Case Report

Pulmonary lymphangiomatosis: a report of two cases*

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Abstract

Lymphangiomatosis, a rare disease of controversial origin, occurs in individuals of any age, regardless of gender, but is predominantly seen in younger individuals. It often presents with thoracic involvement, although, the bones, spleen and liver can also be affected. Histologically, pulmonary involvement includes proliferation, complex anastomoses and secondary dilatation of the lymphatic vessels. Clinically, the presentation is variable. Although radiographic findings can be suggestive of the disease, the final diagnosis is made histologically. We report two cases of lymphangiomatosis, both in females: one was oligosymptomatic and was being treated for the disease; the other had a more progressive form, was diagnosed quite late and ultimately died of the disease.

Keywords: Lymphangioma; Lymphatic System; Pleural Effusion; Lymphatic Diseases; Lymphatic System/abnormalities; Lung Diseases, Interstitial.

Introduction

Lymphatic system disorders can develop in any tissue in which lymphatic vessels are normally found but have a certain predilection for the cervicothoracic region.[1]

Diffuse lymphangiomatosis is a rare disease of the lymphatic system, still of controversial etiology, which occurs predominantly in children and young adults, regardless of gender.[1-4] There are cases reported in individuals from birth to 80 years of age.[1,4] Respiratory symptoms are generally the initial manifestation of the disease and, when the abnormality involves only the thoracic lymphatic vessels, the disease is known as diffuse pulmonary lymphangiomatosis.[1]

In this report, we present two cases of the disease. Case A, an oligosymptomatic patient, was treated with daily subcutaneous (sc) doses of interferon-alpha 2a. In case B, the disease presented a more aggressive, persistent course, and the definitive diagnosis was delayed. After repeated episodes of exacerbation and despite the treatment given, the patient in case B evolved to progressive respiratory failure and death.

Case A

A 30-year-old female patient presented with a history of productive cough with colorless sputum and dyspnea upon exertion since childhood, without other complaints. The patient described herself as a nonsmoker, and had no significant occupational exposure or environmental exposure. The physical examination was normal except for a respiratory frequency of 24 breaths/min and pulse oximetry

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of 88% on room air. She presented normal results in the chest X-ray and blood workup, as well as for electrolytes, inflammatory activity and immunoglobulin levels. A high-resolution computed tomography (HRCT) scan of the chest showed diffuse pulmonary infiltrate, characterized by multiple small, predominantly centrilobular, nodules, some of which presented ground glass attenuation halos (Figure 1). Spirometry findings and the analysis of the pulmonary volumes were normal. However, the diffusing capacity of the lung for carbon monoxide was reduced (63% of predicted). Using an echocardiogram, we estimated the systolic pulmonary artery pressure to be 24 mmHg.

Two transbronchial biopsies showed that the pulmonary parenchyma were unaltered. The patient was then referred to biopsy through video-assisted thoracoscopy. The histological analysis revealed vascular alterations – principally in lymphatic vessels, which were found extremely dilated, especially in the region of pleura and septa – accompanied by intra-alveolar hemorrhagic foci. The histological profile suggested diffuse pulmonary lymphangiomatosis and, based on that, treatment with interferon-alpha 2a in a dose of three million units (sc) per day was initiated.

Case B

A 19-year-old female patient was admitted to the intensive care unit with acute respiratory failure and hemodynamic instability secondary to multiple episodes of hemoptysis. She had presented recurrent chylothorax and chylopericardium for five years and had been submitted to thoracic drainage and biopsies of pleura and pericardium with nonspecific results. She began to present recurrent episodes of hemoptysis and acute respiratory failure one year prior. At admission, the patient presented generally poor health status. She presented tachypnea, pallor, and depletion. Upon pulmonary auscultation, there were diffuse fine rales. Cardiac auscultation was normal. The abdomen was distended with signs suggestive of ascites. The patient presented edema of the lower limbs. Initial laboratory tests revealed normocytic normochromic anemia and hypoproteinemia, without coagulation alterations. The chest X-ray showed moderate bilateral pleural effusion and diffuse pulmonary infiltrate, thickening of the conjunctive septa, especially in the basal segments, in both lungs, without signs of abnormalities in the trachea and pre-segmenting bronchi. There was widening of the superior and medial mediastinum, suggesting pericardial effusion.

The HRCT scan of the chest revealed pronounced bilateral infiltration, especially in the lymphatic interstitium, with thickening of the conjunctive septa, bronchovascular cuffs and fissures, as well as bilateral pleural effusion (Figure 2).

