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Aspergillus spondylitis in immunocompetent patients

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Abstract Four immunocompetent patients with neurological deficit underwent anterior decompression for *Aspergillus* osteomyelitis of the spine. All patients improved neurologically following anterior spinal decompression and antifungal therapy. This study emphasizes the importance of obtaining a tissue diagnosis as these unusual infections may mimic tuberculosis, which is more common.

Résumé Quatre patients immunocompétents souffrant de déficit neurologique ont eu une décompression de la colonne antérieure pour une ostéomyélite *Aspergillus* de la colonne vertébrale. La condition neurologique de tous les patients s'est améliorée suite à la décompression et une thérapie antifongique. Cette étude fait ressortir l'importance de l'obtention d'un diagnostic à partir de tissus puisque ces infections rares peuvent en certains cas imiter la tuberculose qui est plus fréquente.

Introduction

Fungal infections have become increasingly more important causes of morbidity and mortality in patients with depressed immunity [3, 6, 8, 11, 14]. Isolated *Aspergillus* osteomyelitis may occur without evidence of systemic disease but rarely in the absence of a detectable underlying disorder [4, 7, 12]. We report on four normal hosts who developed *Aspergillus* osteomyelitis of the spine, which was successfully treated with surgery and antifungal therapy.

Patients and methods

Between 1992 and 1997 we treated 4 patients with *Aspergillus* osteomyelitis (Table 1). The presenting complaints in our patients

were unremitting neck pain, back pain and weakness of the lower extremities. The mean duration of pain and weakness was 6 weeks (range 4–9 weeks). Cases 1 and 4 were farm laborers and case 3 had been treated in childhood for pulmonary tuberculosis. Anti-tuberculosis treatment was prescribed for 1 patient (case 3) by the referral hospital without any improvement. General and systemic evaluation of the patients revealed no manifestations of AIDS or any underlying immunosuppressive disorder. The radiographs revealed single body involvement and in case 1 the posterior elements were also affected (Figs. 1, 2). Apart from a raised erythrocyte sedimentation rate (ESR, mean 46 mm/h, range 27–58 mm/h Westergren), anemia in 2 patients (9.4 g% and 8.7 g%, respectively) and decreased albumin (27 g/dl) in case 1 all hematological investigations were normal. The CD4/CD8 ratios were normal and the HIV status in 2 patients (cases 2 and 3), who consented to testing, were negative. Chest radiographs revealed no pulmonary lesions and sputum cultures were negative for acid fast bacilli. The Mantoux skin test was positive in cases 2 and 3.

The patients underwent elective anterior decompression after improving their nutritional status. An extended anterior cervical approach was used to decompress lesions involving the upper thoracic spine. The intra-operative findings were similar to tuberculosis but the granulation tissue was gelatinous in all patients. In three patients the anterior column defect was reconstructed with structural allografts and in case 1 instrumentation was used to provide additional stability after resecting the involved posterior elements. The allografts were obtained from the National Tissue Bank (Bone SA) and the methods for harvesting and preparation have been reported previously [5]. Three patients were treated with Amphotericin B and 5 flucytosine. The daily intravenous dose (0.25 mg/kg) of Amphotericin B was increased gradually over a period of 6 to 9 weeks to 0.7 mg/kg and 5 flucytosine was administered orally in a daily dose of 200–400 mg/kg. Fluconazole (400 mg daily) as used in case 4 due to persistent nausea and vomiting following Amphotericin B. Liver function, renal function, and complete blood count were monitored weekly. The treatment was continued for 6 to 9 weeks with the response being assessed clinically and hematologically.

Results

The mean follow-up time was 4.7 years (range 2.3–7.5 years). Three patients tolerated the medication (Amphotericin B, 5 flucytosine) and apart from nausea during the first 2 weeks of treatment there were no complications relating to kidney or liver function. All the patients improved neurologically. *Aspergillus fumigatus*

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Table 1 Clinical details of patients

Case	Sex	Age (years)	Level of lesion	Preoperative neurological status	Postoperative neurological status	Treatment
1	M	54	L4	C	E	Anterior decompression allograft and posterior instrumentation
2	F	29	T1	C	E	Anterior decompression and allograft
3	F	18	T7	B	E	Anterior decompression, allograft and anterior instrumentation
4	M	33	T1	A	D	Anterior decompression and iliac graft

Fig. 1 Platyspondyly of L4 with destruction of the pedicle (AP and lateral view) (arrows)**Fig. 2** Platyspondyly of L4 with destruction of the pedicle (long-term follow up) (arrows)**Fig. 3** Remodeling and incorporation of allograft at 7.5 years post-surgery

was isolated in our patients on tissue culture and histological examination. The iliac graft fused at 5 months and allograft incorporation occurred between 2 and 3 years. The criteria of Bridwell et al. [2] was used to classify allograft incorporation and a grade 1 fusion with remodeling occurred in 3 patients. At 2-year follow-up the ESR decreased to a mean of 21 mm/h, (range 11–27 mm/h). At long-term follow-up there was no clinical or radiological evidence of pulmonary involvement, or recurrence of local infection (Fig. 3).

