Granulomatous Mediastinitis Due to Aspergillus flavus in a Nonimmunosuppressed Patient

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A patient with granulomatous mediastinitis due to Aspergillus flavus is described. A 22 year old black man presented with cough, fever and a right hilar mass. Mediastinal biopsies revealed granulomatous fibrosing mediastinitis with fungal elements compatible with aspergillus species. A. flavus was isolated on culture of this material and later from sputum and bronchial washings. Studies of the patient's immune status revealed normal humoral and cellular immunity. No underlying neoplasm was found. The patient was treated with amphotericin B and 5-fluorocytosine but esophageal and superior vena caval compression developed and he died. This is the first reported case of granulomatous mediastinitis due to A. flavus in a patient whose immune responses were not suppressed (nonimmunosuppressed patient). Infection with Aspergillus species should be considered in the differential diagnosis of granulomatous mediastinitis.

Aspergillus species are ubiquitous in nature, and are saprophytes in the upper respiratory tract and contaminants in the laboratory. Although many of these species may produce disease in man, the organism most commonly responsible for infection in man is Aspergillus fumigatus. Other species occasionally pathogenic for human beings are A. niger, A. flavus, A. glaucus, A. nidulans, A. oryzae and A. sydowi [1]. The tissue response to aspergillus is characterized by a granulomatous reaction. When the infection is most invasive, necrosis may be observed in addition to granuloma formation.

Infections produced by Aspergillus may be characterized as “primary” and “secondary,” the former representing invasion of tissue in a previously healthy person and the latter infection developing in a person with diminished host resistance. Secondary aspergillosis has been recognized with increasing frequency in patients with leukemia and other hematologic neoplasms [2], but primary infection remains uncommon.

Primary aspergillosis of the lungs is a chronic granulomatous infection which, on the roentgenogram, is manifest by nonsegmental pneumonitis which may progress to abscess formation [3]. Mediastinal invasion is exceedingly rare. We describe a patient without underlying disease and a normally functioning immune system in whom granulomatous mediastinitis due to A. flavus developed. To our knowledge a similar patient has not previously been described.

CASE REPORT

A 22 year old black man was well until late September 1977 when a nonproductive cough developed. One week later he was evaluated by a physician who recorded “flu-like” symptoms and a temperature of 101°F. Oral penicillin was
prescribed. Cough and fever persisted. One month after the onset of the patient's illness, dysphagia developed. A physical examination disclosed no abnormalities. The temperature was 100°F. A chest roentgenogram demonstrated a pulmonary infiltrate extending from an enlarged right hilum. A tuberculin Tine test result was negative. Five days later another chest roentgenogram revealed extrinsic compression of the bronchus in the upper lobe of the right lung and progression of infiltrate in the upper lobe of the right lung. The patient was hospitalized. Moderate respiratory distress and a prominent nonproductive cough were noted. The findings on physical examination were within normal limits. A complete blood count, urinalysis, heterophil titer, sputum gram and acid-fast stains, and sputum bacterial culture revealed no abnormalities. The patient was transferred to the Cleveland Clinic Hospital on November 11, 1977.

At the time of admission, the patient complained of unrelenting cough, progressive dysphagia, occasional night sweats, intermittent scant hemoptysis and mild exertional dyspnea accompanied by wheezing. He had worked as a laborer in a factory which produced galvanized steel pipe. There was no history of cigarette smoking, and there had been no weight loss. The physical examination was within normal limits, save for inspiratory and expiratory wheezing over the anterior portion of the upper lobe of the right lung. There was no lymphadenopathy or organomegaly. A complete blood count, sequential multiple analyzer-18, electrocardiogram and urinalysis were within normal limits. Serum fibrinogen was 580 mg/100 ml (normal 200 to 400 mg/100 ml). The serum muramidase level was 58.4 μg/ml (normal 9 to 17.5 μg/ml). Multiple fasting blood sugar levels were normal.

A chest roentgenogram revealed a right hilar mass with atelectasis of the upper lobe of the right lung. Figure 1. Chest roentgenogram showing a right hilar mass with atelectasis of the upper lobe of the right lung.

Compression of the mid-esophagus was present on a barium swallow. Pulmonary function tests revealed a moderately severe restrictive ventilatory abnormality without evidence of obstruction. At bronchoscopy, complete occlusion of the bronchus of the upper lobe of the right lung with extrinsic compression of the intermediate bronchus was observed. Mediastinoscopy was performed. A large mediastinal mass, extending into the right hilum, was found. Biopsy of the mass demonstrated a single non-necrotizing granuloma. Fungal stains revealed septate septicra branching hyphae compatible with Aspergillus species. A flavus was later isolated on culture of this material.

