Chronic forms of pulmonary aspergillosis

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Aspergillus is a genus of fungi commonly found in all environments. Remarkably, only a few species cause disease and equally remarkably, those same species cause multiple diseases. In the lung, exposure to the fungus, the immunological status of the individual and the condition of the lung determine the pattern of disease. In asthmatic patients and those with cystic fibrosis, allergic bronchopulmonary aspergillosis (ABPA) is a complication that reduces pulmonary function and, in asthmatics, is substantially improved by itraconazole therapy. Patients with pre-existing lung cavities develop aspergillomas (fungal masses inside the cavity). Aspergillomas carry a 40% 5 years survival, and it not clear whether antifungal therapy is helpful. Similar in presentation to aspergilloma is chronic necrotizing pulmonary aspergillosis (CNPA). Development of new or expansion of existing pulmonary cavities with surrounding paracavitary shadowing is the hallmark of CNPA These two entities are probably a continuum of the same pathological process. Patients with CNPA respond to systemic antifungal therapy, but this may need to be lifelong. Surgery is appropriate for isolated aspergillomas, but not pleural or multicavity lesions. *Aspergillus* empyema is a complication of aspergilloma and CNPA, or surgery for these diseases and is slow to respond to treatment.

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INTRODUCTION

Aspergillosis is the name given to all diseases caused by the fungus in the genus *Aspergillus* and includes allergic, superficial, saprophytic and invasive disease. Although over 150 species of *Aspergillus* are described only a few cause disease with any regularity; *A. fumigatus, A. flavus, A. terreus* and *A. niger* group species. The pathogenic *Aspergilli* are found the world over. Soil isolation rates increase towards the equator. *Aspergilli* are common saprophytes in the environment, especially in composting facilities. Most aerobiology studies have been done in Europe. Most do not show a seasonal variation in airborne *Aspergillus* counts. However, some studies have shown an increase in the winter in temperate climates in the Northern Hemisphere. The *Aspergilli* comprise from 0.1% to 22% of the total air flora outside and, if speciated, *A. fumigatus* comprises from 4 to 41% of the total of *Aspergilli*. The usual concentration of conidia in outside air is 2–30 conidia/m^3 air but can rise to as high as $68 \times 10^6/m^3$ inside a barn following hay or straw disturbance. In hospitals conidia concentrations in air also vary typically from 1.0 to 2000/m^3 with much variation in the same site. Inside human dwellings *Aspergilli* may be found in high concentrations in potted plants (50 conidia/g soil), damp cellars, dusty crawl spaces and condiments, especially pepper (10^6 conidia/g in one study) and ground spices.

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ABPA

Wheezing in patients exposed to *Aspergillus* was recognized in the late 1800 s, but was ill-understood. First reported in three patients in 1952 from the London Chest Hospital [1], allergic bronchopulmonary aspergillosis (ABPA) is an extreme variety of continuing local allergy to *Aspergillus*. ABPA complicates asthma and cystic fibrosis (CF). Patients either develop exacerbations of asthma and/or CF, but are commonly are 'difficult-to-control' patients, in the pulmonary sense. Characteristic presentations include new pulmonary shadows which resolve with steroids, coughing up plugs of material, and after positive *Aspergillus* precipitins or an extremely elevated IgE is discovered. The diagnosis is made by a combination of criteria, of which episodic wheezing (asthma), transient pulmonary shadows, elevated serum total IgE and *Aspergillus* specific IgE, positive *Aspergillus* precipitins and central bronchiectasis are the most important. Central bronchiectasis is not a useful

diagnostic criterion in CF, as it is universally present. Some patients, especially those with long-standing disease, have barely detectable *Aspergillus* precipitins. Other criteria that have been used include peripheral eosinophilia and a positive immediate skin test to *Aspergillus*. The first of these is usually artificially low in those on steroids, and the second usually correlates with the serum *Aspergillus* specific IgE.

