Progressive Dyspnea With Recurrent Pneumothoraces

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CASE PRESENTATION: A 34-year-old previously healthy man of Korean descent (height, 174 cm; weight, 47.4 kg) demonstrated dyspnea with cough and chest tightness. The patient had no relevant occupational exposures and no history of illicit drug or tobacco use. His medical history was notable for chronic sinus tachycardia of undetermined cause, hypertension, gout, glaucoma of the right eye, and a remote history of an intracranial malignancy 24 years prior treated with unspecified chemotherapy, craniotomy, and ventriculoperitoneal shunt placement. His active medications included diltiazem, candesartan, and colchicine as needed. Because of decreasing exercise capacity, he was referred for evaluation with a treadmill stress test at that time and was found to have an arterial oxyhemoglobin saturation of 77% on room air. The patient was transferred urgently to the ED, where he was diagnosed with a pneumothorax and admitted to pulmonary medicine for high-flow oxygen therapy and serial chest radiography. He was not treated with chest tube placement at that time. The patient’s symptoms resolved and his arterial oxyhemoglobin saturation recovered to its baseline of ≥ 95% on room air. He was discharged from the hospital the day after admission.

The patient continued to deteriorate clinically in the community and subsequently was readmitted six times for recurrent pneumothoraces. Each time, he underwent pigtail catheter placement and serial radiography over the course of admissions averaging 3 to 5 days. The patient declined consultation with thoracic surgery for consideration of decortication on several occasions. One year and 11 months after the initial hospital admission, during the patient’s seventh hospital admission for recurrent pneumothorax, the pneumothorax failed to improve with pigtail catheter placement and he was transferred urgently to the thoracic surgery service for an uneventful right video-assisted thoracoscopic bullectomy, pleurectomy, and pleurodesis. He was believed to have aspirated during the perioperative period, resulting in significant hypoxia requiring reintubation and intensive care. On admission day 10, he was transitioned to venovenous extracorporeal membrane oxygenation support and was listed for lung transplantation. He continued to receive venovenous extracorporeal membrane oxygenation therapy for a total of 5 weeks until an appropriate set of donor lungs became available.

On admission day 42, the patient underwent bilateral orthotopic sequential lung transplantation. During

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surgery, severely fibrotic lungs were noted with extensive dense right pleural adhesions and a large left pleural effusion. His recovery from transplantation was uneventful, and he was discharged from the hospital on day 79.

A baseline outpatient chest radiograph (Fig 1C) ordered by the patient’s family physician showed bilateral fibrotic changes with retraction in both apices. No further investigations were pursued at that time, and the patient remained in the community until his first ED visit and hospital admission 1 year and 7 months later, at which time chest radiography showed progressive changes, including right-sided pneumothorax with upper-lobe predominant subpleural opacities, volume loss, and apical pleural thickening. During the same admission, high-resolution CT (HRCT) imaging of the chest confirmed right pneumothorax with traction bronchiectasis, dilation of the main pulmonary artery, multifocal perilymphatic nodules up to 2.3 cm in diameter, and bilateral upper lobe subpleural reticulations and cysts. Subsequent HRCT imaging of the chest showed bilateral hydropneumothoraces, upper-lobe predominant pleuroparenchymal thickening, upper-lobe predominant bilateral perilymphatic nodularity, patchy ground-glass attenuation in the left lower lobe, and bilateral lower lobe peribronchial nodules (Figs 1, 2).

On pathologic assessment, the right and left explanted lungs weighed 550 and 373 g, respectively. Gross examination of both lungs revealed similar changes, which included a variably roughened pleural surface with areas of adherent tan soft tissue and focal hemorrhage (Fig 2A). Thick fibrous regions dominated the upper and middle lobes, with involvement of the
oblique and horizontal fissures. Sectioning revealed rubbery, tan, fibrous areas distributed peripherally and along the fissures, contiguous with the previously described fibrous pleura. Encasement of the central airways and vessels was present. The most pronounced fibrosis was found in the apical and peripheral upper lobe and the inferior lower lobe. The central portion of the upper lobe contained cystic areas, 0.8 cm in maximum dimension, filled with serosanguineous fluid. No emphysematous changes, consolidation, or masses were identified in either lung.

Histopathologic examination showed extensive bilateral pleural fibrosis and subpleural parenchymal fibroelastosis (intra-alveolar fibrosis with septal elastosis) with entrapment of small dilated airways and vessels. In central regions of the involved lung, similar sharply demarcated fibroelastic changes were observed encasing bronchovascular bundles. These features were found in the upper and lower lung lobes bilaterally and confirmed with Masson’s trichrome and Verhoeff’s elastic stains (Figs 3, 4). Decreased staining intensity of fibroelastosis is seen in the left lower lobe, representing an earlier phase of disease involvement (Fig 4). Perl’s Prussian blue stains showed negative results for hemosiderin deposition. The visceral pleura also showed focal eosinophilic pleuritis, characterized by increased intravascular and extravasated eosinophils (Fig 4), consistent with a history of prior pneumothorax. In addition to these findings, both lungs showed hemorrhagic changes attributable to vv-ECMO.

