-prednisone-vincristine.

Keywords: diffuse, fever of unknown origin, intravascular, large B-cell, lymphoma, non-hodgkin, R-CHOP protocol

1. Introduction

Intravascular large B-cell lymphoma (IVLBCL) was initially known as malignant angioendotheliomatosis, a rare and fatal disease that was thought to be a neoplasm of endothelial cells. This tumor occurs in adults with a median age of 67 years at presentation (range, 13–85 years) with no gender predilection. [1] The patient's geographical origin, either from the West or the Far East, being of Asian descent, demarcates the stark contrast in frequency and clinical presentation. The initial description of this entity was first chronicled in 1986 as a Western variant. [1] Being a lymphomatous entity, the involvement of lymph nodes is astonishingly spared in both. To date, only a few cases and larger case series have been reported. The diagnosis of IVLBCL poses a significant risk of delay in diagnosis mainly due to the wide range of clinical presentations, non-specific laboratory results, and imaging studies. It is a rare subtype of large cell lymphoma, characterized by the discerning growth of lymphoma cells within the lumina of small blood vessels, without an obvious extravascular tumor mass or presence of circulating lymphoma cells in the peripheral blood. Clinical signs and symptoms at presentation are non-specific and are usually related to the main organ involved. Bone marrow involvement is reported to be uncommon in patients with IVLBCL.[2] Here, we describe a patient with IVLBCL who presented with fever of unknown origin, abdominal pain, and bone marrow involvement.

2. Case report

A 68-year-old woman was referred to our center for further investigation and management of myelodysplastic syndrome. She

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

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initially presented with a prolonged fever of three months duration associated with constitutional symptoms. The patient had temperature spikes of 39.0°C on and off since admission. Other than mild pallor, clinical examination was rather unremarkable, and no neurological symptoms or skin lesions were noted. A complete blood count showed hemoglobin 10.3 g/dL, total white blood cells 9.8 x 10^9/L (absolute neutrophil count; 4.1 x 10^9/L and absolute lymphocyte count; 2.4 x 10^9/L) and platelet 366 x 10^9/L while a peripheral blood film examination showed normochromic normocytic anemia and a few atypical and reactive lymphocytes which indicatied inflammatory process. Liver function test showed mildly elevated total bilirubin (22.63 μmol/L) and alkaline phosphatase (151 U/L), while other liver function parameters were within the normal range. The lactate dehydrogenase level was also elevated (311 U/L), and serum ferritin level was markedly elevated (2096 μg/L). A full panel of infectious disease screening including hepatitis B surface antigen, treponema IgM and IgG; dengue IgM, IgG, and NS1; melioidosis; blood film for malaria parasite; *Salmonella typhi* IgM and IgG; and HIV 1 and 2 IgG were negative. Serial blood cultures were negative for growth. However, inflammatory markers were elevated, including C-reactive protein (14.7 mg/L) and procalcitonin (0.11 μg/L). Because of prolonged fever, she was screened for autoimmune disorder using complement levels C3 (1.07 mg/L) C4 (0.17 mg/L) and tumor markers including α-fetoprotein, carcinoembryonic antigen, and several cancer antigen (CA) markers (CA 125, CA 15-3 and CA 19-9), and the results were unremarkable. Further investigation to find the inflammatory or infective source included an echocardiogram that was normal with no vegetation. The skeletal survey did not reveal any lytic lesions. Chest radiography revealed clear lung fields. Computed tomography (CT) of the abdomen and thorax did not reveal any significant abnormalities. Upper and lower endoscopy studies to further investigate the cause of persistent fever were also unremarkable. She was given a trial of antibiotics and prednisolone at tapering doses and was discharged.

However, she was readmitted 2 months later to another hospital as she became increasingly unwell and presented with persistent fever and lethargy associated with abdominal pain and diarrhea. Physical examination revealed pallor with neither lymphadenopathy nor hepatosplenomegaly. A repeat upper and lower gastrointestinal endoscopy examination revealed only mild antral gastritis and colitis. Tissue biopsies of multiple sites including the cecum, ascending and descending colon, sigmoid, and rectum showed non-specific moderate colitis and adenomatous polyps. Stool examination was positive for occult blood. The Spot test result for tuberculosis was negative. Subsequent ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/CT (PET CT) scan showed diffuse marrow uptake, which was attributed to a reactive response to anemia with no evidence of increased FDG uptake elsewhere. Thus, it was concluded that the scan did not reveal any FDG-avid tumor lesions or pathology.

