

Intravascular B-cell Lymphoma Following Nodal Diffuse Large B-cell Lymphoma

Deborah A. Katz, MD¹
Ira J. Miller, MD, PhD²
Stephanie A. Gregory, MD³

¹Department of Internal Medicine; ²Department of Pathology;
³Section of Hematology, Rush University Medical Center/Rush
University, Chicago, Illinois

Intravascular lymphoma was first described in the literature as *angioendotheliomatosis proliferans systemisata* approximately 50 years ago.¹ At that time, it referred to malignant cells that were almost completely restricted to intraluminal spaces and were thought to arise from endothelial cells. In the mid-1980s, some studies suggested an association between malignant angioendotheliomatosis and lymphoma and raised the possibility that these conditions might be a single disease with hematopoietic origins.^{2,3} Advances in immunophenotyping ultimately revealed that these neoplastic cells were actually lymphocytes.⁴

Intravascular lymphomas are a rare subtype of large cell lymphoma characterized by the proliferation of malignant lymphocytes within the lumina of small blood vessels with little to no extravascular involvement.¹ The malignant cells usually have a B-cell phenotype, although some cases of intravascular T-cell lymphoma have been reported. Since intravascular lymphoma is rare—with most cases discovered postmortem—most of the information about this condition comes from case reports and small case series.

Case Report

A 68-year-old woman presented with pancytopenia, abdominal pain, generalized fatigue, and fever in September 2006. Medical history included diagnoses of type 2 diabetes mellitus and 2 cerebral vascular accidents with no residual deficits. The patient reported a 2-month history of symptomatic anemia, for which she had undergone evaluation at another hospital. Prior to presenting to our medical center, the patient had undergone multiple blood transfusions for severe anemia and had been diagnosed with idiopathic pericarditis, for which she underwent a pericardial window. The patient reported being told that

the etiologies of her anemia and pericarditis were unclear despite extensive testing.

On admission to our facility, the patient underwent further work-up, including a bone marrow biopsy that demonstrated extensive infiltration of the marrow with CD20-positive large B cells. Computed tomography (CT) scans of the neck, chest, abdomen, and pelvis revealed mediastinal lymphadenopathy, small bilateral pleural effusions, splenomegaly, and multiple splenic infarcts. Positron emission tomography revealed metabolically active lesions in the spleen. The patient was diagnosed with stage IVB diffuse large B-cell lymphoma, and she began treatment with rituximab (Rituxan, Genentech), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

Following the initial cycle of chemotherapy, the patient was noted to have altered mental status and severe headaches. Magnetic resonance imaging (MRI) of the brain revealed a meningeal pattern of enhancement consistent with meningeal lymphomatosis (Figure 1A). The patient underwent multiple lumbar punctures; however, analysis of the cerebral spinal fluid was consistently nondiagnostic. The patient underwent a right frontal craniotomy with random dural and brain biopsies because the suspected sites of disease were not safely accessible for biopsy. These pathology results were negative for malignancy. Given the strong suspicion for central nervous system (CNS) disease, the patient was treated with intrathecal methotrexate.

A post-treatment brain MRI revealed almost complete absence of meningeal enhancement, which suggested a likely CNS disease response to intrathecal chemotherapy (Figure 1B). The patient was treated with 6 cycles of R-CHOP; the treatment course was complicated by febrile neutropenia, the development of *Clostridium difficile* colitis with toxic megacolon necessitating colectomy, and multiple lower extremity deep venous thromboses requiring inferior vena cava filter placement and anticoagulation. Upon restaging in January 2007, the patient was believed to be in a complete clinical remission.

Address correspondence to:

Deborah A. Katz, MD, Resident, Department of Internal Medicine, Rush University Medical Center, 1653 West Congress Parkway, Chicago, IL 60612; Phone: 312-942-5382; Fax: 312-563-4101; E-mail: deborah_katz@rush.edu.

