Fibrosing Mediastinitis

Clinical Presentation, Therapeutic Outcomes, and Adaptive Immune Response

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Abstract: Fibrosing mediastinitis (FM) is a rare disorder characterized by the invasive proliferation of fibrous tissue within the mediastinum. FM frequently results in the compression of vital mediastinal structures and has been associated with substantial morbidity and mortality. Its pathogenesis remains unknown. However, in North America most cases are thought to represent an immune-mediated hypersensitivity response to *Histoplasma capsulatum* infection.

To characterize the clinical disease spectrum, natural disease progression, responses to therapy, and overall survival, we retrospectively analyzed all 80 consecutive patients with a diagnosis of FM evaluated at Mayo Clinic, Rochester, MN, from 1998 to 2007. Furthermore, we characterized the adaptive immune response in 15 representative patients by immunohistochemistry.

The majority of patients presented with nonspecific respiratory symptoms due to the compression of mediastinal broncho-vascular structures. Chest radiographic imaging most frequently revealed localized, invasive, and frequently calcified right-sided mediastinal masses. Most patients had radiographic or serologic evidence of previous histoplasmosis.

In contrast to earlier reports summarizing previously reported FM cases, the clinical course of our patients appeared to be more benign and less progressive. The overall survival was similar to that of age-matched controls. There were only 5 deaths, 2 of which were attributed to FM. These differences may reflect publication bias associated with the preferential reporting of more severely affected FM patients in the medical literature, as well as the more inclusive case definition used in our consecutive case series.

Surgical and nonsurgical interventions effectively relieved symptoms caused by the compression of mediastinal vascular structures in these carefully selected patients. In contrast, antifungal and antiinflammatory agents appeared ineffective. Histologic examination and immunostaining revealed mixed inflammatory infiltrates consistent with a fibroinflammatory tissue response in these histoplasmosis-associated FM cases. The immune cell infiltrates included large numbers of CD20-positive B lymphocytes. As B lymphocytes may contribute to the pathogenesis of the disease, therapeutic B-cell depletion should be investigated as a therapeutic strategy for FM.

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Abbreviations: CT = computed tomography, FM = fibrosing mediastinitis, PET = positron emission tomography, SVC = superior vena cava.

INTRODUCTION

Fibrosing mediastinitis (FM) is a rare disorder characterized by the proliferation of locally invasive fibrous tissue within the mediastinum.[11,19] Its etiology remains unknown. FM may represent a clinical-pathologic syndrome rather than a single disease.[29] A number of triggers with variable geographic frequencies have been associated with FM, including fungal infections, tuberculosis, and sarcoidosis.[12,29] In the absence of a specific identifiable cause, FM is categorized as idiopathic.[29]

In North America, FM is most commonly associated with *Histoplasma capsulatum* infections and considered to represent an immune-mediated hypersensitivity reaction to this fungal organism.[23,33,39] However, these abnormal host responses are exceedingly rare. Only 3 of 100,000 patients with histoplasmosis developed FM during an outbreak of this fungal infection in Indianapolis between 1978 and 1979.[40] The precise pathogenetic mechanisms of FM remain unknown. The exuberant mediastinal fibrosis has been attributed to chronic inflammation in response to various antigens.[11] The reported association of FM with 1 of the MHC class I antigen presentation molecules, HLA-A2, supports the involvement of host-specific immune factors.[27]

In the absence of universally accepted diagnostic criteria, the clinical diagnosis of FM remains challenging. Chest radiographic findings frequently help to distinguish between FM and mediastinal malignancies such as lymphomas. Although tissue sampling is generally not required to establish a diagnosis of FM at experienced referral centers, diagnostic uncertainty by primary treating physicians often leads to surgical biopsies in these patients.

Clinical, radiographic, and histopathologic criteria have been proposed for FM.[11,23] Once malignancy has been excluded, FM needs to be distinguished from other nonmalignant processes, such as mediastinal necrotizing granulomatous lymphadenitis (also called mediastinal granuloma).[11]

The current understanding of FM is derived from single case reports, small case series, and synopses of cases reported in the literature.[3,4,7,9–11,23,24,26,28,29,32,33,35,36,39] Many of these reports do not clearly distinguish between FM and mediastinal necrotizing granulomatous lymphadenitis (mediastinal granuloma).[4,10,32,36]

In North America most cases of mediastinal necrotizing granulomatous lymphadenitis are also attributed to infection with *H. capsulatum*. Most of these patients are asymptomatic, and the diagnosis is made when radiographic abnormalities are discovered incidentally. The long-term prognosis of mediastinal necrotizing granulomatous lymphadenitis is excellent.[11]

In contrast, compression or occlusion of vital mediastinal structures, including the tracheobronchial tree, pulmonary arteries and pulmonary veins, the superior vena cava (SVC), or the esophagus, caused by FM has been associated with high morbidity and mortality.[7,23,24,33,39] The optimal therapeutic approach to FM remains controversial. Isolated case reports have suggested that some patients with FM may benefit from antiinflammatory, antifungal, or antifibrotic medications.[15–17,21,31,33,39] However, larger case series have not confirmed these observations.[23] Similarly the reported results of surgical and nonsurgical interventions to relieve the compression of mediastinal structures range from very successful procedures to therapeutic failures associated with high peri- and postoperative mortality in excess of 30%.[4–7,10,13,18,23,24,30,34,36,38,39]

We conducted the present review of 80 consecutive patients with FM evaluated and treated at Mayo Clinic, Rochester, MN, between 1998 and 2007 to analyze the clinical presentation, radiographic and pathologic findings, therapeutic interventions, and clinical outcomes of the disease. In addition, we characterize the adaptive immune response within FM lesions using 15 representative FM tissue biopsy specimens.

PATIENTS AND METHODS

Patients in the Clinical Case Series

The Institutional Review Board approved this study. The Mayo Clinic electronic medical record database was queried using the terms *fibrosing mediastinitis, sclerosing mediastinitis*, and *mediastinal fibrosis* to identify patients diagnosed with FM during the 10 years from January 1, 1998, to December 31, 2007. The medical records of all identified cases were reviewed, and all patients meeting our clinical case definition for FM were included. Data regarding their clinical presentation, diagnostic evaluation, treatment response, and long-term outcomes were extracted from their medical records.

Definitions

Clinical Definition of FM

Patients included in this study had chest radiographic evidence of an infiltrative mediastinal process and associated vascular, airway, or esophageal compression (n = 78), or, in the absence of any compromised mediastinal structures, histologic features of FM (n = 2) as described below. Patients with mediastinal malignancies and/or prior mediastinal radiation therapy were excluded.

