0025-7974/0000-0000$02.00/0
MEDICINE

Vol 00, No 0
Printed in U.S.A.

Chronic Necrotizing Pulmonary Aspergillosis: A Discrete Clinical Entity[1]

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Introduction

Reviews of pulmonary disease due to the fungus *Aspergillus* have emphasized that this organism causes a spectrum of illness from saprophytic colonization of the bronchial tree to rapidly invasive and disseminated disease (4, 12, 14, 21, 48, 56, 61, 65, 67, 69). Although several nosological schemes include a chronic, slowly progressive form of invasive pulmonary aspergillosis (14, 23, 61), the recent literature has emphasized the acute process most commonly seen in the immunocompromised host (2, 36, 40, 66, 67). Hence, the "chronic granulomatous" form of aspergillosis which was described over 50 years ago (20, 28, 51, 53, 60) is unfamiliar to most clinicians. During the last 3 years we have seen four patients with chronic necrotizing pulmonary disease due to *Aspergillus* species. This report includes a description of these cases, a review of 22 similar cases collected from the literature, and a classification of the many manifestations of pulmonary aspergillosis.

Methods

Chronic necrotizing pulmonary aspergillosis is defined as an indolent, cavitating process in the lungs due to invasion of lung tissue by a fungus of the *Aspergillus* species. The diagnosis of chronic necrotizing pulmonary aspergillosis was considered in persons with roentgenographically demonstrated persistent or progressive cavitary lesions, often with mycetomas. Confirmation of the diagnosis was considered to be most firmly established by the demonstration in lung tissue of septate hyphae, consistent with *Aspergillus* species, preferably with the culture of *Aspergillus* species from tissue specimens. Clinical diagnostic criteria were also considered acceptable for confirmation when tissue was not available for study or when tissue invasion was not demonstrated. These criteria included the growth of *Aspergillus* species from a lung biopsy, bronchoscopic or percutaneous lung aspirate or sputum, combined with a clinical response to specific antifungal therapy. Failure to demonstrate the presence of other bacterial, fungal or mycobacterial pathogens by culture or pathologic means was required in all cases. Additionally, there had to be no evidence of disseminated aspergillosis at the time of diagnosis.

Chronicity was defined as duration of the disease process for more than 30 days prior to the institution of therapy, as documented roentgenographically or clinically. We excluded patients who were severely immunocompromised such as persons with hematologic malignancy, renal transplantation or those recently treated with intensive immunosuppressive chemotherapy.

The English literature of the last 60 years was reviewed. Cases were accepted for analysis only if there was sufficient information to assess the criteria listed.

Case Reports

Case 1

A 71-year-old man with severe obstructive lung disease and recurrent right lower lobe pneumonia was admitted to another hospital on September 2, 1980 with a 1 month history of productive cough, weight loss, and increasing shortness of breath. The patient had been treated with oral metronidazole 3 months earlier in Canada for bilateral pneumonia; however, a chest film in July 1980 showed only hyperinflated lungs and attenuated peripheral vascular markings. The patient had also intermittently taken prednisone, 5 to 15 mg per day, over the past 3 months for his obstructive lung disease.

Physical examination disclosed a cachectic man who was afebrile and had diminished breath sounds with widespread crackles and wheezes on chest auscultation. His white blood cell count was 24,500/mm^3 and a chest roentgenogram showed extensive consolidation of the right upper lobe.

Several sputum cultures were negative for bacterial and mycobacterial pathogens. Bronchoscopy was performed 10 days and 1 month following admission. No endobronchial lesion was noted and cytologic examination revealed no malignant cells. Cultures of the bronchoscopic specimens were negative for *M. tuberculosis*. However, bronchoscopic washings on both occasions and several sputum specimens grew an *Aspergillus* species later identified as *Aspergillus flavus*.

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[1] Supported in part by the Division of Lung Diseases, National Heart, Lung, and Blood Institute Program Project Grant, HL-19717.

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The patient was initially treated with 3 days of intravenous cefazolin, 12 g daily, followed by a 5 week course of oral tetracycline, 2 g per day. He also received two 3 week tapering courses of prednisone, beginning at 30 mg per day, for his respiratory insufficiency.

While receiving this therapy, the patient's chest roentgenograms failed to improve, and on September 9, 1980 a small cavity with an air-fluid level was noted in the anterior segment of the right upper lobe. A film 3 weeks later showed the appearance of multiple small cavities within the consolidated right upper lobe along with new pleural thickening. On October 5, 1980 extensive cavitation was apparent within the right upper lobe anteriorly.

Because the patient was considered not to be a suitable candidate for either amphotericin B therapy or a thoracotomy, he was transferred to the Bedford VA Medical Center on November 3, 1980. He weighed 110 pounds, having lost 30 pounds since July, 1980 and was afebrile. White blood cell count was 10,400/mm^3. A chest roentgenogram was unchanged from that of October 5, 1980 except for the appearance of an intracavitary mass (Fig. 1A). Cultures of sputum and bronchoscopic washings again grew *Aspergillus* species and failed to grow other bacterial or mycobacterial pathogens. Serum precipitins for *Aspergillus* were positive in a Titer of 1:64. An intermediate strength PPD skin test was negative as was skin testing with control antigens.

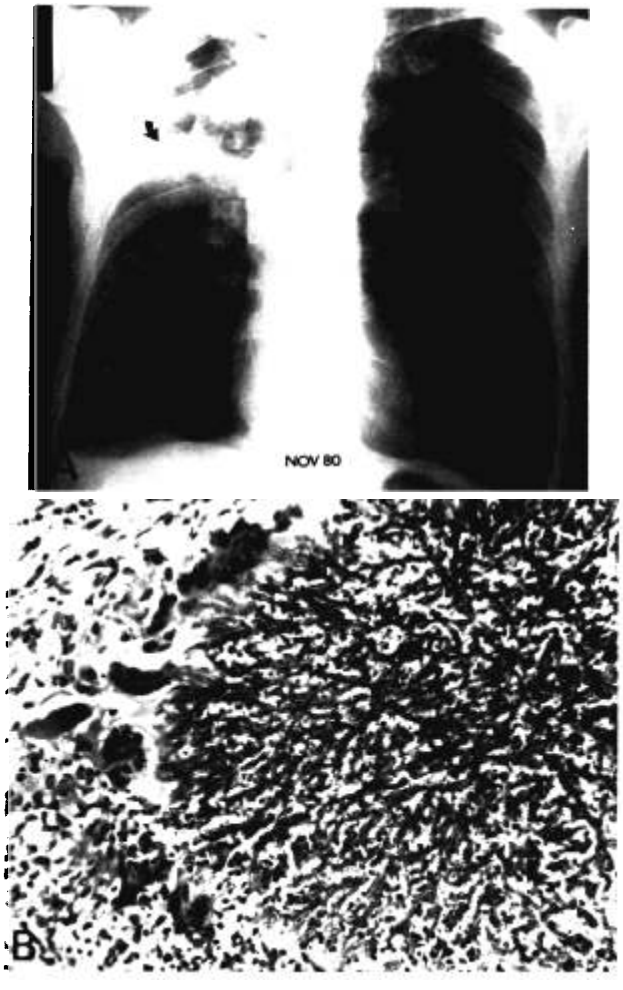

FIG. 1. A. PA Chest Roentgenogram (November 1980). A large cavity with an air-fluid level is evident within the right upper lobe. An intracavitary mass compatible with a mycetoma is present (arrow). B. A section of the wall of patient's right upper lobe abscess cavity demonstrating tissue invasion by numerous septate hyphae surrounded by multinucleated giant cells and other inflammatory cells (260 ×).

Beginning in early December, the patient was started on a 4 week course of intravenous aqueous penicillin G, 8 million units per day, as treatment for a possible chronic, anaerobic, lung abscess. He also received frequent chest postural drainage, was begun on a high-calorie high-protein diet, and prednisone was tapered and stopped.

The patient remained chronically ill, although afebrile. His weight in mid-December was 108 pounds and a white blood cell count was 14,000/mm^3. On January 2, 1981, the patient developed increasing respiratory distress and died. An autopsy was performed.

Pathology: Both lungs exhibited generalized emphysema, congestion, and consolidation. Numerous reddish thrombi were noted within medium sized pulmonary arteries throughout both lower lobes and the right middle lobe. A large cavity measuring 15 × 15 × 10 cm occupied most of the right upper lobe. The cavity was nearly filled with thick, greenish-yellow purulent material and contained several large, irregular, friable mycetomas measuring up to 8 cm in their greatest dimension.