A right transaxillary thoracotomy was performed on December 2, 1977. Biopsy of the upper lobe of the right lung, mediastinum and mediastinal lymph nodes revealed a granulomatous fibrosing pleuritis and mediastinitis. Fungal elements were again noted. There was no evidence of malignancy.

An extensive evaluation of the patient's immune status revealed no specific abnormalities. A serum protein electrophoresis demonstrated a diffuse increase in the globulin fraction with a normal albumin. A bone marrow biopsy revealed a mild plasmacytosis. Serum immunoglobulin levels were elevated: immunoglobulin G (IgG) 2,250 mg/100 ml (normal 1,380 ± 250 mg/100 ml), immunoglobulin A (IgA) 350 mg/100 ml (normal 156 ± 92 mg/100 ml), immunoglobulin M (IgM) 300 mg/100 ml (normal 145 ± 105 mg/100 ml) and immunoglobulin E (IgE) 1,400 U/ml (normal 25 to 570 U/ml). The test for isohemagglutinins revealed the presence of anti-A and anti-B. Complement fixing titers for Blastomyces dermatitidis and Histoplasma capsulatum were negative. Cryptococcal antigen was absent. Precipitin bands for Aspergillus species (flavus, fumigatus and niger) were present. The Schick test was negative. The serum complement assays were normal: total hemolytic complement (CH50) 113 mg/100 ml (normal 70 to 190 mg/100 ml), third component of complement (C3) Beta-IC/ Beta-1A 210 mg/100 ml (normal 80 to 250 mg/100 ml), and fourth component of complement (C4) 40 mg/100 ml (normal 14 to 51 mg/100 ml). Quantitative B and T cell counts demonstrated B cells 10.5 percent (normal 14.7 ± 4.3 percent) and T cells 64.9 percent (normal 75.2 ± 6.3 percent).

There were reactions to intradermal administration of Candida antigen at 24 hours and streptokinase-streptodornase at 48 hours. An intermediate strength tuberculin skin test was nonreactive. There was an immediate reaction to intradermal administration of an A. flavus antigen, but there was no delayed reaction. The antigen preparation, which had been preserved in phenol, failed to induce either the transformation of the patient's cultured lymphocytes or the production of migratory inhibition factor. The patient's lymphocytes did undergo transformation when exposed to phytohemagglutinin, pokeweed mitogen and concanavalin A. Migratory inhibition factor was produced in response to Candida antigen.

Amphotericin B therapy, 40 mg/day intravenously (0.6 mg/kg/day), was initiated on October 23, 1977. Intermitent fever and renal failure complicated the administration of amphotericin B. The administration of 5-fluorocytosine, 3 g orally four times a day, was added on December 12, 1977.

By February 12, 1978, the patient had received a total of 3 g of amphotericin B, with concurrent 5-fluorocytosine therapy. He was afebrile, his cough had diminished. He had gained
weight, and objective improvement had been seen on the esophagram.

On April 7, 1978, the patient was readmitted to the Cleveland Clinic Hospital with a new onset of odynophagia and progressive dysphagia for solids, a 10-day history of nonproductive cough and an oral temperature of 100°F. A chest roentgenogram revealed atelectasis of the upper lobe of the right lung. There had been no significant change in the roentgenogram since November 1977. The patient underwent esophageal dilatation to a No. 60 French scale, improved and was discharged. He was admitted again on April 28, 1978, with recent onset of facial edema, hoarseness, recurrent dysphagia and a temperature of 101°F. The chest roentgenogram was unchanged. Prednisone, 60 mg every other day, was administered in an attempt to halt the progression of the patient's superior vena cava compression.

On June 23, 1978, he was readmitted with worsening of the superior vena cava compression, the recent onset of scant hemoptysis and intermittent fever. Diffuse extrinsic narrowing of the thoracic trachea, right mainstem bronchus and right intermediate bronchus was noted at bronchoscopy. The carina was fixed, and the bronchus in the upper lobe of the right lung was extrinsically occluded. No site of bleeding was identified. A. flavus was cultured from bronchial washings. The prednisone dose was gradually decreased, and a second course of amphotericin B, 40 mg intravenously daily, combined with 5-fluorocytosine, 3 g orally four times a day, was initiated. Hemoptysis continued, with blood loss sufficient to require transfusion. Sputum cultures continued to yield A. flavus.

