

Intravascular Large B-cell Lymphoma – Morphological Diagnosis in the Molecular Era

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ABSTRACT

Intravascular large B-cell lymphoma (IVLBCL) is a rare variant of diffuse large B-cell lymphoma, characterized by its unique morphology. Modern-day diagnostic methods like flow cytometry have limitations in accurate diagnosis of the disease making morphology the mainstay for its diagnosis and adequate management. Here, we present a case of IVLBCL with emphasis on diagnostic aids and adjuncts. A 63-year-old female presented with fever of unknown origin, seizures, hepatosplenomegaly, and peripheral cytopenias. Bone marrow aspirate shows a small number of atypical lymphoid cells. Flow cytometry done on the aspirate yielded 7% abnormal lymphoid cells; however, further, subclassification of this non-Hodgkin lymphoma was not aided by it. Bone marrow biopsy revealed the intrasinusoidal localization of the tumor cells, which were positive for CD20, BCL2, and Mum1 and along with flow cytometric expression of CD5 and lambda restriction of tumor cells; a diagnosis of IVLBCL was made. IVLBCL is a rare entity with protean clinical presentation which frequently leads to a delay in diagnosis. Modern diagnostic modalities like flow cytometry help in picking up even a small number of tumor cells; however, it is limited by failure to subcategorize the entity making morphology and immunohistochemistry as the backbone of its diagnostic workup.

KEY WORDS: Bone marrow, CD5, diffuse large B-cell lymphoma, flow cytometry, immunophenotype, intravascular lymphoma.

Introduction

Intravascular large B-cell lymphoma (IVLBCL), formally known as angiotropic large cell lymphoma, was first described in 1959 by Pfleger and Tappeiner.^[1] It comprises <1% of all non-Hodgkin lymphomas (NHL) and is characterized by neoplastic lymphoid cells growing inside the lumen of medium and small vessels. It virtually involves all organs; however, lymph nodes are usually spared. Clinical presentation of IVLBCL varies according to the geographic region; the main organs affected include the skin and central nervous system (CNS). The tumor cells are seldom found in peripheral blood.^[2,3] Due to the varied modes of presentation and its rarity, the diagnosis is often delayed. Here, we present a

case of a 63-year-old female presenting with stroke, fever of unknown origin, and peripheral cytopenias.

Case Report

A 63-year-old female, known case of type 2 diabetes mellitus and hypertension controlled on medication presented with recurrent low-grade fever for the past 6 months and recent episodes of seizures. A detailed history revealed two episodes of cerebrovascular accidents in the past 3 years, for which she was conservatively managed. On examination, hepatosplenomegaly was found. A review of her laboratory data revealed a persistent thrombocytopenia for the past 3 years and a leukoerythroblastic peripheral blood picture. Magnetic resonance imaging (MRI) of the brain revealed multiple small hyperintensities and hypointensities and a differential diagnosis of vasculitis, metastasis, or lymphoma was suggested. Persistent thrombocytopenia, hepatosplenomegaly, and MRI finding of brain prompted a bone marrow examination. Bone marrow aspirate was dilute, however, showed 7% atypical cell count. Flow

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cytometric evaluation of bone marrow showed 0.5% abnormal cells. These abnormal cells gated by bright CD45 and CD19 expression and low side scatter, showed expression of CD20, CD5, CD79a, and lambda and were negative for CD10, CD3, CD7, kappa, Myeloperoxidase (MPO), and CD34. With the above immunophenotype, a diagnosis of bone marrow infiltration by B-cell lymphoproliferative disorder was suggested; however, the low yield of abnormal cells did not clarify the diagnostic dilemma. Thereafter, the bone marrow biopsy sections were received and showed proliferation of large abnormal cells with a round to convoluted nuclei, coarse chromatin, and scant cytoplasm with intrasinusoidal localization (Figure 1). On immunohistochemistry (IHC), the tumor cells were positive for CD20, Bcl2, and MUM1 (Figure 2) and negative for CD3. The Ki67 index was 50% (Figure 2). Keeping up with the flow cytometry, morphology, and IHC features, a diagnosis of IVLBCL was made.

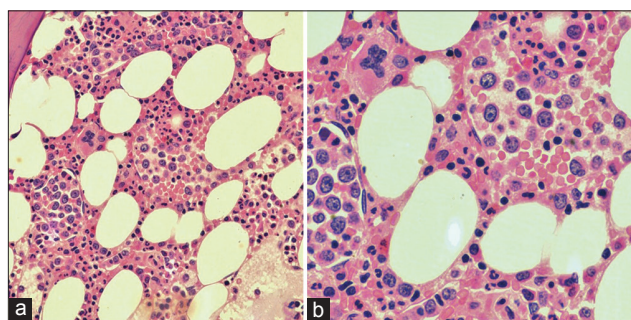


Figure 1: (a) Large lymphoid cells with intrasinusoidal localization (H and E, ×100). (b) Tumor cells are large with round to convoluted nuclei, coarse chromatin, and scant cytoplasm. Tumor cells are seen limited by the endothelial lining of sinusoids (H and E, ×200)