Histologic Case Definition of FM

The histopathologic diagnosis of FM is based on the finding of a predominance of extensive pauci-cellular fibrous tissue (keloid scar tissue) infiltrating and obliterating adipose tissue with or without patchy infiltration of mononuclear cells in the absence of malignancy. All diagnoses of FM were based on this diagnosis provided in the Mayo Clinic clinical pathology reports documenting the review of the pathology specimens by a pathologist at our institution. The 15 cases evaluated by immunostaining were reviewed and confirmed by 1 of the authors (TVC). Because most of the biopsy specimens had been obtained elsewhere, a central re-review of all samples was not feasible.

Histoplasma capsulatum Infection

A *conclusive* diagnosis of infection was assumed in the presence of a positive fungal stain (Grocott methenamine silver) or culture of the biopsy tissue and/or serologic titer ≥1:32 and/or presence of an M or H band by complement fixation/immunodiffusion. A *suggestive* diagnosis was defined as a serologic titer >1:8 and/or radiographic features (pulmonary, splenic, and/or hepatic granulomas) suggestive of previous granulomatous infection.

Outcome Assessments

Therapeutic Response

All patients with more than 3 months of follow-up were included in the analysis of therapeutic benefit. According to the Mayo Clinic standard of care, all chest computed tomography (CT) scans were interpreted by chest radiologists unaware of clinical treatment information for the patient. This clinical interpretation routinely includes comparing the current examination to previous studies. Data regarding radiographic response or progression were collected from these original radiology reports. In addition, all serial CT images were reviewed again by 1 of the coinvestigators (TP) prior to and independent of the tabulation of therapeutic interventions.

Mortality

To evaluate the mortality, we conducted a search of the Social Security Administration death master file using the internet site Ancestry.com (http://Ancestry.com; Ancestry.com Inc, Provo, UT). In addition, we searched the comprehensive commercial database Accurint (http://accurint.com; LexisNexis, Dayton, OH). Based on the Accurint database, the last confirmed date to be alive was defined for all patients 6 months prior to the day of the search, July 1, 2007.

Patients With Tissue Specimens Obtained at Mayo Clinic

A search of the Mayo Clinic pathology database between 1985 and 2006 identified all biopsy specimens with a clinical histopathologic diagnosis of FM. The medical records and pathology slides from these patients were reviewed (n = 15).

Immunostaining

Immunostaining was performed using a DAKO autostaining system (DAKO, Carpinteria, CA). Consecutive sections of formalin-fixed, paraffin-embedded tissues were stained using antibodies against CD3, CD8, CD20, CD138, and S100 (all DAKO). All histopathologic specimens from these 15 patients with FM were evaluated for the presence and distribution of CD3+ and CD8+ T cells, CD20+ B cells, CD138+ plasma cells, and S100+ dendritic cells. After scanning the entire slide at low power in all cases, inflammatory infiltrates, CD8+ T cells, CD20+ B cells, CD138+ plasma cells, and S100+ dendritic cells were semiquantitatively scored as 0 = absent/rare, 1 = moderate, or 2 = frequent. The distribution of these cells was also recorded.

All antibodies used were developed for use in fixed and paraffin-embedded tissues. The staining protocols used were developed in the Clinical Laboratory Improvement Amendments (CLIA)-certified Mayo Clinic pathology laboratory and performed in a research core facility. Representative tissue sections were identified by an expert pulmonary pathologist (TVC).

The immunohistochemistry studies were supported by an IST (investigator sponsored trial) from Genentech, Inc. (South San Francisco, CA). Genentech played no role in designing the study; collecting, analyzing, interpreting the data; or drafting the manuscript. The final manuscript was reviewed and approved by Genentech.

Statistical Analysis

We analyzed patient data using GraphPad Prism 5.0 (La Jolla, CA). Continuous variables were analyzed using the

TABLE 1. Clinical Characteristics of the Clinical and Histologic Series

	Clinical Series* (n = 71)	Histologic Series* (n = 15)	P
Age, median (range), yr	42 (21–75)	36 (27–65)	NS (P = 0.33)
Female sex, %	52	73	NS (P = 0.16)
Anatomic distribution of FM within the mediastinum, % bilateral	18	33	NS (P = 0.29)
Organ compression, no. of patients			
Vascular	34	4	
Bronchial	19	4	
SVC (only)	14	6	NS (P = 0.18)
Esophagus	2	1	
None†	2	0	
Long-term follow-up >3 mo, median mo (no. of patients)	32 (55)	84 (10)	NS (P = 0.12)
Evidence of histoplasmosis (conclusive or suggestive), %	83	80	NS (P = 0.72)

Abbreviations: NS = not significant.

*Series are described in the Methods section. Clinical series includes all Mayo Clinic patients with FM, 1998–2007, excluding the 9 patients in the histologic series. Histologic series includes surgical FM cases at Mayo Clinic, 1985–2006.

†These 2 patients did not meet the clinical criteria for FM (lack of radiographic evidence for mediastinal organ invasion/compression), but both cases had classic histologic findings of FM on histologic examination of their tissue biopsy.

