Case reports

Non-tuberculous mycobacterial lung infection complicated by chronic necrotising pulmonary aspergillosis

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Abstract

We report four cases of pulmonary mycobacterial disease (three due to *Mycobacterium malmoense* and one to *Mycobacterium avium intracellulare*) complicated by the development of chronic necrotising pulmonary aspergillosis. Difficulties with treatment and the potential benefits of steroids are discussed.

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Case 1

In October 1996 a 49 year old woman with chronic obstructive pulmonary disease (COPD) and a history of pulmonary tuberculosis, successfully treated with standard chemotherapy six years earlier, presented with cough and dyspnoea. On examination she was unwell and chest radiography showed left upper lobe consolidation and cavitation. Her sputum was smear positive for acid and alcohol fast bacilli (AAFB) and treatment was started with rifampicin, isoniazid, and pyrazinamide. *Mycobacterium avium intracellulare* was isolated from a sputum culture eight weeks later and treatment was changed to rifampicin, ethambutol (15 mg/kg), and clarithromycin.

After initial improvement she deteriorated both clinically and radiologically. Four months after commencing treatment she had lost 8 kg in weight and the chest radiograph showed increased consolidation and cavitation. *Aspergillus fumigatus* was cultured from bronchial washings and *Aspergillus* precipitins were positive (1:64). There was no obvious immunological abnormality (immunoglobulins and CD4 were normal) and the serum IgE level and eosinophils were within normal limits.

Itraconazole was started in a dose of 200 mg three times daily (suspension initially, capsules later) but she continued to deteriorate, losing another 6 kg with further radiological deterioration. Prednisolone (initially 60 mg/day and gradually reducing) was started which resulted in rapid clinical improvement. Two years following presentation she remains well. Her sputum has remained culture negative for *Mycobacteria* and *Aspergillus* spp since August 1997. Antimycobacterial drugs, itraconazole, and prednisolone have been stopped.

Case 2

In July 1997 a 76 year old man with a history of moderate COPD and previously stable pulmonary function (FEV_1/FVC 1.3/3.4) presented with worsening dyspnoea, a cough with purulent sputum, and weight loss (6 kg in less than a year). His chest radiograph showed bilateral upper lobe consolidation with cavitation and fibrosis. Sputum was smear positive for AAFB and, on culture, *M malmoense* (resistant to rifampicin in vitro) was isolated. Quadruple chemotherapy with rifabutin, ethambutol, clarithromycin, and ciprofloxacin was started. However, three months later he was more dyspnoeic, was producing copious quantities of purulent sputum, had lost more weight, and was persistently pyrexial. Radiologically there had been marked deterioration. *A fumigatus* was cultured from the sputum and precipitins were positive (1:16). A computed tomographic (CT) scan of his chest showed extensive consolidation, cavitation, and scarring in both upper lobes. There was no eosinophilia and his serum IgE level was normal.

He was treated with intravenous amphotericin and oral itraconazole capsules (200 mg three times a day) but after three weeks of antifungal treatment he remained unwell. Prednisolone (60 mg) was added with rapid improvement; he became afebrile and the sputum volume and purulence were reduced. Unfortunately, he developed uveitis due to rifabutin, and rifampicin was substituted. He remained stable for six months on maintenance treatment with rifampicin, ethambutol, clarithromycin, ciprofloxacin, itraconazole, and prednisolone. However, in April 1998 there was further clinical and radiological deterioration. His sputum was culture negative for *Mycobacteria* but had a heavy growth of *Aspergillus*. No other pathogens were isolated. He was treated with intravenous amphotericin (Ambisome, Nexstar, Cambridge, UK) for three weeks with slight clinical improvement.

In July 1998 his sputum remains positive for *Aspergillus* although his radiographs are stable. He remains on antimycobacterial drugs, itraconazole, and prednisolone. However, we have

had difficulty achieving therapeutic levels of itraconazole in spite of high doses (300 mg three times a day).