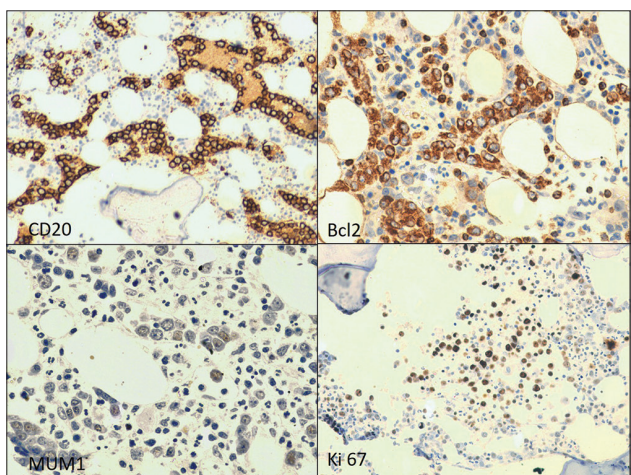


Figure 2: The tumor cells are positive for CD20 (×100), Bcl 2 (×200), MUM 1 (×200). The Ki67 index of 50%

Discussion

IVLBCL is an uncommon form of B-cell NHL which is seen most commonly in patients with a wide age range of 13–85 years with a median age of 65 years and an equal gender predilection.^[3] Three forms of IVLBCL have been documenting based on the geographical region and the clinical presentation. The classical form is usually seen in the west and present predominantly with features of CNS and skin involvement and hemophagocytic syndrome.^[4] The Asian forms seen most commonly presents with multiorgan failure, hepatosplenomegaly, and pancytopenia. Murase *et al.*^[5] in their study on the Japanese population suggested a similar clinical profile. An isolated cutaneous variant has been described recently which is limited to the skin and has a better prognosis. B symptoms like a fever are seen in approximately 75% of cases. Yamada *et al.*^[6] and Khan *et al.*^[7] reported stroke as an initial presentation of intravascular lymphomas. The present case is a 63-year-old female with a history of cerebrovascular accidents, hepatosplenomegaly, cytopenias, and B symptom of fever resembling the Asian form in the presentation.

IVLBCL is characterized microscopically by malignant lymphoid cells localized in the lumina of small and intermediate size vessels in the involved organs.^[3,4] Bone marrow involvement was reported to be as high as 75% by Murase *et al.*^[5] The tumor cells were limited to the sinusoids of the bone marrow and interstitial infiltration was limited to sparse foci. The intrasinusoidal localization is hypothesized to be due to loss of adhesion molecules such as CD29 and CD54. CNS involvement is a rare phenomenon in the Asian variant and CNS relapse can occur in the form of extravascular masses. A brisk mitotic activity is usually noted in these tumors.^[4]

Immunophenotyping of hematopoietic neoplasms by flow cytometry has emerged as a primary aid for prompt diagnosis and for assessing prognosis in recent times. IVLBCL arises from a transformed peripheral B cell and expresses mature B-cell markers. Tumor cells are positive for CD5 (38%) and CD10 (13%).^[8] A rare CD10-negative immunophenotype has also been described and has been shown to be consistently positive for IRF4/MUM1.^[4,5] In the present case, abnormal cells in the bone marrow aspirate were CD19, CD20, CD5, CD79a positive, and clonal (lambda restricted) and negative for CD10, CD3, CD7, kappa, MPO, and

CD34. The above immunophenotype although was enough to derive a diagnosis of a B-cell non-Hodgkin's lymphoma even in case of a low cell yield (0.5% of events) but was not sufficient to further categorize it.

Bone marrow biopsy showed a characteristic pattern of intrasinusoidal infiltration by the tumor cells. The individual cells were large with high N/C ratio, coarse chromatin, and prominent nucleoli. A few tumour cells have a convoluted nuclear morphology. A brisk mitotic activity noted in the background. The interstitial infiltration by tumor cells was not seen. For further subcategorization of lymphoma, an IHC panel of five markers comprising of CD3, CD20, Bcl2, Mum1 and Ki67 was done. The tumor cells were positive for CD20, Bcl2, MuM1, and Ki67 which were 50%. In conjunction with flow cytometry, morphology, and IHC, a final diagnosis of IVLBCL was made.

The main diagnostic differentials with intrasinusoidal localization of lymphoma cells include intravascular NK/T cell lymphoma, in which the tumor cell is positive for CD3 and is usually associated with an EBV infection; and intralymphatic anaplastic large cell lymphoma in the tumor cells shows positivity for CD3, CD5, and CD30 is usually ALK negative.^[4]

Murase *et al.*^[5] reported that the CD5+CD10-IVLBCL shows a more aggressive course than CD5+CD10- DLBCL. The presence of organ involvement and B symptoms in IVLBL does not have any significant prognostic information. Murase *et al.*^[5] and Shimada *et al.*^[9] reported that, a disease limited to skin and rituximab chemotherapy are important prognostic factors for IVLBCL. The delay in diagnosis of IVLBCL is usually due to non-specific presenting features; however, the 3-year survival rates are now as high as 60–80% with anti-CD20 chemotherapeutic regimens. The post-rituximab era is marred by the frequent CNS relapse in the patients with extravasation of tumor cells and formation of extravascular masses. A follow-up with appropriate imaging modality like fluorodeoxyglucose-positron emission tomography can help in monitoring and early detection of a relapse.^[4,6,9]

Conclusion

IVLBCL is rare, morphologically distinct entity than other large B-cell lymphomas with a more aggressive

clinical course. The clinical presentation of this entity is protean and hence frequently leads to a delay in diagnosis. Modern diagnostic modalities like flow cytometry are useful in detecting even a low burden of disease, however, are limited by its inability to subcategorize it. Bone marrow morphology and IHC help to narrow down the diagnosis and serve as important prognostic indicators.

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