

# Review of Intravascular Lymphoma With a Report of Treatment With Allogenic Peripheral Blood Stem Cell Transplant

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*Intravascular lymphoma (IVL) is a non-Hodgkin lymphoma in which atypical lymphocytes accumulate within small blood vessels. Patients most commonly present with neurologic and cutaneous findings; however, any organ system may be affected, which leads to difficulties in diagnosis.*

*The objectives of this article are to review the current IVL literature and stress the importance of multiple skin biopsies in diagnosis. We also describe, to our knowledge, the first case of IVL treated with allogenic peripheral blood stem cell transplant (PBSCT).*

*Intravascular lymphoma should be considered in the differential diagnosis of unexplained erythematous tender indurated plaques, nodules, and telangiectases. Single biopsy is not sufficient to rule out this entity. Intravascular lymphoma is a recalcitrant malignancy, and we describe a case that quickly recurred after treatment with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R), and necessitated allogenic bone marrow transplantation (BMT).*

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## Case Report

A 44-year-old woman presented to the emergency department with a 1-year history of painful nodules and plaques and a 2-month history of weakness, night sweats, and fatigue.

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The lesions on her legs had presented 1 year prior with sudden onset of bilateral medial thigh pain associated with large, erythematous, and edematous plaques and nodules. Throughout the year, lesions recurred involving the anteromedial thighs and lower legs. The lesions would resolve, leaving telangiectases and mild induration. Concurrently, the patient had asymptomatic, slightly red, urticarial, round plaques on her torso, arms, legs, and dorsal feet. Initial skin biopsy revealed a septal panniculitis with no vasculitis consistent with erythema nodosum. No underlying cause of the presumptive erythema nodosum was identified and the patient was treated with supersaturated potassium iodide with rapid response. In the 2 months prior to admission at our institution, the patient developed night sweats, anorexia, and debilitating fatigue, which were associated with a recurrence of the skin findings despite ongoing therapy.

On examination, the patient had no appreciable lymphadenopathy. Neurologic examination did not reveal any abnormalities. Abdominal examination also did not reveal any abnormalities, including no masses or organomegaly. Cutaneous examination revealed large, poorly demarcated, symmetrical areas of diffuse telangiectases with mild induration of the anteromedial thighs and lower legs (Figure 1). On the right medial thigh, there was a small eroded area with a hemorrhagic crust. There were several faintly red, 2- to 5-cm urticarial plaques on the abdomen and upper chest (Figure 2). On the right lower back, there was a 1-cm, solitary, firm subcutaneous nodule in the center of an irregularly shaped area of telangiectases and erythema.

Laboratory examination revealed microcytic anemia and an elevated lactate dehydrogenase (LDH) level (839 U/L; reference range, 100–200 U/L). Peripheral smear demonstrated nonspecific abnormalities.



**Figure 1.** Symmetrical areas of diffuse telangiectases with mild induration of the antero-medial thighs. The area biopsied is seen on the left leg.

The erythrocyte sedimentation rate was elevated at 71 mm/h (reference range, 0–20 mm/h). The remainder of an exhaustive panel of blood work did not reveal any abnormalities, except for a decreased albumin level at 26 g/L (reference range, 35–50 g/L).

A computed tomographic scan of the chest, abdomen, and pelvis demonstrated mild hepatosplenomegaly but no lymphadenopathy.

Each morphology was sampled; a punch biopsy was taken from an abdominal plaque, and incisional biopsies were taken from a nodule and an area of marked telangiectases. Histopathology revealed microvascular thrombosis with an abundance of bizarre lymphocytes with pleomorphic and hyperchromatic nuclei (Figure 3). Polymerase chain reaction and immunohistochemistry identified the cells as a clonal B-cell population. These features were diagnostic for intravascular lymphoma (IVL).

