Young patient with generalized lymphangiomatosis: Differentiating the differential

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Abstract

We present the case of a 19-year-old man who was extensively evaluated in multiple centres for long-standing cough, dyspnea, and hemoptysis without a definitive diagnosis. His chest radiograph at presentation showed mediastinal widening, bilateral pleural effusions, and Kerley B lines. Computed tomography of the thorax showed a confluent, fluid-density mediastinal lesion enveloping the mediastinal viscera without any mass effect. There were bilateral pleural effusions, prominent peribronchovascular interstitial thickening, interlobular septal thickening and lobular areas of ground glass density with relative sparing of apices. There were a few dilated retroperitoneal lymphatics and well-defined lytic lesions in the bones. In this case report, we aim to systematically discuss the relevant differentials and arrive at a diagnosis. We also briefly discuss the treatment options and prognosis along with our patient’s course in the hospital and final outcome.

Key words: Cystic mediastinal mass; generalized lymphangiomatosis; pulmonary interstitial thickening; pulmonary lymphangiectasia

Introduction

Generalized lymphangiomatosis is an uncommon developmental disorder characterized by abnormal proliferation and dilatation of lymphatic channels involving multiple systems. Systemic manifestations include multiple low-density or cystic lesions within the neck, mediastinum and abdomen, pulmonary interstitial thickening, and lytic bone lesions. Poor knowledge of this condition among radiologists and clinicians often leads to a delayed diagnosis. In this case report, we discuss the radiological findings in a young man with generalized lymphangiomatosis and systematically arrive at the diagnosis.

Case History

A 19-year-old student presented with complaints of productive cough and progressive dyspnea for 18 months and hemoptysis for 6 months. He did not have palpitations, chest pain, or fever. He did not smoke and there was no history of tuberculosis or biomass exposure. He was extensively evaluated in multiple centres and was diagnosed with probable tuberculosis based on computed tomography (CT) findings of probable necrotic mediastinal lymphadenopathy and pericardial effusion. Histopathological examination of CT-guided and mediastinoscopy-guided nodal biopsies...
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and thoracoscopy-guided pericardial and lung biopsies done elsewhere were inconclusive. Bronchoscopy showed inflamed tracheobronchial mucosa. He was treated with empirical anti-tubercular therapy (ATT) for 6 months following which there was no clinical improvement. He required repeated pericardial drainages and, therefore, underwent pleuropericardial shunt insertion for recurrent hemorrhagic pericardial effusions. Because there was no clinical improvement, he presented to our institution for further evaluation. Chest radiograph showed mediastinal widening, bilateral pleural effusions (left more than right), prominent interstitial lung markings, and Kerley B lines [Figure 1]. CT thorax and abdomen with intravenous contrast showed confluent, sheet-like, hypodense mediastinal lesion (HU-28) encasing the mediastinal viscera without mass effect [Figure 2]. No discrete mediastinal lymph nodes could be visualized. There were moderate pericardial and bilateral pleural effusions. Extensive interlobular septal thickening, peribronchovascular interstitial thickening, and patchy, lobular areas of ground glass density were seen in both the lungs with relative sparing of the lung apices [Figure 3].

A few well-defined lytic lesions with prominent primary trabeculae were seen in the sternum [Figures 2 and 4] and a few vertebrae. Mottled lucencies with a coarse trabecular pattern were seen in a few vertebral bodies, a few ribs, and pelvic bones [Figure 4]. Minimal, ill-defined, hypodense soft tissue was also seen in the lesser omentum along with a few dilated retroperitoneal lymphatics [Figure 5]. Lab investigations revealed Iron deficiency anemia, normal total and differential white blood cell counts, negative sputum acid-fast bacilli, and negative XPERT polymerase chain reaction for Mycobacterium tuberculosis. Pleural fluid was hemorrhagic and analysis showed multiple red blood cells, lymphocytosis, elevated lactate dehydrogenase, elevated protein, and low glucose. Pleural fluid culture was negative. Combination of the lung findings (smooth interlobular septal thickening, peribronchovascular interstitial thickening, and lobular areas of ground glass density) and hypodense soft tissue lesion insinuating around the mediastinal viscera made us consider the following differentials: Pulmonary lymphoma, pulmonary veno-occlusive disease (PVOD), Erdheim Chester disease, lymphangiomatosis, and histiocytosis. The fluid-density nature of the mediastinal lesion, lack of infiltration and absence of mass effect on the mediastinal structures made lymphoma less likely. PVOD and Erdheim Chester disease could show similar lung findings, but the mediastinal lesion and the lack of CT findings of pulmonary arterial hypertension excluded PVOD. Erdheim Chester disease typically shows a rim of soft tissue around the kidneys, adrenal fossa, and aorta which were not seen in our patient. Although Langerhans cell histiocytosis (LCH) can also present with multiple lytic lesions in the bones, the lesions in LCH tend to be ill-defined, with adjacent bone marrow edema, periosteal reaction, and enhancing soft tissue[1]. Skeletal lesions in lymphangiomatosis are typically well-defined lytic lesions similar to our case. Finally, generalized lymphangiomatosis was thought to be the most likely diagnosis because of the multi-system involvement (mediastinal, pulmonary and bone involvement, retroperitoneal dilated lymphatics, and pericardial effusion), typical lung findings, and the low-density, nonenhancing nature of the mediastinal lesion. These imaging findings are summarized in Table 1.

