Fibrosing Mediastinitis

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ABSTRACT

Fibrosing mediastinitis is an uncommon thoracic disorder characterized by the extensive proliferation of fibrous tissue in the mediastinum. This disorder frequently develops following Histoplasma capsulatum *infection with involvement of mediastinal lymph nodes. The fibrous tissue can invade and compress mediastinal structures, including vessels, large airways, and the esophagus. These patients may present with cough, sputum production, and dyspnea depending on location and extent of fibrosis. The radiographic presentation depends on the type and extent of obstruction. Diagnosis requires computed tomography with angiography, ventilation-perfusion scans, and pulmonary function tests. Management depends on the structures involved and the extent of infiltration and/or compression. Possible approaches include the use of endobronchial stents, intravascular stents, vascular bypass grafts, and the resection of nonfunctional pulmonary tissue. Extensive surgical procedures are usually not warranted. These patients usually do not respond to antifungal or anti-inflammatory medications. Several patients have responded to rituximab, and this drug is a possible consideration in patients with ongoing inflammation in the mediastinum.*

Keywords: fibrosing mediastinitis, venous stenosis, arterial stenosis, tracheal/bronchial stenosis

INTRODUCTION

Fibrosing mediastinitis (FM) is an uncommon diagnosis, that usually involves the proliferation of extensive dense fibrous tissue infiltrating mediastinal structures.[1] The pathological findings typically include thick, "woody," hard fibrotic tissue encasing mediastinal structures, occasionally extending into the interlobular and interalveolar septa of the lung parenchyma and thickening the mediastinal pleura.[2,3] This fibrous tissue can compress and obstruct pulmonary vessels, the trachea and bronchi, and the esophagus.[2] The etiology of FM is diverse; it has been most commonly associated with fungal infections, especially with histoplasmosis in the United States. Mycobacterial infections and non-infectious causes, such as rheumatologic or neoplastic diseases (e.g., lymphoma), have also been reported in these cases.[3]

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PATHOGENESIS

The exact mechanisms causing the proliferation of fibrous tissue in FM remain unknown. Histological findings demonstrate an evolving fibro-inflammatory process which produces continuous morphologic changes similar to the formation of keloids.[4] Mononuclear cells are frequently found within the collagenous tissue.[1] Immunohistochemical staining for IgG4 positive plasma cells in some biopsies has revealed a possible immunologic overlap between granulomatous FM and the IgG4-related disease, suggesting that the B-lymphocytes may be a link between these two highly fibroproliferative disorders.[5] Patients with FM do not have elevated plasma immunoglobulin

levels, like patients with IgG4-related disease, but treatment with B cell targeting therapy (rituximab) has produced clinical improvement in a small number of patients with these two disorders.[6,7]

The exact etiological trigger for the fibrotic process may be difficult to establish. A history of infections, such as histoplasmosis, tuberculosis, blastomycosis, and aspergillosis, are commonly reported in patients with FM; however, cultures are usually negative.[1,3] Non-infectious etiologies, such as autoimmune diseases, sarcoidosis, Hodgkin's disease, retroperitoneal fibrosis, Riedel's thyroiditis, idiopathic, etc. have also been described.[3] HLA-A2 has been associated with FM.[8] Table 1 provides diagnostic factors that can help identify the primary cause of FM.

Table 1. Diseases associated with fibrosing mediastinitis

Conditions associated with FM	Relevant history	Laboratory test	Histology	Radiology
Histoplasmosis	Central and eastern states in the USA	Antibodies titer, fungal cultures	Necrotizing granuloma, +/– yeast on a stain	Calcifications, cavitation
Tuberculosis	Foreign-born, immunocompromised	QuantiFERON test, mycobacterial cultures	Tuberculous granuloma; acid-fast bacilli smear	Reactivated TB: apico-posterior segments, volume loss, calcification, cavitation, bilateral lung involvement, fibrosis
Aspergillosis	Immunocompromised	B-D Glucan, Aspergillus antigen, Aspergillus PCR, fungal culture	Septate, branching hyphae	Infiltrates, halo sign, cavitation
Sarcoidosis	African-American ethnicity, family history	Hypercalcemia, hypercalciuria, elevated ACE	Sarcoid granuloma	Hilar adenopathy, parenchymal involvement
Riedel's thyroiditis	F > M, goiter with hard consistency, predominantly euthyroid	Commonly normal TSH	Infiltration of surrounding tissues by fibrotic tissues, occlusive phlebitis	Hypodense infiltrative mass
Antiphospholipid antibody syndrome[26]	Male: Female = 1:3.5 History of arterial/venous thrombosis, unexplained abortions, placental insufficiency, association with SLE	Lupus anticoagulant; Ig anticardiolipin antibody, IgG/M anti-beta2 glycoprotein-I antibody	—	—
Retroperitoneal fibrosis	Male: Female = 2-3:1 History of radiation, trauma, surgery, malignancies, *M. tuberculosis*, infliximab, ergot alkaloids, dopamine agonists, dull, constant back/flank pain	Hematuria (urethral injury/obstruction), autoimmune tests (ANA, anti-smooth-muscle antibodies)	Spindle-shaped cells, collagen bands; inflammatory infiltrate	Homogenous periaortic mass, non-infiltrative, involvement of ureters

PCR- Polymerase chain reaction, ACE- angiotensin converting enzyme, ANA- Antinuclear antibodies.

