IDCases 2 (2015) 116–117

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case Report

The successful use of amphotericin B followed by oral posaconazole in a rare case of invasive fungal sinusitis caused by co-infection with mucormycosis and aspergillus

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ARTICLE INFO

Article history:
Received 21 August 2015
Received in revised form 30 September 2015
Accepted 1 October 2015

Keywords:
Mucormycosis
Aspergillus
Co-infection
Amphotericin B
Posaconazole

ABSTRACT

We report on an unusual case of oro-rhinocerebral disease caused by mucormycosis and aspergillus co-infection in a 54-year-old insulin dependent diabetic patient. Although she was successfully treated with parenteral amphotericin B followed by oral posaconazole, she was left with irreversible blindness of the right eye and multiple cranial nerve palsies.

Case report

A 54-year-old insulin dependent diabetic female presented to a district hospital, where she was found to be in diabetic ketoacidotic coma (DKA), with peri-orbital cellulitis and neurological impairment. She was stabilized and thereafter transferred to a central tertiary hospital for further management. On arrival at the referral hospital, the ENT surgeons elicited a two-day history of right sided facial and eye swelling, associated with progressively decreasing vision of the right eye. The patient was HIV negative and had no other medical or surgical history of note besides diabetes mellitus.

On physical examination, she was found to be well orientated with a Glascow coma scale of 15/15, blood pressure of 102/52 mm/Hg, a pulse rate of 112 and a respiratory rate of 15. She was noted to have an extensive right sided periorbital cellulitis with marked proptosis of the right eye. Opthalmological examination of the right eye, revealed opthalmoplegia (frozen eye) with mild chemosis, a clear cornea and lens, with the presence of a pale optic disc. The patient was assessed as having irreversible blindness of the right eye secondary to optic atrophy. On neurological examination, she was found to have multiple cranial nerve palsies, involving cranial nerves 4, 5, 6, 7, 8 and 9. The rest of the examination was unremarkable. Routine laboratory investigations revealed a glucose level of 12.5 mmol/l with 1+ ketones present on urine dipstick testing. The C reactive protein was raised to 38, whilst the full blood count, urea and electrolytes, and liver function tests were all within normal ranges. The patient was commenced on intravenous amoxicillin/clavulanate.

An urgent computerized tomography (CT) scan of the paranasal sinuses showed partial opacification of the right maxillary, bilateral ethmoid and right sphenoid sinuses, with a possible filling defect of the right cavernous sinus. In view of these findings, a diagnosis of invasive fungal sinusitis was made.

The patient was booked for an emergency endoscopic antrostomy for debridement of the necrotic tissue, as well as an external fronto-ethmoidectomy (EFE). Intra-operative findings revealed extensive right sided intra-nasal necrotic tissue requiring autoethmoidectomy. The inferior and middle turbinates were extensively destructed. Although the mucosa of the superior turbinate had a dusky appearance, it remained intact. The normal anatomy of the sphenoid sinus was distorted and there was difficulty accessing the ostium. Antrostomy of the right maxillary sinus revealed a large defect in the wall caused by the disease process. The maxillary sinus itself, was clear. EFE revealed that the

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http://dx.doi.org/10.1016/j.idcr.2015.10.001

frontal sinus was clear with no evidence of pus or mucosal damage. In light of these intra operative findings, the patient was commenced empirically on intravenous amphotericin B.

The patient was clinically stable post operatively. However, on consultation with the neurologist, a CT scan of the brain was ordered to exclude a possible infarct in the temporal lobe. CT scan findings showed a right medial hypodensity with possible early cerebritis. A magnetic resonance imaging (MRI) of the brain was therefore requested and showed extensive sinus disease involving the orbit with spread to the extra ocular muscles. A non enhancing hypo-density of the right temporal lobe, representing ischaemia was seen. Changes were in keeping with a right temporal cerebritis or phlegmon formation.

Intra-operative specimens from the right nasal cavity, middle turbinate and maxillary sinus were submitted to the laboratory for histology and microbiological investigation. Microscopy of these specimens revealed broad, aseptate hyphae suggestive of *Zygomycetes* sp. and thin, septate hyphae with dichotomous branching suggestive of *Aspergillus* sp. However *Rhizopus* sp. was the only organism cultured. Histology confirmed invasive co-infection with *Rhizopus* sp. and *Aspergillus* sp.

