CASE REPORT

Fibrosing mediastinitis: a rare complication of histoplasmosis

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SUMMARY

We report a case of a 29-year-old man who presented with intermittent haemoptysis for about 18 months. Previously, his symptoms had been diagnosed as musculoskeletal pain and later as pneumonia. CT found a venous infarct in the right lung in addition to extensive lymphadenopathy in the mediastinum and pulmonary hila, with associated calcifications almost completely occluding the superior vena cava and azygos vein. Further questioning revealed that the patient had once worked on an organic farm in Colorado. Subsequent work up was positive for histoplasmosis yeast antibodies. The patient was diagnosed with fibrosing mediastinitis (FM) and started on itraconazole for 3 months. We note that FM is a rare complication of histoplasmosis and can present as chronic haemoptysis. Travel history is an important aspect of the clinical evaluation. Antifungal agents have shown some efficacy in treating histoplasmosis-related FM.

BACKGROUND

Fibrosing mediastinitis (FM), also called sclerosing mediastinitis, or collagenosis, is a rare but serious idiosyncratic infiltration of mediastinal fat by dense fibrous tissue.^{1–2} To date, FM lacks universally accepted diagnostic criteria, and the worldwide literature on it consists of 180 cases described before 1969 and, thereafter, a number of single case reports, small case series and case reviews.^{3–6} Focal granulomatous and diffuse non-granulomatous forms of FM have been described, although work up for both is identical.^{1–7} Granulomatous FM is more frequently reported in North America, where it is most commonly associated with infection by *Histoplasma capsulatum*.^{6–8–9} FM is incidentally diagnosed in about 40% of cases but, when symptomatic, it can mimic malignancy and cause pulmonary and/or vascular compromise, including superior vena cava (SVC) syndrome.^{1–2} Prognosis is usually good as most FM cases do not progress.⁴ However, in a minority of cases, death occurs when FM causes recurrent postobstructive pneumonia, pulmonary heart disease and/or massive haemoptysis.⁶

CASE PRESENTATION

A 29-year-old non-smoking man from Missouri, with no significant medical history, presented to the emergency department (ED) with chronic intermittent haemoptysis that had worsened in volume and frequency over the past 5 days. The patient was a disaster relief fieldworker and in the past 5 years had visited Mexico, Panama and Spain. He also

reported diving in underwater caves in Missouri and collecting chicken eggs as a worker on an organic farm in Colorado. The haemoptysis started around the time he moved to New York, 18 months earlier, to take a desk job. Initially, it consisted of flecks of blood in sputum, occurred only in the morning, and was accompanied by right-sided chest pain worsened by deep inspiration. The patient had visited an urgent care clinic around this time, obtained a normal ECG, and was told that he had musculoskeletal pain.

In the past year, the patient unintentionally lost 10–15 lbs and occasionally experienced night sweats and fever. He also had ‘head rushes’ with strenuous exercise and recalled that his face had once turned ‘beet red’ while picking up a child. He denied dyspnoea, fatigue or changes in exercise tolerance. About 8 months prior to presentation, he had visited another urgent care clinic and was told that he had atypical pneumonia. He was prescribed a course of antibiotics without radiological follow-up. His symptoms did not resolve. When his haemoptysis worsened 5 days before admission, the patient presented to his primary care physician, who performed a chest X-ray, found an abnormality and directed him to go to the ED for further work up.

On physical examination, the patient was a young, well-appearing and well-developed man. He was afebrile with stable vital signs. Crackles were present at the right lung base.

INVESTIGATIONS

CT of the chest and abdomen were performed to evaluate the patient’s pulmonary problems. It found extensive abnormal adenopathy, soft tissue and associated calcifications, in the mediastinum and both hila, with resultant near-occlusion of the SVC and azygos vein (figures 1 and 2). Numerous collateral vessels were visualised. Pulmonary vein occlusion leading to a venous infarct in the right lobe was also noted. The spleen had many calcified nodules. These findings were concerning for a granulomatous process, malignancy and/or FM.¹⁰

Given a concern for tuberculosis, interferon γ release assay (QuantiFERON-TB Gold) and serial-induced sputum samples with acid-fast bacillus (AFB) staining were also performed, and determined to be negative. Flow cytometry found no evidence of lymphoma.

