Chronic Cavitary and Fibrosing Pulmonary and Pleural Aspergillosis: Case Series, Proposed Nomenclature Change, and Review

David W. Denning,[1] Kostantinos Riniotis,[1] Richard Dobrashian,[2] and Helen Sambatakou[1]

[1]School of Medicine, University of Manchester, and [2]Department of Radiology, North Manchester General Hospital, Manchester, United Kingdom

We describe 18 nonimmunocompromised patients with chronic pulmonary aspergillosis. Duration of the disease ranged from several months to >12 years. All 18 patients had prior pulmonary disease. Weight loss, chronic cough (often with hemoptysis and shortness of breath), fatigue, and chest pain were the most common symptoms. All 18 patients had cavities, usually multiple and in 1 or both upper lobes of the lung, that expanded over time, with or without intraluminal fungal balls. All had detectable *Aspergillus* precipitins and inflammatory markers. Elevated levels of total immunoglobulin E were seen in 78% of patients and of *Aspergillus*-specific immunoglobulin E in 64%. Directed lung biopsies showed chronic inflammation, necrosis, or granulomas without hyphal invasion. Antifungal therapy with itraconazole resulted in 71% of patients improved or stabilized, with relapse common. Interferon-γ treatment was useful in 3 patients. In azole nonresponders, modest responses to intravenous amphotericin B (80%) followed by itraconazole were seen. Surgery removed disease but postoperative pleural aspergillosis was inevitable. Indicators of good long-term medical outcomes were mild symptoms, thin-walled quiescent cavities, residual pleural fibrosis, and normal inflammatory markers.

Aspergillus species cause a wide spectrum of illnesses in humans, including allergy, superficial infection related to local trauma, and invasive disease [1]. The lung is the most frequent site of disease. The host immune system is a major determinant of which particular form of aspergillosis develops, if any. Acute invasive pulmonary aspergillosis (IPA) affects severely immunocompromised persons [2]. Less acute invasive disease (perhaps best termed subacute IPA) has been described, notably in patients with AIDS and chronic granulomatous disease [3, 4]. Aspergilloma is another form of *Aspergillus* infection that has been well described, in which preexisting pulmonary cavities become colonized

by *Aspergillus*. Aspergillomas have been subdivided into simple and complex according to the radiological appearance [5]. Other chronic forms of *Aspergillus* infection that have systemic symptoms have been described. These entities include chronic necrotizing pulmonary aspergillosis (CNPA), semi-invasive aspergillosis, chronic invasive pulmonary aspergillosis, symptomatic pulmonary aspergilloma, and *Aspergillus* pseudotuberculosis. The distinction between subacute IPA, CNPA, and aspergilloma has not been rigorously defined, and an overlap in clinical and radiological features between these different entities probably exists.

In the course of clinical practice, we have observed patients who have chronic pulmonary disease undoubtedly caused by *Aspergillus fumigatus,* with clinical features or a course often different from that described in the literature. We have been able to discern 3 distinct radiological patterns of infection. The first is characterized by the formation and expansion of multiple cavities, some containing fungus balls, which we have termed chronic cavitary pulmonary aspergillosis (CCPA). In some cases, this progresses to marked and

extensive pulmonary fibrosis, which we have termed chronic fibrosing pulmonary aspergillosis (CFPA; second category). We have documented pleural involvement in some cases, either as direct invasion of the pleural cavity or as fibrosis. The third category is the progressive enlargement of a single cavity, usually with a thin wall, in some cases to substantial dimensions, occurring slowly over months or rapidly in weeks. This last group of patients probably have slowly progressive invasive aspergillosis, a disease entity similar to or identical to the previously described CNPA. These patients differ slightly from those with CCPA and CFPA because they usually have minor or moderate degrees of immune dysfunction, such as diabetes or corticosteroid use. We suggest that this condition be called subacute IPA. Herein we use the terms "subacute IPA" and "CNPA" interchangeably.

We describe 18 patients with these 3 forms of subacute or chronic pulmonary aspergillosis (CPA). We describe their clinical courses, diagnostic features, serological patterns, and treatment outcomes. We argue the case for these new terms to describe these chronic destructive conditions. We specifically examined cavity size to establish whether it could be used as a radiological criterion for diagnosis (cavity expansion) and assessing therapeutic response (cavity shrinkage). We also propose diagnostic criteria for CPA and response parameters. The distinction between aspergilloma and these other entities is discussed.

PATIENTS AND METHODS

Patients included all of those referred to one of us (D.W.D.) before the year 2000 who fulfilled the criteria below. On the basis of our experience in managing these cases, and contrasting this experience with the literature, the diagnosis of CPA in this series required all of the following 5 features: chronic (duration of >3 months) pulmonary or systemic symptoms with exclusion of other pulmonary pathogens, such as mycobacteria, that could account for disease; no major discernible immunocompromising factors (e.g., AIDS, leukemia, or transplantation) except for patients with CNPA (see below); radiological evidence of a progressive (over months or years) pulmonary lesion with surrounding inflammation, with or without an intracavitary mass; precipitating (IgG) antibody to *Aspergillus* (Microgen Bioproduct) in serum (*A. fumigatus* precipitins test result >1:2, or detectable arcs on immunodiffusion); persistently elevated inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, or plasma viscosity).

After careful and extensive review of the data and the literature, all cases described were subclassified into 3 categories, and pleural disease was classified as primary or secondary (to intervention). The criteria for these subclassifications are primarily radiological and based on observations over time. Several

patients appeared to manifest a different form over time, particularly a transition to fibrosis without treatment or to a necrotizing pattern with corticosteroid therapy.

Patients with CNPA (patients 7, 12, and 14) had an identifiable immune defect described in clinical terms, such as diabetes mellitus, corticosteroid use, prior methotrexate or other immunocompromising treatment, or AIDS, and had radiological evidence of expanding cavities, usually with thin walls. The cavity might contain hyphae visible on microscopy, or *Aspergillus* might be detected in culture, but not usually.

Patients with CCPA (patients 1–6, 8–13, and 15–18) had multiple cavities, usually small initially, with surrounding inflammatory infiltrates and evidence of progression over months or years. Progression was usually characterized by coalescence of cavities to form larger ones, or fibrosis. Hyphae could be found in the cavity, but the wall of the cavity was composed of chronic inflammatory cells and fibrosis, without hyphal invasion.

Patients with CFPA (patients 3, 6, and 8) were a subset; their disease was the end result of either CNPA or, more commonly, CCPA that was untreated. Fibrosis could be limited to one or both upper lobes but also commonly involved the whole hemithorax.

Some patients also had elevated titers of total IgE (level >20 IU/mL) and *Aspergillus*- specific IgE (fluoroenzyme immunoassay [RAST]) (>0.35 Ua/mL) (Immunocap; Pharmacia) in serum. Repeated samples of sputum were cultured for fungus. Some patients had undergone a lung biopsy or resection. Percutaneous lung biopsy (under CT or fluoroscopic guidance) and bronchial biopsy samples were cultured and usually examined histologically (if adequate amounts were obtained). Histological evaluation of tissues included routine and silver staining for fungal hyphae, to document tissue invasion, and acid-fast staining, to exclude mycobacterial coinfection. Scans were analyzed both prospectively and retrospectively, and cavity size was determined by measuring the greatest cavity diameter.

Treatment was given according to need, acceptability, tolerance, efficacy, and availability. Serum azole levels were determined by bioassay and doses tailored to the results (aiming for random itraconazole concentrations of ≥5 μg/mL). Intracavitary amphotericin B was given as described elsewhere ([6] and "Treatment of specific noninvasive *Aspergillus* diseases: Aspergilloma," available at: www.aspergillus.man.ac.uk/homepagenew/indexhome.html). The MEDLINE database was used for the review of the English-language medical literature.

CASE REPORTS

Patient 2. This 45-year-old smoker with a mild degree of airflow obstruction presented with a right upper-lobe lesion seen on a chest radiograph in December 1991 in Vancouver,

Canada. He underwent a right upper lobectomy because of presumed malignancy. Macroscopic examination of the specimen revealed a 2-cm cavity with necrotic contents associated with local bronchiectasis and thickening of the parietal pleura. Between the cavity and the lung apex was parenchymal fibrosis. The remainder of the lung specimen showed severe emphysema with fibrosis. Microscopically, the cavity was in an area of cystic bronchiectasis with erosion of the mucosa. The cavity contents were purulent and contained a fungus ball without apparent invasion or tissue eosinophilia. A fibrosing (necrotizing) granuloma was seen superior to the cavity. Stains for acid-fast organisms yielded negative results. Cultures of the lung specimen for *Mycobacterium tuberculosis* yielded negative results, and cultures for fungus were not done. It was thought that he was cured, because the whole lesion was resected.

