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Disseminated zygomycosis with involvement of the central nervous system

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Abstract

Zygomycosis of the central nervous system (CNS) can manifest in three distinct clinical forms, as rhinocerebral zygomycosis, as disseminated zygomycosis with CNS involvement, and as isolated cerebral zygomycosis. We present a case of a 2-year-old boy with leukaemia and disseminated zygomycosis, caused by *Absidia corymbifera*, involving the brain, spinal cord, lung and liver. The child received treatment with liposomal amphotericin B and posaconazole for 6 months. Although the lesions of the lungs and liver resolved, those of the CNS persisted and the child is in a vegetative state. A review of the literature after 2004 identified ten additional cases of disseminated zygomycosis with cerebral involvement, all but one of which had concurrent lung infection. The most common underlying disease in these cases was haematological malignancy and the mortality rate was 70%. Disseminated zygomycosis with cerebral involvement is a fatal disease. Early recognition and prompt intervention with combined medical and surgical treatment may improve the outcome.

Keywords: Amphotericin B, CNS, disseminated, posaconazole, spine, zygomycosis

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Introduction

Zygomycosis is an invasive, life-threatening fungal infection that mainly affects immunocompromised hosts. Zygomycetes can invade virtually any tissue or organ, resulting in a variety of clinical presentations. The central nervous system (CNS) can be invaded by Zygomycetes either contiguously from adjacent paranasal sinuses, or haematogenously from a remote site of infection. Zygomycosis of the CNS can present in three distinct clinical forms, as rhinocerebral zygomycosis, as disseminated zygomycosis with CNS involvement, and as isolated cerebral zygomycosis. Rhinocerebral zygomycosis is the most frequent form of CNS zygomycosis and has been well described in the literature [1], whereas disseminated zygomycosis with brain involvement and isolated cerebral zygomycosis are rarer forms of the disease. In this report, we present a boy with acute myeloid leukaemia and disseminated zygomycosis with involvement of the CNS and we review the relevant literature.

Illustrative Case Report

A 2-year-old boy was admitted to hospital because of acute myeloid leukaemia. Two days after admission, he received induction chemotherapy with cytosine-arabinoside, thioguanine and idarubicin. Two weeks later, while on antimicrobial treatment for a febrile episode, his fever recurred and his leukocyte count was 310 cells/μL. The antimicrobial regimen was changed to meropenem and teicoplanin, and liposomal amphotericin B (L-AmB) (5 mg/kg) was added. Over the next 3 days the patient developed multiple focal seizures. Computed tomography (CT) of the brain revealed a ring-enhanced lesion extending into both parietal lobes and the patient was started on corticosteroids and phenytoin (Fig. 1a). Chest CT showed extensive infiltrates in both lungs with bilateral pleural effusion. A CT scan of the abdomen revealed two low density areas in the liver (Fig. 1b). Subsequently, the patient developed status epilepticus and quadriparesis, was intubated and was transferred to the intensive care unit. Direct microscopy of the pleural fluid revealed fungal hyphae. All cultures from blood, pleural fluid, bronchoalveolar lavage and cerebrospinal fluid were negative for bacteria and fungi. Serum galactomannan and polymerase chain reaction (PCR) for *Aspergillus* were negative. A brain