Given the patient's clinical deterioration, a bone marrow aspirate and trephine biopsy examination was performed. Her hemoglobin level during this presentation was lower at 8.8 g/dL. Bone marrow examination was initially reported to have features of myelodysplastic syndrome. A re-examination of the BMAT at our center revealed a hypercellular marrow with abnormally large cells with evenly dispersed chromatin, some with prominent nucleoli, basophilic cytoplasm, and cytoplasmic vacuolation. Hemophagocytic activity was increased with macrophages containing red cells, granulocytes, and mononuclear cells within the cytoplasm (Fig. 1A). Trephine biopsy showed hypercellular bone marrow for age (approximately 90%) accompanied by focal areas of fibrosis. Trilineage hematopoietic activity was observed. However, the abnormal lymphoid cells were arranged in small wavy clusters. These neoplastic cells were medium to large in size with dispersed chromatin and prominent nucleoli in some of the cells (Fig. 1B). The cells were arranged within the blood vessel lumen in a sinusoidal distribution pattern (Fig. 1C). This pattern was apparent with CD34 staining, which highlighted the thin vascular walls containing the neoplastic cells (Fig. 1D). The neoplastic cells expressed B-cell lineage markers with strong CD20 (Fig. 1C) and CD79a and PAX5 positivity. The cells were also positive for MUM-1 with the presence of the anti-apoptotic factor BCL2overexpression. CD30 was expressed in some of the larger neoplastic cells but was negative for CD15. The cells were also positive for OCT2 and BOB1. Ki67 immunostaining showed a very high proliferation fraction (> 80%) in neoplastic cells. *In situ* hybridization for the detection of Epstein-Barr virus-encoded RNA was negative. Histiocytes stained strongly for CD163 within hematopoietic spaces (Fig. 1E). No clonal chromosomal abnormalities were detected using conventional cytogenetics. She was diagnosed with IVLBCL of the marrow and was started on a combination of rituximab and CHOP (R-CHOP) regimen. Over the course of the first cycle of chemotherapy, her clinical symptoms quickly improved. Her fever resolved, and her blood counts recovered. She completed 6 cycles of R-CHOP (five months after diagnosis) without significant therapy-related complications. At two-year follow-up, a repeat bone marrow surveillance examination showed that the patient remained in complete remission.

3. Discussion

IVLBCL is a rare, aggressive, extranodal non-Hodgkin lymphoma that is characterized by the luminal growth of predominantly large neoplastic lymphoid cells. It is often associated with cytopenias, prolonged fever, neurological symptoms, and skin lesions, and involves widely disseminated extranodal sites including the spleen, bone marrow, liver, adrenal gland, brain, lung bone, and uterus.[3,4] The lymph nodes are usually spared. This entity was first described in 1986 and has since been studied as case report, some large case series, and literature reviews.[5,6] It has two major patterns of clinical presentations. First, the so-called classic form, which is mostly present in Western countries, characterized by predominantly neurological and cutaneous symptoms. The second is the Asian variant, which is associated with a hemophagocytic syndrome or hemophagocytic syndrome-associated form. The latter seems to be more uncommon than the former, where patients deteriorate rather quickly with multi-organ failure.[1] Hemophagocytic lymphohistiocytosis is also a rare entity that is potentially life-threatening. This disorder is characterized by the presence of at least five of the following features for diagnosis: fever, cytopenia, hepatosplenomegaly, hemophagocytosis, hypertriglyceridemia, hyperferritinemia, low natural killer cell activity, and elevated soluble CD25.[7] In this case, only diffuse expression of CD163 on bone marrow histiocytes was observed, while other criteria were not assessed.

Tumor lymphocytes are mainly located in the lumen of small- or medium-sized blood vessels in many organs. In some cases, fibrin, thrombosis, bleeding, and necrosis may occur. The tumor cells are large with obvious nucleoli, and frequent mitosis is observed. In rare cases, the cells may be small or anaplastic.[8]

