

INTRAVASCULAR LARGE-CELL LYMPHOMA: REPORT OF AN UNUSUAL CASE

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Intravascular large cell lymphoma (IVL) is characterized by a massive proliferation of neoplastic mononuclear cells within the lumina of vascular channels. It was originally thought to represent an endothelial neoplasm, however, recent studies have clearly established its lymphoid nature. It usually occurs in the middle-aged or elderly. The clinical course is characterized by unexplained fever, microvascular skin lesions, dementia, neurologic changes, and progressive multisystem failure.^{1,2}

A characteristic histopathologic feature of this disorder is the extensive intravascular proliferation of atypical mononuclear cells within the lumens of venules, arterioles, capillaries and small arteries. The lymphoma has a tendency to involve small blood vessels of the skin and central nervous system. Other organs, such as kidneys, heart, spleen, lymph nodes, lungs and endocrine organs, may be involved as well. Various clinical abnormalities have been frequently described in this disease, including low serum levels of albumin, sodium and chloride, high erythrocyte sedimentation rate, disturbance of liver and renal functions and positive rheumatoid factor and antinuclear antibodies. The diagnosis is often made postmortem.³⁻⁵

The first case of IVL was reported by Pflieger and Tappeiner in 1959.¹ Several cases and small series have since been published. The majority of these cases were diagnosed postmortem. We are reporting a case of IVL which had an unusual clinical course, with absence of skin or CNS symptoms, and which initially had a good response to chemotherapy.

Case Report

A 57-year-old female presented to our hospital in June 1996 with a few months' history of fever and chills lasting for two hours, and then resolving spontaneously. This had later increased in frequency to three attacks per day.

The fever was not associated with diaphoresis, arthralgia, body aches, skin rash, chest pain, cough or shortness of breath. On examination, the patient was found to be pale, with muscle tenderness and splenomegaly (2 cm below costal margin). There was no peripheral lymphadenopathy or hepatomegaly.

Investigations revealed a hemoglobin of 82 g/L (normocytic, normochromic), with an ESR of 80 mm/hour. She had raised liver enzymes, ALT 60 units/L (normal 10-50), alkaline phosphatase 22 μ /L (30-125), AST 128 μ /L (10-45), the total bilirubin was 11 (0-21) nmol/L, and albumin 32 g/L (36-48). LDH on admission was 3604 IU (297-537). Ultrasound of the abdomen revealed an enlarged spleen (19 cm), with no focal lesions. The liver showed normal parenchyma and there was no para-aortic lymphadenopathy. CT scan of the abdomen revealed mild hepatomegaly and moderate splenomegaly without focal changes. The density of the liver on non-contrast images was slightly higher than normal. No evidence of lymphadenopathy was noted. Blood cultures were negative and bone marrow and liver biopsy were taken. A bone marrow biopsy revealed a hypercellular marrow with large intravascular, mononuclear cells in the small blood vessels and sinusoids (Figure 1). The liver biopsy showed focal plugging of sinusoids with large lymphoid cells (Figure 2). Immunohistochemical staining on both biopsies revealed that most of the mononuclear cells stained for LCA and L-26 showed no staining with CD3, indicating that the cells were of a B-cell phenotype (Figure 3).

The patient was treated as intermediate/high-grade malignant lymphoma, and started on CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin and prednisone) chemotherapy. CT scan of the head revealed no focal brain lesion and no enhanced abnormality was detected. However, mild generalized brain atrophy was seen with enlarged ventricles. She received six cycles and went into complete remission, as evidenced by the absence of her symptoms, normalization of her liver function tests, and radiological views of her spleen and liver, and negative bone marrow. She was disease-free for four months before her fever recurred, with splenomegaly and positive bone marrow. She was treated intensively with second-line chemotherapy, followed by high-dose chemotherapy at an overseas center. However, her disease

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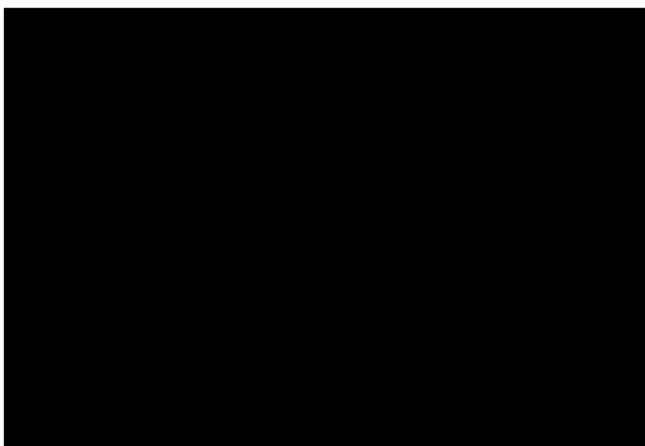


FIGURE 1. Bone marrow biopsy with mononuclear cells in small blood vessels.

persisted and she developed several complications, including septic shock that was fatal.

