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CASE REPORT

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Combination therapy of disseminated *Fusarium oxysporum* infection with terbinafine and amphotericin B

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Abstract A case of disseminated infection with *Fusarium oxysporum* following chemotherapy of acute myelogenous leukemia is reported. Antifungal treatment was successful with a 13-day course of oral terbinafine 250 mg t.i.d. in combination with amphotericin B deoxycholate 1.0–1.5 mg/kg qd and subsequently intravenous liposomal amphotericin B 5 mg/kg qd. Preceding monotherapy with amphotericin B deoxycholate 1.0–1.5 mg/kg qd had not stopped the progression of infection. The combination therapy described here represents a novel approach to the treatment of *Fusarium* spp. in the immunocompromised host in whom *Fusarium* spp. are known to cause disseminated infection with high mortality.

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Case report

We report on a 59-year-old male patient with acute myeloblastic leukemia secondary to myelodysplastic syndrome. The patient received a first induction chemotherapy with thioguanine, cytarabine, and daunorubicin followed by a second induction chemotherapy with high-dose cytarabine and mitoxantrone resulting in an expected overall neutropenia (<500 neutrophils/µl) of 6 weeks' duration. Complete remission was achieved after the first course and the second course was administered in time according to the protocol while the patient was still neutropenic. On the 20th day of neutropenia the patient developed fever of 38.6°C and was treated with ceftriaxone 2 g and gentamicin 5 mg/kg once daily. Six days later, an oval dark-red and itching papulous skin lesion of 5 mm diameter appeared on the right foot (Fig. 1, left). Because of persistent fever and metastatic spreading of the skin lesions, therapy was changed to meropenem 1 g t.i.d., vancomycin 1 g b.i.d., and amphotericin B deoxycholate 1 mg/kg qd.

The sequence of anti-infective agents administered in relation to clinical symptoms is given in Table 1. Over the next 3 days, several blood cultures were positive for molds that were morphologically suggestive of *Acremonium* or *Fusarium* species. Pulmonary infiltrates were ruled out by multislice computed tomography. Despite antifungal treatment, the patient did not defervesce. Physical exams revealed numerous additional skin lesions with central necrosis (Fig. 1, right). Nearly 25% of the patient's skin was covered by these lesions. Septic vasculitis on the basis of a mold fungemia was verified histologically and by culture (Fig. 2). The skin lesions were extremely painful requiring continuous intravenous morphine infusions. The patient's condition deteriorated despite increase of the amphotericin B dose to 1.5 mg/kg qd. On the 35th day of neutropenia, i.e., 9 days after the occurrence of the first skin lesion, preliminary in vitro antifungal susceptibility testing suggested rather low susceptibility to amphotericin B, but possible susceptibility to terbinafine. Therefore, oral terbinafine 250 mg t.i.d. was added to the treatment regimen.

After 3 days of antifungal combination therapy, the patient developed septic shock complicated by acute renal and pulmonary failure. Amphotericin B deoxycholate was replaced by liposomal amphotericin B 5 mg/kg qd IV. The patient required intermittent dialysis and respiratory ventilation over a period of 6 weeks. Progression of the skin lesions stopped after 1 week of antifungal combination therapy. Due to acute hepatotoxicity (bilirubin 10 mg/dl) antifungal treatment was stopped after 13 days of combination