After appropriate examination, the patient received a diagnosis of stage IV cancer. Treatment was initiated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) chemotherapy. The treatment was well-tolerated and drastic improvements in energy and cutaneous findings were noted as well as normalization of the complete blood cell count. The LDH level returned to within reference range. These findings were deemed a complete response, which endured for 5 months. Relapse was characterized by reappearance of cutaneous findings in association

with a rapidly elevated LDH level. Salvage chemotherapy was administered with gemcitabine, cisplatin, and dexamethasone. After 2 cycles, a dramatic response was noted, with resolution of cutaneous findings and the LDH level returned to within reference range. The patient then received cyclophosphamide and total body irradiation in preparation for an HLA antigen–matched allogeneic peripheral blood stem cell transplant (PBSCT) from her sister. The procedure was complicated by acute graft versus host disease affecting the colon, which was controlled with prednisone and cyclosporine. The allograft was further consolidated with intrathecal prophylactic central nervous system chemotherapy delivered in 10 doses. The patient was off all immunosuppressive therapy 5 months after the allograft. Currently, the patient is doing well with no evidence of relapse 31 months posttransplant.

### Comment

Intravascular lymphoma is an uncommon and frequently fatal malignancy in which clonal B cells aggregate in the lumen of small blood vessels. The clinical presentation is quite varied.<sup>1</sup> Because it is rare, few epidemiologic data are available. There is no geographic variance.<sup>2</sup> Elderly patients are most commonly affected, though patients as young as 34 years of age have been diagnosed. There is no gender predilection.<sup>2</sup>

The World Health Organization classifies IVL as a subtype of diffuse large B-cell lymphoma (DLBCL).<sup>3</sup> Intravascular lymphoma is synonymous with older terminology, including intravascular lymphomatosis, angiotropic large cell lymphoma, malignant angioendotheliomatosis, and proliferative endotheliosis.<sup>4</sup> The latter 2 terms demonstrate the early misconception that the malignant cells causing thrombosis in IVL were of endothelial cell origin. Advances in immunohistochemistry have now correctly identified the pathogenic cells in IVL. Most cases of IVL are of B-cell origin, though rare T-cell and histiocytic variants have been reported.<sup>5</sup> No characteristic genetic alteration has been found in the malignant cells; however, clonal rearrangements of immunoglobulin genes have been demonstrated.<sup>6</sup>

The purported pathogenic mechanism of IVL is thought to be mediated by the malignant cells' propensity to aggregate in the luminal microvasculature, causing thrombosis and other reactive changes. It has been theorized that there are specific antigen/receptor interactions between the lymphoid and endothelial cells that halt migration through the endothelial wall.<sup>7</sup> One study of 9 patients demonstrated malignant cells that expressed CD11a and CD49d (VLA-4 [very-late-antigen 4]).<sup>8</sup> The endothelial cells expressed CD54 and CD106, the ligands of those respective markers. This interaction could contribute to the intravascular localization of malignant B cells. An alternate theory proposes that the inability of the cell to leave the luminal space is caused by a lack of, or aberrant expression of, other necessary surface antigens or adhesion molecules.<sup>8</sup>

The clinical signs and symptoms of IVL are caused by obstruction of blood flow by the monoclonal lymphoid cells.<sup>9</sup> The skin and central nervous system are most commonly involved,<sup>10</sup> followed by the adrenal glands, thyroid, pancreas, lungs, liver, spleen, lymph nodes, heart, stomach, and kidneys.<sup>1</sup> Fever of unknown origin, mental status changes, and rash were found to be the most common clinical features in a series of 10 patients with IVL.<sup>11</sup> Occasionally, fever of unknown origin may be the only presenting symptom.<sup>12</sup> Unlike other lymphomas, the lymph nodes, spleen, and liver are less commonly involved.<sup>10</sup> Clinicopathologic findings of IVL from a study of 38 patients included an elevated LDH level (86% [25/29]), anemia (63% [24/38]), B symptoms (55% [21/38]), bone marrow infiltration (32% [12/38]), hepatosplenic involvement (26% [10/38]), and nodal involvement (11% [4/38]).<sup>2</sup> Unusual presentations of IVL have included progressive hypoxemia<sup>7</sup> and subacute spinal cord degeneration.<sup>13</sup> There is a skin-limited variant of IVL that occurs primarily in females and is associated with



