Intravascular Lymphomatosis (Malignant Angioendotheliomatosis) Presenting as Pulmonary Hypertension

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Intravascular lymphomatosis is a rare lymphoma characterized by proliferation of malignant cells within the lumen of small blood vessels. We describe a case of intravascular lymphomatosis resulting in pulmonary hypertension, hypoxemia, and dyspnea. This lymphoma occasionally responds to combination chemotherapy, suggesting that pulmonary hypertension secondary to intravascular lymphomatosis may be reversible. Intravascular lymphomatosis should be considered in the differential diagnosis of pulmonary hypertension. (Chest 1989; 96:1199-1200)

Intravascular lymphomatosis is a rare lymphoma with its primary clinical manifestations in the CNS and skin. It is characterized by proliferation of malignant cells within the lumen of small blood vessels including capillaries, veins, and arteries.1,2 The disease frequently involves many organs, including the lung, liver, kidney, spleen, and adrenal glands. Organ involvement without cutaneous manifestations can occur and portends a poor prognosis.

Approximately 60 cases of intravascular lymphomatosis have been reported in the literature. The clinical features of the disease are varied and include cutaneous manifestations (plaques, nodules), neurologic symptoms (dementia, ischemic infarcts), hematologic abnormalities (hemolytic anemia), and nonspecific systemic symptoms (fever, weight loss, malaise). Lung involvement can be demonstrated pathologically at autopsy in approximately 60 percent of cases, although pulmonary symptoms are distinctly unusual at presentation.3,4 This report describes the first case, to our knowledge, of intravascular lymphomatosis resulting in pulmonary hypertension, profound hypoxemia, and breathlessness.

CASE REPORT

A 79-year-old man, a nonsmoker, presented with a six-week history of dyspnea, fatigue, and intermittent fever. Physical examination revealed a blood pressure of 120/80 mm Hg, pulse 110 beats/min, and a respiratory rate of 32 breaths/min. Results of abdominal and neurologic examinations were normal; cardiopulmonary examination showed a right ventricular heave with no murmurs, and the lungs were clear.

Laboratory examination results revealed a hemoglobin of 11.5 g, WBC count of 5,400/cu mm, Westergren ESR of 68 mm/h, BUN of 47 mg/dl, creatinine of 1.6 mg/dl, bilirubin of 2.6 mg/dl (0.9 direct); arterial blood gas levels were: pH, 7.44; Po2, 46 mm Hg; Pco2, 21 mm Hg on room air; ANA positive at 1:64 (speckled pattern), and a reticulocyte count of 6.5 percent. The chest roentgenogram showed chronic right apical pleural thickening, normal cardiac size, enlarged central pulmonary arteries and small bilateral pleural effusions. Pulmonary function testing revealed an FEV1, 2.6 L (88 percent predicted); FVC, 3.7 L (96 percent predicted); TLC 7.1 L (111 percent predicted); and corrected Dsb severely reduced, 11.2 ml/min/mm Hg (47 percent predicted).

Echocardiographic examination showed right ventricular enlargement with moderate to severe right ventricular dysfunction. Doppler studies documented moderate to severe increases in right-sided flow.

FIGURE 1. Immunoperoxidase stain of lung for common leukocyte antigen. Positively staining tumor cells are located in the capillaries. A 79-year-old nonsmoker presented with a six-week history of dyspnea, fatigue, and intermittent fever. Cardiopulmonary examination revealed a right ventricular heave with no murmurs, and the lungs were clear. Laboratory examination results revealed a hemoglobin of 11.5 g, WBC count of 5,400/cu mm, Westergren ESR of 68 mm/h, BUN of 47 mg/dl, creatinine of 1.6 mg/dl, bilirubin of 2.6 mg/dl (0.9 direct); arterial blood gas levels were: pH, 7.44; Po2, 46 mm Hg; Pco2, 21 mm Hg on room air; ANA positive at 1:64 (speckled pattern), and a reticulocyte count of 6.5 percent. The chest roentgenogram showed chronic right apical pleural thickening, normal cardiac size, enlarged central pulmonary arteries and small bilateral pleural effusions. Pulmonary function testing revealed an FEV1, 2.6 L (88 percent predicted); FVC, 3.7 L (96 percent predicted); TLC 7.1 L (111 percent predicted); and corrected Dsb severely reduced, 11.2 ml/min/mm Hg (47 percent predicted).

