Commentary

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Aspergillus is a rare pathogen in patients with AIDS and its manifestations include chronic cavitatory, invasive, and allergic bronchopulmonary aspergillosis.[1] The chest radiographic findings have been divided into three categories: (1) cavitating upper lobe disease resembling non-invasive or chronic necrotising aspergillosis; (2) focal alvelolar opacities similar to those seen in invasive aspergillosis, a focal infiltrate that remains stable for several months; and (3) bilateral interstitial disease. Patients with chronic cavitatory disease have a high mortality from haemoptysis, while patients with bilateral pulmonary infiltrates die from disseminated disease.[2]

The frequency with which neutropenia or steroid therapy are seen as predisposing factors for the development of *Aspergillus*-related disease[3–6] has only served to emphasise the controversial role of HIV-1 itself. Neutrophil function is not clinically impaired following infection by HIV-1[7] and, although invasive pulmonary aspergillosis is typically seen in patients with a CD4 count of <50/μl,[3 6] these patients often also have a neutrophil count of $<1 \times 10^9$/l as part of an AIDS-related pancytopenia.

In the report by Höhler *et al,* although *Aspergillus fumigatus* and atypical mycobacteria were cultured on several occasions, the authors do not discuss the possibility of both organisms being pathogenic. The patient did not receive any treatment for atypical mycobacterial disease. In the context of AIDS, it is common for several pathogens to cause significant clinical disease at the same time. Atypical mycobacteria are considerably more common as a cause of disease than *Aspergillus* in these patients, and are more likely to lead to the death of the patient than invasive aspergillosis from an aspergilloma.

It is also interesting to note that *Aspergillus* has been isolated with *Pneumocystis carinii* in patients receiving corticosteroids as adjuvant therapy for *Pneumocystis carinii* pneumonia[5 6] and from the respiratory tract of patients with *Cryptococcus neoformans* infections. In these cases the authors concluded that the isolation of *Aspergillus* from the respiratory tract during the course of cryptococcosis was not of pathogenic significance.[8] The association of pulmonary aspergillosis with pulmonary mycobacterial disease has also been reported.[9]

Like aspergillosis, histoplasmosis has several clinical manifestations which range from acute self-limiting disease to chronic pulmonary or disseminated disease. In heavily endemic areas acute infection is usually asymptomatic and of no clinical consequence. Symptomatic, acute pulmonary histoplasmosis results from a heavy exposure.[10 11] Whilst chronic pulmonary histoplasmosis often reflects an immunological or a structural defect in the lung,[12] disseminated histoplasmosis is usually seen in the severely immunocompromised host.[13] Individuals with a normal immune system have a short incubation period, tiny miliary infiltrates on chest radiography, no hilar lymphadenopathy, and no subsequent calcification. Early chronic histoplasmosis usually results in a segmental infiltrate and the scattered densities within areas of interstitial pneumonitis are due to necrosis. Larger necrotic areas may contract to give a linear scar which resembles an infarct and which can calcify years later. Cavities can be static or may enlarge, and aspergillomas can develop within them.[12]

Most patients with chronic pulmonary histoplasmosis have a single lesion. Two or more lesions are seen in one third of patients and these can occur simultaneously or sequentially. Recurrence more than six months after the acute infection occurs in about 20% of patients, but the interval between infection and recurrence can be as long as six years. The type of treatment given for the initial episode does not appear to influence either the frequency or the time to recurrence.[12]

I wonder whether the case described by Kneale and Turton was a manifestation of the rare complication of fibrosing mediastinitis, a condition which is almost always associated with histoplasmosis. Goodwin *et al*[14] have studied the condition of mediastinal granuloma and fibrosis due to histoplasmosis and found that it represents a spectrum of disease. At one end are those patients with primary granulomatous "ordinary" capsules which are 2–5 mm thick, and at the other end are cases in which the capsules of the granuloma are "fibroma-like", being up to 2·5 cm thick and all but obscuring the granulomatous histological pattern. Between these extremes are cases in which the capsular fibrosis is "excessive" and ranges from 6 mm to 9 mm. A significant number of the patients they described had some degree of bronchial obstruction.[15 16]

