Fibrosing mediastinitis

Author: Steven E Weinberger, MD
Section Editor: Kevin R Flaherty, MD, MS
Deputy Editor: Geraldine Finlay, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: May 2018. | **This topic last updated:** Sep 13, 2017.

INTRODUCTION — Fibrosing mediastinitis, also known as sclerosing mediastinitis or mediastinal fibrosis, is a disorder characterized by an excessive fibrotic reaction in the mediastinum. It can result in compromise of airways, great vessels, and other mediastinal structures, with morbidity directly related to the location and extent of fibrosis. Fibrosing mediastinitis is usually a sequel of histoplasmosis [1,2].

The etiology, natural history, clinical presentation, diagnosis, treatment, and outcome of fibrosing mediastinitis are reviewed here. The presentation and treatment of pulmonary histoplasmosis are discussed separately. (See "Pathogenesis and clinical features of pulmonary histoplasmosis" and "Diagnosis and treatment of pulmonary histoplasmosis".)

ETIOLOGY — Fibrosing mediastinitis usually results from an excessive host response to a prior infection that involved the mediastinal lymph nodes.

Histoplasmosis — The vast majority of cases of fibrosing mediastinitis are thought to be sequelae of infection with *Histoplasma capsulatum*, a dimorphic fungus that is found commonly in the southeastern, mid-Atlantic, and central United States. Infection with *H. capsulatum* is subclinical in the vast majority of patients. It begins as an asymptomatic pulmonary infection and disseminates to the mediastinal lymph nodes and other reticuloendothelial organs before specific cell-mediated immunity develops and contains the fungus. Depending upon the inoculum and the extent of host response, the involved mediastinal lymph nodes can enlarge and coalesce into an inflamed caseous mass referred to as a mediastinal granuloma, or can lead to a sclerosing process called fibrosing mediastinitis:

- Mediastinal granuloma – Mediastinal granuloma is more common (comprises 5 to 10 percent of mediastinal masses in most surgical series [3]) and more benign than fibrosing mediastinitis. It usually presents as a mediastinal mass that is discovered either incidentally or because it compresses compliant mediastinal structures such as the superior vena cava (SVC) or esophagus. The mediastinal granuloma consists of encapsulated caseous lymph nodes that are easily removed surgically.

- Fibrosing mediastinitis – The events that lead to the development and perpetuation of fibrosing mediastinitis are incompletely understood. It is believed that fibrosing mediastinitis results from the leakage of fungal antigens from lymph nodes into the mediastinal space, leading to a hypersensitivity reaction followed by an exuberant fibrotic response [1]. Fibroblasts adjacent to evolving granulomata are stimulated and proliferate, leading to fibrosis, entrapment, and invasion of adjacent normal structures. The resulting tissue pathology consists of caseous central foci surrounded by mature, concentrically deposited acellular collagen [1].

Fibrosing mediastinitis is not believed to reflect extranodal infection because the organism cannot typically be cultured from biopsy specimens [1,3]. (See "Diagnosis and treatment of pulmonary histoplasmosis".)

It is unknown why only a minority of patients infected with *H. capsulatum* develop fibrosing mediastinitis. However, genetic influences on the immune response may play a role. This was suggested by a case-control study that included 19 consecutive patients with fibrosing mediastinitis and 21,086 cadaveric kidney donors serving as controls [4]. The study found that the relative risk of fibrosing mediastinitis was 3.3 among persons with the HLA-A2 antigen. (See "Human leukocyte antigens (HLA): A roadmap".)

Some investigators contend that mediastinal granuloma and fibrosing mediastinitis are separate disease processes, with fibrosing mediastinitis occurring idiosyncratically in people predisposed to excessive fibrogenesis in response to antigenic stimuli [1]. Others believe that fibrosing mediastinitis is due to the rupture of mediastinal granulomas into the mediastinal space, leading to a fibrotic host response. In support of the latter hypothesis, one series of 31 patients with mediastinal granuloma found that 11 patients (35 percent) developed fibrosing mediastinitis over a two-year period [5].

