Massive intracerebral aspergillosis responding to combination high dose liposomal amphotericin B and cytokine therapy without surgery

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This report describes a patient with intracranial *Aspergillus flavid* infection in whom it was impossible to remove the fungal mass surgically. Progressive fungal infiltration of the optic nerves was reversed and the extensive intracranial fungal burden was managed successfully with combination antifungal-immunomodulatory therapy alone.

**Patient and methods**

A 25-years-old female patient had presented 3 years previously with epistaxis associated with progressive bi-frontal headache treated with unknown intranasal medications. She was alert but disorientated to time and place. Short-term memory recall was poor. There was moderate difficulty in performing simple arithmetic tasks accurately. A left partial third nerve palsy with ptosis was evident. Bilateral chronic papilloedema was present. A magnetic resonance imaging (MRI) scan of the paranasal sinuses indicated extensive disease in the paranasal sinuses, extending through the cribiform plate and medial orbital walls, into the frontal lobes and beyond (Fig. 1).

ENT examination revealed a polypoid bulge involving the whole length of the left middle turbinate. There was an extensive hard mass suggestive of a malignant tumour which filled most of the ethmoidal labyrinth.

Biopsies showed extensive areas of non-caseating granulomatous inflammation comprised of lymphocytes, macrophages, eosinophils and multinucleate giant cells. Fungal hyphae were present. Culture of the biopsy grew *Aspergillus flavus*. The MICs to amphotericin B and itraconazole were 2 mg/L and 0.125 mg/L, respectively.

The peripheral white cell count and differential were normal. Blood glucose, renal profile, hepatic profile, serum ferritin, vitamin B12, folate, serum IgA and IgM were normal. The IgG was 22.78 g/L (normal range 9–18 g/L). HIV, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were negative. The total IgE was 433 IU/mL (normal range 1–120 IU/mL). Pheno-typing of peripheral lymphocytes showed normal T- and B-cell numbers and percentages but indicated alteration in T-cell subsets. Both relative and absolute numbers of CD4+ T cells were low (31% and 458 cells/μl respectively) and were accompanied by an increased percentage of CD8+ cells. These findings resulted in a low CD4+/CD8+ T-cell ratio of 0.6. The absolute number and percentages of B cells were within the normal range, while percentages of CD3+, CD15+, CD56+ and natural killer (NK) cells were low normal (5%). Quantitative nitroblue tetrazolium (NBT) reduction following ingestion of latex particles indicated a 31% reduction in neutrophil oxygen-dependent bactericidal activity. Stimulation with opsonised zymosan indicated a 50% weaker NBT reduction response of the neutrophils in comparison with control values. Total complement activity was slightly above normal as evaluated by dynamic haemolysis-based testing (137, 4%).

**Results**

Treatment (Fig. 2) was commenced (day 1) with liposomal amphotericin B (LAB, AmBisome) 4 mg/kg/day, rifampicin 600 mg daily, dexamethasone 4 mg three times daily and diamox 250 mg twice daily for raised intracranial pressure, and granulocyte-mono-cyte colony-stimulating factor (GMCSF) 200 μg three times weekly. Neurosurgical intervention was technically impossible as serious permanent iatrogenic damage was inevitable. On day 11 visual acuity in the right eye had fallen to perception of finger
Fig. 1. MRI series of patient before treatment. (a) Sagittal SE, post-gadolinium, shows extensive abnormal uptake of para-nasal sinuses with gadolinium. Note interruption of cortex and dura in cribriform plate area and contiguous uptake in fronto-basal brain, and spread of fungal disease on plenum sphenoidal posteriorly to perisellar area and from paranatal sinus area posteriorly to clivus. (b) Coronal SE T1-weighted shows extension of disease through medial orbital walls into the orbits. (c) Axial fast-spin echo T2-weighted shows extensive frontal lobe disease with oedema involving subcortical structures, white matter, corpus callosum and basal ganglia.
movements only. The ptosis had become more apparent. Repeat MRI examination confirmed progressive fungal disease with bilateral fungal infiltration of both optic nerves (Fig. 3a). Antifungal management was modified as follows: LAB 6 mg/kg/day, 5-flucytosine (5FC) 2 g four times daily and recombinant γ-interferon (γ-IFN) 100 μg three times weekly. Rifampicin was discontinued because of hepatotoxicity. By day 19 visual acuity had substantially improved (20/100 in the symptomatic right eye and 20/25 in the clinically unaffected left eye). Central vision improved progressively thereafter. Repeat MRI at day 40 showed substantial clearing of the optic nerve infiltration (Fig. 3b) and cavernous sinus infiltration and a 35% reduction in the anterior fossa fungal mass (Fig. 3c). Only the posterior ethmoid sinus showed evidence of fungus. White matter oedema was grossly reduced (Fig. 3d). LAB (cumulative dosage 35 050 mg), 5FC and GMCSF were discontinued on day 73. The dose of dexamethasone was gradually tapered off and discontinued on day 61. On day 73 the patient was clinically well, with no headache or visual disturbance. Visual field testing was normal. She was discharged from hospital on itraconazole 800 mg daily and γ-IFN 100 μg twice weekly. The γ-IFN was discontinued on day 210. MRI at day 210 showed further substantial improvement of the intracranial fungal disease (Fig. 3c). The ethmoid sinuses had virtually cleared. The patient has taken itraconazole 800 mg daily for the following 12 months with stable minimal clinicoradiological disease.

