

Refractory pleural effusion as a rare complication of pulmonary vascular stenosis induced by fibrosing mediastinitis: a case report and literature review

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Abstract

Fibrosing mediastinitis (FM) is a progressive, life-threatening disease characterized by extrinsic compression of mediastinal bronchovascular structures, and the clinical manifestations largely depend upon the affected structures. Pleural effusion is rarely reported in patients with FM. We herein describe a 70-year-old man who presented with recurrent breathlessness and refractory left pleural effusion. He was misdiagnosed with and treated for tuberculous pleurisy for several months. Thoracentesis revealed a transudative pleural effusion, and a contrast-enhanced computed tomography scan of the thorax showed an extensive mediastinal soft tissue mass consistent with FM. Pulmonary angiography demonstrated pulmonary artery stenosis on the right side and pulmonary vein stenosis mainly on the left side. After measurement of the pulmonary arterial pressure by right heart catheterization, the patient was diagnosed with pulmonary hypertension associated with FM. He underwent balloon angioplasty and stent implantation of the stenosed pulmonary vessels, which led to long-term improvement in his breathlessness and pleural effusion. Our systematic review of the literature highlights that pleural effusion can be an uncommon complication of FM and requires careful etiological differentiation.

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Keywords

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Introduction

Fibrosing mediastinitis (FM) is a rare disease characterized by proliferation of fibrous tissue in the mediastinum that encases the mediastinal viscera, eventually presenting as a progressive and insidious disease with a variable natural history.^{1,2} The clinical manifestations and imaging characteristics of FM largely depend upon the affected mediastinal structures. Some patients with FM are asymptomatic, while others may have cough, chest pain, and dyspnea with severe compression of mediastinal bronchovascular structures.³ However, pleural effusion, especially unilateral refractory pleural effusion, is rarely reported in patients with FM.⁴⁻⁶ The purpose of this case report is to describe a patient with FM complicated by recurrent massive pleural effusion that was significantly relieved after percutaneous interventional therapy and to review previous studies involving pleural effusion in patients with FM.

Case report

A 70-year-old man with essential hypertension was referred to our hospital because of a 5-month history of persistent dyspnea on exertion due to recurrent left-sided pleural effusion. The patient had been diagnosed with drug-sensitive pulmonary tuberculosis 5 years previously and was successfully treated with anti-tubercular therapy for 6 months. Before referral to our hospital, the initial workup was negative for tuberculosis, but anti-tubercular therapy was

empirically re-initiated for 3 months because of suspicion of tuberculous pleurisy. The patient also underwent multiple thoracentesis procedures; however, the initial pleural fluid examination results were unavailable for review because the thoracentesis procedures were performed in another hospital. Because of the recurrent effusions, a left-sided tunneled intrapleural catheter was placed for palliation, leading to mild symptom improvement and intermittent removal of pleural fluid. On arrival to our hospital, the pleural catheter had been removed and the patient reported experiencing persistent dyspnea on exertion and coughing.

On examination, the patient was afebrile and tachypneic, had a normal blood pressure; had a regular heart rate and rhythm with a loud second pulmonary heart sound; and had an oxygen saturation of 90% on room air at rest. Jugular venous distension, peripheral edema, and cyanosis were present without clubbing. Auscultation revealed diminished breath sounds with dullness on percussion in the lower two-thirds of the left hemithorax. The serum C-reactive protein concentration, erythrocyte sedimentation rate, autoimmune antibody levels, immunoglobulin G4 concentration, carcinoembryonic antigen concentration, and interferon gamma release assay were all unremarkable. Thoracentesis revealed a clear yellow transudative pleural effusion (total protein fluid/plasma ratio, 0.33; lactate dehydrogenase fluid/plasma ratio, 0.48) with an

adenosine deaminase concentration of 10 U/L. The effusion contained 248/ μ L leukocytes and 3% neutrophils. Pleural fluid Gram staining, cytology, and microbiological culture were negative for bacterial organisms and malignancy.