Other precipitants — Tuberculosis is often included as a potential precipitant of fibrosing mediastinitis, but it rarely stimulates an invasive fibrotic reaction similar to that seen following histoplasmosis. However, mediastinal granulomas due to tuberculosis are well described [3,6]. Case reports have also described the development of fibrosing mediastinitis secondary to mediastinal radiation [7] or infection with *Aspergillus* [8-10], *Wuchereria bancrofti* [11], or *Blastomyces* [12].

In a series of 27 patients from France with pulmonary hypertension due to fibrosing mediastinitis, the most common underlying cause was sarcoidosis (13 patients or 48 percent), while tuberculosis was found in nine patients (33 percent). The absence of suspected histoplasmosis suggests that the cause of fibrosing mediastinitis is highly dependent upon location and the likelihood of an underlying endemic fungus.

An idiopathic form of fibrosing mediastinitis has also been described [13,14]. Unlike patients with fibrosing mediastinitis believed to be due to histoplasmosis, patients with the idiopathic form lack calcification on imaging studies. The idiopathic form of fibrosing mediastinitis may be autoimmune and can in some cases be associated with fibrosing processes in other sites, such as retroperitoneal fibrosis, orbital pseudotumor, and Riedel's (fibrous) thyroiditis [13,15].

EPIDEMIOLOGY — Precise data regarding the incidence of fibrosing mediastinitis are not available, but the condition appears to be rare. While it has been estimated that over 500,000 people per year in the United States are infected with Histoplasma and over 80 percent of inhabitants of endemic regions have a positive Histoplasma skin test [16], less than 1 percent of patients with histoplasmosis develop fibrosing mediastinitis (figure 1) [17].

The largest series of fibrosing mediastinitis was from an institution in an endemic region and it described only 94 patients over a nine-year period [18]. The average age at diagnosis was 33 years, 81 percent of patients were white, and there was a slight male preponderance. Similar demographics have been reported by other series [3].

NATURAL HISTORY — Fibrosing mediastinitis is an insidious, progressive disease with a variable natural history. One series of 23 patients found that 10 patients (43 percent) had improvements in symptoms, 11 patients (48 percent) had no significant change, and two patients (9 percent) had progressive disease [13]. In contrast, a second series of 71 patients noted a far worse prognosis, with 21 patients (30 percent) dying during follow-up [3]. The mean interval between the development of symptoms and death was less than six years in these patients, and death resulted most frequently from cor pulmonale or relentless respiratory compromise due to recurrent infection, bronchial obstruction, or hemoptysis. Disease involving subcarinal structures conferred a worse prognosis because bilateral lung involvement was more common in these patients.

CLINICAL PRESENTATION — The signs and symptoms of fibrosing mediastinitis depend upon which structures of the mediastinum are involved and the degree to which those structures are compromised. Typical complications result from compromise of the airways, heart and great vessels, or esophagus:

- Airway compression can lead to postobstructive pneumonia or atelectasis, while bronchial erosion by calcific lymph nodes can lead to broncholithiasis. These complications are most common in the right upper lobe [16].

- Heart and great vessel involvement can cause pulmonary artery and/or pulmonary vein obstruction, constrictive pericarditis, or superior vena cava (SVC) syndrome (image 1). Not all patients with SVC compromise become symptomatic. SVC obstruction due to fibrosing mediastinitis typically develops slowly over a period of years, allowing the formation of an extensive collateral circulation that may be adequate to prevent both stasis and elevated pressure in the tributaries of the SVC [3,18]. SVC obstruction is a less common presentation of fibrosing mediastinitis than tracheobronchial narrowing [3,19].

- Esophageal compression can lead to dysphagia and/or odynophagia. Tracheoesophageal fistula formation may also be seen.

Hemoptysis may also occur in fibrosing mediastinitis. It is a consequence of any of four possible mechanisms. Fibrous tissue can invade a bronchus and extend into the mucosa, leading to a friable intraluminal lesion. Airway obstruction may result in a postobstructive necrotizing pneumonia. Obstruction of pulmonary venous return may produce pulmonary venous hypertension (pseudo-mitral stenosis). And, finally, obstruction of pulmonary arteries can lead to extensive functional anastomoses between the intercostal or bronchial arteries and the pulmonary arteries.