The serological response to *Aspergillus* infection has been well characterized in allergic bronchopulmonary aspergillosis and aspergilloma. The earliest means of detecting *Aspergillus* antibody was immunodiffusion but this methodology is not very sensitive although it is generally highly reproducible [2,3]. Concentration of serum improves sensitivity. Radioimmunoassay (RIA) and ELISA methods have also been developed and are routine in some laboratories [2]. RIA and ELISA test results vary substantially with the antigens used. There are other methods in use including latex agglutination and complement fixation. This subject has been reviewed in detail [2,3]. Commercially available tests have also been compared [4].

ABPA can be classified into five stages. These are acute remission, exacerbation, corticosteroid dependent, asthma and fibrotic. Patients may present in any stage, although it is a difficult diagnosis to make with confidence in the fibrotic stage. The staging system has less meaning in cystic fibrosis because of the progressive deterioration in respiratory status.

Patients in remission whose respiratory status is good with well-controlled asthma or CF require no therapy. Acute exacerbations are best treated with systemic corticosteroid therapy, usually a daily dose of 40–60 mg prednisolone for 7–10 days. Response to corticosteroid therapy can be gauged clinically and radiologically; wheezing and breathlessness should improve, and radiological infiltrates should clear. In patients with frequent exacerbations, inhaled corticosteroids are useful in reducing the frequency of attacks. Probably this also lowers the risk of fibrosis in later years, which is thought to be frequent otherwise. Many of these patients, however, require continuous systemic corticosteroid therapy to sustain remission.

Given the natural history of the disease, which is to wax and wane, convincing evidence of benefit requires a controlled study. For steroid-dependant patients a number of different antifungal strategies have been tried. Oral ketoconazole and inhaled natamycin are ineffective. Itraconazole 200–400 mg per day showed benefit in several open studies [5,6]. Recently a controlled trial of oral itraconazole vs. placebo was completed and there was a clear benefit of itraconazole over placebo in patients who were corticosteroid dependent [7]. Very few patients with CF have been studied. However, itraconazole treatment is associated with lower steroid usage and fewer acute ABPA episodes [8] Endpoints for studies in CF patients are problematic. Serum concentrations of itraconazole CF patients may be low and measurement of serum concentrations may be useful as a guide to appropriate dosing. There are no useful data available on whether corticosteroids and/or antifungal agents slow the progression of ABPA to pulmonary fibrosis which generally occurs between 5 and 11 years after the diagnosis in the preinhaled steroid era. It is likely that they will.

ASPERGILLOMA AND CHRONIC NECROTIZING PULMONARY ASPERGILLOSIS COMPARED

Aspergilloma is the term given to the colonization of an intrathoracic cavity by *Aspergillus*. A fungus ball is formed when spores are deposited in the cavity and germinate on the wall, where mycelia and debris attach to form an amorphous mass (Figure 1). Occasional cases are the result of other fungi, such as the *Mucorales* or *Pseudallescheria boydii* but these other fungi comprise less than 5% of cases of fungal colonization of pulmonary cavities.

Frequency and underlying factors

An aspergilloma may form in any pre-existing lung cavity. There are many causes of pulmonary cavities, including tuberculosis, sarcoidosis, pneumoconiosis, histoplasmosis, bullae and others. Some idea of the prevalence of aspergilloma can be gained from a reported review of 60 000 chest radiographs: aspergillomata were identified in 0.01%. During an 11-year period, 15 patients with aspergilloma were admitted to a Veteran's Administration Hospital, representing 0.02% of admissions. The frequency is high in patients with cavities 2 cm or more in diameter. For example, in tuberculosis cavities of this size, 15–20% of UK patients developed an aspergilloma