Complement fixation (CF) testing for histoplasmosis antibodies proved positive for yeast but negative for mycelia. This supported a clinical diagnosis of FM secondary to histoplasmosis.¹¹ Tissue biopsy

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Figure 1 CT of the chest with contrast, axial view. Red arrow indicates nearly occluded superior vena cava. Blue arrows indicate mediastinal calcifications.

was deferred due to the high risk of complications in patients with pulmonary hypertension and pulmonary haemorrhage.

DIFFERENTIAL DIAGNOSIS

Intermittent haemoptysis carries a broad differential that includes infectious, inflammatory and malignant aetiologies. For this patient, an infectious aetiology was most likely, given his personal history of frequent travel and outdoor exposures. From this standpoint, the bilateral hilar adenopathy and the numerous calcified mediastinal and hilar nodules seen on CT imaging were consistent with histoplasmosis and confirmed by the presence of yeast antibodies on CF testing.

Nevertheless, the patient's cough, night sweats, unintentional weight loss and nearly occluded SVC, in the setting of a mediastinal mass, merited investigation for possible comorbid lymphoma and/or tuberculosis.¹² His white cell count (WCC) and differential were within normal limits, and flow cytometry found no evidence of lymphoma. Likewise, he had negative QuantiFERON-TB Gold and serial-induced sputum AFB stains.

Radiographic findings of bilateral hilar lymphadenopathy with calcified lymph nodes can be concerning for sarcoidosis, but it was less likely for this patient as he lacked systemic symptoms of sarcoidosis such as arthralgia and erythema nodosum. He also had normal serum ACE and vitamin D levels.

Figure 2 CT of the chest with contrast, coronal view. Red arrow indicates extensive fibrosis around a nearly occluded superior vena cava. Blue arrow indicates similar fibrosis around a partially occluded azygos vein.

Lastly, mediastinal granuloma is another complication of histoplasmosis that, similar to FM, can present with a mediastinal mass. However, mediastinal granuloma is characterised by caseation necrosis of multiple massively enlarged lymph nodes, which this patient lacked.¹¹ Diagnosis of FM was therefore made from the clinical and radiographic findings.

TREATMENT

FM presently lacks standardised treatment regimens.¹¹ Cases may be managed by medication or surgery, with the latter usually reserved for patients with severe compression syndromes, or used to establish diagnosis when malignancy is the initial leading diagnosis.^{2 8} A limited number of case reports and case series have investigated the role of antifungal, antifibrotic and anti-inflammatory medications in treating FM.⁴ Itraconazole, the current drug of choice for treating mild to moderate histoplasmosis, has demonstrated extensive anecdotal efficacy in symptomatic improvement for patients with FM.^{6 8 13} Therefore, our patient was started on 200 mg of itraconazole two times a day for 3 months.

DISCUSSION

FM is the most serious late complication of histoplasmosis infection. Although rare, it is the most common non-malignant cause of mediastinal compression syndromes.¹⁴ Infiltrative proliferation of fibrous tissue compromises mediastinal structures, most commonly the SVC, pulmonary hilar vessels and major airways.^{1 2} Case reports of cardiac and oesophageal involvement also exist in the literature.^{10 15 16}

In our patient, near occlusion of the SVC occurred. This would explain his reported occasional 'head rushes' with exercise and manoeuvres that increase intrathoracic pressure. In addition, the patient had complete occlusion of his anterior pulmonary vein, contributing to a venous infarction of his right lower lobe and providing the most likely aetiology of his haemoptysis. This process developed over an extended period of time, and the patient was able to develop the significant collateral circulation seen on imaging. His young age and general good health further minimised his symptomatic burden.

