

CASE REPORT

Intravascular Large B-Cell Lymphoma: Clinical and Histopathologic Findings

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Intravascular large B-cell lymphoma (IVLBCL) is a rare subset of extranodal non-Hodgkin lymphoma characterized by neoplastic lymphocytes within the lumina of small to medium-sized blood vessels. IVLBCLs are B-cell tumors that can present in essentially any organ system, including the skin. Cutaneous manifestations vary greatly and can mimic other skin disease which may delay diagnosis; in the absence of skin lesions, blind skin biopsies can be utilized for diagnosis. Early studies suggested that IVLBCL is a very aggressive lymphoma with high overall mortality rate and short survival times. However, earlier diagnosis and use of new treatment modalities have shown promise in recent studies. This case series illustrates the heterogeneity of clinical and pathologic presentations of this uncommon lymphoma.

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare extranodal lymphoma in which neoplastic lymphocytes are present primarily within small to medium-sized blood vessels in a variety of organs [1]. The most recent World Health Organization classification classifies IVLBCL as a subtype of diffuse large B-cell lymphoma, although other intravascular tumors with a T-cell phenotype have been reported [2,3]. There is no strong association

with Epstein-Barr virus (EBV) but rare EBV-positive cases have been described, particularly in AIDS patients [4,5]. IVLBCL has traditionally been viewed as an aggressive disease with a poor prognosis, though early recognition of cases with rapid institution of treatment has improved outcomes significantly, particularly in the era of rituximab [6,7].

IVLBCL is separated into three variants based upon the clinical presentation and organs involved [1,2]. The classical variant is the most common form in the United

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Abbreviations: IVLBCL, intravascular large b-cell lymphoma; EBV, Epstein-Barr virus; AIDS, acquired immunodeficiency syndrome; CBC, complete blood count; CRP, c-reactive protein; LDH, lactate dehydrogenase; PET, positron emission tomography; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; BEAM, carmustine, etoposide, cytarabine, and melphalan.

Keywords: intravascular large b-cell lymphoma, IVLBCL, diffuse large b-cell lymphoma, classical variant, cutaneous variant

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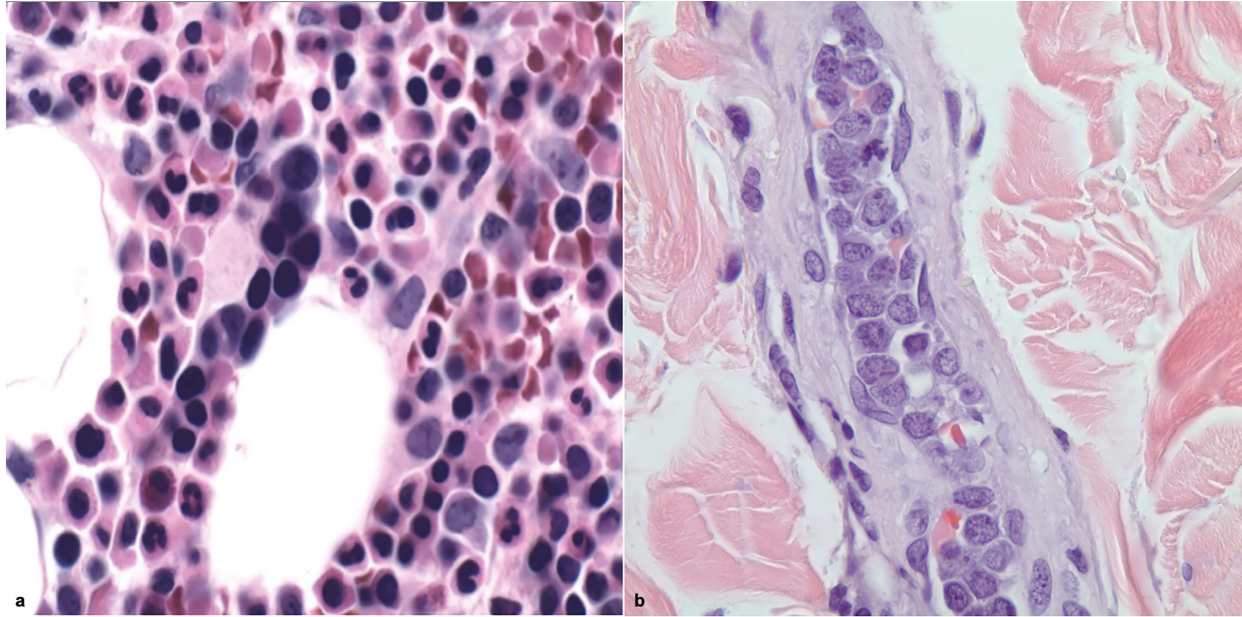


