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Case report/Cas clinique

Successful treatment of a recurrent *Aspergillus niger* otomycosis with local application of voriconazole

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ABSTRACT

Fungal otitis (otomycosis) is a common infection encountered by otolaryngologists. Nevertheless, its management can be challenging because of its high recurrence rate and of the limited therapeutic options. A 45-year-old woman suffered from recurrent otomycosis. The ineffectiveness of successive antibiotic cures and repeated topical treatments with nystatin and then with econazole cream led to perform microbiological analyses. Culture of ear swab grew *Aspergillus niger*. The use of a 1% voriconazole sterile solution previously validated for treatment of eye infections was considered after ensuring the absence of known ototoxic effects of the antifungal and of the excipients. The patient was advised to apply locally this voriconazole solution daily for 14 days (3 drops, 3–4 times a day). Full recovery was obtained at the end of the treatment, and no relevant side effects were noticed. More than one year after completion of therapy, there was no recurrence. Our observation shows that voriconazole 1% solution is an interesting option for treating otomycosis which failed to respond to usual therapeutic options. Further prospective studies are now warranted to confirm these findings.

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1. Introduction

Otomycosis is a fungal infection of the outer ear canal (OEC). It accounts for approximately 10% of all acute otitis externa cases [1]. Anatomical characteristics of the OEC indeed provide ideal conditions for such infections, which mainly involve species belonging to the *Aspergillus* (especially *A. niger* and *A. fumigatus*) or *Candida* genus [2]. Risk factors for such infections include warm, moist weather, and excessive accumulation of cerumen in the OEC. This is particularly true when the OEC remains wet after swimming or bathing. Although usually benign, management of otomycosis may be challenging because of its high recurrence rate [1], the paucity of therapeutic options and the emergence of antifungal resistance [3,4]. Besides patient's discomfort, its possibility to evolve towards an invasive fungal infection justifies appropriate care. Here, we report the first case of recurrent *A. niger* otomycosis that was successfully treated by topical administration of a 1% voriconazole solution along with a literature review of antifungal therapy of *A. niger* otomycosis.

2. Case report

In March 2015, a 45-year-old woman practicing swimming consulted her family doctor complaining of left auricular pain, hearing loss, and tinnitus, along with changes in her tone of voice. Eardrum was undamaged. The patient was given ofloxacin eardrops, 1.5 mg bid for 7 days, followed by a 5-day course of cefpodoxime per os 100 mg bid. Despite compliance to treatment, the symptoms did not improve and black residues appeared in the OEC. Fifteen days later, during an otorhinolaryngology consultation, an ear cleaning suction was performed and a local treatment with nystatin (Auricularum[®], Grimberg) was prescribed for 15 days; eardrops were instilled twice daily. There was a marked improvement but clinical signs reappeared quickly. Microbiological examination was undertaken and mycological cultures from a swab taken from the OEC grew *Aspergillus niger*, which was identified morphologically according to standard descriptions [5]. The same local treatment was prescribed for a further 15 days, along with custom-made earplugs to prevent water penetration into the ear canal during aquatic activities.

In July 2015, during a consultation in mycology, and following another 15-day course of local nystatin, a yellowish material was sampled from the left OEC, but cultures remained sterile. Despite clinical recurrence and significant discomfort, the possibility of

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using an oral antifungal agent (either itraconazole or voriconazole) was rejected given the potential side effects associated with systemic delivery and the lack of consensus on its implementation in this indication. The patient no longer used the earplugs and stopped going to the swimming pool.

Seven months later, i.e., about one year post-onset of symptoms, the patient came back to our hospital. A total of 4 clinical recurrences were noticed, and the symptoms worsened with the appearance of eczema-like lesions at the level of the tragus and antitragus, discharge flowing down the left earlobe, and severe itching. Blackish debris were removed from the left ear, allowing the recovery of *A. niger* again by cultures (Fig. 1A and 1B). In this context, an antifungal susceptibility testing was performed on the patient's isolate using nystatin and voriconazole by the disk diffusion and E-test methods, respectively (Fig. 1C). A very slight inhibition zone (11 mm) was noticed around the nystatin disk, indicating little activity against this strain, which probably contributed to disease relapses. By contrast, voriconazole exhibited excellent in vitro activity, with a minimal inhibitory concentration of 0.064 µg/mL, which is markedly lower than the epidemiological cutoff value reported for voriconazole against *A. niger* [6]. Meanwhile, a treatment with econazole cream was started but such formulation was difficult to apply due to the deep, peritympanic spread of the fungus. The hospital pharmacy was contacted to investigate the possibility of using an azole-based aqueous solution as eardrops. Finally, a 1% voriconazole ophthalmic solution was chosen, used outside of marketing authorisation, after excluding ototoxicity risks due to the eye drop components.

