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Clinical and microbiological efficacy of micafungin on Geosmithia argillacea infection in a cystic fibrosis patient

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1. Introduction

Geosmithia argillacea is presently considered as an emerging opportunistic fungus that causes systemic infections in immunocompromised patients with low efficacy of current antifungal therapy despite the use of combinations of 2 to 4 antifungal agents [1–4]. In cystic fibrosis (CF) patients who are at high risk for fungal infections, pathogenic effect of G. argillacea can be expected, particularly in case of lung transplantation, since it shares the thermophilic and chronic colonization characteristics of other pathogenic fungi commonly found in the CF context such as Aspergillus fumigatus or Scedosporium apiospermum, another emerging invasive fungal agent [5–7].

2. Case history

We report the case of a young female patient diagnosed at birth (1996) with F508Del-CFTR homozygous CF. She presented with recurrent severe asthma-like exacerbations not associated with allergy and was chronically colonized by multi-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa since 1997 and 2007, respectively. From 2001 to 2006, A. fumigatus was recurrently detected in airway secretions, while investigations did not provide evidence for allergic bronchopulmonary aspergillosis or invasive pulmonary aspergillosis. In the context of asthma-like exacerbations, she was alternately treated with oral voriconazole (V-FEND, Pfizer, 200 mg bid.) and itraconazole (Sporanox, Janssen-Cilag, 300 mg per day) from 2004 to 2008, which resulted in A. fumigatus eradication in 2006. Nevertheless, due to the detection of other fungi from respiratory specimens, this treatment was continued until 2008. On 2005 and 2006, the presence of Penicillium sp. and Paecilomyces sp. in sputum specimens was recorded at 3 and 2 occasions, respectively. However these findings were not considered as clinically relevant. On May 23, 2007 (Day 0), G. argillacea was recovered for the first time from respiratory secretions, and chronic colonization of the airways by this filamentous fungus was considered as the likely cause of recurrent asthma-like symptoms and of lack of clinical efficacy of antibiotic and antifungal agents (Fig. 1). Morphological identification of G. argillacea was confirmed by molecular analysis as described [1]. Briefly, DNA extracted from fungal cultures was amplified by PCR...
using primers targeting the internal transcribed spacer (ITS-) regions of the rRNA operon. The resulting amplicons were sequenced and the obtained sequences were used in individual BLASTn (Basic Local Alignment Search Tool) searches using NCBI (National Center for Biotechnology Information) BLAST and UNITE databases [8]. In addition, all available G. argillacea isolates from this patient were compared by random amplification of polymorphic DNA (RAPD) using the three-primer set M13, NS3 and NS7 which were found the most discriminant among 10 RAPD primers tested with 12 epidemiologically unrelated isolates (Fig. 2). In this patient, chronic colonization with G. argillacea lasted 1230 days since day 0. There were 23/28 fungus positive sputum samples, and RAPD analysis of the available isolates revealed that all belonged to the same genotype.

In 2008 (day +533), the patient was treated with posaconazole (Noxafil, Schering-Plough, 400 mg per day) orally, but G. argillacea persisted in sputum samples (Fig. 3). In 2009 (from day +882 to day +903), a 3-week caspofungin (Cancidas, MSD) course at a dose of 70 mg per day, later reduced to 50 mg per day due to altered liver enzyme levels, resulted in improved lung function with a FEV1 predicted value increase from 47% to 64% in the absence of G. argillacea eradication. In 2010, deterioration in clinical status was observed with frequent severe dyspnoea episodes and a FEV1 predicted value decline to 47% (day +1191). A first 3-week course of micafungin (Mycamine, Astellas Pharma, 75 mg per day, IV) was administered from day +1139 to day +1160 without either clinical improvement or disappearance of G. argillacea in sputum. A second course of micafungin started 2 months later (i.e. 100 mg bid for 3 weeks and 100 mg per day from day +1219 to day +1261), resulted in clinical and microbiological improvement, with a FEV1 predicted value increase to 68% and G. argillacea eradication, mycological cultures from sputum samples remaining sterile for 21 months after initiation of high dose micafungin therapy. No side effect attributable to micafungin therapy was noticed.

In vitro susceptibility to antifungal drugs was assessed for 6 G. argillacea isolates using the microdilution broth reference method (Clinical Laboratory Standards Institute (CLSI) M38-A protocol). The median (range) minimal inhibitory/effective concentrations (MIC/MEC, mg/ml) were: 1.0 (0.25–1), 8.0 (2.0–16.0), 4 (16.0), 4.0 (2.0–8.0).