DIAGNOSIS

General approach — The average interval from initial symptoms to diagnosis is five years for women and 2.2 years for men [1]. Imaging studies are necessary to confirm the diagnosis of an infiltrative process in the mediastinum, to help exclude malignancy, and to assess the integrity of mediastinal structures. We feel that a biopsy should not be done if the patient has a typical clinical and radiologic presentation with associated calcification. Biopsies are difficult because of the dense fibrosis and calcification and may be hazardous as a result of bleeding from engorged collateral vessels. Serologic studies are of limited benefit because they frequently fail to establish the diagnosis.

Diagnostic studies — Diagnostic studies performed on patients with suspected fibrosing mediastinitis may include chest radiography, computed tomography (CT), CT angiography, and/or magnetic resonance imaging (MRI).

- Chest radiographs – The findings of fibrosing mediastinitis on chest radiographs are nonspecific, with common findings including hilar or mediastinal adenopathy, lobar or segmental consolidation or atelectasis, a unilateral small pulmonary artery, septal lines, pleural effusion, or cardiomegaly. The extent of disease is often underestimated, with the chest radiograph appearing relatively normal even in patients with extensive disease (ie, disease causing major central airway obstruction and vascular occlusion) [3,13].

- Computed tomography – CT can reveal an infiltrative mediastinal process that obliterates fat planes, with or without a discrete mass [3,20,21]. It often demonstrates calcifications within the mediastinal process, which are not evident on the chest radiograph but suggest nonmalignant disease. In one series, 86 percent of patients had calcification on their CT scan, approximately 50 percent of which were not visible on the chest radiograph alone [22]. CT may also reveal evidence of prior Histoplasma infection, such as calcified lymph nodes and splenic calcifications.

- CT angiography – CT angiography is useful in assessing the degree of vascular occlusion and demonstrating collateral blood flow around obstructed vessels [19,21]. Increased lung attenuation, thickened interlobular septa, and peribronchial cuffing are usually seen with pulmonary venous obstruction. When these findings are combined with an area of tracheobronchial narrowing, the diagnosis of fibrosing mediastinitis is favored over lymphoma [22].

- Magnetic resonance imaging – MRI of fibrosing mediastinitis typically reveals a mass of heterogeneous signal intensity [23,24]. Decreased signal intensity on T2-weighted images is suggestive of fibrosis. MRI may be superior at defining the extent of disease (particularly the degree of vascular involvement) compared to CT, but is less useful for demonstrating intralesional calcifications [21,24].

Generally speaking, invasive procedures may be hazardous because of pulmonary hypertension and/or the potential for pulmonary hemorrhage. This was demonstrated by a case series of 71 patients, which reported two deaths from hemorrhage complicating bronchoscopy and two deaths complicating cardiac catheterization [3].

TREATMENT — There is no curative therapy for fibrosing mediastinitis. Antifungal agents are generally ineffective, although several case reports have suggested a potential benefit [3,18,20,25]. Glucocorticoids do not appear to be beneficial in typical cases of fibrosing mediastinitis, although controlled trials have not been performed [3,26]. However, in fibrosing mediastinitis due to sarcoidosis, improvement may sometimes be seen [27]. Another possible exception is autoimmune fibrosing mediastinitis, which may respond more favorably to glucocorticoid therapy, although these cases are difficult to identify prospectively [13]. Based upon the finding of CD20-positive B lymphocytes in tissue samples from patients with fibrosing mediastinitis, a preliminary report of off-label treatment with rituximab reported a therapeutic response and reduction of both lesion size and metabolic activity in three patients with progressive and refractory disease [28].

Bronchoscopically placed airway stents and percutaneously placed vascular stents have been used to treat airway obstruction and vascular obstruction, respectively [29,30]. Vascular stents may be effective in improving symptoms in patients with central vascular obstruction due to fibrosing mediastinitis. In a series from Vanderbilt University of 77 vascular stents placed in 40 patients to relieve lesions in the pulmonary artery, pulmonary vein, or superior vena cava, there were significant increases in vessel caliber and reductions in pressure gradients [31]. Symptomatic improvement was reported in 87 percent of patients for whom follow-up was available. Procedure-related complications occurred in 24 percent, and symptomatic recurrent stenosis requiring further intervention occurred in 28 percent.

