Case Report

Fatal disseminated fusariosis presenting initially as tonsillitis

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Introduction: Disseminated fusariosis is a devastating disease in severely immunocompromised patients and is associated with high lethality.

Case presentation: We describe a patient with severe disseminated fusariosis presenting initially as tonsillitis. Fusarium solani was isolated from cultures of the tonsils, skin and blood, while histological evidence for fungal tissue invasion was detected in tissue samples of the tonsils, tongue, oesophagus, lungs, myocardium, intestine, kidney, mediastinal lymphnodes and skin. Susceptibility testing revealed resistance to voriconazole, posaconazole and caspofungin, and susceptibility to amphotericin B. The patient died, despite treatment with amphotericin B, due to multiorgan failure and refractory cardiac arrhythmia.

Conclusion: Tonsillitis was the primary clinical manifestation of disseminated fatal fusariosis in this immunocompromised patient. It is important to know the spectrum of primary manifestations of less commonly encountered moulds in order to guide clinical decisions and early targeted therapy.

Keywords: fungi; fusariosis; immunocompromised; tonsillitis.

Introduction

Disseminated fusariosis is a devastating disease in severely immunocompromised patients and is associated with high lethality. The organ-specific clinical symptoms reported in the literature are predominantly pulmonary disease and skin and soft-tissue infections. Here, we describe a patient with severe disseminated fusariosis presenting initially as tonsillitis.

Case report

A 60-year-old patient presented with fever and symptoms of tonsillitis 2 weeks after the start of a second chemotherapy cycle. The previously healthy man had been diagnosed with acute myeloid leukaemia 2 months earlier and treated with two cycles of induction chemotherapy. The second cycle was administered before regeneration of the bone marrow due to refractory leukaemia. The patient had been neutropenic since the time of diagnosis and presumably for weeks before. Several infectious complications including pneumonia with Pneumocystis jirovecii and colitis with Clostridium difficile had occurred during the first induction chemotherapy. At current presentation, he was treated with broad-spectrum antibiotics, and prophylactic fluconazole (initiated since the first chemotherapy cycle) was increased to a therapeutic dose after detection of Candida albicans in a swab of the tonsil. Neutropenic fever relapsed after initial clinical improvement, and he developed progressive pain on swallowing. Empiric antifungal treatment with caspofungin was initiated. Several blood cultures were negative at this point. Multiple abscesses were seen in the peritonsillar space and in the left tonsil in a computed tomography scan of the neck. A bilateral tonsillectomy was performed. The patient was transferred to the intensive care unit, as he required mechanical ventilation to secure the airway due to local swelling after the intervention. He remained febrile and on the second day after surgery, about 10 new livid skin lesions with central necrosis occurred on both legs and on the face (Fig. 1). On the same day, the microbiological laboratory reported growth of a mould in the culture of the resected tonsils. Histology of the tonsils revealed extensive fungal angioinvasion.
Caspofungin was stopped and liposomal amphotericin B at a dose of 5 mg kg\(^{-1}\) was started for suspected systemic mould infection evolving under echinocandin treatment. Massive fungal invasion of all skin layers and blood vessels was detected by skin biopsy (Fig. 2). Furthermore, blood cultures drawn on the third post-operative day and culture of the skin biopsy grew a mould, identified as *Fusarium solani* on the basis of macroscopic and microscopic morphology and DNA sequencing using a MicroSeq D2 LSU kit (Applied Biosystems). Susceptibility testing by Etest (bioMérieux) showed no inhibition by voriconazole, posaconazole and caspofungin (MICs \(\geq 32 \mu g \text{ ml}^{-1}\)). The MIC for amphotericin B was 1.0 \(\mu g \text{ ml}^{-1}\) after 48 h of incubation. Because the mould had grown well, this MIC was reported from the microbiology laboratory and the strain was considered susceptible. The patient’s condition did not improve over the next few days, and he died from multiorgan failure and refractory cardiac arrhythmia 7 days after treatment initiation with amphotericin B.

Infiltrative mycosis affecting the base of the tongue and the oesophagus, as well as mycotic emboli in multiple mediastinal lymph nodes, the myocardium, intestine, left kidney and skin was detected in the autopsy. No emboli were found in the brain.