In June 1992, he presented with hemoptysis. CT of the thorax revealed a cavity measuring 6.24 cm^2 with surrounding parenchymal infiltration in the area of previous surgery. Investigations for tuberculosis yielded negative results. A bronchoscopy was done, and culture of the bronchial aspirate yielded *A. fumigatus*. Culture of material obtained by needle aspiration of the cavity yielded *A. fumigatus*, but findings of histological examination were unremarkable. At this time, his *A. fumigatus* precipitins test result was 3+, and this fell to 0 after treatment with itraconazole (200 mg b.i.d. for 1 year, July 1992 to July 1993). However, his cough persisted, and no radiological improvement was seen. CT of his thorax (July 1993) confirmed recurrence of disease (the area of the cavity increased to 16 cm^2, and there was de novo formation of small cavities in the same vicinity with a fluid level). In November 1993, CT revealed an intracavitary fungus ball together with pleural involvement. He was then treated with voriconazole (200 mg b.i.d. for 7 months, November 1993 to May 1994). Response to this was incomplete; culture of sputum continued to yield *A. fumigatus*, and *A. fumigatus* precipitins test results were 2+. CT in March 1994 showed persistence of the cavity mass and irregular subpleural consolidation (figure 1). Contrast instilled in the lung cavity descended all the way down to the pleural space on the right, indicating extensive pleural involvement with invasive aspergillosis. He was subsequently treated with iv amphotericin B (0.5–0.7 mg/kg/day), together with granulocyte colony-stimulating factor (G-CSF; 300 µg sc for 6 weeks), and amphotericin B paste (50–70 mg/day), locally administered through a percutaneous catheter into the cavity on a weekly basis, was given for ~1 month. CT in September 1994 showed a slight reduction in cavity size (area, 15 cm^2), more pleural involvement (small pneumothorax), and no evidence of fungus ball. The patient's *A. fumigatus* precipitins test result was unchanged (2+). With this therapy, his general condition and symptoms improved, as did the radiological findings. The pleural involvement cleared radiographically, and the right upper lobe cavity was unchanged
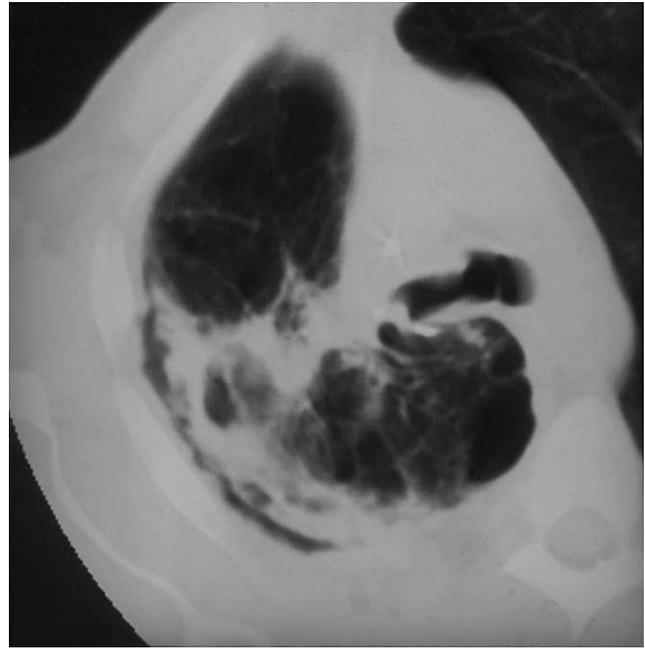

Figure 1. CT scan of the chest of patient 2 done in March 1994, showing multiple cavities, localized consolidation, and irregular infiltration of the pleura, with a new, small pleural space containing air not seen on a CT scan done in in July 1993.

in size (area, 15 cm^2). However, culture of sputum continued to yield *A. fumigatus*, *A. fumigatus* precipitins test results remained weakly positive, and his IgE level was 238 IU/mL.

In October 1997, the patient recommenced treatment with itraconazole (200 mg b.i.d., reduced to 100 mg b.i.d.). In May 1999, plasma itraconazole concentrations were 11 µg/mL during treatment with this lower dose. Results of culture of sputum became negative, as did *A. fumigatus* precipitins test results in serum. He remained nearly asymptomatic, continuing to take itraconazole. No appreciable change was seen on chest radiography for 4 years. In mid-2002, chest radiography showed a large thin-walled apical cavity, with some pleural thickening, and no pulmonary inflammatory infiltrates. He stopped therapy with itraconazole in June 2002. He remained healthy until November 2002, when cough, fatigue, and weight loss recurred. His *A. fumigatus* precipitins test result rose from 1+ to 4+, and levels of inflammatory markers rose. He made a partial improvement over the next 8 weeks in response to itraconazole treatment but remains unwell. A selection of the patient's chest radiographs and CT scans can be viewed online ("Chronic necrotising invasive pulmonary aspergillosis," patient RW, in the Image Library section of the *Aspergillus* Web site, available at: www.aspergillus.man.ac.uk/homepagenew/indexhome.html). He was found to be heterozygous for a 54 mutation in mannose-binding protein [7].

The patient had CCPA at the time of his surgery, without

Figure 2. Chest radiograph of patient 8 done in November 1992, showing marked loss of volume, fibrosis, cavitation, and pleural thickening within the left upper lobe, consistent with a previous tuberculous infection.

tissue invasion, and an intraluminal aspergilloma. However, 6 months later, CCPA developed again, manifest as a new cavity in previously uninvolved lung, and a percutaneous biopsy sample was positive for *Aspergillus.* This was a new infection, because chest radiography after surgery documented complete clearance. His initial response to itraconazole was mediocre, and his infection rapidly relapsed after its discontinuation. Likewise, his response to voriconazole was also mediocre. A more favorable response was noted when the patient received treatment with amphotericin B combined with G-CSF. G-CSF was given on theoretical grounds to augment neutrophil function, although there was no evidence in this patient that his function was defective. It is not possible to evaluate its contribution to success in this patient. A proinflammatory cytokine, such as IFN-γ or granulocyte-macrophage colony-stimulating factor (GM-CSF), might also have been considered. This case is also of interest because CCPA progressed over time to form a new adjacent pulmonary cavity and then to involve the pleura. Stability was achieved with long-term antifungal therapy, with relapse after nearly 5 years of itraconazole treatment.

Patient 8. A 37-year-old woman from Gujarat, India, had pulmonary tuberculosis in 1986, was successfully treated, but was left with bilateral upper lobe scarring and a cavity in the left upper lobe. In 1989, she visited Mecca (in Saudi Arabia) and experienced smoke inhalation, with some additional damage to her left lung (figure 2). In March 1994, she became ill, with productive cough, dyspnea, and weight loss (figure 3). CT in June 1994 revealed 3 cavities in her left upper lobe, with areas measuring 12.6, 3.6, and 2.4 cm^2. Fungus balls consistent with aspergillomas were found in the 2 larger cavities. *A. fu-*

migatus precipitins test results were 2+, her total serum IgE level was 1800 IU/mL, and culture of sputum yielded *A. fumigatus.* Findings on bronchoscopy were unremarkable, but fluid obtained by bronchial lavage yielded *A. fumigatus.* Histological examination of the biopsy sample did not reveal anything abnormal. She decided not to undergo surgery.

In November 1997, her condition deteriorated. She had gross finger clubbing, dyspnea on mild exertion, cough, frequent episodes of mild hemoptysis, and weight loss. A prior chest radiograph showed complete opacification of the left lung, with multiple cavities, at least 2 of which contained fungal balls (figure 4), widespread consolidation, and a pleural effusion. Itraconazole treatment, 200 mg b.i.d., was started, but she had continual hemoptysis, so in February 1998, intracavitary amphotericin B paste was added. She received this for 3 weeks, but the catheter became infected with *Staphylococcus aureus* and had to be removed.

In July 1998, CT identified only 1 cavity in the left lung, measuring 15.3 cm^2, with no visible evidence of aspergilloma. The whole of the left lung showed extensive fibrosis and consolidation. However, she continued to have hemoptysis, and her plasma viscosity was 203 (normal, <175 centipoise $\times$ 100). Intravenous amphotericin B (1 mg/kg) was also given, and a left bronchial artery embolization was done. A percutaneous lung biopsy of the left lower lobe with an 18-gauge needle was done. Histological examination revealed a core of fibrotic lung tissue containing carbon pigment and focal chronic inflam-

Figure 3. Chest radiograph of patient 8 done in June 1994, showing features suggestive of at least 1 aspergilloma, with a solid fungus ball surrounded by a radiolucent air-halo sign. The patient received no antifungal therapy.

Figure 4. Chest radiograph of patient 8 done in September 1997, showing a further deterioration in appearance, with enlargement of cavities, extensive lower lobe fibrosis, and presence of pleural effusion. A possible fungus ball persists, with an air-halo sign in the left midzone. The patient received no antifungal therapy.

mation. *Aspergillus* organisms were not seen with special stains, and culture results were negative. In September 1998, her serological profile was as follows: *A. fumigatus* precipitins test result, 3+; C-reactive protein, 70 mg/L (normal, <10 mg/L); IgE, 1000 IU/mL; and *Aspergillus*-specific IgE, 26 Ua/mL. Because her symptoms and weight had only partially improved, amphotericin B was discontinued and itraconazole, 200 mg b.i.d., was recommended. In October 1998, treatment with IFN-γ, 55 μg sc 3 times weekly, was added to itraconazole treatment.

By January 1999, her weight had increased, and the bouts of hemoptysis were less frequent. *A. fumigatus* precipitins test result was now 2+, and IgE level was 550 IU/mL. Her plasma viscosity, however, remained elevated at 220, as it had been for 18 months. In April, she had another episode of hemoptysis, and a second bronchial embolization was done. In July 1999, her *A. fumigatus* precipitins test result was 1+, IgE level had declined to 400 IU/mL, and RAST test results had declined to 7 Ua/mL. At this time, she underwent another bronchial artery embolization to control severe hemoptysis. Since then she has gained weight, felt much better, and had no further episodes of hemoptysis. She continued to take itraconazole and IFN-γ until December 1999 and has remained reasonably well under treatment with itraconazole only since then (February 2003). Her course is depicted in figure 5. She was found to be homozygous for a 54 mannose-binding protein mutation [7].

This case is one of the most severe in this series. Over a period of 10 years, the patient's disease progressed from apical scarring with a small cavity, in 1987, to complete destruction of the whole left lung with replacement by large, fungus-containing cavities and fibrosis (CFPA). Pulmonary damage from smoke inhalation may have contributed to her deteriorating pulmonary function. Itraconazole alone and amphotericin B intravenously alone both made small contributions to the improvement in her condition. Instillation of amphotericin B paste into the cavity was ineffective and complicated by bacterial infection. Most impressive in this case is the response to treatment with a combination of itraconazole and IFN-γ following amphotericin B therapy. Her weight and the serological markers of the disease mirrored clinical improvement. There has been essentially no radiological change.

RESULTS

Clinical, pathological, and radiological data and procedures for 18 patients are summarized in table 1. Of the 18 patients, 16 were white, and 13 were male. The ages ranged from 20 to 77 years, with a median age of 59 years. The duration of disease was variable and not possible to determine accurately for all patients, but the longest duration was in patient 2 (described above), now 12 years.

Predisposing conditions. None of the patients were immunocompromised. All 18 had prior pulmonary disease (table 1). Nine patients had had tuberculosis, in 5 instances due to atypical organisms. Thirteen patients were cigarette smokers, and 3 had previously consumed excessive amounts of alcohol. One patient was heterozygous for α_1-antitrypsin deficiency.

Signs and symptoms. Constitutional symptoms were prominent in all patients, with varying degrees of weight loss, malaise, and fatigue (table 1). There were 3 common clinical presentations. The most common was a chronic productive cough, associated with weight loss and shortness of breath. The second was hemoptysis, usually in association with a chronic cough and general ill health. The least common presentation was that of weight loss associated with fatigue, and general ill health, usually with a minor cough. Overall, the most common symptoms were weight loss (17 patients [94%]), cough (14 [78%]), shortness of breath (9 [50%]), hemoptysis (10 [58%]), moderate to severe fatigue and malaise (5 [28%]), chest pain (3 [17%]), substantial sputum production (2 [11%]), and fever (2 [11%]). Wheezing and anorexia were seen in only 1 patient each. Shortness of breath was a common feature, but in many patients this was related to underlying lung disease. Hemoptysis varied from severe to trivial but in no case was fatal. Two patients had episodic fevers due to empyema, chest infections, or exacerbations of bronchiectasis.

Radiological examination. All patients had radiological evidence of a cavitary lesion in the lung (table 1). The commonest site of involvement was the left upper lobe in 9 cases; however, the right upper lobe was involved in 5 cases, and in 3 it was
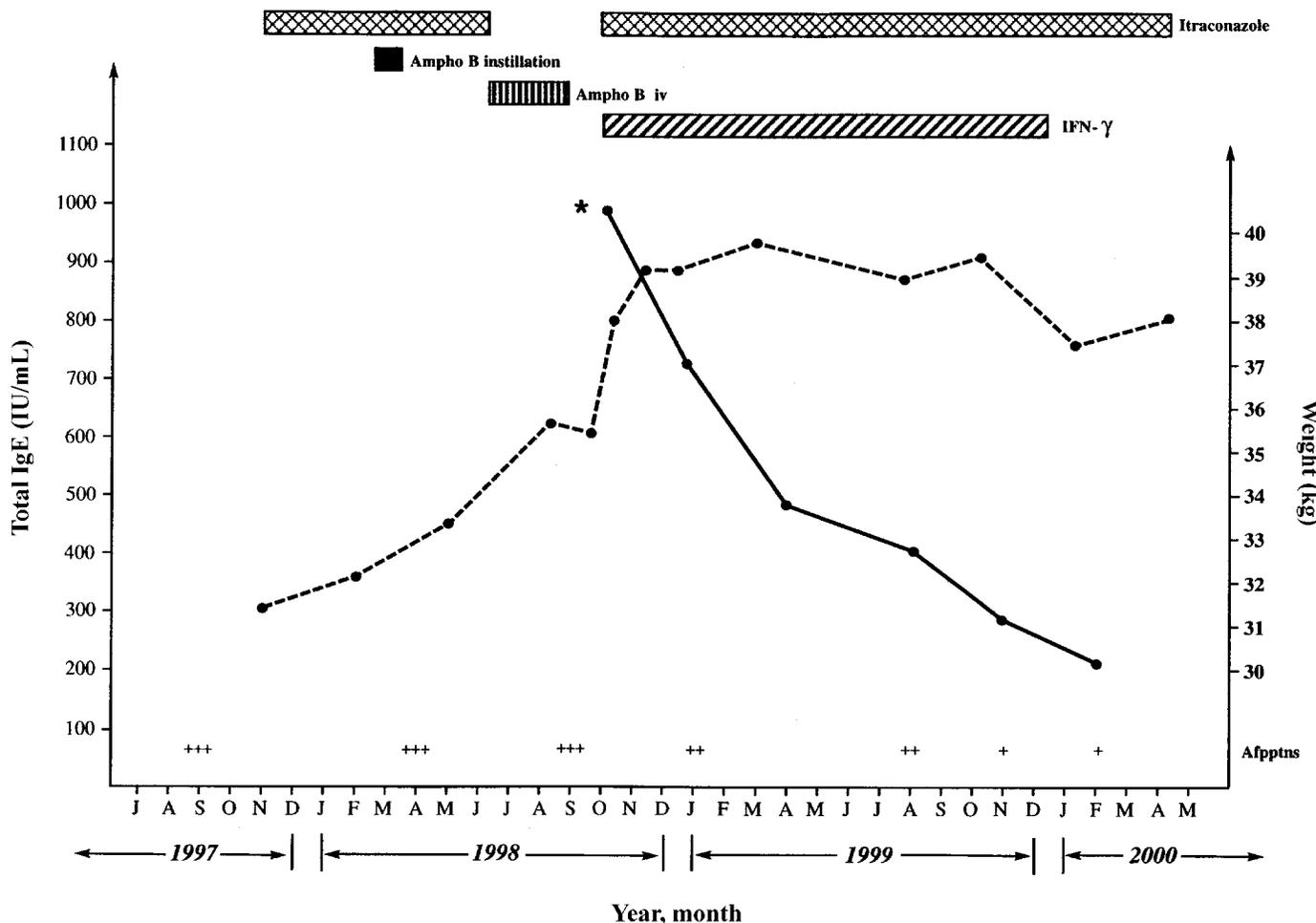
Figure 5. Treatment and serological course of patient 8. Ratings for *Aspergillus* precipitin test results are shown along the bottom of the figure. Afpptns, *A. fumigatus* precipitins; ampho B, amphotericin B; +, quantitation of lines of precipitating antibody. *IgE, 1800 IU/mL in March 1994.

bilateral. The left lower lobe was involved in 1 case. In CCPA, the infiltrates were initially ill-defined areas of consolidation that progressed to form well-defined cavities. These cavities often contained intracavitary masses (fungus balls), debris, or fluids. Commonly there were multiple cavities, some large and others small. The size of the cavities was measured on CT where possible. The areas varied from 2 cm^2 (2nd cavity in patient 2) to 110 cm^2 (patient 1). Some cavities had thick walls and were adjacent to thickened pleura, but more commonly they were thin-walled without pleural thickening. In those cases in which cavities preexisted (i.e., in cases of previous tuberculosis or bronchiectasis), in addition to intracavitary fungus ball formation, cavity expansion and paracavitary infiltrates were seen, which often coincided with clinical relapse or deterioration. Cavity expansion correlated well with continuing ill health as a radiological marker of disease progression, with arrest of expansion with successful therapy. However, cavity wall thickness measured on CT (range, 0.2–2 cm) was not a useful marker of disease activity. Relatively rapid

expansion of a cavity (few weeks) was most consistent with subacute IPA or CNPA, compared with the much slower expansion seen with CCPA. One remarkable case of cavity expansion (CNPA) over many months is demonstrated in a series of images from patient 14 [8].

Substantial pleural thickening was noted in 3 of 6 patients with intracavitary fungus balls (aspergillomas) and in 6 patients with no evidence of aspergilloma. Extensive pleural thickening of the left lung preceded CCPA in patient 12. Pleural involvement in 1 case resulted in the formation of a bronchopleural fistula.

One patient (patient 10) presented initially with a solitary pulmonary lesion that was suggestive radiologically of malignancy (the side opposite from his prior squamous cell carcinoma). Levels of inflammatory markers were raised, and *A. fumigatus* precipitins were detectable. Results of biopsy were inconclusive, and he responded clinically to itraconazole over 4 months. The mass then expanded, and the patients developed

Table 1. **Clinical characteristics, and radiological, serological, and mycological findings of 18 patients with pulmonary aspergillosis.**

Patient no.	Age (y)/sex	Underlying pulmonary disease	Categorization of aspergillosis	Signs and symptoms	Radiological findings	Serological findings	Results of culture for *Aspergillus*	Procedures performed	Histological results from procedure
1	51/M	Ankylosing spondylitis, mild COPD, *Mycobacterium malmoense* tuberculosis	CCPA	Cough, weight loss	LUL cavities, aspergilloma, pleural thickening	*Aspergillus fumigatus* precipitins titer rating, 3+; IgE, 20 IU/mL; RAST, positive	Sputum, positive; drain fluid, positive; BAL fluid, positive	LUL resection; bronchoscopy	Chronic inflammation, abscess cavities, caseous material, Langhans giant cells; none
2	45/M	Emphysema	CCPA + pleural aspergillosis	Cough, weight loss, chest pain, SOB, hemoptysis	RUL cavity, with infiltrates and pleural thickening	*A. fumigatus* precipitins titer rating, 2+; IgE, 238 IU/mL; RAST, ND	Sputum, positive; BAL fluid, positive; lung biopsy, positive	RUL resection; bronchoscopy; lung biopsy	2-cm cavity with local bronchiectasis and intraluminal fungal ball; negative
3	73/F	Emphysema, *M. malmoense* tuberculosis	CCPA then CCFA	Cough, weight loss, SOB, hemoptysis	LUL cavity, aspergilloma, infiltrates, pleural thickening	*A. fumigatus* precipitins titer rating, 3+; IgE, 10 IU/mL; RAST, ND	Sputum, positive	Bronchoscopic biopsy	Negative
4	20/F	Kyphoscoliosis and bronchiectasis	CCPA then pleural aspergillosis	Cough, weight loss, malaise, episodic fever	LLL infiltrates + cavity, pulmonary abscess, pleuritis	*A. fumigatus* precipitins titer rating, 3+; IgE, 1200 IU/mL; RAST, ND	Sputum, positive; pleural fluid, positive	LLL resection thoracoplasty	Chronic inflammation with eosinophils, *Aspergillus* hyphae in cavity
5	67/M	Mild COPD	CCPA	Cough, SOB, hemoptysis, weight loss	Infiltrates, consolidation, LUL cavity, pleural thickening	*A. fumigatus* precipitins titer rating, 1+; IgE, 5000 IU/mL; RAST, ND	Sputum, positive	Lung biopsy	Negative
6	72/F	Mild COPD, tuberculosis	CCPA then CCFA	Hemoptysis, cough, weight loss	LUL cavity, infiltrates, aspergilloma, pleural thickening	*A. fumigatus* precipitins titer rating, 4+; IgE, 4500 IU/mL; RAST, 8 Ua/mL	Sputum, positive	Lung autopsy biopsies	Chronic inflammation
7	54/M	*Mycobacterium kansasii* tuberculosis, COPD during steroid treatment	Subacute IPA/CNPA	Cough, SOB, chest pain, weight loss, hemoptysis	Infiltrates, consolidation, LUL cavities, aspergilloma	*A. fumigatus* precipitins titer rating, 2+; IgE, 3400 IU/mL; RAST, 32 Ua/mL	Sputum, positive; BAL fluid, negative; sputum cytology, positive	Bronchoscopic biopsy	Granulomas
8	37/F	Tuberculosis, smoke inhalation	CCPA then CFPA	Cough, SOB, weight loss, hemoptysis	LL cavities, infiltrates, aspergilloma, pleural thickening	*A. fumigatus* precipitins titer rating, 3+; IgE, 1800 IU/mL; RAST, 26 Ua/mL	Sputum, positive; BAL fluid, positive	Bronchoscopic biopsy; lung biopsy	Negative; carbon pigment and focal chronic inflammation
9	46/F	R pneumothoraxes, pleurodesis	CCPA	Cough, malaise, weight loss, recurrent chest infections, episodic fever	RUL cavity, bronchiectasis, infiltrates	*A. fumigatus* precipitins titer rating, 3+; IgE, 1 IU/mL; RAST, positive	Sputum, positive; BAL fluid, positive	CT lung biopsy; bronchoscopic biopsy	Chronic inflammatory reaction; negative

10	77/M	COPD, squamous cell carcinoma, LUL segmentectomy	CCPA	Cough, hemoptysis, weight loss, wheezing	Infiltrates, LUL cavity, pleural thickening	*A. fumigatus* precipitins titer rating, 1+; IgE, 260 IU/mL; RAST, 5 Ua/mL	Sputum, positive; BAL fluid, negative; lung biopsy, negative	Bronchoscopic biopsy; lung biopsy	Negative; chronic inflammation with fibrosis
11	43/M	Emphysema, tuberculosis	CCPA	Hemoptysis, weight loss, SOB	LUL cavity, fluid level, infiltrates	*A. fumigatus* precipitins titer rating, 2+; IgE, 260 IU/mL; RAST, negative	Sputum, negative; BAL fluid, negative	Bronchoscopic biopsy	Negative
12	66/M	Pleural thickening, hypertension	CCPA, then subacute IPA/CNPA with steroids, then pleural aspergillosis	SOB, cough, weight loss	LUL cavity, pleural thickening	*A. fumigatus* precipitins titer rating, 3+; IgE, 14 IU/mL; RAST, negative	BAL fluid, positive; pleural fluid, positive; autopsy, positive	Bronchoscopic biopsy; lung biopsy; pneumonectomy; autopsy	Negative; hyphae; cavity with fibrosis, granulomas, fungal ball; negative
13	70/M	*M. malmoense* tuberculosis	CCFA	Weight loss, SOB, sputum production	RUL contraction, pleural thickening, RUL mass, bilateral UL bronchiectasis	*A. fumigatus* precipitins titer rating, 1+; IgE, 180 IU/mL; RAST, 2 Ua/mL	Sputum, negative; lung biopsy, negative	Lung biopsy	Lymphoid, plasma cell infiltrate with epithelioid and mast cells and eosinophils
14	59/M	Asthma, *Mycobacterium avium* tuberculosis, diabetes	Subacute IPA/ CNPA	Weight loss, fatigue, sputum production, mild hemoptysis	10-cm thin-walled RUL cavity with fluid, expanding over 2 y from 2 cm, containing aspergilloma	*A. fumigatus* precipitins titer rating, 1+; IgE, 300 IU/mL; RAST, 7 Ua/mL	Sputum, negative; lung aspiration, *Staphylococcus aureus*	Cavity aspiration	None
15	76/M	Emphysema, multiple bullae, R basal pneumothorax	CCPA	Weight loss, anorexia, fatigue	Extensive fibrotic shadowing, LUL and RUL, with L apical pleural fibrosis	*A. fumigatus* precipitins titer rating, 3+; IgE, 260 IU/mL; RAST, negative	Sputum, negative	None	None
16	59/M	RLL lobectomy for *Legionella* infection, chronic bronchitis	CCPA	Severe weight loss, nonproductive cough, SOB	R extensive pulmonary scarring, pleural thickening, cavitation R apex	*A. fumigatus* precipitins titer rating, 1+; IgE, 600 IU/mL; RAST, 1 Ua/mL	Sputum, negative; BAL fluid, negative	Bronchoscopy	None
17	59/M	Emphysema, ? pigeon fancier's lung	CCPA	Weight loss, dull central chest pain, cough	Fibrotic destruction of both ULs, pleural thickening	*A. fumigatus* precipitins titer rating, 1+; IgE, 360 IU/mL; RAST, 1 Ua/mL	Sputum, negative; BAL fluid, negative	Bronchoscopic biopsy	Negative
18	44/M	Tuberculosis, alcohol abuse	CCPA	Hemoptysis, productive cough, fatigue	Fibrosis both ULs, pleural thickening, bronchiectasis, cavitation	*A. fumigatus* precipitins titer rating, 1+; IgE, 17,000 IU/mL; RAST, 900 Ua/mL	Sputum, negative; lung tissue, negative	Lung biopsy	None

NOTE. BAL, bronchoalveolar lavage; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; F, female; IPA/CNPA, invasive pulmonary aspergillosis/chronic necrotizing pulmonary aspergillosis; L, left; LL, left lung; LLL, left lower lobe; LUL, left upper lobe; M, male; ND, not done; R, right; RAST, *Aspergillus*-specific IgE fluoroenzyme immunoassay; RLL, right lower lobe; RUL, right upper lobe; SOB, shortness of breath; UL, upper lobe; y, years; ?, possible/uncertain.

superior vena cava obstruction. Additional biopsies showed chronic inflammation, and he died a few weeks after insertion of a stent and radiotherapy; an autopsy was not done. Whether he had had CFPA or a squamous cell carcinoma that evaded 3 directed biopsies is uncertain.

Serological testing. All 18 patients had positive results for *A. fumigatus* precipitins. This was required as part of the definition of disease in this series. The titer of antibodies varied over time and, in a very few instances, precipitins test results reverted to negative at some time in the illness. High titers of antibodies were more common in more seriously ill patients, and generally the titer would rise during exacerbations. One patient with otherwise typical features of CFPA was excluded because of negative results of testing for *A. fumigatus* precipitins on 2 occasions. It is possible therefore that some patients with CFPA do not mount an IgG serological response to *A. fumigatus.*

All 18 patients had elevated acute-phase markers (C-reactive protein, plasma viscosity, or erythrocyte sedimentation rate). However, in the same patient, an inflammatory marker could be normal and another raised, so >1 measurement of inflammation is required for full documentation. Rarely did inflammatory markers fall to normal, even with apparently successful therapy.

Elevated levels of total IgE were seen in 14 (78%) of 18 patients, of whom 13 had levels >200 IU/mL and 7 had levels >400 IU/mL (table 1) early in the course. Some patients seen in the early 1990s did not have *Aspergillus*-specific IgE measured, but of the 14 patients who did have it measured early in their course, it was present in 9 (64%). It was present in all those with total IgE levels of >400 IU/mL.

Histological examination. The procedures undertaken for diagnostic and therapeutic purposes are shown in table 1. They included examinations of sputum samples, bronchial washings, percutaneous lung or pleural aspirates, and tissue obtained during thoracotomy. Bronchoscopic biopsy samples yielded negative findings in 7 of 8 instances and showed granulomas (but no hyphae) in 1 patient. Percutaneous lung biopsies were done antemortem in 7 cases and showed hyphae in 1 case (patient 12). However these biopsies did yield some histological information in that chronic inflammation and fibrosis was common, and in 1 case (patient 13), plasma cells, eosinophils, and epithelioid giant cells were seen.

Among the 4 patients who had lung resections, the histological appearance of the lung tissue was similar. Hyphae were found in abnormal cavities in all cases and were not seen to invade lung tissue. In each case, hyphae were found in cavities rather than within the lung parenchyma or cavity walls. The pathological findings described above for patient 2 were typical. Localized bronchiectasis with cavity formation, chronic inflammation, and associated fibrosis appears to be the histological hallmark of CCPA. Fibrosis was prominent in CFPA. In ad-

dition, some patients had a prominent eosinophilic infiltrate. Granulomas were often seen sparsely distributed and in some cases were the so-called naked granulomas associated with sarcoidosis. The volume of tissue examined may be important, because only in those who underwent surgery were hyphae demonstrated, with 1 exception. In patient 12, who had remarkable expansion of disease during treatment with corticosteroids, small abscesses containing fungal hyphae were seen in the pleura, surrounded by dense fibrosis, without any such appearances in the lung tissue.

Microbiologic testing. Culture of sputum yielded positive results for *A. fumigatus* in 10 cases, and in all instances the fungus was the sole pathogen isolated. Positive culture results were infrequent, however, and often occurred months or years after the patient first presented. Cytological examination of sputum revealed *Aspergillus* hyphae in only 1 case. Ten patients underwent bronchoscopy with bronchoalveolar lavage, and in 4 of them, culture of the fluid samples yielded *A. fumigatus.* One bronchoscopic biopsy sample yielded *A. fumigatus.* Lung biopsy samples or fluid obtained by aspiration were cultured for fungus in 5 instances and yielded *A. fumigatus* on 1 occasion (patient 2) and *S. aureus* on another (patient 14). Culture of pleural fluid yielded *A. fumigatus* on the 3 occasions that it was done, usually after surgery for patients with postpneumonectomy or postlobectomy empyema.

Treatment. The patients were treated with corticosteroids, amphotericin B, itraconazole, or voriconazole alone or in combination with IFN-γ or G-CSF. The duration of therapy varied from 12 days to >10 years.

One patient (patient 12) progressed from CCPA to CNPA during corticosteroid treatment, and eventually surgical resection was attempted. He developed *Aspergillus* empyema and died some months after surgery. Another patient (patient 7), given corticosteroids and itraconazole in combination for 6 months, had a slight reduction in the size of the cavity but an increase in the amount of material in the cavity and no improvement of systemic features of disease. Two patients who received no therapy for long periods (patients 3 and 8) had CCPA that progressed to CFPA.

All patients took itraconazole at some time during the course of their disease, and all had detectable blood levels of itraconazole that exceeded 5 μg/mL. In 17 instances, itraconazole was given as primary therapy, and 12 (71%) patients had improvement or stabilization in their condition, without need of further therapy (table 2). Three patients developed severe ankle edema; in 2 of them it prevented further therapy. Even though itraconazole treatment failed in 5 patients, all subsequently were treated with itraconazole as maintenance therapy after amphotericin B, and itraconazole seemed to be effective in maintaining improvement (table 2).

Eleven courses of amphotericin B (0.5–1 mg/kg/day iv) were

Table 2. Outcomes of treatment in series of 18 patients with pulmonary aspergillosis.

Therapy administered	No. of courses of treatment	Stable or improved	Treatment failure due to progression of disease	Toxicity[a]
Itraconazole primary	17	12	5	3
Voriconazole	2	2	0	2[b]
Amphotericin B, iv[c]	11	9	2	7
Amphotericin B, intracavitary[d]	4	3	1	1[e]
IFN-γ in addition to itraconazole	3	3	0	3
Itraconazole maintenance (after amphotericin B)	6	6[f]	0	0

[a] Clinically significant toxicity resulting in discontinuation of therapy (except skin reactions with voriconazole).
[b] Both photosensitivity skin reactions.
[c] Any preparation, usually Fungizone, but course could include 2 or 3 preparations during 1 hospitalization.
[d] In association with iv amphotericin B in 2 cases and with itraconazole in 1 case.
[e] Sepsis due to *Staphylococcus aureus*.
[f] Stable condition during therapy; relapse was usual when therapy was stopped.

given to 10 patients. Eight patients had a marked or moderate response to therapy (assessed after discharge from hospital) (table 2). Two patients had no response to amphotericin B treatment and needed immediate institution of alternative therapy. Seven patients had significant toxicity requiring reductions in dosage or curtailing of therapy, even with the substitution of lipid-based amphotericin B.

In 4 patients, amphotericin B paste was instilled into lung cavities through a flexible pigtail catheter that was left in situ. In 1 patient, amphotericin B instillation was directly into the pleural cavity (simply dispersed in dextrose), by means of a rigid needle and syringe. In 3 cases, local therapy was accompanied by systemic therapy. One patient (patient 8) developed local sepsis due to *S. aureus*, and the catheter was removed. Two of the 3 other patients appeared to benefit in a minor way and 1 not at all. Reduction in the amount of intracavitary material was seen, but was rarely complete.

IFN-γ was given sc as adjunctive therapy to 3 patients, and all showed improvement. Low dosages were used: initially 50 μg 3 times weekly, reduced to dosages as low as 20 μg 3 times weekly if adverse events, such as chills and fever, were severe.

Treatment was evaluated in accordance with clinical, radiological, serological, and microbiological parameters of response. During treatment, improvements were seen in some, but not all, of these parameters. Particularly useful parameters of response were weight gain (early [<8 weeks]), reduction of coughing (early), falling inflammatory markers (middle [~6 months]), falling IgE (middle), improvement in inflammation surrounding cavities (late [>1 year]), and eventually a reduction in cavity size and thinning of the wall of the cavity (late). In no patient did the radiological appearance return to normal, but a good outcome in patients with CCPA and CNPA was a stable thin-walled cavity, with little or no pleural thickening (figure 6). Patients with CFPA did not achieve any radiological response. Titers of *Aspergillus* precipitins usually fell with im-

provement, but in some cases precipitins were only just detectable at baseline. The most important parameter of response was the patients' general well-being and energy level. Hemoptysis was not a good guide to progression, because it was intermittent and would often continue despite other improvements or be arrested by embolization without other markers of response.

Attempts were made to stop oral itraconazole therapy, usually after 1–2 years of therapy. Late relapse was common (exemplified by patients 1 and 3) (figures 7–9). Thus, long-term clinical, serological, and radiological follow-up is mandatory. An argument could be made for not discontinuing therapy, but most patients prefer not to be taking medication. The optimal duration of therapy remains to be established.

