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Fusarium fungaemia in immunocompromised patients

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ABSTRACT

Fusarium spp. cause infections only rarely in immunologically competent hosts, but disseminated infection may occur in severely immunocompromised patients. Symptoms of disseminated infection are persistent fever, despite broad-spectrum antibacterial and antifungal treatment, associated with skin lesions, most commonly on the extremities, in 60–80% of patients. A mortality rate of 50–75% has been reported for patients with disseminated fusariosis. Despite treatment failures, amphotericin B remains the preferred drug, in part because of lack of alternatives. Voriconazole is a promising new agent, but more clinical experience is required.

Keywords Fungaemia, *Fusarium*, immunocompromised host, mycoses

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The genus *Fusarium* comprises a large number of species, most of which are common soil saprophytes or plant pathogens [1,2]. The main characteristic (Fig. 1) of the genus is the production of multi-septate sickle-shaped macroconidia, with a more or less pronounced foot cell [1]. In immunologically competent hosts, *Fusarium* spp. cause infections only rarely and, when they do, the infections are mainly skin infections in surgical wounds, burns or deep ulcers, nail infections or keratitis [1–3]. Less commonly, these organisms have been documented as aetiological agents in localised tissue infections, including septic arthritis, endophthalmitis, cystitis, peritonitis and brain abscesses [1–3].

In contrast, in severely immunocompromised patients, disseminated infection may occur. Symptoms are persistent fever despite antibacterial and antifungal treatment, with skin lesions in 60–80% of cases [1–4]. The lesions are seen most commonly on extremities and appear as widespread, violaceous or erythematous indurated elements, sometimes progressing to necrosis resembling ecthyma gangrenosum [2–5].

Most disseminated *Fusarium* infections have been reported from warm climate zones. In Nordic countries, disseminated *Fusarium* infections in humans seem to be rare [1], with only a single published case [5]. However, in our own hospitals, four cases of blood culture-proven disseminated fusariosis were diagnosed during 2000–2002 among patients with haematological diseases.

The first case involved a 65-year-old woman with acute lymphoblastic leukaemia who became febrile during a second course of chemotherapy. Broad-spectrum antibacterial agents were without effect, and localised erythematous papular lesions appeared on the extremities and face. Intravenous amphotericin B (Ambisome), 300 mg daily, was started. The fever resolved after treatment for 18 days, and the patient was discharged. Blood cultures obtained 15 and 17 days after admission yielded growth of *Fusarium*. Species identification was not performed.

The second case involved a 65-year-old man receiving chemotherapy for relapsing chronic lymphatic leukaemia. The patient became febrile with lung infiltrates 7 days after admission, and treatment with broad-spectrum antibacterial agents and intravenous amphotericin B (Fungizone), 50 mg daily, was commenced. Despite this,

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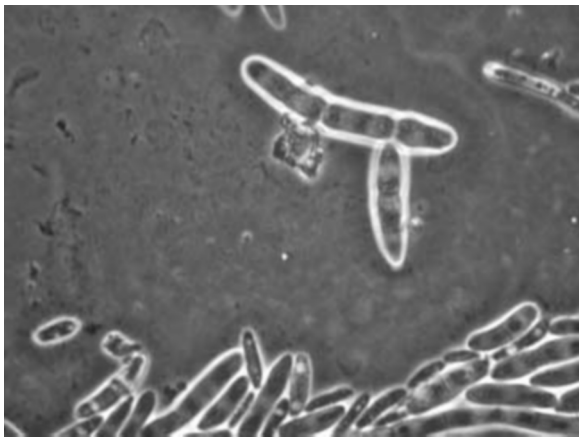

Fig. 1. Typical microscopical appearance of *Fusarium verticillioides* showing septate macroconidia.

the fever continued and an erythematous indurated area mimicking erysipelas was observed on the right lower leg. Although treatment was changed to intravenous amphotericin B (Ambisome), 300 mg daily, after 19 days, the patient died after 23 days. Blood cultures yielded growth of *Fusarium*, which was identified subsequently as *F. verticillioides* (syn. *F. moniliforme*).

The third case involved a 52-year-old woman with acute myeloid leukaemia who was admitted with fever. Bone marrow examination revealed disease relapse, and chemotherapy was initiated. Broad-spectrum antibacterial treatment was initiated at the time of admission. After 4 days, painful localised erythematous papular lesions were detected on the patient's right foot sole and both ear lobes. A blood culture taken after 16 days yielded growth of *Fusarium*, and treatment with intravenous amphotericin B (Ambisome), 300 mg daily, was initiated. More erythematous papular lesions developed on the neck and face, and the fever continued, with progressive infiltrates in the right lung. The patient died 14 days after the initiation of amphotericin B following a cerebral event. The *Fusarium* isolate was subsequently identified as *F. verticillioides* (syn. *F. moniliforme*).

The fourth case involved a man aged 69 years with non-Hodgkin's lymphoma who was admitted with persistent fever. As bone marrow examination revealed massive lymphoid infiltration, the patient received three courses of chemotherapy, in conjunction with intermittent broad-spectrum antibacterial treatment for neutropenia and fever. Two weeks after the third course of chemotherapy, the patient was again hospitalised with fever, neutropenia and symptoms of respiratory tract infection. Broad-spectrum antibacterial treatment and fluconazole were initiated, but when *Fusarium* was detected in blood cultures after 4 days, the antimycotic treatment was changed to intravenous amphotericin B (Ambisome), 200 mg daily. The patient stabilised initially, but remained deeply neutropenic and died 9 days after the initiation of amphotericin B with a clinical picture of heart failure. The *Fusarium* isolate was identified subsequently as *F. solani*.

A mortality rate of 50–75% has been reported for patients with disseminated fusariosis [4,6,7], which is in accordance with the survival of only one of the four patients described above. The high mortality rate presumably reflects both the infection and the serious underlying disease of this group of patients. With the grave prognosis for disseminated fusariosis and the lack of efficient antimycotic drugs, early detection and resolution of neutropenia should be emphasised, possibly aided by the use of exogenous growth factors [1,4], and on removal of any primary infected focus, such as infected nails [2] or intravenous catheters [6–8], whenever possible. The portal of entry was not established in the patients described above. Three had pulmonary infection of uncertain aetiology, and inhalation of spores followed by pulmonary involvement has been suggested previously as a likely mode of acquisition of *Fusarium* infection [1–4,6].

Isolates of *Fusarium* can be resistant to most, if not all, available antimycotic drugs [9–12]. A discrepancy has been reported between microdilution MICs and Etest endpoints for amphotericin B [13], and more extensive investigations are required to establish which method best predicts the clinical outcome of treatment [3,11,12]. Despite the equivocal in-vitro susceptibility results and treatment failures [7,10], amphotericin B has remained the drug of choice for the treatment of disseminated fusarial infections, as there is a lack of alternatives [1,6]. Voriconazole is a promising new agent [9,14–16], but more clinical experience is required.

In countries with a warmer climate than Denmark, disseminated fusarial infections occur throughout the year, but are frequently clustered during rainy summer seasons [3,4,17]. In Denmark, precipitation is fairly constant, but as the four infections described above occurred in the summer months, the environmental temperature

may also be important in determining the number of aerial spores, and hence the risk of acquiring the infection. It has been shown that the aerial spore concentration of two other moulds, *Alternaria* and *Cladosporium*, is highest between June and September [18]. Thus, even in northern Europe, a clinical picture of persistent fever, despite broad-spectrum antibacterial treatment, in a severely immunocompromised patient with skin lesions, or the growth of mould in a blood culture, should suggest the possibility of *Fusarium* infection.

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