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A Case of Lymphoma without Lymphadenopathy and Organomegaly

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ABSTRACT

Intravascular large B cell lymphoma (IVBCL) is a rare type of extranodal large B cell lymphoma characterized by selective growth of lymphoma cells within the microvasculature. We present an illustrative case of intravascular B cell lymphoma suspected by the presence of a very few atypical cells on peripheral smear. The diagnosis was confirmed by bone marrow biopsy, immunohistochemistry and flow cytometry.

INTRODUCTION

The WHO classification of tumors of haematopoietic and lymphoid tissues defines intravascular large B-cell lymphoma (IVLBCL) as a rare sub type of extranodal diffuse large B-cell lymphoma (DLBCL) characterized by the selective growth of lymphoma cells within the lumina of vessels, particularly capillaries with the exception of larger arteries and veins.[1] Few cases of intravascular lymphoma exhibiting a T-cell or Natural Killer-cell phenotype have also been described.[2]

IVBCL is a rare disease and occurs in less than one person per million population[.3] It occurs mostly in middle aged and elderly. Usually it is widely disseminated with involvement of bone marrow, spleen, liver, lungs, CNS and skin with an aggressive and rapid progressive clinical course. The heterogeneity of clinical presentation and lack of detectable tumor mass or lymphadenopathy often hampers timely and accurate diagnosis. In recent years, the increased awareness of IVLBCL has resulted in more patients being diagnosed during life, whereas in the past diagnosis was made post-mortem[4,5].

CASE HISTORY

A 77 year-old man presented with a history of four months of recurrent fevers, weight loss, headache, proximal limb girdle pain and mild cough. Physical examination was unremarkable. There was no organomegaly or lymphadenopathy. He had no neurological deficit and cardiovascular examination disclosed no significant abnormalities. Peripheral blood analysis revealed hemoglobin of 8.6g/dl and a leucocyte count of 8,900/µl with neutrophilic predominance and 5 % of large atypical cells of size around 3 times that of normal lymphocyte with large irregular nuclei, coarse chromatin, basophilic cytoplasm and convoluted/ folded nuclei (fig. 1). Platelet count was 304,000/µl, ESR was raised (137mm at 1st hour), liver enzymes were elevated with SGOT 62U/L, Alkaline phosphatase 227U/L. SGPT was 37U/L. Lactate dehydrogenase (LDH) 1264UI/L (reference range 230-480 UI/L) and ferritin (502.60ng/ml) were raised.

Blood, urine and stool cultures were negative.

Ultrasonography of abdomen demonstrated grade II prostatomegaly, cholelithiasis. and computed tomography scan of chest demonstrated bilateral minimal pleural effusions. In view of peripheral smear findings, hematological disorder was suspected and a bone marrow aspiration and trephine biopsy were performed. Cytomorphologic evaluation of the bone marrow smear revealed 08% atypical, large sized lymphoid cells (Fig. 2). On Flow cytometry (Fig. 3a and b), these 5-8 % atypical lymphoid cells expressed CD19, CD22 along with CD45. These cells also expressed CD10, CD5, CD38 and kappa light chains. Histopathologic evaluation of the bone marrow biopsy confirmed the presence of large lymphoid cells with irregular nuclei within the sinusoidal vessels (Fig. 4a). These atypical cells were not seen outside the vessels. The rest of the marrow elements were unremarkable. On immunohistochemistry, these atypical cells

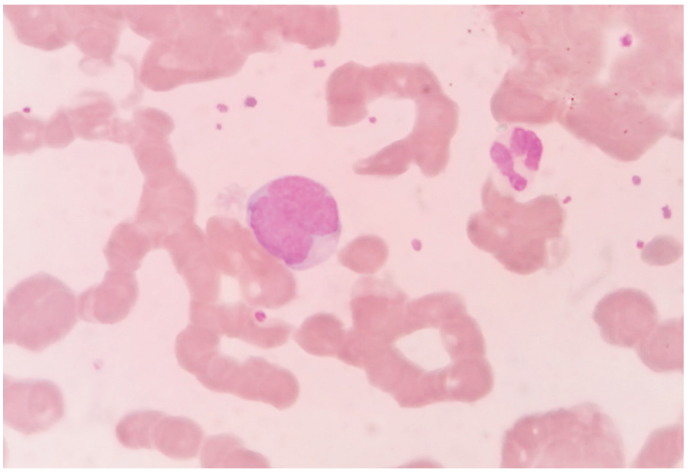

Figure 1 : Peripheral smear shows large atypical cell with high nucleo cytoplasmic ratio and irregular nuclei.

