Acremonium sclerotigenum-Acremonium egyptiacum: a multi-resistant fungal pathogen complicating the course of aplastic anaemia

J. Guitard[1,*], A. Degulys[2,*], G. Buot[1], A. Aline-Fardin[3], E. Dannaoui[4], B. Rio[2], J. P. Marie[2], S. Lapusan[2] and C. Hennequin[1]

1) *Department of Parasitology and Mycology, Saint-Antoine Hospital, AP-HP,* 2) *Department of Haematology, Saint-Antoine Hospital, AP-HP and Université Pierre et Marie Curie,* 3) *Department of Pathology, Saint-Antoine Hospital, AP-HP and* 4) *Department of Parasitology and Mycology, Hôpital Européen Georges Pompidou, AP-HP, Paris, France*

Abstract

A patient with aplastic anaemia, successively treated with caspofungin then liposomal amphotericin, developed a disseminated infection due to *Acremonium,* further confirmed as resistant *in vitro* to these drugs. Successful treatment was achieved with voriconazole. Multiple antifungal treatments may expose to the risk of breakthrough of multi-resistant pathogens in haematology patients.

Keywords: *Acremonium*, amphotericin B resistance, caspofungin resistance, opportunistic infections, severe aplastic anaemia
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Corresponding author: J. Guitard, laboratoire de Parasitologie Mycologie, Hôpital St Antoine, 184 rue du faubourg St Antoine, 75012 Paris, France
E-mail: juliette.guitard@sat.aphp.fr

*These two authors have equally participated in this work.

Introduction

A 25-year-old male native of French Polynesia was diagnosed in January 2011 with severe idiopathic bone marrow aplasia. Working as an employee in naval construction, the patient was used to manipulating chlorhydric acid, dye stuffs and solvents. When admitted to our institution, the patient was febrile at 39.5°C. Complete blood count revealed leucocytes at 1.21 G/L. Initial antibiotic therapy consisted of piperacillin–tazobactam plus gentamycin. In the absence of a genotypically matched donor, the patient started at Day 0 (D0) a 3-month course of immunosuppressive treatment combining anti-thymocytic globulin, cyclosporin and methylprednisolone followed by granulocyte–colony-stimulating factor administration for 70 days. As fever persisted, antibiotic treatment was changed at D6 leading to apyrexia within 24 h. However, a blood culture sampled at D12 because of the re-emergence of the fever, returned positive for yeasts, further identified as *Candida metapsilosis*. Liposomal amphotericin B at 3 mg/kg/day was added, and produced a rapid recovery from the fever. However, this resulted in renal function impairment (blood creatinine at 130 mg/dL), which forced, at D20, a switch to caspofungin (50 mg/day after a loading dose of 70 mg). On D41, while the patient was still neutropenic (leucocytes at 0.08 G/L), multiple cutaneous lesions appeared on his back, trunk and all extremities, but sparing his palms and soles. They were well-circumscribed, non-blanching, non-purpuric, non-pruritic, erythematous nodules, approximately 8–14 mm in diameter. Pathological examination of these nodules showed dermal, epidermal and vascular fungal infiltration, with blood-vessel fungal thrombosis. Periodic acid-Schiff staining revealed thin septate hyaline hyphae and cultures grew with a filamentous fungus suggestive of *Acremonium*. At the same time, the patient complained of pain of the right great toenail, which appeared with an inflammatory partial onycholysis. Direct examination of the nail scrapping demonstrated the presence of thin septate hyaline hyphae with a positive culture for *Acremonium*. Similarly, a blood culture sampled on D42 grew positive for *Acremonium*. Total body computed tomography (CT) scan revealed micro-hypodensities disseminated in the lung fields but no further bronchopulmonary investigation was performed. Serological galactomannan antigen (BioRad, Hercules, CA, USA) assayed twice a week remained negative. Caspofungin was changed for oral voriconazole (5 mg/kg twice a day). From then, the cutaneous lesions progressively healed, the patient became apyretic and systematic blood cultures remained negative. The patient was discharged 3 months later while a CT scan demonstrated the disappearance of the chest nodules. Oral voriconazole was continued for 6 months. Neutrophil count only returned to normal at D77.

Acremonium isolates were tested for their *in vitro* antifungal susceptibility using the Etest method (BioMérieux, Marcy l'Etoile, France), according to the manufacturer's recommendations. The MIC of amphotericin B, fluconazole, itraconazole,

voriconazole, caspofungin and 5-fluorocytosine were 12, >256, 1.5, 0.125, >32 and >32 mg/L, respectively. The *in vitro* resistance was confirmed using a conventional microdilution assay (CLSI methodology) showing MICs of amphotericin B, itraconazole, voriconazole and posaconazole at 2, >8, 1 and 1 mg/L, respectively. This strain is now included in the CBS collection (CBS135846; CBS-KNAW Fungal Biodiversity Centre, Utrecht, the Netherlands).

Aspergillus and *Candida* remain the leading cause of invasive fungal infections in haematology patients [1,2]. However, during the last decades unusual pathogens, such as zygomycetes or *Fusarium*, have emerged in these populations and cause difficulties in diagnosis and therapeutic management because of their reduced susceptibility to different classes of antifungal drugs.