Airway dilation and placement of a silicone airway stent may be useful in selected cases of fibrosing mediastinitis complicated by severe extrinsic obstruction of central airways. In a report of seven patients from The Mayo Clinic undergoing airway dilation and silicone stent placement, airway remodeling allowing stent removal occurred in five patients [32]. However, because of potential concomitant vascular obstruction in these patients, bronchoscopy may be associated with an increased risk of bleeding [3].

Surgery has been performed to palliate symptoms by relieving airway, vascular, and esophageal obstruction, as well as managing tracheoesophageal fistulas [18,26]. However, its success has been variable. Extensive fibrosis, calcification, and collateral vessels limit the benefits of surgery and are responsible for substantial morbidity and mortality [3,18,26]. This was illustrated by a series of 18 patients with fibrosing mediastinitis secondary to histoplasmosis, which reported three deaths (19 percent) during the early postoperative period [26].

- Resection of the stenotic airway and/or the distal lung parenchyma has been done in cases of fibrosing mediastinitis complicated by recurrent postobstructive infection or poor gas exchange secondary to shunt physiology. Sleeve lobectomy, carinal resection, or pneumonectomy may be required [26]. Airway surgery is technically difficult and associated with significant mortality [26].

- Superior vena cava (SVC) bypass surgery with a spiral vein graft has been used for symptomatic relief in some patients with SVC obstruction. The saphenous vein is harvested and then opened longitudinally through its entire length. It is then wrapped around a stent in a spiral manner and sutured together to create a bioprosthesis of the desired length and diameter. The stent is then removed and the graft is placed in the mediastinum anterior to the aorta. The largest series of patients treated in this fashion included four individuals with SVC syndrome due to fibrosing mediastinitis; all were symptom-free two years after the operation [33,34].

SUMMARY AND RECOMMENDATIONS

- Fibrosing mediastinitis is a rare disorder characterized by an excessive fibrotic reaction in the mediastinum. (See 'Introduction' above and 'Epidemiology' above.)
- Fibrosing mediastinitis usually results from an excessive host response to a prior infection that involved the mediastinal lymph nodes. The vast majority of cases are thought to be sequelae of *Histoplasma capsulatum* infection. (See 'Etiology' above.)
- Fibrosing mediastinitis is an insidious, progressive disease with a variable natural history. Morbidity is directly related to the location and extent of the fibrosis. (See 'Natural history' above.)
- The signs and symptoms of fibrosing mediastinitis depend upon the structures of the mediastinum that are involved and the extent to which they are compromised. Typical complications result from compression and obstruction of the airways, heart and great vessels, or esophagus. Hemoptysis may also occur. (See 'Clinical presentation' above.)
- Imaging studies are necessary to confirm the presence of an infiltrative process in the mediastinum, to help exclude malignancy, and to assess the integrity of mediastinal structures. A biopsy should not be done if the patient has a typical clinical and radiologic presentation with associated calcification. Biopsies may also be hazardous because of a significant risk of bleeding. (See 'Diagnosis' above.)
- There is no curative therapy for fibrosing mediastinitis. Bronchoscopically placed airway stents and percutaneously placed vascular stents have been used for ameliorating central airway and vascular obstruction, respectively. Surgery has been performed to palliate symptoms by relieving airway, vascular, and esophageal obstruction, but its success has been variable. (See 'Treatment' above.)

REFERENCES

1. Goodwin RA, Nickell JA, Des Prez RM. Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine (Baltimore) 1972; 51:227.
2. http://www.idsociety.org/Content.aspx?id=9088 (Accessed on December 12, 2011).
3. Loyd JE, Tillman BF, Atkinson JB, Des Prez RM. Mediastinal fibrosis complicating histoplasmosis. Medicine (Baltimore) 1988; 67:295.
4. Peebles RS, Carpenter CT, Dupont WD, Loyd JE. Mediastinal fibrosis is associated with human leukocyte antigen-A2. Chest 2000; 117:482.
5. Dines DE, Payne WS, Bernatz PE, Pairolero PC. Mediastinal granuloma and fibrosing mediastinitis. Chest 1979; 75:320.

