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Case Report

Late diagnosis of generalized lymphangiomatosis in a woman presenting with respiratory distress [☆]

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ABSTRACT

Generalized lymphangiomatosis (GLA) is a rare lymphatic abnormality, mostly affects children and young individuals and can be a diagnostic challenge because of wide spectrum of clinical manifestations. A 26-year-old woman presented to the emergency department of our institution with respiratory distress and hypoxia. The patient reported similar episodes for the past 10 years without a definite diagnosis. The imaging study demonstrated findings suggestive of GLA with pulmonary, retroperitoneal and osseous involvements which was confirmed on pathological studies from a lung biopsy. A concise review of the clinical, imaging and pathological findings of GLA is provided in this study. A comprehensive history and physical examination, laboratory and pathological work up and imaging is required to make the diagnosis of GLA. The characteristic imaging findings play an essential role to rule out other possible diagnoses and raise the possibility of GLA.

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Introduction

Generalized lymphangiomatosis (GLA) is a rare lymphatic abnormality, mostly affects children and young individuals with an equal gender prevalence [1,2]. It can be a diagnostic challenge because of broad spectrum of manifestations and variety of organs involved [3]. The systemic manifes-

tations are wide and may include chylothorax, pleural and pericardial effusion, lung infiltration, mediastinal soft tissue and cystic masses, lytic bone lesions, abdominal organs and mesenteric involvement, disseminated intravascular coagulation and skin lesions, and cervical lymphadenopathy [2–7]. In this study a rare case of GLA is described with characteristic imaging and laboratory findings who was not diagnosed for about 10 years.

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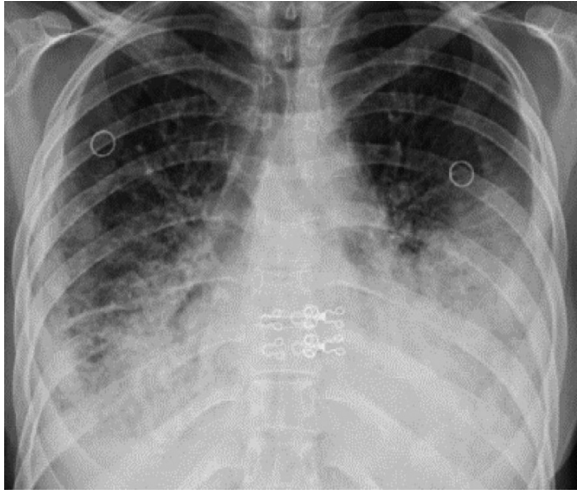


Fig. 1 – Chest radiograph shows mediastinal widening, patchy opacifications and increased reticular interstitial markings of both lung fields with Kerley B lines and pleural effusions.

Case report

A 26-year-old woman presented to the emergency department (ED) of our institution with respiratory distress and emergently intubated due to hypoxia. Patient had multiple similar episodes during the last 10 years including recurrent pleural effusions, shortness of breath, lower extremity edema, and proteinuria. On one of the prior similar ED admissions about 9 years ago, patient underwent chest tube placement and video assisted thoracoscopic surgery (VATS) for chylothorax which demonstrated multiple dilated lymphatic vessels in the pleural space. The lung biopsy was performed at that time and revealed multiple dilated lymphatic vessels lined by endothelial cells and spindle cells. The smooth muscle actin (SMA) marker was positive and the human melanoma black (HMB-45) marker was negative. The previous laboratory studies on pericardial and pleural effusion was negative for malignant cells and granulomatous inflammation. A complete blood count on the current admission showed leukemoid reaction with increased white blood cells with neutrophil predominance.

A chest radiograph (Fig. 1) was performed and demonstrated mediastinal widening, patchy opacifications and increased reticular interstitial markings of both lung fields with Kerley B lines. There was blunting of the both costophrenic angles, suggestive of pleural effusions. Computed tomography (CT) of the chest and abdomen and pelvis (Fig. 2) revealed confluent cystic mediastinal masses enveloping mediastinal structures without compression effect. Lungs parenchyma showed interlobular septal thickening, prominent peribronchovascular interstitium and multifocal ground glass opacities. Dilated lymphatic vessels were identified in the retroperitoneum. A chest tube was placed for pleural effusions and the laboratory study of the pleural fluid was consistent with chylothorax with elevated lactate dehydrogenase and triglyc-

eride and chylomicrons. The patient underwent a CT-guided biopsy of mediastinal lymph nodes which was in favor of reactive lymphadenopathy without evidence of malignancy. Multiple lucent lesions were present throughout the spine on CT which were confirmed on magnetic resonance imaging (Fig. 3). A Technetium-99 whole body bone scan (Fig. 4) demonstrated multiple foci of abnormal increased radiotracer uptake throughout the spine, ribs and pelvic girdles. An echocardiography was performed which was unremarkable. The characteristic imaging findings and laboratory tests were suggestive of GLA with a possible superimposed pulmonary infection.

