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CASE REPORT

CLINICAL CASE

Fibrosing Mediastinitis Caused by Histoplasmosis in an Adolescent

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ABSTRACT

Fibrosing mediastinitis (FM) is a rare, potentially progressive disease resulting from an idiosyncratic immune response to a variety of stimuli that lead to fibrous infiltration of the mediastinum and possible narrowing of the bronchovascular structures. We report an unusual case of FM in a pediatric patient presenting as myopericarditis and progressing to pericardial thickening and encasement of the mediastinal vascular structures needing surgical intervention. Imaging, including transthoracic echocardiography, cardiac computed tomography, and cardiac magnetic resonance played a crucial role in the diagnosis, assessment, and follow-up. Contrast-enhanced computed tomography can be especially helpful to demonstrate potential findings associated with FM. (J Am Coll Cardiol Case Rep 2024;29:102161)

HISTORY OF PRESENTATION

A 16-year-old African-American male presented with a 1-week history of chest pain.

LEARNING OBJECTIVES

- To highlight the importance of fibrosing mediastinitis as a rare etiology for mediastinal vascular compression.
- To understand the implication of multimodality imaging in the diagnosis and treatment of fibrosing mediastinitis.

PAST MEDICAL HISTORY

His past medical history was significant for acute pericarditis progressing to pericardial tamponade requiring drainage 1.5 years prior. At the 3-month follow-up after his initial presentation, he was asymptomatic, but transthoracic echocardiography revealed a new finding of mild right pulmonary artery narrowing. He was subsequently lost to follow-up until his current presentation.

DIFFERENTIAL DIAGNOSIS

Recurrent pericarditis secondary to infectious and noninfectious causes such as tuberculosis and lupus were high on the differential diagnoses.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

FM = fibrosing mediastinitis

INVESTIGATIONS

Imaging including transthoracic echocardiography and contrast-enhanced cardiac computed tomography (CT) revealed a confluent heterogeneous masslike soft tissue thickening centered predominantly in the superior mediastinum but occupying the pericardial space with encasement and compression of the main and right pulmonary arteries, right pulmonary veins, and superior vena cava. There was an hourglass deformity of the main pulmonary artery with at least moderate supravalvular pulmonary stenosis (Figure 1). Cardiac magnetic resonance to characterize the mass confirmed the CT findings, with T1-weighted and T2-weighted cardiac magnetic resonance suggesting inflammation and fibrosis of the visceral pericardium (Figure 2). His symptoms improved with nonsteroidal anti-inflammatory medications. Further work-up was significant for elevated histoplasma antibody levels (complement fixation titers: mycelial 1:8 and yeast 1:128). Urine histoplasma antigen was negative. There was no evidence of another infectious, autoimmune, or malignant process. Based on the serologic and imaging findings, a diagnosis of fibrosing mediastinitis (FM) secondary to histoplasmosis infection with compression of the mediastinal vascular structures was made.

MANAGEMENT

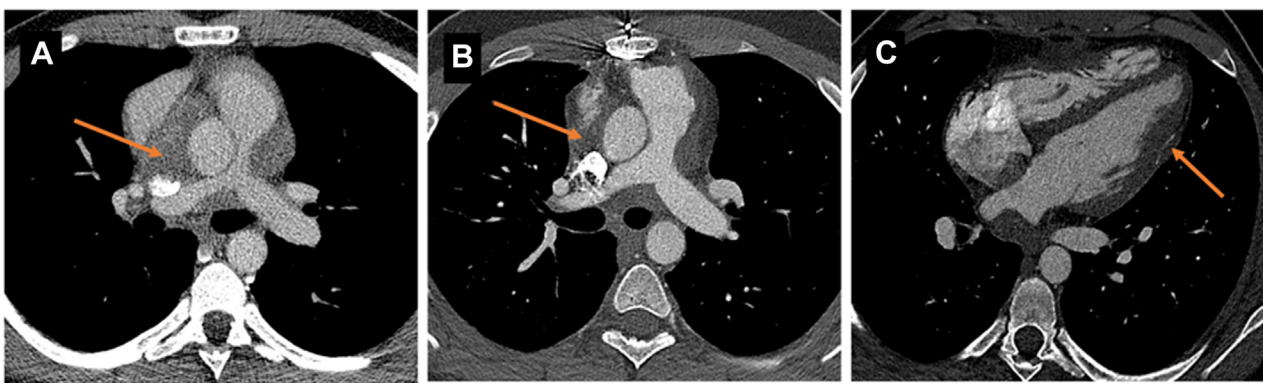
After extensive discussions with the family, he underwent surgery. The mass was tightly adherent to the vascular structures on inspection. An incision was made to open the pericardial mass, allowing partial removal and improvement of the compression. Microbiological cultures of the surgical specimen, including for fungal growth, were negative. Pathological findings of necrotizing granulomas were consistent with FM (Figure 3). He was treated with approximately 3 months of oral itraconazole therapy with adequate drug levels demonstrated during this time.

