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Skull base osteitis following fungal sinusitis

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Abstract

Aspergillus sp. sinusitis is not uncommon in immunocompromised patients but is unusual in patients who are not immunocompromised. The disease may occur as a saprophytic condition, as an allergic sinusitis or as a potentially lethal invasive disease. The differentiation between non-invasive and invasive *Aspergillus* sp. sinusitis is crucial and this distinction is fully discussed. The treatment options are also considered. Invasive disease requires aggressive treatment with long-term antifungal agents in sufficient doses combined with wide surgical excision.

We present a patient who presented with invasive *Aspergillus fumigatus* sinusitis and subsequently developed cranial neuropathies and skull base osteitis. She was initially treated with oral itraconazole (400 mg daily) for 18 months but due to lack of response this was changed to a new experimental oral azole (voriconazole) which was continued for a further 14 months. She has since remained well for the last five years.

Key words: Fungal sinusitis; *Aspergillus.*

Introduction

Aspergillus is a fungus which is ubiquitous throughout the environment being found in soil and organic debris. Since the spores are airborne the main portal of entry is via the respiratory tract and the fungus can often be cultured from the mouth and the sputum of asymptomatic subjects.

However, fungal sinusitis is uncommon unless the host is immunocompromised. Patients with diabetes, leukaemia and lymphoma are particularly at risk and may become infected with a range of fungi such as *Aspergillus, Candida* and the mucorales (Ericcson *et al.*, 1993; Ishida *et al.*, 1993; Morrison and McGlave, 1993). Infections in this group of patients can lead a fulminant course and may be life-threatening (McGill *et al.*, 1980).

Aspergillus infections are usually due to one of four species: *A. fumigatus*, *A. niger*, *A. flavus* and *A. terreus.* Infections are classified as either being non-invasive or invasive depending on the presence of tissue destruction. Thus, *Aspergillus* may act as a saprophyte and form a fungus ball or be associated with sinusitis without invasion of mucosa or bone. This non-invasive condition is usually seen in a normal host and only progresses to an invasive form on rare occasions. It is sometimes associated with dental work to the upper molars (Stammberger, 1991). Invasive disease may be acute (or fulminant) or chronic and when acute carries a mortality of 66 per cent despite therapy (Denning, 1996). Acute invasive *Aspergillus* rhinosinusitis occurs in immunocompromised patients, particularly leukaemic and bone marrow transplant patients, whereas chronic invasive *Aspergillus* sinusitis occurs in normal or mildly immunocompromised patients. The incidence of invasive disease is increasing due to increasing immunosuppression and there are probably more than 600 new cases per year throughout the UK, although this figure includes pulmonary disease as well (Wilson and Denning, 1993).

The commonest species to cause sinusitis in the UK is *Aspergillus fumigatus* but, interestingly, in the Sudan, *Aspergillus flavus* has been reported to be the most common cause of fungal sinusitis. The hot dry, dusty atmosphere of the Sudan is thought to be an important aetiological cause. There is an associated granulomatous pathology and orbital invasion has occurred in about 60 per cent of such patients (Veress *et al.*, 1973).

Skull base osteitis is a rare but potentially lethal disease which may complicate invasive fungal sinusitis. The other potential route of entry of infection is via the temporal bone secondary to ear disease (Farrior, 1989). However, the latter is usually due to a *Pseudomonas* otitis externa. The principles of treatment are similar for the two conditions and both require early diagnosis, long-term chemotherapeutic agents and adequate surgical debridement for effective control.

Fungal sinusitis is being increasingly recognized in non-immunocompromised patients. We report details of chronic invasive disease in a patient in whom temporary cranial nerve palsies were observed. She subsequently developed skull base disease for which she received antifungal treatment for 32 months. This included treatment with a new oral azole (voriconazole) on a trial basis.

