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**A B S T R A C T**

Cystic fibrosis (CF) patients are at high risk of colonization of the airways by a number of fungi, including the emerging opportunistic fungus *Geosmithia argillacea*. We report the eradication of respiratory *G. argillacea* associated with clinical resolution of severe symptoms by high-dose and prolonged micafungin therapy in a young CF patient.

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1. Introduction

*Geosmithia argillacea* is presently considered as an emerging opportunistic agent that causes systemic infections in immuno-compromised 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), 416.0 (4–16.0), 4.0 (2.0–8.0), 4.0 (2.0–8.0), 4.0 (2.0–8.0).
MEC compared with caspofungin [2]. Until now, all azole compound absorption in CF patients. In agreement with sensitivity may be due to prolonged therapy or deficient intestinal nevertheless, they were found less sensitive to itraconazole and found resistant to voriconazole and to amphotericin B. Never- lower posaconazole MICs than itraconazole MICs, and all were to be defined, and their indoor environment are presently climate. The origin of the contamination of the patients remains in 11/156 CF patients followed-up in Rouen (Normandy, France) in whom no clinical consequence of the fungus. This contrasts with a previous series of 8 CF patients 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 pathogeni- city [10].

In the present patient, the presence of G. argillacea in respira- tory 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. Never- theless, 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 intestinal azole 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