Discussion

Aspergillus, which is a ubiquitous species of fungus and a normal commensal of the upper respiratory tract, has

been isolated from soil and decomposing organic materials. It behaves as a pathogen by invading the tissues of patients whose normal immunological defenses are impaired by prolonged use of antibacterial or immunosuppressive therapy [3, 13]. Invasion may also occur in patients with malignancy, uncontrolled diabetes, organ transplant recipients, AIDS, chronic granulomatous disease and long-term steroid therapy [3, 9, 11]. *Aspergillus* is the most common cause of infection and death in individuals with chronic granulomatous disease [6, 8, 14]. The infection often begins in the lungs with contiguous spread to the spine occurring in most cases. Despite aggressive medical and surgical therapy, reported cases have been associated with treatment failure and recurrence [1, 6, 8]. The prognosis is good in immunocompetent hosts [4, 7, 11].

Microscopically *Aspergillus* appears as fragments of dichotomously branched septate hyphae 4–6 mm in diameter. Colonies of aspergillosis can be isolated easily on Sabourauds glucose agar at 30°–37°C [3]. The immunodiffusion test is an effective and specific method for the diagnosis of Aspergillosis in patients with an intact immune system. In patients suspected of having in-

vase Aspergillosis with serum negative for antibodies, counter immunoelectrophoresis and radioimmunoassay should be performed [3, 13]. The most commonly implicated species is *Aspergillus fumigatus* and less commonly *A. flavus*, *A. niger*, *A. nodulans* and *A. terreus* have been isolated [7].

The radiological features of *Aspergillus* spondylitis are non-specific and they may involve single or multiple bodies, present as primary discitis and as extradural extraosseous infection [4, 7, 10, 12]. The preoperative clinical and radiological diagnosis was tuberculous spondylitis in 3 of our patients since spinal tuberculosis is endemic in our region and moreover there are no distinguishing radiological characteristics in differentiating it from *Aspergillus* spondylitis. In case 1 a diagnosis of a malignant lesion (plasmacytoma, 2° deposit) was considered in view of the patient's age and radiological presentation. We have previously reported 5 cases of *Aspergillus* osteomyelitis [4]. One patient had discitis and the remaining 4 patients had 2 contiguous bodies involved. Four patients had been treated for pulmonary tuberculosis in the past and 1 patient had active pulmonary tuberculosis. A recent case report described pulmonary tuberculosis and *Aspergillus* spondylitis involving L2/L3 [9]. Although *Aspergillus* was not cultured from the sputum, the spinal involvement was possibly from a primary pulmonary focus. It is important to exclude a pulmonary focus in patients with isolated *Aspergillus* osseous lesions.

Anterior spinal decompression is our preferred method since it facilitates thorough cord decompression and reconstruction of the anterior column. We have reported successful incorporation of allografts in spinal tuberculosis and in this study, the allografts incorporated with no evidence of rejection or late infection [5]. Several studies have shown that surgery together with antifungal treatment is most effective in managing *Aspergillus* osteomyelitis [7, 9, 12].

Although Amphotericin B and 5 flucytosine, which have a synergistic effect were effective in 3 patients, the side effects have to be monitored carefully. Amphotericin B combines with sterols in the plasma membrane resulting in increased permeability and cell death. Intravenous administration is recommended as absorption is negligible following oral absorption [10]. The duration of medical treatment is unknown and needs to be individualized with respect to side effects and therapeutic response. Amphotericin B lipid complex (ABLC) has been successfully used in patients who develop renal impairment following treatment with Amphotericin B [1].

As a result of the poor absorption and the side effects of Amphotericin B synthetic antifungal imidazoles and triazoles (ketoconazole, fluconazole and itraconazole) have been introduced. They inhibit fungal growth by blocking the biosynthesis of fungal lipids especially ergosterol in cell membranes. Fluconazole is well absorbed and diffuses readily into the cerebrospinal fluid where the concentrations are 50–90% of simultaneous values in plasma following a daily oral dose of 100–400 mg [10].

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