

## Rhinoorbital and pulmonary zygomycosis post pulmonary aspergilloma in a patient with chronic lymphocytic leukaemia

Andrew Barr<sup>1</sup>, Marianne Nolan<sup>2</sup>, William Grant<sup>3</sup>, Christine Costello<sup>1</sup>, Michael A. Petrou<sup>2</sup>

<sup>1</sup> Department of Haematology, Chelsea and Westminster Hospital, London, UK, <sup>2</sup> Mycology Department of Microbiology, Hammersmith Hospital, London, UK; <sup>3</sup> Department of ENT, Charing Cross Hospital, London, UK

**Abstract.** A patient with an 18-year history of chronic lymphocytic leukaemia developed zygomycosis of the orbit, sinuses and nasal bones together with pulmonary fungal nodes due to *Absidia corymbifera* while on high dose steroids and four months after successful treatment of pulmonary aspergilloma with liposomal amphotericin B followed by oral voriconazole. He was treated successfully with extensive surgical debridement, intravenous liposomal amphotericin B and intravenous itraconazole. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Chronic lymphocytic leukaemia, immunosuppression, pulmonary Aspergilloma, rhinoorbital and pulmonary zygomycosis

### Introduction

The term zygomycosis is used to refer to uncommon but frequently fatal infections caused by fungi belonging to the order *Mucorales* that includes *Absidia corymbifera*, *Apoophysomyces elegans*, *Cunninghamella bertholletiae*, *Mucor* species, *Rhizopus* species, *Rhizomucor pusillus* and *Saksenaea vasiformis*. These ubiquitous, mainly thermotolerant moulds can be found in soil and decomposing organic matter, such as fruit, bread and cereals. Their spores become airborne easily entering the respiratory system via inhalation, where they are deposited in the nasal passageways and may subsequently reach the pulmonary alveoli. After germination of the spores the resulting hyphae proliferate and as the *Mucorales* have a particular predilection for blood vessels, angioinvasive disease is common, often leading to thrombosis and infarction of surrounding tissue. The type, extent and severity of the disease depend on the host defences and different risk factors.

The risk factors for developing Zygomycosis include uncontrolled diabetes mellitus, ketoacidosis,

burn wounds, haematological malignancies (particularly during neutropenia), corticosteroid therapy, desferrioxamine therapy for iron or aluminium overload and receipt of solid or haematopoietic stem cell transplant (HSCT) (1). Rhinocerebral is the most devastating infection and mainly occurs in patients with diabetes who have ketoacidosis whereas patients with haematological malignancies tend to have pulmonary infection that may become disseminated with multi organ involvement (2).

Prophylaxis in patients with haematological malignancies, particularly for allogeneic haematopoietic stem cell transplant (HSCT) to prevent invasive fungal infections, is mainly directed against *Aspergillus* species. Over the last two years a number of institutions have switched prophylactic agent from fluconazole or itraconazole to voriconazole as the latter has been shown to have an excellent activity not only against *Aspergillus* species and *Candida* species but also *Fusarium* species and *Scedosporium apiospermum*. However, despite its broad spectrum of activity, voriconazole has no activity against the *Zygomycetes* thus many reports since indicate a sharp increase in Zy-

gomycosis as a direct result of treatment or prophylaxis with voriconazole (3). We report a case of invasive Zygomycosis in a patient who after the completion of a two week treatment with liposomal amphotericin B for a pulmonary aspergilloma due to *Aspergillus fumigatus* was converted to a 4 week course of oral voriconazole followed by high doses of methylprednisolone.

### Case report

A fifty-nine year old welder was diagnosed with chronic lymphocytic leukaemia (CLL) in 1986 and received several courses of chlorambucil and prednisolone at diagnosis and again in 1990. He remained well without treatment until November 1999 when he became anaemic (haemoglobin 8.2 g/dL, direct antiglobulin test negative) and thrombocytopenic (platelets  $73 \times 10^9/L$ ) with the bone marrow showing extensive diffuse and interstitial infiltration with CLL cells. The peripheral blood lymphocyte count was  $13.2 \times 10^9/L$ , neutrophils  $1.7 \times 10^9/L$ , monocytes  $0.8 \times 10^9/L$ , a few small lymph nodes were palpated in the neck and there was no splenomegaly.

