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Intravascular Large B-Cell Lymphoma

A Brief Review of Current and Historic Literature and Cautionary Tale of Pertinent Pitfalls

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• Context.—Intravascular large B-cell lymphoma (IVLBCL) is a rare hematopathologic entity, posing both a clinical and histologic challenge for diagnosis. Numerous pitfalls can hinder making the diagnosis.

  Objective.—To summarize recent developments in literature pertaining to IVLBCL and point out key pitfalls pathologists should be prepared to encounter.

  Data Sources.—Literature review via PubMed search and hospital (Darnall Medical Library) resources.

Intravascular lymphoma is an uncommon neoplasm first recognized more than half a century ago. Terminology has been continually updated since the first reported discovery. 1 It was originally recognized by the distinctive growth pattern and thought to be of endothelial origin, thus classified as “angioendotheliomatosis.” Utilization of immunohistochemistry and Southern blot techniques in the late 1980s led to its definitive classification as a hematolymphoid process and renaming as angiotrophic large cell lymphoma before current day nomenclature. 2–3 One commonality among observers over the decades has been recognition of intravascular lymphoma as a high-grade neoplasm with poor outcomes. B-cell origin represents the most common cell lineage. Exceedingly rare T-cell and natural killer cell intravascular lymphomas have been identified but remain separate entities according to the World Health Organization (WHO). 4 This review will focus on the B-cell type of the disease. The most recent WHO classification defines intravascular large B-cell lymphoma (IVLBCL) as lymphoma that is restricted to intravascular growth (particularly capillaries), as the name implies. 4 Because neoplastic cells are not usually seen circulating in the peripheral blood and IVLBCL does not form an extravascular tumor mass, many cases had been historically diagnosed postmortem, with the exception of cutaneous involvement or incidental detection. Owing to the diagnostic challenges, IVLBCL remains a difficult diagnosis, replete with various pitfalls.

Conclusions.—The 3 primary pitfalls of IVLBCL include masking of IVLBCL, mimicry by IVLBCL, and mimicry of IVLBCL. These scenarios illustrate the importance of histologic pattern recognition and subsequent usage of immunohistochemistry, especially in context of a clinical history that may be noncharacteristic.

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EPIDEMIOLOGY, CLINICAL PRESENTATION, AND DIAGNOSIS

IVLBCL usually occurs in patients between the ages of 34 and 90 years with a variable reported median range of 60 to 70 years. 5–7 The age-adjusted incidence within the United States was 0.095 per 1 million people between the years 2000 and 2013. 7 Symptoms at presentation are based on the site of involvement with central nervous system (CNS) and skin being the most common locations. Around 55% to 76% 4 of patients also present with some form of B symptomatology, in particular fever, and rare case reports have also identified atypical findings such as paraneoplastic syndromes (eg, syndrome of inappropriate antidiuretic hormone secretion). 8 It is not uncommon, however, for patients to be asymptomatic in settings where the diagnosis is incidental.

Initial screening diagnostics are highly limited in part because IVLBCL is rarely identified on peripheral blood smear, 5,9 and complete blood counts may only show nonspecific findings such as anemia, thrombocytopenia, or leukopenia. 5,10 Oncologists and radiologists alike regard IVLBCL as a “great mimicker,” masquerading as reactive processes that pose diagnostic challenges. 18F-fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) scans may be useful in evaluating...
symptomatic patients by identifying hypermetabolic areas in tissues involved by IVLBCL amenable to biopsy.\textsuperscript{11–13} PET/CT scans also serve to monitor patients for posttreatment relapse. While no IVLBCL-specific staging system exists, studies suggest that the use of more conventional staging parameters including imaging, bone marrow biopsy, various blood chemistry analytes, and evidence of organ infiltration might be of value to assess the presence and progression of the disease.\textsuperscript{4,5}