Sections of the mycetomas showed recognizable pulmonary tissue with mild anthracotic pigmentation infiltrated and engulfed by masses of uniform, septate hyphae. Large numbers of polymorphonuclear neutrophils were also present. Sections from the wall of the cavity (Fig. 1B) demonstrated a small number of microabscesses containing clusters of septate hyphae surrounded by numerous neutrophils, cell debris and multinucleated giant cells. Acid-fast stains of the cavity wall were negative; however a moderate number of acid-fast bacilli were seen in sections of the mycetomas. Fungal cultures of the mycetomas and the right upper lobe grew *Aspergillus* species. Unfortunately, cultures of lung tissue for mycobacteria were not performed.

Microscopic examination of other lung lobes disclosed an extensive, necrotizing pneumonia and postmortem lung cultures grew *Staphylococcus aureus* and *Hemophilus influenzae*. The numerous, organized pulmonary arterial thrombi did not contain septate hyphae, and no evidence of disseminated *Aspergillus* infection was detected.

Comment: Pathologic evidence of tissue invasion by *Aspergillus* species along with the repeated isolation of *Aspergillus flavus* from pulmonary secretions and failure to isolate another pulmonary pathogen prior to our patient's death strongly favor the diagnosis of chronic necrotizing pulmonary aspergillosis. The significance of the acid-fast bacilli visualized within the cavity is unclear. Repeated failure to culture mycobacteria from sputum or bronchoscopic aspirates during his illness, and the absence of acid-fast bacilli associated with caseating granulomas within the walls of the cavity or involving lung parenchyma makes tuberculosis unlikely. The acid-fast rods may represent colonization by non-tuberculous mycobacteria. Of interest was the discovery of necrotic lung parenchyma within the intracavitary mycetomas supporting a recent report

(42) which noted that some mycetomas may arise in foci of *Aspergillus* bronchopneumonia as a result of the peripheral dissolution of infected lung tissue with sequestrum (mycetoma) formation. This patient died from a nosocomial pneumonia and pulmonary emboli.

Case 2

A 52-year-old man with chronic rheumatoid arthritis was admitted to another hospital in October 1977 with productive cough, a six-pound weight loss, and a right upper lobe (RUL) infiltrate (Fig. 2A). He reported taking prednisone, 15 mg every other day, for the past 8 years. There was no history of travel in

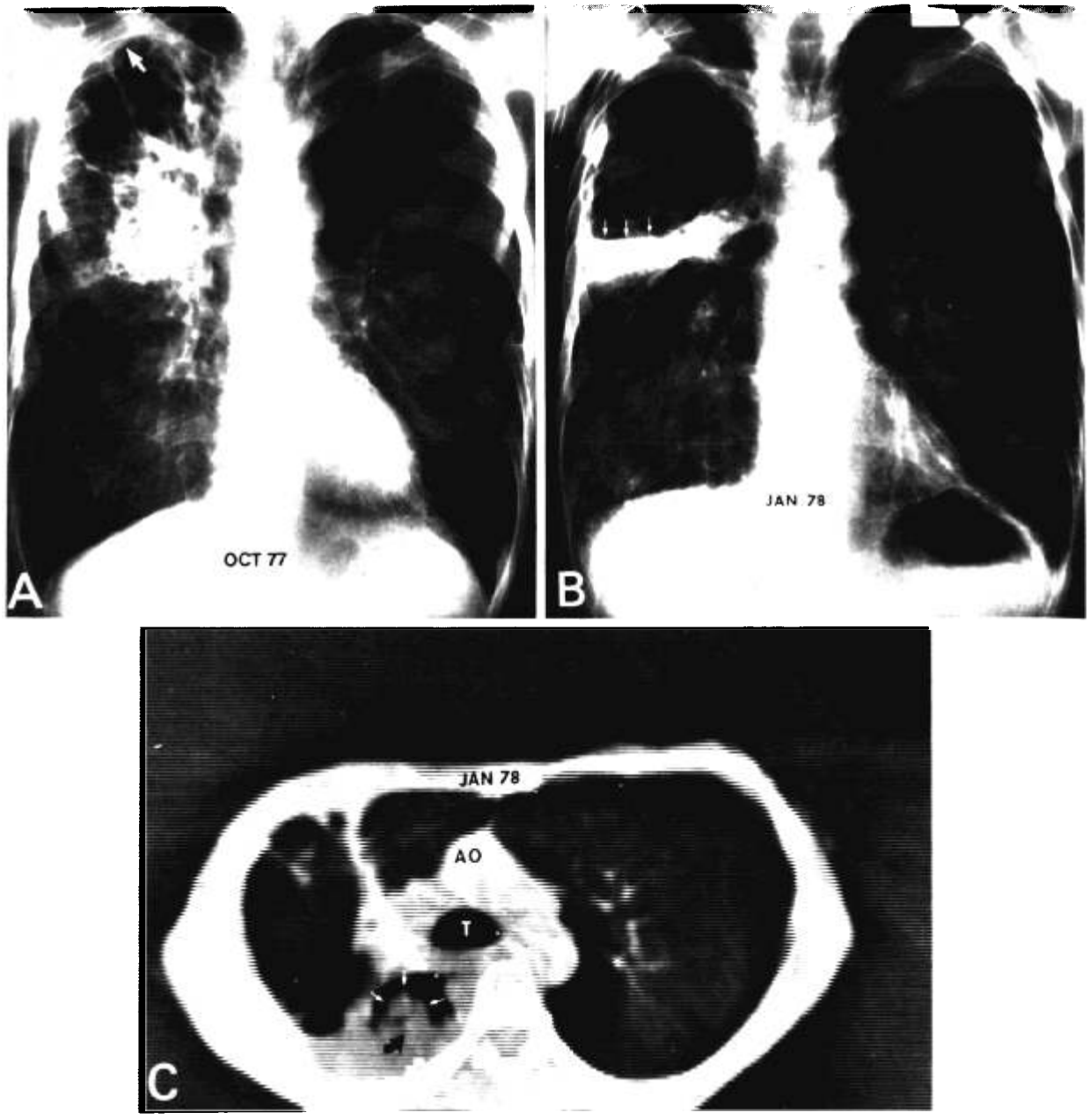

FIG. 2. A. Case 2—PA Chest Roentgenogram (October 1977). An infiltrate with varying sized cystic spaces is present in the right upper lobe. Minimal pleural thickening is evident laterally (arrow). B. PA Chest Roentgenogram (January 1978). A large cavity containing an air-fluid level (arrows) now occupies the right upper lung zone. Progressive pleural thickening is evident laterally. No mycetoma is evident. C. 2½ Minute Supine CT Scan (January 1978). Posteriorly in the right upper lobe an intracavitary mass (black arrow) is capped by air anteriorly and laterally (white arrows). A prone scan confirmed the mobility of this mycetoma. The mycetoma was not visible on standard tomograms. AO = aortic arch, T = tracheal lumen.

an area endemic for histoplasmosis. A chest roentgenogram taken 6 months earlier was normal. Physical examination revealed a cachectic, edentulous man weighing 81 pounds. He was afebrile, had deforming arthritis of the hands and feet, and exhibited scattered wheezes on chest auscultation. The white blood cell count was 18,600/mm^3.

Multiple sputum cultures for both bacterial and mycobacterial pathogens were negative. Bronchoscopy was performed on two occasions. No endobronchial lesions were seen and cytologic examination did not reveal malignancy. Cultures of the bronchoscopic specimens were negative for *M. tuberculosis*. However, bronchoscopic washings and three subsequent sputum specimens grew *Aspergillus fumigatus*.

Despite 10 weeks of drug treatment for tuberculosis and antimicrobial treatment consisting of 4 weeks of oral phenoxymethyl penicillin, 2 grams daily, followed by 3 weeks of intravenous penicillin G, 20 million units daily and clindamycin, 1.8 grams daily, the patient's condition deteriorated. He lost eight pounds and his chest roentgenogram demonstrated progressive cavitation and pleural reaction involving the RUL (Fig. 2B). The patient was transferred to the Boston Veterans Administration Medical Center (BVAMC) for further evaluation and management.