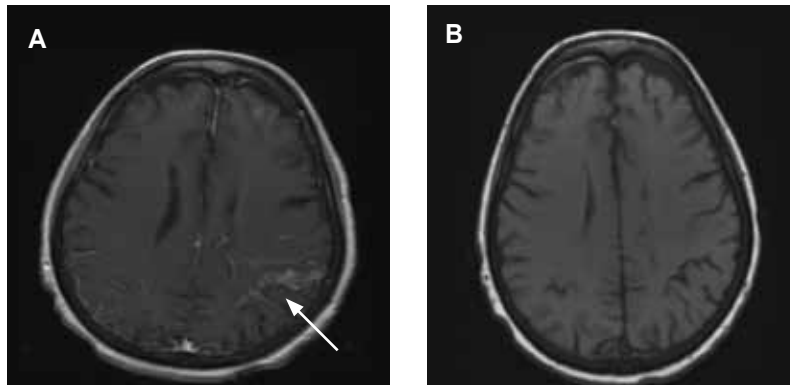


Figure 1. (A) Magnetic resonance imaging (MRI) scan of the brain demonstrates right central sulcus meningeal enhancement consistent with meningeal lymphomatosis. (B) Post-chemotherapy MRI brain scan demonstrates resolution of the area of meningeal enhancement.

The patient did well until April 2009, when she presented to our medical center with symptomatic anemia, low-grade fevers, chills, bilateral thigh pain, shoulder pain, and lower back pain of 3–4 weeks duration. The patient reported no weight loss, bone pain, bleeding, headaches, visual changes, shortness of breath, dysphagia, diarrhea, or dysuria.

Vital signs on admission revealed a temperature of 99.4°F, pulse rate of 98 beats per minute, blood pressure of 112/52 mm Hg, respiratory rate of 16 breaths per minute, and oxygen saturation of 97% on room air. Physical examination was notable for an area of induration and erythema on the medial aspect of the right thigh, which was warm and tender to palpation. The right lower extremity was noted to be significantly larger than the left. The patient reported a size discrepancy between her lower extremities that had existed since 2007, though not to the degree that was noted on examination.

Laboratory studies revealed the following values: white blood cell count of 7,540/mcL, hemoglobin of 9.6 g/dL, hematocrit of 29.3%, and platelet count of 220,000/mcL. A comprehensive metabolic profile revealed the following levels: sodium of 138 mmol/L, potassium of 4.1 mmol/L, chloride of 114 mmol/L, bicarbonate of 18 mmol/L, blood urea nitrogen of 15 mg/dL, creatinine of 1.0 mg/dL, glucose of 126 mg/dL, calcium of 8.5 mg/dL, total protein of 7.0 g/dL, albumin of 3.1 g/dL, total bilirubin of 0.6 mg/dL, alkaline phosphatase of 112 U/L, aspartate aminotransferase of 20 U/L, and alanine aminotransferase of 8 U/L. Additional laboratory studies revealed lactate dehydrogenase (LDH) of 451 U/L (normal level: 84–240 U/L) and an erythrocyte sedimentation rate (ESR) of 72 mm/hr (normal level: 0–27 mm/hr).

A Doppler ultrasound of the lower extremities revealed wall thickening of the right common femoral and proximal femoral artery consistent with chronic fibrosis. There was no evidence of acute deep vein thrombosis. CT scans of the chest, abdomen, and pelvis did not reveal adenopathy, hepatosplenomegaly, or masses.

A bone marrow biopsy failed to reveal any evidence of recurrent lymphoma. A comprehensive infectious disease evaluation failed to elucidate the etiology of the patient's fevers and bilateral thigh pain.

To evaluate the possibility of polymyalgia rheumatica, additional imaging studies were obtained. An MRI of the right lower extremity revealed extensive subcutaneous and fascial edema. A CT scan of the right lower extremity revealed soft tissue inflammatory stranding with mild extension to deep muscular compartments and a small amount of central fluid.