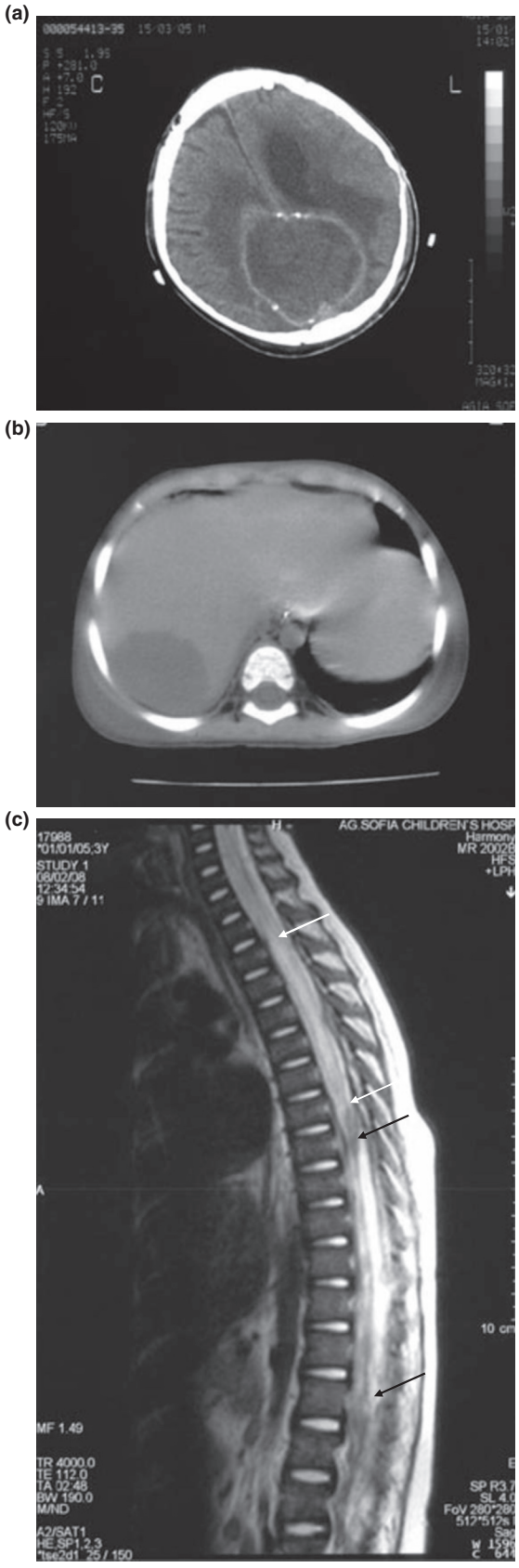

FIG. 1. (a) Computed tomography (CT) scan showing a large, hypodense, interhemispheric mass lesion with ring contrast enhancement compressing both lateral ventricles with extensive surrounding oedema. (b) Abdominal CT scan showing two low density areas, one in the right liver lobe and the other in the border between the right and left lobes. (c) Spine magnetic resonance imaging T2-weighted image showing extensive intramedullary oedema of the thoracic spinal cord (white arrows) and epidural fluid entrapment at the thoracolumbar junction (black arrows).

biopsy revealed fungal hyphae consistent with *Aspergillus*. The child was treated with voriconazole and caspofungin along with intraventricular AmB for 1 month. He remained febrile and his clinical condition was unchanged. Magnetic resonance imaging (MRI) of the brain revealed new lesions and MRI of the spine showed hypodense lesions extending from the cervical to the lumbar spinal cord area (Fig. 1c). In light of these findings, paraffin-embedded brain tissue was re-examined using a semi-nested PCR specific for Zygomycetes and sequencing of the amplicon identified the fungus to be *Absidia corymbifera* [2]. The patient was then treated with posaconazole (25 mg/kg) and L-AmB (7 mg/kg) for 6 months. He defervesced, the lung and liver lesions disappeared, but the brain and spinal cord lesions remained unchanged. Six months after discontinuation of antifungal therapy, the patient is alive but in a vegetative state and his leukaemia is in remission.

Discussion

The case presented here underlines the diagnostic and therapeutic difficulties involved in the management of cerebral fungal infections. The diagnosis of CNS zygomycosis is often difficult because the clinical and radiological findings are non-specific. For a definitive diagnosis, histology and culture are needed. Histological identification of fungus, however, may be incorrect and cultures are positive in <70% of cases [3]. In our patient, the fungus had been misidentified as *Aspergillus* based on hyphal morphology, which resulted in the administration of inappropriate treatment for a month. The correct identification of fungus as *Absidia corymbifera* was made by PCR in paraffin-embedded tissue after conventional means had failed to allow the diagnosis. In addition to the diagnostic difficulties, the management of fungal infections with CNS involvement is problematic as a result of the poor response of the CNS to standard antifungal therapy. With the administration of L-AmB and posaconazole, the lung and liver lesions resolved, whereas those of the CNS remained unchanged.

The CNS can be invaded by Zygomycetes either contiguously from adjacent structures (i.e. the sinuses) or haematogenously from a remote site of infection in the lungs, gastrointestinal tract, skin or other organ. In a recent study analysing all cases of zygomycosis published up to 2004, among 283 patients with CNS involvement, 196 (69%) had rhinocerebral infection, 42 (15%) had disseminated disease with involvement of the brain, and 45 (16%) had isolated cerebral zygomycosis without any other foci of infection [3]. In the same study, patients who had received deferroxamine therapy presented more frequently with generalized disseminated zygomycosis, compared with other host categories. There were no patients with diabetes who had haematogenous dissemination to the brain. Instead, all CNS infections in patients with diabetes occurred in those with rhinocerebral infection. By contrast with rhinocerebral and disseminated zygomycosis, isolated cerebral zygomycosis was found mainly in immunocompetent patients who were abusing drugs intravenously [3].

In a review of the English literature since 2004, we identified ten additional cases of disseminated zygomycosis with cerebral involvement (Table 1). Of these ten patients and the case presented here, ten had concurrent lung infection (90%). The most common underlying disease was haematological malignancy (64%). A total of 63% of the patients had positive cultures: five yielded *Rhizopus* spp., one *Rhizomucor* spp., one *Cunninghamella bertholletiae*, and in the patient presented here the fungus species was identified as *Absidia corymbifera* by a Zygomycetes-specific PCR [2].

