Short reports

Chronic necrotising pulmonary aspergillosis treated with itraconazole

J A ELLIOTT, L J R MILNE, D CUMMING

From the Chest Unit, Heathfield Hospital, Ayr, and the Mycology Unit, Central Microbiological Laboratories, Western General Hospital, Edinburgh

ABSTRACT A patient with longstanding ankylosing spondylitis developed chronic necrotising pulmonary aspergillosis, which was successfully treated with itraconazole.

Upper lobe fibrobullous pulmonary changes and aspergilloma formation are recognised complications of ankylosing spondylitis.¹ More recently chronic necrotising pulmonary aspergillosis has been described as a complication of pre-existing lung disease, including ankylosing spondylitis.² Though systemic antifungal treatment is of little value in the treatment of aspergilloma,³ encouraging results have been reported for itraconazole in chronic necrotising pulmonary aspergillosis.⁴

Fig 1 Posteroanterior chest radiograph at admission to hospital, showing large right apical cavity, intracavitary mass, and right lower lobe consolidation.

Address for reprint requests: Dr J A Elliott, Chest Unit, Heathfield Hospital, Ayr KA8 9DZ.

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Case report

A 58 year old man with a 35 year history of ankylosing spondylitis complained of a productive cough and mucopurulent sputum of two months' duration. Over the same period he had had intermittent febrile symptoms and weight loss of 6 kg. He failed to respond to treatment with amoxycillin (250 mg three times daily for 10 days) and ciprofloxacin (500 mg twice daily for 10 days) was substituted. A chest radiograph showed a large, thick walled cavity at the right apex as the only abnormality.

Despite antibiotic treatment the patient's sputum volume and purulence had increased and he became breathless with an effort tolerance of 100 metres on the level. A repeat chest radiograph (fig 1), three weeks after the initial one, showed pronounced deterioration. The cavity at the right lung apex now contained an intracavitary mass and there was extensive homogeneous right lower lobe consolidation. He appeared ill, with a temperature of 38.4°C, and showed the classical stigmata of advanced ankylosing spondylitis. He was anaemic (haemoglobin 9.8 g/dl) with peripheral blood leucocytosis ($23.7 \times 10^9/l$, 85% neutrophils) and an erythrocyte sedimentation rate of 108 mm in one hour.

A 24 hour collection of sputum was sent for mycological investigation. Direct microscopy showed numerous hyphae characteristic of both aspergilloma and invasive infection (see discussion). Culture yielded *Aspergillus fumigatus* 10 700 colony forming units (cfu)/ml. Examples of both "wild type" and "variant" colony morphology were seen. The latter confirmed the diagnosis of aspergilloma⁶ and the presence of a large proportion of wild type colonies was consistent with invasive aspergillosis. Fibreoptic bronchoscopy showed extensive inflammatory changes; microscopy and culture of bronchial aspirate gave results similar to those for sputum. Histological examination of transbronchial lung biopsy specimens from the right lower lobe showed a non-specific inflammatory exudate but cultures were negative and special stains failed to identify any microorganisms.

Treatment was started with itraconazole at an initial dose of 400 mg daily, which was reduced after two weeks to 200 mg daily; this was continued for a further six months. Repeat tomography one month after initiation of treatment confirmed disappearance of the intracavitary mass and chest radiograph after treatment showed substantial clearing of the right base (fig 2). These changes were accompanied by weight gain (4 kg), a fall in the erythrocyte sedimentation rate (to 35 mm in one hour), resolution of anaemia, and considerable clinical improvement, enabling the patient to return to work.

After one week of treatment sputum microscopy showed

Fig 2 Posteroanterior chest radiograph after six months' treatment with itraconazole.

abundant mycelial fragments of both aspergilloma and invasive forms, though culture produced only a scanty growth of *A. fumigatus* (30 cfu/ml), implying that a large proportion of the hyphae were non-viable. A 24 hour sputum collection two weeks after the start of treatment failed to show evidence of fungi from microscopy or culture.