A computerized tomographic (CT) scan of the chest confirmed the plain chest radiographic findings but also showed a large moveable intracavitary mass consistent with a mycetoma (Fig. 2C). At bronchoscopy purulent secretions were present in the RUL. A plugged, telescoping catheter (PTC) brush was used to obtain a specimen for bacterial culture without upper airway contamination (63). All aerobic, anaerobic, and mycobacterial cultures were again negative. A post-bronchoscopic sputum showed mycelia on wet mount and grew *Aspergillus fumigatus* on culture. Serum precipitins for *Aspergillus fumigatus* were strongly positive. The patient was begun on intravenous amphotericin B, oral 5-fluorocytosine (5-FC), and high caloric nutrition via a nasogastric tube. His prednisone was tapered and stopped. Over a four month period he received 1.5 grams of amphotericin B; the 5-FC was discontinued after 6 weeks of therapy because of diarrhea. A chest tube was placed into the right apical cavity because of a persistent air-fluid level, and a stoma was eventually made by a rib resection to provide open drainage.

On this regimen the patient gradually improved. He gained 17 pounds, his white blood cell count returned to normal, and he resumed ambulation with an improved sense of well being. At the time of discharge, his chest roentgenogram showed a persistent RUL cavity with no air fluid level and resolution of the pericavitary infiltrate. Except for a persistent bronchocutaneous fistula, the patient remained clinically well until late August 1981 when he developed *Pseudomonas aeruginosa* pneumonia and died. No evidence of *Aspergillus* infection was found at autopsy.

Comment: Although we do not have pathological evidence of invasive aspergillosis in this case, the clinical evidence in favor of this diagnosis is substantial. *Aspergillus fumigatus* was isolated from multiple sputum specimens and bronchoscopic washings while vigorous attempts to isolate another bacterial, mycobacterial, or fungal organism were unsuccessful. The chest roentgenogram showed progressive RUL cavitation along with marked pleural reaction, and a CT scan revealed an intracavitary mass consistent with a mycetoma. These roentgenographic findings are classic for *Aspergillus* infection, especially in the absence of any other process known to cause an "air-crescent" sign (11, 24, 31, 43, 62). Our patient's clinical improvement while on antimycotic therapy in contrast to his deterioration while on antituberculosis and high dose antibiotic therapy supports the diagnosis of chronic necrotizing pulmonary aspergillosis. Persistent cavitation following treatment commonly occurs in this disorder.

Case 3

A 58-year-old woman, with a past history of resection of her right middle and upper lobes for an undifferentiated large cell carcinoma of the lung in 1975, was admitted to the BVAMC in October, 1979 with a 1 month history of productive cough, fever, and night sweats. She had not recently travelled outside of New England. Chest roentgenograms revealed right apical pleural thickening and a right upper lung field infiltrate (Fig. 3A). Multiple sputum cultures for bacteria and mycobacteria were negative. Bronchoscopy was performed and a PTC brush was used to obtain an uncontaminated specimen for aerobic and anaerobic bacterial culture (63). The orifice of the superior segment of the right lower lobe was narrowed, but no endobronchial lesions were seen and cytologic preparations were negative for malignancy. Bacterial, mycobacterial, and fungal cultures of the bronchoscopic specimens, as well as similar cultures from a percutaneous needle aspirate of the infiltrate, were all negative.

The patient did not respond to a 7-day course of oral ampicillin, 2 g daily, and was discharged on a regimen of phenoxymethyl penicillin, 3 g daily. She took this medication sporadically, did not receive regular follow-up care, and returned to the hospital 2 months later in January 1980, with persistent fever, and a ten pound weight loss. Physical examination revealed a cachectic woman who weighed 75 pounds and had a temperature of 101.4°F. Her white blood cell count was 12,500/mm^3. A chest roentgenogram showed increased pleural reaction at the right apex and progression of her right upper lung field infiltrate with possible early cavity formation. Multiple sputa for bacterial and mycobacterial culture were again negative. Despite treatment with phenoxymethyl penicillin, 2 g daily, she remained febrile during the next month and her chest radiograph showed an enlarging cavity containing a moveable mass most consistent with a mycetoma (Fig. 3B). A percutaneous needle aspiration of the cavity was performed and grew *Aspergillus fumigatus* on fungal culture. Aerobic, anaerobic, and mycobacterial cultures of the aspirate were negative. Serum precipitins for *Aspergillus fumigatus* were strongly positive.

High caloric nutrition via nasogastric feeding tube was initiated, and the patient received 1.0 g of intravenous amphotericin B during the next 3 months. She became afebrile, gained 6 pounds, and resumed ambulation with an improved sense of well-being. On discharge, 4½ months after admission, her chest roentgenogram showed persistence of the cavity, almost total resolution of the right apical infiltrate and disappearance of the intracavitary mass.

The patient was readmitted to the BVAMC in early October 1980 and died shortly later following a cardiac arrest. There was no clinical evidence of pulmonary aspergillosis during this admission. An autopsy showed only an acute myocardial infarction.

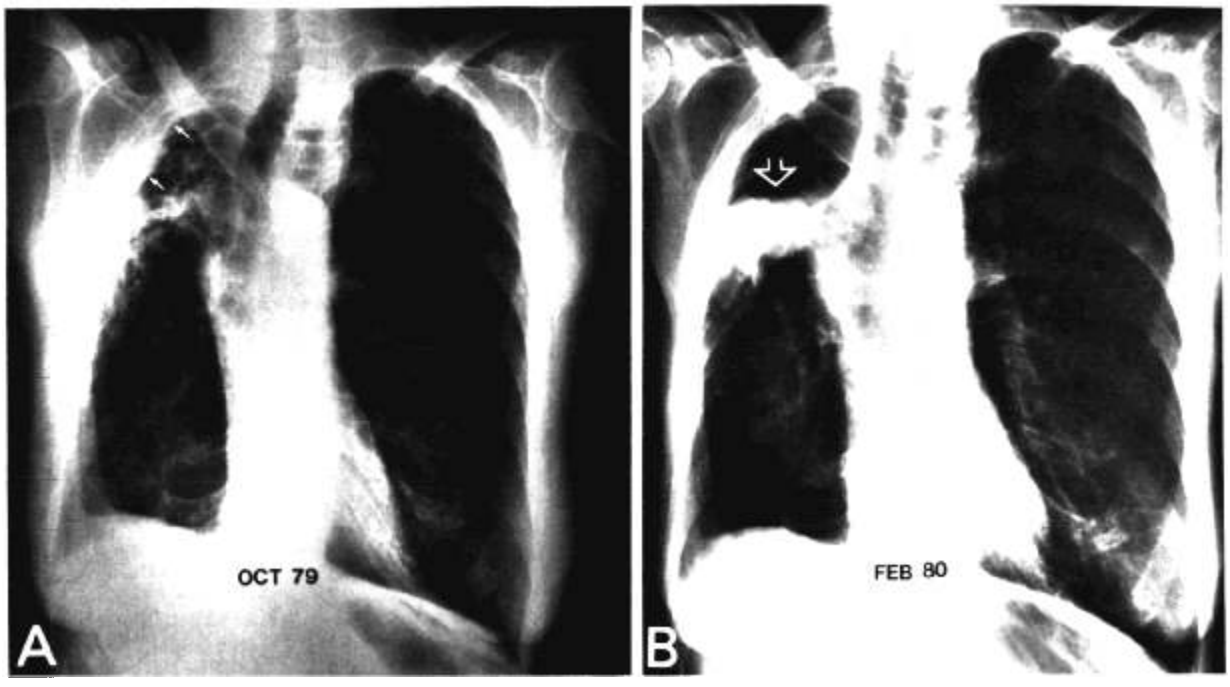

FIG. 3. A. PA Chest Roentgenogram (October 1979) (Case 3). Right lateral and apical pleural thickening (arrows) as well as a poorly defined right upper lung zone infiltrate are present in this patient. A right sided thoracotomy had been performed 4 years prior to this radiograph. B. PA Chest Roentgenogram (February 1980). The right upper lung zone is now occupied by a large cystic space. Its superior and lateral aspect are marginated by thickened pleura. In the inferior aspect of this cavity a mass lesion has appeared which is capped by air (open white arrow). Decubitus views demonstrated the mobility of this intracavitary mycetoma.