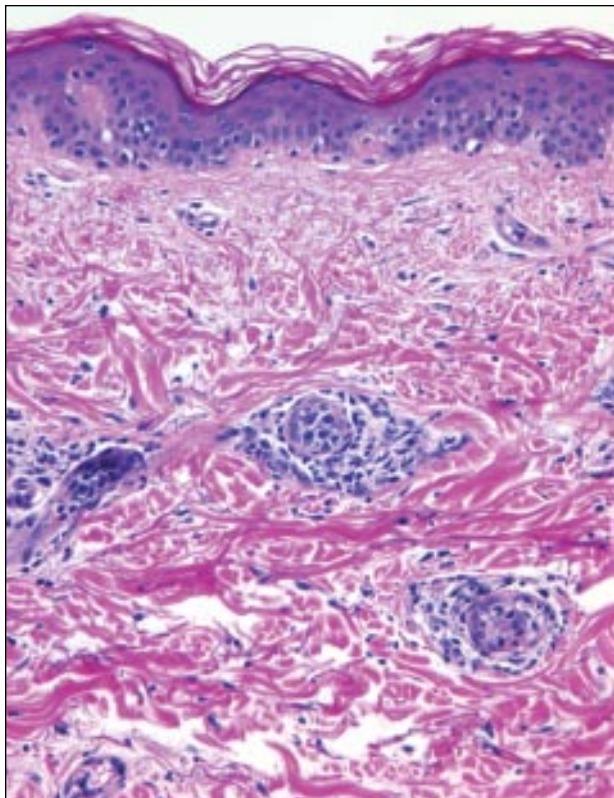
**Figure 2.** Faintly red, 2- to 5-cm urticarial plaques on the upper chest.

an unaffected platelet count (thrombocytes) and has a better prognosis.<sup>2</sup> Not surprisingly, IVL has been dubbed the “great imitator” by some authors.<sup>14</sup> This moniker is deserving, as it has been described in initial presentations ranging from Guillain-Barré syndrome,<sup>15</sup> diverse neurologic manifestations,<sup>13</sup> pyrexia of unknown origin,<sup>16</sup> hemophagocytic syndrome,<sup>17</sup> pulmonary hypertension,<sup>18</sup> and sudden hearing loss.<sup>19</sup>

The cutaneous findings in IVL are varied, with the following morphologies described: erythematous tender plaques, nodules, tumors, panniculitislake lesions, and telangiectases. Thicker lesions may have a propensity to ulcerate.<sup>1</sup> Telangiectatic plaques often are observed on the inner thighs and lower abdomen.<sup>20</sup> Ankle edema is a common finding.<sup>1</sup>

Neurologic involvement occurs in as many as 85% of patients. It may manifest as dementia, mental sluggishness, cerebrovascular accidents, seizures, peripheral neuropathies, paresthesia, visual disturbances, headaches, and other neurologic signs.<sup>1</sup>

Laboratory and imaging tests usually are not helpful for diagnosis, except for magnetic resonance imaging of the cerebral cortex. Classically, parenchymal hypodensities can be demonstrated.<sup>10</sup> Diagnosis is made based on histologic and immunohistochemical findings, with the skin being the most readily sampled organ. Histology reveals dilated vessels in the dermis and upper subcutaneous fat that are filled with fibrin thrombi and large, atypical, monomorphic cells. Cytologic features



**Figure 3.** Microvascular thrombosis with pleomorphic and hyperchromatic nuclei (H&E, original magnification  $\times 20$ ).

include hyperchromasia and numerous mitotic figures.<sup>4,10,12</sup> Immunohistochemistry demonstrates different leukocyte markers depending on classification of malignant cells as B-cell, T-cell, or histiocytic lineage (Table).<sup>6,10</sup>