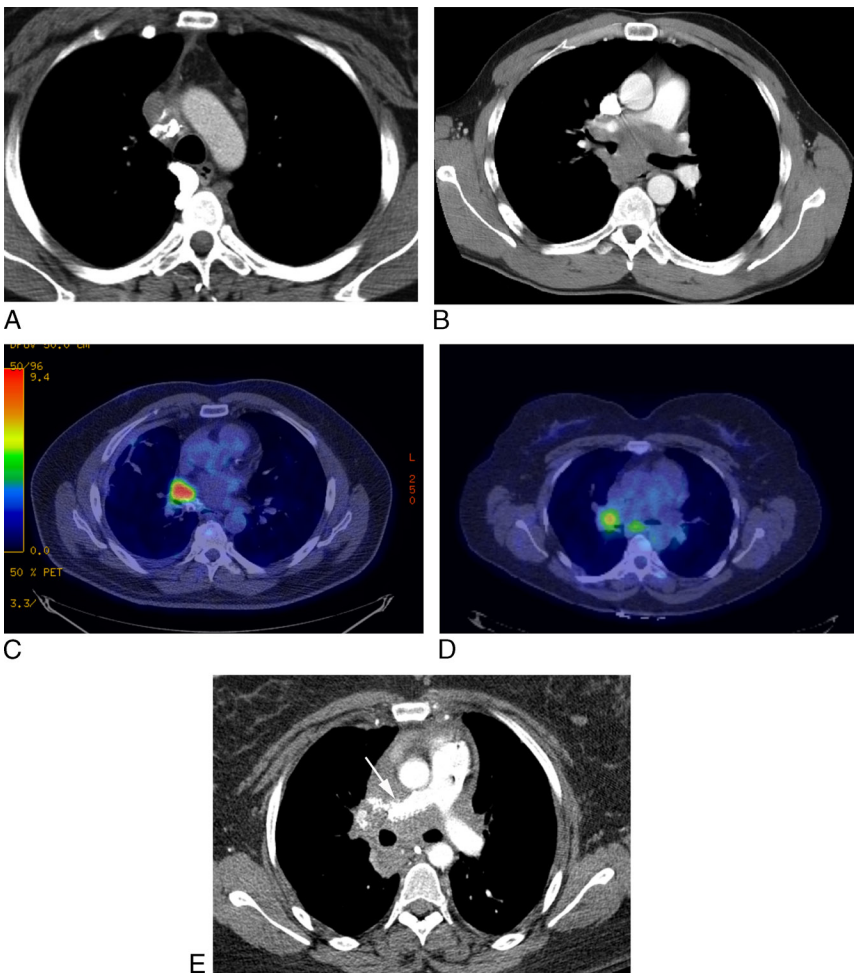

FIGURE 1. Radiographic patterns in fibrosing mediastinitis. A, Localized, calcified mass lesion. B, Diffuse, noncalcified mediastinal infiltration. C and D, PET scans demonstrating increased fluorodeoxyglucose (FDG) uptake of representative FM lesions. E, Representative CT scan demonstrating pulmonary artery compression by FM lesion (white arrow).

Mann-Whitney test and categorical data were compared by either the Fisher exact test or the chi-square test. Survival curves were constructed using the Kaplan-Meier method.

RESULTS

Patients

A search and review of the Mayo Clinic electronic records between 1998 and 2007 identified 80 patients with FM (considered the "clinical series"). Paraffin-embedded biopsy specimens were available for 9 of these patients, and a search of the Mayo Clinic pathology database identified biopsy specimens from 6 additional patients with FM obtained between 1985 and 1997. The clinical characteristics of these 15 patients (considered the "histologic series") were compared to the remaining 71 patients of the clinical series (Table 1). There were no significant differences in clinical, radiographic, or histologic characteristics or survival between the 2 groups. Therefore, we concluded that the cases in the smaller histologic series are representative of the larger clinical series, and we used these specimens to characterize the adaptive immune response by immunostaining.

Demographics and Presenting Symptoms

Eighty patients with FM were identified between 1998 and 2007. The median age was 42 years (range, 21–75 yr). Fifty-four percent were women, and 94% resided in endemic areas for *H. capsulatum* at the time of evaluation at Mayo Clinic.

Only 4 patients (5%) were asymptomatic at the time of presentation. Reported symptoms included respiratory complaints such as dyspnea on exertion (n = 39, 47%), cough (n = 17, 21%), facial swelling, head fullness, or headaches consistent with SVC syndrome (n = 17, 21%), chest pain (n = 16, 20%), and hemoptysis (n = 16, 20%). Twenty-seven patients (34%) presented with multiple symptoms.

Chest Imaging

Chest CT scans were available for review in 74 patients (93%). Focal mediastinal abnormalities were identified in 70 of the 74 patients (95%) (Figure 1A). Diffuse mediastinal infiltration was found in only 4 patients (5%) (Figure 1B). Radiographic abnormalities localized to the right side in 53 (72%) and to the left in 4 patients (5%); bilateral lesions were found in 17 patients (23%). Calcifications were detected in 54 patients (73%).

Positron emission tomography (PET) scans were obtained in 7 patients (9%). Clinical indications included suspicion for malignancy (for example, lymphoma) at the time of diagnosis (n = 5) or concerns about malignancy raised by a new lung lesion during FM follow-up. All PET scans showed increased metabolic activity within the FM-associated mediastinal lesions. PET images were routinely interpreted as highly suspicious for malignancy. Subsequent surgical biopsies (n = 5) revealed FM in 3 cases and granulomatous inflammation in 2 cases. Both patients with granulomatous inflammation had a typical clinical presentation of FM characterized by large airway compression. PET images of 2 representative cases are shown in Figure 1C and 1D.

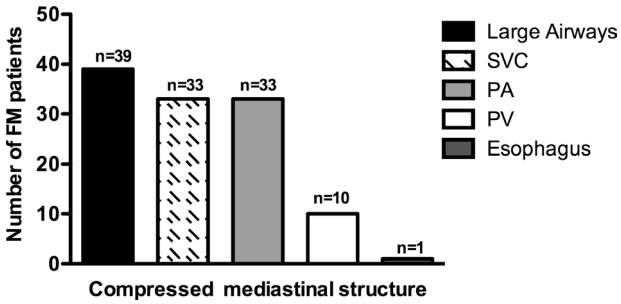

FIGURE 2. Radiographic compression of mediastinal structures in FM (n = 78 patients).

TABLE 2. Therapeutic Interventions for Mayo Clinic FM Patients, 1998–2007 (n = 80 Patients)

Medical therapy	
Antifungal therapy	
Itraconazole	28
Other antifungals	3
Antiinflammatory therapy	
Prednisone	5
Tamoxifen	2
Other agents	2
Nonsurgical procedural interventions	
SVC balloon angioplasty/stent	10*
Endobronchial balloon dilatation/stent	2
Pulmonary artery balloon angioplasty/stent	3*
Pulmonary vein balloon angioplasty	1
Surgical procedures	
Debulking/decompression procedures	4
SVC bypass procedures	
Spiral vein grafts	3
PTFE graft	2
Right ventricle to pulmonary artery conduits	2
Pulmonary resection for uncontrollable hemoptysis	
Lobectomy	4
Pneumonectomy	1
Pulmonary vein reconstruction	1

Abbreviations: PTFE = polytetrafluoroethylene.

*One patient underwent balloon angioplasty and stent placement of both the pulmonary artery and SVC.

Compression of Mediastinal Structures

Anatomic structures within the mediastinum were compressed or obstructed in 78 patients (98%), and more than 2 mediastinal structures were affected in 28 (35%) (Figure 2).

Histopathologic Findings

Surgical resections with diagnostic (n = 29) or therapeutic (n = 14) intent, or autopsy (n = 1) were performed in 44 patients (55%), and tissue for histologic examination was obtained in 43 of 44 cases (98%). A histologic diagnosis of FM was established in 34 of 43 patients (79%). In 6 of the remaining 9 specimens only excessive fibrosis, chronic mixed inflammatory infiltrates, and granulomatous inflammation were described, but no diagnosis of FM was specified in the pathology report. The remaining 3 cases demonstrated only granulomatous inflammation. All 9 cases met the clinical diagnostic criteria for FM. In 8 of these cases compression of the large airway, pulmonary artery, pulmonary vein, or SVC—or a combination thereof—was detected. One individual had isolated compression of the esophagus.