Comment: The diagnosis of chronic necrotizing pulmonary aspergillosis is based on clinical criteria in this patient. Despite vigorous attempts to identify another pathogen, only *Aspergillus fumigatus* was isolated following a percutaneous needle aspiration of her cavitary disease. Progression of the apical infiltrate to cavitation, with the development of an intracavitary mass is typical of *Aspergillus* infection (11, 24, 31, 43, 62). In addition, she deteriorated while on conventional antibiotic therapy and improved markedly following treatment with amphotericin B. An autopsy 4.5 months later disclosed no evidence of pulmonary aspergillosis.

Case 4

A 57-year-old man was admitted to the BVAMC in October, 1979 with a 1-month history of productive cough, anorexia, a 6-pound weight loss, and a left upper lobe (LUL) infiltrate. Sixteen months prior to admission the patient received a 3-month course of cis-platinum and bleomycin for a squamous cell carcinoma of the pharynx. The tumor recurred, and 7 months prior to admission he underwent resection of the tumor and a left radical neck dissection followed by radiation therapy with 5500 rads delivered to the left neck and upper chest. The patient had not recently travelled outside of the New England area. His current physical examination revealed a well developed, well nourished man in no acute distress. Temperature was 101.4°F. Head and neck examination showed no evidence of recurrent carcinoma, and the chest examination was normal. His white blood cell count was 16,900/mm^3, and a chest roentgenogram showed a LUL infiltrate (Fig. 4A) not present on a film taken 2 months previously.

Multiple sputum cultures were negative for bacterial and mycobacterial pathogens. He remained clinically ill despite 3 days of oral ampicillin, 2 g daily, 5 days of intravenous pencillin G, 12 million units daily, and 7 days of intravenous clindamycin, 2.4 g daily. His chest roentgenogram worsened with the development of cavitation within the LUL infiltrate, extensive pleural reaction at the left apex, and a new infiltrate in the lingula (Fig. 4B).

One week following admission, bronchoscopy with transbronchial lung biopsy was performed, and a PTC brush was passed through the bronchoscope to obtain uncontaminated material for aerobic and anaerobic bacterial culture (63). All bronchoscopic specimens were negative for bacterial and mycobacterial pathogens. The transbronchial lung biopsy showed only nonspecific inflammation. Culture of the biopsy, bronchial washings, and subsequent sputum cultures all grew *Aspergillus fumigatus*. A percutaneous needle aspirate of the infiltrate performed 3 weeks after admission also grew only *Aspergillus fumigatus*.

One month following admission the patient was begun on intravenous amphotericin B. Shortly thereafter he developed a superinfection characterized by rapid clinical deterioration with a temperature of 104°F and a new left lower lobe (LLL) infiltrate. Culture of sputum and a percutaneous needle biopsy of the lung now grew *Pseudomonas maltophilia*. Amphotericin B was discontinued after a total dose of only 136 mg and the patient promptly defervesced on tobramycin and ticarcillin. During the second month of hospitalization, his chest x-ray showed progres-

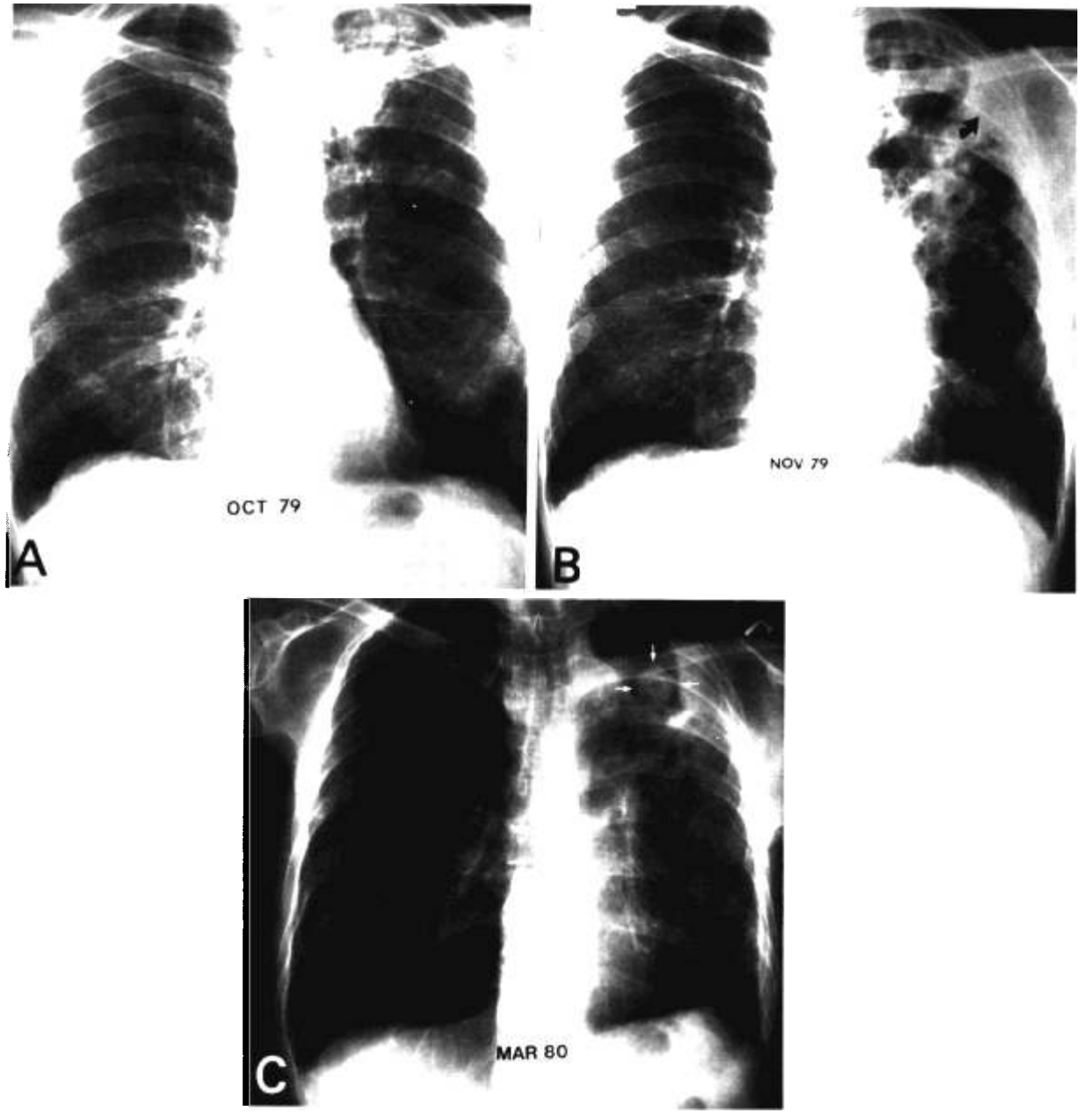

FIG. 4. A. PA Chest Roentgenogram (October 1979) (Case 4). A left upper lobe infiltrate is demonstrated. No associated pleural changes are seen. B. PA Chest Roentgenogram (November 1979). The left upper lobe infiltrate has progressed, cavitated and involved the lingula. Pleural thickening is seen laterally (arrows). C. Overpenetrated PA Chest Roentgenogram (March 1980). This view demonstrates the mycetoma (arrows) in the left upper lobe cavity.

sion of his left apical pleural disease, the gradual development of a LUL intracavitary mass consistent with a mycetoma, and partial clearing of the pericavitary, lingular, and LLL infiltrates. However, because of his clinical improvement, antimycotic therapy was not reinstituted, and he was discharged 2 months following admission. Except for further clearing of the pericavitary infiltrate, these roentgenographic findings persisted 3 months following discharge from the hospital (Fig. 4C). The patient was clinically well until the autumn of 1980 when he developed metastases from his pharyngeal cancer. No autopsy was obtained after his death in December 1980; however, a chest roentgenogram in November 1980 disclosed further resolution of his LUL infiltrates and mycetoma.

Comment: This patient is atypical in that he developed an obvious pulmonary superinfection with an unusual bacterial pathogen and appeared to stabilize his pulmonary aspergillosis without having completed an adequate course of amphotericin

B. Nevertheless, we believe that our patient's initial illness was chronic necrotizing pulmonary aspergillosis. His chest roentgenogram showed progressive worsening during a 4-week period when multiple diagnostic attempts yielded no aerobic, anaerobic, or mycobacterial pathogens; however, *Aspergillus fumigatus* grew from cultures of sputum, bronchoscopic biopsy and washings, as well as from a percutaneous lung aspirate. These findings along with his failure to respond to high dose penicillin or clindamycin therapy are consistent with invasive *Asperigillus* infection.