Clinical presentation

Patients with FM range in age from childhood to late adulthood.[3,9] The clinical presentation depends on the mediastinal structures encased or compressed by the fibrous tissue. The fibrosis is usually limited to the mediastinum, but in rare cases the fibrotic tissues spread through the diaphragm and involve the descending aorta.[10] Large airways have been the most commonly obstructed structures, followed by vascular structures, and the esophagus.[1] Patients commonly present with exertional dyspnea, cough, hemoptysis, pleuritic chest pain, and/or superior vena cava syndrome.[1,3] Peikert et al reported an overall survival similar to age-matched controls, in contrast to previous reports.[1]

The pliability and a low intraluminal pressure of the superior vena cava (SVC) makes it susceptible to compression and/or obstruction;[10] SVC obstruction often presents with nasal congestion, headaches, facial and upper chest congestion, and upper gastrointestinal bleeding from esophageal varices.[1,11] Fibrotic stenosis of the pulmonary artery can mimic thromboembolic obstruction.[12] Pulmonary vein constriction causes symptoms of pulmonary vascular congestion.[13] Fibrotic tissue invasion of the cardiac structures can compress the left atrium and can cause coronary artery stenosis;[14] these patients often develop chest pain.[1]

Radiological and pulmonary function assessment

The principal finding on radiographic studies of the chest is a widened mediastinum with a hilar mass and/or paratracheal mass. Obstruction of the SVC usually presents with a mass in the right superior mediastinum. Calcification suggests prior fungal or mycobacterial infection.[1,9] Localized edema and septal thickening suggest pulmonary venous congestion. Compression of bronchial structures can cause pulmonary infiltrates secondary to post-obstructive pneumonia and/or atelectasis.[15]

Computed tomography (CT) of the chest provides a detailed map of the soft tissue in the mediastinum and bronchial involvement;[15] CT angiography is helpful to assess vascular involvement with more detail. The role of conventional chest x rays is limited due to non-specific findings.[16] Enlarged or calcified lymph nodes suggest exposure to *H. capsulatum* infection and may help in the differential diagnosis.[17] Vascular involvement secondary to compression and obstruction of mediastinal structures is best identified by contrast angiography studies that clearly demonstrate stenotic vessels.

Ventilation-perfusion scans can reveal both ventilation and perfusion defects.[12] These scans help localize the involved lung segments, provide functional information about the overall impairment in either ventilation or perfusion, and provide estimates of the potential benefits with vascular and bronchial procedures to open up compressed structures.[18,19,20] Pulmonary angiography can detect pulmonary arterial obstruction, and venography provides for the diagnosis of SVC syndrome or proximal SVC occlusion. Pulmonary function results depend on the type and extent of occlusion and provide an overall assessment of ventilatory impairment.[2] Magnetic resonance imaging of the chest and positron emission tomography (PET) in the assessment and management of FM may provide additional information about disease location and activity but needs more study.

Unfortunately, there is no general consensus regarding diagnostic criteria for FM. Tissue biopsy should provide a histological and etiological diagnosis, but decisions regarding biopsy need careful risk-benefit analysis.

Treatment

There is no established pharmacologic treatment for FM or its complications. Medications, such as anti-inflammatory drugs and antifungals, have been used, but their effects on slowing down the progression of FM are inconclusive.[1] Fibrosing mediastinitis is usually a late-stage complication of a *Histoplasma* infection. Therefore, treatment with antifungals should be reserved for patients with active histoplasmosis, and this probably requires biopsy and cultures.[21] The benefit of corticosteroids and other agents has not been conclusive; several reports have found different

outcomes.[1,22] Westerly et al reported the use of rituximab in three patients with FM secondary to histoplasmosis. These patients had positive PET scans. Clinical symptoms, radiographic images (mass size), and PET imaging all improved with treatment. This study suggests that some patients have ongoing B cell mediated inflammation which responds to B cell depletion.[6]

Surgical intervention with exploratory mediastinotomy can help in the assessment of the extent of vascular involvement and provides an opportunity to decompress the involved structures. However, fibrous tissue excision is risky and complex due to invasion of nearby vessels, infiltration, and excessive tissue growth. Therefore, the treatment approach should be tailored to the individual case. In patients with nonfunctional lung parenchyma, lobectomy or pneumonectomy has been performed.[20]

