

Intravascular Lymphomatosis With Bone Marrow Involvement

A Case Report and Review of the Literature

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● We describe the case of a 56-year-old man who presented with numbness and tingling of the extremities, weakness, and fatigue. Laboratory findings included anemia and thrombocytopenia. A diagnosis of intravascular lymphomatosis was established when liver, omentum, and bone marrow samples were examined. A review of the literature reveals that most cases of intravascular lymphomatosis have cytopenias, mainly anemia and thrombocytopenia, but bone marrow involvement is rare. In our case, a subtle neoplastic infiltrate in the marrow sinusoids was highlighted with a B-cell marker. While immunohistochemical analysis was not performed in most reported cases in the literature, our studies suggest that a systematic search in bone marrow of cases of intravascular lymphomatosis may reveal unsuspected neoplastic cells. We conclude that bone marrow involvement in intravascular lymphomatosis appears to be rare, has subtle features, and is difficult to diagnose if unsuspected and not searched for.

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Intravascular lymphomatosis is a rare and insidious non-Hodgkin lymphoma that is a peculiar variant of large cell lymphoma.^{1,2} It may be considered as a "malignant lymphoma, high grade, immunoblastic" in the Working Formulation,³ and it could be considered as an "unclassified large B-cell lymphoma" in the REAL classification.⁴ The tumor is characterized by multifocality and exclusive or predominant growth within the vasculature.^{1,2} Since some of the neoplastic cells line the luminal side of the blood vessels, intravascular lymphomatosis was formerly considered a neoplasm of endothelial or subendothelial cells² and was called neoplastic endotheliomatosis and malignant angioendotheliomatosis, among other names.

Afflicted patients usually are middle-aged or elderly and present with central nervous system or skin manifestations.^{1,5,6} The neurologic symptoms usually are nonspecific and may not be localized. They may result from mul-

tipl infarcts secondary to vascular occlusion.^{1,2,5,6} Virtually any organ can be involved, but the bone marrow is usually spared.^{2,6,7} Except for hypocellularity or hypercellularity, bone marrow findings in intravascular lymphomatosis are usually described as unremarkable,^{8,9} and neoplastic cells are noted in rare cases.^{5,6,10,11}

We describe the case of a 56-year-old man with intravascular lymphomatosis who presented with neurologic manifestations and inconspicuous bone marrow involvement, suspected by light microscopy and confirmed by immunohistochemical studies. To better define the characteristics and significance of bone marrow involvement in intravascular lymphomatosis, we have compared our findings with those reported in the literature.

REPORT OF A CASE

A 56-year-old white man presented to the emergency department with hematemesis, weakness, and fatigue. For the prior 2 years he had complained of chest pain, numbness, and tingling in his upper extremities. He underwent a cervical spine laminectomy because a bone spur was suspected of impinging on the spine. The patient had no relief following this procedure. The physical examination was not significant, and an upper gastrointestinal tract double-contrast radiographic examination and barium enema revealed no significant abnormalities. An exploratory laparotomy performed because of a clinical suspicion of an undetected gastrointestinal lesion did not reveal discrete lesions. Because of unexplained anemia, he was transferred to a university hospital.

His medical history included epilepsy secondary to meningitis since he was 10 years old. His seizures were poorly controlled with phenobarbital, phenytoin, and diazepam.

Significant laboratory findings on admission included leukocyte count of $3.0 \times 10^9/L$ (normal, $4.5-10 \times 10^9/L$); hemoglobin, 8.4 g/L (normal, 13.5-17.5 g/L); hematocrit, 0.26 (normal, 0.40-0.45); mean corpuscular hemoglobin concentration, 20 mmol/L (32.4 g/dL) (normal, 19-22 mmol/L [30-36 g/dL]); reticulocytes, 0.034 (normal, 0.005-0.015); and platelets, $57 \times 10^9/L$ (normal, $150-450 \times 10^9/L$). The peripheral blood showed a normochromic microcytic anemia with an occasional nucleated red blood cell. No abnormal cells were noted. Flow cytometry of the peripheral blood showed a predominance of T-helper cells (Leu-4 [CD3], Leu-3 [CD4], Leu-9 [CD7]) and a small B-cell population (Leu-12 [CD19]) expressing polytypic immunoglobulin light chains.