Case 3

A 66 year old man with long standing COPD was referred in April 1992 with persistent right upper zone shadowing on the chest radiograph. Bronchoscopic washings were positive for AAFB and culture grew *M malmoense*. He was started on treatment with isoniazid, rifampicin, and ethambutol which were continued for a total of 14 months. His sputum had been culture negative for AAFB during the last six months of treatment, the chest radiograph improved, and treatment was stopped in September 1993. In July 1994 his chest radiograph showed patchy consolidation in the right mid zone and *M malmoense* was again isolated from the sputum. Isoniazid, rifampicin, and ethambutol were recommenced in October 1994. In February 1995 isoniazid was stopped and ciprofloxacin and clarithromycin were added. By March 1996 his sputum was still culture positive for *M malmoense* and chest radiographs were worse. In September 1996 he had a right upper lobectomy and antimycobacterial treatment was stopped. In February 1997 further right mid zone consolidation was observed on the chest radiograph. Rifampicin, ethambutol, ciprofloxacin, and clarithromycin were re-started but he continued to deteriorate both clinically and radiologically. His sputum grew both *M malmoense* and *A fumigatus*. The serum IgE level was normal, there were no eosinophils in the sputum, and no excess in the blood. Serum precipitins for *Aspergillus* were positive (titre 1:64). Despite a high dose of oral itraconazole (200 mg three times daily) there was little clinical improvement. However, after adding prednisolone he improved rapidly. In May 1998 he was clinically stable on four antimycobacterial drugs, itraconazole, and corticosteroids. His sputum has remained culture negative for AAFB and *Aspergillus* since October 1997.

Case 4

In July 1995 a 64 year old woman with severe COPD (FEV_1 0.4 l) presented with increasing dyspnoea and weight loss. The chest radiograph showed left apical consolidation and cavitation. Sputum was smear positive for AAFB so she was commenced on Rifater (Hoechst Marion Roussel, Uxbridge, UK). However, *M malmoense* was isolated and treatment was changed to ethambutol, rifabutin, isoniazid, and clarithromycin which resulted in clinical and radiological improvement within three months.

Antimycobacterial treatment was stopped in October 1997 after two years. However, within one month of stopping she had become unwell with persistent fever and new right upper lobe consolidation on the chest radiograph. Her sputum remained culture negative for AAFB but *A fumigatus* was isolated and serum precipitins were strongly positive (>1:64). Itraconazole was commenced in a dose of 200 mg three times daily, following which there was clinical and radiological improvement. Itraconazole was discontinued in June 1998. She did not require any other treatment and remains well.

Discussion

The incidence of non-tuberculous mycobacterial pulmonary disease has increased in the last few years.[1] The organisms most frequently isolated in the UK are *M xenopi, M avium intracellulare* (MAI), and *M malmoense*.[2 3] Typically, as in the cases described, patients have pre-existing chronic lung disease and present with increased respiratory symptoms and deteriorating lung function and radiological appearance.

Current guidelines for treatment of MAI pulmonary disease recommend a three (or more) drug regimen including ethambutol (E), rifampicin (R), and clarithromycin (Cl) (or azithromycin), continued for 12 months after the sputum is culture negative.[4] For *M malmoense* isoniazid (H), E, and R are recommended with the optional addition of streptomycin (SM) for the initial 3–6 months.[4 5] However, regimens including Cl and/or ciprofloxacin (Ci) are currently being evaluated by the British Thoracic Society.

Because treatment is protracted and often complicated by drug intolerance, response to treatment may be difficult to evaluate. However, as in our patients, a failure to respond to antimycobacterial treatment or a relapse during treatment may be caused by concomitant infection with *Aspergillus*. In all four cases clinical and radiological deterioration was associated with isolation of *A fumigatus* from the sputum and positive *Aspergillus* precipitins. It may be appropriate to evaluate fully patients with damaged lungs and non-tuberculous mycobacterial infection for coexisting *Aspergillus* infection at the start of the treatment. In the cases reported here the stage at which *Aspergillus* infection was diagnosed was different for each patient. Patient 1 deteriorated after four months of antimycobacterial treatment; patient 2 deteriorated steadily despite apparently complying with all his treatment; patient 3 relapsed following 14 months of E, R, H (six months sputum negative)—despite reintroduction of chemotherapy he remained persistently sputum positive with *M malmoense* over a three year period; and in patient 4 clinical deterioration occurred within one month of completion of antimycobacterial treatment. In patients 2 and 3 the microbiological response to antimycobacterial treatment occurred only when the concurrent *Aspergillus* infection was also treated.