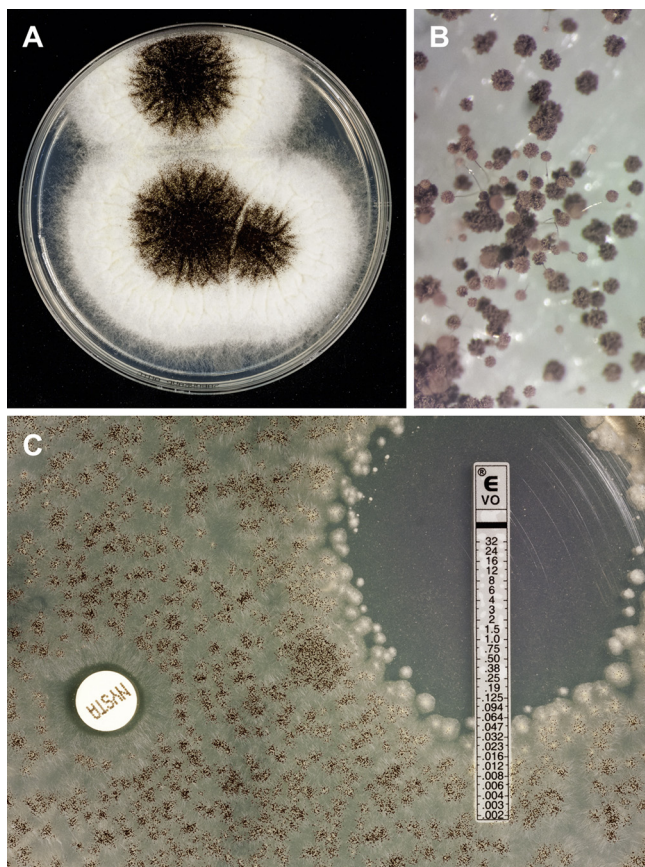


Fig. 1. Mycological investigations performed on ear wax mass. A. Macroscopic aspect of culture on Sabouraud's agar, consistent with *Aspergillus niger*. B. Observation of an *A. niger* colony with a binocular magnifier, showing hyaline conidiophores bearing dark-brown conidial heads. C. Susceptibility testing of *A. niger* against nystatin (disk diffusion) and voriconazole (E-test).

Eardrops were thus prescribed, to be added for 10 to 15 minutes, 3 to 4 times a day for 14 days.

Complete recovery was achieved at the end of treatment with voriconazole without any side effects. The skin of the OEC became normal and the patient was advised to avoid swimming for some time and reuse of the silicone earplugs to prevent further fungal colonization. At the two-month follow-up visit, otoscopic examination was unremarkable and ear swab cultures remained sterile, indicating mycological cure. More than one year after completing treatment, the patient had no recurrence of otitis.

3. Discussion

In France, nystatin is the only antifungal licensed as a powder or as suspension (in combination with oxytetracycline, polymyxin B and dexamethasone) for local treatment of otomycosis [7]. Since other antifungals are not available in a formulation suitable for auricular use, the prescription of nystatin is recommended as the first-line treatment of otomycosis for up to 15 days. Like amphotericin B, nystatin exhibits a broad spectrum including the aspergilli and *Candida* yeasts, which are mostly responsible for otomycosis. However, lack of efficacy has been reported in several cases of *Aspergillus* otomycoses [8,9]. Several other otological antifungals are available in some countries, but the most effective drug in this context remains to be defined. Clotrimazole is the most widely used topical imidazole [9]. In the USA, it is considered as the drug of choice for treatment of uncomplicated otomycosis [10]. It displays a high in vitro activity against most yeasts and molds [11] and success rates ranging from 50% to 100% have been reported [12–14]. However, all these studies were conducted on a limited number of patients, and effectiveness was often based on symptom resolution rather than mycological assessments.