Acremonium spp. are common soil and plant saprophytes but can be the aetiological agent of superficial infections such as onychomycosis [3], and more rarely invasive infections [4–6]. Haematological patients, particularly allogeneic haematopoietic stem cell transplant or acute leukaemia patients, are the most frequently involved [1,2] but, to our knowledge, we report the first case occurring in a patient suffering severe aplastic anaemia. The characteristics of disseminated *Acremonium* infection are very similar to those of *Fusarium* infections [7]. The triad skin lesions–pneumonia–blood culture positive for a filamentous fungus in a patient with adapted antibiotic therapy suggests the diagnosis of infection with either *Fusarium* or *Acremonium* [5]. In our case, the pulmonary involvement could not be documented but is likely considering the favourable outcome of the lesions that were visible on CT scans when appropriate antifungal therapy was initiated. As already reported for *Fusarium* infection [8], onychomycosis may have been the starting point of dissemination and, it must be remembered that nails should be systematically examined before the initiation of cytotoxic chemotherapy.

The taxonomy of *Acremonium* has been reviewed in depth and supports the need for a molecular approach for definitive identification [9]. The internal transcribed spacer sequence of our strain, (accession number KF156781), was identical to the AY138844 sequence in GenBank, deposited as *Acremonium strictum* (strain UW836). However, the revision of the taxonomy considered this strain as belonging to the *Acremonium sclerotigenum- Acremonium egyptiacum* group (group P), as does our strain and the majority of clinical isolates tested in this study, with the possible exception of mycetoma [9].

There is little information regarding the susceptibility of *Acremonium* species to antifungals, but they are characteristically resistant to the anti-Candida agents, fluconazole and flucytosine. Although there is a lack of breakpoint data for those organisms, MICs against amphotericin B are commonly elevated, which suggests poor activity of this drug. *Acremonium sclerotigenum-A. egyptiacum* group seems to be less susceptible to amphotericin B [9], as supported by our results showing an amphotericin B MIC at 12 mg/L and 2 mg/L using the Etest and the CLSI method, respectively, of which the latter has been shown to be less sensitive than Etest for detection of resistance to amphotericin B at least in *Candida* [10].

Finally, posaconazole and voriconazole may be the best therapeutic alternative. The clinical history of our patient correlated with these *in vitro* peculiarities: breakthrough of the *Acremonium* infection while the patient had been treated with liposomal amphotericin B and was receiving caspofungin and favourable outcome using a prolonged course of voriconazole. However, it should be mentioned that this outcome also correlates with the progressive recovery of a normal neutrophil count, which remains an essential prognosis factor of invasive fungal infection. With the wider use of anti-Candida agents and liposomal amphotericin B, clinicians must be aware of the list of fungal pathogens resistant to these drugs among which *Trichosporon* spp. [11], *Aspergillus ustus* [12] and *Acremonium* spp. are predominant.

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Contribution to Authorship

AD collected the clinical data and drafted the manuscript. JG carried out the mycological identification, susceptibility tests and molecular studies, analysed the data, and drafted the manuscript. GB and CH carried out the mycological identifications and susceptibility tests, and helped to draft the manuscript. AFA, AB, MJP and LS collected the clinical data and participated in the manuscript revision. ED carried out the MIC determinations using CLSI method. All authors read and approved the final manuscript.

Transparency Declaration

The authors declare that there are no conflicts of interest.

References

1. Pagano L, Caira M, Candoni A *et al.* The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* 2006; 91: 1068–1075.

2. Kurosawa M, Yonezumi M, Hashino S *et al.* Epidemiology and treatment outcome of invasive fungal infections in patients with hematological malignancies. *Int J Hematol* 2012; 96: 748–757.
3. Kan SF, Tsai TH, Hu CH, Lee WR. Cutaneous hyalohyphomycosis caused by *Acremonium* in an immunocompetent patient. *Br J Dermatol* 2004; 150: 789–790.
4. Schell WA, Perfect JR. Fatal, disseminated *Acremonium strictum* infection in a neutropenic host. *J Clin Microbiol* 1996; 34: 1333–1336.
5. Herbrecht R, Letscher-Bru V, Fohrer C *et al. Acremonium strictum* pulmonary infection in a leukemic patient successfully treated with posaconazole after failure of amphotericin B. *Eur J Clin Microbiol Infect Dis* 2002; 21: 814–817.
6. Foell JL, Fischer M, Seibold M *et al.* Lethal double infection with *Acremonium strictum* and *Aspergillus fumigatus* during induction chemotherapy in a child with ALL. *Pediatr Blood Cancer* 2007; 49: 858–861.
7. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. *Clin Microbiol Rev* 2007; 20: 695–704.
8. Boutati EI, Anaissie EJ. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: ten years' experience at a cancer center and implications for management. *Blood* 1997; 90: 999–1008.
9. Perdomo H, Sutton DA, Garcia D *et al.* Spectrum of clinically relevant *Acremonium* species in the United States. *J Clin Microbiol* 2011; 49: 243–256.
10. Pfaller MA, Messer SA, Bolmstrom A. Evaluation of Etest for determining in vitro susceptibility of yeast isolates to amphotericin B. *Diagn Microbiol Infect Dis* 1998; 32: 223–227.
11. Kataoka-Nishimura S, Akiyama H, Saku K *et al.* Invasive infection due to *Trichosporon cutaneum* in patients with hematologic malignancies. *Cancer* 1998; 82: 484–487.
12. Pavie J, Lacroix C, Hermoso DG *et al.* Breakthrough disseminated *Aspergillus ustus* infection in allogeneic hematopoietic stem cell transplant recipients receiving voriconazole or caspofungin prophylaxis. *J Clin Microbiol* 2005; 43: 4902–4904.