A biopsy of subcutis and fascia of the right thigh revealed small foci of fat necrosis accompanied by a mild lymphoplasmacytic perivascular infiltrate (Figure 2A). Rare vessels demonstrated clustered, large cells within the lumen (Figure 2B). Occasional small vessels revealed fibrin thrombi with admixed cells and apoptotic debris (Figure 2C). Immunostains for Pax-5 and CD20 demonstrated clustered, intraluminal, large B cells (Figure 2D). Immunohistochemistry was negative for Epstein-Barr virus. Based on the histopathologic findings, the patient was diagnosed with intravascular large B-cell lymphoma. The patient is currently receiving treatment with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH).

Discussion

The incidence of intravascular lymphoma is estimated to be less than 1 person per million.¹ The mean age at diagnosis is 70 years, although cases have been reported in patients ranging from 39–90 years. There is no gender predilection.¹ Patients with intravascular lymphoma have varied clinical presentations, with the majority of cases involving the CNS and skin in Western countries,⁵ and with hemophagocytic syndrome frequent in Asian countries.⁶ In cases with CNS involvement, patients can present with focal neurologic deficits, generalized weakness, seizures, and altered mental status, making the initial diagnosis very difficult. Cutaneous involvement is a

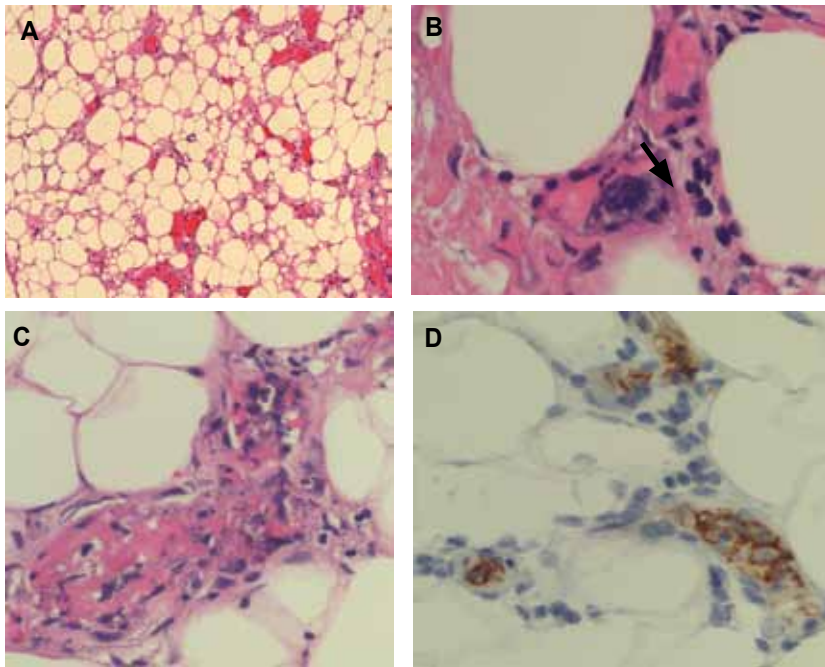


Figure 2. A right fascial thigh biopsy demonstrates the characteristic morphology of intravascular B-cell lymphoma. (A) A low-power field reveals vascular congestion and fat necrosis. (B) A cluster of atypical cells adheres to the inside of the lumen of a capillary (arrow). (C) Atypical cells associated with occlusive fibrin thrombi. (D) CD20 immunostaining illustrates medium to large lymphocytes within the lumen of small vessels.

common presenting feature, occurring almost exclusively in women.⁷ Patients often present with variable types of skin lesions that are often misdiagnosed. B symptoms, including fevers, night sweats, and weight loss, are often present. It is rare to find involvement or evidence of lymphoma in the spleen, lymph nodes, cerebrospinal fluid, bone marrow, or peripheral blood. Although there are no diagnostic laboratory studies, the most common abnormalities in patients with intravascular lymphoma include anemia, elevated LDH, and elevated ESR.¹ A definitive diagnosis is based upon characteristic pathology that demonstrates malignant lymphocytes filling the lumen of small vessels. Immunostains are used to identify the specific immunophenotype of the malignant lymphocyte. Because the diagnosis of intravascular lymphoma is often difficult to make, one study evaluated the potential benefit of “random” skin biopsies of healthy looking skin in patients who were clinically suspected of having intravascular lymphoma.⁸ The findings suggested that random skin biopsies should be considered, even in patients with no evidence of cutaneous disease, in order to aid in the early diagnosis and treatment of intravascular lymphoma.