### HISTOLOGY, VARIANTS, IMMUNOHISTOCHEMISTRY, AND MOLECULAR FINDINGS

Histologic evaluation is the key to definitive diagnosis of IVLBCL. Sometimes, random biopsies, especially of skin, may be performed in the context of patients with fever and neurologic signs of no definitive origin. If there is clinical suspicion of intravascular lymphoma, skin is an easily accessible site for sampling. When symptoms and clinical findings suggest specific organ dysfunction, biopsy samples of those organ sites might be obtained. Other cases are diagnosed incidentally. From a clinical perspective, IVLBCL has a propensity to mimic other benign or malignant processes, and benign processes can mimic IVLBCL. In both of these instances, the mimicry does not typically extend far into the pathologic differential, as most of these processes look significantly different from lymphoma, both grossly and microscopically.

### Case Reports Noting Unexpected Intravascular Large B-Cell Lymphoma Diagnoses and/or Collision Tumors

<table>
<thead>
<tr>
<th>Patient age, y/sex</th>
<th>Initial presentation</th>
<th>CBC findings</th>
<th>Initial imaging studies</th>
<th>Primary tissue site</th>
<th>Primary diagnosis</th>
<th>Secondary diagnosis</th>
<th>Positive IHC</th>
<th>Negative IHC</th>
<th>IVLBCL Ki-67 index, %</th>
<th>Postdiagnosis clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muftah et al,\textsuperscript{26} 2012</td>
<td>73/F</td>
<td>Fever, generalized weakness; progression to right-sided weakness, lethargy, vomiting</td>
<td>Anemia</td>
<td>CT and MRI head and neck Central nervous system/meninges</td>
<td>Meningioma</td>
<td>IVLBCL</td>
<td>CD45, CD20, MUM1, Bcl6 (+/−)</td>
<td>CD10, EBV, EMA, cytokeratin</td>
<td>Near 100%</td>
<td>Skin biopsy positive for IVLBCL; palliative measures taken; died &lt;30 d post surgery</td>
</tr>
<tr>
<td>Zhang et al,\textsuperscript{27} 2015</td>
<td>61/F</td>
<td>Fever, fatigue, hematemesis, melena</td>
<td>Anemia</td>
<td>CT abdomen, Pancreas</td>
<td>Gastrointestinal stromal tumor (GIST)</td>
<td>IVLBCL</td>
<td>CD20, MUM1</td>
<td>CD10, CD3</td>
<td>Near 100% Patient declined surgical intervention; died 4 mo post surgery</td>
<td></td>
</tr>
<tr>
<td>Yuan et al,\textsuperscript{28} 2021</td>
<td>54/F</td>
<td>Fever and fatigue</td>
<td>NR</td>
<td>Ultrasound neck</td>
<td>Gastrointestinal stromal tumor (GIST)</td>
<td>CD20, PAX5, p53, Bcl6, MUM1</td>
<td>CD3, CD10, CD20, Bcl2, EBV-ISH</td>
<td>CD3, CD5, AE1/AE3, EMA, S100, factor VIII, CD34, CD31</td>
<td>“High”</td>
<td>Near 100% Negative bone marrow biopsy, PET/CT without further evidence of disease, received R-CHOP; in remission (6 y)</td>
</tr>
<tr>
<td>Linnik et al,\textsuperscript{29} 2018</td>
<td>78/F</td>
<td>Transient ischemic attack symptoms</td>
<td>No abnormalities</td>
<td>Ultrasound neck</td>
<td>Thyroid</td>
<td>IVLBCL</td>
<td>-</td>
<td>CD45, CD20, PAX5, Bcl6, MUM1</td>
<td>NR</td>
<td>Follow-up imaging negative, bone marrow biopsy negative, cerebrospinal fluid sample negative; received CHOP and adjuvant radiation (local); in remission (27 mo)</td>
</tr>
<tr>
<td>Nixon et al,\textsuperscript{30} 2005</td>
<td>64/F</td>
<td>Local irritation and discomfort of scalp</td>
<td>NR</td>
<td>CT head/neck, chest, abdomen, pelvis</td>
<td>Skin (scalp)</td>
<td>CD20</td>
<td>CD3</td>
<td>CD10, CD3, MPO, TdT</td>
<td>NR</td>
<td>Follow-up imaging negative, received CHOP, 33-mo remission, then recurrence; stem cell transplant; in remission (15 mo)</td>
</tr>
<tr>
<td>55/F</td>
<td>Increased size of left shoulder skin lesion</td>
<td>NR</td>
<td></td>
<td></td>
<td>Skin (shoulder), Recurrence on thigh</td>
<td></td>
<td></td>
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**Abbreviations:** CBC, complete blood count; CT, computed tomography; EBER-ISH, Epstein-Barr virus encoding region in situ hybridization; EBV, Epstein-Barr virus; EBV-ISH, Epstein-Barr virus in situ hybridization; EBV-LMP, Epstein-Barr virus latent membrane protein; EMA, epithelial membrane antigen; HHV8, human herpesvirus-8; HLH, hemophagocytic lymphohistiocytosis; HMB-45, human melanoma black 45; IgG, immunoglobulin G; IHC, immunohistochemistry; IMP3, insulin-like growth factor II messenger ribonucleic acid binding protein 3; IVLBCL, intravascular large B-cell lymphoma; MGUS, monoclonal gammopathy of undetermined significance; MPO, myeloperoxidase; MRI, magnetic resonance imaging; MUM1, multiple myeloma 1; NR, not reported; PET, positron emission tomography; R-CHOP/CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/cyclophosphamide, doxorubicin, vincristine, and prednisone; TdT, terminal deoxynucleotidyl transferase.
There are 2 main histologic variants of IVLBC, historically classified by geographic region: classic or “Western” type and hemophagocytic syndrome–associated or “Asian” type. Both variants consist of classically large atypical lymphoid cells that may have open chromatin, 1 or more prominent nucleoli, scant to moderate cytoplasm, frequent mitotic figures, and solely intravascular distribution favoring small to intermediate vessels. Cell size on rare occasion can be variable with both anaplastic and small cell forms. The presence of histiocytes imbibing other inflammatory cells such as erythrocytes or leukocytes and their precursor cells suggests the hemophagocytic syndrome–associated type. A third clinically relevant primary cutaneous variant has also been well described in literature, possessing histologic features of the classic IVLBC type, but is isolated to cutaneous intravascular involvement. This cutaneous clinical variant represents up to 25% of IVLBC cases within Western countries (compared to only 3% in Asian countries), has a predilection for young females, and is associated with a better prognosis and outcomes as compared to systemic involvement.