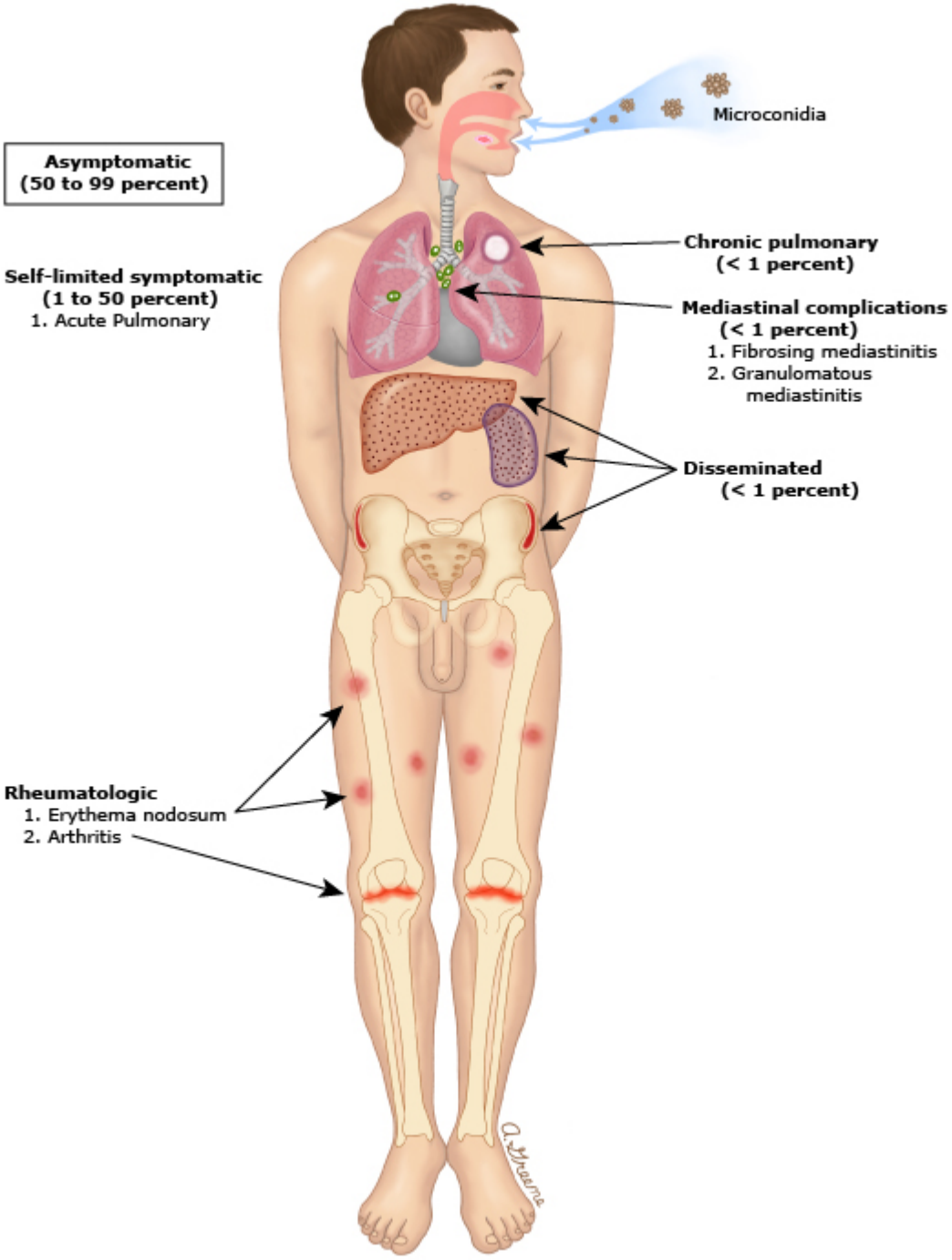
6. SALYER JM, HARRISON HN, WINN DF Jr, TAYLOR RR. Chronic fibrous mediastinitis and superior vena caval obstruction due to histoplasmosis. Dis Chest 1959; 35:364.
7. Morrone N, Gama e Silva Volpe VL, Dourado AM, et al. Bilateral pleural effusion due to mediastinal fibrosis induced by radiotherapy. Chest 1993; 104:1276.
8. Puri S, Factor SM, Farmer P. Sclerosing mediastinitis. Presumed to be due to primary aspergillosis. N Y State J Med 1977; 77:1774.
9. Ahmad M, Weinstein AJ, Hughes JA, Cosgrove DE. Granulomatous mediastinitis due to Aspergillus flavus in a nonimmunosuppressed patient. Am J Med 1981; 70:887.
10. Schowengerdt CG, Suyemoto R, Main FB. Granulomatous and fibrous mediastinitis. A review and analysis of 180 cases. J Thorac Cardiovasc Surg 1969; 57:365.
11. Gilbert HM, Hartman BJ. Short report: a case of fibrosing mediastinitis caused by Wuchereria bancrofti. Am J Trop Med Hyg 1996; 54:596.
12. Lagerstrom CF, Mitchell HG, Graham BS, Hammon JW Jr. Chronic fibrosing mediastinitis and superior vena caval obstruction from blastomycosis. Ann Thorac Surg 1992; 54:764.
13. Sherrick AD, Brown LR, Harms GF, Myers JL. The radiographic findings of fibrosing mediastinitis. Chest 1994; 106:484.
14. Worrell JA, Donnelly EF, Martin JB, et al. Computed tomography and the idiopathic form of proliferative fibrosing mediastinitis. J Thorac Imaging 2007; 22:235.
15. Mitchell IM, Saunders NR, Maher O, et al. Surgical treatment of idiopathic mediastinal fibrosis: report of five cases. Thorax 1986; 41:210.
16. Wheat LJ, Slama TG, Eitzen HE, et al. A large urban outbreak of histoplasmosis: clinical features. Ann Intern Med 1981; 94:331.
17. Wheat LJ. Histoplasmosis susceptibility in humans. In: Fungal Disease, Jacobs PH, Nall L (Eds), Marcel De kker, New York 1997. p.239.
18. Garrett HE Jr, Roper CL. Surgical intervention in histoplasmosis. Ann Thorac Surg 1986; 42:711.
19. Feigin DS, Eggleston JC, Siegelman SS. The multiple roentgen manifestations of sclerosing mediastinitis. Johns Hopkins Med J 1979; 144:1.
20. Peikert T, Colby TV, Midthun DE, et al. Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response. Medicine (Baltimore) 2011; 90:412.
21. McNeeley MF, Chung JH, Bhalla S, Godwin JD. Imaging of granulomatous fibrosing mediastinitis. AJR Am J Roentgenol 2012; 199:319.
22. Weinstein JB, Aronberg DJ, Sagel SS. CT of fibrosing mediastinitis: findings and their utility. AJR Am J Roentgenol 1983; 141:247.
23. Farmer DW, Moore E, Amparo E, et al. Calcific fibrosing mediastinitis: demonstration of pulmonary vascular obstruction by magnetic resonance imaging. AJR Am J Roentgenol 1984; 143:1189.
24. Rholl KS, Levitt RG, Glazer HS. Magnetic resonance imaging of fibrosing mediastinitis. AJR Am J Roentgenol 1985; 145:255.
25. Urschel HC Jr, Razzuk MA, Netto GJ, et al. Sclerosing mediastinitis: improved management with histoplasmosis titer and ketoconazole. Ann Thorac Surg 1990; 50:215.
26. Mathisen DJ, Grillo HC. Clinical manifestation of mediastinal fibrosis and histoplasmosis. Ann Thorac Surg 1992; 54:1053.