On August 17, 1978, the patient experienced the sudden onset of retrosternal chest pain and dyspnea. Asymmetry in calf diameter was noted. Venograms demonstrated phlebothrombosis involving the deep venous system of the left calf. Because of the patient's hemoptysis, heparin was not administered. A vena cavagram demonstrated narrowing of the superior vena cava to 8 mm, precluding insertion of the Mobinud-Din umbrella capsule. On August 18, 1978, an inferior vena cava ligation and feeding gastrostomy were performed. Intraoperative biopsy specimens of the liver and retroperitoneal lymph nodes revealed no abnormalities. Pulmonary edema developed during the immediate postoperative period and the patient died. Permission for an autopsy was not granted.

COMMENTS

Extension to the mediastinum is extremely rare in primary pulmonary aspergillosis. One previously described patient, a 25 year old carpenter and farmer who died of extensive invasion of the mediastinal contents and lymph nodes, had infection due to A. fumigatus [4]. Postmortem examination in that case demonstrated that the marked fibrous tissue proliferation and invasion produced by the fungus had resulted in a frozen mediastinum which required removal of the entire thoracic contents.

Although different aspergillus species were responsible for the conditions in the previously described patient and the present patient, there were similarities in the two. Both patients were in their twenties and had no apparent occupational exposures or underlying diseases. In both patients the granulomatous fibrosing mediastinitis was extensive and led to death. The diagnosis of A. flavus-induced granulomatous mediastinitis was documented in our patient by demonstration of the fungus on smears and subsequent culture of the organism from mediastinal tissue, sputum and bronchial washings. No underlying neoplasm was discovered, and an immunologic investigation demonstrated normal cellular and humoral immunity and ability to form antibodies.

The etiology has not been established in the majority of cases of granulomatous mediastinitis. A specific etiology was defined in 33 (32 percent) cases reviewed by Schowengerdt et al. [5]—histoplasmosis in 14, tuberculosis in 13, sarcoidosis in four, silicosis in one and nocardiosis in one. No cases were attributed to Aspergillus species, either in these studies or in several other reviews of mediastinal granulomatosis [6,7]. In the majority of instances, sclerosing mediastinitis most probably represents the end stage of chronic granulomatous infection, and in one review of 77 patients [5], there were only three (two with histoplasmosis and one with tuberculosis) in whom the responsible microorganism could be determined.

The patient we describe presented with a large hilar mass, and later manifestations of sclerosing mediastinitis developed, which led to compression of the esophagus and superior vena cava and death. Corticosteroids, administered in an attempt to inhibit the sclerosing component of the mediastinitis, proved ineffective.

Various antifungal agents [8-10-13], including amphotericin B, nystatin, natamycin, hydroxystilbamidine, iodides and 5-fluorocytosine, have been employed in the therapy of pulmonary aspergillosis. Amphotericin B has been demonstrated to be effective in some patients [14,15], but a cooperative study of the efficacy of this agent in pulmonary aspergillosis yielded inconclusive results [16]. The American Thoracic Society's Ad Hoc Committee on microbiology, infection and immunity has recommended amphotericin B as the drug of choice for the treatment of aspergillosis [17]. However, because of the rarity of mediastinal invasion with Aspergillus, there is no current evidence demonstrating the efficacy of this agent in this condition. 5-fluorocytosine as a single agent and in combination with amphotericin B has proved effective in some cases of pulmonary aspergillosis [13]. In one study reported from Sudan, two of three patients with primary pulmonary aspergillosis due to A. flavus died despite therapy with amphotericin B; the survivor had localized disease and recovered after lobectomy [18]. None of the patients had mediastinal invasion. In the present patient, there was no evidence that amphotericin B and 5-fluorocytosine modified the clinical course of the infection. Jesiotr [19] reported successful treatment of a patient with primary pulmonary aspergillosis due to A. flavus with emetine hydrochloride after demonstration of in vitro susceptibility of the fungus to this compound. Mediastinal involvement was not present, and the diagnosis was based
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solely on isolation of the fungus from a culture of the sputum.

Aspergillus species (both flavus and fumigatus) must be considered to be possible etiologic agents of granulomatous mediastinitis even in nonimmunocompromised patients, particularly when the fungus is observed on smears and cultured from tissue specimens. Since a microorganism is not discovered in the majority of patients with granulomatous mediastinitis, it is quite possible that Aspergillus species, which are ubiquitous in nature, may be responsible for some of these infections. These fungi must not be dismissed as laboratory contaminants. In our patient, therapy with amphotericin B and 5-fluorocytosine proved to be ineffective.

ACKNOWLEDGMENT
We wish to thank Dr. John D. Clough from the Department of Rheumatic and Immunologic Diseases for his assistance in the interpretation of the immunologic studies conducted on our patient.

REFERENCES