**Discussion**

To our knowledge, this is the first report of fatal disseminated fusariosis presenting initially as tonsillitis with peritonsillar abscesses. The organ-specific clinical symptoms reported in the literature are predominantly pulmonary disease (87 % in one study) and skin and soft-tissue infections (71 %) (Campo et al., 2010). Sinonasal involvement accounted for 29 % of the cases. We hypothesize that the patient had been colonized with *Fusarium* spores by inhalation, and local invasive disease then developed during the period of long neutropenia. The clinical clue for diagnosis in our patient – as culture results of the tonsils were still pending – was the evolvement of skin eruptions, which occurs frequently in disseminated fusariosis (Nucci & Anaissie, 2002). Unlike aspergillosis, infection with *Fusarium* spp. is associated with a high incidence of positive blood cultures (Boutati & Anaissie, 1997), as also present in this case.

Disseminated disease occurs primarily in severely immunocompromised patients. In recent decades, an increase in the incidence of invasive fusariosis has been observed, possibly due to extensive use of antifungals (Campo et al., 2010). Lethality in this population is reported to be as high as 50–70 % (Campo et al., 2010; Nucci & Anaissie, 2002). In a retrospective analysis of 84 patients with invasive fusariosis, persistent neutropenia and treatment with corticosteroids were associated with a poor outcome (Nucci et al., 2003). Importantly, the survival was 0 % for patients with both risk factors (neutropenia and corticosteroid therapy) and 4 % in patients with persistent neutropenia, as in our case.

*Fusarium* is variably resistant to many antifungals, and guidelines for treatment are lacking. Our patient was under empirical treatment with caspofungin, which was changed to liposomal amphotericin B as systemic fusariosis was suspected. *Fusarium* spp. are intrinsically resistant to echinocandins (Diekema et al., 2003), and therefore amphotericin B is often used for treatment (Campo et al., 2010). In an analysis of data from the Collaborative Exchange of Antifungal Research (CLEAR) database, 12 (46 %) of 26 evaluated patients were cured or improved when treated with liposomal amphotericin B (Perfect, 2005). However, MICs of amphotericin B for *Fusarium* spp. seem to be higher than for other moulds (Paphitou et al., 2002). To date, no breakpoints have been defined for mould MICs, and only very limited *in vivo* data are available.
The newer azoles (voriconazole and posaconazole) show variable in vitro activity against Fusarium spp. (Paphitou et al., 2002). There are clinical data supporting the effectiveness of voriconazole in vivo in a series of 73 patients with invasive fusariosis treated with voriconazole, the 90-day survival rate was 42% (Lortholary et al., 2010). In a retrospective analysis of 21 patients with refractory disease or who were intolerant of conventional antifungal treatment, posaconazole proved effective as a salvage therapy in 48% (Raad et al., 2006). Although some experts recommend a combination therapy of an azole with liposomal amphotericin B, data for this recommendation are lacking. None of the newer azoles was added to liposomal amphotericin B in this case, as the isolate tested resistant to both voriconazole and posaconazole.

In addition to antifungal treatment, surgical debulking of infected tissue is recommended, especially in a solitary cutaneous lesion, in order to prevent local progression or dissemination (Al-Abdely, 2004). Regeneration of the neutrophils is the cornerstone in a favourable outcome of infection (Boutati & Anaissie, 1997). In patients without recovery of the bone marrow – as in our case – clearance of the fungal disease is very rare (Nucci et al., 2003). Therefore, the use of granulocyte transfusions or cytokines (such as granulocyte colony-stimulating factor or granulocyte–macrophage colony-stimulating factor) as immunostimulatory measures have been reported, although trials to document their benefit are missing (Hospenthal, 2009).

To conclude, tonsillitis was the primary clinical manifestation of disseminated fatal fusariosis in this patient. The hallmark of fungal infection in an immunocompromised host is extended fever refractory to antibacterial therapy during prolonged neutropenia. However, a subset of patients does present initially with more specific clinical features. It is important to know the spectrum of primary manifestations of less commonly encountered moulds in order to guide clinical decisions and early targeted therapy.

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**References**