Immunohistochemical evaluation is also required in diagnosing IVLBC. The neoplastic cells should be positive for 1 or more pan-B-cell markers including CD19, CD20, CD22, CD79a, PAX5, OCT2, and BOB1. Positivity for CD5 (38%) and CD10 (13%) may be observed. Reports of BCL6 positivity are variable with ranges of 22% to 86%. When tumor cells are negative for germinal center markers (ie, CD10 and BCL6), MUM1/IRF4 is usually expressed. Other markers displaying positivity can include BCL2 and rarely CD23. Expression of uncommon markers such as myeloperoxidase and CD30 have also been described. Ki-67 proliferation indices are frequently high, with expression above 50% in most cases.

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CD34 and CD31 mark the endothelial cells and can be useful in confirming the intravascular nature of the tumor cells. T-cell–specific markers such as CD3 should display negativity. Fluorescence in situ hybridization may be used to identify MYC, BCL2, and/or BCL6 aberrations. Most genetic studies have demonstrated nongerminal center B-cell (ie, activated B cell) gene expression profiles in IVLBCL. Case series of genetic sequencing have implicated nuclear factor-κB pathway, immune system evasion, and other oncogenes of interest in IVLBCL to include MYD88 L265P, CD79B Y196, other CD79B mutations, PD-L1/PD-L2, SETD1B, and HLA-B. These findings have been identified across both systemic IVLBCL and primary cutaneous IVLBCL variant. The genetic profile of IVLBCL thus draws comparison to entities with a similar panel of aberrations such as primary CNS lymphoma and primary cutaneous diffuse large B-cell lymphoma (DLBCL), leg type.