Figure 1. Case 1. Small to medium-sized intrasinusoidal lymphocytes in the bone marrow (a, H&E, 400x) in comparison with the intravascular large, atypical lymphocytes in the subsequent blind skin biopsy (b, H&E, 400x).

States, encompassing approximately 75% of cases. Skin and central nervous system involvement is seen in 40% and 30% of classical variant cases, respectively. Other organs typically involved include the lung, kidney, liver, and adrenal glands [8,9]. The hemophagocytic syndrome-associated variant (also known as the Asian variant), classically presents with fever, thrombocytopenia, splenomegaly, and bone marrow involvement. Finally, the cutaneous variant, comprising around 25% of cases in the United States, presents with one or more cutaneous lesions and negative workup for additional sites of involvement. In this series, we present clinical and pathologic correlation for three cases of IVLBCL, two of the classical variant and one presumed to be the cutaneous variant.

CASE PRESENTATIONS

Patient 1

A 69-year-old man with unremarkable past medical history presented with a multiple week history of gait instability, chronic dry cough, 15-pound weight loss, and fever. Complete blood count (CBC) showed mild normocytic anemia without leukocytosis or thrombocytopenia. Ferritin and C-reactive protein (CRP) were elevated at 1140 ng/mL and 190 mg/L, respectively, while lactate dehydrogenase (LDH) was within normal limits. A positron emission tomography (PET) scan was performed which showed a hypermetabolic and enlarged spleen with patchy bone marrow hypermetabolism. The bone marrow biopsy showed small collections of small to medium-sized lymphocytes within the sinusoids (Figure

1a). No hemophagocytosis was identified. Corresponding flow cytometry showed a clonal B-cell population comprising approximately 5% of total cellularity. The immunophenotype of this population was CD19+, CD20+, CD5dim+, CD23-, CD10-, CD103-, CD38dim+, CD11c-, FMC7dim+, CD43-, IgG-, IgM-, and kappa light chain restricted. Ki-67 showed a proliferative index of approximately 70% within the abnormal lymphocyte population. EBER, BCL2 and BCL6 were negative by immunohistochemical staining. Karyotype and FISH results for the IGH, BCL6, MYC, 15q, 17p (TP53), 13q, CDKN2C, and CKS1B loci were normal and a PCR test for cyclin D1 mRNA level was not elevated. Concurrent flow cytometry performed on peripheral blood showed a B-cell population with identical immunophenotype which comprised less than 1% of cellularity.

Given the sinusoidal pattern of the bone marrow infiltration, consideration was given to splenic marginal zone lymphoma, splenic diffuse red pulp small B-cell lymphoma, as well as IVLBCL. While this differential is often distinguished morphologically, the intermediate size of the lymphocytes could not clearly delineate between these entities, and additional workup was necessary. Random skin biopsies were pursued and showed medium to large-sized lymphocytes within small to medium-sized blood vessels (Figure 1b) which stained positively with CD20, confirming the diagnosis of IVLBCL.

The patient received numerous cycles of R-CHOP with significant improvement in his symptoms, followed by dose-modified BEAM with autologous stem cell rescue. He is currently in complete remission.