Figure 2 – Correlation between CT imaging and pathologic examination. A, Gross surgical specimen of resected bilobed left lung showing dense pleural fibrosis, predominantly in the upper lobe with notable lower lobe involvement, extending subpleurally and along fissure lines to encase central airways and pulmonary vasculature. B, CT scan in lung window settings of the left lung demonstrating architectural distortion, upper lobe volume loss, traction bronchiectasis and bronchiolectasis, subpleural cysts, and subtle lower lobe ground-glass opacity. C, Coronal CT scan slice in lung window settings from the same study again demonstrating upper lobe fibrosis and volume loss (slice thickness, 1 mm; reconstruction algorithm, mediastinal [B40f] and lung [B60f]; contrast rate, 5 mL/s; timing of contrast, bolus tracking over main pulmonary artery; contrast volume, 75 mL; type of contrast, Omnipaque 350); GE Healthcare.
Figure 3 – Photomicrographs showing results from the right upper lobe of explanted lungs. A, D, G, Hematoxylin and eosin staining of peripheral right upper lung lobe sections showing dense pleural fibrosis (*), prominent subpleural (**) and parenchymal (***) fibroelastosis, and entrapment of small dilated airways and vessels (white arrows). B, C, E, F, H, I. Collagenous fibrosis is highlighted in dark blue with Masson trichrome stain (B, E, H), and elastin deposition is highlighted in dark black with Verhoeff-Van Gieson stain (C, F, I). Total magnification of images: ×25 (A, B, C); ×50 (D, E, F), and ×200 (G, H, I).
Figure 4 – Photomicrographs showing results from the left lower lobe of explanted lungs. A, Hematoxylin and eosin staining of the central left lower lung lobe section showing rigid demarcation between background uninvolved alveoli (*) and regions of parenchymal fibroelastosis (**), with fibroelastosis involving bronchovascular bundles (white arrows). B, C, E, F, Fibrosis is highlighted in dark blue with Masson Trichrome stain (B, E), and elastin deposition is highlighted in dark black with Verhoeff-Van Gieson stain (C, F). E, F, Higher magnification views of areas with less well-developed intra-alveolar fibroelastosis. D, Hematoxylin and eosin staining of peripheral left upper lobe lung section showing eosinophilic pleuritis with abundant eosinophils (black arrow in insert). Total magnification of images: ×25 (A, B, C), ×50 (D, inset at ×400), and ×200 (E, F).

What is the diagnosis?
Diagnosis: Idiopathic pleuroparenchymal fibroelastosis

Discussion

Clinical Discussion

Pleuroparenchymal fibroelastosis (PPFE) is a rare idiopathic interstitial pneumonia characterized by chronic, well-demarcated fibrosis and elastosis in a characteristic subpleural distribution. We report a case of idiopathic PPFE in a young man that illustrates the importance of recognizing this condition in its early stages and shows that changes may not be restricted to upper lobes or subpleural regions.

PPFE most frequently affects individuals between 40 and 70 years of age, although ages have ranged from 13 to 85 years. Several conditions have been associated with PPFE, including hematopoietic stem cell and lung transplantation, pulmonary infections, chemotherapy, autoimmune diseases, chronic hypersensitivity pneumonitis, and exposures to asbestos or aluminum. The characteristic clinical presentation of PPFE is progressive dyspnea associated with cough, weight loss, and pleuritic chest pain. The main differential diagnosis includes hypersensitivity pneumonitis, sarcoidosis, other fibrotic interstitial lung diseases, remodeling after lung injury, pneumoconioses, malignancy, and apical pleural cap after infection.

Radiologic Discussion

In 2012, Reddy et al proposed pathologic and HRCT scan criteria for the diagnosis of PPFE. In their schematic, histopathologic patterns compatible with PPFE are subdivided based on the presence or absence of certain features into three categories: definite PPFE, consistent with PPFE, and inconsistent with PPFE. From the imaging perspective, definite PPFE is characterized by pleural thickening with subpleural fibrosis predominantly in the upper lobes with less marked or no lower lobe involvement. When the characteristic pleural thickening and subpleural fibrosis is not concentrated in the upper lobes or features of coexistent disease are seen on HRCT imaging, the case is considered consistent with PPFE. Reddy et al also noted that in up to 25% of PPFE patients, usual interstitial pneumonia changes can be noted in the lower lobes.

Additional features on HRCT imaging suggestive of PPFE include architectural distortion, upper lobe volume loss, traction bronchiectasis or bronchiolectasis, coexistent usual interstitial pneumonia or nonspecific interstitial pneumonia, and rarely, subpleural cysts. PPFE typically is more progressive and more diffuse than apical fibrosis resulting from other causes. Honeycombing points to the alternative diagnosis of usual interstitial pneumonia and chronic hypersensitivity pneumonitis. It should be noted that assessment with CT scan may not be adequate for determining the degree of pleural involvement in PPFE.

Pathologic Discussion

The histopathologic hallmark of PPFE is dense collagenous and elastic tissue that fills alveolar spaces. This finding is referred to as intra-alveolar fibrosis and elastosis. The demonstration of intra-alveolar fibrosis and elastosis is a requirement for the histopathologic diagnosis of PPFE. An additional histopathologic finding of visceral pleural fibrosis strongly supports, but is not a requirement for, the diagnosis of PPFE. The subpleural fibroelastotic changes that characterize PPFE typically are concentrated in the upper lobes.

Despite the proposed criteria citing the absence of lower lobe involvement as characteristic of PPFE, we report a case of idiopathic PPFE in which prominent fibroelastotic change around more central airways and significant lower lobe involvement, notably in the left lung, were present. Histopathologic examination of these lower lobes and central changes confirmed that these changes were indistinguishable from the microscopic...
appearance of the upper lobe changes in this patient. Both upper and lower lobe involvement have been described in PPFE, as has more diffuse involvement with centrilobular involvement. Thus, recent literature and the present patient together illustrate how a unified primary process of idiopathic PPFE may extend outside of its classically described upper lobe distribution.

Conclusions

PPFE is a rare pulmonary interstitial pneumonia that can follow a rapidly progressive course leading to respiratory failure and death. Diagnostic criteria have been established, but currently no effective medical therapy for this condition is available. It is important to recognize PPFE at an early stage such that patients may be listed as candidates for lung transplantation with no unnecessary delay, particularly in young individuals.

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References