Zygomycetes rapidly invade the walls of blood vessels, resulting in infarction, haemorrhage or abscess formation. When cerebral zygomycosis occurs in the context of disseminated infection, mainly in immunocompromised patients, the involved areas may be the eye, the optic nerve or the brain parenchyma (including the frontal and temporal lobes). Alternatively, zygomycosis may present as cavernous sinus thrombosis. In addition, zygomycotic lesions may be found in the spinal cord as a result of acute or subacute infarction. Various patterns are seen on MRI, but the central grey matter is usually the most severely affected [4]. The infarction is more common in the thoracolumbar junction, especially in the conus medullaris, because the collateral supply to the anterior spinal artery is relatively sparse in this region. Infarction of the cervical segment is rare because of the abundant blood supply by radicular arterioles of this area [4]. By contrast, most cases of isolated cerebral zygomycosis are localized at the basal ganglia or the thalamus and the lesions are usually unilateral [5,6].

Treatment of CNS zygomycosis is most successful when a multi-modal approach, using surgery and antifungal medication, is used. The prognosis, however, remains dismal, especially in disseminated infections. In the past, high doses of AmB deoxycholate were the only available option. Lipid formulations of AmB provide a useful alternative in that they allow the administration of higher doses for longer periods of time. The most commonly used antifungal therapy in CNS zygomycosis is L-AmB. Its use is also supported by studies in animals. In a murine model of disseminated zygomycosis, Ibrahim *et al.* [7] showed that high-dose L-AmB (7.5 mg/kg) treatment was more effective than standard AmB or a lower dose of L-AmB (2.5 mg/kg). In a maximum-tolerated dose study of L-AmB, dosages as high as 10 mg/kg per day were

TABLE 1. Case reports of disseminated zygomycosis with central nervous system involvement published after 2004

References	Age, years	Sex	Underlying disease	Organs involved	Fungal species	Treatment	Outcome
Almyroudis *et al.* [11]	45	M	Lung transplantation	Brain, lung, myocardium, kidney, small and large intestine and thyroid gland	Culture negative	Amphotericin B	Death
Horger *et al.* [4]	62	F	Multiple myeloma	Brain, spinal cord, heart, lung	*Rhizopus* sp.	None	Death
	43	M	AML	Lung, ethmoid, sphenoid and maxillary sinus, orbit, brain	*Rhizopus* sp.	AmBisome	Death
Hampson *et al.* [12]	68	M	Diabetes, desferroxamine therapy	Soft tissue, pericarditis, kidney, spleen, brain	*Cunninghamella bertholletiae*	None	Death
Kannan *et al.* [13]	18	M	Allogeneic BMT, GVHD	Brain, lung	*Rhizopus* sp.	Systemic antifungal	Survival
Revankar *et al.* [14]	46	M	Diabetes mellitus	Rhinocerebral, lung	*Rhizopus* sp.	Abelcet, AmBisome	Cure
Vahid *et al.* [15]	32	M	AML	Lung, liver, brain	Unspecified	NA	NA
Singh *et al.* [16]	65	M	Rheumatoid arthritis, anti-TNF (adalimumab)	Lung, brain	NA	Amphotericin B	Death
Uckay *et al.* [17]	40	F	BMT, GVHD, deferroxamine, hyperglycaemia	Lung, heart, brain	*Rhizomucor* sp.	None	Death
	35	M	BMT, GVHD	Rhinocerebral, stomach, intestines, lung	*Rhizopus* sp.	Amphotericin B deoxycholate	Death
Current case	2	M	AML	Lung, liver, brain, spinal cord	*Absidia corymbifera*	AmBisome, posaconazole	Survival, with neurological sequelae

M, male; F, female; AML, acute myelogenous leukaemia; BMT, bone marrow transplantation; GVHD, graft-versus-host disease; NA, not available; TNF, tumour necrosis factor.

suggested as beneficial in CNS fungal infections that do not respond to standard doses [8]. In isolated cerebral zygomycosis there have been reports of treatment with endoscopic debridement and intralesional administration of AmB in conjunction with systemic L-AmB [9]. In recent years, posaconazole has been added to the antifungal armamentarium against zygomycosis, with promising results [10]. The mortality rates of disseminated zygomycosis with cerebral involvement in cases reported before and after 2004 were 98% [2] and 70% [4,11–17], respectively (Table 1).

Conclusions

In conclusion, disseminated zygomycosis with cerebral involvement is a fatal disease. Early recognition and prompt intervention with combined medical and surgical treatment may improve the outcome.

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Transparency Declaration

The authors declare no conflicts of interest.

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