While in hospital, a repeat endoscopic debridement of the nasal cavity was performed a week later. Intra-operative findings revealed extensive bony and tissue necrosis of the septum, lamina papyracae and maxillary sinus. All necrotic and non-viable tissue was debrided and biopsies were taken from the septum and inferior turbinate. Microbiology and histology of intra operative specimens were negative for both *Rhizopus* sp. and *Aspergillus* sp.

2 weeks later, a repeat debridement of the right nasal cavity was performed. Intra operative findings included crusts involving the right nasal cavity and maxillary sinus with an anterior septal perforation. Crusts were removed and the nasal cavity flushed and suctioned. Once again, specimens received at the laboratory did not reveal any fungi on microscopy and culture. Histology indicated no active disease, with only chronic inflammatory changes seen.

The patient remained clinically stable and the CT prior to discharge revealed residual disease in right nasal cavity and sphenoid. A naso-endoscopy was performed which revealed right sided crusting due to possible inadequate douching. A mucosal tissue biopsy was negative on microscopy and culture.

The patient completed 4 weeks of amphotericin B and was thereafter discharged on oral posaconazole 200 mg three times daily. On follow up 6 weeks later, the irreversible blindness in the right eye as well as cranial nerve palsies were still present. She was otherwise disease free.

Acute invasive fungal sinusitis is an aggressive disease seen particularly in immunocompromised individuals with neutropenia, HIV and diabetes mellitus. Mortality rates remains very high, especially if the diagnosis and appropriate management is not timely instituted. Etiological agents responsible for invasive fungal sinusitis include *Aspergillus* spp.; that are more commonly seen in patients with neutropenia; and Zygomycetes (*Rhizopus* spp., *Mucor* spp., *Absidia* spp.) that are more commonly seen in diabetic patients, particularly in the setting of DKA as was seen in this patient [1]. Invasive fungal infections of the oro-rhinocerebral area, due to mixed mucormycosis and aspergillosis infections have rarely been reported [2–6].

The disease is acquired by inhalation of fungal spores into the nasal cavity with subsequent invasion of the sinus mucosa. Fever, headache and nasal congestion, accompanied by facial pain and swelling are the earliest symptoms reported. Disease thereafter rapidly progresses with extensive involvement of the cavernous sinus, orbit or intracranial compartment. Subsequently, periorbital cellulitis, restriction of ocular movements, ptosis, proptosis and visual deterioration due to occlusion of the central retinal artery may follow, which is highlighted in this case report [1,7].

Diagnosis is currently dependent on microscopy and culture as well as histological examination of specimens [1,7]. However, microscopic identification of fungal species is highly dependent on the quantity and quality of hyphae present. Identification of mixed fungal infections is even more challenging, as illustrated in this case, wherein, the mixed infection resulted in only the *Rhizopus* sp. being cultured. This was attributed to the rapid growth of *Rhizopus*, which hindered the growth of *Aspergillus* sp. This illustrates the important role that initial direct microscopy plays in making the diagnosis of mixed fungal infections. The introduction of molecular techniques that use broad-range PCR amplification and reverse line blot hybridization (PCR/RLB) also allow for the detection and differentiation of mixed fungal infections. Although these molecular methods have the advantage of providing a rapid diagnosis; they are not freely available in low resource countries.

In the diagnosis of invasive sinusitis, CT is sensitive for the detection of changes in the ostium; however MRI remains superior for the evaluation of intracranial and intraorbital extension [8]. These investigations were an integral part of the management in this patient.

A combination of early surgical intervention, appropriate antifungal therapy and the correction of underlying causes such as metabolic acidosis improves prognosis. In addition, serial endoscopic debridements have been shown to improve cure rates, as was illustrated in this patient.

Limited data is available on the management of fungal co-infections. Amphotericin B remains the drug of choice for these infections [9]. A disadvantage is that it can only be administered parenterally and is also potentially nephrotoxic. Posaconozole is the only triazole with activity against both *Rhizopus* sp. and *Aspergillus* sp. [10]. Its availability in oral formulations has facilitated the outpatient management of patients with severe fungal disease.

This case highlights the importance of close liaison between clinicians and the laboratory in the management of rare and complicated infections.

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