Surgery. Four patients underwent surgical resection. In 2 cases, this established a previously unsuspected diagnosis (although in case 4, *Aspergillus* had already been isolated by culture), and in 2 it was a therapeutic procedure. Three of the 4 patients did well initially. The patient who did not (patient 12) received very little antifungal therapy postoperatively, despite spillage of cavity contents into the pleura. It is notable that patient 2 had a recurrence in the lung after resection surgery, and pleural aspergillosis developed postoperatively in the other 3 patients (patients 1, 4, and 12). Surgery was offered at an early stage to patient 8 when she had CCPA, which she declined, but after progression to complete involvement of the left lung over 3 years with CFPA, her condition prohibited surgery.

Eventual outcome. Ten of 16 patients for whom recent follow-up data are available are still alive. One died of an episode of pneumonia (patient 6), 3 of respiratory failure (patients 3, 10, and 11) (figures 7–9), another of superior vena cava obstruction (patient 13), and another of postoperative complications (empyema and chest wall abscess) 6 months after surgery (patient 12). None of the remaining 10 patients are unequivocally cured, and all have variable degrees of disability

Figure 6. Radiological appearance of the chest of patient 7, after ~7 years of maintenance therapy with itraconazole in 2002. The original chest radiograph obtained in 1994, when the diagnosis of chronic pulmonary aspergillosis was made, showed 2 cavities in the left upper lobe, with thick walls and a rounded shadow at base of the largest cavity, consistent with aspergilloma. The largest cavity had an area of 65 cm² on the radiograph. The fluid level on the chest radiograph reproduced here is related to the very small communication between the cavity and the bronchial tree and the recurrent bacterial infection of the cavity. The remarkable change over 8 years is the gradual thinning of the cavity wall and the complete absence, now, of paracavitary infiltrates.

and symptomatology. For example, patient 1 has a bronchopleurocutaneous fistula that discharges pus from time to time, patients 7 and 14 have large pulmonary cavities that become secondarily infected intermittently, and patient 9 has had to give up work and spends a part of each day in bed because of fatigue and night coughing, despite treatment. Patient 14 (who has CNPA) developed a squamous cell carcinoma of the lung immediately superior to a large pulmonary cavity.

DISCUSSION

CPA tends to affect middle-aged persons who are mildly or not immunosuppressed, with a predominance of males. It has an indolent progressive course lasting for years. Chronic productive cough and weight loss with mild hemoptysis, dyspnea, and fatigue are the usual presenting symptoms. Pleural fibrosis and *Aspergillus* empyema appear to complicate some cases of CPA. The combination of characteristic clinical and radiological find-

ings and either serological results positive for *Aspergillus* or the isolation of *Aspergillus* from respiratory samples is highly indicative of CPA.

We have attempted to divide CPA into 3 subcategories: subacute IPA or CNPA, CCPA, and CFPA (figure 10). The distinctions among these subcategories are not absolute but reflect the dominant clinical and radiological manifestations. CPA should be distinguished from acute and subacute IPA at one end of the spectrum and from a simple aspergilloma at the other. Acute IPA occurs in highly immunocompromised patients, such as those with profound neutropenia or who have undergone transplantation [2]. Subacute IPA has been associated with diseases such as AIDS [3], chronic granulomatous disease [4], diabetes mellitus [9], and alcoholism [9], and with low-dose corticosteroid therapy [10, 11]. Local extension of disease into the chest wall, brachial plexus, or vertebral column is occasionally seen in subacute IPA [3, 4] but not in CPA, in which local extension involves only the pleura.

We have identified a subtle immune defect (mannose-binding protein polymorphisms) in some of the patients described here [7] and postulate that many of the differing manifestations

Figure 7. Chest radiograph of patient 3 obtained in June 1999 by means of advanced multibeam equalization radiography technique, showing a large cavity in the left upper zone surrounded by number of smaller cavities inferiorly and some pleural thickening. There is substantial contraction and fibrosis of the left upper lobe but the apperance of the lower left lobe is nearly normal. Shadows of probable previous tuberculosis are seen at the right apex, and the patient has an indwelling intravenous catheter for administration of amphotericin B.

Figure 8. Chest radiograph of patient 3 obtained in July 2001 by advanced multibeam equalization radiography, showing persistence of the left upper lobe cavity, with additional pleural thickening and the cavity completely filled with an aspergilloma. A typical air crescent surrounds the aspergilloma. Inferior paracavitary infiltrates are obvious, together with some very small cavities. The patient received no antifungal therapy in the interval since 1999, because she could not tolerate either long-term amphotericin B therapy or itraconazole therapy.

of CPA will be genetically determined. Recent data obtained from mice are consistent with the hypothesis that alterations in surfactant D are important in aspergillosis [12, 13], and the genes encoding mannose-binding protein and surfactant are in proximity on chromosome 10, which could imply linkage of defects. Other genetic polymorphisms, such as those described in transforming growth factor β, may be important in determining tissue response to chronic exposure to *Aspergillus*. Several of the patients described in this and other series appear to have had structural pulmonary defects, such as bullae, which could have a similar underlying defect, such as defective surfactant. Some of the clinical and radiological features of CPA are also found in chronic pulmonary histoplasmosis [14] and coccidioidomycosis [15, 16], suggesting that host factors may be as important as which fungus is causing chronic infection, given the rather different features of these fungi. Patients with fibrocystic chronic sarcoidosis also develop pulmonary cavities that may develop into CPA, and this common host response could be partly or completely genetically determined.

A remarkable feature of some of these cases of CPA is the slow progression to unilateral pulmonary fibrosis surrounding pulmonary cavities of those untreated with antifungal drugs.

The cases of patients 3 and 8 are particularly extreme examples (figures 1–3 and figures 7–9). Long-term antifungal therapy probably arrested progression, as illustrated by several cases, including those in patients 2, 4, 7, 11, 17, and 18. Patient 12 had progressive disease, with cavity expansion as a result of corticosteroid treatment (evolution from CCPA to subacute IPA/CNPA) and patient 14 with diabetes had remarkable cavity expansion with little fibrosis (subacute IPA/CNPA). These differing expressions of CPA are the basis of the subcategorization proposed. The observation of progression to extensive fibrosis over many years as a result of chronic *Aspergillus* infection has not been systematically described previously. The lack of any immunocompromising factors in some of these patients has been noted by investigators who have described CNPA, but the radiological evolution over time and the long-term outcomes of survivors remained obscure [8, 10, 17–27]; such patients may have had either subacute IPA or CCPA.

The clinical distinction between CPA and a simple aspergilloma can be problematic and in many cases may be semantic

Figure 9. Chest radiograph of patient 3 obtained in April 2002, showing slight shrinkage of the left upper zone cavity because of additional pleural thickening. The aspergilloma and the cavity persist, but there is remarkable development of complete obliteration of the left lower lobe, with loss of diaphragmatic contour. CT of the lungs revealed a dense fibrotic appearance of the whole left lung with the exception of the large cavity containing the aspergilloma. The patient was given no antifungal therapy in the interval between July 2001 and April 2002.
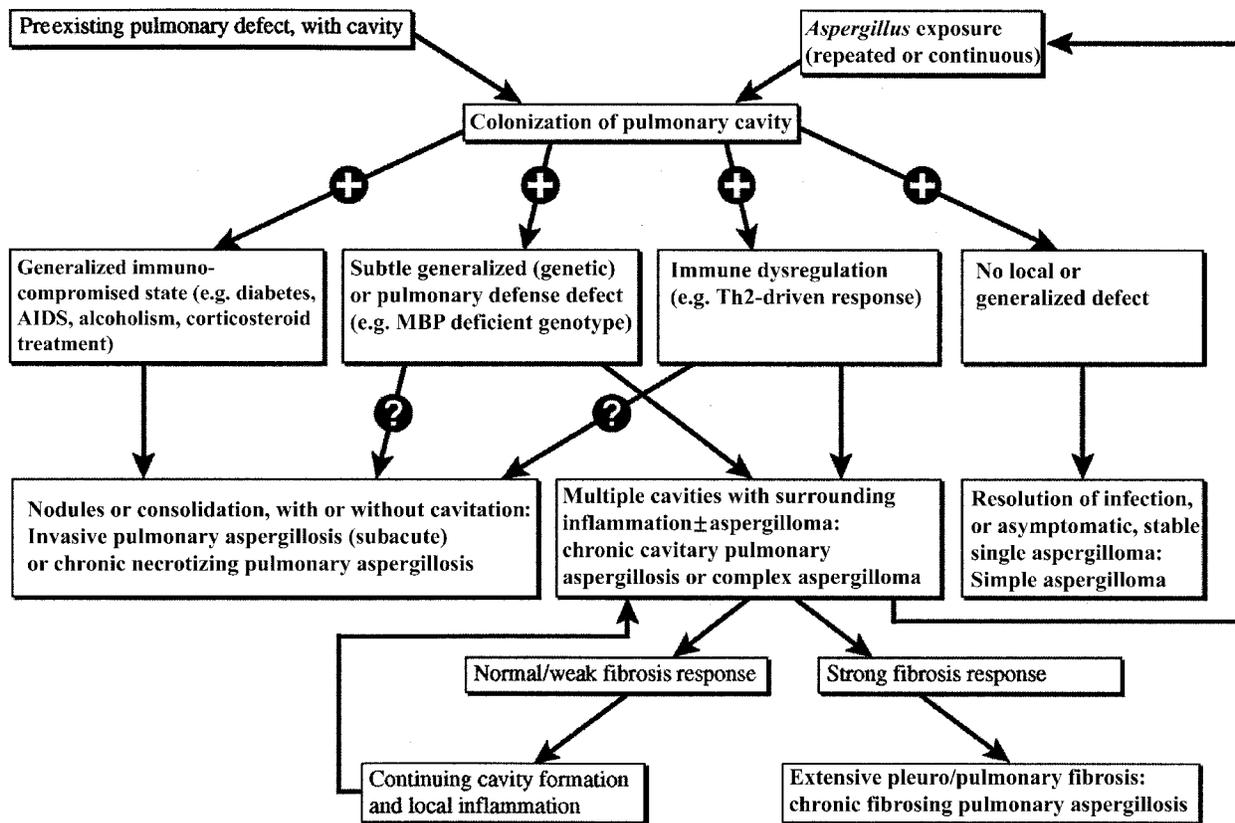
Figure 10. Proposed classification and pathogenesis of chronic pulmonary aspergillosis. The pathways proposed *(arrows)* are speculative, and one or more may or may not be operative in a given patient.