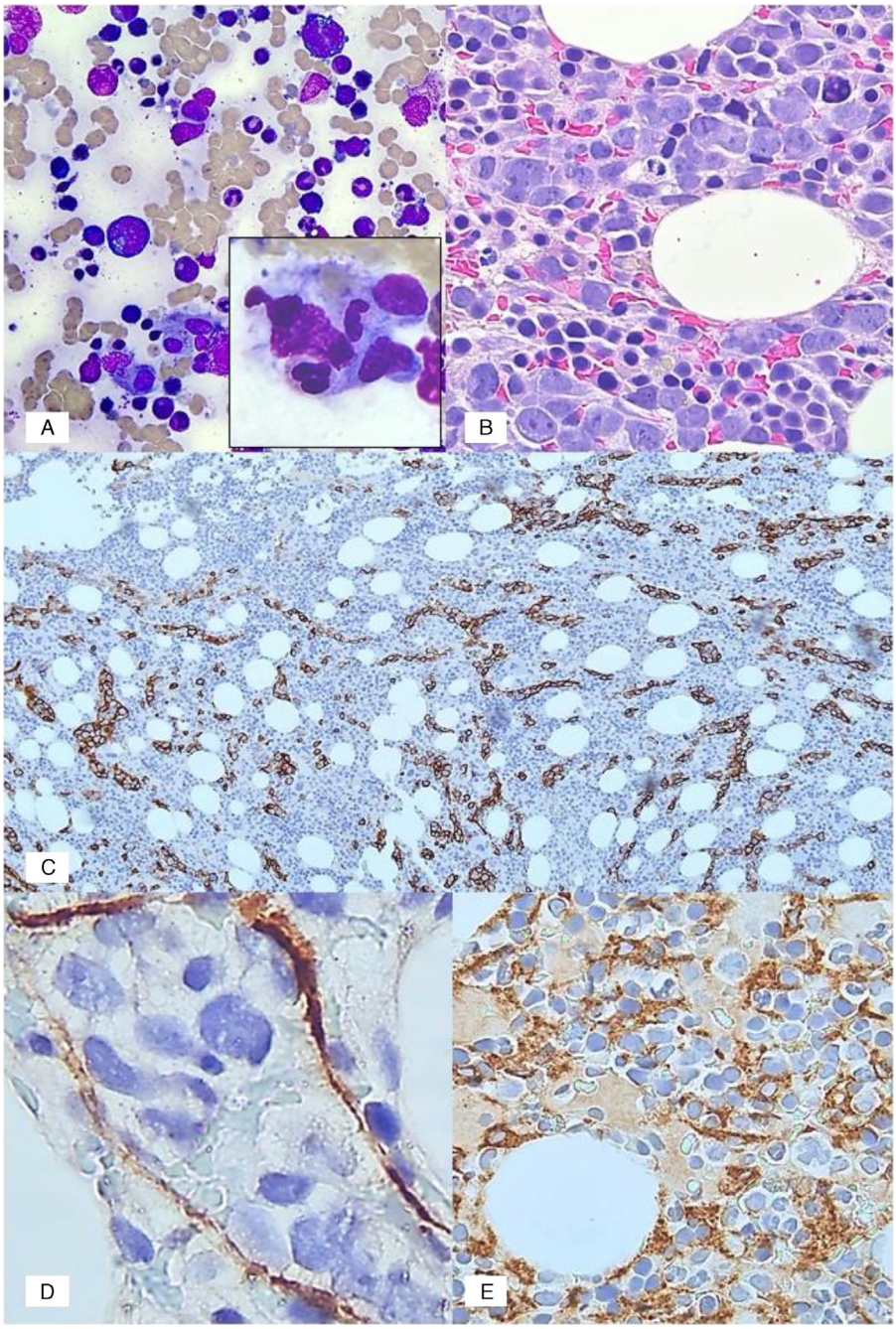

Figure 1. A) Large atypical cells in bone marrow aspirate with irregular nucleus, basophilic cytoplasm, and vacuolation (May-Grunwald-Giemsa, 40X). Inset shows hemophagocytic activity (100X). B) Neoplastic cells with multiple prominent nucleoli within blood vessel lumen (H&E, 100X). C) Cells express CD20 highlighting a sinusoidal pattern (Immunostain, 10X). D) CD34 outlines thin blood vessel wall (Immunostain, 100X). E) Histiocytic activity is increased expressing strong CD163 (Immunostain, 20X).

Tumor cells positioned in the interstitium of the involved tissues are usually minimal. In the central nervous system type, recurrence of the tumor may be related to extravascular brain masses.[9] Thin venous sinusoidal involvement is observed in the liver, spleen, and bone marrow. Circulating malignant cells may occasionally be found in peripheral blood, although this does not occur in the majority of cases observed.[10] The same patient may exhibit several different patterns of tumor distribution. Neoplastic cells located in the central part of the blood vessel lumen exhibit a free-floating appearance, while in the more 'cohesive or sticky' mode, the tumor cells almost completely fill the lumen, and it is often difficult to assess the vascular structure. A marginating pattern is discerned when tumor cells have an affinity to adhere and skirt along the sides of endothelial cells, where the central part of the lumen appears void.[11]

In most cases, tumor cells are large and have a high nuclear-to-cytoplasmic ratio with very little cytoplasm. The nuclear outline is usually smooth, whereas irregular contours are less commonly

reported. Neoplastic cells characterized by smaller cells with irregular nuclear contours have been reported in isolated cases.[10] The nucleolus may be single, conspicuous, or multiple nucleoli, but is easily identified. Therefore, IVLBCL shows a morphological spectrum involving centroblasts to more atypical features of immunoblasts or plasmablasts[10,12] including rare forms with anaplastic morphology.[8] Except for major blood vessels, almost all other blood vessels may be affected in IVLBCL.[10] In this case, the presence of mitotic figures and high proliferation fraction of cells highlighted by Ki67 immunostaining confirmed active replication within the vascular space.