Etiology

Antibodies against *H. capsulatum* were measured by enzyme-linked immunosorbent assay, immunodiffusion, and/or complement fixation in 58 of 80 patients (73%). Antibody

titers established a conclusive diagnosis of histoplasmosis in 17 of 58 patients (29%). Furthermore, yeast forms typical of *H. capsulatum* were seen on Grocott methenamine silver stains in 11 of 43 tissue specimens (26%), and these organisms were always found in the necrotic areas of old necrotizing granulomas. However, fungal tissue cultures remained negative when performed (n = 5). Taken together, a conclusive diagnosis of histoplasmosis was established in 22 of 68 patients (32%) who had either serologic tests or tissue stains for the organism.

Twenty-one additional patients had antihistoplasma antibody titers and radiographic findings suggestive of histoplasmosis. Radiographic evidence of a prior granulomatous infection was detectable in 46 of 74 patients (62%) by chest CT, and based on these radiographic findings another 24 patients were classified as having a suggestive diagnosis of prior histoplasmosis. Therefore, overall serologic and/or radiographic evidence of histoplasmosis was detected in 67 of 80 patients (84%). None of the 80 patient with FM had a history of granulomatous mediastinitis progressing to FM.

Two of the 13 patients without evidence of previous histoplasmosis had radiographic findings of diffuse mediastinal infiltration. One of these 2 individuals and another patient had associated retroperitoneal fibrosis, both features typically detected in patients with idiopathic FM. No other possible etiologic factors were identified.

Treatment

Therapeutic interventions were recommended for 54 patients, and observation was advised in 26. The specific medical, interventional, and surgical treatments used are outlined in Table 2. Primary therapeutic interventions consisted of antifungal and antiinflammatory drug therapy (n = 23 patients), nonsurgical procedural interventions (n = 6 patients) and surgical procedures (n = 14 patients). In 11 patients nonsurgical interventions (9 patients) and surgical procedures (2 patients) were combined with medical therapies.

Observation alone was recommended for patients without symptoms, or those with mild and nonspecific symptoms that could not be attributed clearly to the compressed mediastinal structures. Medical therapy consisted predominantly of antifungal medications in patients with serologic evidence of histoplasmosis.

In contrast, nonsurgical procedural interventions and surgical procedures were primarily aimed at relieving symptoms caused by compression of mediastinal structures in patients judged to be candidates for these procedures. Moreover, nonsurgical procedural interventions were often needed as secondary interventions to manage recurrent symptoms during follow-up (Tables 3 and 4). Follow-up information (follow-up ≥3 mo; median, 37 mo; range, 3–382 mo) to evaluate the long-term therapeutic outcomes of these strategies was available for 69 patients, 52 treated and 17 untreated.

Therapeutic Outcomes

Follow-up of longer than 3 months was available for 17 of 26 (65%) untreated patients (median, 68 mo; range, 6–357 mo). None of these experienced disease progression.

Medical Therapy

Follow-up was available for 28 of 34 (82%) patients treated with a variety of medical therapies. Drug therapy was

TABLE 3. Therapeutic Outcome of All Nonsurgical Interventions for FM Patients (n = 15 Patients)

Indication	Nonsurgical Intervention	Success of Intervention	Complication	Follow-Up Duration (mo)	Follow-Up (≥3 mo)
SVC syndrome	SVC angioplasty/stent	Yes	No	49	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	Yes	No	10	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	Yes	No	89	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	Yes	Cardiac tamponade	59	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	No	No	94	Need for spiral vein graft*
SVC syndrome	SVC angioplasty/stent	Yes	No	116	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	Yes	No	46	Need for repeat angioplasty/stent, stable
SVC syndrome	SVC angioplasty/stent	Yes	No	13	No recurrence
SVC syndrome	SVC angioplasty/stent	Yes	No	30	No recurrence
SVC syndrome/PA compression†	SVC/PA angioplasty/stent	Yes	No	130	Need for repeat angioplasty/stent, stable
Airway compression	Balloon dilatation and stent LMSB	No	Stent occlusion requiring removal	12	Stable
Airway compression	Balloon dilatation bronchus intermedius	No	No	8	Stable
PA compression	PA angioplasty/stent	Yes	No	13	No recurrence
PA compression	PA angioplasty/stent	No	No	23	Stable
PV compression	PV angioplasty	Yes	No	NA	NA (died)

Abbreviations: LMSB = left main bronchus, NA = not available, PA = pulmonary artery, PV = pulmonary vein.

*Due to failed SVC angioplasty, a spiral vein graft was placed.

†Both SVC and PA were treated with angioplasty.

TABLE 4. Therapeutic Outcome of All Surgical Procedures for FM Patients (n = 17 Patients)

Surgical Indication	Surgical Procedure	Surgical Success	Surgical Complication	Follow-Up Duration (mo)	Follow-Up (≥3 mo)
SVC syndrome	Spiral vein graft	Yes	No	46	Need for repeat angioplasty/stent, stable
SVC syndrome	Spiral vein graft	Yes	No	94	Need for repeat angioplasty/stent, stable
SVC syndrome	Spiral vein graft	Yes	Pericarditis	382	No recurrence
SVC syndrome	PTFE graft	Yes	No	51	No recurrence
SVC syndrome	PTFE graft	Yes	No	NA	NA
Hemoptysis	Lobectomy	Yes	No	208	Stable, recurrence with need for bronchial artery embolization 4 yr later
Hemoptysis	Lobectomy	Yes	Stroke with minimal residual defect, respiratory failure	18	No recurrence
Hemoptysis	Lobectomy	Yes	Empyema	70	No recurrence
Hemoptysis	Pneumonectomy	Yes	No	NA	NA
Airway compression	Surgical decompression BI	Yes	No	24	No recurrence
Airway compression	Surgical decompression RMSB	Yes	No	NA	NA
Airway compression	Bronchoplasty LMSB	No	Unscheduled pneumonectomy	162	RMSB stent
PA compression	Bypass	Yes	Tricuspid regurgitation	83	No recurrence
PA compression	Bypass	Yes	No	106	No recurrence
PV compression	Surgical decompression PV	Yes	No	145	Need for repeat angioplasty/stent, stable. Died of non-small cell lung cancer.
PV compression	Surgical decompression and enlargement PV	Yes	No	NA	NA
Esophageal compression	Surgical decompression esophagus	Yes	No	NA	NA

Abbreviations: See previous tables. BI = bronchus intermedius, RMSB = right main bronchus.

administered for a median duration of 8 months (range, 3–129 mo). No patient achieved complete remission, and only a minority (5 of 28, 18%) experienced partial radiographic and/or symptomatic responses. Itraconazole therapy resulted in the radiographically detected decrease in size of the mediastinal lesions in 3 patients, and 1 of these also reported improved dyspnea. A fourth individual experienced a reduction in chest pain following therapy with itraconazole. The clinical significance of the 2 isolated radiographic improvements remains unclear.