A contrast-enhanced computed tomography scan of the thorax demonstrated bilateral pleural effusion mainly on the left side, an extensive soft tissue mass in the mediastinum, and severe stenosis of the right lower pulmonary artery consistent with FM (Figure 1). Echocardiography suggested dilated right heart chambers and right ventricular hypokinesis with a peak tricuspid regurgitation velocity of 3.64 m/s. The 6-minute walking distance was 308 m. Bronchoscopy revealed extensive mucosal carbon deposition, mucosal hyperemia and edema, and multiple bronchial slit-like stenoses. Further bronchoalveolar lavage, brushings, and biopsies were negative for malignancy, sarcoidosis, fungal organisms, and acid-fast bacilli. Pulmonary

angiography suggested that the openings of the right middle pulmonary artery and right lower pulmonary artery were severely narrowed, and the left upper pulmonary vein was not seen with contrast (Figure 2 (a)–(c)). The pulmonary arterial pressure (PAP) measured by right heart catheterization was 73/38 (53) mmHg. Therefore, the patient was diagnosed with pulmonary vein stenosis (PVS), pulmonary artery stenosis (PAS), and pulmonary hypertension associated with FM, which was considered to have been caused by previous tuberculosis.

The anti-tubercular therapy was discontinued because there was no evidence of tuberculosis activity or tuberculous pleurisy. The patient underwent balloon angioplasty of the right middle pulmonary artery and right lower pulmonary artery (Figure 2(d), (e)), leading to an increase in the PAP [from 73/38 (53) to 52/23 (34) mmHg] and 6-minute walking distance (from 308 to 415 m) and a decrease in the depth of left pleural effusion (from 8.4 to 2.7 cm). Stents were

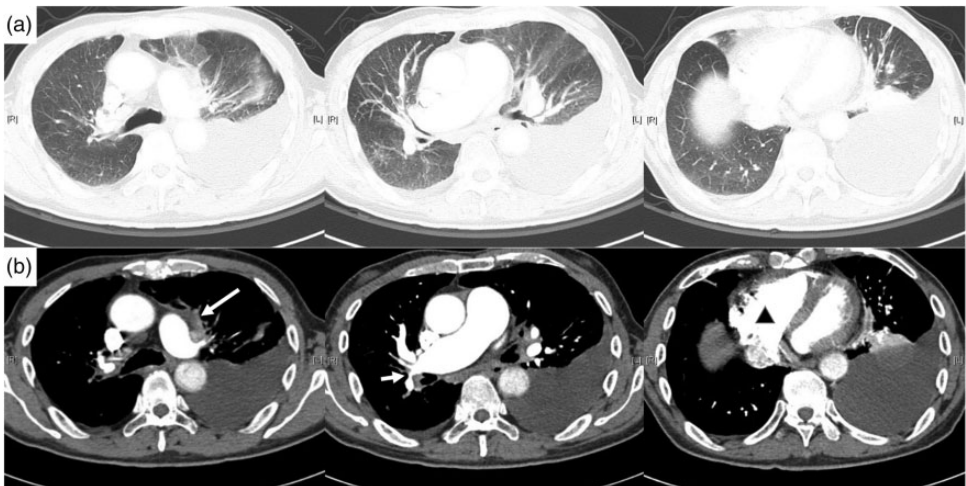


Figure 1. Contrast-enhanced computed tomography scans of the thorax at admission. **a** Axial lung window showed parenchymal and pleural signs of hydrostatic pulmonary edema, including central ground-glass attenuation, bilateral pleural effusion, and thickening of the interlobular septa. **b** Axial mediastinal window showed an extensive soft tissue mass in the mediastinum (white long arrow), severe stenosis of the right lower pulmonary artery (white short arrow), right heart enlargement (black arrowhead), and bilateral pleural effusion mainly on the left side with left lower lobe compressive atelectasis.