Discussion

Intravascular (angiotropic) large cell lymphoma is an extensive proliferation of neoplastic mononuclear cells within the lumina of blood vessels. The disease is characterized by involvement of the skin and central nervous system, and disseminates rapidly with involvement of multiple organs. The prognosis is usually extremely poor, with rapid death despite chemotherapy.¹ Most patients present with fever of unknown origin and nonspecific cutaneous and neurologic manifestations. Cutaneous lesions may be confused with mycosis fungoides, sarcoidosis, vascular neoplasms, or cutaneous involvement by lymphoma or leukemia.^{5,6} The histogenesis of IVL is still controversial. Benign forms have been described in association with bacterial endocarditis and are distinguished by their clinical and histological features.^{3,7}

Originally, these intravascular cells in IVL were thought to be of endothelial origin. This observation was based on the presence of tumor cells attached to the endothelium of involved blood vessels. However, immunohistochemical stains have failed to demonstrate consistent staining for factor-VIII-related antigen, an endothelial cell marker.³ Ansell et al. and Bhawan et al. were the first to demonstrate that the neoplastic intraluminal cells are of lymphoid origin of B-cell lineage.^{8,9} Otrakji et al. demonstrated specific B-cell immunoglobulin gene rearrangement by Southern blot hybridization analysis on deoxyribonucleic acid (DNA) extracted from neoplastic cells present in the adrenal tissue obtained at autopsy from a patient with IVL. This study provided the first genotypic evidence for the monoclonal proliferation of B-cells in this condition. They also demonstrated strong positive reaction with anti-Kappa light chain antibody in cryostat cut fresh frozen section.⁷

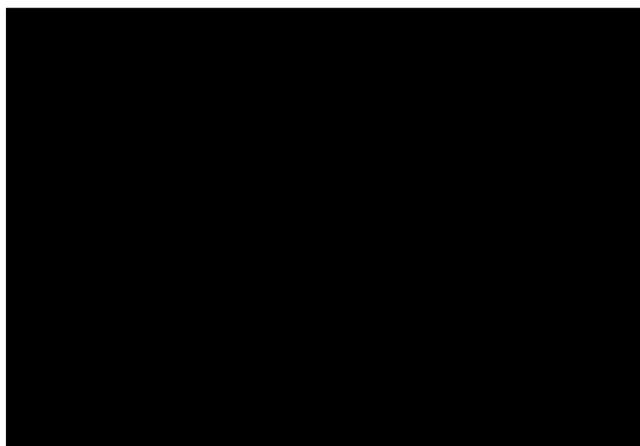


FIGURE 2. Liver biopsy shows plugging of sinusoids in large mononuclear cells.

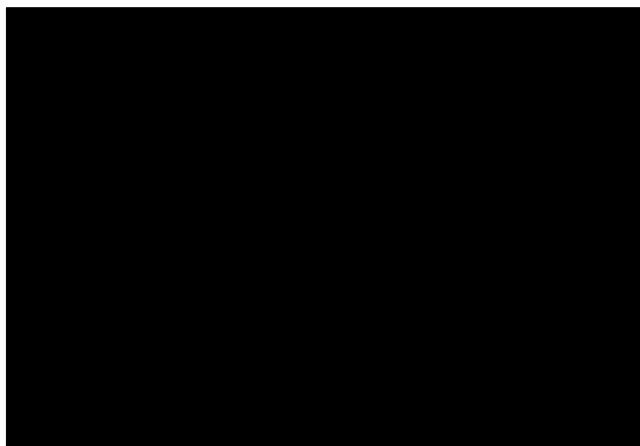


FIGURE 3. Immunohistochemical stain on the mononuclear cells stain for L-26.

Obviously, intravascular lymphomatosis represents an unusual type of lymphoproliferative disease in which many aspects are as yet poorly understood, e.g., site of origin and types of lymphoid cells involved (heterogeneity of the disease). Also misunderstood are the mechanisms that mediate the exclusive affinity of the lymphoma cells to certain types of blood vessels (capillaries, postcapillary venules) and prohibit the colonization of the organs most commonly linked to lymphoma, such as lymph nodes, spleen and bone marrow.^{2,10}

Histopathologic diagnosis of IVL on biopsy material is usually problematic, since many pathologists are still not aware of this entity. Most of the reported cases in the literature have been diagnosed at autopsy.^{11,12} In our case, bone marrow biopsy was initially interpreted as reactive, however, a liver biopsy revealed atypical large lymphoid cells in the sinusoids, which revealed a B-cell phenotype, suggesting the diagnosis of IVL. A review of bone marrow biopsy showed similar involvement. This is the first case of IVL reported in Saudi Arabia, and we believe that

increased awareness of this type of lymphoma will result in recognition of additional cases.

Most of the patients with IVL present with skin and CNS involvement, however, in our case, careful evaluation of the patient failed to reveal dermal and CNS involvement. Our patient had abnormal liver function tests with transaminases and a high level of LDH. She had hypoalbuminemia, hyponatremia, anemia, and elevated ESR. She responded to CHOP chemotherapy and the fever subsided. Among 35 patients reported in the literature who received chemotherapy, 43% attained complete remission. This suggests that IVL is a high-grade, non-Hodgkin's lymphoma and long-term survival may result in patients who are treated with aggressive combination chemotherapy.¹³

In the literature, several synonyms have been used to describe this entity, such as malignant angioendotheliosis, neoplastic angioendotheliosis, malignant angioendotheliomatosis, hemangioendotheliosis, angioendotheliomatosis proliferans and intravascular lymphomatosis. In view of conclusive evidence favoring a lymphoid phenotype of the tumor cells, it is believed that intravascular large cell lymphoma would be a more appropriate name for this disease, since it accurately describes the clinical, histological and biological features seen in this disorder.^{2,3}

In summary, it is hoped that this report of an unusual case of IVL which had no CNS or skin involvement and which initially responded well to chemotherapy, will increase awareness among pathologists and oncologists regarding this entity.

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