The prognosis of IVL is poor, with a median survival rate of 5 months.<sup>21</sup> In 1997, the Dutch Cutaneous Lymphoma Working Group reported a 5-year survival rate of 50%.<sup>6</sup> The overall mortality rate has been reported to be more than 80%, with most patients dying within 1 year of diagnosis.<sup>1</sup>

Treatment of IVL is primarily with aggressive chemotherapy, though irradiation and corticosteroids also have been used.<sup>1,4,10,12,22</sup> Chemotherapy regimens are modeled on the treatment of aggressive non-IVL DLBCL and consist of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).<sup>23,24</sup> The addition of rituximab to CHOP (CHOP-R) has proven to be superior to CHOP alone in the treatment of DLBCL and has been successfully used in IVL.<sup>25-28</sup> Despite these advances, the overall prognosis for IVL is still poor and better treatment options are needed.

Autologous bone marrow transplantation (BMT) has been described as a second-line treatment for relapsed IVL.<sup>29,30</sup> The data on this therapeutic

option are preliminary and based on several case reports. Patients with a chemosensitive relapse are ideal candidates.<sup>31</sup> Sawamoto et al<sup>31</sup> and Yamaguchi et al<sup>32</sup> both observed long-term remissions in patients with IVL following autograft.

In reviewing the literature, no reports of patients with IVL treated with allogenic PBSCT were identified. Our patient had a complete response to this modality and is currently disease free 31 months posttransplant. Choosing between autologous and allogenic BMT in the treatment of relapsed IVL is difficult, primarily because of the paucity of experience with either modality in this rare malignancy. Several cases of IVL treated with autologous BMT have been published,<sup>29,31,32</sup> while our patient treated with allogenic PBSCT stands alone. Allogenic PBSCT offers a theoretical advantage of a graft versus lymphoma effect. However, in the DLBCL literature, allogenic procedures carry a higher procedure-related mortality rate.<sup>33-35</sup> Some insight can be provided by examining outcomes of autologous versus allogenic PBSCT in high-grade non-IVL DLBCL. Peniket et al<sup>34</sup> analyzed the data for these groups from the European Bone Marrow Transplant Registry in a match-paired fashion, comparing the overall survival, relapse rate, and treatment mortality rates for allogenic and autologous BMT. Patients with high-grade non-Hodgkin lymphoma (n=255) who had received allografts were matched with patients receiving autografts. The data revealed that the treatment mortality rate was higher in the allogenic group, and consequently, the overall survival was lower as compared to autografts. However, the relapse rate in the allogenic group was lower than the autologous group.<sup>34</sup> In an attempt to take advantage of the graft versus lymphoma effect of allogenic transplants while decreasing the transplant-related mortality of allogenic PBSCT, reduced-intensity allogenic PBSCTs have been developed. Further reports of allografts in patients with IVL are needed to clarify the role of allotransplantation in the treatment of IVL.<sup>35</sup>

## Conclusion

Intravascular lymphoma should be considered in the differential diagnosis of unexplained erythematous tender indurated plaques, nodules, and telangiectases. Often, multiple skin biopsies are required to diagnose IVL. This is the second published report in which the diagnosis was not identified on the first biopsy.<sup>36</sup> With respect to our patient, the diagnostic biopsy was done on a more recent, less tender, edematous, faintly red urticarial plaque on the patient's upper chest. The biopsies taken from the indurated telangiectatic areas on her inner thighs were only read as positive for IVL retrospectively.

## Immunophenotyping in Intravascular Lymphoma

### B Cell

CD19

CD20

CD22

CD45RA

CD79a

### T Cell

CD1

CD3

CD4

CD8

CD43

CD45RO

### Histiocyte

MAC387

CD68

Our patient has had a prolonged complete response to allogeneic PBSCT after a rapid relapse following CHOP-R. We report this case to question if allogeneic PBSCT should be the preferred salvage regimen in relapsed IVL.

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