27. Seferian A, Steriade A, Jaïs X, et al. Pulmonary Hypertension Complicating Fibrosing Mediastinitis. Medicine (Baltimore) 2015; 94:e1800.
28. Westerly BD, Johnson GB, Maldonado F, et al. Targeting B lymphocytes in progressive fibrosing mediastinitis. Am J Respir Crit Care Med 2014; 190:1069.
29. Qanadli SD, El Hajjam M, Mignon F, et al. Subacute and chronic benign superior vena cava obstructions: endovascular treatment with self-expanding metallic stents. AJR Am J Roentgenol 1999; 173:159.
30. Kalra M, Gloviczki P, Andrews JC, et al. Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. J Vasc Surg 2003; 38:215.
31. Albers EL, Pugh ME, Hill KD, et al. Percutaneous vascular stent implantation as treatment for central vascular obstruction due to fibrosing mediastinitis. Circulation 2011; 123:1391.
32. Kern R, Peikert T, Edell E, et al. Bronchoscopic Management of Airway Compression due to Fibrosing Mediastinitis. Ann Am Thorac Soc 2017; 14:1353.
33. Doty DB. Bypass of superior vena cava: Six years' experience with spiral vein graft for obstruction of superior vena cava due to benign and malignant disease. J Thorac Cardiovasc Surg 1982; 83:326.
34. Doty JR, Flores JH, Doty DB. Superior vena cava obstruction: bypass using spiral vein graft. Ann Thorac Surg 1999; 67:1111.