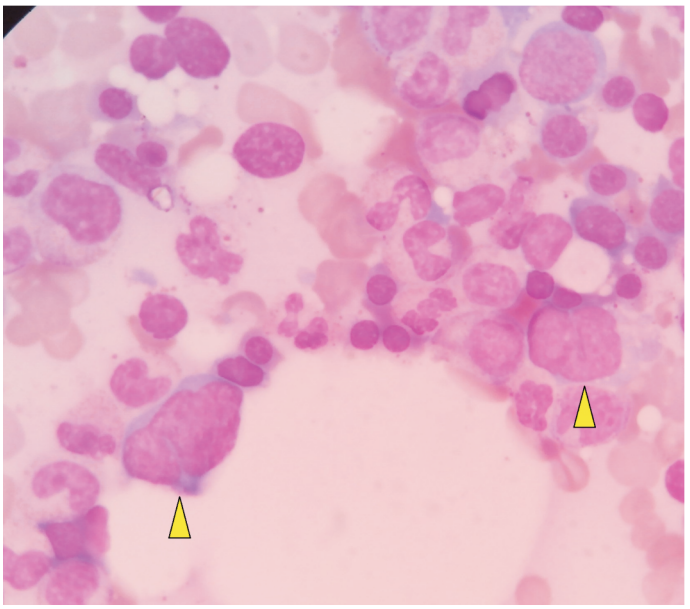

Figure 2a : Bone marrow aspirate shows large atypical cells with high nucleo cytoplasmic ratio and irregular nuclei (arrow heads).

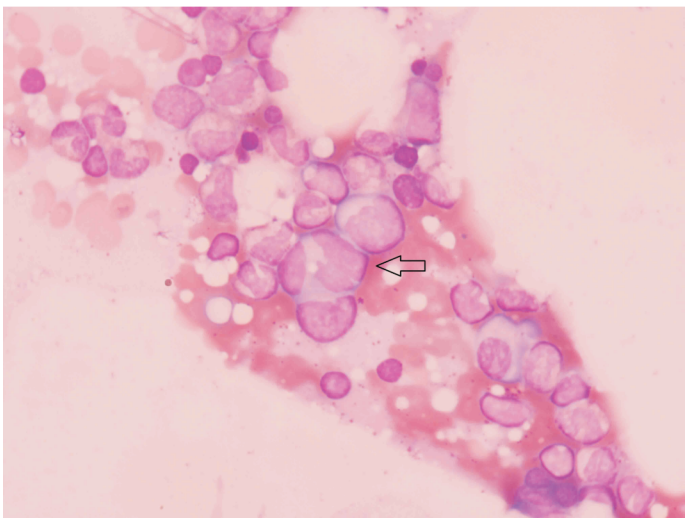

Figure 2b : Bone marrow imprint shows large atypical cell with high nucleo cytoplasmic ratio and irregular nucleus (arrow).

expressed CD20 (Dako, L26 clone) (Fig. 4b), confirming the diagnosis of intravascular large B cell lymphoma. CD31 (Dako, JC70A clone) confirmed the intravascular localization of the lymphoma cells. Patient is asymptomatic with 6 cycles of RCHOP with improved hematological parameters. He is on regular follow up for the last 3 years without any signs or symptoms of recurrent disease. Meanwhile he was treated for acid peptic disease.