Figure 2. Case 2. At presentation, indurated plaques, stellate scars, focal crusting, and associated telangiectasia (a). Skin lesions progressed over time with erythematous, indurated plaques with focal foul-smelling non-healing ulcerations on the left upper thigh (b) and eschar-covered ulcer on the abdomen (c).

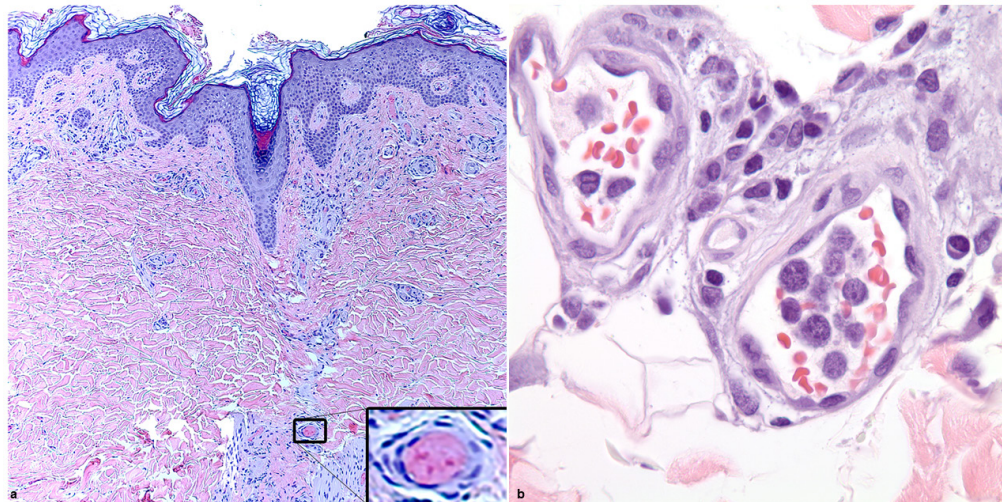


Figure 3. Case 2. Small vessels with fibrin thrombi (a, H&E, 100x). Atypical lymphocytes, ranging from small to large, within small vessels in the subcutis. (b, H&E, 400x).

Patient 2

A 69-year-old man with extensive past medical history including stroke three years prior to presentation and two years of recurrent falls attributed to leg weakness initially presented to the dermatology clinic with painful, erythematous plaques (Figure 2a). A skin biopsy was performed which showed occlusion of small vessels within the dermis by fibrin thrombi (Figure 3a). These findings were interpreted as thrombotic coagulopathy. Subsequent hypercoagulability workup was negative.

Over the next six months, the patient's skin lesions worsened significantly and he was admitted for altered mental status. By this time, he had developed multiple reticulated (retiform, branching) purpuric indurated

plaques with necrotic eschars and ulcers on his abdomen, bilateral thighs, calves, and buttocks, as well as reticulated hyperpigmented patches and dozens of telangiectasias on his back (Figure 2b,c). An additional skin biopsy was taken from the thigh which showed no evidence of thrombotic changes, vasculitis, or lymphoproliferative disorder. Bone marrow biopsy and flow cytometry performed at this time was negative for involvement by a lymphoproliferative disorder. Subsequent rheumatologic and additional coagulopathy workup was negative.

Approximately four months later, the patient was admitted for failure to thrive and an additional skin biopsy was pursued which showed atypical lymphocytes, ranging in size from small to large, within both small- and medium-sized vessels (Figure 3b). These cells were pos-

