Intravascular Lymphoma: The Oncologist’s “Great Imitator”

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LEARNING OBJECTIVES
After completing this course, the reader will be able to:
1. Describe the clinicopathologic features of IVL that distinguish it from the other large-cell lymphomas.
2. Discuss the diagnostic tests helpful in evaluating a case of suspected IVL.
3. Explain the rationale for treatment approaches in patients with IVL, including the role of hematopoietic stem cell transplantation.

ABSTRACT
Intravascular lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma with a distinctive presentation. Anatomically the disease is characterized by the proliferation of clonal lymphocytes within small vessels with relative sparing of the surrounding tissue. The clinical symptoms of the disease are dependent on the specific organ involvement, which most often includes the central nervous system and skin. Because of the various modes of presentation and the rarity of IVL, the diagnosis is often made postmortem. The diagnosis is almost exclusively made by surgical biopsy of a suspected site of involvement. Advances in imaging and immunohistochemistry have led to increasing antemortem diagnosis of this lymphoma. Although some patients with this disease may be curable with aggressive therapy, further research into novel treatment strategies is needed to improve outcome. Some potential insights into future therapies may be drawn from the small amount of basic science literature relevant to this entity. This review provides a concise, up-to-date summary of IVL.

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INTRODUCTION
Intravascular lymphoma (IVL) is defined as the intravascular proliferation of clonal lymphocytes with little to no involvement of the organ parenchyma and is a unique subset of diffuse large B-cell lymphoma (DLBCL). The surprising degree of sparing of the surrounding tissue and the absence of lymphoma cells in the lymph nodes and reticuloendothelial system is a hallmark of the disease. The B-cell immunophenotype is most common, although cases with T-cell receptor rearrangements have been reported. It is an uncommon disease that has been the focus of limited research. This disorder has been described using many terms over the years (Table 1), but in accordance with the World Health Organization (WHO) classification of the hematologic malignancies, the term intravascular lymphoma is used in this review [1]. The disease was first reported in the literature in 1959 by Pfleger and Tappeiner in Germany and was described as “angioendotheliomatosis proliferans...”
Table 1. Historical names for intravascular lymphoma

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<th>Name</th>
<th>Kiel Classification</th>
<th>Lukes-Collins Classification</th>
<th>REAL Classification</th>
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<td>Angioendotheliomatosis proliferans systemica</td>
<td>Angio-endotheliotropic</td>
<td>Angiotropic large cell lymphoma</td>
<td>Diffuse large B-cell lymphoma</td>
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<td>Malignant angioendotheliomatosis</td>
<td>(intravascular) lymphoma</td>
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<td>Kiel Classification: Angio-endotheliotropic (intravascular) lymphoma</td>
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Abbreviation: REAL, Revised European-American Lymphoma.

systemisata” [2]. The remarkable restriction of malignant cells to the intraluminal space and the absence of malignant cells in the adjacent tissue led the authors to believe that the neoplastic cells derived from the endothelium. It was not until the mid 1980s that immunophenotyping demonstrated that the neoplastic cell of origin is the lymphocyte and not the endothelial cell [3]. Despite the 45 years that have passed since the first description of this syndrome, our understanding of the pathophysiology and appropriate therapy for this disease has made minimal advances. Because this disease is rare, nor randomized trials have been possible, and only one retrospective series has reported a substantial number of patients [4]. Most of the available information on this rare lymphoma has been collected from individual case reports over several decades. Similarly, treatment recommendations are extrapolated from results of trials in more common subtypes of lymphoma. In this article, the latest information on the epidemiology, genetics, biologic characteristics, clinical presentation, and therapy of IVL is presented.

Epidemiology and Risk Factors

IVL is a rare disease with an estimated incidence of less than one person per million based on its rate of appearance in the literature. It has been described in patients ranging from 34–90 years of age, with a median age of 70 years. It occurs equally in women and men [4]. There is some evidence to suggest that disease occurs more often in Asian populations, particularly a variant of IVL associated with hemophagocytosis, although this may be a reflection of a higher disease awareness in Japan [5]. There are no known risk factors for IVL; however, there are several instances of IVL arising in the setting of a diagnosis of DLBCL [6] and even follicular lymphoma [7]. It is unclear whether this represents embolization of neoplastic lymphocytes into the vascular lumina or clonal evolution of nodal lymphoma with loss of expression of chemokine receptors critical for migration across vascular walls [8]. There are also a few cases of IVL arising in the setting of treated solid tumors or arising concurrently [4], although, as with most rare diseases, reporting bias obscures the true incidence of this association.