Other significant laboratory findings included albumin, 20 g/L (normal, 35-55 g/L); total protein, 40 g/L (normal, 6.5-8.5 g/L); total lactate dehydrogenase (LDH), 725 U/L (normal, 100-190 U/L); LDH-LD3, 33% (normal, 12%-22%); alkaline phosphatase, 411 U/L (normal, 50-136 U/L); aspartate aminotransferase, 125 U/L (normal, 15-37 U/L); alanine aminotransferase, 25 U/L (normal, 37-77 U/L); γ -glutamyltransferase, 437 U/L (normal,

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15–85 U/L); total creatine kinase, 6 U/L (normal, 35–232 U/L); serum urea nitrogen, 13.6 mmol/L (38 mg/dL) (normal, 2.1–7.1 mmol/L [6–20 mg/dL]); creatinine, 150 μ mol/L (1.7 mg/dL) (normal, 53–106 μ mol/L [0.6–1.2 mg/dL]); calcium, 1.75 mmol/L (7.0 mg/dL) (normal, 2.10–2.55 mmol/L [8.4–10.2 mg/dL]); phosphorus, 0.42 mmol/L (1.3 mg/dL) (normal, 0.87–1.45 mmol/L [2.7–4.5 mg/dL]); and magnesium, 0.60 mmol/L (1.2 mEq/L) (normal, 0.75–1.20 mmol/L [1.5–2.4 mEq/L]). A chest radiograph showed changes consistent with right lower lobe pneumonia, and a computed tomography of the abdomen showed splenomegaly and ascitis.

An exploratory laparotomy was performed for diagnostic purposes. Splenectomy, wedge biopsy of the liver, omentectomy, and a mesenteric lymph node biopsy were performed. No gross intraoperative abnormalities were noted.

On diagnosis, a bone marrow biopsy was performed, and the patient was treated with intrathecal methotrexate and folinic acid; a pump was placed for administration of systemic vincristine, Adriamycin, and cytoxan. About the time systemic chemotherapy was started, he developed anasarca. In the subsequent weeks he experienced multiple mouth and throat ulcers as well as sepsis due to a methicillin-resistant *Staphylococcus aureus* and *Pseudomonas multocida* infection. The patient refused further treatment and was discharged with termination of all chemotherapy. The patient died less than 2 months later; an autopsy was not performed.

PATHOLOGIC FINDINGS

Gross and Histopathologic Finding

The spleen weighed 1164 g. The gross examination showed congested parenchyma, but no focal lesions. Microscopic examination revealed red pulp congestion with an unremarkable white pulp. No abnormal cells were identified.

Wedge biopsy of the liver showed numerous noncohesive large cells in hepatic sinusoids. The cells showed moderately abundant clear cytoplasm and large vesicular nuclei with central nucleoli (Figure 1, A). In addition, focal chronic portal inflammation and mild macrovesicular fatty change were noted.

The omentum measured 8.0 \times 3.5 \times 1.0 cm. Grossly, small yellow indurated foci were noted; histologically, the foci showed necrosis and granulation tissue. Small and medium-sized vessels contained large noncohesive cells, similar to those described above; some vessels had microthrombi. The lymph node showed large noncohesive cells in subcapsular sinuses.

The bone marrow biopsy showed about a 60% cellularity with trilineage hematopoiesis and normal maturation of megakaryocytes, myeloid, and erythroid elements. Subtle small sinusoids appeared to contain large cells with moderate amount of cytoplasm, vesicular nuclei, and punctate nucleoli, morphologically similar to immature myeloid cells (Figure 1, B). These findings were considered suspicious but insufficient for a diagnosis of involvement by tumor cells.

Immunohistochemical Studies

Immunohistochemical studies performed in the bone marrow, liver, and omentum showed that the large abnormal cells marked as B cells (leukocyte common antigen positive, L26 [CD20] positive, CD3 negative, and cytokeratin [AE1/AE3] negative) (Zymed Lab Inc, South San Francisco, Calif). The large abnormal cells were inside hepatic sinusoids (Figure 2, A), small omental vessels and in bone marrow sinusoids (Figure 2, B). In the bone mar-