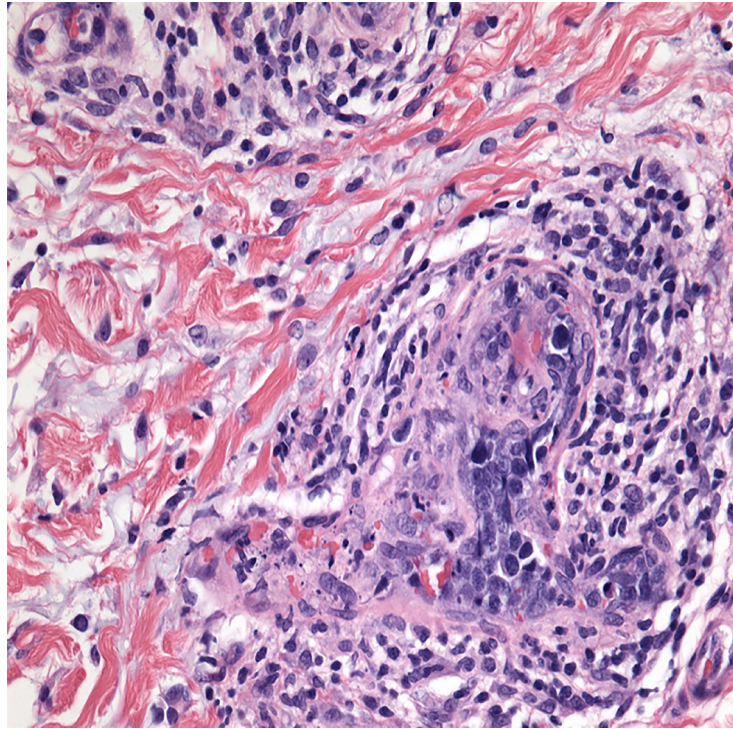


Figure 4. Case 3. Large, hyperchromatic lymphocytes and small fibrin thrombi filling the lumina of blood vessels within the dermis (H&E, 200x).

itive for CD45 and CD20, lambda light chain predominant, and negative for CD30, EBER, BCL2, BCL6, CD5, and CD10 by immunohistochemical staining, consistent with a diagnosis of IVLBCL. CBC on this admission showed a mild normocytic anemia without leukocytosis. CRP, Ferritin, and LDH were elevated at 86.5 mg/L, 676 ng/mL, and 525 U/L, respectively. The patient opted to not pursue chemotherapy and passed away shortly after diagnosis.

Patient 3

A 93-year-old woman presented with retiform purpura and violaceous, indurated plaques on her anterior and medial thighs bilaterally. CBC performed at this time showed a mild normocytic anemia without leukocytosis and LDH was within normal limits. A biopsy was performed which showed occlusion of small vessels of the superficial and deep dermis by large atypical lymphocytes and small fibrin thrombi (Figure 4). The atypical cells had the following phenotype by immunohistochemistry: CD3-, CD20+, CD79a+, CD30-, MUM1+, BCL2+, BCL6var+, CD10-, CD23-, CD43-, CD5-, CyclinD1-, CD56-, TIA1-, CD68-, myeloperoxidase-, TdT-, ALK-, EBER-, EMA-, and HHV8-. Ki-67 stain showed a proliferative index of approximately 90%. These findings were consistent with the diagnosis of IVLBCL. Subsequent PET scan showed no systemic involvement with mild uptake in the

thigh lesions bilaterally. Peripheral blood flow cytometry and bone marrow studies were not performed.

The patient was treated with rituximab monotherapy with complete resolution of her cutaneous lesions. Approximately two years later, the patient began experiencing transient numbness of her left leg of unclear etiology. One year later (three years after initial diagnosis), the patient developed new lesions on her left lower leg and subsequent biopsy showed relapse of her IVLBCL. Rituximab monotherapy was again pursued, with progression of additional violaceous plaques on her thighs. At this time, given the age and frailty of the patient, localized radiation therapy was pursued with complete resolution of the lesions.

DISCUSSION

Intravascular large B-cell lymphoma is rare, with limited large series to date [7,8,10-12]. This issue is compounded by the fact that IVLBCL has numerous variants with different presentations and associated prognoses: a classical variant, a cutaneous variant, and a hemophagocytic syndrome-associated variant described predominantly in Asian countries [2]. Cutaneous involvement is particularly complex in that it is seen both as the only site of involvement in the cutaneous variant, but also as one of the most frequently involved sites at in the classical variant of IVLBCL. Skin lesions are present in about

40% of classical variant IVLBCL at presentation [8]. Both cases of the classical variant in our series had skin and neurologic involvement (*e.g.* gait instability and leg weakness).