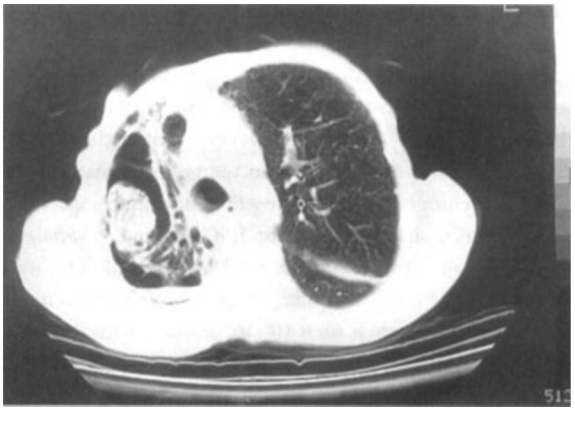

Figure 1 CT scan of the upper thorax in a patient showing multiple cavities and a large irregular aspergilloma in the right upper lobe. Some pleural thickening is apparent, as are some paracavitary infiltrates. This patient is a poor candidate for surgery. The diagnosis is probably chronic necrotizing pulmonary aspergillosis.

[9]. In another series in patients with pulmonary sarcoidosis, 10 of 19 (53%) patients with cystic parenchymal damage from sarcoidosis had aspergillomas compared with none of 81 patients with noncystic pulmonary sarcoidosis [10].

The incidence of chronic necrotizing pulmonary aspergillosis (CNPA) is not known. Most patients with CPNA, if not all, have prior pulmonary disease [11]. A healed tuberculous cavity, whether the result of typical or atypical mycobacteria, is common. Sometimes distinguishing an aspergilloma and CNPA can be difficult, particularly if a previous chest radiograph is not available. Other underlying pulmonary conditions include chronic obstructive pulmonary disease, ankylosing spondylitis, recurrent pneumothorax, thoracic surgery and kyphoscoliosis [12]. Corticosteroid therapy may be implicated but, if so, tends to lead to a more severe and rapid course. Diabetes mellitus, excess alcohol consumption and chronic liver disease are occasional antecedents. In a recent report of aspergillomas in AIDS [13], progression of 'aspergillomas' over time was seen with considerable morbidity and some mortality. This probably reflects invasion of cavity walls by *Aspergillus* rather than simple colonization of *Pneumocystis* cavities by *Aspergillus* and is either CNPA or invasive aspergillosis. Mitochrondrial defects (Pearson and MELAS syndromes) have recently been associated with invasive aspergillosis [14,15]. We have also recently described mannose binding protein deficiency as a probable association with CNPA (Crosdale *et al.*, unpublished data).

Clinical presentation

The symptomatology of aspergilloma is variable in individual patients over time. Most patients are asymptomatic when an aspergilloma first forms. The commonest presentation is that of hemoptysis, which initially is usually minor. In association with this, most patients have cough and productive sputum. About 40% of patients are 'sensitized' to *Aspergillus* and develop wheezing, weight loss and malaise with or without fever. The patient is typically in the 4th–6th decade of life and more men than women are affected. Hemoptysis may be progressive and is frequently severe ($\geqslant$ 150 mL blood daily). A considerable proportion of patients die directly as a result of exsanguinating hemorrhage.

CNPA presents in three ways. Constitutional symptoms are prominent in all patients with weight loss, malaise and fatigue. The most common presentation is a chronic productive cough. The second common presentation is hemoptysis, which varies from severe to trivial. The third is with only constitutional symptoms. Dyspnea is a common feature but usually reflects underlying lung disease unless CNPA is very distinctive. Chest pain is uncommon, but does occur. Features of bronchiectasis are also common and may coexist. Finger clubbing also occurs.

Radiology

Plain radiography of the chest in cases of aspergilloma shows a number of typical features, including a round solid mass within a cavity separated from the wall of the cavity by a rim of air [16]. This rim of air is known as the 'crescent sign' (not to be confused with the 'air crescent' sign in invasive aspergillosis) and is virtually diagnostic of an aspergilloma (Figure 1). Typically, pleural thickening is also present and this may vary from several millimetres to 2 cm. Pleural thickening may antedate the appearance of the aspergilloma on chest radiographs and is therefore a clue to the diagnosis of aspergilloma in patients with other pulmonary disease such as sarcoidosis. Computed tomographic (CT) scans are useful in dubious cases. However, some pleural thickening is also common following pulmonary tuberculosis. The aspergilloma may be mobile within the cavity. Mobility of the mass is most easily demonstrated on CT scans by rotating the patient.