Four months and seven months after the end of treatment direct microscopy of sputum yielded positive results, showing clumps of interlaced hyphae that failed to grow in culture. Similar findings have been reported in patients with an aspergilloma.⁵ Our patient remained positive for aspergillus precipitins. Radiologically, a large apical cavity persists but so far, eight months after cessation of antifungal treatment, there has been no radiographic or tomographic evidence of recurrence of an intracavitary mass. Clinical improvement has been maintained and the patient continues in full time employment.

Discussion

Invasive aspergillosis usually occurs as a complication during the management of severely immunocompromised patients. Chronic necrotising pulmonary aspergillosis is encountered when the patient's defences are impaired locally and to a lesser degree by chronic bronchopulmonary disease. The clinical manifestations and predisposing factors have been described in ankylosing spondylitis⁷ and were similar to the case reported here. As a further refinement of the diagnostic criteria, we would suggest inclusion of evidence of concurrent invasive aspergillosis and aspergilloma as determined by

morphological features in sputum and the culture characteristics of the fungus.⁵ Invasive aspergillosis is characterised by large, dichotomously branching fungal fragments; in aspergilloma the fungal fragments tend to be short with ragged end walls—a result of abrasion within the mycetoma cavity—and contain few cells, which are often devoid of cytoplasmic contents (that is, "dead" hyphae).⁶

Systemic antifungal treatment with amphotericin B, alone or in combination with flucytosine, may be lifesaving in invasive aspergillosis, but clinical and mycological results in patients with aspergillomas are poor. Two new orally active triazole antifungal agents (itraconazole and fluconazole) appear to show broad spectrum activity with lower potential for toxicity than currently available imidazoles.⁸ Preliminary results have shown that itraconazole has a high degree of activity against *A. fumigatus* in vivo.⁴ Our patient showed a good response to treatment with itraconazole, with eradication of the fungus and complete radiological regression of the aspergilloma. This result may be due to the nature of the aspergilloma associated with chronic necrotising pulmonary aspergillosis or the immaturity of the cavity (or both), as itraconazole has failed in a few cases of longstanding aspergilloma (unpublished data). Since treatment was discontinued recolonisation of the cavity appears to be taking place.

The present case outlines the need for vigilance in the management of pulmonary disease in longstanding ankylosing spondylitis, where chronic necrotising pulmonary aspergillosis is a potential complication. Our results suggest that itraconazole merits further evaluation in the treatment of bronchopulmonary aspergillosis, especially when there is evidence of parenchymal invasion and necrosis.

References

- 1 Rosenow EC, Strimlan CV, Muhm JR, Ferguson RH. Pleuropulmonary manifestations of ankylosing spondylitis. *Mayo Clin Proc* 1977;52:641-9.
- 2 Binder RE, Faling LJ, Pugateb RB, Mahasaen C, Snider GL. Chronic necrotising pulmonary aspergillosis: a discrete clinical entity. *Medicine (Baltimore)* 1982;61:109-24.
- 3 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.
- 4 De Beule K, De Doncker P, Cauwenbergh G, et al. The treatment of aspergillosis and aspergilloma with itraconazole, clinical results of an open international study (1982-87). *Mycoses* 1988;31:476-85.
- 5 Milne LJR. Direct microscopy. In: Evans EGV, Richardson MD, eds. *Medical mycology: a practical approach*. Oxford: IRL Press, 1989:17-45.
- 6 Leslie CE, Flannigan B, Milne LJR. Morphological studies on clinical isolates of *Aspergillus fumigatus*. *Journal of Medical and Veterinary Mycology* 1988;26:335-41.
- 7 Hargis JL, Bone RC, Stewart J, Rector N, Hiller FC. Intracavitary amphotericin B in the treatment of symptomatic pulmonary aspergillosis. *Am J Med* 1980;68:389-94.
- 8 Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. *Antimicrobial agents and chemotherapy* 1988; 32:1-8.