Only 1 of 6 patients treated with antiinflammatory therapies benefited from this intervention (improved symptoms and decreased radiographic infiltration). This patient was 1 of the 3 cases with either diffuse mediastinal involvement or retroperitoneal fibrosis (idiopathic FM). The patient's disease subsequently deteriorated despite therapy, and he died as a consequence of progressive pulmonary artery compression and pulmonary hypertension. In 2 patients treated medically (1 with itraconazole, 1 with prednisone), radiographic disease progression was detected during follow-up. In the remaining 21 patients managed medically, FM remained stable.

Medical therapies were generally well tolerated; however, 1 patient discontinued itraconazole because of hives, and another patient was unable to tolerate tamoxifen.

Nonsurgical Procedural Interventions

Fifteen patients were managed with primary nonsurgical procedures. Endovascular interventions effectively relieved symptoms caused by compression of the SVC, pulmonary artery, and pulmonary vein by FM-associated fibrous tissue (see Table 3; Figure 1E). In contrast, the 2 patients treated with bronchoscopic interventions to restore airway patency did not experience symptomatic relief. The nonsurgical procedures were generally safe, and there were no procedure-related deaths. Cardiac tamponade occurred in 1 patient following SVC stenting, but this complication did not have any lasting consequences.

Long-term follow-up information was available for 14 patients (median, 38 mo; range, 8–130 mo). The majority of patients treated with endovascular procedures experienced stent re-stenosis with recurrent symptoms and required repeated interventions at 6–12 months intervals (see Table 3).

Surgical Therapy

The operations performed in the 17 patients managed surgically (primary surgery in 16 and failed stenting in 1 patient) are outlined in Tables 4 and 5. Despite being technically challenging, all but 1 procedure successfully relieved the symptoms caused by the obstruction of various mediastinal structures. The

TABLE 5. Clinical Characteristics of FM Patients in the Histologic Series, Mayo Clinic, 1985–2006 (n = 15 Patients)

Patient	Age/Sex (yr)	Organ Involvement	Chest Radiography	Histoplasmosis	Treatment	Outcome
1	25/M	SVC	Right mediastinal mass	Suggestive	Surgical	NA
2	32/M	PV	Left hilar mass	Conclusive	Surgical and antifungal	NA
3	65/F	Bronchial tree	Right mediastinal mass	Conclusive	Surgical	Stable, 29 mo
4	51/F	Carotid artery, internal jugular vein	Left cervical and right hilar mass	Conclusive	Surgical	NA
5	31/F	SVC	Right mediastinal mass	Suggestive	Surgical	Stable, 24 mo
6	27/F	PA	Right mediastinal mass	Conclusive	Surgical and antifungal	NA
7	27/F	PV	Diffuse mediastinal infiltration	Conclusive	Interventional	Died
8	48/F	Bronchial tree	Left mediastinal mass	Suggestive	Surgical	Stable, 113 mo
9	35/M	PA and bronchial tree	Bilateral hilar masses	Conclusive	Surgical	NA
10	43/F	SVC	Right mediastinal mass	NA	Surgical	Stable, 207 mo
11	44/M	Chest wall	Anterior mediastinal mass	NA	Surgical	Stable, 224 mo
12	27/F	Bronchial tree	Right mediastinal mass	Conclusive	Surgical and antifungal	Stable, 24 mo
13	59/F	SVC	Right mediastinal mass	Conclusive	Surgical	Stable, 112 mo
14	36/F	SVC	Right mediastinal mass	Conclusive	Surgical	Stable, 95 mo
15	58/F	SVC	Right mediastinal mass	NA	Surgical and antifungal	Stable, 44 mo

Abbreviations: See previous tables.

unsuccessful operation, a failed bronchoplasty of the left mainstem bronchus, required an unscheduled left pneumonectomy. There were 4 surgical complications and no peri- and postoperative deaths (see Table 4). The only peri- and postoperative complication of significance was 1 patient suffering minimal neurologic deficit (mild weakness) following a perioperative stroke.

Long-term follow-up information (median, 89 mo; range, 18–382 mo) was available for 12 of 17 patients (71%) in whom the surgical intervention had a therapeutic intent. The benefits of the surgical interventions were only temporary in 5 of the 12 patients (42%), and they required subsequent procedures for recurrent symptoms: balloon angioplasty/stenting for vascular graft obstruction (n = 3 patients), angiographic embolization for hemoptysis (n = 1 patient), and endobronchial stent placement for airway torsion (n = 1 patient) (see Table 4).

Survival

To determine the survival endpoint for our patient cohort, we searched the Social Security Death Index, and the commercial Accurint database was searched in addition to the available clinical follow-up. Using this approach the median follow-up was 68 months (range, 0–401 mo). Five deaths were identified. Two of these were the result of FM. One patient died shortly after the initial presentation from the hemodynamic consequences of severe pulmonary venous obstruction, despite temporary improvement after angioplasty. The second fatality was a patient with idiopathic FM and associated retroperitoneal fibrosis. He

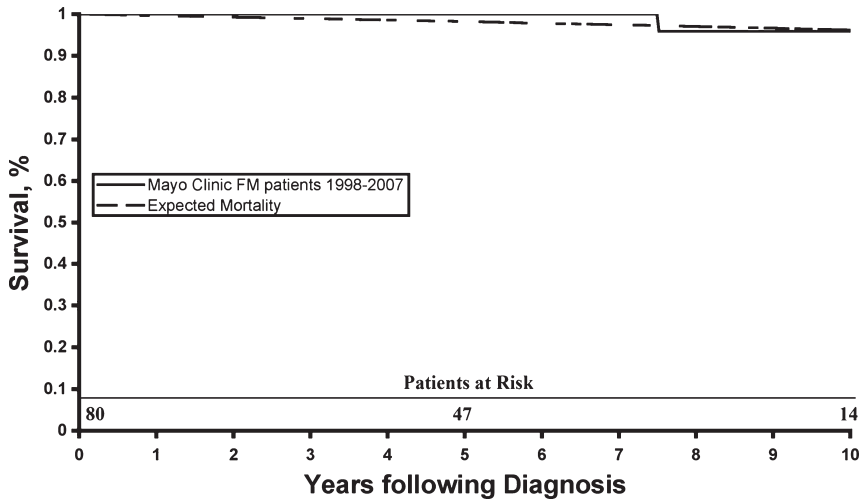

FIGURE 3. Overall survival of FM patients evaluated at Mayo Clinic Rochester, MN, 1998–2007 compared to the survival of age-matched controls (expected mortality) (Kaplan-Meier curve).