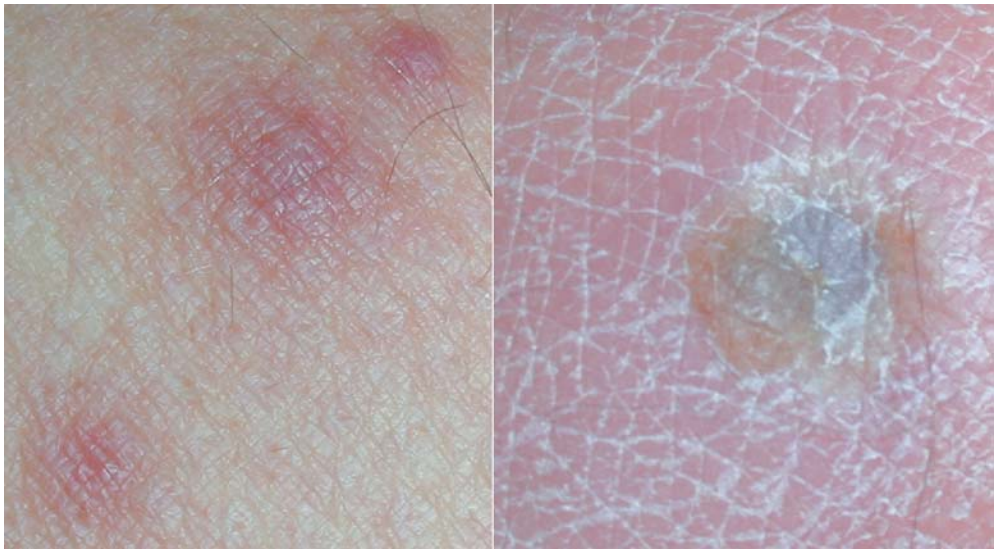

Fig. 1 *Left*: early spreading of papulous skin lesions; *right*: skin lesions developing central necrosis within 3 days (×3)

Table 1 Clinical symptoms and resulting anti-infective treatment during the course of neutropenia

Day	Clinical symptoms	Anti-infective treatment
1	Onset of fever (day 20 of neutropenia)	Ceftriaxone 2 g qd and gentamicin 320 mg qd started
7	Fever relapses and skin lesions occur	Ceftriaxone stopped and ampicillin/sulbactam 3 g t.i.d. started
9	Persistent fever and metastatic spread of skin lesions	Gentamicin and ampicillin/sulbactam stopped Meropenem 1 g t.i.d. started Amphotericin B deoxycholate 1 mg/kg qd started
11	Blood cultures repeatedly positive for *Staphylococcus haemolyticus*	Vancomycin 1 g b.i.d. added
12	Blood cultures positive for molds	Amphotericin B deoxycholate increased to 1.5 mg/kg qd
16	Patient's condition deteriorated (day 35 of neutropenia)	Oral terbinafine 250 mg t.i.d. added
19	Septic shock with acute renal failure	Amphotericin B deoxycholate replaced by liposomal amphotericin B 5 mg/kg qd
23	Progression of skin lesions stopped	
29	Clinically relevant hepatotoxicity	Oral terbinafine and liposomal amphotericin B stopped
30	Neutrophil count at 250/μl	

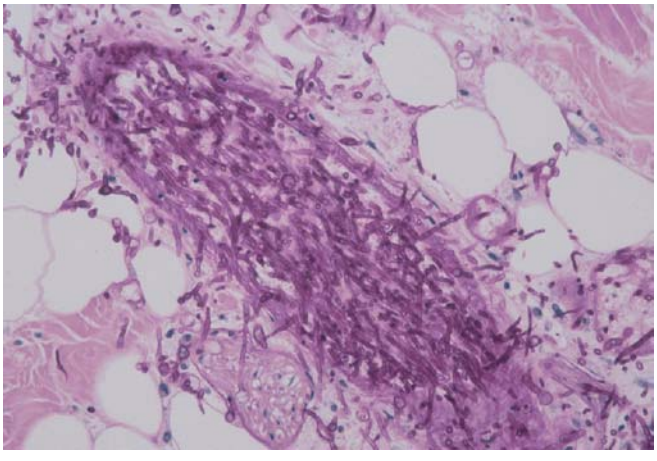

Fig. 2 Vessel occlusion by intravasal hyphae. Diapedesis through the vessel wall and microhemorrhage (PAS ×200)

therapy. However, the skin lesions further improved and completely resolved with neutrophil reconstitution above 1000/μl.

