

Posaconazole responsive cerebral aspergillosis in an immunocompetent adult



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ABSTRACT

Cerebral aspergillosis is a rare manifestation of invasive aspergillosis that usually affects immunocompromised patients. There are few treatment options for recurrent disease and experiences with immunocompetent patients are lacking. We report the clinical course of an immunocompetent patient with recurrent cerebral aspergillosis, following initial treatment with burr hole aspiration and voriconazole, who showed remarkable response to posaconazole. The patient remains clinically well with no evidence of recurrence on MRI 7 years following diagnosis. To our knowledge this is the first reported experience with posaconazole in an immunocompetent patient with cerebral aspergillosis.

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1. Introduction

Cerebral aspergillosis is a rare manifestation of invasive aspergillosis caused by members of the *Aspergillus* genus of saprophytic fungi. It is usually associated with immunocompromised states and only rarely affects immunocompetent patients [1]. Outcomes are poor and many survivors are left with significant disability [2]. Diagnosis requires a biopsy, but operative procedures may also serve a therapeutic role in terms of drainage or excision of the abscess, although the mainstay of treatment is systemic antifungals. Recurrent disease presents additional challenges due to limited treatment options. We report the clinical course of an immunocompetent patient with recurrent cerebral aspergillosis who showed remarkable response to posaconazole.

2. Case report

A 67-year-old, male, retired civil servant presented with right-sided facial pain and lower motor neuron facial palsy (House-Brackmann Grade V). His past medical history included bilateral hearing loss secondary to otitis media, and right-sided mastoiditis, treated with bilateral grommets and mastoidectomy, respectively. He had no underlying cause of immunocompromise and all haematological tests were within the normal range. MRI demonstrated several ring enhancing lesions in the right temporal lobe, contiguous with the right petrous temporal bone (Fig. 1).

The patient underwent an image-guided burr hole biopsy and *A. fumigatus* was isolated, which showed susceptibility to voriconazole (minimal inhibitory concentration 0.5 mg/l). Voriconazole treatment was therefore commenced. Unfortunately, the patient also received a concurrent diagnosis of prostate cancer and was

commenced on hormonal therapy with bicalutamide and goserelin.

After 3 months of therapy with voriconazole, there was no change in symptoms and only minimal radiological improvement. However, therapy was continued and further treatment decisions were withheld until completion of radiotherapy. MRI at 12 months following commencement of treatment demonstrated a significant reduction in enhancing tissue size and surrounding oedema (Fig. 2), with accompanying resolution of the patient's facial pain. Voriconazole was therefore continued.

At 18 months post-diagnosis the patient presented with left-sided hemiparesis and a right sixth cranial nerve palsy. MRI demonstrated a significant increase in the size of the abscesses and surrounding oedema (Fig. 3). He underwent a craniotomy with total excision of the abscesses and adjacent petrosectomy. Post-operatively, his sixth nerve palsy persisted, although his hemiparesis resolved and there was no residual disease visible on imaging. *A. fumigatus* was cultured from operative specimens and showed susceptibility to posaconazole (minimal inhibitory concentration/ minimal fungicidal concentration to itraconazole 1/8 mg/L, amphotericin 1/2 mg/L, voriconazole 1/2 mg/L and posaconazole 0.12/2 mg/L; fully susceptible). The patient was therefore commenced on posaconazole (400 mg twice daily) and seen 6 monthly to check levels. Therapy was continued for a period of 5 years without incident and serum levels remained therapeutic throughout (range 1.33–1.92 mg/l, target >1.25 mg/L for invasive fungal disease). At 7 year follow-up, the patient remains fully independent without evidence of recurrence.

3. Discussion

Management of cerebral aspergillosis involves a combination of surgical and medical approaches, although the best surgical option is unclear when comparing biopsy, drainage or excision. Usually, surgery is necessary only for diagnostic purposes, although complete operative removal of infected tissue may be necessary in