**PITFALLS IN DIAGNOSIS**

Numerous cases have been reported in the medical literature where IVLBCL has been masked by background...
inflammation and where it has been identified in addition to primary epithelial or stromal tumors, in keeping with its reputation for mimicry. Case reports have described IVLBCL diagnosed within meningiomas, gastrointestinal stromal tumors, benign thyroid nodules, hemangiomas, silicone breast implant inflammatory reactions, renal cell carcinomas, and other primary neoplastic or reactive conditions (Table). In most of these collision cases, IVLBCL is discovered incidentally. Occasionally, reverse mimicry can occur. There have been cases of intravascular reactive lymphoid proliferations mimicking IVLBCL in the background of primary inflammatory lesions. In one case where an endometrial curettage was diagnosed as endometritis, there were reactive intravascular “lymphoid blasts” mimicking IVLBCL that were CD3+ T cells rather than B cells, with no further phenotypic or T-cell receptor aberrations. The 3 primary pitfalls of IVLBCL thus include masking of IVLBCL, mimicry by IVLBCL, and mimicry of IVLBCL.

Figure 3. Atypical lymphoid cells are CD20+ (A; arrowheads). CD10 displays negativity in the atypical lymphoid cells with nonspecific staining of background cervical stroma (B). The atypical lymphoid cells are also MUM1+ (C) and highlighted by a Ki-67 proliferation index of greater than 90% (D), sharply delineated from background cervical stroma (original magnifications ×40 [A and D] and ×100 [B and C].

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primary lesions; however, it must also be considered that the risk of missing an incidental neoplasm highly depends on level of subtlety. IVLBCL falls into a category of variable subtlety, of which various factors can affect the degree on histologic examination. For example, it can be difficult to identify an incidental IVLBCL in context of primary cervical evaluation for squamous dysplasia with a background of dense lymphoid infiltrate (Figure 1, A and B; Figure 2, A and B). An incidental IVLBCL within a meningioma, gastrointestinal stromal tumor, or hemangioma, in which cases may lack a background dense inflammatory infiltrate, are less likely missed. Low-power diagnosis becomes key for pattern recognition and draws a parallel to identifying lymphovascular space invasion by carcinoma. The packeted but sometimes discohesive nature of intravascular malignant lymphoid populations conforming to vessel lumens seen in IVLBCL can be recognized in these masked contexts. When the characteristic pattern is recognized, immunohistochemistry becomes paramount (Figure 3, A through D). In certain cases, the IVLBCL may be represented only in a focal region of histologic sections, limiting performance of immunohistochemistry and ancillary genetic testing. Additional difficulty may arise when the clinical history is that of an asymptomatic patient or of a patient who otherwise presents nonclassically.

Mimicry by IVLBCL can take place when a predominant organ system is involved with the lymphoma, simulating clinical scenarios such as acute inflammatory, infectious, neurologic, or ischemic processes (eg, cutaneous rash, cholecystitis, bowel obstruction, cerebrovascular accident). IVLBCL is known for its propensity to elicit signs, symptoms, and laboratory findings congruent with site of involvement. It is well within the realm of possibility to receive a routine surgical specimen and identify IVLBCL on histologic sections. Appropriate specimen sampling at gross examination thus remains imperative, especially when gross and histologic findings do not match the clinical scenario.