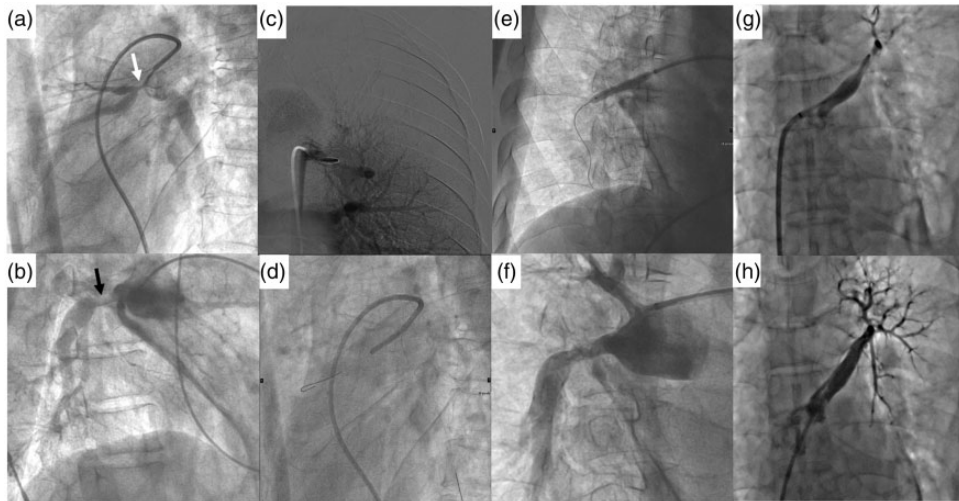


Figure 2. (a–f) Pulmonary angiography and (g, h) pulmonary venography. **a** The opening of the right middle pulmonary artery was severely narrowed (white arrow). **b** The opening of the right lower pulmonary artery was severely narrowed (black arrow). **c** The left upper pulmonary vein was not seen with contrast. **d** Use of balloon angioplasty (3-mm diameter) to dilate the right middle pulmonary artery. **e** Use of balloon angioplasty (6-mm diameter) to dilate the right lower pulmonary artery. **f** The stenosis of the right lower pulmonary artery was significantly relieved after stenting. **g** The left upper pulmonary vein exhibited localized severe stenosis. **h** The flow of the left upper pulmonary vein was restored after stenting.

then implanted into the right lower pulmonary artery (6.0/18 mm) (Figure 2(f)) and left upper pulmonary vein (9.0/29 mm) (Figure 2 (g), (h)), and the patient's breathlessness disappeared. One month following the procedure, the left pleural effusion was 1.1 cm in depth as shown by chest ultrasound. The patient underwent 8 months of anticoagulant therapy with rivaroxaban at 20 mg/day and aspirin at 100 mg/day. The therapy was then changed to rivaroxaban monotherapy at 20 mg/day. We followed up the patient through a telephone survey every year thereafter. At the time of this writing, he stated that he felt good and could go for a walk or shopping without obvious breathlessness.

Discussion

FM is a rare and benign but potentially life-threatening condition characterized by

proliferation of fibrous tissue in the mediastinum, causing extrinsic compression of mediastinal bronchovascular structures.⁷ The causes of FM have been attributed to a variety of etiologies, including tuberculosis,^{2,5} histoplasmosis,^{1–3,8} sarcoidosis,⁹ fungal infections,¹⁰ autoimmune diseases,^{10,11} drug exposure,¹² and mediastinal radiation therapy.⁴ An idiopathic form of FM with no known etiological factor has also been reported.¹³ In high-income countries, such as those in North America, the main causes of FM are histoplasmosis and sarcoidosis.^{7,8} In contrast, tuberculosis is a common etiology of FM in low- and middle-income countries, such as China.¹⁴ The etiology of FM in our patient was determined according to his history of tuberculosis and his epidemiological history.

The clinical manifestations of FM largely depend upon the affected structures of

the mediastinum.¹⁵ Because of the invasiveness of biopsy, confirmation of FM usually based on the imaging features of mediastinal soft tissue infiltration and compression on computed tomography and magnetic resonance imaging as well as a suggestive clinical context.¹⁶ Typical complications include tracheobronchial tree compression leading to obstructive pneumonia or atelectasis, and vascular compression resulting in superior vena cava syndrome, PVS, PAS, and pulmonary hypertension.^{16–18} However, to the best of our knowledge, only a few cases of pleural effusion as a complication of FM have been reported in the literature.^{4,6,19}