DISCUSSION

IVLBCL is a rare form of extra nodal diffuse large B cell lymphoma which is usually widely disseminated at the time of presentation. It is characterized by presence of lymphoma cells nearly exclusively within small and medium sized vessels. At times these lymphoma cells can be observed in immediate vicinity of the blood vessels. These cells can also be seen in sinusoidal vessels of liver, spleen and bone marrow.[1].It is proposed that the homing of tumor cells in IVLBCL is related to expression of molecules (CD11a and CD49d) on surface of lymphocytes that allow preferential binding within vascular channels. It is also found that these tumor cells lack CD29 and CD54 both of which are necessary for lymphocyte homing and trans vascular migration [3,5]. The clinical presentation of an intravascular lymphoma is extremely variable and caused by occlusion of small vessels. Geographic differences have been noted in the presentation of the disease. Two different modes of clinical presentation have been recognized: a Western variant (classic-type) and an Asian variant, each having its own pattern of organ infiltration. Cases diagnosed in Western countries display a relatively high frequency of central nervous system (CNS) and skin involvement while hepatosplenomegaly is reported in 26% cases. Patients from Asian countries preferentially present with haemophagocytic syndrome, bone marrow involvement, fever, hepatosplenomegaly (in 73-100% of cases) and thrombocytopenia. Lymphadenopathy is usually absent in both the variants.[6] A third type of clinical presentation has been described, where lymphoma infiltration is strictly limited to the skin. Almost all patients with this cutaneous variant are females with a good performance status, this is in contrast with the other presentation forms without male or female predominance.[7-13] Peripheral blood involvement is rarely observed (5 to 9% cases). Laboratory findings are usually non specific. Anemia (65%), increased serum LDH and β2-micro globulin concentrations (80 to 90%) are the most frequently observed abnormalities. Liver enzymes may be elevated in case of liver involvement. [7-10,12] In our case, elevation of live enzymes may suggest sub clinical involvement of liver. Liver biopsy was not performed in this case. There are no pathognomonic laboratory or imaging findings of IVLBCL. Magnetic resonance imaging in cases with central nervous system involvement commonly shows cortical, subcortical metachronous lesions that are hyperintense on T2-weighted and fluid- attenuated inversion recovery images. These findings often suggest alternative diagnosis of CNS vasculitis.[6] Computed tomography of liver can show infiltrative lesion with no enhancement and no mass effect. Even in the absence mass lesion, a random skin, liver or bone marrow biopsy can aid in diagnosis of IVLBCL when suspected.[3] Suspicion of intravascular lymphoma is mainly based on cytologic recognition of large atypical lymphoid cells on bone marrow smears. In contrast to the well described spectrum of cytologic characteristics of IVLBCL cells on haematoxylin and eosin stained smears (large cells with vesicular nuclei, prominent nucleoli, frequent mitotic figures or coarse nuclear chromatin or

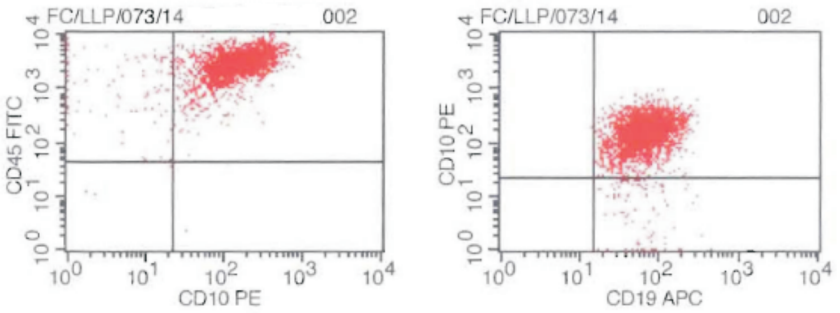

Figure 3a : On flowcytometry, these cells express CD45, CD19 and CD10.

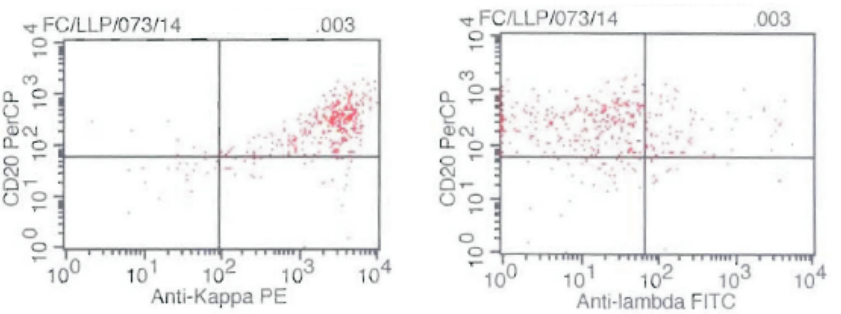

Figure 3b : On flowcytometry, these cells express CD20 and kappa light chain.

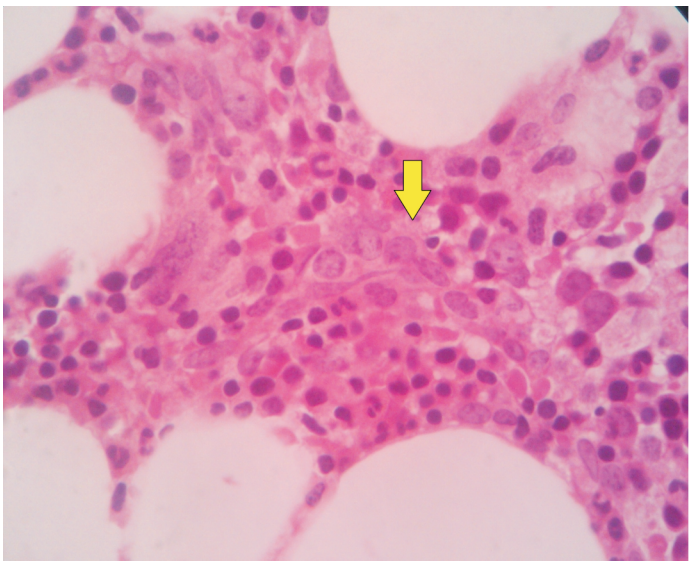

Figure 4a : Bone marrow biopsy (H&E stain X400) shows large atypical cells within the sinusoid (arrow).