All patients with intravascular lymphoma should be considered to have disseminated disease. Anthracycline-containing chemotherapy regimens have been reported to improve clinical outcome in patients with intravascular lymphoma.⁹ Most of the literature advocates the use of combination anthracycline-based chemotherapy with rituximab as palliative therapy. This regimen is largely based on the success of this program for the treatment of nodal diffuse large B-cell lymphoma.¹⁰ One retrospective

analysis evaluating the safety and efficacy of rituximab-containing chemotherapy regimens for treatment of intravascular lymphoma suggests an overall improved clinical outcome.¹¹ Some case reports support the use of high-dose chemotherapy followed by autologous stem cell transplantation in younger patients with good performance status. Monitoring response to therapy in patients with intravascular lymphoma is difficult because most patients lack measurable disease. Further research is needed to assess whether there are useful laboratory studies that can be used to measure disease response to treatment.

The patient described in this case report was treated with R-EPOCH based on data regarding treatment of both intravascular lymphoma and diffuse large B-cell lymphoma.^{12,13} Research has demonstrated that the R-EPOCH regimen is very effective in the treatment of relapsed/refractory aggressive non-Hodgkin lymphoma (NHL) in patients who had received prior anthracycline-based treatment. Results from these studies reveal a low incidence of toxicity despite prior exposure to anthracyclines.^{12,13}

This case is unique in the fact that this patient developed intravascular lymphoma following treatment and remission of nodal diffuse large B-cell lymphoma. The diagnostic marrow biopsy at presentation showed an interstitial pattern of infiltration accompanied by fibrosis, but there was no evident intravascular component. In a review of the literature, there are a few reported cases of patients who developed intravascular lymphoma following treatment and remission of a prior lymphoma. One case report described a patient who first presented with

nodal diffuse large B-cell lymphoma that relapsed 2 years later as intravascular lymphoma.¹⁴ However, in this case, the initial biopsy specimen at the time of the nodal diffuse large B-cell lymphoma diagnosis revealed intranodal small vessels that contained large lymphoma cells. Further studies revealed that the 2 lymphomas had identical morphologic and immunophenotypic characteristics. The authors of that case report theorized that the intravascular component of the original diffuse large B-cell lymphoma was indicative of the subsequent development of intravascular lymphoma. The original pathology was reviewed in our patient and revealed considerable fibrosis precluding an assessment of the endothelial lined spaces. One article described several patients with intravascular lymphoma associated with a solid tumor, as well as patients with intravascular lymphomas associated with other NHLs.⁵ Most of these cases occurred concurrently or following treatment for another NHL. Another case report describes a patient diagnosed with intravascular lymphoma in the setting of untreated follicular small cleaved cell lymphoma.¹⁵

Conclusion

Intravascular lymphoma is a rare type of NHL. Most information about intravascular lymphoma has been gained from small case reports and case studies. However, the precise mechanisms that characterize this type of lymphoma are largely unknown. Although there appears to be a possible association between intravascular lymphoma and nodal NHL, the pathophysiologic relationships are poorly understood. At a recent international consensus meeting, future strategies to investigate a possible clonal relationship between nodal NHL and intravascular lymphoma were proposed in order to better diagnose and treat this disease.⁷

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Review

Intravascular Lymphoma Occurring in Patients With Other Non-Hodgkin Lymphomas

Maurilio Ponzoni, MD,^{1,2} Elias Campo, MD, PhD,³ and Andrés J.M. Ferreri, MD^{2,4}

¹Pathology Unit, ²Unit of Lymphoid Malignancies, San Raffaele Scientific Institute, Milan, Italy; ³Department of Pathology, Hospital Clinic, University of Barcelona, Barcelona, Spain; ⁴Department of Oncology, Medical Oncology Unit, San Raffaele Scientific Institute, Milan, Italy