Topic 4397 Version 12.0

GRAPHICS

Clinical course following exposure to Histoplasma capsulatum



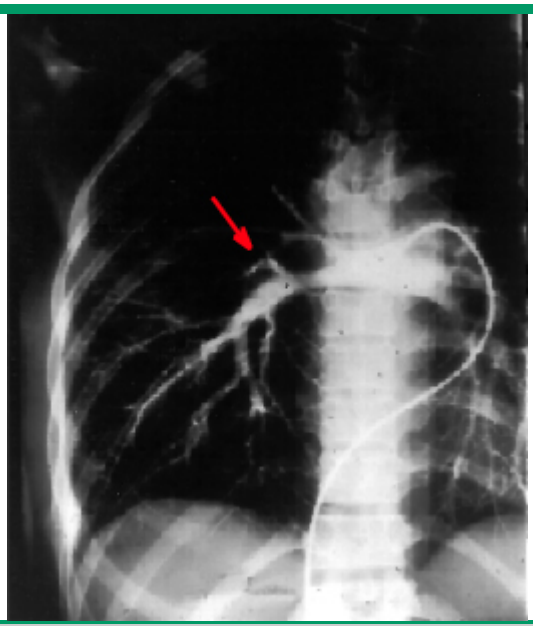
Histoplasmosis remains asymptomatic in most healthy individuals following low level exposure. Symptomatic infection usually causes self-limited pulmonary illnesses, rheumatologic manifestations, erythema nodosum, or pericarditis, but a heavy inoculum can cause diffuse pulmonary involvement. The variation in clinical course noted in the illustration above depends on the extent of exposure to the organism (ie, ~1 percent of individuals exposed to a low inoculum develop self-limited symptomatic infection compared with ~50 percent of individuals exposed to a high inoculum). Persons with emphysema may develop chronic pulmonary histoplasmosis with cavity formation, and individuals at the extremes of age or with underlying immunosuppressive conditions can develop progressive disseminated

disease. Rarely, patients manifest chronic inflammatory conditions such as fibrosing mediastinitis or a sarcoidosis-like illness.

Courtesy of Joseph Wheat, MD.

Graphic 75641 Version 6.0

Pulmonary arteriogram in fibrosing mediastinitis



Pulmonary arteriogram reveals an abrupt cutoff (red arrow) of a right pulmonary artery branch in a patient with fibrosing mediastinitis.

Courtesy of Joseph Wheat, MD.

Graphic 50957 Version 4.0

Contributor Disclosures

Steven E Weinberger, MD Nothing to disclose **Kevin R Flaherty, MD, MS** Grant/Research/Clinical Trial Support: Boehringer Ingelheim [IPF (Nintedanib)]; Roche/Genentech [IPF (Pirfenidone)]. Consultant/Advisory Boards: Boehringer Ingelheim [IPF (Nintedanib)]; Genetech [IPF (Pirfenidone)]; Roche [IPF (Pirfenidone)]; Veracyte [IPF]; Fibrogen [IPF]; Celgene [ILD]; Sanofi-Genzyme [IPF]. **Geraldine Finlay, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy