中文題目：Terbinafine 用於 Azole 抗藥性的侵襲性中樞神經系統麴菌病:病例報告

英文題目：Terbinafine in Azole-resistant Invasive CNS Aspergillosis: A Case Report

作　　者：陳嘉俊[1], 王竣令[1]

服務單位：[1]國立成功大學醫學院附設醫院內科部

Background

The case-fatality rate of central nervous system aspergillosis was the highest comparing to other forms of invasive aspergillosis [1]. And the mortality rate was as high as 100% in the literature [2,3]. The current IDSA guideline recommended Voriconazole as the standard treatment of CNS aspergillosis based on open-label studies [4,5,6]. Also, Liposomal AmB (amphotericin B) has demonstrated favorable results towards CNS aspergillosis[7,8,9]. For azole-resistant CNS aspergillosis, an international expert panel favors Liposomal AmB as core therapy [10]. As alternatives, itraconazole, posaconazole, caspofungin and micafungin have been used in the treatment of CNS aspergillosis in some studies [11,12]. As another option, a case report showed the activity of Terbinafine against refractory pulmonary aspergillosis [13]. But lack of clinical data limits recommendation for its use, especially in CNS aspergillosis.

We herein report a case of an 83-year-old man with skull base osteomyelitis and pachymeningitis resulting from an azole-resistant Aspergillus flavus. Combination of high-dose micafungin and liposomal AmB was used in the first place but the titer of aspergillus antigen (Ag) remained high. Thus, oral terbinafine was prescribed as a salvage therapy, which successfully lowers the titer of Aspergillus Ag in the case.

Case report

A 83-year-old male patient with coronary artery disease, heart failure with preserved ejection fraction, type 2 diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, was admitted due to left ear pain and otorrhea for 6 months and intermittent conscious disturbance including lethargy, disorientation and visual hallucination for 2 months (day 0, d0).

There was no specific pathogen isolated from the bacteria, fungus and mycobacterium culture of the ear discharge. For the survey of the peripheral facial palsy, an osteomyelitis scan (day) (d8) revealed left mastoiditis with osteomyelitis in mastoid part of the left temporal bone, left petrous part and body of the sphenoid bone, and possible skull base involvement. The presence of CNS infection was

excluded by lumbar puncture(d10). A CT scan(d31) and gallium scan(d38) verified the presence of osteomyelitis. Meanwhile, the rising CRP and leukocytosis suggested a limited response despite prolonged empiric antibacterial therapy. However, the surgical risk was too high for this patient considering a deep and broad involving area of the osteomyelitis. At this point, the patient received conservative treatment with broad spectrum antibacterial therapy for one month, but there was no clinical improvement.

Subsequently, a highly elevated serum Aspergillus Ag (titer 4.2, positive: ≥0.5) was found on d35. Intravenous Voriconaozle and liposomal Amphotericin B (3mg/kg) were started due to the likelihood of invasive aspergillosis with CNS involvement. In addition, fungus culture of left ear discharge obtained on d46 yielded Aspergillus flavus. The titer of serum Aspergillus Ag kept rising (6.42 on d51 and >7.76 on d59), when the patient was empirically treated with combination of both Voriconaozle plus liposomal Amphotericin B(d37-d51) and Voriconaozle plus Caspofungin(d51-d63). On d57, a brain MRI revealed temporal, sphenoid, occipital osteomyelitis and pachymeningitis at left temporo-parieto-occipital region (Fig1).

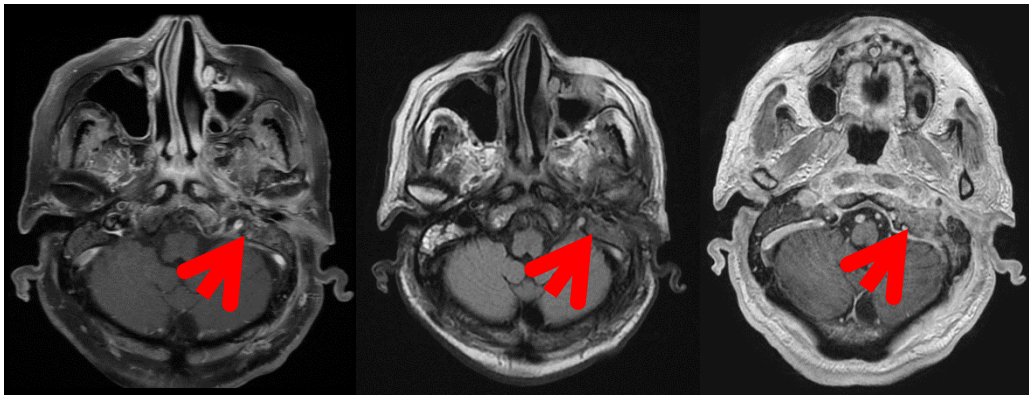

Fig 1. MRI of head without and with contrast medium images
(A) T1 FLAIR with gadolinium; (B) T2 FLAIR; (C) 3D T1 with gadolinium
Red arrows showed left otitis media with osteomyelitis involving the petrous portion of left temporal bone and pachymeningitis at left temporo-parieto-occipital region.