Classification of aspergillomas into simple and complex may be therapeutically useful. Simple aspergillomas have thin-walled cysts with little surrounding parenchymal disease. Complex aspergillomas have thick-walled cavities with associated parenchymal infiltrates (Figure 1). In such instances, the aspergilloma consists of an irregular mass containing air spaces. Many, if not all, of these complex aspergillomas are in fact CNPA (see below). In addition, aspergillomas may be primarily pulmonary, pleural or bronchial in location.

All patients with CNPA exhibit radiological evidence of a cavitary lesion in the lung, usually in one or both upper lobes. Initially, infiltrates are ill-defined areas of consolidation or small cavities that progressed to form well-defined cavities (Figures 2–7). Cavities may be large or small. The cavities often contain an aspergilloma, debris or fluid. Over time, these cavities became multiple with thickened walls (Figure 8). In those cases where cavities pre-existed (i.e. in cases of prior tuberculosis or bronchiectasis), cavity expansion and paracavitary infiltrates are characteristic. Such new findings in a patient previously diagnosed with CNPA are characteristic of clinical relapse or deterioration. Some patients have pleural thickening and this may progress to form a broncho-pleural fistula.

Serology

Aspergillus precipitins (IgG antibody) are detectable in over 95% of patients with aspergilloma. Some have IgM antibodies as well. Successful surgical removal of an aspergilloma will result in a fall of *Aspergillus* antibody to (usually) undetectable levels over the following few months. The precipitin test may, however, be positive in some patients with cavities who do not have an overt aspergilloma, and these patients probably have CNPA. Most patients with aspergilloma have positive

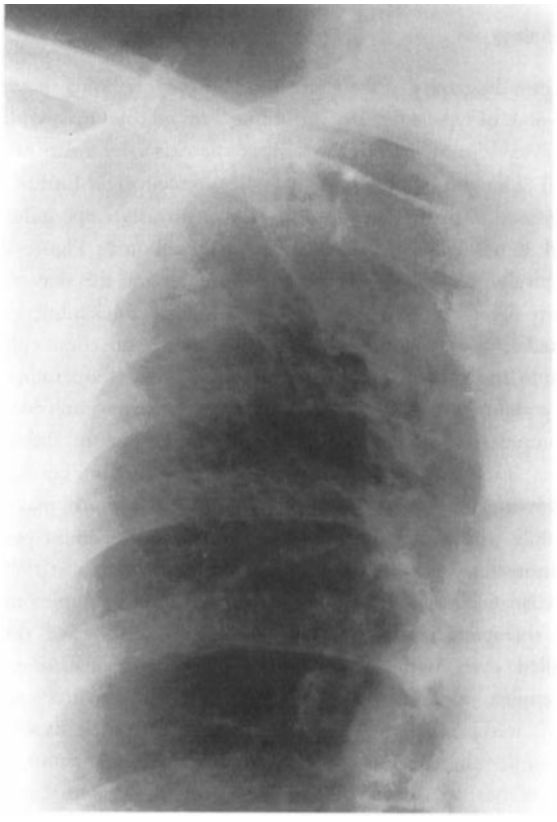

Figure 2 Right upper lobe from a male patient (MS) of 54 years with diabetes mellitus and pulmonary *Myobacterium avium* infection, showing small cavitary lesion, October 1995.

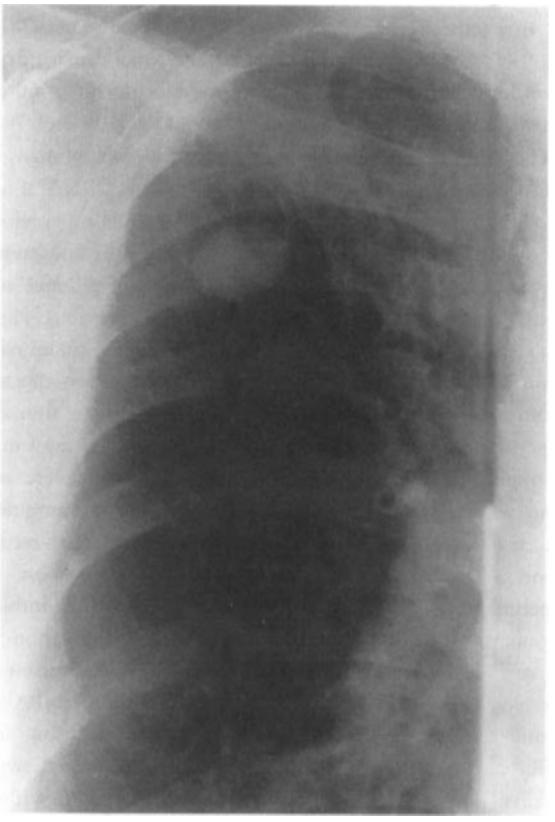

Figure 3 Right upper lobe from patient MS with the formation of a circular shadow, partly filled by a mass, June 1997.

respiratory cultures of *Aspergillus*, usually *A. fumigatus*. In a retrospective series, 25% of those with pulmonary aspergillomas, 100% of those with a sinus aspergilloma, and 8% with disseminated aspergillosis had calcium oxalate crystals identified in tissue [17]. *A. niger* may be a more prolific producer than *A.fumigatus*. Occasionally renal oxalosis is observed [17].

All, or almost all, patients with CNPA have *A. fumigatus* precipitins in blood. The titer of antibodies varies over time and may occasionally be negative at some time in the course of CNPA. Elevation of acute phase markers such as C-reactive protein, plasma viscosity are a useful clue to the diagnosis, if the distinction between CNPA and aspergilloma is difficult to draw. Two-thirds of patients have elevated levels of total IgE and *Aspergillus* specific IgE.

Other diagnostic measures

Patients with aspergillomas usually grow *Aspergillus* from sputum with ease and multiple variants and genotypes may be recovered.

Sputum cultures may be positive in CNPA and *Aspergillus* is typically the sole pathogen isolated. However positive cultures are infrequent and may occur years after the patient first presents. Bronchoscopy samples may also be positive by culture. Confirmation of the diagnosis can be difficult and the characteristic radiological and serological findings are sufficient. Histologically hyphae may be found in abnormal cavities without invading tissue. Lung resection may be necessary to identify such hyphae as bronchoscopic and percutaneous biopsies have usually been negative histologically. Other findings compatible with CNPA include chronic inflammatory reaction, with or without nonspecific granuloma formation without hyphae being visualized. In contrast, percutaneous biopsies were positive microbiologically on two or three occasions.

Natural history

Spontaneous resolution of aspergillomas is recognized to occur in 10% of cases within 3 years [9]. However the consequences of this type of *Aspergillus* infection can be dramatic. One report focussed on the long-term outcome of 23 patients with aspergilloma, five of whom died directly from complications of this infection [18]. Many patients with aspergillomas are elderly and have significant underlying disease, including