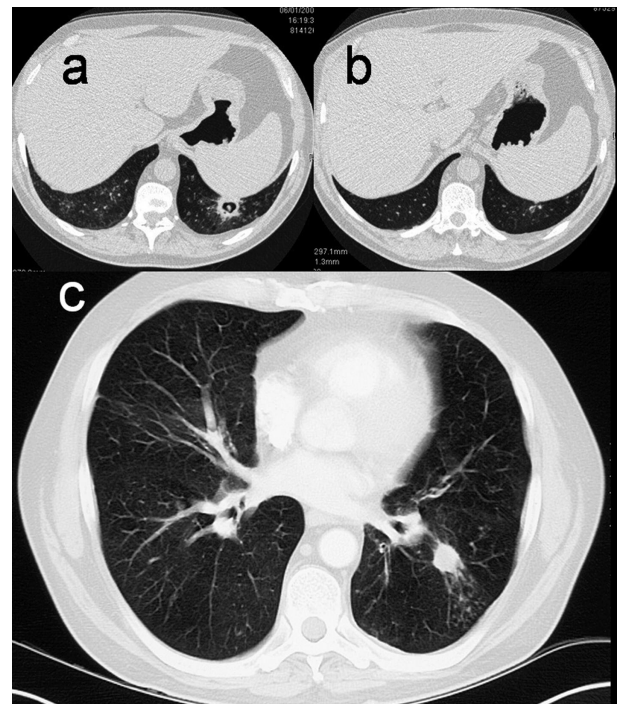
The patient received six courses of fludarabine between 1999 and 2000 after which he entered a good nodular partial remission with a normal blood count. He remained well apart from recurrent chest infections related to bronchiectasis and he received three weekly infusions of intravenous immunoglobulin since the IgG level was below normal and both IgA and IgM levels were reduced.

In November 2003, three years after receiving the fludarabine, there was evidence of relapse with increasing pancytopenia and a densely infiltrated marrow. Treatment was not initially started due to the patients wish to travel to Thailand. However he was repatriated in January 2004 when he developed fever, haemoptysis and headache. A CT chest identified diffuse nodular shadowing in both lungs and a cavitating lesion (Figure 1a). A bronchoalveolar lavage grew *Aspergillus fumigatus*. His pulmonary aspergilloma was treated successfully with a two week course of intravenous liposomal amphotericin B and he was converted, on 14/01/2004, to oral voriconazole for 4 weeks. A

CT scan of the head and sinuses revealed a little fluid within the frontal sinuses but was otherwise unremarkable. A CT chest on 25/03/2004 showed resolution of the nodes and cavitating lesion (Figure 1b).

At the end of March 2004 he developed a cough, shortness of breath and fever and he was found to be neutropenic ( $0.26 \times 10^9/L$ ). He was admitted on 01/04/2004 and treated appropriately for neutropenic sepsis associated with a lower respiratory tract infection. He was also commenced on oral itraconazole 200mg capsules OD dose and maintained on it thereafter as prophylaxis.

A relapse of his CLL was noted on 21/04/2004 but a four-week course of prednisolone 60 mg daily failed to improve the cytopenias. He was admitted to hospital on 24/5/04 for a five-day course of methylprednisolone with the intention to introduce fludarabine when the peripheral blood count permitted. Antibacterial prophylaxis was introduced along with the ongoing itraconazole, now changed to oral solution



**Figure 1.** a) CT chest identifying the cavitating lesion of a pulmonary aspergilloma. b) CT chest confirming resolution of lesion following liposomal amphotericin B and voriconazole. c) CT chest identifying a lesion that was later confirmed as pulmonary zygomycosis

and at a higher dose of 200mg twice daily for better bioavailability (4). A fortnight before admission a neutropenia ( $0.3 \times 10^9/l$ ) and monocytopenia ( $0.1 \times 10^9/l$ ) had been noted. The patient had been started on daily granulocyte colony stimulating factor (G-CSF) in view of right cheek ulceration. This was continued on admission in view of ongoing neutropenia ( $0.5 \times 10^9/l$ ). His neutrophil count continued to improve but his monocytopenia persisted ( $0.1 \times 10^9/l$ ) during his admission.