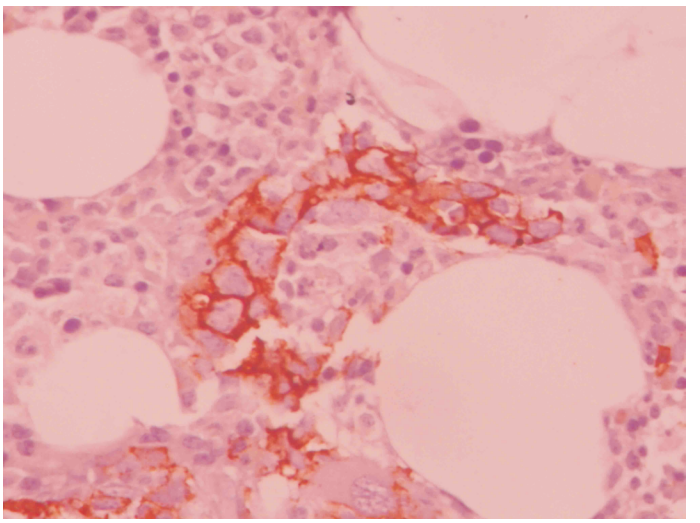

Figure 4b : Immunohistochemistry with CD20 highlights the intravascular atypical B lymphocytes.

irregular and indented nuclei), only limited information is available about the cytomorphologic aspects of these neoplastic cells in May-Grünwald-Giemsa stained bone marrow smears.[1,5] Additional histopathology and immunohisto chemistry are necessary to confirm the selective growth of neoplastic lymphoid cells in the lumina of small blood vessels which can be demonstrated using endothelial cell markers such as CD31, CD34 or FVIII. A concomitant minimal extra vascular localization of neoplastic cells, usually surrounding involved vessels, may occasionally be observed.[5] Differential diagnoses for intravascular neoplastic lymphocytes include B cell chronic lymphocytic leukaemia, mantle cell lymphoma and splenic marginal zone lymphoma. However, these cases cases have predominant extravascular component and small size of lymphoma cells and immunophenotyping help in diagnosis.[4]. Tumour cells in IVLBCL typically express B-cell antigens such as CD19, CD20, CD22 and CD79a. The reported frequency of CD5 positivity varies considerably (22- 75%). A subset of IVLBCL cases also expresses CD10. In most cases the neoplastic cells are reactive for BCL2 with at least 25% of cells being positive for BCL6. Molecular studies have been performed only in a limited

number of cases and most have shown clonal immunoglobulin heavy chain gene rearrangements supporting a B-cell origin.(3,4,7,8) Clonality can also be determined by flow cytometric analysis for light chain surface immunoglobulin distribution. However, flow cytometry is often hampered by the low number of neoplastic lymphoid cells present. Gain/ losses involving chromosome 18 and abnormalities of 8p21 and 19q13 have been reported in several case reports. (12,14). In clinical practice, treatment strategy is similar for DLBCL and IVLBCL, bearing in mind the less favourable prognosis when IVLBCL is suspected[4]. However, for the cutaneous variant local therapy (and radiotherapy) could be considered.[4] Cases of long term remission have been reported in literature with response rate of 59%.[15] In our case also follow up is uneventful till date after 6 cycles of RCHOP. Some patients achieved complete remission, however response rates and overall median survival rates are consistently lower than that of diffuse large B cell lymphoma.[3]

CONCLUSION

Clinicians & pathologists should be aware that intravascular lymphomas may present with atypical clinical symptoms and high serum LDH levels but without obvious lymphadenopathy or without detectable tumour mass. In patients presenting with these findings, it is important to perform a bone marrow biopsy. Indeed, in our patient diagnosis of IVLBCL was made or confirmed by bone marrow biopsy. This case report illustrates that the presence of (even few) atypical large lymphoid cells on a peripheral smear and bone marrow smear may be the first clue pointing to a diagnosis of intravascular B-cell lymphoma before histopathology data are available. The final diagnosis however should still be based on histopathology and immunohistochemistry. The recognition of these cells may lead to a more rapid diagnosis of this lymphoma entity frequently missed by clinical features. Early diagnosis and treatment of this aggressive lymphoma may have a favourable impact on outcome.

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