The molds were identified morphologically as *Fusarium oxysporum* (Fig. 3). The results of in vitro susceptibility testing are given in Table 2. Terbinafine, administered by mouth and by nasogastric tube, achieved maximal plasma concentrations of 0.433 μg/ml (Fig. 4).

Table 2 Susceptibility testing of antifungal agents for *Fusarium oxysporum*. *MIC* minimal inhibitory concentration

Antifungal	MIC (μg/ml)
Amphotericin B	2
Fluconazole	>64
Itraconazole	>2
5-Flucytosine	>64
Terbinafine	0.03

The acute myelogenous leukemia relapsed after 3 months of complete remission. The patient then received allogeneic bone marrow transplantation from a matched unrelated donor and was discharged 2 months later without secondary antifungal prophylaxis being given. Two months after discharge, the patient was readmitted with severe graft-versus-host reaction, developed a fever, and subsequently died of cerebral hemorrhage. Blood cultures were again positive for *Fusarium oxysporum* suggesting a reoccurrence of fungal infection. However, these results were communicated only after the patient's death.

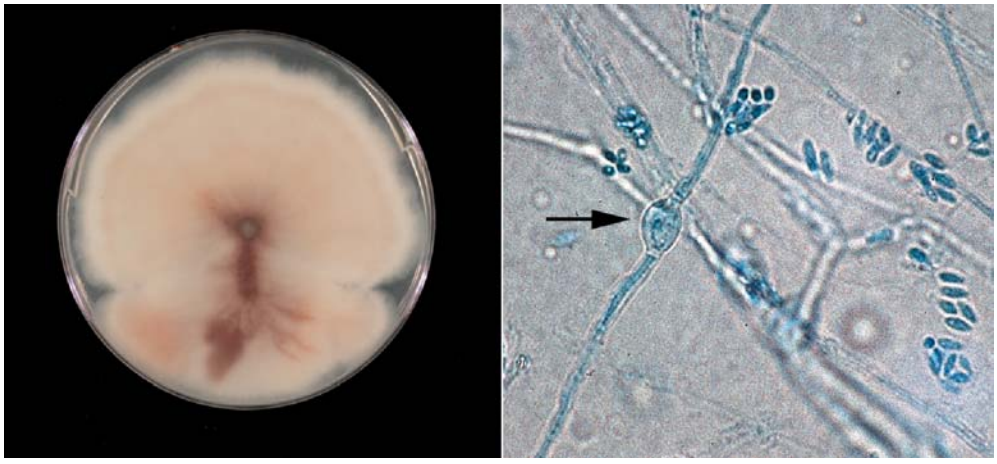

Fig. 3 *Left*: subculture of *Fusarium oxysporum* showing whitish aerial mycelium. Reverse side with typical purple pigmentation. *Right*: mycelium producing abundant ellipsoidal to cylindrical microconidia in clusters. *Arrow*: intercalary chlamydospore

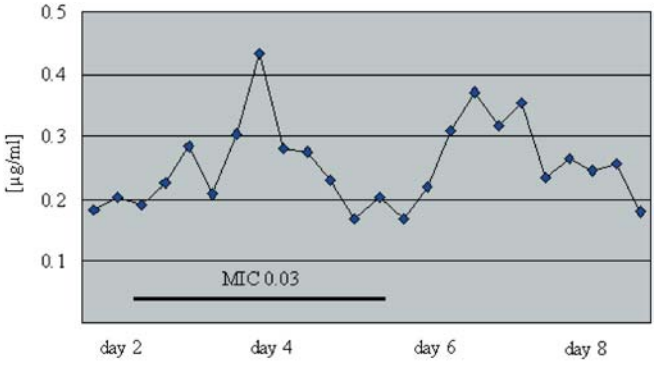

Fig. 4 Terbinafine plasma concentration at a dose of 250 mg t.i.d. and MIC determined for *Fusarium oxysporum*

Discussion

We describe the remission of a disseminated *Fusarium oxysporum* infection refractory to amphotericin B deoxycholate monotherapy. Subsequent antifungal combination therapy with liposomal amphotericin B and terbinafine was successful.