**Fig. 1.** Microscopic appearance of *Geosmithia argillacea* cultured on Sabouraud dextrose agar medium (magnification ×200). *Geosmithia argillacea* can be recognized by the presence of hyaline, septate and often branched conidiophores bearing biverticillate or triverticillate (occasionally monoverticillate) asymmetrical penicilli, and its smooth-walled, one celled, cylindrical to ellipsoidal conidia produced at the apex of phialides with a cylindrical base tapering more or less abruptly to a narrowed conidium-bearing tube.

**Fig. 2.** Electrophoretic patterns of *Geosmithia argillacea* isolates. Electrophoretic patterns of epidemiologically independent isolates recovered from sputum samples collected from March 2009 to February 2011 from distinct patients with CF followed-up in Angers, Giens, Rouen and Paris Necker Hospitals (lanes 1 to 8: 100112439-01, 0908654817-01, 110089119-01, 090676598-01, 100421474-01, 090213107-01, 090482165-01 and 110063519-02, respectively). Electrophoretic patterns of patient’s isolates (lanes 9 to 18: isolates recovered from sequential sputum samples collected on 2007/04/20, 2007/06/26, 2007/11/12, 2008/10/01, 2008/12/08, 2009/03/16, 2009/06/10, 2010/04/14, 2010/05/17 and 2010/12/13, respectively). Amplicons generated by RAPD using primers M13, NS3 or NS7 were separated on 1.5% agarose gels. Lanes M, DNA size markers (100-bp ladder from GE Healthcare Life Sciences).

**Fig. 3.** Evolution of FEV1 predictive values in the course of *Geosmithia argillacea* infection.
0.25 (0.03–0.25) and 0.015 (0.015–0.03) for amphotericin B, itraconazole, voriconazole, posaconazole, caspofungin and micafungin, respectively. From December 2010 (day +1300) until now (day +1846), the patient received posaconazole prophylaxis.

3. Discussion

The pathogenic role of G. argillacea in CF is still under discussion. In this patient, G. argillacea respiratory colonization was retained as consistent with the deterioration of clinical status and lung function. Each of the three episodes of recovery from the fungus was associated with a dramatic increase in FEV1 predicted values. Moreover, results from RAPD showed that the patient was constantly infected by the same genotype, further supporting chronic colonization of the airways by the fungus. In addition, unchanged bacterial colonization before, during, and after G. argillacea colonization, and clinical and functional improvement of the patient after prolonged high dose micafungin-based G. argillacea eradication are consistent with a pathogenic role for the fungus. This contrasts with a previous series of 8 CF patients in whom no clinical consequence of G. argillacea colonization was reported. However, that only 2/8 patients were persistently colonized and no G. argillacea eradication was achieved seems to preclude conclusions [9]. Documented intraspecies sequence divergences in the ITS regions of G. argillacea raise also the hypothesis of an heterogeneity of isolates in terms of pathogenicity [10].

In the present patient, the presence of G. argillacea in respiratory secretions was ascertained since May 2007, although due to morphological similarities, some 2005 or 2006 isolates may have been misdiagnosed as Penicillium and/or Paecilomyces species. Respiratory colonization by G. argillacea was currently identified in 11/156 CF patients followed-up in Rouen (Normandy, France) University hospital, which questions the role of a mild and wet climate. The origin of the contamination of the patients remains to be defined, and their indoor environment are presently investigated.

As previously reported, isolates from this patient exhibited lower posaconazole MICs than itraconazole MICs, and all were found resistant to voriconazole and to amphotericin B. Nevertheless, they were found less sensitive to itraconazole and posaconazole than those previously studied [2–4]. Differences in sensitivity may be due to prolonged therapy or deficient intestinalazole compound absorption in CF patients. In agreement with other antifungal susceptibility assays, micafungin exhibited lower MEC compared with caspofungin [2]. Until now, all G. argillacea-colonized patients treated with antifungal drugs presented with invasive pulmonary infection due to underlying immunodeficiency [2,3]. One patient who received a tritherapy including terbinafine survived. Likewise, another patient survived after receiving a combination of micafungin and posaconazole, while all other patients who received only one antifungal without lung surgery died [2,3]. In the present case, the first micafungin course given at the commonly recommended dose was inefficient, and G. argillacea eradication was achieved only after a prolonged high dose micafungin course.

In summary, the present observation provides first clue for the clinical relevance of G. argillacea airway colonization in CF patients. Data prompt further investigation of first intention anti-G. argillacea therapy with adapted regimens of micafungin in colonized CF patients.

Conflict of interest

There are none.

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References