Biology

The predilection of the tumor cells for capillary endothelium is likely related to the expression of molecules on the surface of lymphocytes that allows for preferential binding within the vascular channel. Two alternative theories have been suggested. Aberrant expression of CD11a and CD49d (VLA-4) on IVL cells has been proposed as a possible mechanism because these adhesion molecules would enable tumor cells to home to CD54 (CD11a ligand) and CD106 (CD49d ligand), which are expressed on endothelial cell surfaces [9]. Alternatively, a more recent study of six cases demonstrated that IVL cells were consistently lacking in CD29 (β2 integrin) and CD54 (ICAM-1), both of which are regarded as essential for lymphocyte homing and transvascular migration [8]. Other explanations have included a deficiency in the Hermes-3-defined homing receptor antigen and lack of the receptor for peanut agglutinin [10, 11]. Comprehensive studies of the expression of integrins and their ligands in a larger group of cases is needed to define the relative importance of these observations in the pathogenesis of IVL. Recent studies in follicular lymphoma have identified polymorphisms in Fcγ receptors as critical elements in the response of these lymphomas to therapy with rituximab [12]. Although this possibility has not been examined in IVL, it is conceivable that systemic expression of integrin or chemokine receptor polymorphisms among different populations might cause a lymphoma to present preferentially in the intravascular space.

Pathologic Characteristics

Histology

The histologic appearance of IVL involvement of brain, renal parenchyma, and thyroid are shown in Figures 1–3, demonstrating the classic appearance of large malignant lymphocytes filling small vascular lumina.

Immunophenotype

The classic immunophenotype of the malignant lymphocyte in IVL is B-cell-associated antigen-positive CD19+CD20+CD22+CD79a+. Several cases have been reported to express CD5 [9, 13]. In a summary of cell lineages from 1985–1999, the B-cell phenotype was seen in 78 of 86 (91%) IVL cases, and the T-cell phenotype was identified in 8 of 86 (9%) cases [14]. Most recently, the first two cases of an IVL of the natural killer cell phenotype were reported [15]. Some cases of IVL may have apparent
staining for factor VIII, which is classically associated with endothelial cells; however, this may represent absorption of this protein as opposed to expression [16].

**Chromosomal Abnormalities**
One study of genetic alterations in IVL describes chromosomal abnormalities in 1p (4 of 6 cases) and trisomy 18 (4 of 6 cases) [17].

**Clinical Features**
IVL is extremely heterogeneous in its clinical presentation and has been described in the small vessels of nearly every organ. Although IVL is a clonal proliferation of lymphocytes, it is uncommon to find significant adenopathy, hepatosplenomegaly, or circulating cells in the peripheral blood. It is this absence of IVL in the traditional sites of presentation of lymphoma that makes accurate and timely diagnosis so difficult. In Table 2, we compare clinical presentation, laboratory findings, organ site involvement, and outcomes in seven of the largest series of patients with IVL. The majority of cases can be grouped into a few discrete presentations: (a) central nervous system (CNS) involvement, (b) cutaneous involvement, (c) fever of unknown origin, and (d) hemophagocytic syndrome. We postulate that the “classic” presentations of IVL in the CNS and skin are more likely reflections of the exquisite intolerance of the CNS to any vascular perturbations and the skin’s easy accessibility, rather than a predilection for any organ beyond that for the vasculature itself. Proof of this supposition, however, can only come from extensive evaluation of integrin expression in IVL cases from disparate organs. Beyond these major presentations, there are single case reports of IVL presenting primarily in almost every organ system; as interstitial lung disease [18], adrenal failure [19], pulmonary hypertension [20], nephrotic syndrome [21], myocardial infarction [22], and symmetric polyarthritis [23].

**CNS Involvement**
In the largest series of IVL, 13 of 38 patients presented with neurologic symptoms as either their exclusive symptoms or prominent associated symptoms, and the literature is replete with individual case reports of IVL affecting the CNS [4, 24–26]. Patients can present with focal

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**Figure 1.** Intravascular large B-cell lymphoma. (A): The large lymphoma cells fill the vessel in this brain biopsy. (B): The tumor cells in the vessel are highlighted by immunohistochemical staining for CD20. (C): The vessel wall in the brain is highlighted by immunohistochemical staining for factor VIII.

