

CLINICAL VIGNETTE

Fibrosing Mediastinitis Presenting as Angioedema in a Geriatric Patient

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Case Presentation

An 83-year-old female with hypertension, presented to the emergency room with sudden onset lip swelling associated with an itchy rash. She denied cough, weight loss, or night sweats. Her medical history includes hyperlipidemia, hypothyroidism, osteopenia, and heart failure with preserved ejection fraction. Medications include furosemide, metoprolol, levothyroxine, aspirin and atorvastatin. She was a lifelong non-smoker with no alcohol use, and worked as a homemaker.

She was diagnosed with angioedema and urticaria and given diphenhydramine and prednisone with improvement in her symptoms. At follow up, additional testing for new onset angioedema revealed an elevated sedimentation rate (ESR) of 91 mm/hr and C-reactive protein (CRP) of 1.1mg/dL. Rheumatologic evaluation did not show any evidence of connective tissue disease. Serum protein electrophoresis revealed polyclonal hypergammaglobulinemia with negative immunofixation with concern for malignancy. Computerized tomography (CT) scans of the chest, abdomen and pelvis were obtained. Chest imaging showed confluent matted lymphadenopathy in the mediastinal, hilar, subhilar regions and associated narrowing of the bronchi and pulmonary vasculature consistent with fibrosing mediastinitis. Abdominal imaging showed bulky, hypoenhancing retroperitoneal, iliac and right inguinal lymphadenopathy. Subsequent CT-guided biopsy of an inguinal lymph node revealed granulomatous lymphadenitis with fibrosis with negative congo red stain, negative stain for organisms. Flow cytometry showed no discrete monotypic B cell population. Testing for tuberculosis, aspergillus, coccidioides and histoplasmosis were all negative. Given the patient's minimal symptoms and goal to limit invasive procedures, treatment was deferred and the patient was monitored closely. Within six months the patient developed mild, progressive dyspnea and repeat imaging revealed interval mild progressive confluent lymphadenopathy with focal areas of fibrosing mediastinitis concerning for sarcoidosis. Angiotensin converting enzyme level was elevated at 92 U/L and repeat ESR was elevated at 128 mm/hr. After discussion with the patient, treatment for possible sarcoidosis was deferred given the patient's atypical presentation and limited symptoms.

Unfortunately, six months later, the patient developed progressive dyspnea and repeat CT scan showed uniform, progressive increase in size of massive intrathoracic lymphadenopathy and mediastinal fibrosis. Repeat biopsy of cervical lymph node showed granulomatous lymphadenitis with fibrosis. Acid-fast

culture and stain, fungal culture, and bacterial culture and gram stain were all negative. She was started on prednisone, however, within six weeks developed worsening dyspnea and required hospitalization. Given lack of response to prednisone, steroids were tapered. On hospital day two she developed acute on chronic hypercarbic respiratory failure requiring BiPAP (bilevel positive airway pressure). The patient and her family were not interested in further diagnostic workup or aggressive interventions and she was discharged on hospice care.

Discussion

Fibrosing mediastinitis, which is also known as mediastinal fibrosis or sclerosing mediastinitis, is an uncommon disorder characterized by fibrous tissue proliferation in the mediastinum. While technically a benign condition, the disease can be life-threatening depending on the aggressiveness of the fibrosis and near vital structures. Symptoms also vary depending on the severity of the disease and location of the fibrosis, and typically include cough, dyspnea, chest pain, hemoptysis, recurrent pulmonary infection and presence of superior or inferior vena cava syndrome.^{1,2}

Fibrosing mediastinitis can have multiple etiologies. In the United States, *Histoplasma capsulatum* is thought to be the most common trigger for the disease via an altered immunologic response to the organism.³⁻⁷ Although the exact mechanism in which *H. capsulatum* incites this fibro-inflammatory response is unknown, genetic factors are likely contributory given only a small subset (3:100,000) of those infected with *H. capsulatum* will develop fibrosing mediastinitis.^{3,7} Other infections associated with fibrosing mediastinitis include *Mycobacterium tuberculosis*, *Wucheria bancrofti*, *Aspergillus*, mucormycosis, *Blastomyces* and *Cryptococcus*.^{3,4} Non-infectious causes of fibrosing mediastinitis include Behçet's disease, orbital pseudotumor, Riedel's (fibrous) thyroiditis, sarcoidosis, sclerosing cholangitis, and rheumatic fever.^{3,4} Interestingly, methylsergide maleate, a drug previously used to prevent migraines and cluster headaches, was taken off the market due to concerns of fibrosis. Radiation therapy can also lead to mediastinal fibrosis.⁴ Often, the etiology of the fibrosis is unclear, and the patient is classified as having idiopathic fibrosing mediastinitis.³

Fibrosing mediastinitis can be characterized as focal or diffuse. Diffuse disease or nongranulomatous fibrosing mediastinitis is

less common, making up 10-20% of all cases and has been commonly idiopathic, autoimmune, radiation or medication related.⁵ Focal or granulomatous fibrosing mediastinitis makes up 80-90% of all cases and is most often due to an abnormal immunologic response to *Histoplasma capsulatum* or inflammatory conditions such as sarcoidosis.⁵