DISCUSSION

FM is a rare fibroinflammatory disorder characterized by dense mediastinal fibrous tissue proliferation and infiltration.[1] Although the exact etiology of the exaggerated inflammatory response has been elusive, in North America, *Histoplasma* infection is believed to be the most common triggering factor.[2-4] Parasitic infections (eg, *Wuchereria bancrofti*), mycobacterial infections, noninfectious etiologies such as sarcoidosis, systemic lupus erythematosus malignancies such as Hodgkin lymphoma, and mediastinal radiation or some medications such as methysergide can all present with an FM-like picture.[5-7] Pathology of tissue reveals an abundance of fibrous tissue with a patchy mononuclear cell infiltrate.[3] In rare cases, there may be infiltration of the heart and pericardium.[8]

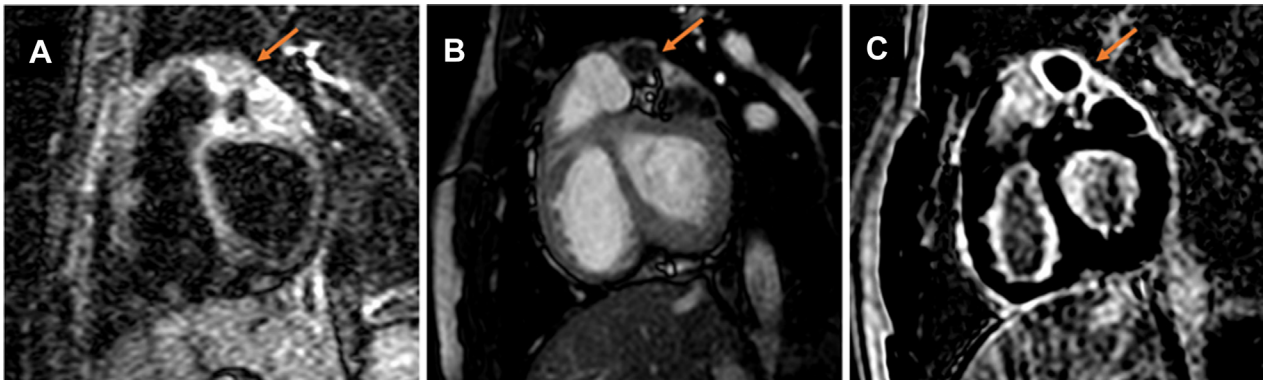
Most patients remain asymptomatic, and diagnosis is usually made incidentally on cross-sectional radiography. However, some patients develop significant compression of mediastinal structures such as the tracheobronchial tree, esophagus, systemic and

FIGURE 1 CT Scan Images



(A) A preoperative contrast-enhanced chest computed tomography (CT) image showing a pericardial mass and hourglass narrowing of the main pulmonary artery and a narrowed superior vena cava (SVC). (B) A postoperative electrocardiography-gated contrast-enhanced cardiac CT showing an improved but persisting pericardial mass and narrowing of the main pulmonary artery. There is also a marked decrease in soft tissue thickening to the right of the aorta and a decreased mass effect over the SVC (arrow). (C) A postoperative gated cardiac CT angiogram demonstrating pericardial thickening with minor calcification along the lateral left ventricular wall (arrow).