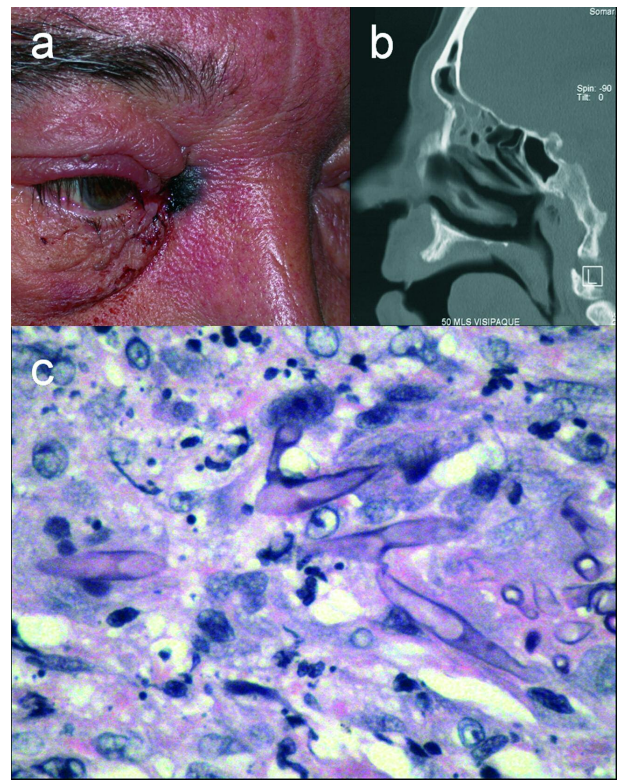
Towards the end of the course of methylprednisolone, on 27/5/2004, he developed a right sided headache and tender swelling superior and medial to the right orbit. Bilateral peri-orbital oedema was noted and he developed a 1 cm black patch of skin medial to the right medial canthus, raising suspicions of zygomycosis (Figure 2a).

A CT sinus scan showed normal orbital bones, opacification of the ethmoidal and frontal sinuses (Figure 2b) with no evidence of bony destruction or of an orbital or retro-orbital abscess.

Empirical therapy with tazocin and metronidazole was commenced and a radical endoscopic ethmoidectomy debridement carried out with biopsy of the right medial canthal skin lesion. Fungal hyphae were seen macroscopically in the right nasal cavity and confirmed histologically (Figure 2c). Tissues from the bilateral anterior ethmoid and frontal sinuses were cultured for bacteria and fungi. Cultures of the tissue taken on 03/06/2004 grew *Absidia corymbifera*. MIC testing was performed according to CLSI guidelines with minor modifications (5). Extremely low MICs were found for Amphotericin B and Itraconazole, 0.03 and 0.01  $\mu\text{g/mL}$  respectively and very high to Fluconazole, Voriconazole and 5-Flucytosine MICs  $>64$ ,  $>8$  and  $>32 \mu\text{g/mL}$  respectively.

Caspofungin did not exhibit any activity against this isolate, including at the maximum concentration of 8  $\mu\text{g/mL}$  tested.

Treatment with intravenous liposomal amphotericin (AmBisome, 5 mg/kg/day) was commenced with good initial response however the patient then deteriorated with worsening peri-orbital oedema and discharge from both eyes. CT scan of the brain showed no evidence of intracranial extension. Aggressive excision of all involved tissues in the mid face was carried