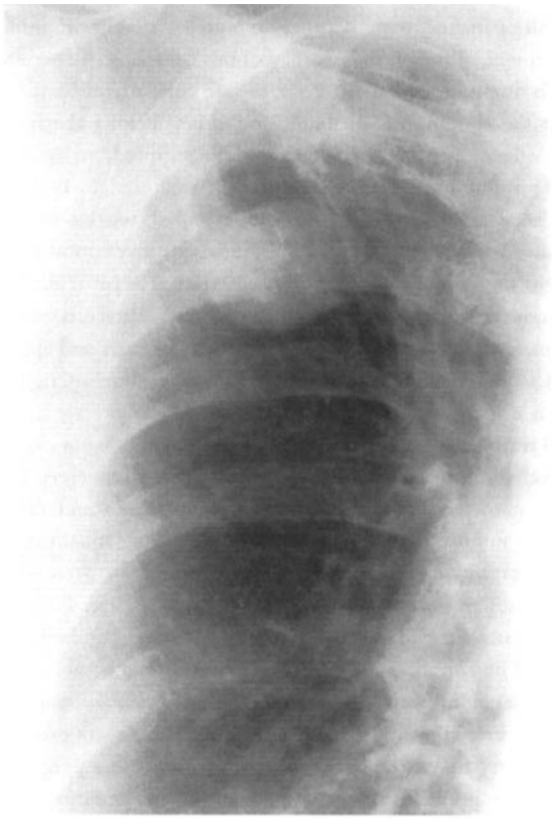

Figure 4 Right upper lobe from patient MS showing the expansion of the shadow, still partially filled with a mass, March 1998.

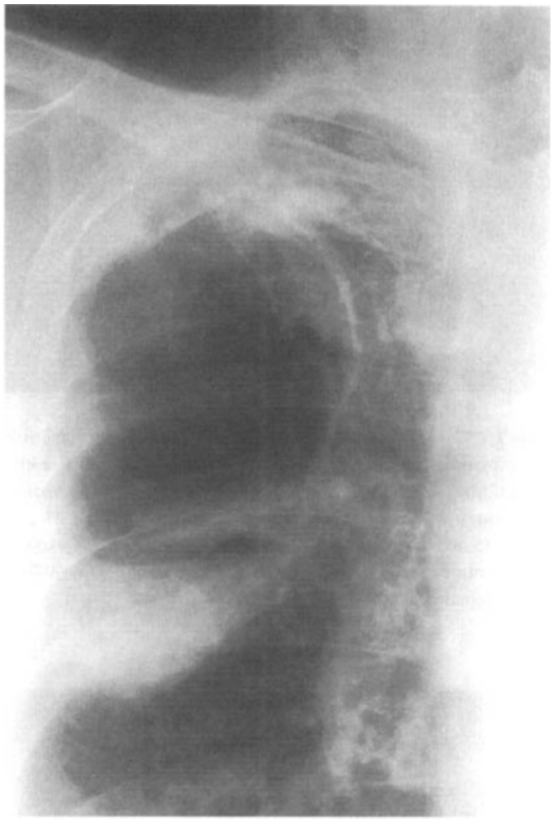

Figure 5 Right upper lobe from patient MS with a huge cavity containing some debris, with positive *Aspergillus* precipitins. Needle aspiration did not yield *Aspergillus*, but he responded to itraconazole (weight increase, reduced coughing and reduced fatigue), May 2000.

severe respiratory compromise in addition to the aspergilloma. Thus, many patients die with an aspergilloma rather than of it.

Untreated CNPA runs a slowly progressive course over months or usually years. Cavities expand reducing pulmonary capacity, local pulmonary fibrosis occurs and eventually the patient is left with little functional lung. Sometimes the systemic features are more prominent and cachexia, mimicking carcinoma, is the eventual outcome. Fatal hemoptysis occasionally occurs.

Treatment

Several therapeutic strategies have been used in treating aspergillomas. Systemic antifungal therapy with ketoconazole is ineffective. Itraconazole 200 mg daily is of marginal symptomatic benefit and little radiological benefit [19]. Work from Japan has shown that the drug does accumulate in the fungal ball and cavity [20], but responses are incomplete.