**Figure 2.** Intravascular large B-cell lymphoma. (A): The large lymphoma cells fill the capillaries in this renal glomerulus. (B): High-power view showing extensive capillary and surrounding vascular involvement of the glomerulus. (C): The tumor cells in the vessels are highlighted by immunohistochemical staining for CD20.

**Figure 3.** Intravascular large B-cell lymphoma. (A): The large lymphoma cells fill the vessels in this thyroid tissue. (B): The tumor cells in the vessels are highlighted by immunohistochemical staining for CD20.
sensory or motor deficits, generalized weakness, altered sensorium, rapidly progressive dementia, seizures, hemiparesis, dysarthria, ataxia, vertigo, and transient visual loss [24, 27–29]. Initial diagnoses of stroke, encephalomyelitis, Guillain-Barré syndrome, vasculitis, and multiple sclerosis are often made, and the diagnosis of IVL is often not established until autopsy [25–27, 30]. Most often there are abnormalities on brain magnetic resonance imaging (MRI), particularly multiple, metachronous cortical or subcortical lesions that are hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, suggestive of small vessel ischemia or demyelination [28, 31]. There are no pathognomonic neuroradiological findings for IVL, although the most common alternative diagnosis entertained in cases of IVL with these MRI findings is CNS vasculitis [26, 27, 32]. In the largest series of IVL patients with CNS disease, six of seven patients had a lymphocytosis in the cerebrospinal fluid (CSF), although only one of seven patients had CSF cytopathology that was positive for malignant cells. Two of the seven patients had malignant cells identified by polymerase chain reaction (PCR) for IgH gene rearrangement [31].

Cutaneous Involvement
IVL involvement of the skin was seen as a predominant feature in 15 of 38 patients in the largest series, with 10 of 38 patients presenting with skin lesions alone [4]. Of these 15 patients, four had a solitary skin lesion and 11 had multiple...
lesions. Again, the clinical features of cutaneous IVL are remarkably protean—lesions can appear as maculopapular eruptions, nodules, plaques, tumors, hyperpigmented patches, palpable purpura, ulcers, and infiltrative “peau d’orange” and have been misdiagnosed as cellulitis, gangrene, vasculitis, squamous cell carcinoma, and Kaposi’s sarcoma [4, 33, 34]. Some authors contend that the skin lesions of IVL tend to favor the proximal extremities, lower abdomen, and submammary areas [4]. In almost all descriptions of lesions being biopsied, the results have shown IVL on the first biopsy attempt.

**Fever of Unknown Origin**

Fever is a prominent sign in IVL and is seen in approximately 45% of cases [4]. An exhaustive search for an infectious etiology often contributes to the delay in diagnosis. There are at least three examples of IVL being diagnosed by a random skin biopsy in the setting of fever of unknown origin [35, 36].

**Hemophagocytic Syndrome**

There are extensive reports within the Japanese literature to suggest the existence of an Asian variant of IVL characterized by fever, anemia, thrombocytopenia, and hepatosplenomegaly [5, 37, 38]. In contrast to typical IVL, there is involvement of the reticuloendothelial system and the bone marrow. Marrow involvement is characterized by malignant lymphocytes within vessel lumina and hemophagocytosis [5, 14]. These cases of IVL with hemophagocytosis are reported almost exclusively in Asian patients, suggesting a possible genetic or environmental influence in the development of IVL. There is an association of infection with *Fasciola* and *Anisakis* and the development of Asian variant IVL, although there is no clear causative link [39].

**Laboratory Features**

Anemia, elevated lactate dehydrogenase, and elevated erythrocyte sedimentation rate are the most common laboratory abnormalities seen in IVL. Thrombocytopenia and leukopenia are seen less often [4]. The majority of studies have shown IVL to be absent in peripheral blood by histologic examination of the peripheral smear, although one group has described a series in which five of five patients diagnosed with IVL had malignant lymphocytes in the peripheral blood smear at varying concentrations and four of five had IVL in the bone marrow biopsy [14].

**Therapy**

There are no randomized, controlled trials comparing treatments in IVL. Our recommendations are based on the collective literature, observations made at our institution, and extrapolation from the treatment of nodal DLBCL. IVL is in most cases disseminated at the time of diagnosis and warrants treatment with systemic therapy. We advocate an anthracycline-based chemotherapy regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with the addition of the monoclonal antibody rituximab (R-CHOP) in cases with a B-cell immunophenotype. Given the poor long-term prognosis of patients with noncutaneous IVL, we suggest consideration of autologous hematopoietic stem cell transplantation in first complete remission (CR) in young patients with good performance status.

