Thirty-one patients with mediastinal granuloma and fibrosing mediastinitis were seen at the Mayo Clinic from 1975 through 1977. Review of this series reveals that surgery is necessary to establish a diagnosis if the lesions are noncalcified and indeterminate. Fibrosing mediastinitis most likely develops after rupture of the fibrocaceous material from mediastinal lymph nodes into the mediastinum. Thoracotomy, with evacuation of the granulomas, is recommended, especially when the lesions are large, in order to prevent subsequent fibrosing mediastinitis with involvement of the contiguous structures, such as the superior vena cava, azygos vein, trachea, esophagus, and left atrium. In most patients, obstruction of the superior vena cava develops slowly, and efficient collateral venous circulation occurs, allowing long-term survival and minimal disability.

Mediastinal granuloma with fibrosing mediastinitis generally is considered a complication of histoplasmosis. With healing of the acute infection, caseous and fibrocaceous granulomas develop in the regional mediastinal lymph nodes, typically located adjacent to the main-stem bronchi. Occasionally, these granulomas rupture, spreading their caseous material into the mediastinum, where an intense inflammatory reaction develops. During the ensuing months and years, the resultant inflammation heals, producing variable amounts of collagen, which is now recognized as fibrosing mediastinitis. Because dense collagen can entrap vital structures (such as the superior vena cava, trachea, esophagus, and left atrium), fibrosing mediastinitis becomes a formidable therapeutic problem to the surgeon. Currently, there is no universally acceptable treatment for the complications of fibrosing mediastinitis. Consequently, prevention by prophylactic removal of the mediastinal granuloma, especially when large, has become our treatment of choice.

It is difficult to prove that all cases of mediastinal granuloma and fibrosing mediastinitis are due to histoplasmosis when the cultures and silver stains are so often negative; however, we have not seen fibrosing mediastinitis with tuberculosis or sarcoidosis, and we have seen the complication with histoplasmosis. It is also difficult to prove that fibrosing mediastinitis does develop from preexisting established mediastinal adenopathy. We have encountered the complication in histoplasmosis, and data from one such patient with active granulomatous disease, fibrosing mediastinitis, and positive cultures are included in this review. We have not seen preexisting established mediastinal adenopathy in primary tuberculosis or stage 1 sarcoidosis give rise to the complication of fibrosing mediastinitis. We think

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Patients Tested</th>
<th>Results Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests for histoplasmosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement-fixation</td>
<td>23</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Immunodiffusion</td>
<td>23</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Culture of sputum</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Culture of tissue</td>
<td>26</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Culture of material from fiber-optic bronchosopic procedure</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Histopathologic study for caseous granuloma</td>
<td>26</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Silver stain for <em>H. capsulatum</em></td>
<td>22</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Test with PPD</td>
<td>24</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Tests for acid-fast bacilli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Material from fiberoptic bronchosopic procedure</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Culture of tissue</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
</tbody>
</table>

*From the Mayo Clinic and Mayo Foundation, Rochester, Minn. Read before the First International Histoplasmosis Conference, Atlanta, April 10-12, 1978.

**Professor of Medicine.
†Assistant Professor of Surgery.

Manuscript received April 3; revision accepted July 27.
Reprint requests: Section of Publications, Mayo Clinic, Rochester, Minnesota 55901.
that the association is a real one, but there is no proof.

Several previous reports from the Mayo Clinic have summarized our experience with mediastinal granuloma and fibrosing mediastinitis. In 1954, Kunkel and associates\(^1\) described a series of 16 patients with mediastinal granuloma. In 1967, Sakulsky and co-workers\(^2\) added 30 patients seen between 1954 and 1964. In 1975, Strilman and associates\(^3\) reported the findings from 47 patients seen between 1965 and 1974. In 1976, Dukes and co-workers\(^4\) described ten patients with esophageal involvement from mediastinal granuloma. In addition, Dozois and co-workers\(^5\) in 1968 described two patients with fibrosing mediastinitis involving major bronchi. The present report involves 31 additional patients with mediastinal granuloma and fibrosing mediastinitis who were seen at the Mayo Clinic from 1975 through 1977.

**MATERIALS AND METHODS**

Of the 31 patients, 21 were men and 10 were women, with ages ranging from 17 to 76 years (mean, 45 years). Eight patients were asymptomatic, and mediastinal granuloma was discovered because of an abnormal mass evident on the routine roentgenogram of the chest. Twenty-three patients had one or more symptoms of cough (18 patients), pain in the chest (ten patients), dyspnea (10 patients), and hemoptysis (three patients). Three patients had dysphagia. Five patients had wheezing, five had distention of the veins in the neck, and two had distention of the veins in the neck along with distended collateral veins in the wall of the chest.