Discussion

Intracranial aspergillosis associated with contiguous sinusitis is a rare, poorly understood entity in the apparently immunocompetent host. This patient had all the features associated with A. flavus aetiology described in patients mainly from Sudan [1].

Prolonged severe neutropenia and corticosteroid use are two factors implicated in the pathogenesis of invasive aspergillosis in immunocompromised patients, particularly those with haematological malignancy. The patient described here had neither of these. However, the modest phagocyte dysfunction in this patient may have been one factor in failing to eradicate the Aspergillus infection. The importance of normal phagocytic function has been highlighted by others [2]. In addition low CD4+ counts were detected in this patient. There was no evidence of humoral immuno-
deficiency but an increased IgE level in the absence of allergic manifestations. These findings are compatible with the notion of a selective Th1-type cell deficit which is of paramount importance in controlling infection with *Aspergillus* spp. [3]. Intranasal administration of corticosteroids has also been implicated [4]. It was not possible to determine whether the patient described here had received these in the past.

The mortality of immunocompromised patients with cerebral aspergillosis is 99% [5]. In contrast, the mortality of cerebral aspergillosis in apparently normal hosts, where the sinus disease is the epicentre, is c. 13–50% [5]. Most clinicians would favour a combined surgical–medical approach in patients with sinus–cerebral aspergillosis, as survival is extremely rare with medical treatment alone. In a recent literature review of patients who had survived CNS aspergillosis there were only two patients without underlying disease with primary sinus site who had medical treatment (conventional amphotericin B with or without 5FC) alone [6]. Surgical excision in the patient described in this report carried a substantially high risk of mortality and morbidity as the lesions were large, noncapsulated and multifocal and their resection would have resulted in serious and permanent neurological sequelae. This patient received non-surgical multimodality medical therapy, with an excellent response.

LAB was selected as the initial key systemic antifungal agent. The radiological evidence of the absence of capsule around the fungal mass suggested that LAB might penetrate the brain tissue favourably. Rapidly progressive fungal disease occurred which was interpreted as due to sub-therapeutic concentrations of drug at the site of the fungus. Dose escalation to 10 mg/kg/day was based on anecdotal reports of successes in treating cerebral aspergillosis with very high doses of LAB [6]. However, disease progression can still occur despite LAB doses of up to 15 mg/kg/day [6].

GMCSF was given concomitantly with LAB; it is known to enhance neutrophil, monocyte and macrophage antifungal activities *in vivo* [7]. This translates into clinical benefit [7] and was probably useful in this patient. Surprisingly, there was clinical and radiological deterioration of progressive sight-threatening fungal disease. The further addition of recombinant γ-IFN appeared to halt and improve the cause of the disease, as shown by a temporal relation between its introduction and rapid improvement in vision and MRI appearances. γ-IFN improves the antifungal properties of polymorphonuclear cells and of helper T cells by tilting their activities towards a Th1 response and inducing neutrophil-mediated fungal lyphal damage [7]. Furthermore, mononuclear cells play a major role in host defence against *Aspergillus* in the neutropenic patient, possibly through the activity of tumour necrosis factor and macrophage inflammatory protein 1α [8]. It is foreseeable, although not proven, that these activities were enhanced by treatment of the patient described here with γ-IFN.

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**Fig. 3.** MRI series of patient during and after combination anti-fungal immunomodulatory treatment. (a) Day 11 of treatment: SE T1 post-contrast, fat suppressed shows new appearance of optic nerves infiltration by fungus, with ill-defined margins of the nerves. (b) Day 40 of treatment with additional cytokine treatment: axial SE T1-weighted post-contrast shows clearing of optic nerve infiltration and reduction of disease in sinuses and orbits. (c) Day 56 of combination treatment: Coronal SE T1-weighted post-gadolinium shows extensive reduction of disease throughout. (d) Day 100 of combination therapy: Axial fast-spin echo T2-weighted shows gross reduction of frontal lobe vasogenic oedema. (e) Day 210 of combination treatment: Coronal SE T1 post-contrast shows extensive reduction of the disease in paranasal sinuses, orbits and frontobase.
However, predisposition to invasive aspergillosis in apparently immunocompetent hosts may be due to qualitative cellular or subcellular immunodeficiency that is either unrecognized or poorly characterized. In patients with invasive aspergillosis who fail to respond to conventional treatment with antifungal drugs, adjunctive treatment with immunomodulators should be considered.

References