Non-surgical interventions, such as balloon angioplasty with intravascular stenting, are effective in the management of vascular compression and provide symptomatic relief in up to 87% of patients (Table 2).[23] The procedure may be difficult due to a higher pressure requirement for the deployment of the stent in compressed vessels and due to a tendency for stents to migrate into a non-involved area of the vessel. The need for restenting secondary to progressive fibrous tissue growth, thrombosis, or stent collapse has been reported in up to 28% of cases with a median time to recurrence of 115 months.[23]Albers concluded that percutaneous interventions improved clinical outcomes and the five year survival rate in cases with bilateral but not unilateral vascular occlusion.[23] Bronchial stents can open up compressed airways.

Table 2. Surgical management strategies in patients with mediastinal fibrosis

Study	Patient characteristics	Complications	Follow-up
Peikert,[1] 2011 80 patients	15 patients: Endovascular interventions (SVC angioplasty; PA angioplasty; PV angioplasty; stent placement); endobronchial stent placement	One cardiac tamponade after SVC stenting	Median 38 months 8/14 patients developed stent restenosis and required interventions at 6–12 months interval 1 died
	17 patients: Graft placement; bypass; surgical decompression	Pericarditis, empyema, Tricuspid regurgitation, stroke, pneumonectomy	Median 89 months in 12 patients: 5/12 patients required repeated intervention
Gustafson,[24] 2012 1 patient with bilateral PA stenosis	1 patient underwent bilateral PA stents placement		Restenosis within 6 months; required repeated intervention with PA homograft
Dunn,[27] 1990 6 cases	1 patient with right PA stenosis underwent Dacron graft placement		Restenosis after two and a half years, no intervention performed
	1 patient with SVC syndrome underwent saphenous vein bypass graft		No additional interventions at the follow-up (no exact date of follow-up)
	3 patients had pneumonectomy	Bronchopleural fistula in 2/3 patients	No additional interventions at the follow-up
	1 patient had a mass excision		No additional interventions at the follow-up

Table 2. Surgical management strategies in patients with mediastinal fibrosis (*continued*)

Study	Patient characteristics	Complications	Follow-up
Satpathy,[28] 2007 1 patient with right PA stenosis	PA Stent placement		No restenosis for 4 years
Phillips,[29] 2011 2 patients with SVC syndrome	SVC Stent placement		No restenosis at 13 and 18 months follow-up
Arbra,[20] 2014 3 patients	1 patient had lobectomy		No recurrence of symptoms at 8 months follow-up
	1 patient had lobectomy		No recurrence of symptoms at follow-up
Johansen,[30] 2013 1 patient with SVC syndrome	Patient underwent angioplasty and stent placement		No clinical signs of restenosis at 1 year follow-up
Guerrero,[31] 2001 1 patient with PA stenosis	PA angioplasty and stent placement		No symptoms at 3 months follow-up
Dechambre,[32] 1998 1 patient with bronchial stenosis	Endobronchial stent		Distortion of RMB and the distal portion of trachea required longer stent placement after 1 year
Kang,[33] 2006 3 patients with SVC obstruction	1 Patient underwent Dacron graft and PTFE stents placement		Restenosis of prosthesis with required dilation after 1 year
	1 patient underwent surgical resection		Asymptomatic at 3 year follow-up
	1 patient underwent PTFE stent grafting	CHF symptoms	
Dye,[34] 1977 1 patient with PV stenosis	Bilobectomy		Symptoms free after 16 months
Mathisen,[21] 1992 20 patients	18/20 patients: 6 had resection of mass, 5 had right middle and lower lobectomies, 4 had carinal pneumonectomy, 4 had esophagoplasty, 3 had sleeve resection, 1 had right upper lobectomy, 1 had middle lobectomy, 1 had bronchoplasty.	3 patients died after complications of carinal pneumonectomy, 1 patient with tracheobronchial obstruction died during the dilation procedure	

Surgical vascular reconstruction techniques with bypass grafting using silicone prostheses, homografts, or saphenous vein grafts should be considered as an alternative to stenting, especially in younger patients and in patients with unsuccessful percutaneous interventions.[24] Doty et al reported a patency in 87.5% of patients with a mean clinical follow-up of 10.9 years after spiral graft placement for the SVC obstruction relief.[25]

Conclusion

In summary, fibrosing mediastinitis usually becomes clinically important only when the disease has progressed and complications occur, especially with infiltration and compression of major mediastinal structures. Current diagnostic tools, such as CT angiography and ventilation-perfusion studies, are essential to determine the involved structures and appropriate treatment. Endovascular stents and endobronchial stents can open up compressed structures. The possibility of ongoing active inflammation should be considered; PET scans can help in this assessment.

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