A magnetic resonance imaging scan showed the following: bilateral diffuse pleural thickening; interstitial pulmonary lesion, with thickening of the peribronchovascular cuff, diffusely impairing the

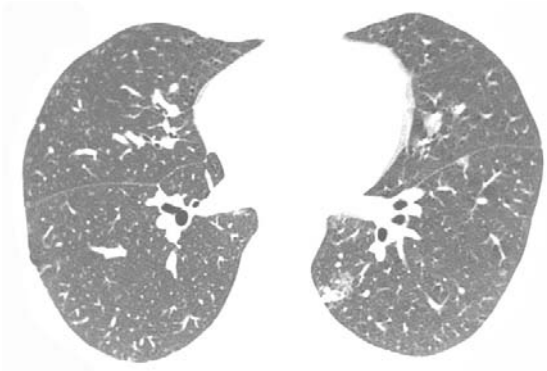

Figure 1 - High-resolution computed tomography slices obtained at the level of the inferior pulmonary veins and of the costophrenic spaces show small pulmonary nodules with random distribution and irregular subpleural opacity in the lower left lobe, surrounded by a ground-glass attenuation halo.

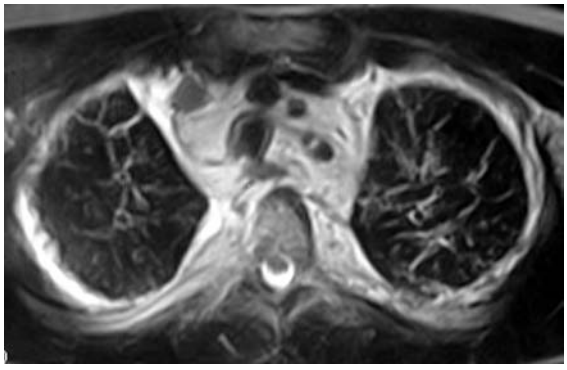

Figure 2 - Computed tomography slice at the level of the lower lobes showing diffuse thickening of the central lung interstitium, of the interlobular septa and of the subpleural interstitium. Some irregular and peripheral opacities, contiguous to the thickening of the central interstitium, can also be observed.

lungs; enlargement of pulmonary hila; and mediastinal obliteration (Figure 3).

Fiberoptic bronchoscopy revealed lymph drainage bilaterally through the bronchi. An echocardiogram showed slight pericardial effusion. An abdominal ultrasound presented a hepatic image suggesting generalized fibrosis, a renal image consistent with cortical edema, and moderate clotted ascites. Examination of the pleural fluid, whose aspect was chylous, revealed predominance of mononuclear cells and unspecific mesothelial hyperplasia.

The review of previous pulmonary biopsy slides showed pronounced diffuse fibromuscular thickening, involving lymphatic vessels throughout the submesothelial layer (fat and connective tissue) at the expense of the proliferation of elongated cells (fibroblasts and smooth muscular cells), which were arranged in bundles, leading to traction and ectasia of the lymphatic vessels. An immunohistochemical study showed positivity for the antigens desmin, muscle actin, smooth muscle actin and vimentin, whereas the patient tested negative for estrogen and progesterone receptors. This finding is consistent with pulmonary lymphangiomatosis.

The patient evolved to a worsening of the clinical profile and arterial blood gas pattern. On day 67 of hospitalization, interferon-alpha 2a was started at 4.5 million units sc per day. However, there was no clinical improvement. The patient died 18 days after the initiation of the interferon treatment.

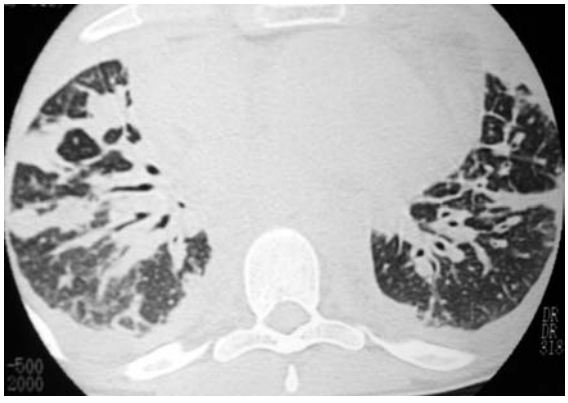

Figure 3 - Magnetic resonance imaging slice obtained at the axial plane over T2 shows thickening of the central and peripheral interstitium, principally subpleural. Note also the hyperintense tissue diffusely involving the mediastinal structures.