TABLE 6. Histologic and Immunohistochemistry Staining of FM Tissue Samples (n = 15 Patients)

Patient	Inflammation	CD20	Pattern	CD8	CD138	S100
1	++	++	Peripheral rim	+	++	0
2	++	++	Peripheral rim, follicles	+	++	+
3	++	+	Follicles	+	+	+
4	+	++	Follicles	+	+	+
5	++	++	Peripheral rim	++	+	++
6	+	+	Follicles	0	+	0
7	++	++	Peripheral rim, follicles, sheets	+	0	0
8	+	+	Follicles	+	+	0
9	+	+	Peripheral rim, follicles	0	0	0
10	++	++	Peripheral rim	+	+	+
11	+	+	Follicles	+	0	+
12	+	+	Follicles	0	+	0
13	+	++	Peripheral rim, sheets	++	0	0
14	++	++	Peripheral rim, follicles	+	+	0
15	0	+	Follicles	0	0	0

initially responded to immunosuppressive therapy but eventually died 10 years after the diagnosis from pulmonary hypertension caused by progressive pulmonary artery compression. We note that both of these patients had bilateral mediastinal involvement. Two additional patients died of non-small cell lung cancer, which developed 12 and 29 years after the diagnosis of FM, respectively. One additional patient died of an unknown cause. This patient originally presented with right-sided bronchial compression and broncholithiasis, for which he underwent bilobectomy. The death occurred 8 years following his diagnosis and surgical intervention.

Overall, the Kaplan-Meier analysis did not reveal a difference between the observed and predicted mortalities (Figure 3). However, the small number of deaths (n = 5) precludes a

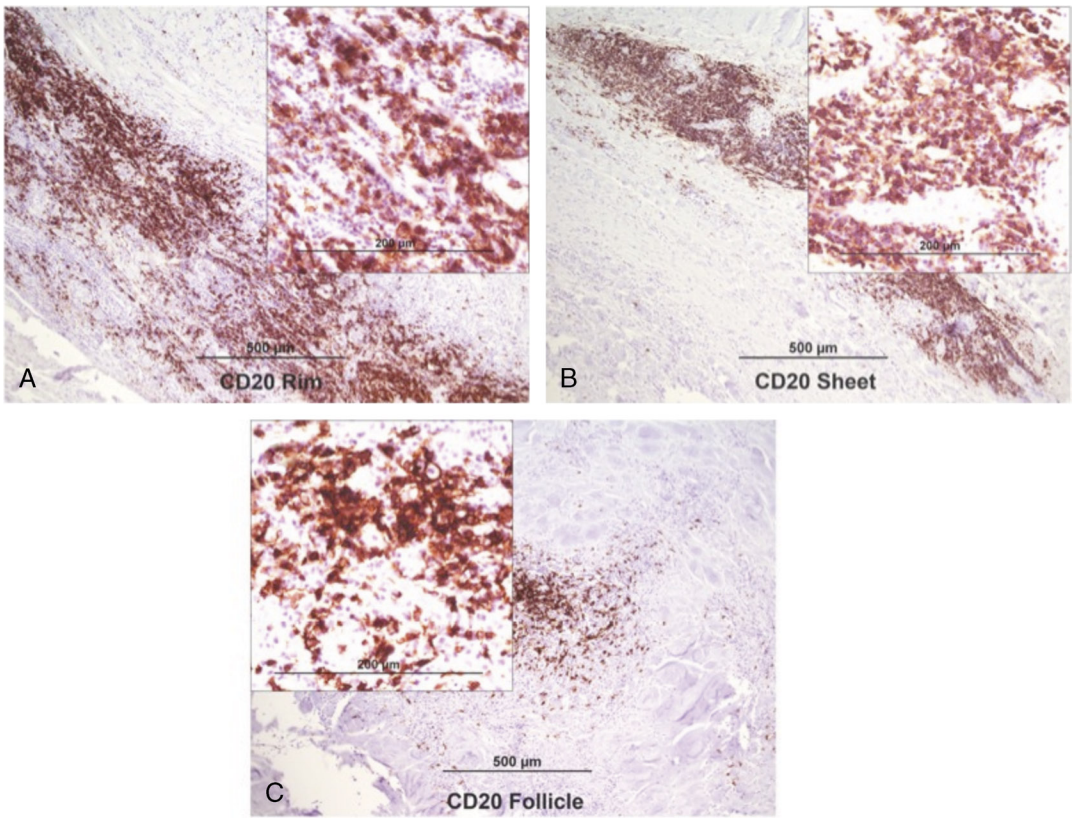

FIGURE 4. B lymphocytes in FM. Representative photomicrographs of the immunostaining for CD20-positive B lymphocytes. A, Peripheral rim of B lymphocytes. B, Infiltrating sheet of B lymphocytes. C, Poorly formed lymphoid follicle without germinal center.

meaningful statistical analysis of the Kaplan-Meier curves. It is noteworthy that both FM-related fatalities occurred in patients with bilateral mediastinal involvement, suggesting that such individuals are perhaps at a higher risk for adverse outcomes.

Characterization of the Adaptive Immune Response

Paraffin-embedded tissue samples were available for 15 FM cases evaluated at Mayo Clinic between 1985 and 2006 (the histologic series). Based on their clinical characteristics and therapeutic outcomes, these patients were representative of our larger clinical cohort (see Table 1). The clinical characteristics, treatments, and therapeutic outcomes are summarized in Table 5.

Detailed results of the histologic and immunohistochemical analysis are listed in Table 6. Mixed, lymphocytic inflammatory infiltrates were almost universally present (14 of 15 patients). CD20-positive B lymphocytes accounted for a large proportion of these cells and were seen in all cases examined. These cells either formed a peripheral rim surrounding the fibrotic lesion or clustered within infiltrating sheets of cells (Figure 4A and 4B). Alternatively, they formed poorly structured lymphoid follicles without germinal centers (Figure 4C). These distribution patterns varied between patients but were simultaneously detected in the same cases. CD3- and CD8-positive lymphocytes were also frequently detected (11 of 15 patients), but their distribution was distinct from the CD20-positive B lymphocytes (see Table 6). T lymphocytes predominately infiltrated into fibrotic