Repeated instillations of nystatin or amphotericin B into the cavity have yielded some benefit in some cases (especially with amphotericin B) [21]. Communication between the cavity and the airways is usual so the instilled agent usually leaks into the airways. Repeated instillations are labor intensive and not very effective for complex and/or bilateral aspergillomas. The more

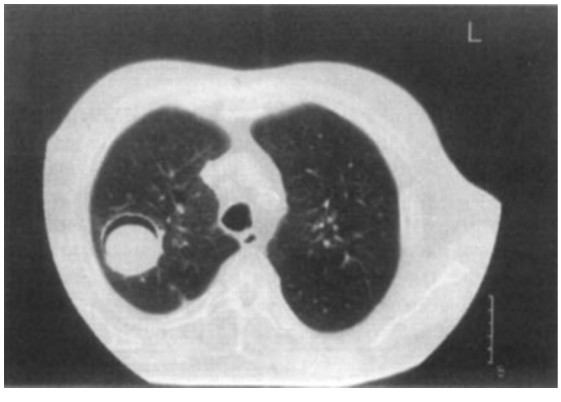

Figure 6 CT scan (single cut) of the upper thorax of patient MS showing a textbook example of an air crescent so typical of an aspergilloma, but without any pleural thickening, which is unusual for an aspergilloma, September 1998.

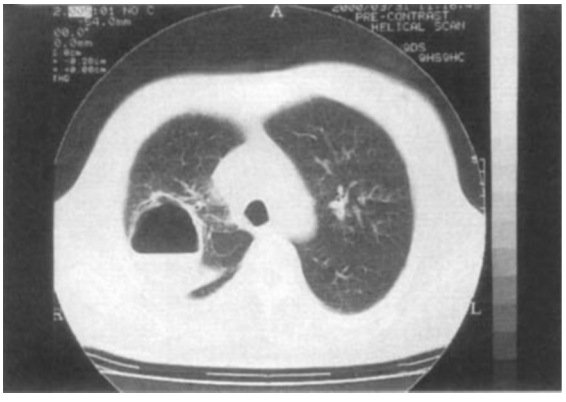

Figure 7 CT scan (single cut) of the upper thorax of patient MS showing marked progression of the lesion over 18 months, with no treatment, March 2000. Collectively these images show the evolution over 5 years from a very small cavity presumably from the *M. avium* infection, to the development of an aspergilloma, which expanded slowly to a huge cavity. He improved with antifungal therapy, although the cavity remains large.

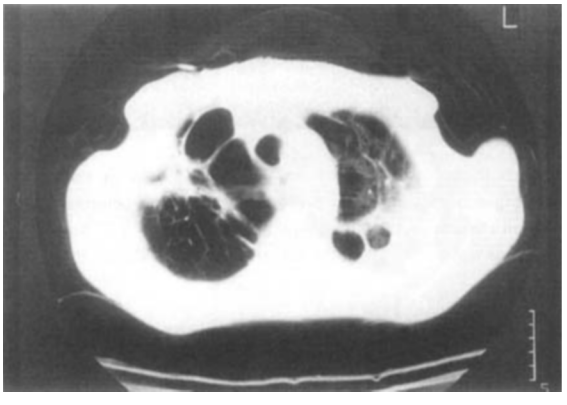

Figure 8 A CT scan of the thorax in a patient with CNPA presenting with profound weight loss and coughing on a background of emphysema and smoking. The scan shows multiple cavities bilaterally, with an aspergilloma on the left in one small cavity and much pleural thickening. He was thought to have carcinoma by *Aspergillus* precipitins and sputum cultures were positive. He responded partially to itraconazole, but developed ankle edema and did poorly with intravenous amphotericin B with renal dysfunction and pulmonary decompensation.

recent use of amphotericin B in gelatin or glycerin that solidifies at 37 °C and instilled through a flexible plastic catheter have been successful [22–24]. Details of how to make up this preparation and instill it are described on www.aspergillus.man.ac.uk/secure/treatment. It is important to ensure that little or none leaks into the airways in patients with precarious pulmonary function.