Discussion

Lymphangiomatosis is a rare disease of the lymphatic system and principally affects individuals under 20 years of age.[3,6] It typically manifests as a lung disease, although the bones, spleen, and liver can also be affected. By definition, diffuse lymphangiomatosis affects a variety of tissues, and the term diffuse pulmonary lymphangiomatosis is used when the alterations are restricted to the chest. Diffuse lymphangiomatosis is the most common form, since the bones are concomitantly affected in up to 75% of the cases.[1]

Its origin remains controversial. It is believed to be caused by abnormalities in the development of the lymphatic canals.[1,7] The proliferative aspect of the vessels might suggest neoplastic etiology and the structural disorganization, present in some samples, indicates hamartomatous origin.[6]

Some authors[1] divide the diseases of the thoracic lymphatic system, according to their clinical and pathological characteristics, into lymphangioma, lymphangiectasia, lymphatic dysplasia syndrome, and lymphangiomatosis. Lymphangiomas are characterized by focal benign proliferation of dilated lymphatic canals aligned by the endothelium and cysts of conjunctive tissue, forming a mediastinal mass. In lymphangiectasia, however, there is dilatation without proliferation of the lymphatic vessels. Lymphatic dysplasia syndrome presents as chronic pleuritis, fibrosis, and lymphatic dilatation. Lymphangiomatosis, therefore, differs from the other diseases in that it presents proliferation, complex anastomoses, and, secondarily, dilatation of the lymphatic vessels.[1,2,8,9] In the chest, the process develops along the lymphatic drainage ways, in the subpleural, paraseptal, perivascular, and peribronchial regions. The vessels might contain acellular, eosinophilic and proteinaceous material, surrounded by bundles of collagen fibers and smooth muscle cells. Immunohistochemical study reveals positivity for the antigens vimentin, actin, and desmin, as well as for the factor VIII-related antigen, with negativity for the estrogen receptor, as was observed in case B.[2,10] The adjacent pulmonary parenchyma is preserved, although macrophages with hemosiderin have been described and mediastinal fat might be diffusely infiltrated.[2,4,7]

In addition to lymphangioma and lymphangiectasia, other authors[2] indicate

hemangiomatosis, Kaposi's sarcoma, kaposiform hemangioendothelioma, and lymphangioleiomyomatosis as possible sources of diagnostic confusion in diffuse pulmonary lymphangiomatosis.

Patients with lymphangiomatosis, whether diffuse or restricted to the chest, generally present symptoms since childhood,[2] and those symptoms vary according to the organs affected, as in case A. Since such patients can present dyspnea and wheezing, they might be misdiagnosed as having bronchial asthma.[1,3,7] Some even respond to therapy with bronchodilators.[2] Chylous effusions are common. Chyloptysis, hemoptysis, chylopericardium, chylous ascites, protein-losing enteropathy, peripheral lymphedema, lymphopenia, and disseminated intravascular coagulation can also be part of the clinical profile.[1,4] The combination of lytic bone lesions and chylothorax favors a diagnosis of lymphangiomatosis.[3]

In individuals with lymphangiomatosis, the chest X-ray shows bilateral interstitial infiltrate, associated with pericardial or pleural effusions. According to the HRCT scan, there is thickening of the interlobular septa and of the bronchovascular cuffs, with infiltration of the mediastinal fat and of the perihilar region, most with areas of ground-glass attenuation, due to small alveolar hemorrhages.[7] Fiberoptic bronchoscopy is typically inconclusive but can reveal thin-walled vesicles, with opaque secretion upon compression, along the bronchial tree.[4] In the literature, we found only one report of such a pattern, which was also observed in our study, in case B. The lymphangiography shows the areas and the extent of the disease.[9] However, lymphangiography is now rarely performed due to its inherent risks. Spirometry findings are of a restricted, obstructive, or mixed pattern.[1,2,7] Case A, despite the fact that the pulmonary function tests showed no alterations, presented diffusion disorder. We found no reports of this type of presentation in the literature. The biopsy of the lesions, with histological and immunohistochemical study, allows a definite diagnosis.

The disease is progressive and the prognosis, in general, is poor.[1,6,9] The evolution tends to be slow, with recurrent chylous accumulation and mediastinal compression. The main cause of death is respiratory failure secondary to infections and accumulation of chylous fluid.[3,4,6]

The best treatment for lymphangiomatosis has yet to be defined. Thoracic surgery is useful in cases of the localized form of the disease.[3,7,9,11] In cases of disseminated intravascular coagulation and splenic involvement, splenectomy and embolization have been described.[8] Recurrent chylothorax can be treated with drainage and pleurodesis.[3] The use of radiotherapy, corticosteroids, somatostatin, tamoxifen, vincristine, interferon-alpha 2a, and interferon-alpha 2b has been reported.[3,5] Most of these treatments have proven to be only palliative.

In our patients, we opted for the daily use of interferon-alpha 2a sc. Lymphangiomatosis is probably a proliferative disease, and interferon is a cytosine that regulates cell growth and differentiation.[5] Interferon has proven effective in the treatment of childhood hemangioma,[12] and there are reports of therapeutic success with its use in lymphangiomatosis,[5,13] with improvement of clinical, spirometric, and radiological parameters. In the initial stages of lymphangiomatosis, interferon can prevent disease progression and improve the prognosis. In advanced phases of the disease, however, the results are less impressive.[5]

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