The patient was started on wide spectrum antibiotic therapy with improvement of clinical and pulmonary radiological findings. At 6-month follow-up visit the patient was symptom free without a new complaint.

Discussion

Generalized lymphangiomatosis is a rare lymphatic developmental disorder which is thought to originate from a persistence of dilated lymphatic channels during embryonal growth [2,8,9]. Lymphangioma consists of a localized or diffuse proliferation of lymphatic vessels; the localized form are mostly multicystic and involves chest wall or mediastinum whereas diffuse type presents with thickened pulmonary interlobular septa, and pleural and pericardial effusions [10]. The exact pathophysiology of the GLA is not clearly defined and the vascular endothelial factor receptor 3 may play a role in the development of lymphangiomatosis [2,4,11,12].

Clinical and imaging presentations

Patients with GLA may be asymptomatic, or may present with respiratory symptoms like our patient. The pulmonary symptoms include shortness of breath, productive cough, hemoptysis, chest pain, wheezing and recurrent respiratory tract infection [5–8]. Pulmonary function test in patients with GLA may show restricted or mixed patterns [13]. The most common presenting lesions in patients with thoracic lymphangiomatosis are chylothorax and chylopericardium (49%), followed by a mediastinal mass (47%) and pulmonary infiltration (45%) [14]. The chest CT most commonly shows smooth interlobular septal thickening and pleural effusion, and less commonly centrilobular small ground glass nodules and patchy lobular areas of ground glass opacities [9,11,12,15]. Fluid may be accumulated in the lymphatic malformations and patients may present with well-defined mediastinal or retroperitoneal cystic lesions encasing adjacent structures without significant effect [9,12,15], or cervical lymphadenopathy [13,14]. Other less common manifestations include bone lesions, splenic lesions, disseminated intravascular coagulation, skin involvement [14], and mesenteric thickening [1]. Skeletal manifestations can be seen in 75% of patients with GLA and are characterized by lytic lesions involving multiple bones on radiographs and CT exams, which histologically represent lymph filled septate cysts [11,16]. The MRI may show abnormal bone marrow signal and multiple lesions with increased signal on