Intravascular large B-cell lymphoma (IVL) is an uncommon type of aggressive lymphoma characterized by almost selective, if not exclusive, growth of neoplastic cells within the blood vessel lumina.¹ Usually, this lymphoma does not form neoplastic masses, and, therefore, its recognition is frequently delayed. The diagnosis is often based on a biopsy taken for organ-related signs and symptoms. Although the prognosis of this lymphoma remains poor, a significant improvement has been made with the introduction of anti-CD20 immunotherapy into upfront therapy.^{2,3}

Address correspondence to:

Maurilio Ponzoni, MD, Pathology Unit, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy; Phone: 0039-02-26432544; Fax: 0039-02-26432409; E-mail: ponzoni.maurilio@hsr.it.

Katz and colleagues report a case of a patient with a stage IV, nodal, diffuse large B-cell lymphoma (DLBCL) with IVL features at relapse after treatment with rituximab (Rituxan, Genentech), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).⁴ This case report directs further interest to the topic of the relationship between IVL and other non-Hodgkin lymphomas; only a few reports in the literature address this issue from either pathogenetic or therapeutic standpoints.

Two interesting aspects may play an important role in the interpretation of the pathogenesis of IVL. The first one concerns the potential association between IVL and lymphomas not characterized by large cell morphology. This association is rare, but the literature contains reports of IVL associated with small lymphocytic lymphoma,⁵ follicular small cleaved-cell lymphoma,⁶ and gastric mucosa-associated lymphoid tissue lymphoma-type.⁷ To date, no relationship between these histotypes has been clarified. The second aspect, which is more important and intriguing, concerns the potential association between IVL—which is characterized mostly by B cells with large cell morphology—and “conventional” DLBCL in the same patient. It is currently not possible to know whether the 2 lymphomas are reciprocally independent. When IVL and DLBCL occur in the same patient, they may have at least 3 different temporal relationships. For example, we have observed patients who presented with classic features of IVL and, later in the course of the disease, extravasated and developed “conventional” nodal DLBCL.⁸ These cells, in both components, shared somewhat overlapping immunophenotypic markers. An alternative form of presentation may occur for IVL simultaneously with lymphomatous mass; this condition seems to occur particularly in the central nervous system.⁹

Katz and colleagues present a case of IVL following a conventional DLBCL, a presentation that parallels previous experience.^{10,11} Intriguingly, in both this report and one by Zhao and associates,¹⁰ the DLBCL biopsy specimen showed small vessels within the nodal parenchyma containing large lymphoma cells. IVL following DLBCL may also involve extranodal sites, such as the skin.¹² Although both of these lymphomas share large B-cell features, it remains to be ascertained whether these neoplasms belong to the same clone or in fact represent 2 independent *de novo* lymphoproliferative disorders that occur in a patient at different time points or simultaneously. Theoretically, attention could be paid in these instances to the presence of a minor “intravascular” component at diagnosis—for example, in the vessels surrounding the lymph node effaced by DLBCL. However, we have observed patients with these latter features who did not eventually develop IVL during their course and, therefore, a minor intravascular component within the

context of DLBCL may not per se represent a predictive marker for the development of IVL.

These proteiform modes of occurrence support the need for a comprehensive analysis aimed to find analogies and differences between IVL and DLBCL. A reliable working hypothesis would be to comprehensively analyze all these anecdotal cases with a systematically similar methodologic approach. This approach would involve immunophenotypic characterization of both neoplastic cell populations and, through immunoglobulin receptor analysis followed by direct sequencing of resulting polymerase chain reaction products, would allow the suggestion of a common molecular origin. If classic cytogenetic data are available for the DLBCL sample, it would be easier to assess any single chromosomal abnormality through a fluorescence in situ hybridization test on the IVL sample. Promising technologies include gene expression profiling and array-comparative genomic hybridization, which are starting to become available on paraffin-embedded material. Such approaches are required to further define the molecular signatures carried both by DLBCL and IVL and would shed light on these complex issues. Accordingly, the case of IVL described by Katz and colleagues should not be regarded as an unequivocal “relapse” of nodal DLBCL until a clonal relationship between these 2 disorders is proven.⁴

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