We speculate that our patient's gram-negative superinfection was responsible through unknown mechanisms for his clinical and radiologic improvement. Survival of patients with pulmonary aspergillosis complicating neoplastic disease is often related to the outcome of the underlying disease rather than the total dose of antifungal therapy (8, 40). Also, lysis of intracavitary aspergillomas has been reported to occur spontaneously (18) and in association with pyogenic infections (17, 44).

Review of the Literature

Search of the literature disclosed 22 cases which met our diagnostic criteria for chronic necrotizing pulmonary aspergillosis (5, 9, 10, 16, 19, 22, 23, 34, 35, 37, 39, 52, 57). The diagnosis was confirmed pathologically in 11 cases; 10 by lung biopsy, resection or autopsy, and 1 by pleural biopsy. In 11 cases, the diagnosis was based on clinical criteria. Our 4 cases are very similar to those previously reported and all are combined for analysis. Table 1 summarizes the pertinent clinical, laboratory, roentgenographic, treatment, and outcome data of these 26 patients.

Clinical Features

Most patients were middle aged, 77 percent being 40 years of age or older (Table 2). There were 18 males and 8 females. Nineteen patients (73%) had a previous history of documented or suspected lung disease. Five patients had chronic obstructive lung disease, four had inactive mycobacterial infection, three had undergone previous pulmonary resection, and two had nonspecific cystic changes on their chest roentgenograms. Pulmonary sarcoidosis with insulin-dependent diabetes mellitus, longstanding pneumoconiosis, recent influenza, a chronic unspecified respiratory illness and radiation therapy to the area of subsequent disease were each noted in one patient. Of interest, 3 of the 26 patients had an underlying connective tissue disorder, rheumatoid arthritis in 2 and ankylosing spondylitis in 1.

Seven patients (27%) had recently received corticosteroid therapy or were taking these drugs at the time of diagnosis. In the six patients in whom steroid dosage was recorded, one patient was taking dexamethasone 16 mg twice daily, one was taking predisone 10 mg daily, one had intermittently taken predisone 5 to 15 mg per day, and the others were taking less than 20 mg of predisone every other day. Only one patient had received cytotoxic chemotherapy, and his chemotherapy had been discontinued 1 year prior to the onset of pulmonary aspergillosis. The most frequent complaints were fever, cough, and sputum production with one or more of these symptoms in about two-thirds of the patients (Table 3). Adequate data were available in 21 cases for judging the duration of the process from the onset of clinical abnormality until the institution of specific therapy. In 16 cases (76%) the duration was 1 to 6 months, in 3 cases (14%) it was 6 months to 2 years, and in 2 cases (10%) it was more than 2 years.

Laboratory Findings

White blood cell counts were available in only 12 of the 24 cases. Of these, nine had white blood cell counts greater than 10,000/mm^3. Fungal cultures grew *Aspergillus fumigatus* in 22 patients (85%) and *Aspergillus niger* (4%), *Aspergillus niveus* (4%) and *Aspergillus flavus* (4%) in one patient each. Culture results were not reported in one patient whose lung biopsy showed infiltration by a fungus characteristic of *Aspergillus* species. Branching septate hyphae consistent with *Aspergillus* infection were observed in lung tissue from all 12 patients who had a biopsy, surgical resection or autopsy. The tissue sample was generous in all but two patients. Serum precipitins against *Aspergillus* antigens were present in 16 of 17 patients tested.

Roentgenographic Findings

The chest roentgenogram showed an infiltrative process with parenchymal necrosis in 21 of the 26 patients (81%) (Table 4). Of the 21, 10 also demonstrated an intracavitary mass which was consistent with a mycetoma. The five patients without this typical chest roentgenographic picture included two persons with only a cavity on chest film but with parenchymal invasion by *Aspergillus* on pathologic examination, one person with total opacification of the left lung and extensive invasion of the lung by *Aspergillus* at autopsy, one child with an *Aspergillus* empyema associated with a parenchymal infiltrate, and one person with only a parenchymal infiltrate on chest film but with abscess formation on pathological examination.

In general, the chest x-ray abnormalities most often involved the upper lobes or the superior segments of the lower lobes when the upper lobe had been previously resected (Table 4). Exceptions in-

TABLE 1. Clinical Characteristics of 26 Patients with Chronic Necrotizing Pulmonary Aspergillosis*

Patient no	Reference	Age-Sex	Underlying condition	Recent steroid therapy	Symptoms and signs	Clinical course prior to diagnosis (mo.)
1	(16)	44 M	None	None	None	Greater than 1
2	(57) (Case 2)	63 F	Chronic unspecified respiratory illness	None	F, C, S	2
3	(39)	32 F	Old *M. tuberculosis*	None	F, C, S	5
4	(22)	25 M	None	None	C, wt. loss	Greater than 24
5	(10)	7 F	None	None	wt. loss	6
6	(52) (Case 3)	24 M	Diabetes mellitus, RUL resection	None	None	Indeterminate
7	(34) (Case 3)	58 M	Recent influenza	None	C, S	5
8	(23)	40 F	None	None	F, C, S	Greater than 24
9	(5) (Case 2)	47 M	Nonspecific left apical fibrosis	None	F, C, S	1½
10	(5) (Case 4)	62 M	None	None	C	Indeterminate
11	(5) (Case 6)	43 F	Sarcoidosis, diabetes mellitus	Yes, dosage not recorded	F	4
12	(5) (Case 7)	46 M	Old atypical mycobacteriosis	None	F, C, S	3
13	(5) (Case 8)	54 M	Nonspecific RUL cystic	None	F, C, S, weight loss	Greater than 6
14	(5) (Case 10)	57 M	Pneumoconiosis	None	F, Weight loss	Indeterminate
15	(9)	55 M	Old tuberculosis	None	C, S	6
16	(35) (Case 3)	55 M	Old tuberculosis, LUL resection	None	F, C, weight loss	12
17	(19) (Case 1)	69 F	COPD, Raynaud's disease	Prednisone 10 mg daily	F, weight loss	5
18	(19) (Case 2)	61 M	COPD, Rheumatoid arthritis	Prednisone 5–20 mg every other day	F, C, S	Indeterminate
19	(19) (Case 3)	56 M	COPD, Ankylosing spondylitis	Prednisone 5–20 mg every other day	F, S, weight loss	Greater than 1
20	(19) (Case 4)	68 M	None	None	F, C, S	Indeterminate
21	(19) (Case 5)	22 M	None	None	F, C, S	10

* F, fever; C, cough; S, sputum; NR, not recorded, IV Ampho B, intravenous amphotericin B; IC Ampho B, intracavitary amphotericin R; 5-FC, 5-fluorocytosine; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; BPF, bronchopleural fistula; COPD, chronic obstructive pulmonary disease.