Owing to significant vascular compromise in our patient, further progression of his FM may necessitate surgical management. Urgent thoracotomy is indicated in cases of massive haemoptysis (>300 mL) in order to control haemorrhage of lung parenchyma.¹ Less severe haemorrhage may be treated with endobronchial laser coagulation or transcatheter embolisation.⁶ Resection of fibrous tissues, however, is considered a last resort given the high risk of haemorrhage, damage to involved mediastinal structures and intraoperative mortality.² Balloon angioplasty and stenting can improve symptoms of SVC syndrome and pulmonary vessel stenosis.^{2 12} In the case of pulmonary vein or artery obstruction, stenting has been performed with improved post-operative exercise tolerance up to 4.5 years.¹⁷

Our patient may benefit from a stenting procedure if his symptoms worsen despite antifungal therapy. Reconstruction of the SVC with prosthetic grafts, utilised for patients with poor vascular collateralisation, may eventually be justified for our patient if there is subsequent infiltration of existing collateral vessels.² Pulmonary venous involvement is usually not amenable to vascular reconstruction, and, in such cases, pneumonectomy becomes the remaining option.

The exact mechanism of FM is not well understood, but it is thought to involve an immune-mediated delayed hypersensitivity reaction to histoplasmosis antigen.^{10 11 13} Rupturing of caseous granulomas in the regional mediastinal lymph nodes

after acute infection has also been postulated as a source of prolonged inflammation.¹² FM shares histopathological overlap with IgG4-related disease (IgG4-RD), mediastinal granuloma, retroperitoneal fibrosis and others.^{5 18}

CD20-positive B lymphocytes may mediate the development of FM as they have demonstrated accumulation in tissue samples and corresponding circulatory depletion in patients with FM.⁴ Antineutrophil cytoplasmic antibody positivity may be found in patients with FM, although, to date, only a single case report in the literature has noted this finding.¹⁹ Class II human leucocyte antigen, specifically DQB1*04:02, has also been associated with FM in a recent case-control cohort study.⁶

While these findings appear supportive of an immune-mediated hypersensitivity model for FM, the majority of patients with FM respond suboptimally to immunosuppressive, antimicrobial and antifibrotic therapies.¹⁸ The rarity and idiosyncratic natural history of FM complicate investigations of potential therapies, and modifiable patient factors such as smoking may affect disease progression.⁵ Success with rituximab has recently been reported in three cases of FM.²⁰ However, as in other attempted pharmacological interventions including non-steroidal anti-inflammatory drugs (NSAIDs), prednisone, tamoxifen, amphotericin B and azoles, these findings have yet to be substantiated by larger, more rigorous studies.^{4 5 13}

Because FM is rare but potentially fatal, our case highlights three important aspects of clinical practice. First, good clinical history should include a patient's recent travels and exposures, and these findings should be incorporated into a broad and thorough differential diagnosis. Our patient's differential included histoplasmosis because we discovered his history of exposure to caves and poultry in areas of the USA known to be endemic for *Histoplasma capsulatum*.^{8 9} His international travel history was also examined, but histoplasmosis remained the most likely infectious aetiology for his haemoptysis, fever and night sweats.²¹

Second, radiological findings should be pursued in outpatients with high clinical suspicion. Our patient presented to two urgent care centres over an 8-month period, reporting thoracic pain and haemoptysis. A chest X-ray would have revealed mediastinal abnormalities and prompted further evaluation earlier in his disease course. Although treatment options for FM have mixed results, earlier diagnosis might have delayed or spared

our patient from acquiring a pulmonary venous infarct and extensive vascular compression.

Lastly, young patients presenting with chronic symptoms as severe as haemoptysis should be approached with an elevated level of suspicion. Often, young patients are able to compensate and appear well despite extensive disease, while their subsequent decompensation may be rapid and catastrophic. The chronicity of symptoms often serves as a clue into the underlying disease process and, for a patient with inconclusive prior work ups, may indicate an uncommon aetiology.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Fibrosing mediastinitis is a rare complication of histoplasmosis infection and can present as chronic haemoptysis.
- Travel and exposure history is an important aspect of a patient's clinical history and should be incorporated into a thorough differential diagnosis.
- Well-appearing young patients with chronic haemoptysis should be approached with an elevated level of clinical suspicion for uncommon aetiologies.

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