Important historical points in the evaluation of a patient with fibrosing mediastinitis include history of living in a histoplasmosis endemic region, such as along the Ohio and Mississippi River Valley. Diagnosis can be established with imaging, with CT scan with contrast the preferred modality. CT findings include localized infiltrative mediastinal soft tissue, commonly with calcifications. In nongranulomatous disease, calcifications are rare and diffuse infiltrative tissues typically involve multiple compartments.^{3,5}

Treatment of mediastinal fibrosis is largely directed at treating the complications of the disease. For example, progressive fibrosis can lead to airway stenosis and, ultimately airway obstruction. Some cases respond to balloon dilation and stenting of the airway.^{5,6} Encasement of the arteries and veins can also lead to complications. Unilateral constriction of the pulmonary artery will lead to hypoperfusion of the lung tissue.^{5,6} Chronic venous obstruction and lymphatic congestion can cause dyspnea and hemoptysis, also known as pseudomitral stenosis syndrome.⁵ Superior vena cava (SVC) involvement can lead to SVC syndrome. Angioplasty and stent placement have been used to treat symptomatic vascular obstruction.^{5,6,8} In addition debulking and decompression surgeries have been used.⁹ Antifungal and anti-inflammatory agents have shown limited efficacy in treating fibrosing mediastinitis.⁶ However, there is one report of successful control of idiopathic disease with high dose pulsed steroids followed by maintenance steroids and methotrexate.¹

The prognosis of fibrosing mediastinitis is poorly studied and relies on case series. Disease mortality was similar to matched controls in one study, however subsequent study reported mortality of 30% in fibrosing mediastinitis patients.⁹ The variability and rarity of fibrosing mediastinitis makes it challenging to diagnose and treat. However, it is important to consider in patients presenting with symptoms of possible fibrosing mediastinitis.

REFERENCES

1. **Joury AU, Al Boukai AA, Kashour TS.** Severe fibrosing mediastinitis with atypical presentation: Effective control with novel therapeutic approach. *Ann Thorac Med.* 2017 Jul-Sep;12(3):209-212. doi: 10.4103/atm.ATM_47_17. PMID: 28808494; PMCID: PMC5541970.
2. **Rossi GM, Emmi G, Corradi D, Urban ML, Maritati F, Landini F, Galli P, Palmisano A, Vaglio A.** Idiopathic Mediastinal Fibrosis: a Systemic Immune-Mediated Disorder. A Case Series and a Review of the Literature. *Clin Rev Allergy Immunol.* 2017 Jun;52(3):446-459. doi: 10.1007/s12016-016-8584-1. PMID: 27553003.

3. **Rossi SE, McAdams HP, Rosado-de-Christenson ML, Franks TJ, Galvin JR.** Fibrosing mediastinitis. *Radiographics.* 2001 May-Jun;21(3):737-57. doi: 10.1148/radiographics.21.3.g01ma17737. PMID: 11353121.
4. **Ferrer Galván M, Rodríguez Portal JA, Serrano Gorrarredona MP, Gómez Izquierdo L.** Fibrosing mediastinitis mimicking sarcoidosis. *Clin Respir J.* 2015 Jan;9(1):125-8. doi: 10.1111/crj.12107. Epub 2014 May 15. PMID: 24405501.
5. **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 May-Jun;39(3):651-667. doi: 10.1148/rg.2019180143. Epub 2019 Apr 5. PMID: 30951437.
6. **Peikert T, Colby TV, Midthun DE, Pairolero PC, Edell ES, Schroeder DR, Specks U.** Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. *Medicine (Baltimore).* 2011 Nov;90(6):412-23. doi: 10.1097/MD.0b013e318237c8e6. PMID: 22033450.
7. **Strock SB, Gaudieri S, Mallal S, Yu C, Mitchell D, Cogan J, Mason W, Crowe D, Loyd JE.** Fibrosing mediastinitis complicating prior histoplasmosis is associated with human leukocyte antigen DQB1*04:02 - a case control study. *BMC Infect Dis.* 2015 May 5;15:206. doi: 10.1186/s12879-015-0943-7. PMID: 25940591; PMCID: PMC4424560.
8. **Albers EL, Pugh ME, Hill KD, Wang L, Loyd JE, Doyle TP.** Percutaneous vascular stent implantation as treatment for central vascular obstruction due to fibrosing mediastinitis. *Circulation.* 2011 Apr 5;123(13):1391-9. doi: 10.1161/CIRCULATIONAHA.110.949180. Epub 2011 Mar 21. PMID: 21422386; PMCID: PMC3095436.
9. **Fender EA, Widmer RJ, Knavel Koepsel EM, Welby JP, Kern R, Peikert T, Bjarnason H, Holmes DR Jr.** Catheter based treatments for fibrosing mediastinitis. *Catheter Cardiovasc Interv.* 2019 Nov 15;94(6):878-885. doi: 10.1002/ccd.28152. Epub 2019 Feb 21. PMID: 30790443.