Cultures for histoplasmosis are almost always negative in cases with prominent fibrosis even when the organism is demonstrated in tissue samples using special stains. *H capsulatum* is not always found by staining in cases of far advanced fibrotic disease, in contrast to its more ready demonstration in granulomatous material. The inability to grow *H capsulatum* from biopsy specimens in cases of fibrosing mediastinitis has led to the conclusion that this condition is not the result of active fungal proliferation but a hypersensitivity reaction to healed infection. Goodwin *et al* have suggested that the process begins at the site of the primary infection and the lymph nodes which drain that area. With the development of delayed hypersensitivity, both the parenchymal fascia and the draining lymph nodes undergo intense in-

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flammation resulting in focal caseous necrosis. Metabolically inactive, but still viable, organisms persist in these tissues despite gradual infiltration with calcium salts. Healing occurs by encapsulation with fibrous tissue. The process so far is analogous to tuberculosis. Occasionally, however, in the case of histoplasmosis, the encapsulating fibrosis continues with collagen being added over a period of several years resulting in a mass which can be 3–4 cm in diameter. Theoretically, ongoing seepage of antigens from the necrotic centre of the granuloma stimulates the process to continue in the rare host who is hypersensitive. Fibroblasts are stimulated in normal tissues adjacent to the nodule and this results in the destruction of bronchi, lung, and blood vessels by what appears to be invading fibrosis.[17] Amphotericin B is not indicated because active infection is not the cause. Corticosteroids have been used in the course of granulomatous disease when vital structures are involved, but reports of their success are largely anecdotal.

The patient described by Kneale and Turton received approximately 2·4 g amphotericin B and ketoconazole for eight months. However, the authors note that the most dramatic response was seen when high dose prednisolone was started. It would have been interesting to know how long this course of treatment was continued and the relationship between clinical improvement and the course of steroids. If the case described was one of fibrosing mediastinitis secondary to histoplasmosis, it may explain why the authors could not demonstrate the organism in samples taken at fibreoptic bronchoscopy.

Acinetobacter calcoaceticus is a Gram negative bacillus of low virulence which has been implicated as a cause of both community acquired and nosocomial infections.[18] In a review of positive blood cultures from a Denver teaching hospital *Acinetobacter* was the cause of 2% of all Gram negative bacteraemias,[19] and in a more recent series 33% of true bacteraemias with *Acinetobacter* were polymicrobial in nature.[20 21]

There are several points worth noting in the report by Bilgiç *et al.* Firstly, *Acinetobacter* are rod shaped organisms during periods of rapid growth and coccoid when in the stationary phase. Although usually encapsulated, nonmotile, aerobic, Gram negative organisms, they can retain crystal violet and this can lead to their misidentification as Gram positive cocci. The salutary tale from this case report is that clinicians should not base their choice of antibiotics upon the identification of a *species* of organism solely from a Gram stain.

Secondly, as a significant number of *Acinetobacter* bacteraemias are polymicrobial in nature, I find it difficult to accept the authors' conclusion that this is a case of community acquired *Acinetobacter* pneumonia only. *Klebsiella pneumoniae* was isolated from one sputum specimen; in my opinion, this is a serious pathogen and its presence in the context described here should be taken seriously, even if it is only isolated from a single sample.

Finally, the predisposing factors for *Acinetobacter* and *Klebsiella* pneumonia are similar and both can give rise to cavitation and pleural effusions. The choice of treatment for serious, deep seated *Acinetobacter* infections should be based on the sensitivities of the organism isolated because there are considerable differences in local sensitivity patters. Antibiotics with significant activity against this organism include imipenem, ciprofloxacin, and high dose ceftazidime. A combination of one of these with amikacin can result in clinically useful synergy.

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