Cases associated with the Asian variant of hemophagocytic syndrome are accompanied by non-neoplastic histiocytes containing red blood cells or mononuclear cells. Cells displaying phagocytic activity may also be easily observed in peripheral blood smears. In a small number of cases, IVLBCL is diagnosed following the identification of a preceding lymphoma involving indolent types such as small lymphocytic lymphoma and follicular lymphoma, and the more aggressive type diffuse large cell lymphoma not otherwise specified.[11] A clear clonal origin has recently been reported in a patient with lymphoplasmacytic lymphoma and subsequent IVLBCL.[13] In this case, the diagnosis was made only after the examination of the trephine biopsy with extensive immunostaining. Tumor cells express antigens associated with mature B cells. Co-expression of CD5 and CD10 was observed in 38% and 13% of the cases, respectively. Almost all CD10 negative cases arre positive for IRF4/MUM1 in favor of a non-germinal center B subtype. More EBV-positive tumor cells are seen in intravascular NK/T cell lymphomas, and a very small number of ALK-negative intralymphatic large cell lymphomas have been reported, but separating these entities must be considered.[1] It has been hypothesized that the intravascular growth pattern is secondary to defects in the localization of receptors on tumor cells, such as the lack of adhesion β molecules CD29 (integrin β1) and CD54 (ICAM1). Further studies are needed to better understand the evolution of this rare lymphoma. New and emerging evidence indicates the utility of PET/CT in the diagnosis of lymphoma.[14] However, its role in IVLBCL is still largely unknown due to its rarity and non-specific findings on clinical and other supporting diagnostic tools. A characteristic pattern of FDG capture has been proposed, mainly involving diffuse accumulation in organs that are rich in small blood vessels, such as the lungs, kidneys, and bone marrow.[15] This is because autopsies revealed a high frequency of involvement in these organs.[15] Cytogenetic abnormalities and molecular changes have not been well characterized under these conditions.[16]

Only one other case of IVLBCL has been reported in Malaysia, where the patient presented with neurological symptoms and was initially diagnosed with acute demyelinating encephalomyelitis.[17] After the symptoms worsened a month later, a biopsy of the brain was performed, which showed B-lymphoid cells within the vascular lumina.[17] Our patient presented with fever of unknown origin and was later diagnosed with IVLBCL. Unfortunately, there is no fever pattern pathognomonic of cancer. Classically, cancer fever may be less associated with rigors, tachycardia, and hypotensive episodes than other causes. The patient did not respond to intensive and prolonged antibiotic therapy, which tended to exclude any involvement of bacteriologic etiology. Antipyretic agents such as aspirin and paracetamol usually have no effect on cancer fever, unlike fever caused by infection.[18,19] The mechanisms underlying cancer-induced fever are not fully understood. High levels of IL-6 and IL-10 have been observed in lymphomas, and the presence of B symptoms correlates with the serum levels of IL-6.[20] The heterogenous presenting features of IVLBCL among patients make early diagnosis difficult. Delay in diagnosis was considerable as the time it took from initial presentation until the definitive diagnosis of IVBCL was nearly six months in this patient. Bone marrow involvement is associated with a poor prognosis.[21] The first choice of treatment in patients with IVLBCL is the use of combination chemotherapy comprising cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) regimen. Patients with IVLBCL treated with CHOP achieved an overall response rate of 59%.[22] Rituximab has improved the outcomes of IVLBCL. The addition of rituximab to CHOP chemotherapy (R-CHOP) has yielded an 88% complete remission rate, 91% overall response rate, and 3-year OS in 81% of patients.[23,24] The positive effect of rituximab may be explained by the high drug bioavailability and elevated complement concentrations in the lumina of small vessels. Our patient received six cycles of R-CHOP and remained in complete remission. However, the overall survival rate for this aggressive disease is poor. Autologous stem cell transplantation has been reported to prolong survival; however, further studies are warranted.[25]

Clinical recognition of this entity remains a challenge. Standard staging and therapeutic approaches need to be addressed to further elucidate the characterization and management of this rare disease.

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Author contributions

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