WBC count	Aspergillus precipitins	Predominant roentgenographic findings	Diagnosis	Therapy	Outcome	Follow-up time after therapy (mo.)
'Normal'	NR	RUL infiltrate with cavity	Pathologic (lung resection)	RUL resection	Improved	18
NR	NR	LUL infiltrate with cavity	Clinical	Iodides, external drainage	Improved	unknown
10,100	NR	RUL infiltrate with cavity	Clinical	IV Ampho B, 1.5 g	Improved	7
'Normal'	NR	Opacification left lung	Pathologic (autopsy)	Iodides	Died, progressive disease	—
10,000–20,000	NR	RML infiltrate with empyema	Pathologic (lung biopsy)	IV Amph B, 770 mg	Improved, 7 mo. after therapy completed	24
NR	NR	Right apical cavity	Pathologic (lung resection)	RML and apical segment of RLL resected	Improved	6
6,200	NR	RUL infiltrate with cavity	Pathologic (lung resection)	Apical and posterior segments of RUL resected	Improved (taking Nystatin post-surgery)	2
10,800	NR	RUL and LUL infiltrates with cavitation and mycetoma	Clinical	IV Ampho B, 2.2 g	Improved for 2 yr, then died from recurrent disease	24
NR	Positive	LUL infiltrate with cavity and mycetoma; RUL infiltrate	Clinical	5-FC, 6 g daily × 3 mo. LUL resection	Improved, Post-op empyema. Responded to further antimycotic therapy	6
NR	Positive	RUL infiltrate	Pathologic (lung resection)	Abscess resected; 5-FC, 10 g daily × 3 mo.	Improved	18
NR	Positive	RLL infiltrate with mycetoma	Pathologic (lung resection)	5-FC, 6 g daily × 2 wk, RLL resection	Improved, Post-op BPF	9
NR	Positive	LUL infiltrate with cavity	Clinical	5-FC, 12 g daily × 3 mo.	Died, bacterial superinfection and resistant *Aspergillus*	—
NR	Positive	RUL infiltrate with necrosis, RML and RLL infiltrates	Clinical	5-FC, 12 g daily × 6 wk	Improved	12
NR	Positive	RUL infiltrate with BPF	Pathologic (pleural biopsy)	5-FC, 12 g daily × 3 mo.	Improved	12
22,000	Positive	LUL infiltrate with cavity	Pathologic (transbronchial lung biopsy)	IV Ampho B, 1.2 g, LUL resection	Improved, Post-op abscess and empyema	unknown
NR	NR	Left apical infiltrate with cavity and BPF	Pathologic (lung resection)	LLL resection	Died, post-op empyema and hemoptysis	—
NR	Positive	LUL infiltrate with cavity and mycetoma	Clinical	IV Ampho B, 1.95 g, IC Ampho B, 500 mg	Improved	24
NR	Positive	LUL infiltrate with cavity	Clinical	IC Ampho B, 500 mg	Improved	24
NR	Positive	RUL infiltrate with cavity	Clinical	IV Ampho B, 1.95 g, IC Ampho B, 500 mg	Improved	8
NR	Positive	LUL infiltrate with cavity and mycetoma	Clinical	IV Ampho B, 500 mg, IC Ampho B, 500 mg	Improved	13
NR	Positive	Superior segment RLL infiltrate with cavity and mycetoma	Clinical	IC Ampho B, 105 mg, Superior segment RLL resected	Improved	unknown

TABLE 1—*Continued*

Patient no	Reference	Age-Sex	Underlying condition	Recent steroid therapy	Symptoms and signs	Clinical course prior to diagnosis (mo.)
22	(37)	16 F	Severe Asthma	Dexamethasone 16 mg bid	C, weight loss	1
23	This report (Case 1)	71 M	COPD	Prenisone 5–15 mg/day intermittently	C, S, weight loss	1
24	This report (Case 2)	52 M	Rheumatoid arthritis	Prednisone 15 mg every other day	C, S, weight loss	3
25	This report (Case 3)	58 F	RML and RUL resection	None	F, C, S	3
26	This report (Case 4)	62 M	Radiation therapy to left apex	None	F, C, S, weight loss	1

TABLE 2. Clinical Features of 26 Patients With Chronic Necrotizing Pulmonary Aspergillosis

Age (years)	No.	(%)
<20	2	(8)
20 to 35	4	(15)
36 to 60	14	(54)
60+	6	(23)
Previous lung disease	19	(73)
Underlying connective tissue disorder	3	(12)
Previous steroid therapy	7	(27)

TABLE 3. Symptoms and Signs in 26 Patients With Chronic Necrotizing Pulmonary Aspergillosis

	No.	%
Fever	16	(62)
Cough	19	(73)
Sputum production	16	(62)
Weight loss	11	(42)
Asymptomatic	2	(8)

TABLE 4. Chest Roentgenographic Findings in 26 Patients With Chronic Necrotizing Pulmonary Aspergillosis

	No.	(%)
Chest roentgenogram abnormality		
Infiltrate with parenchymal necrosis*	21	(81)
Infiltrate with empyema	1	(4)
Cavity only	2	(8)
Consolidated lung	1	(4)
Infiltrate alone	1	(4)
Total	26	
Predominant site of involvement		
Upper lobe disease	19	(73)
Superior segment of lower lobes following upper lobe resection	3	(12)
Other	4	(15)
Total	26	

* 10 of the 21 (48%) demonstrated mycetoma formation.

cluded one patient who had involvement of the superior segment of the RLL without a history of prior lung resection, one patient with sarcoidosis and diabetes mellitus who had RLL disease, one 7-year-old child with predominantly RML disease, and one patient with complete consolidation of his left lung.

Treatment and Outcome

Overall, patients with chronic necrotizing pulmonary aspergillosis respond favorably to therapy (Table 5). Of the 26 patients reviewed, there were 5 deaths (19%), one due to a complication of therapy and 4 due to the underlying disease; one of these 4 never received antimycotic therapy. Long-term follow-up was not available in most cases, however.

Ten patients underwent surgical resection and 9 survived. Of the five who had received no previous chemotherapy, four had an uncomplicated course and one died from a postoperative empyema and massive hemoptysis; however, one of the survivors received 5-FC following resection of his abscess. Of the five patients who underwent surgical resection following antimycotic chemotherapy, all eventually did well. However, one patient developed a postoperative empyema, one developed a postoperative lung abscess and an empyema, and one developed a postoperative bronchopleural fistula. Resection was required in four of these five patients because

WBC count	Aspergillus precipitins	Predominant roentgenographic findings	Diagnosis	Therapy	Outcome	Follow-up time after therapy (mo.)
17,400	Negative	LUL cavity	Pathologic (lung resection)	IV Ampho B, 1 g, Superior division LUL resected	Improved but died from chronic asthma	50
24,500–10,400	Positive	RUL infiltrate with cavity and mycetoma	Pathologic (autopsy)	No antimycotic therapy	Died prior to antimycotic therapy	—
18,600	Positive	RUL infiltrate with cavity and mycetoma	Clinical	IV Ampho B 1.5 g, 5-FC, 2 g daily × 6 wk, External drainage	Improved but died with bacterial pneumonia	40
12,500	Positive	Right apical infiltrate with cavity and mycetoma	Clinical	IV Ampho B, 1.0 g	Improved but died from an acute myocardial infarction	4.5
16,300	Positive	LUL infiltrate with cavity and mycetoma	Clinical	IV Ampho B, 136 mg	Improved but died from metastatic cancer	12

TABLE 5. Treatment and Outcome in 26 Patients With Chronic Necrotizing Pulmonary Aspergillosis

Treatment	Number	Died	Survived	Comment
Antimycotic Chemotherapy				
A. 5FC	3	1	2	
B. Iodides	2	1	1	Survivor also had a pneumonostomy
C. Ampho B	10	1 (after 2 yr remission)	9	1 IC Ampho B alone, 3 IV and IC Ampho B, 1 IV Ampho B, 5FC, and a pneumonostomy
Surgical Resection and Antimycotic Chemotherapy*				
A. 5FC	3	0	3	1 p.o. BPF 1 p.o. empyema
B. Ampho B	3	0	3	1 p.o. abscess and empyema
Surgical resection	4	1	3	p.o. empyema and hemoptysis in the patient who died
No treatment	1	1		
Total	26	5 (19%)	21 (81%)	

5FC, 5 fluorocytosine; Ampho B, amphotericin B; IC, intracavitary; IV, intravenous; p.o., postoperative; BPF, bronchopleural fistula.
* Chemotherapy preceded surgery in 5 of these 6 patients.

of complications from either intravenous amphotericin B or intracavitary amphotericin B in two and failure of 5-FC therapy in the other two patients. Resection in the fifth patient was undertaken shortly following the institution of amphotericin B which was continued postoperatively to complete a course of 1 gram.

Fifteen patients received antimycotic chemotherapy with or without external cavity drainage. Of the three patients who received 5-FC alone, one died after a complicated course, and two improved. Two patients were treated with iodides; one did well after percutaneous tube drainage of her cavity, and one died with progressive intrathoracic disease. Ten patients received amphotericin B. Five patients received intravenous amphotericin B alone and four improved without further intervention. The fifth initially was symptomatically improved, but died with recurrent, progressive disease following a 2 year remission. Three patients failed to improve significantly on intravenous amphotericin B and responded only after intracavitary amphotericin B was also administered. One patient improved on a regimen of intravenous amphotericin B, oral 5-FC and percutaneous drainage of a giant RUL cavity. The tenth patient was treated solely with intracavitary amphotericin B and did well. Although 22 of the 25 treated patients (88%) with chronic necrotizing pulmonary aspergillosis showed symptomatic recovery with therapy, roentgenographic improvement was noted in only 11 patients (44%) of these 22 and failed to occur in 6. One of the latter patients eventually died from recurrent disease. In five patients who improved clinically, follow-up chest roentgenograms were not available.