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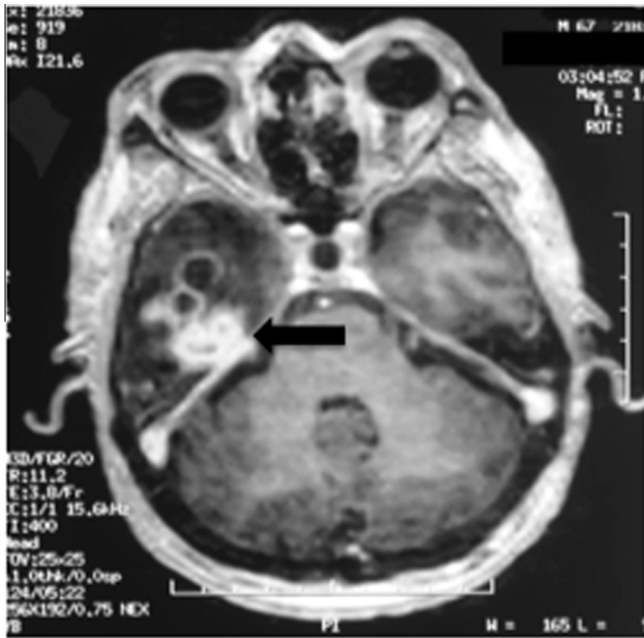


Fig. 1. Axial post-gadolinium T1-weighted MRI demonstrating ring enhancing lesions in the right temporal lobe contiguous with the right petrous bone (black arrow).

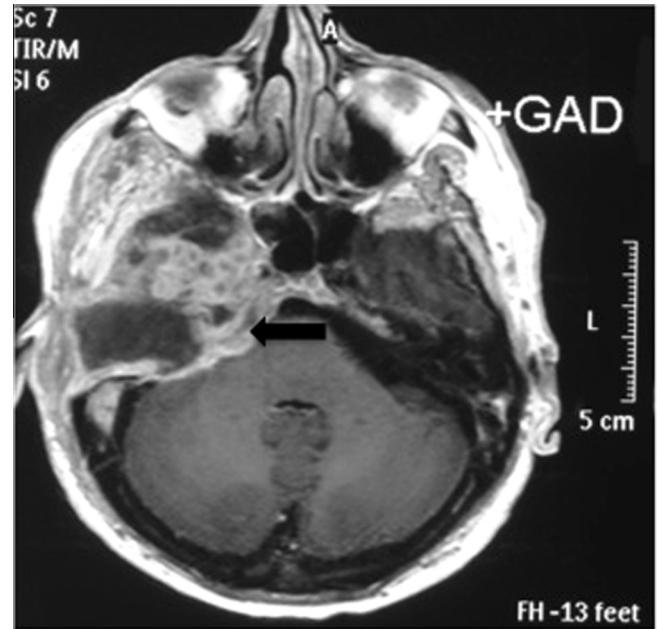


Fig. 3. Axial post-gadolinium T1-weighted MRI demonstrating progression of the right temporal *Aspergillus* abscess with enhancement through the right petrous temporal bone extending into the clivus (black arrow).



Fig. 2. Axial post-gadolinium T1-weighted MRI demonstrating a significant reduction in the enhancing tissue size and surrounding oedema of the focus of cerebral aspergillosis (black arrow).

the absence of response to medical therapy. Some advocate routine surgical resection followed by systemic antifungal therapy and favourable outcomes have been reported [1]. However, this approach can result in significant operative mortality [2].

Posaconazole is a newer extended spectrum triazole antifungal which demonstrates greater *in vitro* activity against *Aspergillus* species compared to voriconazole and itraconazole [3]. Guidelines currently recommend its use as salvage therapy for cerebral aspergillosis after failure of first-line drugs such as voriconazole [4]. Posaconazole was administered in two daily doses, as divided regimens increase its oral bioavailability, and levels were found to be therapeutic throughout the duration of therapy, supporting pharmacokinetic data [5]. Posaconazole proved to be safe and efficacious, which reflects the findings of larger series, which have predominantly included immunocompromised patients [6].

Cerebral aspergillosis should be considered in the differential diagnosis of patients with acute onset of focal neurologic deficit, even in immunocompetent patients. This patient demonstrates that if initial therapy with minimally invasive procedures such as image guided aspiration and first line antifungal therapy with voriconazole fail, more aggressive treatment with surgical excision and administration of the second generation antifungal agent posaconazole can lead to excellent long term control with low morbidity and good neurological outcome. Whether aggressive therapy with excision and posaconazole treatment should be considered as first-line treatment requires further study. Indeed, to our knowledge this is the first reported experience with posaconazole in an immunocompetent patient with cerebral aspergillosis.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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