All patients with CNPA require systemic antifungal treatment, although the urgency of this is variable. Experience with amphotericin B, itraconazole or voriconazole indicates that the condition is incurable and either lifelong therapy or prolonged periods of therapy are required to prevent progression and improve symptoms. Amphotericin B should be used systemically and a dose of 0.5–1 mg/kg per day (conventional) or 4–5 mg/kg (lipid based) gives good results after the patient has completed therapy, particularly if itraconazole is continued subsequently. Itraconazole as primary therapy is effective in about 45% of cases and appears still to be effective suppressive therapy after amphotericin B, even if it fails as primary therapy.

Treatment of CNPA is best evaluated by following clinical, radiological, serological and microbiological parameters. Useful parameters of response include weight gain and energy levels, improved pulmonary symptoms, falling inflammatory markers and total serum IgE, improvement in paracavitary infiltrates and eventually a reduction in cavity size. Haemoptysis is not a useful guide to response – if severe, embolization should be considered. Surgical resection should be avoided, if possible, as this is technically difficult and *Aspergillus* empyema and/or bronchpleural fistula is a common subsequent problem.

Surgery may be appropriate for patients with aspergilloma and hemoptysis. In those patients with major hemoptysis and simple aspergillomas, surgery offers an 84% five year survival compared with a 41% survival with conservative therapy [25]. More recent series have substantially lower mortality rates, particularly if patients are selected carefully [26,27]. Surgical removal of aspergillomas is fraught with difficulty because of the very vascular, adherent pleura and the technical challenge. Aspergillomas in old tuberculous cavities fare less well as do those requiring pneumonectomies [28]. This often results in the spillage of cavity contents into the pleura resulting in the chest cavity becoming infected with *Aspergillus* [29]. Patients with complex aspergillomas (who probably have CNPA) do not fare well with surgery. Surgical removal of pleural aspergillomas and thoracoplasty is also prone to many complications and should be avoided if possible [30]. In addition, many patients have underlying respiratory insufficiency and removal of a lobe of the lung would leave them unacceptably breathless.

In those patients with hemoptysis who are not fit to undergo surgery, embolization of bleeding vessels by a skilled interventional radiologist may be appropriate. In most instances of hemoptysis abnormal and novel vascular connections to the systemic circulation are implicated. Usually, this is the bronchial circulation but it may be any of the other arteries supplying the chest including the internal or external mammary arteries. Several abnormal vascular connections may coexist.

ASPERGILLUS EMPYEMA

The most common cause of *Aspergillus* empyema is rupture or surgical removal of an aspergilloma or CNPA [31]. Sometimes the pleura is directly involved. Symptoms of fever, cough and weight loss are typical. A bronchopleural fistula is a common additional finding. Aspiration of the pleural cavity yields *Aspergillus* and biopsy of the pleura or wall of the cavity confirms the diagnosis histologically. Drainage of an empyema with creation of a deep pleurocutaneous fistula (e.g. an Eloesser flap) [32] is typically necessary. Other approaches have included using free muscle flaps to fill the pleural space. This is usually effective but disfiguring. Local irrigation with saline and/or sugar paste, oral itraconazole and patience will usually allow the cavity to slowly fill in and heal. However this can take months or years. If the patient has very significant pulmonary dysfunction rendering surgery difficult or impossible, a combination of systemic antifungal therapy with instillation of amphotericin B paste into the pleural cavity is the optimal therapeutic approach. As pleural aspergillosis tends to be chronic and indolent many months of therapy are usually required and often the disease can only be stabilized with improvement of symptoms, without full resolution or cure.

OTHER CHRONIC SYNDROMES

Other syndromes possibly or probably completely or partly attributable to *Aspergillus* include extrinsic allergic alveolitis, exacerbation of asthma without ABPA, bronchocentric granulomatosis, some episodes of bronchitis and systemic syndromes related to excessive environmental exposure. These entities require more research to fully understand their relationship to *Aspergillus* and other fungi and to understand better their pathogenesis and optimum treatment.

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