There are examples in the literature of long-term remissions with the use of combination chemotherapy. The largest series includes 22 individuals gathered by the International Extranodal Lymphoma Study Group [40]. In this group, 19 received an anthracycline-based regimen with a response rate of 59% (10 CRs, 3 partial responses [PRs]). Seven of the responders later relapsed. The three patients treated with cyclophosphamide, vincristine, and prednisone (CVP) relapsed, although one had a late spontaneous remission. The group from Johns Hopkins described that all four of the 10 patients in their study who received combination chemotherapy (3 CHOP and 1 ProMACE-CytaBOM [cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone]) achieved CRs and were alive at the time of follow-up (6–48 months) [41]. The response rates and overall median survival rates seen in IVL are consistently lower than those described in DLBCL. We do not know if this indicates a more aggressive underlying biology of IVL or if it is because the disease is so frequently diagnosed at an advanced stage, sometimes within weeks or days of the patient’s death. More intensive therapies such as m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) and ProMACE-CytaBOM [27], as well as dose-dense regimens such as CHOP-14 [24], have also been used with varying degrees of success. The recommendation for the addition of the monoclonal anti-CD20 antibody rituximab is based mostly on the survival advantage seen in elderly patients with nodal DLBCL [42]. There are also nine case reports in the literature that describe the use of rituximab in combination with chemotherapy with varying degrees of success. Interestingly, two cases report sustained remissions after mono-therapy with rituximab [43, 44]. There are now seven case reports of long-term survival after autologous hematopoietic stem cell transplantation: three patients in first CR (one with CNS involvement) [40, 45]; four in second CR [46–49]; and two patients in whom bone marrow transplant in second CR was unsuccessful [40].
Two situations warrant further consideration: neurologic IVL, in which there is evidence of malignant lymphocytes in the CSF, and IVL presenting as a solitary cutaneous lesion. Patients in whom IVL can be found in the CSF, either on cytopathology or PCR for IgH gene rearrangement, are unlikely to respond to R-CHOP alone because of poor penetration of the blood–brain barrier by these agents, and these patients should be treated with regimens similar to those used for primary or secondary CNS lymphoma. Both high-dose methotrexate (MTX) of 8–12 g/m² [31] as well as the methotrexate, BCNU, etoposide, and methylprednisolone regimen [50] have been described as providing benefit. High-dose corticosteroids alone (up to 1 g daily of methylprednisolone) may provide transient clinical improvement but have never been reported to provide sustained therapeutic benefit. Plasmapheresis has also been described in the literature as providing temporary benefit, but does not appear to have sustained efficacy [51, 52]. Although data are extremely limited, patients with a single cutaneous lesion appear to have a better prognosis than those with disseminated disease and have been treated successfully with local radiation therapy [4].

**Ongoing Research**

There are ongoing studies into the molecular, genetic, and cell surface features of IVL. The disease lends itself to studying the basic biology of lymphocyte migration and trafficking. As therapeutic antibodies against surface adhesion molecules are developed, they may prove to be good candidates for targeted therapy for IVL.

**Conclusions**

IVL is a rare subtype of DLBCL in which the tumor cells pack the lumina of small vessels without infiltrating into parenchymal tissue. Given its rarity and the multiplicity of presentations, it is an extremely difficult diagnosis to make antemortem and the practicing oncologist may encounter a case of IVL only once or twice in a career. Nonetheless, several key points about IVL emerge that can be of assistance, particularly to an oncologist who is consulted regarding a potential case of IVL. First, the majority of cases of IVL present as either CNS abnormalities, particularly with diffuse encephalopathy and/or subacute, progressive multifocal neurological deficits and MRI images that resemble vasculitis; cutaneous involvement; or fever of unknown origin. Second, the timely acquisition of a tissue biopsy is critical. We maintain a low threshold to biopsy abnormal brain lesions and to perform a skin biopsy of suspicious lesions. A random skin biopsy can be supported in the setting of fever of unknown origin for several reasons: IVL has been diagnosed in clinically uninvolved skin, other diseases in the differential diagnosis can also be evaluated, and it is generally a safe procedure. Third, most cases of IVL are associated with a poor prognosis and should be treated systemically with an anthracycline-based regimen for aggressive non-Hodgkin’s lymphoma such as R-CHOP. Intrathecal or high-dose systemic MTX should be incorporated if there is evidence of the disease within the CSF.

**Disclosure of Potential Conflicts of Interest**

The authors indicate no potential conflicts of interest.

**References**