**Figure 2.** Right medial canthal skin lesion suggestive of zygomycosis. Opacification of ethmoidal and frontal sinuses. Broad non-septated hyphae seen on the biopsy from the medial canthus was indicative of *Zygomycetes*. The culture grew *Absidia corymbifera*. The lung biopsy had a similar appearance and biopsy culture also grew *Absidia corymbifera*

out – skin was excised from both medial canthi, on the right side this included the lacrimal sac and superior and inferior lacrimal canaliculi, underlying necrotic bone including most of the nasal bone, the ascending process of the maxilla and part of the frontal bone, the anterior lamina papyracea or the medial orbital wall, the superior nasal septum, the frontal intersinus septum and the anterior skull base was also removed. A small cerebrospinal leak was grafted during the surgical procedure. A mid line 1 cm of bone and a strip of median skin remained with soft tissue and bone removal completed back as far as healthy, normal bleeding tissue. The orbital periosteum was thickened and inflamed but did not appear necrotic and was not resected. The wound was left unreconstructed and lightly packed.

A few days later the patient developed haemoptysis. A CT chest scan showed multiple parenchymal no-

dules within both lung fields, some with adjacent tree-in-bud sign and some showing possible early cavitation (Figure 1c). In view of the very low MICs to itraconazole found for *A. corymbifera* and its excellent activity against *Aspergillus* species, intravenous itraconazole 5 mg/kg/day was added and a CT biopsy of the lung nodule carried out. Histology showed fungal hyphae consistent with *Zygomycetes* (as seen in Figure 2c) and culture identified *A. corymbifera*.

The patient was continued on intravenous itraconazole for two weeks and intravenous liposomal amphotericin for a total of eleven weeks following which biopsies of the sinus regions were culture and histology negative. Prophylaxis with oral solution itraconazole 200 mg twice daily was continued and facial reconstruction surgery was planned. The CLL has remained relatively stable and he currently has a normal full blood count and liver function test. G-CSF has been continued and treatment options will be re-examined once the reconstructive process is complete.

## Discussion

Despite the abundance of *Zygomycetes* in nature, the infrequency of disease caused by these organisms, standing at 1.7 cases per million population in the United States (6) confirms their low virulence in normal human host.

Zygomycosis is the third most common invasive fungal infection (after candidiasis and aspergillosis) and accounts for 8.3-13% of all fungal infections discovered at post mortem in haematology patients (7).

An increase in zygomycosis from 8 to 20 per 100,000 admissions between 1989-1993 and 1994-1998 was noted, however in HSCT patients the rate was 10/4020 equivalent to 0.25% (8). Three separate publications reported rates of 8.9%, 3.2% and 4.3% in HSCT patients and all attributed the sharp rise in voriconazole use that became available in late 2002 (9-11).

A high index of clinical suspicion is required for early diagnosis and better prognosis. The clinical manifestations of zygomycosis are dependent on the anatomical site involved. The first sinister manifestation in our patient was the black patch of skin medial to

the right canthus (Figure 2a). This suggested rhinocerebral disease which typically presents with unilateral headache, fever, nasal congestion, nasal discharge and variable orbital cellulitis – most of these were evident in our patient. The development of a black eschar on the nasal mucosa or palate, which is a classical sign, was not present in our patient.

Further manifestations of disease progression include loss of vision, ophthalmoplegia, proptosis, ptosis and ultimately cavernous sinus and/or carotid artery thrombosis. The Mucorales may extend through the ethmoid or sphenoid sinuses to invade the retro-orbital region and then the frontal cerebral lobes. Mucosal thickening may be evident on an early CT scan, and the diagnosis must be suspected in the presence of the appropriate risk factors. Indicators of poor prognosis include delay in treatment (>6 days), symptoms of intracranial involvement such as hemiplegia or hemiparesis, bilateral sinus involvement, palate involvement, orbital involvement and underlying leukaemia (12). Rhinocerebral zygomycosis can be subdivided into three subtypes: rhinomaxillary, rhinoorbital (as in our patient) and rhinoorbitocerebral (13) and if not treated aggressively the condition is invariably fatal.

