

Osteomyelitis caused by *Aspergillus* species: a review of 310 reported cases

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Abstract

Aspergillus osteomyelitis is a rare infection. We reviewed 310 individual cases reported in the literature from 1936 to 2013. The median age of patients was 43 years (range, 0–86 years), and 59% were males. Comorbidities associated with this infection included chronic granulomatous disease (19%), haematological malignancies (11%), transplantation (11%), diabetes (6%), pulmonary disease (4%), steroid therapy (4%), and human immunodeficiency virus infection (4%). Sites of infection included the spine (49%), base of the skull, paranasal sinuses and jaw (18%), ribs (9%), long bones (9%), sternum (5%), and chest wall (4%). The most common infecting species were *Aspergillus fumigatus* (55%), *Aspergillus flavus* (12%), and *Aspergillus nidulans* (7%). Sixty-two per cent of the individual cases were treated with a combination of an antifungal regimen and surgery. Amphotericin B was the antifungal drug most commonly used, followed by itraconazole and voriconazole. Several combination or sequential therapies were also used experimentally. The overall crude mortality rate was 25%.

Keywords: Antifungals, aspergillosis, immunosuppressed patients, osteomyelitis, spondylodiscitis

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Introduction

Aspergillus species have emerged as important causes of morbidity and mortality in immunocompromised hosts [1,2]. Invasive aspergillosis (IA) can occur in most organs, with the lung being the main target of this opportunistic infection. Among the extrapulmonary locations, bone is rarely involved. Osteomyelitis caused by *Aspergillus* species is an infection that is often neglected, and data concerning risk factors, therapies and outcome are lacking [3–68]. Therefore, in order to improve our knowledge of this unusual infection, we reviewed the data presented in the literature concerning this type of IA.

Materials and Methods

To identify eligible studies for this analysis, four investigators searched the PubMed database for English language studies published up to April 2013. The search strategy was based on a combination of the keywords ‘aspergillus’ AND ‘aspergillosis’ AND ‘osteomyelitis’ AND ‘spondylodiscitis’. All references cited in these studies were also reviewed to identify additional studies. Study variables included basic demographics and clinical and laboratory characteristics, such as underlying conditions, clinical signs and symptoms, and outcome. We gave special attention to therapeutic modalities such as surgical and antifungal treatment, as well as bone imaging techniques including standard radiology, computed tomography, and magnetic resonance imaging. Cases were included if they had biopsy-proven osteomyelitis or imaging suggestive of osteomyelitis, and isolation of *Aspergillus* from cultured bone. If articular involvement was evident (e.g. isolation of *Aspergillus* species from a arthrocentesis) without evidence of bone

involvement, the case was excluded from this analysis. The variables collected were analysed as a function of outcome by performing a *t*-test for independent samples when appropriate (e.g. age) or the Fisher exact test for categorical variables. A model of logistic regression was also utilized to evaluate the effect of the factors analysed on the healing of osteomyelitis caused by *Aspergillus* species. All factors that were statistically significant in the univariate analysis and those with significant clinical relevance were included. A *p*-value of <0.05 was considered to be statistically significant.

Results

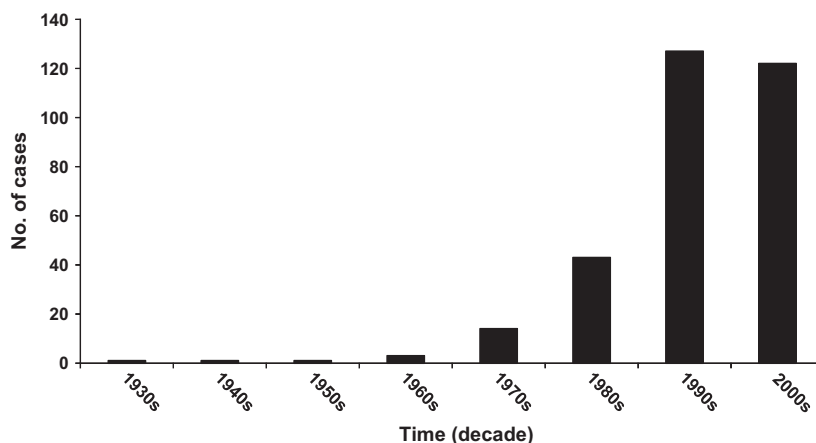
A total of 310 individual cases of osteomyelitis caused by *Aspergillus* species described between 1936 and 2013 were identified. An additional 51 cases found in the literature published during the same time period were excluded from the present analysis, because they did not fulfil the study definition criteria. An increase in the number of reports over time was noted (Fig. 1). Fifty-nine per cent of the patients were male. The median age was 43 years (range, 0–86 years).

The comorbidities identified for *Aspergillus* osteomyelitis included chronic granulomatous disease (CGD) (19%), haematological malignancies (11%), transplantation (11%), diabetes (6%), surgery, trauma and fractures (6%), human immunodeficiency virus infection (4%), steroid therapy (4%), pulmonary disease (4%), previous *Aspergillus* infection (4%), intravenous drug use (3%), otitis and sinusitis (3%), and cancer (1%). Among cancer patients, 50% had lung cancer, 25% breast cancer, and 25% vertebral condrosarcoma. Some patients had multiple comorbidities, and in 36 patients (12%) comorbidities were not reported (Fig. 2a). The most common sites of infection included the spine (49%) (20% thoracic, 20% lumbar

and sacral, and 3% cervical), base of the skull, paranasal sinuses and jaw (18%), ribs (9%), long bones (9%), sternum (5%), chest wall (4%), hand or foot bones (3%), and hips (2%) (Fig. 2b).

Aspergillus species were isolated from 278 individual cases. In four patients, multiple species were isolated, and in 61 patients the *Aspergillus* species was not specified. The most common infecting *Aspergillus* species were *Aspergillus fumigatus* (55%), *Aspergillus flavus* (12%), and *Aspergillus nidulans* (6.7%). Less frequently isolated species included *Aspergillus terreus* (2.3%), *Aspergillus niger* (2.3%), *Aspergillus versicolor* (0.7%), and *Aspergillus flaviparus* (0.3%) (Fig. 2c). Although a given species of *Aspergillus* was not associated with a particular risk factor, there was a trend towards a high prevalence of *A. flavus* in diabetic patients (25% of patients with osteomyelitis caused by *A. flavus* were diabetic). There were significant differences between the paediatric/young (≤ 18 years) and adult (> 18 years) populations concerning risk factors, and the localization and distribution of *Aspergillus* species. In particular, CGD was found in 75% and 4% of the paediatric and the adult populations, respectively ($p = 0.0001$). Conversely, transplantation and diabetes were both significantly more frequent in adults (19% vs. 1.5%, $p = 0.0001$; and 11% vs. 1.5%, $p = 0.009$). Chest wall involvement and long bone involvement were significantly more frequent in the paediatric/young population than in the adult population (40% vs. 16%, $p = 0.0001$; and 17% vs. 8%, $p = 0.04$). Finally, *Aspergillus* species other than *A. fumigatus* were significantly more frequent in the paediatric/young population than in the adult population (32% vs. 20%, $p = 0.04$).

Along with non-specific and systemic symptoms (e.g. fever, asthenia, and weight loss), local symptoms related to the specific site of infection were often reported. Most commonly, local pain and hyposthenia or loss of organ function for systems innervated by the compressed nerve (e.g. cranial nerve palsy, paraplegia, and incontinence) were reported. Of



*For the 2000s, 20 cases diagnosed after the year 2010 are included.

FIG. 1. Number of osteomyelitis cases caused by *Aspergillus* species over a period of eight decades.

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