**RESULTS**

**Clinical Findings**

Routine laboratory tests were not helpful in establishing a diagnosis. Some of the diagnostic studies were pertinent (Table 1), but there were no tests specific for the diagnosis of mediastinal granuloma. Complement-fixation tests for histoplasmosis were positive in nine of 23 patients, and the immunodiffusion test for histoplasmosis was positive in one of 23 patients.

Cultures of sputum and of material from the fiberoptic bronchoscopic procedure were negative for histoplasmosis in 16 and 19 patients, respectively. Culture of tissue was positive for histoplasmosis in one of 28 excised specimens. Staining with methenamine silver was performed in 22 cases but was positive for *Histoplasma capsulatum* in only four.

A positive test with purified-protein derivative of tuberculin (PPD) was found in three of 24 patients, but cultures of sputum, fiberoptic bronchoscopic washings, and tissue all were negative for acid-fast bacilli. Of the 31 patients, 26 had a histologic diagnosis made at surgery, and the specimen showed caseous granuloma, with or without fibrosing mediastinitis.

The roentgenographic findings were abnormal in all 31 patients. Eighteen patients had a right paratracheal mass, nine of these with superior mediastinal widening (Fig 1). Other roentgenographic findings and the number of patients with each were as follows: calcified granuloma with hilar enlargement, five; hilar enlargement with collapse of right middle lobe, three; hilar enlargement with collapse of right lower lobe, two; left hilar mass with loss of volume of left lower lobe, two; and calcified granuloma with left hilar enlargement, one.

An angiogram was performed in one patient (Fig 2) and showed decreased perfusion to the right upper lobe, compression of superior and inferior pulmonary veins, and decreased venous return. A superior venacavogram was performed in one patient (Fig 3) and showed obstruction to the superior vena cava.

A bronchoscopic procedure was performed in 18 patients and an esophagoscopic examination in four. Nine patients had obstruction of a bronchus, and two had an esophagobronchial fistula.

**Complications**

The most common complications of mediastinal granuloma were fibrosing mediastinitis (11 patients) and obstruction of the superior vena cava (six patients). Other complications and the number of patients with each were as follows: obstruction of innominate vein, three; obstruction of azygos vein,
However, surgery was performed in 26 of the 31 patients, both to establish a diagnosis in patients with a noncalcified mediastinal mass and to remove as much granuloma as was technically feasible. The types of surgery and the number of patients with each were as follows: thoracotomy with biopsy, 14; mediastinoscopic examination followed by thoracotomy and removal of granuloma, six; mediastinoscopic examination, two; thoracotomy with resection and closure of esophagobronchial fistula, two; thoracotomy and right pneumonectomy, one; and thoracotomy and angioplasty of vena cava, one. Five patients had asymptomatic calcified granulomas and were observed.

Twenty-four patients underwent either thoracotomy or mediastinoscopic examination followed by thoracotomy. The mediastinoscopic procedure is an excellent means of investigating superior mediastinal disease, but the procedure does carry more risk of bleeding in patients with obstruction of the superior vena cava, and there is an increased chance of ligating important collateral vessels in an effort to control bleeding. In many of the patients in our series, the mediastinum was frozen in place with dense collagen, and normal anatomic structures could not be identified. Because of these reasons, mediastinoscopic examination should be avoided in patients with fibrosing mediastinitis and obstruction of the superior vena cava. One patient with massive involvement and obstruction of the right superior pulmonary vein (Fig 4) required a pneumonectomy to remove the extensive fibrosing mediastinitis. Thoracotomy and angioplasty of the superior vena cava was performed in only one patient, and the superior vena cava was obstructed again within six months of surgery, due to fibrosing mediastinitis. One patient with extensive granulomatous disease documented at thoracotomy had smears and cul-

---

Figure 2. Pulmonary angiograms of patient with fibrosing mediastinitis. A (top), Decreased perfusion to right upper lobe. B (bottom), Decreased venous return from right upper lobe caused by compression of superior and inferior pulmonary veins.

One; obstruction of right superior pulmonary vein, one; obstruction of right middle lobe bronchus, three; obstruction of right lower lobe bronchus, two; obstruction of left lower lobe bronchus, two; pericardial involvement, three; esophageal compression, two; traction diverticulum of esophagus, two; esophagobronchial fistula, two; and widening carina and involvement of right main-stem bronchus, two.

One patient died of cardiopulmonary failure 26 years after the diagnosis was made in 1950 by exploratory thoracotomy. Postmortem examination showed massive mediastinal involvement with obstruction of the superior vena cava and compression of pulmonary veins.