The long-term course of these patients is uncertain since they are often left with destroyed lung and persistent cavities, and have serious underlying medical disorders. Follow-up information, 7 or more

months after completion of therapy, was available in 15 patients, including 2 of our own; 11 were well 7 months to 2 years following therapy, one had died from recurrent disease two years after symptomatic improvement with intravenous amphotericin B, 1 died from non-pulmonary causes, 1 patient died from the complications of severe, longstanding asthma, and 1 died with a bacteremic gram-negative pneumonia. Another patient of ours died 4.5 months after hospital discharge from an acute myocardial infarction.

Discussion

Previous reports have comprehensively reviewed several major manifestations of disease caused by *Aspergillus* in the lungs, including allergic bronchopulmonary aspergillosis (ABPA) (48), hypersensitivity pneumonitis (65), aspergilloma (58), and acute invasive disease both localized (14, 36, 66, 67) and disseminated (36, 67). Our discussion will focus on the chronic necrotizing form of pulmonary aspergillosis which has been inadequately emphasized in the past.

Lung infection by *Aspergillus* was first described in the 1800s (6). It was generally believed to be a chronic disease and was noted to commonly afflict persons with an occupational exposure to the fungus such as pigeon feeders or hair sorters (41). In the early 1900's, it was frequently confused with tuberculosis (28, 29, 51, 53). Roentgenographically, the disease was characterized by chronic and progressive pulmonary infiltrates, often with cavitation, and usually involved the upper lung zones. The patients had malaise, fever, and a cough frequently productive of dark particulate sputum which grew *Aspergillus* species on culture. Hemoptysis was occasionally observed. Many patients had a prolonged chronic illness and responded symptomatically to iodide therapy. Some of the patients described in the early literature probably had chronic necrotizing pulmonary aspergillosis, but many appeared to have had allergic bronchopulmonary aspergillosis with mucoid impaction and proximal bronchiectasis or *Aspergillus*-induced hypersensitivity pneumonitis. Others likely had tuberculosis or another chronic lung disease with *Aspergillus* colonization. Since tissue invasion by *Aspergillus* was rarely documented in these cases, and because the clinical evaluation was frequently too incomplete to establish a firm diagnosis, the existence of a "chronic granulomatous" form of the disease has been questioned by many authors.

Careful review of our 4 cases and the 22 cases culled from the medical literature leads us to conclude that chronic necrotizing pulmonary aspergillosis is an identifiable clinical entity. This form of aspergillosis is shown schematically in relation to the other forms of lung disease produced by *Aspergillus* in Figure 5. We speculate that patients initially inhale the fungus and colonize their respiratory tracts. *Aspergillus* species have a low order of pathogenicity for humans and although aspergillosis may rarely occur in an apparently normal host following a large inoculum of organisms (55, 59), some evidence of altered host defense is usually present. Fulminant, acute pneumonia due to *Aspergillus*, often with dissemination, occurs almost always in persons who are seriously immunocompromised because of administration of immunosuppressive drugs after organ transplantation or following treatment of a neoplasm with high-dose radiation, antineoplastic drugs or corticosteroids. Influenza (15), chronic alcoholism (7, 50, 68), or fibrotic lung disease (47) may also predispose to acute pneumonic aspergillosis.

Aspergillomas without evident tissue invasion are a complication of persistent, large airspaces within the lungs, whether these are a result of bullous emphysema or some destructive inflammatory process such as tuberculosis which has been treated with antituberculosis drugs. Allergic bronchopulmonary aspergillosis is associated with asthma.

In the chronic necrotizing form of pulmonary aspergillosis, which is the subject of this report, evidence of some abnormality of host defenses is also frequently present. This may take the form of abnormalities in pulmonary defense mechanisms related to lung disease such as previous resectional surgery, ionizing radiation therapy, pulmonary infarction (4), inactive mycobacterial disease, chronic obstructive lung disease, or a pneumoconiosis. Although the fibrobullous stage of pulmonary sarcoidosis is frequently complicated by *Aspergillus* colo-

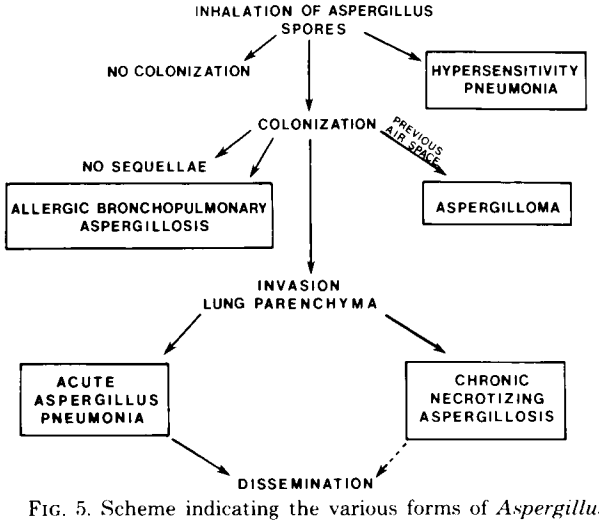

FIG. 5. Scheme indicating the various forms of *Aspergillus* lung disease. See text for discussion.

nization and mycetoma formation, invasive disease is unusual (25, 26, 64). Mild systemic immunocompromise may also be present as with connective tissue disorders, poor nutrition, diabetes mellitus, or low-dose corticosteroid therapy. These abnormalities are not frequent in young persons, which appears to explain the predominant occurrence of chronic necrotizing pulmonary aspergillosis in middle-aged adults.

The predilection of *Aspergillus* for vascular invasion results in tissue necrosis and often cavity formation. If a large area of lung parenchyma is involved, residual necrotic material, blood or fungal hyphae may remain in the cavity to give the typical "air-crescent" sign of an intracavitary mass on chest roentgenograms (11, 36, 38, 42, 43). This roentgenographic appearance is often referred to as a "fungus ball" or "mycetoma." In chronic necrotizing pulmonary aspergillosis, mycetomas form in cavities that are the result of tissue invasion and necrosis by the fungus. We wish to stress that the main feature which distinguishes chronic necrotizing pulmonary aspergillosis from pulmonary aspergilloma is the very obvious evidence of tissue invasion and destruction due to the fungus in the former, whereas in the latter, the mycetoma colonizes a pre-existent cavity and evidence of tissue invasion is subtle or altogether wanting.

Although they were not seen in plain chest roentgenograms taken prior to the onset of the active phase of their lung disease, the presence of preexisting airspaces in the lungs of our four patients cannot be excluded. The main radiographic feature of their disease was progressive parenchymal necrosis and excavation; mycetomas became manifest relatively late in their course. Also noteworthy is that *Aspergillus* was cultured from the lungs of our patients shortly after the onset of their disease without the isolation of other pulmonary pathogens; on the other hand, most large airspaces which eventually become the site of mycetoma formation are roentgenographically visible for long periods prior to the isolation of *Aspergillus* or other mycetoma-forming organisms.

We and others (14, 23, 61) have classified chronic necrotizing pulmonary aspergillosis as a form of invasive aspergillosis distinct from aspergilloma, allergic bronchopulmonary aspergillosis, and acute pneumonic and disseminated aspergillosis. While this distinction is clinically and therapeutically useful, reports documenting overlap of the various manifestations of pulmonary aspergillosis suggest a continuum of disease. Allergic bronchopulmonary aspergillosis has occurred following the development of an aspergilloma (13) and the converse has also been reported (49). Limited tissue invasion has been observed in bronchopulmonary aspergillosis (45) and a pneumonic illness has followed the development of an aspergilloma (30). Additionally, disseminated infection has occurred in association with aspergilloma alone (33) or aspergilloma complicating allergic bronchopulmonary aspergillosis (3).

Chronic necrotizing pulmonary aspergillosis is slowly progressive and can eventually involve an entire lung, spread to the contralateral hemithorax, or invade the pleural space, mediastinum or chest wall. Patients appear chronically ill, often with weight loss, and almost always with respiratory tract symptoms. Fever and an elevated white blood cell count are usually present and signal infection as the most likely cause of the patient's illness. Distant spread is uncommon because the organism has low virulence and because a defect in pulmonary clearance is probably the significant factor leading to focal invasion and infection. Like centrilobular emphysema, postprimary tuberculosis, and chronic pulmonary histoplasmosis, this disease has a predilection for the upper lung zones; apical localization may be due to the consequences of the upright position on human pulmonary physiology (54). The appearance of considerable pleural thickening adjacent to a parenchymal process may be an early sign of *Aspergillus* infection (32). Three of our four patients had significant pleural reaction associated with their chronic necrotizing pulmonary aspergillosis.