Other recent case reports have identified concomitant infection with *Aspergillus* spp as a possible reason for failure to respond to antimycobacterial chemotherapy. Bollert *et al* reported co-infection by *M malmoense* and *Aspergillus* in three patients, all of whom died despite antimycobacterial and antifungal treatment. Two of the three patients had evidence of an aspergilloma at post-mortem examination.[6] Similarly, Debieuvre *et al* reported a fatal case of *M malmoense* complicated by co-infection

with *A fumigatus*.[7] Two other case reports have described complex mycetomas complicating *M kansasii* and *M xenopi* infections.[8 9]

The radiological appearances of our patients were in keeping with chronic necrotising pulmonary aspergillosis (CNPA) or semi-invasive aspergillosis. CNPA is characteristically an indolent cavitating process in the lungs caused by invasion by *Aspergillus* spp.[10–12] As seen in our patients, constitutional disturbance with fever and weight loss is accompanied by radiological signs of upper lobe infiltration, cavitation, and lung destruction. It is striking that three of our patients only began to improve after addition of corticosteroids, although there was no evidence of allergic bronchopulmonary aspergillosis (ABPA). We postulate that the better response compared with the (scant) literature was because of this. In the light of this we suggest that a local hypersensitivity reaction (type III) contributes to tissue destruction. Histological studies provide some support for this.[13] Constitutional symptoms of fever and sputum production in patients with ABPA and aspergilloma have been attributed to a type III hypersensitivity reaction in the lung surrounding the fungus, which is present intrabronchially.[14 15]

The optimal treatment for CNPA is unclear. Itraconazole (with starting doses of 200 mg twice daily) has been used with clinical benefit.[12 16–18] The bioavailability of itraconazole solution is much better than that of capsules, which is important for patients with damaged gut or those receiving enzyme inducers. The pharmacological interaction between rifampicin/rifabutin and itraconazole is complex. Itraconazole inhibits liver enzymes resulting in increased levels of rifabutin which are associated with uveitis (as in case 2).[19] Rifampicin, a liver enzyme inducer, has been shown to lower itraconazole levels. The effect of rifabutin, which has different enzyme inducing properties,[20] on itraconazole levels is less clear but the available evidence suggests that they will be reduced.[21] Adequate levels were achieved with capsules in our patients apart from patient 2 who is being changed to the suspension.

Our patients have received treatment with itraconazole for periods ranging from seven months (patient 4) to 20 months (patient 1) and treatment is still ongoing in patients 2 and 3 (both >12 months). Despite this, patient 2 has remained sputum positive for *Aspergillus*. He also had partial responses to intravenous amphotericin B during two periods of exacerbation of symptoms. The variable response to treatment may be partly a result of the degree of lung destruction and extent of disease at the time of presentation. Patient 2 had the most extensive radiological changes at the start of treatment. Intravenous amphotericin B has a place in the management of patients who are failing to respond to itraconazole after attempts have been made to optimise bioavailability.[12] Surgery may be an option in patients with focal disease and good lung function, but it may be associated with significant mortality,[22] in contrast to patients with haematological malignancy.[23] Intralesional amphotericin may be used when cavities are present.[24]

Although the role of corticosteroids in treating CNPA requires clarification, they seemed to result in considerable benefit for three of the patients in this series. Furthermore, in contrast to the poor outcome described in previous reports of aspergillosis complicating atypical mycobacterial lung disease, all of our patients are alive at the time of writing.

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