Cutaneous involvement shows impressive heterogeneity, with indurated, erythematous eruptions, violaceous plaques, painful nodular discoloration, ulceration, desquamative plaques, peau d'orange, cellulitis, hyperpigmented patches, and palpable purpura having all been described [8,13,14]. Colonization of cutaneous hemangiomas and other benign neoplasms by neoplastic cells has also been reported [15,16]. No relationship has been found between type of skin lesion and prognosis or systemic involvement. Our cases are consistent with previous reports and show heterogeneity of skin lesions in Case 2 as well as biopsy-confirmed involvement of normal-appearing skin (Case 1). Case 2 highlights the potential need for multiple biopsies for definitive diagnosis, which is well documented in the literature [17].

Two of our three presented cases had retiform purpura, which is classically associated with coagulopathy but can be due to any vaso-occlusive process. As Case 2 had fibrin thrombi within vessels in the first biopsy, a coagulopathy was suspected. This case emphasizes the importance of not completely ruling out another vaso-occlusive process (like IVLBCL) even when fibrin thrombi are present. While IVLBCL has been reported with fibrin thrombi, large, neoplastic lymphocytes are typically present, as in Case 3 [18]. As demonstrated by Case 2, however, they are not always present, even with careful examination of multiple levels.

The hallmark of IVLBCL is intravascular involvement of small and medium-sized vessels by large, malignant lymphocytes; however, both Case 1 and Case 2 had smaller lymphocytes. In Case 1, the small to medium-sized neoplastic lymphocytes and sinusoidal pattern on bone marrow biopsy, led to consideration of splenic marginal zone lymphoma. However, given the constellation of symptoms, blind skin biopsy was pursued and showed large intravascular B-lymphocytes, securing the diagnosis. This case again highlights the need for additional sampling in IVLBCL, and there should be a low threshold for re-biopsy, particularly of the skin [17].

The pathomechanism behind the presence of tumor cells within the vessels in IVLBCL has not been fully elucidated. Tumor cells may lack expression of molecules necessary for extravasation, such as CD29 and CD54, as well as matrix metalloproteinases like MMP-2 and MMP-9 [19,20]. Despite their presence in vessels, the malignant cells of IVLBCL also do not circulate in the blood in large numbers in most cases, which is supported by the lack of lymphocytosis in the vast majority of cases, including our series. In fact, cytopenias, including leukopenia, are seen in the majority of cases [21]. Additional

laboratory abnormalities, such as elevated LDH, CRP, and ferritin are relatively nonspecific but present in many cases, including Cases 1 and 2 in our series [9,21].

Therapy for IVLBCL has not been firmly established, but classically the disease has been treated as an aggressive lymphoma with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Using CHOP, response rates are around 55%, with about a third of patients alive at three years in classical IVLBCL, and less in hemophagocytic-syndrome associated IVLBCL [10,22]. The addition of rituximab to these regimens (R-CHOP) has resulted in significantly better outcomes: greater than 90% response rate and more than 80% of patients alive at three years [6]. Case 1 highlights the potential for good outcomes in IVLBCL despite traditionally poor prognosis. The treatment of the cutaneous variant of IVLBCL, given its superior outcomes, is less clear, although many authors recommend R-CHOP. Rituximab monotherapy or radiation therapy for cutaneous lesions in older patients or those unfit for aggressive chemotherapy can be considered, and was successfully employed with good response in Case 3. Stem cell transplant has shown additional promise in small retrospective studies [23].

CONCLUSIONS

With the potential for improved outcomes with modern therapies, the timely diagnosis of IVLBCL is particularly critical. This case series promotes awareness of two pitfalls in the diagnosis of IVLBCL: 1) prominent fibrin thrombi without atypical lymphocytes and 2) small to medium-sized (rather than large) lymphocytes. Understanding the spectrum of IVLBCL and having a low threshold for additional sampling can be critical to making the diagnosis.

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