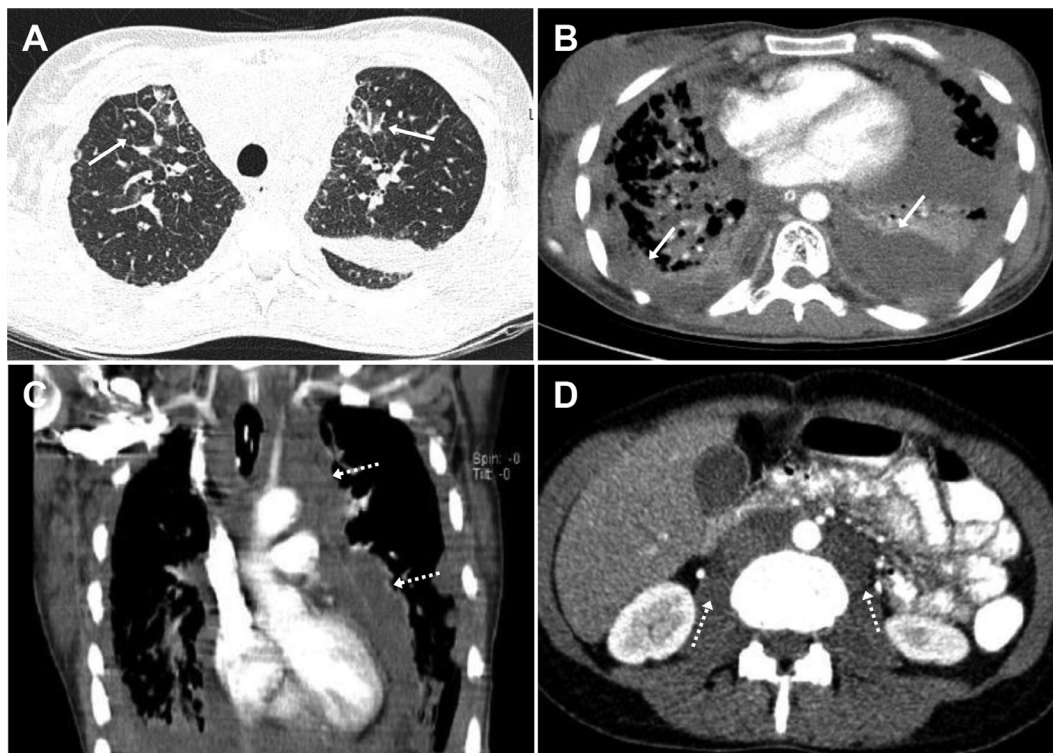


Fig. 2 – Axial postcontrast chest CT in lung (A) and soft tissue (B) windows demonstrate interlobular septal thickening, prominent peribronchovascular interstitium (A, arrows), and pleural effusions (B, arrows). Coronal postcontrast chest CT (C) show confluent cystic mediastinal masses enveloping mediastinal structures without compression effect (C, dotted arrows). Dilated lymphatic vessels are identified in the retroperitoneum on contrast enhanced axial abdominal CT (D, dotted arrows).

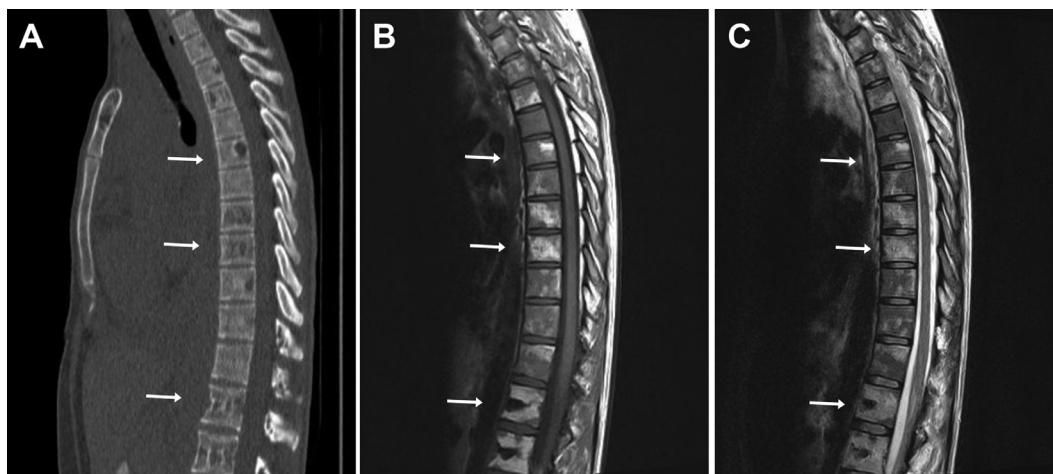


Fig. 3 – Sagittal thoracic spine CT (A) and T1-weighted (B) and T2-weighted (C) MR images show loss of bone marrow signal with multiple lucent lesions (examples with arrows) throughout the thoracic spine.

T1-weighted and on T2-weighted images, as seen in the patient in our study [9,14]. Bone scan with Tc-99 may show increased radiotracer uptake of the osteolytic areas mimicking the osseous metastasis [17]. Lymphangioscintigraphy by the use of radioactive materials demonstrate lymphatic system and it is used to show lymphatic pathology and the extent of the disease [15].

Diagnostic and laboratory tests

Patient with GLA usually present with nonspecific clinical symptoms which makes GLA a diagnostic challenge. Bronchoscopy usually demonstrates nonspecific findings such as airway mucosal edema and erythema, bronchial narrowing in progressive disease and thin walled vesicles containing