Consequently, whether or not treatment failures with clotrimazole could be attributed to a particular pathogen, i.e., *A. niger*, is unknown. Miconazole and bifonazole, as well as ciclopiroxolamine, can also be used. Compared to clotrimazole, the two imidazole drugs exhibit similar activity, but varying from one fungal species to another. For instance, del Palacio et al. [15] investigated the efficacy of topical bifonazole on 40 infected ears and they found a clinical cure for 72.5% of them while mycological cure rate reached 57.5%. Of note, during long-term follow-up (2–5 years), 10 ears were re-infected, 8 of them with *A. niger* at baseline. These results are in line with another study also performed by del Palacio et al. [16]. Among the 40 infected ears treated with a ciclopiroxolamine-based preparation, seven (17.5%) relapses were noticed, of which four (10%) were due to *A. niger* [16]. The effectiveness of ciclopiroxolamine versus miconazole was also investigated [17]. Ciclopiroxolamine showed a narrower spectrum, since it inhibited only 57% of the selected strains compared to 90% with miconazole [17]. Terbinafine also showed a potent in vitro antifungal activity against several aspergilli, including *A. niger* [18,19]. Unfortunately, ototoxic effects of topically administered terbinafine have been reported in an animal model [20], thus limiting its usefulness in the field. Unlike terbinafine, tolnaptate was not ototoxic in animal models [12], but it is ineffective against *A. niger* [11].

In our case, relapse could be attributed to an insufficient activity of nystatin against the causative agent, as attested by our experimental data. Multiple recurrences of otomycosis could also be explained by the use of oral and topical antibiotics, which may have destabilized the local flora and permitted fungal proliferation, or by the use of earplugs during aquatic activities, a possible source of re-infection [12].

To treat these recalcitrant forms, prescribers must seek an alternative among the antifungal medications classically used by

another route of administration than the otic route, and therefore beyond marketing authorization. Such a procedure requires the patient's consent as well as the verification of the tympanic membrane integrity. In the present case, nystatin treatment was switched to econazole cream, but its effect was limited due to poor penetration of this formulation into the OEC. Econazole is also available as a solution but it is applied using a pressurized vial, which is not suitable for direct application into the OEC.

Another therapeutic option compatible with auricular application and effective on the isolated fungus was therefore searched. According to the *European Pharmacopoeia*, auricular solution intended for application to an injured ear should be sterile and free of antimicrobial preservatives and should not induce toxic effects or local irritation [21]. Given the urgency of the situation and the results of antifungal susceptibility testing, it was decided to investigate the opportunity of using a sterile voriconazole solution prepared by the AP-HP (Assistance publique-Hôpitaux de Paris, Paris, France) in the form of eye drops in multi-dose vials (8 mL), and containing voriconazole 10 mg/mL and beta-cyclodextrin sulfobutyl ether sodium salt 160 mg/mL as stabilizing agent. Although the effectiveness of oral voriconazole for the treatment of *Aspergillus* otitis has been reported [22], a twelve-week duration therapy was required, with the risk of side effects. Conversely, the topical use of voriconazole solution for treatment of otomycosis has never been reported to date. The pharmacists' approach was to check the absence of ototoxicity. A bibliographical search did not reveal ototoxic effects regarding the local administration of the eye drop solution components, voriconazole and cyclodextrin, which was confirmed by making inquiries to Pfizer laboratory (which markets voriconazole products) and contacting the Regional Pharmacovigilance Centre. Furthermore, the physicochemical properties of this formulation were considered to be safe and compatible with ear instillation (pH: 7.0 ± 0.1 , osmolarity: 562 ± 10 mosm/L) [23]. Finally, this treatment was prescribed, which allowed to cure the patient. To our knowledge, this is the first report on the safety and efficacy of a 1% sterile voriconazole solution to treat a recurrent, nystatin-resistant otomycosis. The local application of this molecule avoids systemic treatment for an extended period, potentially responsible for undesirable effects. These data should be confirmed by a larger-scale study enrolling patients with recurrent otomycosis unresponsive to standard treatments.

Disclosure of interest

The authors declare that they have no competing interest.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the consent form is available for review by the Editor of this journal.

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