Treatment

There is no universally accepted treatment for mediastinal granuloma and fibrosing mediastinitis;
tures of tissue that were positive for *H capsulatum*, and this patient was treated with amphotericin B for six weeks after surgery.

Corticosteroids were administered to two patients; both had surgically proven disease with no evidence of active infection. One patient was given therapy with steroids because of bronchial obstruction, in an effort to prevent bronchostenosis; the other patient, with involvement of the superior vena cava, was given steroids in order to prevent further scarring and obstruction. No complication occurred from the therapy with corticosteroids during a three-month period in which they were administered every other day, but there was no objective evidence that the steroids prevented scarring and obstruction from the fibrosing mediastinitis. There is no reason to believe that therapy with corticosteroids can alter the chronic long-standing fibrotic process of fibrosing mediastinitis.

**DISCUSSION**

Progressive fibrosing mediastinitis is probably a late stage of mediastinal granuloma due to histoplasmosis. Although about 40 percent of the patients with mediastinal granuloma are asymptomatic (16 of 30 patients in our first series, 20 of 47 patients in our second series, and eight of 31 patients in the present series), the remainder have cough, dyspnea, pain in the chest, fever, wheezing, dysphagia, and hemoptysis. One of the most common physical findings is distention of the veins in the neck from obstruction of the superior vena cava. Mediastinal granuloma with fibrosing mediastinitis is the most common cause of benign obstruction of the superior vena cava.

In our experience, in 25 percent of the patients with mediastinal granuloma, complete excision of the granuloma can be achieved (17 of 30 patients in our first series, four of 47 patients in our second series, and six of 31 patients in the present series).

Complement-fixation and immunodiffusion tests may be positive in some cases and aid in the diagnosis, but these tests are of limited value. Because cultures of sputum are rarely positive, surgery is usually necessary to establish a diagnosis in indeterminate hilar and mediastinal masses. Asymptomatic calcified granulomas can be observed clinically without surgical intervention (five patients in this series). In the present series, only four of 22 cases had positive silver staining for *H capsulatum*. Twelve cases in our previous two reports had positive methenamine silver staining. Ferguson and Burford reviewed 43 cases of mediastinal granuloma and were unable to identify any Histoplasma-like structures in a study from an endemic area. Thus, identifying the yeast forms of the organism with methenamine silver stain is not diagnostic of mediastinal granulomas and fibrosing mediastinitis.

The course of the mediastinal granuloma with fibrosing mediastinitis is usually benign. One patient in our series died of cardiorespiratory failure 26 years after the diagnosis was confirmed by thoracotomy, and postmortem examination revealed massive mediastinal involvement with obstruction of the superior vena cava and compression of pulmonary veins. In most patients, obstruction of the superior vena cava develops slowly, and efficient collateral venous circulation occurs, allowing long-term survival and minimal disability. Reconstructive surgery was performed in one of these patients, but reconstructive surgery for obstruction of the superior vena cava in fibrosing mediastinitis is seldom of benefit and should be advised only when conservative measures cannot control the symptomatic edema.

Therapy with amphotericin B was given to one patient after surgery in our series, but most patients have no evidence of active infection. Administration of corticosteroids was utilized in two patients with surgically proven disease, in order to prevent bronchial obstruction and further scarring of the superior vena cava. No evidence of active infection was seen in either patient. There was no evidence that the therapy with corticosteroids was of any value in preventing further scarring.
Surgery is necessary to establish a diagnosis if the lesions are noncalcified and indeterminate. Fibrosing mediastinitis most likely develops after rupture of the fibrocaseous material from mediastinal lymph nodes into the mediastinum. Thoracotomy with evacuation of the granulomas is recommended, especially when the lesions are large, in order to prevent subsequent fibrosing mediastinitis with involvement of contiguous structures, such as the superior vena cava, azygos vein, trachea, esophagus, and left atrium. We have no proof that excision of noncalcified mediastinal granulomas prevents the development of mediastinal fibrosis, and we are not recommending excision of all nontuberculous mediastinal granulomas. We are recommending evacuation of noncalcified granulomas in the patient with clinical features that are compatible with histoplasmosis in whom lymphoma, tuberculosis, and sarcoidosis have been excluded by histopathologic study of frozen sections.

REFERENCES

UPDATE IN CLINICAL ALLERGY
The Continuing Medical Education Committee of the American Academy of Allergy has planned a course, Update in Clinical Allergy, to be held at the Pheasant Run Resort, St. Charles, Illinois, June 22-24. Contact the Executive Office, AAA, 611 East Wells Street, Milwaukee 53202, for information.