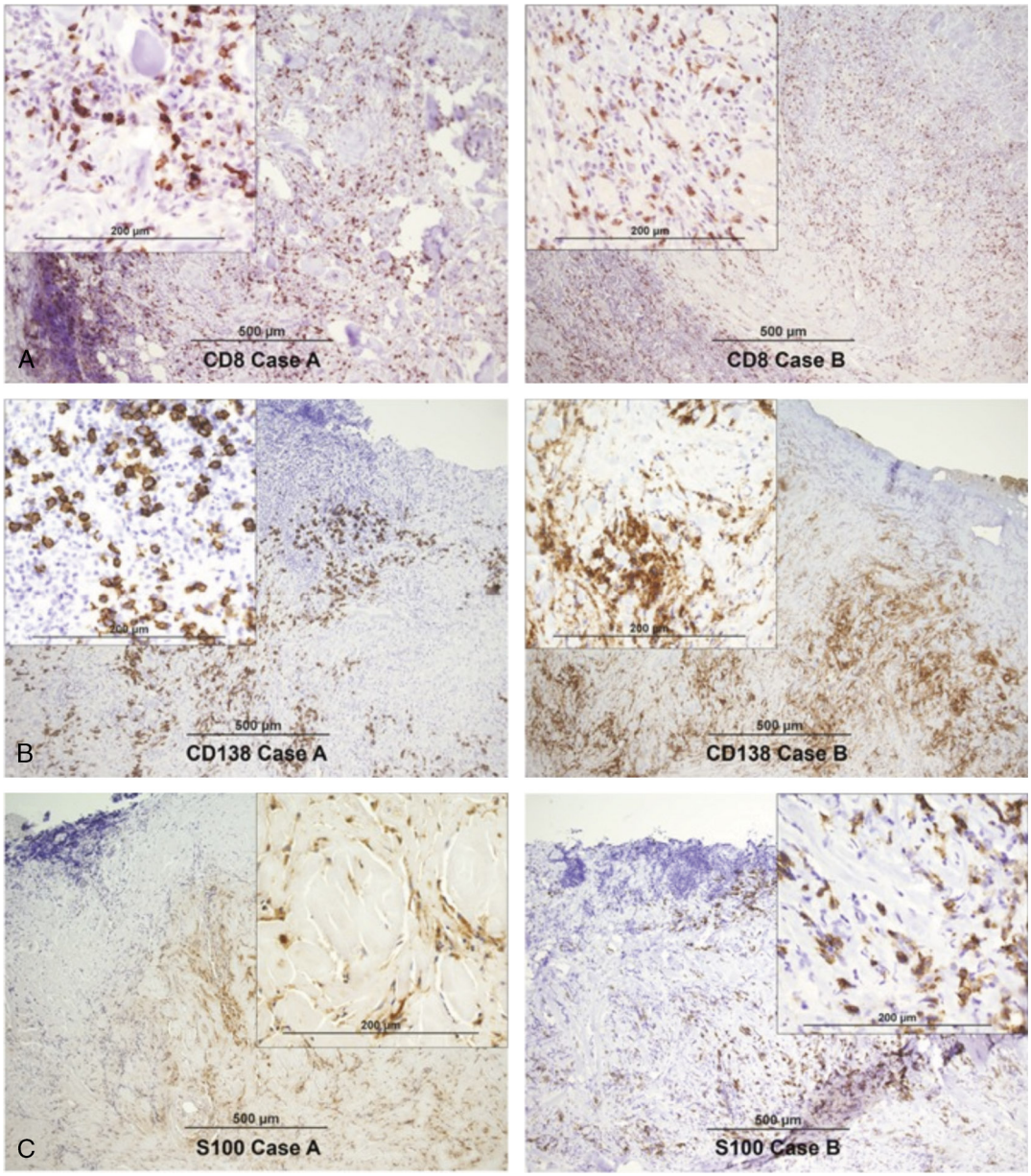

FIGURE 5. A, CD8-positive T lymphocytes; B, CD138-positive plasma cells; and C, S100-positive dendritic cells in FM. Tissue sections are immunostained, and for each cell type photomicrographs of 2 representative cases are displayed.

areas and were found in close proximity to smooth muscle actin-positive fibroblasts rather than in the periphery of the lesions (Figure 5A).

CD138-positive plasma cells (Figure 5B) and S100-positive dendritic cells (Figure 5C) were also frequently seen. Their distribution resembled that of the T lymphocytes.

DISCUSSION

FM is a rare disease, and universally accepted diagnostic criteria are lacking. Previous reports on FM include retrospective case series with limited numbers of patients, synopses of previously reported cases, or studies focusing on specific subgroups of FM patients, such as surgically managed cases, idiopathic cases, or cases referred for the management of airway involvement.[1,3,4,7–11,14,23,24,26,32,33,36,39] Moreover, heterogeneous case definitions have been applied, and frequently FM and necrotizing granulomatous lymphadenitis (mediastinal granuloma) have not been differentiated.[4,7,9,10,24,32,36,39] Consequently, it has been difficult to predict the clinical course of patients with FM and their response to medical therapy or surgical interventions. Moreover, little is known about the pathogenesis, which has hampered the development of novel therapeutic approaches.

The present analysis of 80 consecutive patients with FM from an area where infections with *H. capsulatum* are endemic provides the following novel insights about this rare disease: the prognosis of FM is better than previously thought; therapy with antifungal and antiinflammatory agents provides little benefit; nonsurgical and surgical vascular interventions are safe and provide symptomatic relief but their benefits are of limited duration. Last, but not least, our immunohistochemistry analyses show that B lymphocytes represent a prominent component of the persistent inflammation within the FM lesions.

In North America the majority of patients with FM residing in endemic areas for *H. capsulatum* have either serologic or pathologic evidence of prior histoplasmosis and radiographic findings characteristic of a previous granulomatous infection.[4,23,29,33,39] Earlier studies had proposed the hypothesis that mediastinal necrotizing granulomatous lymphadenitis and FM represent a continuum.[4] However, we did not observe the evolution of necrotizing granulomatous lymphadenitis into FM in our patient cohort. Only a small number of patients (n = 3) had either diffuse mediastinal involvement or associated retroperitoneal fibrosis as evidence of the idiopathic FM.

The disease severity of FM at presentation is variable and ranges from incidentally discovered, asymptomatic mediastinal mass lesions to acute cardiovascular decompensation or life-threatening hemoptysis. The extent of the initial clinical symptoms and their relationship to the compromise of specific mediastinal structures should guide the therapeutic approach. Our data suggest that progressive mediastinal fibrosis is rare in patients with unilateral mediastinal involvement, particularly when symptoms are nonspecific and not clearly attributable to the compression of mediastinal structures. Such patients should be reassured and followed clinically and radiographically for disease progression.

We did not detect convincing evidence of the success of antifungal or conventional antiinflammatory therapy. Therefore, these therapies should be avoided in FM, and glucocorticoid therapy should be reserved for patients with idiopathic FM.