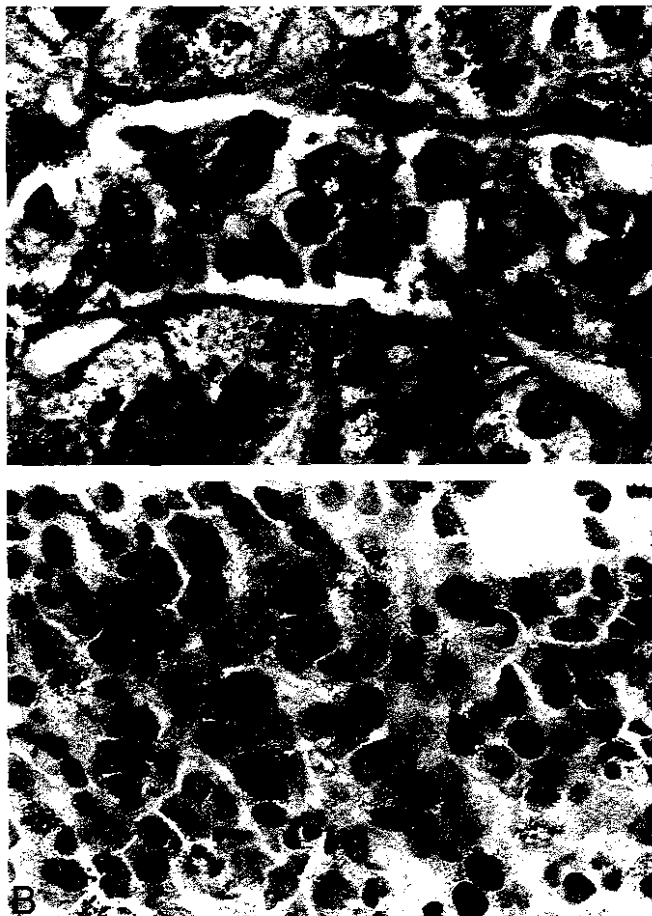


Figure 1. A, Liver, wedge biopsy. Large cells with vesicular nuclei are within sinusoids. B, Bone marrow, core biopsy. Normocellular marrow with trilineage hematopoiesis; sinusoid is not readily identified (hematoxylin-eosin, original magnification \times 1000).

row the large abnormal B cells were not outside the sinusoids.

COMMENT

This is the report of a 56-year-old man who presented with vague neurologic complaints for which he was referred for psychological counseling. Ultimately a diagnosis of intravascular lymphomatosis was established after histologic examination of biopses of liver, omentum, and bone marrow. In this discussion we will focus on the bone marrow findings of intravascular lymphomatosis.

The unexplained presentation of 1 or more of the following neurologic symptoms should alert a clinician or pathologist to the possibility of intravascular lymphomatosis: vascular occlusive syndrome, progressive multifocal cerebrovascular events, paraparesis, pain, incontinence, subacute encephalopathy, and peripheral or cranial neuropathies.^{5,6,12–14}

Histologically, the tumor cells may fill the lumina of small and intermediate-sized blood vessels of almost any organ. The neoplastic cells are discohesive, large, and usually display round nuclei, vesicular chromatin, multiple or single prominent nucleoli, and a moderate rim of amphophilic cytoplasm along with mitotic figures.^{1,2} They are usually enmeshed in fibrin or microthrombi and associated with endothelial proliferation.^{1,2} Although this entity preferentially involves the vasculature, the diagnosis



Figure 2. Immunohistochemistry with the B-cell marker L26. The neoplastic cells are within sinusoids and mark as B cells. A, Liver, wedge biopsy. B, Bone marrow, core biopsy (original magnification $\times 1000$).

should not be excluded in the presence of an extravascular (nodal or extranodal) component.^{1,2}

The diagnosis of intravascular lymphomatosis can be confirmed with immunohistochemical studies, which show that the neoplastic cells react with the leukocyte common antigen (CD45) and usually with B-cell markers (L26 [CD20] and CD19). There are occasional cases of T-cell lineage^{6,13,15} and more rare cases are of histiocytic lineage.^{16,17} The neoplastic cells are negative for endothelial, epithelial, or melanoma cell markers.¹⁷

The differential diagnosis of intravascular lymphomatosis includes other diseases that may have an intravascular component such as disseminated carcinoma, malignant melanoma,¹⁸ acute leukemia, angiocentric immunoproliferative lesions, angiosarcoma, reactive angioendotheliomatosis, and papillary endovascular angioendothelioma.^{2,7,18,19} To narrow the differential diagnosis, immunohistochemistry or flow cytometry markers for leukocytes, B- and T-cell markers, as well as immunohistochemistry for cytokeratin, factor VIII-related antigen, S100, and HMB-45 may be helpful.