[8]. It is likely that what has been termed complex aspergilloma is synonymous with CCPA, although some patients with CCPA do not have aspergillomas within the cavities [5]. There appears to be a spectrum of cavitary pulmonary disease caused by *Aspergillus,* from a simple, single aspergilloma in a single cavity to CCPA and CFPA. Radiological evolution over time (particularly cavity expansion and new cavity formation) is helpful in making or excluding the diagnosis of CCPA and distinguishing it from a simple aspergilloma. The formation or expansion of ⩾1 new cavity over time with surrounding inflammation is typical of CCPA. Evidence of progressive pulmonary (as opposed to pleural) fibrosis is typical of CFPA. Usually there is less pleural thickening in CCPA than in aspergilloma, but more pulmonary fibrosis or an enlarging cavity is seen. Many cavities in CCPA do not have fungal balls in them. The presence of the fungal ball may divert attention away from very significant changes in the surrounding lung or pleura.

The histological diagnosis of invasive aspergillosis requires the presence of invasion of lung tissue by fungus of the *Aspergillus* species [2]. In the 4 cases described here, in which large portions of the lung have been removed, hyphae were visualized, but always within a cavity and not in lung tissue. In immediate proximity to cavities, there is typically chronic inflammation with fibrosis, sometimes with granulomatous inflammation. These features are similar to those classified by Yousem [28] as a granulomatous bronchiectatic cavity. A lung biopsy will also demonstrate chronic inflammation and fibrosis (sometimes with granulomatous features) with or without hyphae present. The major utility of a biopsy in this context is the exclusion of other major conditions, such as carcinoma, lymphoma, or tuberculosis. Granulomas may suggest sarcoidosis or tuberculosis, but these diagnoses should not be made without excluding CPA by serological testing. The absence of hyphae does not exclude the diagnosis of CPA because of the paucity of hyphae in CPA and the sampling error. We suggest that the presence of any hyphae in tissue defines IPA (acute or subacute) and that chronic inflammatory changes, with or without fibrosis, implies CCPA if other diagnostic criteria are met.

Aspergilli are ubiquitous in the environment. At least 100 species are described. The most common species infecting humans are *A. fumigatus, Aspergillus flavus, Aspergillus niger,* and *Aspergillus terreus* [1]. Other species, such as *Aspergillus clavatus,* are potent allergens. Only *A. fumigatus* was isolated from our patients. *Aspergillus* species are almost unique among human pathogens in that they are capable of invoking both invasive and allergic disease, at opposite ends of the immune

Table 3. Proposed enrollment criteria for prospective clinical studies of chronic pulmonary aspergillosis (CPA).

Criterion	Definition
1	Chronic pulmonary or systemic symptoms (duration, 3 months) compatible with CPA, including at least 1 of the following symptoms: weight loss, productive cough, or hemoptysis
2	Cavitary pulmonary lesion with evidence of paracavitary infiltrates, new cavity formation, or expansion of cavity size over time
3	Either positive result of serum *Aspergillus* precipitins test **or** isolation of *Aspergillus* spp. from pulmonary or pleural cavity
4	Elevated levels of inflammatory markers (C-reactive protein, plasma viscosity, or erythrocyte sedimentation rate)
5	Exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests, that are associated with similar disease presentation, including mycobacteria and endemic fungi (especially *Coccidioides immitis* and *Histoplasma capsulatum*)
6	No overt immunocompromising conditions (e.g., HIV infection, leukemia, and chronic granulomatous disease)

NOTE. All criteria must be met to be enrolled; for criterion 3, one or the other condition must be met.

spectrum [29]. When inhalation of airborne conidia takes place, alveolar macrophages in the normal human lung kill them rapidly. In damaged lungs, respiratory tract colonization may occur, which may be temporary or semipermanent. Defective mucociliary clearance appears to be a key defect. This is irreversibly damaged in preexisting lung cavities and in bronchiectasis. One of the more remarkable features of the cases described here is the preexisting pulmonary disease. Phagocyte dysfunction appears to be the common denominator of invasive aspergillosis, generally including subacute cases, such as in AIDS or chronic granulomatous disease. No such defects were demonstrable in the patients studied here. If generalized immunologic defects exist in patients with CPA (such as mannose-binding protein defects), they may not be readily amenable to testing in a routine immunology workup, and perhaps only local defects are sufficient for the disease to be initiated. It may be that the compelling data showing the importance of a strong Th1 immune response to *Aspergillus* species [30–32] for a good outcome in experimental invasive aspergillosis are important in CPA as well.

Although treatment of CPA with systemic antifungal therapy appears from our data, and that of others, to be beneficial, the assessment of response is difficult to gauge. Weight gain and improved energy levels were the earliest and most definitive indicators of response. Inflammatory markers also improved, but more slowly, and usually remained elevated even during long-term therapy. Although the response to amphotericin B appeared to be slightly better than that to itraconazole, it required long hospitalization periods and carried considerable toxicity. Amphotericin B has minor immunomodulating activity [33, 34]. It is possible that this is the explanation for the apparent response to itraconazole as maintenance therapy after amphotericin B yet lack of success as primary therapy. Itraconazole is slightly inhibitory to immune responses likely to be useful for recovery from CPA [35]. This balance between the importance of the antifungal effect and immunomodulation

may be why the addition of IFN-γ was helpful. One study [36] reported good responses to corticosteroid therapy, although the apparent large doses were modulated in many cases by concurrent rifampicin therapy.

Surgery plays a small role in the treatment of CPA because of poor overall lung function in many patients. The first surgical resection to treat aspergilloma dates back to 1943 [37], and in many centers, surgery is regarded as the treatment of choice for symptomatic aspergilloma [38, 39]. This view has been questioned, particularly for patients with so-called "complex" aspergillomas [40–42]. Major postoperative complications, such as respiratory failure, bronchopleural fistulas, resistant air space problems, pleural aspergillosis, and even disseminated disease, can occur [40–42]. For example, in 1 retrospective series, 11 (34%) patients with complex aspergillomas died, compared with 1 (5%) patient with a simple aspergilloma [38]. Postoperative pleural aspergillosis (postpneumonectomy empyema) is particularly common [38, 42–44], probably for 2 reasons. First, the pleura is involved in the disease process, as shown in the patients with CCPA presented here. Second, spillage of cavity contents at surgery is common, because surgery is difficult. Three of the 4 patients who underwent surgical excision in this series developed pleural aspergillosis subsequently. Thus, surgery should be reserved for patients with reasonable respiratory reserve and no other treatment options. Surgery may be appropriate for patients with severe hemoptysis if embolization fails. Surgical resection and thoracoplasty as treatments for pleural aspergillosis are prone to many complications and should be avoided, if possible. In addition, many patients have underlying respiratory insufficiency, and removal of a lobe of the lung would leave them unacceptably breathless.

Improvement in the prognosis for patients with CFPA requires improvements in medical therapy. No prospective trials of this entity have been done, although some patients have been included in clinical trials of azole antifungal drugs, and 1 trial specifically addressed this population of patients [45].