FIGURE 2. Immunoperoxidase stain of lung arteriole with epithelial membrane antigen. In contrast to Figure 1, tumor cells fail to stain for this antigen. Immunostains for both T cell and endothelial markers were also negative (original magnification × 120).
pressures with a pulmonary artery systolic pressure of approximately 60 mm Hg. Left ventricular systolic function was normal. Doppler studies of the lower extremities revealed no evidence of venous thrombosis, and a ventilation-perfusion scan showed low probability for a pulmonary embolus, with a single subsegmental matched defect in the right upper lobe.

During the course of his evaluation, the patient developed a diffuse violaceous rash over his trunk and extremities, which blanched but was nonpalpable. A skin biopsy showed mild nonspecific perivascular and perifollicular inflammation in the dermis without vasculitis. The patient’s presentation and clinical evaluation suggested that the pulmonary hypertension was due to an intravascular process in the lung such as tumor emboli, vasculitis, or capillary hemangiomatosis. However, prior to a scheduled open lung biopsy, a ventricular fibrillation arrest occurred, and resuscitative efforts were unsuccessful.

Pathologic Findings

At autopsy the lungs together weighed 1,300 g, with consolidations at the apices and multiple firm, white nodules measuring 3 mm or less. The heart weighed 425 g with right ventricular dilatation. The right kidney weighed 210 g and the left 240 g. There were multiple small, white cortical and medullary nodules, the largest of which measured 1 cm. Lymph nodes appeared normal in size and consistency except for a small calcification in one node at the pulmonary hilum.

Microscopic examination demonstrated multifocal intravascular lymphomatosis with marked intravascular involvement of the lungs, kidneys, GI tract, and liver. The heart (notably the conduction system), pancreas, and prostate showed moderate intravascular involvement. Lymph nodes, spleen, bone marrow, and skin did not show evidence of intravascular lymphomatosis. Spread outside the vessels was seen only in the kidney.

Immunohistochemistry of the malignant cells was positive for common leukocyte antigen, indicating hematolymphoid cells; LN2 and MB1 antigens were also positive on tumor cells, confirming their B cell origin (Fig 1). Stains for T cells, including MT1, UCHC-1, and Leu M3, as well as epithelial membrane antigen, were negative (Fig 2).

The vasculature of the lung was extensively involved, with lumens of arteries, veins, and capillaries occluded by intraluminal malignant cells. In addition, the arteries demonstrated hypertrophy, intramural tumor cells, and rare intraluminal platelet fibrin thrombi.

Discussion

This report describes the first case, to our knowledge, of pulmonary hypertension and hypoxemia secondary to extensive vascular involvement by intravascular lymphomatosis. Intravascular lymphomatosis is a systemic lymphoma, usually of B cell origin, that occurs primarily in the lumens of small vessels. Many of the protean clinical features and laboratory abnormalities seen in this case, including fever, malaise, hemolytic anemia, and positive ANA, have been reported in other cases.

In our patient, the pathologic findings correlated well with the prominent clinical features of pulmonary hypertension, hypoxemia, dyspnea, and renal impairment. This patient’s pulmonary function tests demonstrated an isolated reduction in the D50 with normal lung mechanics. The severe reduction in the D50 physiologically correlates with the loss of surface area for gas exchange secondary to vascular obstruction by the malignant cells. Extensive involvement of glomeruli as well as the conduction system of the heart likely caused the patient’s renal insufficiency and could have resulted in the arrhythmia and sudden death.

Intravascular lymphomatosis was originally called malignant angioendotheliomatosis because of its intravascular location and presumed endothelial cell origin. Approximately 60 cases have been reported in the literature since it was first described in 1959. Recent evidence from immunohistochemical studies indicate that the intravascular malignant cells are of B cell origin in all cases except a single report of T cell origin. Endothelial and epithelial immunomarkers are negative. Additional supporting evidence for lymphoma comes from a recent report of gene rearrangements in a case of intravascular lymphomatosis.

Intravascular lymphomatosis involves lung, kidney, and brain in over 90 percent of the cases. Other sites of involvement include the genitourinary system, adrenal glands, heart, liver, GI tract, and skin. However, unlike many lymphomas, spleen and lymph node involvement occurs in less than 50 percent of the cases; bone marrow involvement is rare. Diagnosis is established from biopsies of clinically affected organ systems.

Treatment of intravascular lymphomatosis consists of local radiation therapy and systemic chemotherapy. Some patients respond to aggressive combination chemotherapy as used for lymphoma. This suggests that pulmonary hypertension secondary to intravascular lymphomatosis may be reversible.

In summary, intravascular lymphomatosis is a rare B cell lymphoma that can present with extensive pulmonary vascular occlusion, pulmonary hypertension, and hypoxemia. It should be considered in the differential diagnosis of pulmonary hypertension.

References