The initial assessment of patients with pleural effusion should include thoracentesis to categorize the effusion as a transudate or exudate and to obtain specimens for microbiology and cytology.^{20,21} In patients with FM, exudative pleural effusion may be caused by infections such as tuberculous pleurisy and parapneumonic effusion, malignant disease, autoimmune inflammatory diseases, pulmonary embolism, post-radiation therapy, and other miscellaneous factors.^{4,6,20,21} In contrast, a transudate may be associated with congestive heart failure, superior vena cava obstruction, PVS, or hypoalbuminemia.^{5,21} Morrone et al.⁴ reported a case of bilateral exudative pleural effusion due to mediastinal fibrosis induced by radiotherapy. Patterson et al.⁶ diagnosed an 18-year-old man with right exudative pleural effusion caused by focal FM secondary to histoplasmosis. Yangui et al.¹⁹ concluded that FM is an uncommon mechanism of pulmonary edema in patients with sarcoidosis after evaluating a 44-year-old woman with bilateral transudative pleural effusion due to PVS. Wu et al.⁵ recently published a case of a 74-year-old man who was diagnosed with post-tuberculous FM resulting in pulmonary hypertension and left transudative hydrothorax; he was treated with prednisolone and

mycophenolate mofetil. Our patient had a transudative pleural effusion predominantly on the left, without evidence of superior vena cava obstruction or hypoalbuminemia. Thus, we considered that the cause of the pleural effusion in this patient might have been a dual effect of increased hydrostatic pressure secondary to PVS and cardiac insufficiency secondary to pulmonary hypertension.^{21–23} Therefore, pleural effusion can be bilateral or unilateral in patients with FM, and it may be either a transudate or exudate according to the cause of FM and the location of mediastinal tissue compression. Furthermore, based on these pathophysiological features, pleural effusion as an unnoticed complication in patients with FM requires pathogenetic exploration and careful identification.^{16,24}

The optimal therapeutic approach to FM remains controversial, varying from observation or systemic treatment of the primary disease to surgical or endovascular treatment.²⁵ Isolated case reports indicate that some patients with FM may benefit from anti-inflammatory, anti-fungal, or anti-fibrotic drugs. However, these observations have not been confirmed in larger series of cases.²⁶ Off-label use of therapy specific for pulmonary arterial hypertension must be carefully evaluated in patients with FM-associated pulmonary hypertension because involvement of the pulmonary veins and parenchyma may result in drug-induced pulmonary edema and deterioration of arterial oxygen saturation.²⁵ Patients with significant hemoptysis or with bilateral involvement may be candidates for surgical and nonsurgical therapeutic interventions, which are safe and provide symptomatic relief but with short-lived beneficial effects.²⁵

In recent years, percutaneous endovascular stenting has been reported for the treatment of FM-induced PVS, PAS, and superior vena cava syndrome.^{27–29} Although such treatment has emerged as a

promising therapeutic modality, the relevant evidence is restricted to case series and retrospective studies with small samples sizes.^{29–33} The success of hemodynamic and angiographic improvement is temporary, and the long-term prognosis is inconsistent.^{32,33} Restenosis appears to be the most common complication related to interventional treatment of FM-induced PVS and PAS, followed by hemoptysis.^{26,34}

A recent systematic review showed that pulmonary vascular compression in patients with FM can cause pulmonary hypertension and refractory pleural effusion, but no detailed information was provided regarding the use of interventional therapy to relieve pleural effusion resulting from pulmonary vascular stenosis.³⁴ In our patient, the affected pulmonary vasculature was characterized by left-sided PVS and right-sided PAS. Dilation of the right pulmonary arteries can directly decrease PAP and redistribute the blood flow from the left to the right, thus decreasing the hydrostatic pressure of the left hemithorax. The left upper pulmonary vein subsequently expands to further decrease the hydrostatic pressure and reduce the pleural effusion, further verifying the relationship between pleural effusion and FM-induced pulmonary vascular stenosis. Our patient was asymptomatic for more than 2 years following the procedure. His prognosis seemed to be better than that described in most previously published cases using stents to treat FM-induced pulmonary vascular stenosis, which may be attributed to our patient's continuous anticoagulant therapy.^{32,34} Because of the variety of causes of pleural effusion and the complexity of its hemodynamic features, the specific steps of interventional procedures should be further clarified.

This report emphasizes that pleural effusion may not be so rare in patients with FM and that its etiology should be carefully identified. Percutaneous endovascular

interventional therapy may help to alleviate refractory pleural effusion in patients with FM-induced pulmonary vascular stenosis, but the specific procedure needs to be further explored.

Consent to participate and ethics approval

The patient provided written informed consent for the use of his imaging data and publication of this case. The study protocol was approved by the ethics committee of Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, Beijing, China.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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