Well-defined, lytic lesions with prominent primary trabeculae like in our patient could represent hemangiomas or lymphangiomas which cannot be differentiated on CT or

Figure 1: Chest radiograph showing mediastinal widening, bilateral pleural effusion (open arrows), prominent interstitial lung markings (oval), and Kerley B lines (curved arrows)

Figure 2 (A-C): Images of CT thorax in mediastinal window, axial (A, B) and coronal (C) images showing confluent, sheet-like, hypodense (HU-28) mediastinal lesion (straight solid arrows) encasing the mediastinal viscera without mass effect. Left pleural effusion (star) and pericardial effusion (curved arrow) are also evident on coronal image (C). A well-defined lytic lesion is seen in the sternum (open arrow) in image 2A.
MRI. However, in view of the nature of the systemic lesions, these were presumed to be lymphangiomas. Pleural fluid analysis for detection of chylomicrons was suggested based on the imaging diagnosis. It showed elevated pleural fluid triglyceride (225 mg/dl) and was positive for chylomicrons, confirming chylothorax. Review of the histopathology slides from the lung biopsies (thoracotomy and open lung biopsies done earlier) showed congested blood vessels with dilated lymphatic channels lined by endothelial cells, which were positive for D2-40 and CD31. The walls of the vascular channels focally contained spindle cells with elongated nuclei and eosinophilic cytoplasm. The spindle cells were positive for SMA and negative for HMB-45. These histopathological and immunohistochemistry findings were consistent with lymphangiomatosis. Our patient was initiated on medium chain fatty acid diet, even though the usefulness of the same has been disputed. A multidisciplinary team involving pulmonologists, radiation oncologists, medical oncologists, and radiologists met to discuss the treatment options. He was started on 5 mg propranolol which was gradually increased to 20 mg per day while monitoring the heart rate. He was symptomatically better with this treatment. He received 10 fractions of 20 Gy external beam radiotherapy to the thorax which he tolerated well. He was symptomatically better and was discharged from the hospital. Few days later, he presented to the Emergency Department with complaints of small volume hemoptysis, rapidly worsening breathlessness over a few hours, and two episodes of generalized tonic–clonic seizures. On admission, he was found to have metabolic acidosis and hypoxic respiratory failure, either of which could have caused the seizures. Although hypoxia improved with mechanical ventilation, he had worsening hemodynamic compromise requiring inotrope infusions. He had a cardiac arrest and could not be revived.

**Discussion**

Generalized lymphangiomatosis/diffuse lymphangiomatosis is a rare developmental disease involving the lymphatic system characterized by abnormal proliferation, dilatation, and thickening of lymphatic channels. It forms a part of the spectrum of lymphatic disorders and clinical presentation depends on the extent and site of involvement. It can involve any organ except the central nervous system. Imaging findings include pericardial effusion, low-density mediastinal and neck masses, which encase the large vessels and other viscera without compressing them. Pulmonary findings most commonly include smooth interstitial thickening and pleural effusions. Less commonly, centrilobular, small, ground glass-density nodules and patchy, lobular areas of ground glass density may be seen in the lungs. Skeletal involvement is seen in 75% of the cases and is characterized by lytic lesions involving multiple bones. Histologically, these lytic bone lesions represent lymph filled septated cysts. Abdominal findings include confluent, low-density lesions, motled appearance of splenic parenchyma, and cystic lesions within the spleen. Lymphangiomatosis can also extensively involve other abdominal viscera and retroperitoneum, as described by Cutillo et al. Mesenteric thickening may
be seen in a few cases.[10] Lymphangiomatosis is a distinct entity, separate from pulmonary lymphangiectasia which is thought to be due to the pathologic dilatation of pulmonary lymphatics either due to the failure of pulmonary interstitial connective tissues to regress (primary or congenital form) or secondary lymphangiectasia, which is due to a variety of processes that impair pulmonary lymph drainage or increase lymph production. On pathological examination, lymphangiomatosis shows proliferation of complex, anastomosing, endothelial-lined spaces with asymmetrically spaced bundles of spindle-shaped cells and collagen, surrounding the endothelial-lined channels.[11] On immunohistochemical staining, the endothelial cells in lymphangiomatosis are positive for D2-40, CD 31, and Factor VIII-related antigen.[12] In addition, the spindle cells in lymphangiomatosis stain positive for SMA and negative for HMB-45 while the spindle cells in lymphangioleiomyomatosis are positive for both SMA and HMB-45.[13,14] There is no specific treatment for diffuse lymphangiomatosis that is universally effective. Treatment is aimed at alleviating the patient’s symptoms. Recurrent pleural effusions may require pleural fluid drainage or pleurodesis. Palliative options that have been reported to be useful in the literature include radiotherapy,[15,16] medical therapy with interferon-alpha,[17,18] corticosteroids, and other chemotherapy drugs, which may be associated with systemic toxicity. More recently, propranolol has been used with promising results and without any significant systemic side effects.[19] Prognosis and outcome depend on the organs involved and the extent of disease.[20] Chylothorax associated with multiple bone lesions is reported to have a poor prognosis.[21,22] In summary, multi-system involvement with low-attenuation cystic lesions in the neck, thorax, and abdomen along with pulmonary interstitial thickening, chylothorax, and skeletal lesions in a young patient should raise the possibility of generalized lymphangiomatosis. Treatment is supportive and the prognosis is poor. Propranolol has recently shown promising results in a few patients.

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**Conflicts of interest**

There are no conflicts of interest.

**References**