In an effort to facilitate this, we propose enrollment criteria for prospective clinical trials (table 3). Although some patients with CPA may have concurrent infection with *Mycobacterium* species or other pathogens [45], such patients should not be enrolled into clinical trials because the assessment of response is difficult. With current therapies, response time is measured in weeks and months, and studies should therefore be at least 4–6 months long and possibly as long as 12 months, as shown by the chronicity of disease in this series. Relapse months or years later is also problematic, as it is for coccidioidomycosis, and so these studies will require a considerable time investment. Hemoptysis is not a good guide to therapeutic response, because we have seen good clinical and radiological responses with continuing hemoptysis arrested with vessel embolization.

Acknowledgments

References

1. Denning DW. Aspergillus. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. 5th ed. Philadelphia: W. B. Saunders, **2000**:2674–82.
2. Denning DW. Invasive aspergillosis. Clin Infect Dis **1998**; 26:781–805.
3. Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med **1991**; 324:654–62.
4. Segal BH, DeCarlo ES, Kwon Chung KJ, Malech HL, Gallin JI, Holland SM. *Aspergillus nidulans* infection in chronic granulomatous disease. Medicine (Baltimore) **1998**; 77:345–54.
5. Belcher JR, Plummer NS. Surgery in bronchopulmonary aspergillosis. Br J Dis Chest **1960**; 54:335–41.
6. Giron J, Sans N, Poey C, Fajadet P, Fourcade D, Senac JP, Railhac JJ. CT-guided percutaneous treatment of inoperable pulmonary aspergillomas: a study of 42 cases. J Radiol **1998**; 79:139–45.
7. Crosdale D, Poulton K, Ollier W, Thomson W, Denning DW. Mannose binding lectin gene polymorphisms as a susceptibility factor for chronic necrotizing pulmonary aspergillosis. J Infect Dis **2001**; 184:653–6.
8. Denning DW. Chronic forms of pulmonary aspergillosis. Clin Microbiol Infect **2001**; 7(Suppl 2):25–31.
9. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis; review of 2,121 published cases. Rev Infect Dis **1990**; 12:1147–201.
10. Gefter WB, Weingrad TR, Epstein DM, Ochs RH, Miller WT. "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of *Aspergillus* infections of the lung. Radiology **1981**; 140:313–21.
11. Binder RE, Faling LJ, Pugatch RD, Mahasaen C, Snider GL. Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine (Baltimore) **1982**; 61:109–24.
12. Madan T, Kishore U, Singh M, et al. Protective role of lung surfactant protein D in a murine model of invasive pulmonary aspergillosis. Infect Immun **2001**; 69:2728–31.
13. Madan T, Kishore U, Singh M, et al. Surfactant proteins A and D protect mice against pulmonary hypersensitivity induced by *Aspergillus fumigatus* antigens and allergens. J Clin Invest **2001**; 107:467–75.
14. Rubin H, Furcolow ML, Yates JL, Brasher CA. The course and prognosis of histoplasmosis. Am J Med **1959**; 27:278–88.
15. Winn WA. A long term study of 300 patients with cavitary-abscess lesions of the lung of coccidioidal origin. An analytical study with special reference to treatment. Dis Chest **1968**; 54 (Suppl 1):268–72.
16. Salkin D, Hubbert M. Review of 706 cases of pulmonary cavities in the coccidioidomycosis VA-AF Cooperative Study [abstract 12]. In: Proceedings of the 23rd annual Coccidioidomycosis Study Group meeting (Beverly Hills). California Thoracic Society, **1978**.
17. Palmer LB, Greenberg HE, Schiff MJ. Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease. Thorax **1991**; 46:15–20.
18. Rodrigues J, Niederman MS, Fein AM, Pai PB. Nonresolving pneumonia in steroid treated patients with obstructive lung disease. Am J Med **1992**; 93:29–34.
19. Caras WE, Pluss JL. Chronic necrotizing pulmonary aspergillosis: pathologic outcome after itraconazole therapy. Mayo Clin Proc **1996**; 71:25–30.
20. Rello J, Esandi ME, Mariscal D, Gallego M, Domingo C, Valles J. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: report of eight cases and review. Clin Infect Dis **1998**; 26:1473–5.
21. Thommi G, Bell G, Liu J, Nugent K. Spectrum of invasive pulmonary aspergillosis in immunocompetent patients with chronic obstructive pulmonary disease. South Med J **1991**; 84:828–31.
22. Pittet D, Huguenin T, Dharan S, et al. Unusual cause of lethal pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med **1996**; 154:541–4.
23. Conesa D, Rello J, Valles J, Mariscal D, Ferreres JC. Invasive aspergillosis: a life threatening complication of short term steroid treatment. Ann Pharmacother **1995**; 29:1235–7.
24. O'Brien AAJ, Moore DP, Keogh JAB. Pulmonary berylliosis on corticosteroid therapy with cavitating lung lesions and aspergillomata—report on a fatal case. Postgrad Med J **1987**; 63:797–9.
25. Waldhorn RE, Tsou E, Kerwin DM. Invasive pulmonary aspergillosis associated with aspergilloma and sarcoidosis. South Med J **1983**; 76:251–3.
26. Israel HL, Ostrow A. Sarcoidosis and aspergilloma. Am J Med **1969**; 47:243–50.
27. Saraceno JL, Phelps DT, Ferro TJ, Futerfas R, Schwartz DB. Chronic necrotizing pulmonary aspergillosis: approach to management. Chest **1997**; 112:541–8.
28. Yousem SA. The histological spectrum of chronic necrotizing forms of pulmonary aspergillosis. Hum Pathol **1997**; 28:650–6.
29. Casadevall A, Pirofski LA. Host-pathogen interactions: redefining the basic concepts of virulence and pathogenicity. Infect Immun **1999**; 67:3703–13.
30. Cenci E, Perito S, Enssle KH, et al. Th1 and Th2 cytokines in mice with invasive aspergillosis. Infect Immun **1997**; 65:564–70.
31. Cenci E, Menacci A, Del Sero G, et al. Interleukin-4 causes susceptibility to invasive aspergillosis through suppression of protective type 1 responses. J Infect Dis **1999**; 180:1957–68.
32. Clemons KV, Grunig G, Sobel RA, Mirels LF, Rennick DM, Stevens DA. Role of IL-10 in invasive aspergillosis: increased resistance of IL-10 gene knockout mice to lethal systemic aspergillosis. Clin Exp Immunol **2000**; 122:186–91.
33. Louie A, Baltch AL, Franke MA, Smith RP, Gordon MA. Comparative capacity of four antifungal agents to stimulate murine macrophages to produce tumour necrosis factor alpha: an effect that is attenuated by pentoxifylline, liposomal vesicles, and dexamethasone. J Antimicrob Chemother **1994**; 34:975–87.
34. Rogers PD, Stiles JK, Chapman SW, Cleary JD. Amphotericin B induces expression of genes encoding chemokines and cell adhesion molecules in the human monocytic cell line THP-1. J Infect Dis **2000**; 182:1280–3.

35. Kim JH, Ahn YK. The effects of itraconazole on the immune responses in ICR mice. J Toxicol Sci **1994**; 19:7–15.

36. Hafeez I, Muers MF, Murphy SA, Evans EG, Barton RC, McWhinney P. Non-tuberculous mycobacterial lung infection complicated by chronic necrotising pulmonary aspergillosis. Thorax **2000**; 55:717–9.

37. Gerstl B, Weidman WH, Newman AV. Pulmonary aspergillosis. Report on two cases. Ann Intern Med **1948**; 28:662–71.

38. Jewkes J, Kay PH, Paneth M, Citron KM. Pulmonary aspergilloma: analysis of prognosis in relation to haemoptysis and survey of treatment. Thorax **1983**; 38:572–8.

39. Battaglini JW, Murray GF, Keagy BA, Starek PJ, Wilcox BR. Surgical management of symptomatic pulmonary aspergilloma. Ann Thorac Surg **1985**; 39:512–6.

40. Babatasi G, Massetti M, Chapelier A, et al. Surgical treatment of pulmonary aspergilloma: current outcome. J Thorac Cardiovasc Surg **2000**; 119:906–12.

41. Daly RC, Pairolero PC, Piehler JM, Trastek VF, Payne WS, Bernatz PE. Pulmonary aspergilloma: results of surgical treatment. J Thorac Cardiovasc Surg **1986**; 92:981–8.

42. Massard G, Roeslin N, Wihlm JM, Dumont P, Witz JP, Morand G. Pleuropulmonary aspergilloma: clinical spectrum and surgical treatment. Ann Thorac Surg **1992**; 54:1159–64.

43. El-Oakley R, Petrou M, Goldstraw P. Indications and outcome of surgery for pulmonary aspergilloma. Thorax **1997**; 52:813–5.

44. Chen JC, Chang YL, Luh SP, Lee JM, Lee YC. Surgical treatment for pulmonary aspergilloma: a 28 year experience. Thorax **1997**; 52:810–3.

45. Dupont B, Denning DW, Lode H, Yonren S, Troke P, Sarantis N. UK 109,496 (Voriconazole), a novel, wide spectrum triazole derivative for the treatment of fungal infections. Clinical efficacy in chronic invasive aspergillosis [abstract F-81]. In: Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1995**:125.