FIGURE 2 Cardiac Magnetic Resonance (Preoperative) Images



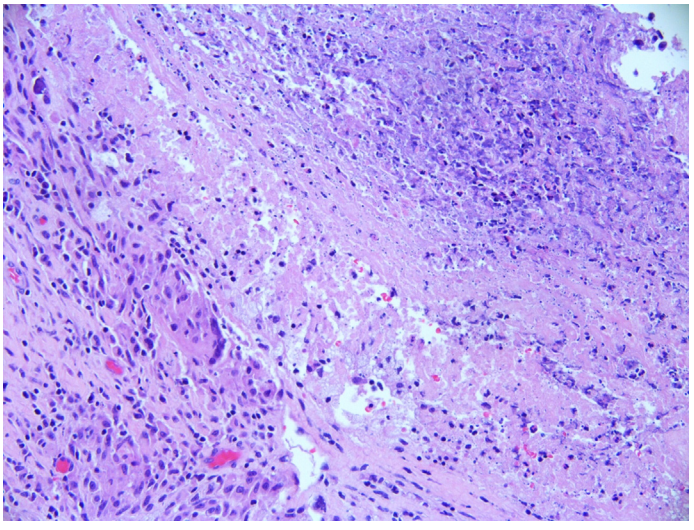
(A) T2-weighted short tau inversion recovery image in the basal ventricular short-axis view showing an increased signal from the pericardial mass in the superior mediastinum (arrow). (B) A still image from a steady-state free precession cine sequence in the basal ventricular short-axis view showing hypointense pericardial mass in the superior mediastinum (arrow). (C) A late gadolinium enhancement image showing the nonenhancing pericardial mass with a brightly enhancing visceral pericardium in the superior mediastinum (arrow).

pulmonary veins, or the great arteries.[9,10] The most common symptoms are dyspnea, chest pain, cough, hemoptysis, and recurrent postobstructive pneumonia.[2,10,11] Cardiac findings may include those resulting from superior vena cava stenosis such as facial swelling, prominent neck veins, and headache as well as bradycardia from heart block and chest pain from pericarditis.[12-14]

The diagnosis is suggested by the demonstration of a mediastinal mass and its effects on mediastinal structures. Chest x-ray findings are usually nonspecific and may include widening of the mediastinum and calcification of the lymph nodes.[3] Transthoracic echocardiography is useful to assess for hemodynamic effects of vascular obstruction and to monitor the progression or resolution with treatment. However, echocardiograms may be inadequate in visualizing the extracardiac structures.

Contrast-enhanced CT is considered the imaging modality of choice for diagnosing FM. It can delineate the extent and severity of disease including the presence and severity of vascular and/or airway stenosis. Calcification and heterogeneous enhancement of the infiltrative soft tissue may be demonstrated.[15] The presence of calcification and enlarged lymph nodes is very common and helpful in the diagnosis. Lung changes resulting from airway narrowing as well as sequelae of prior histoplasmosis infection such as calcified lung granulomas may be observed. Pulmonary arterial stenosis may result in oligemic lung fields, whereas pulmonary vein stenosis may result in pulmonary venous congestion and localized pulmonary edema. Cardiac magnetic resonance is useful to characterize soft tissue infiltration, vascular patency, and any ongoing inflammation. Variable enhancement of the soft tissue structures on T1-weighted and T2-weighted imaging suggests areas of fibrosis and inflammation. In this patient's case, there was evidence of pericardial thickening as well as prominent delayed gadolinium enhancement of the visceral pericardium that encased the mediastinal

FIGURE 3 Pathology Images



A resection specimen with necrotizing granuloma. Note the multinucleated giant cell (solid arrow) and macrophages at the bottom left and the necrosis in the middle and upper right. Hematoxylin-eosin stain, original magnification 200×.

mass, suggesting a fibroinflammatory process primarily involving the pericardium.

Management of FM is dependent on the extent and severity of the disease. Corticosteroids and nonsteroidal anti-inflammatory drugs may have utility, but their reported efficacy is variable. For FM associated with histoplasmosis, antifungal therapy (eg, itraconazole) may improve symptoms and mediastinal mass size, but the optimal duration of therapy is unclear. Other patients exhibit no or limited benefit of antifungal therapy. Interventional procedures may be indicated in the presence of compression and/or obstruction of mediastinal structures and include percutaneous angioplasty to dilate a stenosed vessel, open debulking of the mediastinal fibrous mass and/or decompression, and venous grafting to relieve superior vena cava syndrome.

FOLLOW-UP

At the 1-year follow-up after surgery, the patient remains asymptomatic with a persistent residual pericardial mass with patchy calcification and improved mediastinal vascular compression in the form of mild supravalvular main pulmonary artery and left pulmonary vein narrowing. The systemic and right pulmonary veins and the branch pulmonary arteries appeared widely patent (**Figure 1**).

