Commentary: unusual manifestations of aspergillosis

David W Denning

Four cases of pulmonary aspergilloma in the context of cystic fibrosis are reported in this issue of *Thorax*. In one of the patients the development of an aspergilloma was preceded by allergic bronchopulmonary aspergillosis (ABPA), and in two others there was some evidence of an allergic response to *Aspergillus* but this was insufficient to establish the diagnosis of ABPA. A small number of aspergillomas in patients with cystic fibrosis have previously been reported, including two cases in children from Italy¹ and an adolescent from California.² Two cases have also been reported from St Vincent's Hospital in Dublin,³ although one of these was probably the same as case 1 reported by Maguire *et al* on page 805.

Aspergilloma is an increasingly uncommon condition in the Western world with the decline in cavitary tuberculosis. Cases do, however, occur in patients with other conditions such as sarcoidosis, ankylosing spondylitis, and in patients who have previously had spontaneous pneumothoraces. Although the development of an aspergilloma has been a rare occurrence in patients with cystic fibrosis, it is likely to be seen with somewhat increasing frequency. Invasive aspergillosis is also likely to appear more often than previously,^{4,5} particularly in patients receiving steroids⁶ and/or those undergoing lung transplantation.⁷

The treatment of aspergillomas is problematic. Surgical resection is useful for simple aspergillomas but there is a mortality rate of about 33% for patients with complex (multicavitary) aspergillomas.⁸ In addition, the site of the aspergilloma is critically important to surgical outcome. Pleural aspergillomas carry an extremely high complication rate (100%) following surgery, whereas simple pulmonary or bronchial aspergillomas do well.⁹ For this reason, bronchial or pulmonary aspergillomas without any pleural component should not be a contraindication to lung transplantation. However, in the context of cystic fibrosis, particularly late stage, surgical resection rather than transplantation is unlikely to be a viable option. The administration of oral itraconazole (in a dose of at least 400 mg/day for adult patients),¹⁰ with serial monitoring of serum concentrations or intracavitary amphotericin B, are viable treatment options. In patients who do not have cystic fibrosis repeated administration of amphotericin B into the aspergilloma cavity has shown some efficacy. New means of administering the amphotericin B in gelatin¹¹ or glycerin¹² may be beneficial. Ryan *et al* (pages 809-10) showed that this approach was feasible, despite fears of a pneumothorax.

Another case of pseudomembranous tracheo-

bronchitis caused by colonisation by *Aspergillus* is reported by Nicholson *et al* (pages 807-8). This is a condition first described in 1890 in a non-immunocompromised child¹³ and, to date, over 60 cases have been reported in a variety of clinical settings.¹⁴ Recent reviews have emphasised the disease entity in the context of leukaemia,¹⁵ lung transplantation,⁷ and AIDS.¹⁴ My coworkers and I attempted to classify these diseases and to unify the terminology.⁷ We have suggested that the term "*Aspergillus* tracheobronchitis" should be applied to patients in whom there is evidence of bronchial and/or tracheal inflammation, excess mucus production, with *Aspergillus* as the only pathogen and without invasion of bronchial mucosa on biopsy. Focal, ulcerative, or plaque-like processes, which have been described in AIDS and in patients undergoing lung transplantation we termed "ulcerative *Aspergillus* tracheobronchitis" if histological invasion of the abnormal area of bronchial mucosa and/or cartilage showed hyphae consistent with *Aspergillus*. The term "pseudomembranous *Aspergillus* tracheobronchitis" is reserved for patients with very extensive involvement of the whole of the tracheobronchial tree, with a membranous slough overlying the mucosa containing *Aspergillus*. Separate from these conditions (in which the extensive inflammation and/or invasion of the tracheobronchial tree is absent) is a condition of obstructing bronchial aspergillosis described initially in patients with AIDS¹⁶ and now also in heart transplantation patients.¹⁷ In this condition thick mucous plugs full of *Aspergillus* are coughed up or found in the airways, with little or no inflammation and no evidence of invasion or allergic manifestations. This last group of patients is much more symptomatic than those with *Aspergillus* tracheobronchitis.

The case reported by Nicholson *et al* serves to emphasise that approximately 25% of patients with *Aspergillus* tracheobronchitis are non-immunocompromised or only mildly so. Symptoms are deceptively mild. Without bronchoscopy and antifungal treatment these patients are likely to succumb relatively rapidly as in the case presented. One possibly useful clinical clue to the diagnosis which otherwise is somewhat elusive is unilateral wheeze.¹⁸ It is disappointing that the authors of this case report chose to use fluconazole for aspergillosis as it has no useful clinical activity; the only current therapeutic choices are amphotericin B or itraconazole.¹⁹

Finally, Freixinet *et al* describe a case of *Aspergillus* colonisation of intralobar pulmonary sequestration, the second on record. It is likely

Department of Infectious Disease & Tropical Medicine, North Manchester General Hospital, Manchester M8 6RL and Department of Medicine, Section of Infectious Diseases, University of Manchester, Hope Hospital, Salford, UK
D W Denning

that the cavities observed do not represent an aspergilloma but rather chronic necrotising pulmonary aspergillosis which is a very slowly progressive invasive form of aspergillosis.²⁰⁻²² This sometimes leads to the radiological appearance of an aspergilloma but occurs in patients who have no pre-existing cavitory lesions in the lung. In the case presented we have the benefit of histological data which do not support the diagnosis of chronic necrotising pulmonary aspergillosis as no hyphae were seen within the lung tissue. This could represent a sampling error or a form of progressive disease mediated by extracellular toxins of *Aspergillus* without direct invasion of lung. Clearly much additional work is necessary to elucidate the pathogenesis of these unusual types of aspergillosis which defy accurate classification according to our present knowledge base.

These case reports all focus on relatively rare forms of *Aspergillus* disease. However, invasive aspergillosis is increasingly common. A recent necroscopic survey of 11 000 unselected cases in two Frankfurt hospitals over 12 years has shown a 14-fold increase in invasive aspergillosis from 1978 to 1992.²³ These hospitals have a 70% necropsy rate. In 1992 the pathologists found invasive mycoses at necropsy in 6% of all their patients, with invasive aspergillosis comprising over 60% of these cases. Increased awareness of infections caused by this common mould is clearly appropriate, as the case reports demonstrate.

- 1 Costantini D, Padoan R, Secco Rozzoni C, Giunta A. Aspergilloma in CF: Treatment with itraconazole. *Fourth Annual North American and 1990 International CF Conference, Arlington, Virginia*, 3-6 October 1990.
- 2 Denning DW, Van Wye J, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. *Chest* 1991;100:813-9.
- 3 Logan M, McLoughlin R, Gibney RG. Aspergilloma complicating cystic fibrosis. *AJR* 1993;161:674-5.
- 4 Bhargava V, Tomashefski JF Jr, Stern RC, Abramowsky CR. The pathology of fungal infection and colonization in patients with cystic fibrosis. *Hum Pathol* 1989;20:977-86.
- 5 Guidotti TL, Leutzler J, Di Sant'Agnese PA, Escaro DU. Case report: fatal disseminated aspergillosis in a previously well young adult with cystic fibrosis. *Am J Med Sci* 1982;283:157-60.
- 6 Ng TTC, Robson GD, Denning DW. Hydrocortisone-enhanced growth of *Aspergillus* spp: implications for pathogenesis. *Microbiology* 1994;140:2475-80.
- 7 Kramer MR, Denning DW, Marshall SE, Ross D, Berry G, Lewiston N, et al. Ulcerative tracheobronchitis following lung transplantation: a new form of invasive aspergillosis. *Am Rev Respir Dis* 1991;144:552-6.
- 8 Daly RC, Pairolo PC, Piehler JM, Trastek VF, Spencer Payne W, Bernatz PE. Pulmonary aspergilloma: results of surgical treatment. *J Thorac Cardiovasc Surg* 1986;92:981-8.
- 9 Massard G, Roeslin N, Wihlm J-M, Dumont P, Witz J-P, Morand G. Pleuropulmonary aspergilloma: clinical spectrum and results of surgical treatment. *Ann Thorac Surg* 1992;54:1159-64.
- 10 Campbell JH, Winter JH, Richardson MS, Shankland GS, Banham SW. Treatment of pulmonary aspergilloma with itraconazole. *Thorax* 1991;46:839-41.
- 11 Munk PL, Vellet AD, Rankin RN, Müller NL, Ahmad D. Intracavitary aspergilloma: transthoracic percutaneous injection of amphotericin gelatin solution. *Radiology* 1993;188:821-3.
- 12 Giron JM, Poey CG, Fajadet PP, Balagner GB, Assoun JA, Richardi GR, et al. Inoperable pulmonary aspergilloma: Percutaneous CT-guided injected with glycerin and amphotericin B paste in 15 cases. *Radiology* 1993;188:825-7.
- 13 Wheaton SW. Case primarily of tubercle, in which a fungus (*aspergillus*) grew in the bronchi and lung, simulating actinomycosis. *Trans Pathol Soc London* 1890;41:34-7 (Reproduced in: Denning DW. *Aspergillus tracheobronchitis*. *Clin Infect Dis* 1994;19:1176-7).
- 14 Kemper CA, Hostetler JS, Follansbee SE, Ruane P, Covington D, Leong SS, et al. Ulcerative and plaque-like tracheobronchitis due to infection with *Aspergillus* in patients with AIDS. *Clin Infect Dis* 1993;17:344-52.
- 15 Clarke A, Skelton J, Fraser RS. Fungal tracheobronchitis. Report of nine cases and review of the literature. *Medicine* 1991;70:1-14.
- 16 Denning DW, Follansbee S, Scolaro M, Norris S, Edelstein D, Stevens DA. Pulmonary aspergillosis in AIDS. *N Engl J Med* 1991;324:654-62.
- 17 Hummel M, Schüller S, Hempel S, Rees W, Herzer R. Case report. Obstructive bronchial aspergillosis after heart transplantation. *Mycoses* 1993;36:425-8.
- 18 Tait RC, O'Driscoll BR, Denning DW. Unilateral wheeze due to pseudomembranous *Aspergillus* tracheobronchitis in the immunocompromised patients. *Thorax* 1993;48:1285-7.
- 19 Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. *Rev Infect Dis* 1990;12:1147-201.
- 20 Binder RE, Faling LJ, Pugatch RD, Mahasaen C, Snider GL. Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. *Medicine* 1982;61:109-24.
- 21 Geffer WB, Weingrad TR, Epstein DM, Ochs RH, Miller WT. "Semi-invasive" pulmonary aspergillosis. *Radiology* 1981;140:313-21.
- 22 Karam GH, Griffin Jr FM. Invasive pulmonary aspergillosis in nonimmunocompromised, nonneutropenic hosts. *Rev Infect Dis* 1986;8:357-63.
- 23 Groll A, Shah PM, Mentzel CH, Schneider M. Changing pattern of invasive mycoses at autopsy. *Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida*. American Society for Microbiology, October 1994, Abstract J109.