It is not known why the neoplastic cells of intravascular lymphomatosis remain predominantly in the vessels and tumor is usually not found extravascularly.^{1,2} This may be a result of abnormal interactions between homing receptors of neoplastic lymphocytes and cell adhesion molecules of endothelial cells of high endothelial venules

(HEV). It has been suggested that, if there is such an abnormality, it is more likely to be in the neoplastic lymphocytes than in the endothelial cells.²⁰ LFA-1 (lymphocyte function-associated antigen 1, CD11a/CD18), a lymphocyte adhesion molecule, was not detectable in neoplastic cells of intravascular lymphomatosis,²⁰ suggesting that the absence or deficiency of CD11a/CD18 may contribute to the inability of the neoplastic cells to migrate through the HEV.²⁰ However, LFA-1 is decreased or absent in 50% of B-cell lymphomas,²¹ most of which have an extravascular component, suggesting that LFA-1 may not be the critical factor for the lack of migration of intravascular lymphomatosis cells. Furthermore, the endothelial cell adhesion molecule ICAM-1 (CD54) that is the ligand for LFA-1 appears preserved,^{15,20} but it has also been shown that HEV may lack certain antigens as detected with the antibody HEC-452.¹⁴

Bone marrow examination is performed for staging malignant lymphoma or as part of the workup of patients with protean presentations such as fever of unknown origin. A review of the literature of cases of intravascular lymphomatosis shows frequent anemia and thrombocytopenia, but it is surprising that neoplastic cells in the bone marrow are rarely reported.^{5,7,9,13,19} Therefore, the following is an account of the reviewed literature regarding hematologic and bone marrow findings in cases of intravascular lymphomatosis with emphasis on the presence or absence of neoplastic cells in the bone marrow (Table).

Ansell et al²² reported 1 patient with intravascular lymphomatosis who had leukopenia and a bone marrow questionable for lymphoma. Chapin et al³ reported 1 patient with anemia and a normal bone marrow. Cheng et al¹² reported a patient with anemia and thrombocytopenia, and the marrow was normocellular but with active hemophagocytosis; neoplastic cells were not reported in the bone marrow. Demirel et al⁷ reported bone marrow findings in 3 of 4 cases of intravascular lymphomatosis. The marrow was not involved in 2 cases, and erythroid hyperplasia was noted in a patient with anemia and thrombocytopenia. Devlin et al⁸ reported 2 cases with no marrow involvement; both had anemia and 1 had thrombocytopenia. Domizio et al¹³ reported a patient with anemia, thrombocytopenia, and circulating nucleated red blood cells and unremarkable bone marrow. Ferry et al¹⁴ reported 6 patients with intravascular lymphomatosis, 4 cases had anemia, and 5 had thrombocytopenia; none had bone marrow involvement. Glass et al⁹ reported 4 patients with intravascular lymphomatosis, and the bone marrow was examined in only 1 patient who had thrombocytopenia; the marrow was hypocellular. No hematologic findings were provided for the other 3 cases. Ip et al²¹ reported a patient with pancytopenia, but the bone marrow findings were not mentioned. Jalkanen et al²⁰ reported 3 cases of intravascular lymphomatosis; 1 presented with anemia and the bone marrow findings were not reported. Khalidi et al¹¹ reported 5 cases of intravascular lymphomatosis; 1 showed bone marrow vessels distended by neoplastic cells; bone marrow findings of 4 cases and laboratory findings were not indicated. Setoyama et al¹⁵ reported a patient with mild anemia; the bone marrow was normal. Sheibani et al¹⁰ reported 3 patients with intravascular lymphomatosis and the marrow was examined in 2. One patient presented with anemia and leukopenia, and the marrow had neoplastic cells "in the capillaries"; the other patient had the bone marrow not involved. Stroup et al¹⁹ re-

Bone Marrow (BM) and Hematologic Findings of Intravascular Lymphomatosis: Review of the Literature*

| Source | BM Findings | | Hematologic Findings | | |
|--------------------------------|------------------------------|--------------------------|----------------------|------------|------------------|
| | BM Examined/ Total Cases† | BM Involvement | Anemia | Leukopenia | Thrombocytopenia |
| Ansell et al ²² | 1/1 | Indeterminate | ND | Yes | ND |
| Chapin et al ³ | 1/2 | Negative | Yes (1/1) | No | ND |
| Cheng et al ¹² | 1/1 | Negative | Yes | ND | Yes |
| Demirer et al ⁷ | 3/4 | Negative | Yes (3/3) | ND | ND |
| Devlin et al ⁶ | 2/2 | Negative | Yes (2/2) | Yes (1/2) | Yes (1/2) |
| Domizio et al ²³ | 1/1 | Negative | Yes | No | Yes |
| Ferry et al ¹⁴ | 0/6 | ND | Yes (4/6) | No (6/6) | Yes (5/6) |
| Glass et al ⁶ | 1/4 | Negative | ND | ND | Yes (1/1) |
| Ip et al ²⁴ | 0/1 | ND | No | Yes | Yes |
| Jalkanen et al ²⁰ | 0/3 | ND | No (3/3) | ND | ND |
| Khalidi et al ¹¹ | 1/5 | Tumor cells: 1/1 | ND | ND | ND |
| Setoyama et al ¹⁵ | 1/1 | Negative | Yes | No | ND |
| Sheibani et al ¹⁰ | 2/3 | Tumor cells: 1/2 | Yes (1/2) | Yes (1/2) | No |
| Stroup et al ⁹ | 3/7 | Negative | Yes (2/3) | Yes (2/3) | Yes (2/3) |
| Wick et al ²⁵ | 1/1 | Negative | Yes | No | No |
| DiGiuseppe et al ¹³ | 8/10 | Tumor cells: 1/8 | ND | ND | ND |
| DiGiuseppe et al ²⁶ | 5/5 | Negative | ND | ND | ND |
| Current report | 1/1 | Tumor cells: 1/1 | Yes | Yes | Yes |
| Total | 26/52 | Tumor cells: 4/26 | | | |