In contrast, FM patients presenting with clinical symptoms caused by the compression of mediastinal vascular structures with significant hemoptysis or with bilateral involvement should undergo a detailed evaluation to characterize the extent of the mediastinal involvement. These patients may be candidates for surgical and nonsurgical therapeutic interventions. In contrast to previous reports that raised concerns about the safety and effectiveness of such procedures and even reported fatalities, our observations at a specialized tertiary care center (Mayo Clinic Rochester) reflecting more recent advances in surgical techniques suggest that these interventions are generally safe and effective if performed by experienced providers in these carefully selected patients.[23]

Unfortunately, the durability of the therapeutic success of these interventions is frequently limited. Subsequent stent or graft obstruction often requires repeated nonsurgical interventions to maintain long-term patency. The data presented here expand on the findings of 2 reports from our institution describing 6 patients treated with endovascular stents and 5 who underwent surgical reconstruction of the pulmonary artery.[1,8] The exact reasons for the failure of vascular procedures to provide long-lasting benefits could not be established clearly in all cases. There was no apparent radiographic progression of the lesions in these cases. However, stent collapse, vein graft contraction, and thrombosis were reported in individual cases. The role for bronchoscopic relief of symptomatic airway compression is unclear, as only 2 patient had this intervention and neither appeared to benefit.

The overall survival of our patient cohort was independent of the extent of mediastinal infiltration (bilateral vs. unilateral involvement) at diagnosis and was similar to the survival of age-matched controls. This is substantially better than the survival stated in prior reports.[23] Several factors may contribute to these observed differences in mortality. First, differences in case definitions need to be considered. Second, publication bias may have favored the reporting of more severe cases in the past. Third, recent advances in chest radiography may cause some lead-time bias.

Most patients were able to maintain a functional lifestyle, and severe disability was rare. Overall, there were only 2 confirmed FM-related deaths, both of which occurred in patients with bilateral mediastinal involvement. This is consistent with observations by others indicating that bilateral mediastinal involvement by FM is associated with a distinctly worse prognosis.[3] Novel therapeutic strategies are needed for patients with bilateral mediastinal involvement, progressive mediastinal fibrosis, symptomatic airway compression, and those who experience recurrent vascular obstruction following surgical and nonsurgical interventions.

PET scanning has developed into a widely available and valuable diagnostic tool. It is routinely used to evaluate known or suspected malignant pulmonary lesions and lymphoma. Considering the high frequency of radiographic surveillance in patients with FM and the diagnostic considerations of lymphoma during the evaluation of a mediastinal mass, it is not surprising that 7 of our patients (9%) underwent PET scanning for these indications. Selected previous case reports demonstrated variable metabolic activity within the mediastinal lesions of FM and suggested a possible correlation with disease activity.[2,22,37] Interestingly, all 7 PET scans in our series showed increased ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake, suggesting ongoing inflammation within the lesion. However, none of these patients experienced disease progression.

Based on their histologic review of 30 idiopathic cases of FM, Flieder and colleagues[9] proposed that FM is not a purely fibrotic lesion but rather represents a fibroinflammatory disease with a variable degree of inflammation. Our analysis of 15 patients with predominantly histoplasmosis-associated FM, who were treated with surgical or nonsurgical interventions, confirmed various degrees of mixed inflammatory infiltration in all cases. The immunophenotyping of these inflammatory

infiltrates identified a large number of CD20-positive B lymphocytes. These B cells either accumulate in the periphery or cluster in sheets or poorly formed lymphoid follicles within the fibrous tissue. We propose that these infiltrating B lymphocytes play a pathogenic role in FM, and consequently, represent a rational therapeutic target. In the absence of any effective medical therapy to date, depletion of B lymphocytes may be a potential therapeutic option for those patients with FM who have a poor prognosis (bilateral mediastinal or progressive involvement), suffer symptomatic airway compression, or have recurrent symptoms attributable to obstruction of mediastinal structures.

Further support for such an approach comes from murine models of bleomycin-induced fibrosis as B lymphocytes, specifically CD19 expression, were shown to be required for the development of fibrosis.[20] This is consistent with reports demonstrating effective depletion of B lymphocytes within fibrotic skin lesions and initial therapeutic success of rituximab in scleroderma.[25,41]

The current study is limited by its retrospective design and incomplete long-term follow-up information. Although difficult to perform, prospective studies to confirm and further characterize the disease spectrum, natural history, and outcome of FM are needed. Furthermore, since the disease spectrum and prognosis may be affected by the diagnostic criteria used, it is crucial to standardize the case definitions. Our diagnostic criteria closely resemble the case definitions of FM used by the majority of authors. In addition to clinical and radiographic criteria, our case definition includes information obtained from biopsies. Although the histologic pattern of FM is nonspecific, it is highly characteristic and distinctly different from other processes within the mediastinum, such as mediastinal necrotizing granulomatous lymphadenitis associated with histoplasma infection.[4,9,26,32,33,36,39] In contrast to the largest FM case series reported previously, we decided not to limit our inclusion criteria to the compression of pulmonary arterial, venous, or bronchial structures, but also included cases with invasive mediastinal mass lesions with isolated SVC or esophageal compression, as well as cases with an invasive mediastinal mass and excessive histologic deposition of fibrous tissue and lack of mediastinal compromise.[23] Even if we excluded the 18 patients with isolated SVC or esophageal compression lacking mediastinal compression, the surgical success rates as well as the overall survival remain unchanged. Moreover, if the exclusion criteria (definition of mediastinal granuloma) provided by Loyd et al[23] were applied to the current patient cohort, only 5 patients would have to be excluded. These patients were either asymptomatic (n = 4) or had no organ compression (n = 1). Nevertheless, tissue biopsies and chest-radiographic findings clearly supported a diagnosis of FM in these patients.

This suggests that the observed differences between the current study and previous reports are more likely to be the result of differences in study design than in case definitions. Our cohort of consecutive patients is more likely to reflect the natural disease spectrum than a synopsis of all previously reported cases, which is likely to be confounded by publication bias toward more severe cases with worse outcomes.[23]

In conclusion, most cases of FM can be diagnosed based on clinical and radiographic criteria. Tissue biopsies are needed only if diagnostic uncertainty remains in asymptomatic patients presenting without compression of mediastinal structures. The analysis of this large cohort of consecutive patients with FM indicates that the clinical course of FM overall appears to be more favorable than previously reported, and patients are less likely to progress. In contrast to mostly ineffective medical approaches, surgical and nonsurgical interventions can effectively relieve the symptoms caused by compression of vascular mediastinal structures. The overall survival of FM is similar to age-matched controls. PET scanning and immunophenotyping suggest that FM from histoplasmosis is associated with persistent inflammation characterized by large numbers of CD20-positive B lymphocytes. These B lymphocytes may contribute to the pathogenesis of the disease. Therapeutic B-cell depletion should be investigated as a potential therapeutic strategy for selected patients with FM, particularly those with progressive disease, recurrent compression of mediastinal structures, or the idiopathic variant of the disease.

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