Afterwards, drug susceptibility testing on d63 confirmed that Aspergillus flavus was resistant to Voriconazole(MIC 8 mg/L). Thus, antifungal therapy was changed to high dose Micafungin plus liposomal Amphotericin B(d63-d102). Nonetheless, the titer of serum Aspergillus Ag was still above 5 in six weeks. On d102, the MIC result of Terbinafine was 1 mg/L, and the patient was treated with oral Terbinafine 250mg BID since then. Finally, the clinical condition became stable, and after a 116-day

hospitalization, the patient was discharged. Eventually, the titer of serum Aspergillus Ag decreased to 2.35 on d129 after discharge (Fig 2).

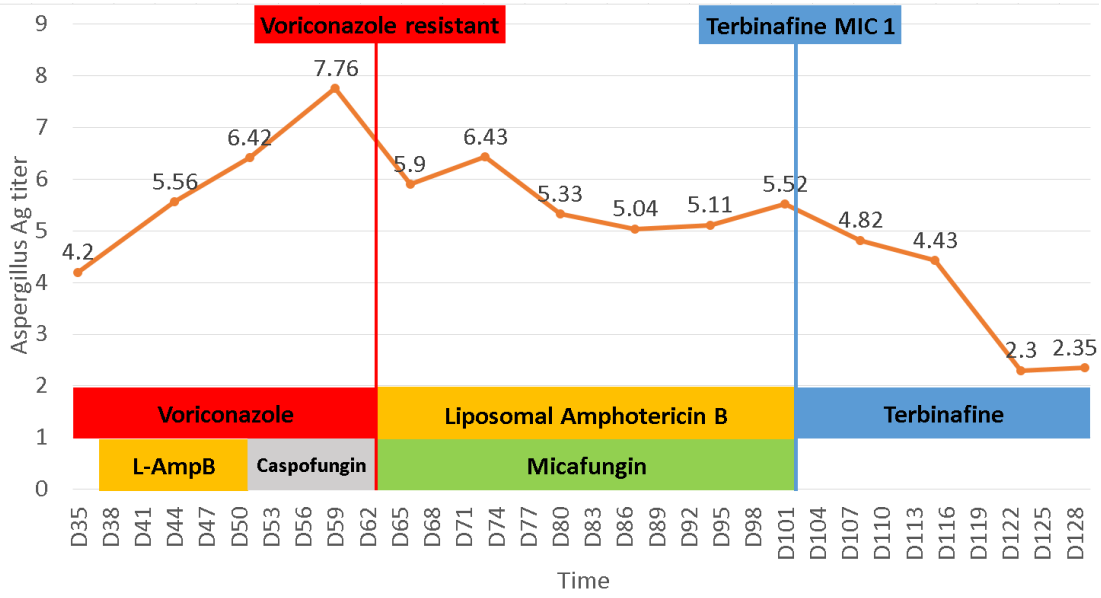

Fig 2. The timeline of the response of Aspergillus Ag titer to the antifungal agents

Discussion

According to an epidemiological report in 2019, Aspergillus flavus is the most common specie of CNS aspergillosis in immunocompetent patients [14]. The outcome of CNS aspergillosis was poor, as both the overall response rate to antifungal therapy and the 1-year overall survival was low in the same study.

Here we present a patient with type 2 diabetes mellitus who developed invasive CNS aspergillosis caused by Aspergillus flavus. As the recommendation in IDSA guideline [15], Voriconazole was chose as a first line therapy. Later, liposomal AmpB and Caspofungin were added as a combination therapy with Voriconazole. However, the rising titer of Aspergillus Ag indicated a poor clinical response of both combinations.

Hence, a drug sensitivity test was carried out and confirmed the resistance to Voriconazole. Then, the voriconazole-based treatment was replaced by liposomal amphotericin B plus high-dose Micafungin. But the clinical response remained poor. Due to relative low MIC, Terbinafine was prescribed as a last resort and demonstrated a good therapeutic response in this patient.

Terbinafine is approved in the treatment of onychomycosis or tinea infection in many regions. However, the clinical data were limited for non-dermatophyte infection.

Terbinafine had already displayed a great primary fungicidal activity against non- A. fumigatus Aspergillus in vitro study [16].

To date, the clinical experience with Terbinafine was mainly in pulmonary aspergillosis when conventional treatment failed [13,17,18,19]. The complete response rate was high within 9-month treatment with a dose of 250-1000 mg/day. A pilot study also showed the effectiveness against pulmonary aspergillosis comparing to Itraconazole [20]. The reported adverse effects included headache, gastrointestinal upset, skin rash, elevated transaminases and test disturbance [21]. In general, the side effects are minor and well-tolerated.

Currently there is no available data of Terbinafine used in CNS aspergillosis. In our case, Terbinafine(250 mg BID) successfully lowered the titer of the Aspergillus Ag. For invasive CNS aspergillosis, though the effective treatment dosage and duration remained unclear, Terbinafine may serve as an alternative treatment option besides azoles, AmpB and Echinocandin in refractory cases.

Conclusions

We successfully treated our patient with Terbinafine for invasive CNS aspergillosis when the conventional therapy including Voriconazole, AmpB and Echinocandin failed. The patient tolerated the therapy well and the titer of Aspergillus Ag decreased at follow-up. Despite no standard dose and duration of treatment, Terbinafine should be considered a potential alternative for invasive CNS aspergillosis.

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