Pulmonary zygomycosis is the second most common site for infection after rhinocerebral. The clinical presentation is indistinguishable from that of invasive pulmonary aspergillosis (14). Cough, fever, haemoptysis (as in our patient) and pleuritic chest pain are the usual symptoms. It can be clearly seen in Figure 1a and 1c that pulmonary zygomycosis has a similar radiographic appearance to aspergillosis and may be difficult to differentiate without histology and or culture. Therefore in the absence of histology and or culture, the choice of antifungal agent must be guided by its spectrum of activity and ought to be active not only against *Aspergillus* species but the *Zygomycetes* as well. Furthermore in patients who relapse soon after successful treatment for *Aspergillus* species infections full investigation of fungal infection by other filamentous fungi is warranted and CT imaging must be used to confirm fungal infection and not the fungus causing the infection.

Definitive diagnosis of zygomycosis is dependent on demonstration of the organism in debrided tissue or biopsy. Fungal hyphae may be seen on routine hi-

stological stains. It is extremely important to culture as the identity of the organism will aid treatment and this is better done when small fragments of tissue "minced meat" rather than ground tissue is used as the unsegmented hyphae will be damaged. Early diagnosis is paramount to any chance of successful treatment as mortality rates of 60-100% have been reported in haematology patients with focal pulmonary disease (3, 15).

Effective treatment includes prompt instigation of an antifungal, reversal of underlying immunosuppression, where possible, and most importantly aggressive surgical debridement (16). Our patient promptly received intravenous liposomal amphotericin on the same day that fungal hyphae were seen at endoscopy and intravenous itraconazole was subsequently added in view of the sensitivities. Though itraconazole does show activity against some *Zygomycetes* in vitro, the new antifungal agent posaconazole has a wealth of evidence supporting its use in zygomycosis (17) and may be the drug of choice in patients who cannot tolerate amphotericin B for such infections. The other new agents, voriconazole and the echinocandins, such as caspofungin have no activity against *Zygomycetes* and their use as monotherapy must be avoided when Zygomycosis is suspected. Concomitant use of granulocyte colony-stimulating factor (G-CSF) may have contributed to the rapid recovery and clearance of the fungus as G-CSF increases the number of mature circulating polymorphonuclear leucocytes as well as enhancing phagocytic activity and oxidative burst responses to opportunistic fungal pathogens (18, 19).

This is the first case of zygomycosis in our haematology patients in the last 15-20 years and the reason for the low incidence might be the absence of the fungus in the patients' environment or the fact that we have been using itraconazole prophylaxis. Given the increase in zygomycosis in centres where voriconazole was used, itraconazole prophylaxis seems to be the most likely reason for the low incidence of zygomycosis in our patients. This case also indicates the need for prophylaxis post-fungal infection as the patient acquired a second infection just eight weeks after resolution of the pulmonary Aspergilloma. Liposomal amphotericin B has been used in prophylaxis (20) whereas the

introduction of the new triazole posaconazole, a similar molecule to itraconazole, which has shown excellent activity against the *Zygomycetes* and was recently licensed in the UK, might prove to be the ideal prophylactic agent in patients unable to attend the clinic or to tolerate liposomal amphotericin B (21). The duration of prophylaxis however is debatable, from six months to the time of full recovery of the underlying disease.

In conclusion we present a case of rhinocerebral and pulmonary zygomycosis in a man with an 18 year history of CLL treated previously with chlorambucil, prednisolone and fludarabine and recently with high doses of methylprednisolone. He was treated successfully with extensive surgical debridement along with intravenous liposomal amphotericin, intravenous itraconazole and granulocyte colony-stimulating factor. The immunosuppressive treatment for his CLL may have precipitated a recurrence of his fungal infections. One year later, our patient is well with normal full blood count, no evidence of recurrence of any fungal infection and he is now undergoing facial reconstruction.

## Acknowledgements

Dr. Anne Sandison and Dr. Ian Clarke of the Department of Histopathology Charing Cross Hospital for biopsy images.

Dr. Mark Pasteur of Norfolk and Norwich University Hospital for the CT chest images.

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Correspondence: Dr. Michael A. Petrou,  
Department of Medical Mycology,  
Hammersmith Hospital, Du Cane Road,  
London, W12 0HS, United Kingdom.  
Tel. +44 208 383 5820  
Fax +44 208 3835824  
E-mail: m.petrou@imperial.ac.uk  
www.actabiomedica.it