Mimicry of IVLBCL can occur in 2 predominant scenarios: reactive conditions where a nonneoplastic yet atypical intravascular large B-cell or T-cell proliferation is a component of an inflammatory infiltrate, or when there is vascular spread by a lymphoma derived from a primary tissue site such as lymph node (eg, DLBCL). For the first scenario, instances of lymphoma-like lesions of various organ sites are well described in medical literature, but are not typically characterized by isolated intravascular involvement. The cases that do involve isolated intravascular atypical or reactive lymphoid populations are of predominantly T-cell origin, with cutaneous cases predominating.\textsuperscript{36–39} This remains a potential pitfall as clinical investigation for suspected cases of IVLBCL often includes skin biopsies, in both the context of positive skin findings on physical examination or lack thereof. Immunohistochemistry, in addition to ancillary studies, remains imperative for classifying the intravascular population. The second scenario, however, is likely more common in disrupting a straightforward diagnosis. Vascular spread by a lymphoma is not uncommon given the nature of the neoplasm (Figure 4, A and B; Figure 5, A through C). In this scenario, lack of other readily identifiable lesions on imaging studies, detailed clinical investigation, and extensive sampling of target tissue are highly contributory in diagnosing IVLBCL. Clinical features such as extensive lymphadenopathy remain an additional context clue against IVLBCL. Lymph node involvement by IVLBCL is possible but is extremely rare. It is up to the pathologist to identify when a sample is limited and only intravascular malignant lymphoid cells are identified, as limited sampling may not be representative of the target process as a whole and may contribute to a nondefinitive diagnosis.

TREATMENT, CLINICAL OUTCOMES, AND PROGNOSIS

First-line treatment for IVBCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone with the addition of rituximab (R-CHOP).\textsuperscript{5,16} CNS recurrence is a concern post treatment with one case series showing CNS recurrence rates as high as 18% in R-CHOP–treated groups even in patients without CNS involvement at initial diagnosis.\textsuperscript{40} Recent studies suggest the addition of intrathecal methotrexate as both CNS treatment and prophylaxis; however, impact on survival outcomes remains in need of further investigation.\textsuperscript{31–33} Autologous stem cell transplants have also been trialed with variable reports of success.\textsuperscript{44,45}
Despite treatment, disease progression is aggressive and prognosis is generally poor.\(^7\) Median overall 5-year-survival (unadjusted) within the United States has been estimated at 46.1%,\(^7\) with studies outside the United States reporting variable findings.\(^{42,43,46}\) Hemophagocytic syndrome–associated IVLBCL generally portends a poorer diagnosis, just as it generally does when seen as secondary to other primary neoplasms.\(^{43}\) Cutaneous involvement by systemic IVLBCL and the primary cutaneous variant of IVLBCL generally portend a better prognosis with case series showing a 3-year overall survival of 56% ± 16% (primary cutaneous variant).\(^{16,17}\) These findings are likely due to earlier detection of cutaneous lesion manifestation and shorter time to treatment, with younger patient age and higher functional status of those with the primary cutaneous variant also playing a role. The available data do not currently suggest a significant correlation of the genetic landscape with disease-specific survival and outcomes of primary cutaneous or systemic IVLBCL. Emerging genetic findings may serve to guide future targeted therapy and clinical trials. Swift detection, diagnosis, and treatment remain key elements for survival.

**CONCLUSIONS**

IVLBCL is a well-described but rare entity in the literature, past and present. IVLBCL can be masked, mimicked, or be mimicked, and can be difficult to definitively diagnose, especially in a small biopsy sample. Incomplete workup, imaging, or limited sampling can leave both pathologists and clinicians with a nondefinitive answer, where IVLBCL can be favored, but other entities cannot be entirely excluded. Corroboration by clinical and radiologic findings, as well as longitudinal patient follow-up, remains crucial to avoid diagnosing IVLBCL in a lesion that is actually a diffuse large B-cell lymphoma or even a reactive inflammatory condition. IVLBCL can be present in any vascularized tissue, so caution must be exercised when evaluating the morphology of any inflammatory or lymphoid infiltrate. Pattern recognition and scrutiny of packeted or discohesive intravascular atypical lymphoid cells is paramount for accurate diagnosis. These statements are especially true when the clinical history is not characteristic or if the primary evaluation is of a nonlymphoid neoplasm.

**References**


**Figure 5.** Sheets of malignant lymphoid cells, of both intravascular and nonvascular distribution, are present on follow-up excision of the intra-abdominal lymph node conglomerate (A). The malignant lymphoid populations show diffuse CD20 positivity (B). CD34 staining of vascular endothelium (C) highlights the intravascular nature of malignant lymphoid cells (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×100 [B and C]).