Diagnosis can be difficult, since *Aspergillus* is a common contaminant of the respiratory tract, and the clinical picture is easily confused with infection by anaerobic bacteria, mycobacteria or other pathogenic fungi. Infection by *Histoplasma capsulatum*, *Coccidioides immitis* and *Blastomyces dermatitidis* should be carefully excluded in those areas which are endemic for these fungi; none of our patients had lived in or recently travelled through such areas. A careful and vigorous search for *Aspergillus* is necessary. Lung biopsy is diagnostic if tissue invasion by septate hyphae, consistent with *Aspergillus* species, are identified in conjunction with growth of the fungus on culture. However, a transbronchial or percutaneous lung biopsy may fail to demonstrate the organism because only a small piece of parenchyma is obtained or because necrotic or infarcted lung is sampled rather than a zone of fungal invasion. Under these circumstances, or when a lung biopsy is considered inadvisable because of excessive risk or poor patient compliance, a clinical diagnosis of chronic necrotizing pulmonary aspergillosis may be based on the following criteria: *Aspergillus* species is cultured from sputum or from bronchoscopic or percutaneous lung aspirates, no other pathogen is identified, and the patient's roentgenographic and clinical features are

consistent with this diagnosis. Serologic tests are useful in confirming that the patient is harboring the fungus and its antigens (27), but cannot be used alone to distinguish invasive from noninvasive disease or to guide therapy. ^{87m}Strontium can localize in the lesions of pulmonary aspergillosis, but this diagnostic technique is still experimental (1, 46).

The decision to institute therapy is a difficult one because of the known hazards of surgery and antimycotic chemotherapy. Progressive lung involvement should be documented and other more frequent causes of necrotizing pulmonary infection must first be considered. As in our cases, many patients ultimately shown to have chronic necrotizing pulmonary aspergillosis, will have received protracted courses of conventional antibiotic and antituberculous chemotherapy before antimycotic therapy is initiated.

The best chemotherapeutic approach to chronic necrotizing pulmonary aspergillosis is not known, but intravenous amphotericin B, with or without oral 5-FC, appears to be a reasonable choice. Large fluid-filled cavities often require percutaneous drainage if they do not drain via the tracheobronchial tree. Three deaths are recorded in the literature following chemotherapy. One patient was treated with iodides alone, one patient developed a severe superinfection and recurrent, drug-resistant aspergillosis, and one patient responded symptomatically to intravenous amphotericin B, but refused resection of residual cavitary disease and died 2 years later of progressive chronic necrotizing pulmonary aspergillosis.

In one recently published series (19) several patients with apparent chronic necrotizing pulmonary aspergillosis failed to improve on intravenous amphotericin B, but responded to intracavitary amphotericin B. These individuals improved clinically, resolved their pulmonary infiltrates and some demonstrated closure or shrinkage of their cavitary disease. Why these patients responded to intracavitary but not intravenous amphotericin B is not clear. Failure of systemic chemotherapy to penetrate cavities due to vascular impairment by *Aspergillus* may have resulted in higher local tissue concentrations of amphotericin B following intracavitary administration.

Except in otherwise healthy young persons with focal disease, surgical therapy as an initial therapeutic choice is probably not warranted. Surgical resection may be considered in persons unable to tolerate chemotherapy, or in those with residual but clearly localized active disease despite an adequate course of chemotherapy. A short course of intravenous amphotericin B immediately before and for several weeks following surgery may be advisable in these cases to prevent postoperative empyema and bronchopleural fistula. Although surgery was completed successfully in 9 of the 10 cases we reviewed, 4 of the 10 (40%) had major postoperative complications, one resulting in death.

Clinical improvement occurs if patients are managed aggressively for their *Aspergillus* infection, are given supplemental caloric nutrition, and receive treatment of underlying systemic disorders. Roentgenographic improvement is not uniform, however, and parenchymal scarring with residual cavitation is common. The long-term prognosis of these patients is not well documented and further follow-up studies are required. Three of our patients died 4.5 to 40 months after hospital discharge from other illnesses.

Can we be absolutely certain that *Aspergillus* species was solely responsible for the destructive pulmonary disease seen in our 4 patients and in the 22 patients culled from the medical literature? It is difficult to unequivocally exclude another unidentified pathogen or a non-infectious destructive process such as Wegener's granulomatosis as a cause for the progressive, necrotizing disease in these patients, with *Aspergillus* only colonizing an abnormal lung or perhaps causing limited clinically insignificant tissue invasion (45). Nevertheless, we believe that the data strongly support chronic necrotizing *Aspergillus* infection as the prime cause of this entity. Progressive excavation of the lung, the isolation of *Aspergillus* species in the absence of other identifiable pathogens or non-infectious etiologies, the demonstration of *Aspergillus* in tissue specimens in 12 of these 26 cases, and clinical improvement during therapy for *Aspergillus* after failure to respond to protracted conventional antibiotics and antituberculosis chemotherapy is powerful evidence in support of this concept. However, we welcome controversy, and hope that this report will stimulate other physicians to search for and report similar cases. If possible, the evaluation of these patients should include a lung biopsy in an attempt to demonstrate *Aspergillus* species histologically in lung tissue and by culture.

While this manuscript was in preparation, Gefter et al (17A) published a report of five patients with chronic cavitary pulmonary aspergillosis very similar to that of our patients. They referred to this form of aspergillosis as "semi-invasive" and pointed out that all of their patients had mild immunosuppression or underlying lung disease. The mean age of their patients was 60.6 (range 49–75) years; four of their five patients were men. In four cases prior radiographs were available and showed normal lung tissue in two and the non-cavitary shadows of sarcoidosis in one patient and radiation fibrosis in another patient. Mild immunosuppression in four of their five patients took the form of prior neoplasm treated with radiation and chemotherapy, sarcoidosis, alcoholism and debilitation. Precipitins

for *Aspergillus* were positive in the three patients in whom the test was done. *Aspergillus* species were recovered from one or more of cultures of sputum, bronchoscopic aspirates, percutaneous needle aspirates or lung tissue in all instances. Lung tissue was available from autopsy or lobectomy specimens in four of their five patients. The authors state that true fungal invasion was not demonstrated microscopically despite considerable lung destruction. This report lends further credibility to our concept that chronic necrotizing pulmonary aspergillosis is a distinct and recognizable clinical entity.

Summary

We conclude that chronic necrotizing pulmonary aspergillosis is a clinical entity which has not usually been recognized as one of the forms of pulmonary disease due to *Aspergillus* species. Patients are middle-aged, and often have some evidence of impairment of host defenses such as diabetes mellitus, a connective tissue disorder, poor nutrition, chronic obstructive lung disease or low dose corticosteroid therapy. They are almost always symptomatic with fever and a productive cough, and their chest roentgenogram shows infiltrative and cavitary disease, typical of a chronic destructive lung process such as tuberculosis or anaerobic infection. Cavity formation is often accompanied by the development of a mycetoma. The disease is usually of 1 to 6 months duration but can be present for years prior to diagnosis. The diagnosis is suggested by the clinical course and the isolation of the fungus from pulmonary secretions; negative cultures for other pathogens and failure to respond to antibacterial or antimycobacterial therapy are characteristic. The diagnosis is confirmed by pathologic evidence of tissue invasion by the fungus or a response to specific antimycotic therapy. The symptomatic response to antifungal chemotherapy, at times combined with surgical drainage or resection, is favorable. However, roentgenographic resolution is not uniform, and many patients have residual cavitary disease. The long-term prognosis is uncertain.

Acknowledgments

We wish to thank Jane Dolan and Kathy Henri for their assistance in preparing this manuscript, Dr. Talia Herman for referring Case 3, and the many physicians and nurses whose meticulous and excellent care assured the recovery of our patients. We also thank Dr. Jordan N. Fink of the Medical College of Wisconsin, Milwaukee, Wisconsin for performing the *Aspergillus* precipitin titers on three of our patients. Mr. Anthony Catanese prepared Figure 5.

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