Fusarium spp. are ubiquitous and may be found on rice, beans, soybeans, and grains as saprophytes or as plant pathogens, as well as in soil specimens. They have also been found in potted plants, and hospital water supply systems have been discussed as a reservoir [1]. *Fusarium* spp. have been reported as pathogens in the immunocompromised host before [2].

Fusarium spp. can cause disseminated fungal infection, but most often present as localized infection such as onychomycosis. In patients with leukemia, sinusitis as well as pneumonia and fungemia have been observed. Skin lesions are documented frequently in hematogenously disseminated infection [2]. In the setting of hemato-oncology, these skin lesions mostly occur during neutropenia or the immediate post-transplantation phase. After solid organ transplantation, fusariosis tends to be rather localized in contrast to the more disseminated forms in patients with hematological malignancies or after bone marrow transplantation [3]. In the latter, antifungal treatment is often unsuccessful [2].

The macroscopic and microscopic exams are decisive for the diagnosis of fusariosis. Molecular methods of identification such as 28S rRNA sequencing may then be helpful to differentiate between different species [4].

In this patient, skin lesions were first noticed on the 26th day of neutropenia. Initially, gram-positive infection was considered to be the most likely cause. However, similar lesions may also be caused by *Candida* spp., *Aspergillus* spp., and *Mucorales* as well as *P. aeruginosa* in ecthyma gangrenosum. In this patient, molds were detected both in blood cultures and in skin biopsy. During treatment with amphotericin B deoxycholate, nephrotoxicity occurred and liposomal amphotericin B had to be administered instead.

Fusarium isolates show in vitro and in vivo resistance to conventional antifungal agents, thus representing a therapeutic challenge. *Fusarium oxysporum* frequently shows reduced susceptibility to amphotericin B [2, 5, 6, 7, 8, 9, 10]. In this patient, amphotericin B monotherapy was clinically ineffective, despite reports indicating a response of fusariosis to conventional or lipid-based amphotericin B. As in this patient, lipid-based amphotericin B was administered when nephrotoxicity occurred under treatment with amphotericin B deoxycholate [11]. In vitro testing of itraconazole suggested ineffectiveness, too. For 5-flucytosine, ketoconazole, miconazole, fluconazole, and itraconazole high MIC levels have been described elsewhere, and primary resistance to caspofungin and other ß-1,3-glucan-synthesis inhibitors has been reported [5, 6, 9, 10, 12, 13, 14]. In data presented to the Food and Drug Administration (FDA), 9 (43%) of 21 patients with fusariosis had a complete or partial response to voriconazole [15]. Meanwhile voriconazole has been approved for the treatment of fusariosis, but was not yet available at the time when this patient required treatment. Terbinafine is an allylamine inhibiting squalene epoxidase, which interferes with the fungal cell membrane synthesis. However, terbinafine is not approved for treatment of invasive fungal infection. Terbinafine minimal inhibitory concentration (MIC) values against *Fusarium* spp. have been

reported in the range of 0.25 to >128 μg/ml; thus, its benefit must be evaluated on a case-by-case basis [7, 16, 17].

Despite the lack of effectiveness in monotherapy, the combination of caspofungin and amphotericin B seemed to be efficacious in vitro in some isolates [10]. In general, combination therapies may be discussed especially in refractory fungal disease, but the pattern of infection (localized versus disseminated) and pharmacokinetic parameters have to be considered. In the patient we report on, a disseminated *Fusarium oxysporum* infection refractory to amphotericin B deoxycholate was successfully treated with combination therapy of liposomal amphotericin B and terbinafine. However, complete eradication of fungal infection cannot be assumed, as *Fusarium oxysporum* was isolated again during a subsequent and eventually fatal episode of severe immunosuppression.

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