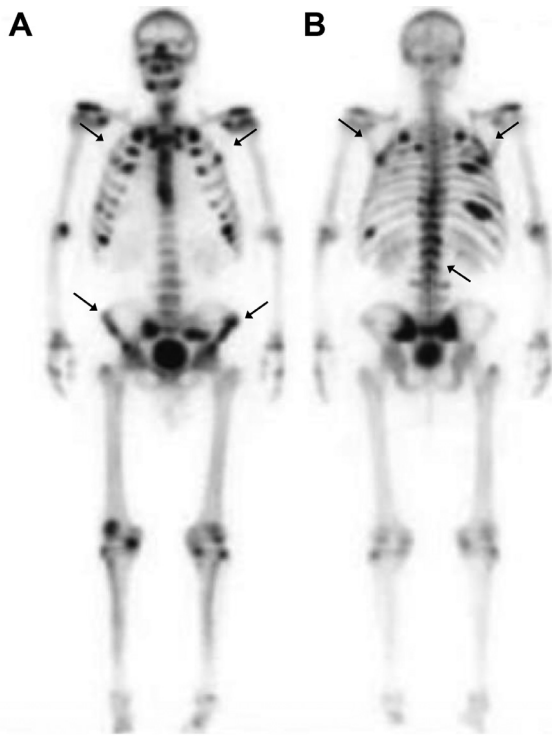


Fig. 4 – A Technetium-99 whole body bone scan on anterior (A) and posterior (B) views demonstrate multiple foci of abnormal increased radiotracer uptake throughout the spine, ribs and pelvic girdles (arrows).

chylous fluid [1]. Lung biopsy and biopsy of the mediastinal cystic lesions can be helpful to confirm the diagnosis, but it may be technically challenging and is associated with complications [1,2]. Trans-bronchial lung biopsy may reveal thick varicose septal veins and intra alveolar macrophages [18]. Microscopic examination on lymphangiomatosis demonstrated proliferation of complex anastomosing endothelial lined, lymphatic channels that causes dilated lymphatic pathway [14]. Immunological staining of endothelial cells in GLA is positive for D₂₋₄₀, CD₃₁, factor VIII-related antigen and SMA, but it is negative for HMB-45 which is characteristic for lymphangiomyomatosis (LAM) [2,3,12]. The lymph node biopsy usually show lymphoid hyperplasia which is difficult to separate from chronic nonspecific inflammation [19].

Differential diagnosis

Differential diagnoses for pulmonary findings of GLA may include pulmonary veno-occlusive disease (PVOD), Erdheim Chester disease, and lymphangiectasis [19-21]. PVOD may present with similar pulmonary involvement but the presence of mediastinal masses and absence of pulmonary hypertension in echocardiography favor GLA [20]. The Erdheim Chester disease is characterized by proliferation of lipid-containing foamy histiocytes in the skeleton and other organs; the absence of sclerotic changes in the diaphysis and metaphysis of long bones may exclude this diagnosis [22]. Pulmonary lym-

phangiectasis is a rare abnormality, defined as dilation of pulmonary lymphatics and can be congenital or secondary to pulmonary hypertension or venous occlusion. Histological analysis can distinguish the two diagnoses; lymphangiectasis is dilation of nonproliferative lymphatic vessels whereas lymphangiomatosis is characterized by an increased number of lymphatic vessels with variable size [2,12]. LAM usually presents with multiple cysts with possible chylothorax, pneumothorax and rarely hemoptysis in a premenopausal woman [2,3,5]. If in doubt, histological analysis may be helpful in differentiating LAM from GLA.

The mediastinal soft tissue masses may be suspicious for lymphoma; although cystic appearance of the lesions without displacement of adjacent structures and negative lymph node biopsy would favor GLA. The differential diagnoses for osseous lesions include Gorham-Stout disease and hemophagocytic lymphohistiocytosis (HLH). The osseous lesions in GLA are well defined and centered in the medullary space while Gorham-Stout disease may result in progressive osseous destruction known as "disappearing bone disease" and LHL lesions are usually ill-defined and associated with bone marrow edema, periosteal reaction and enhancing soft tissues [22].

Treatments and outcome

There is no definitive cure for GLA and all the treatments are mainly supportive and symptomatic. Recurrent pleural effusions may benefit from pleural fluid drainage or pleurodesis. Localized pleural lesion can be resected surgically [23]. Medical treatments with propranolol, corticosteroids, immunosuppressant and radiation therapy can decrease parenchymal involvement and effusions [1,23]. Bevacizumab has shown to decrease lymphatic channels proliferation and pleural fluid effusion [24]. Lung transplantation may considered as the last resort [2]. GLA in infancy or childhood can be fatal and is associated with congenital abnormalities, especially cardiac anomalies [16]. The primary cause of death in patients with GLA are respiratory failure, infection and accumulation of chylous fluid [5-7].

Conclusion

Generalized lymphangiomatosis is a rare disease with non-specific symptoms and may be a diagnostic challenge. A comprehensive history and physical examination, laboratory work up and imaging is required to make the diagnosis. The characteristic imaging findings play an essential role to rule out other possible diagnoses and raise the possibility of GLA.

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