* ND indicates not described. This feature was not described, not examined, or not mentioned.

† Number of cases in which bone marrow was mentioned, either as positive or negative/total number of cases reported.

ported 7 cases of intravascular lymphomatosis, and the bone marrow was examined in 3 patients. Two patients had pancytopenia, and the bone marrow was hypercellular in 1 and necrotic in the other; the third patient had a normal cell blood count and a normocellular bone marrow. No neoplastic cells were detected. Wick et al²⁵ reported 1 patient with anemia, and the bone marrow had plasmacytosis, but it was negative for tumor. DiGiuseppe et al¹³ reported 8 patients with intravascular lymphomatosis, 3 had hemolytic anemia, and the hematologic findings were not mentioned for the other cases. Only 1 had bone marrow involvement, but the features of the involved marrow were not mentioned. In a subsequent study by these authors,²⁶ it was noted that despite using immunohistochemical studies for B cells, the neoplastic cells were not detected in 5 of those cases. However, polymerase chain reaction (PCR) analysis for rearranged immunoglobulin heavy chain (IgH) showed a high rate of clonal populations.²⁶ These findings suggested that the presence of clonal B-cell populations detected by PCR with negative histologic findings may be suggestive of bone marrow involvement by intravascular lymphomatosis.

Therefore, bone marrow was examined in 26 of 52 patients with intravascular lymphomatosis reported in the literature. In the majority, the bone marrow was described as unremarkable or negative for tumor. Four cases had neoplastic cells detected in the bone marrow. The infiltrate was described in 1 case as "within the capillaries"¹⁰ and distending vessels in another.¹¹

The patient who is the subject of our report had pancytopenia and a bone marrow that was normocellular with trilineage hematopoiesis. The bone marrow sinusoids and neoplastic cells were not readily apparent in the hematoxylin and eosin sections, but they were highlighted with immunohistochemistry using the B-cell marker L26 (CD20). We believe that, if the disease is suspected, performing immunohistochemical studies or immunoglobulin gene rearrangement analysis will help avoid further delay in the diagnosis. It can be argued that other authors²⁶ did not detect the neoplastic cells despite using

immunohistochemical studies, probably because of technical variations such as antigen retrieval. The diagnosis of intravascular lymphomatosis is difficult, and about 50% of cases are diagnosed at autopsy.²³ It has been suggested that an early diagnosis and treatment may result in occasional cases of complete remission.^{3,13} Without treatment, death is inevitable, usually in less than 24 months.^{7,19}

In the above analysis we have not included what some investigators consider a variant of intravascular lymphomatosis called malignant histiocytosis-like B-cell lymphoma.²⁷ This variant presented in a group of Asian patients, with a rapidly aggressive clinical course but usually did not have central nervous system or skin manifestations. Anemia, leukopenia, and thrombocytopenia were common. Most cases had bone marrow involvement manifested by neoplastic cells in marrow sinusoids. Some cases had hemophagocytic syndrome.

In summary, it is evident that intravascular lymphomatosis commonly present with cytopenias, usually anemia and thrombocytopenia, findings that may not be explained by the bone marrow findings alone. Some cases of anemia may be due to concomitant hemolytic anemia or bone marrow hypoplasia. The review of the literature discloses that neoplastic cells are not typically noted in the bone marrow of cases with intravascular lymphomatosis. We found that sinusoids and neoplastic cells are highlighted with immunohistochemical studies. Thus, we believe that the immunohistochemical evaluation of bone marrow in cases of intravascular lymphomatosis may reveal unsuspected involvement. Kinetic studies may be helpful to determine the fate of blood cells in cases of intravascular lymphomatosis with cytopenias and their possible relationship with the presence of neoplastic cells in bone marrow sinusoids.

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