CONCLUSION

FM is a rare potentially progressive fibroinflammatory process in which dense fibrous tissue infiltrates the mediastinum and may encase the bronchovascular structures. In the United States, most cases are believed to be caused by previous infection with *Histoplasma capsulatum*. However, other infectious, autoimmune, and malignant conditions should be excluded. Imaging including echocardiography, CT scan, and cardiac magnetic resonance play a crucial role in the diagnosis, assessment, and follow-up of this condition. Contrast-enhanced CT is the most useful diagnostic modality and may demonstrate a variably enhanced soft tissue infiltrative mass with calcification and encasement and/or obstruction of the airway and vascular structures. Thus, FM should be 1 of the differential diagnoses in patients with features of mediastinal vascular compression and the previously described imaging abnormalities. Management is highly dependent on the severity of the disease and may require both medical treatment with anti-inflammatory agents with or without antifungal therapy and interventional procedures. Unfortunately, there is a sparsity of data on the long-term follow-up of these patients.

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REFERENCES

1. Goodwin RA, Nickell JA, Des Prez RM. Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. *Medicine (Baltimore)*. 1972;51(3):227-246. https://doi.org/10.1097/00005792-197205000-00008

2. Loyd JE, Tillman BF, Atkinson JB, Des Prez RM. Mediastinal fibrosis complicating histoplasmosis. *Medicine (Baltimore)*. 1988;67(5):295-310. https://doi.org/10.1097/00005792-198809000-00002

3. Rossi SE, McAdams HP, Rosado-de-Christenson ML, Franks TJ, Galvin JR. Fibrosing mediastinitis. *Radiographics*. 2001;21(3):737-757. https://doi.org/10.1148/radiographics.21.3.g01ma17737

4. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore)*. 2011;90(6):412-423. https://doi.org/10.1097/MD.0b013e318237c8e6

5. Lin J, Jimenez CA. Acute mediastinitis, mediastinal granuloma, and chronic fibrosing mediastinitis: a review. *Semin Diagn Pathol*. 2022;39(2):113-119. https://doi.org/10.1053/j.semdp.2021.06.008

6. Wu Z, Jarvis H, Howard LS, Wright C, Kon OM. Post-tuberculous fibrosing mediastinitis: a review of the literature. *BMJ Open Respir Res*. 2017;4(1):e000174. https://doi.org/10.1136/bmjresp-2016-000174

7. Sengupta A, Williams EE, Dekio F, Beasley MB, Murthy RA. Pneumonectomy for idiopathic fibrosing mediastinitis mimicking neoplasm in a child. *Ann Thorac Surg*. 2022;113(6):e445-e447. https://doi.org/10.1016/j.athoracsur.2021.08.047

8. Bharadwaj R, Madakshira MG, Bharadwaj P, Sidhu HS. Sclerosing mediastinitis presenting as complete heart block. *J Clin Diagn Res*. 2017;11(5):ED12-ED14. https://doi.org/10.7860/JCDR/2017/26349.9786

9. Kalweit G, Huwer H, Straub U, Gams E. Mediastinal compression syndromes due to idiopathic fibrosing mediastinitis-report of three cases and review of the literature. *Thorac Cardiovasc Surg*. 1996;44(2):105-109. https://doi.org/10.1055/s-2007-1011996

10. Schade MA, Mirani NM. Fibrosing mediastinitis: an unusual cause of pulmonary symptoms. *J Gen Intern Med*. 2013;28(12):1677-1681. https://doi.org/10.1007/s11606-013-2528-8

11. Mathisen DJ, Grillo HC. Clinical manifestation of mediastinal fibrosis and histoplasmosis. *Ann Thorac Surg*. 1992;54(6):1053-1057; discussion 1057-1058. https://doi.org/10.1016/0003-4975(92)90069-g

12. Alsunaid S, Holden Van, Fridberg J, Burke A, Pickering E, Sachdeva A. Chronic pericarditis secondary to coxsackie viral infection presenting as fibrosing mediastinitis. *Chest*. 2020;158(4):A378-A379.

13. Gill KPS, Gulhar R, Hayase J, Koppula AS. Fibrosing mediastinitis causing high degree av block in a young female patient. *J Am Coll Cardiol Case Rep*. 2022;7:101717. https://doi.org/10.1016/j.jaccas.2022.101717

14. Eleid M, Mulpuru SK, Asirvatham SJ, Holmes DR Jr. Fibrosing mediastinitis: a squeeze on arterial and venous segments of the heart. *Circulation*. 2014;130(3):290-291. https://doi.org/10.1161/CIRCULATIONAHA.114.010166

15. Garrana SH, Buckley JR, Rosado-de-Christenson ML, Martínez-Jiménez S, Muñoz P, Borsa JJ. Multimodality imaging of focal and diffuse fibrosing mediastinitis. *Radiographics*. 2019;39(3):651-667. https://doi.org/10.1148/rg.2019180143

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