Case report

A 37-year-old lady initially presented with nasal obstruction and a polypoid mass in the left side of her nose. She had a history of having a blow to the left side of her face 20 months previously and complained of having had headaches, purulent rhinorrhoea and nasal obstruction since. She also had acne rosacea and had had several long-term courses of antibiotics for this over a five-year period.

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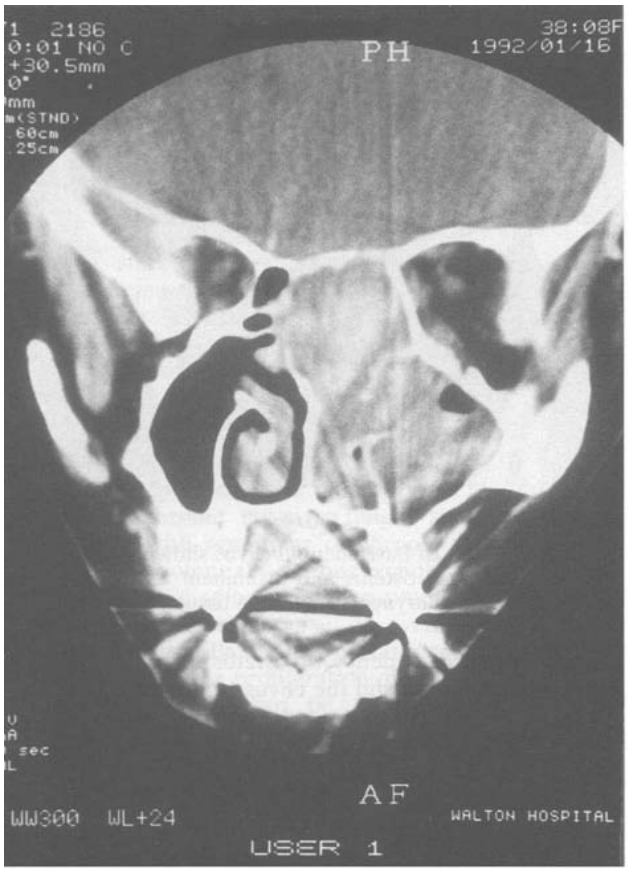

FIG. 1a

Coronal CT scan showing opacity of left ethmoid, maxillary antrum and sphenoid sinus. Note the characteristic bone-dense opacities of fungal sinusitis.

A plain sinus X-ray showed an opaque left maxillary antrum but no evidence of bone destruction. She subsequently underwent an antral washout and faeculent pus was removed from the left maxillary antrum. Ethmoidal polyps were also removed and faeculent material was present in a large ethmoidal cavity. The left orbit was swollen following this procedure and she was treated with intravenous cefuroxime and metronidazole. The histology reported inflammatory nasal polyps and the culture grew *Proteus* spp. and *Aspergillus fumigatus*. She was reviewed one month later and at that time her symptoms were minimal and anterior rhinoscopy was normal. A steroid nasal spray was prescribed and she was subsequently discharged.

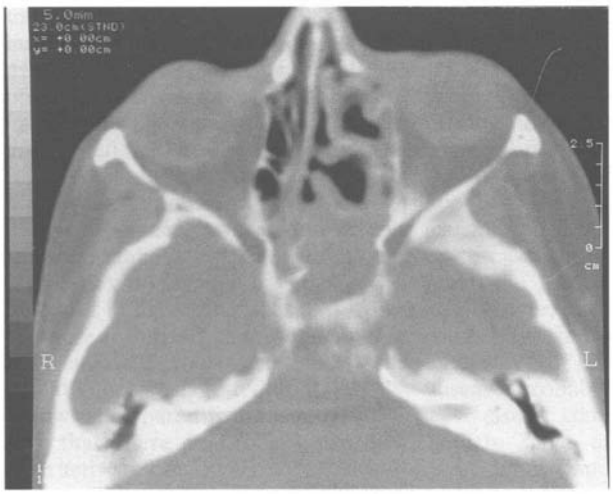

FIG. 1b

Axial CT showing an opaque sphenoid sinus. Note asymmetrical sphenoid septum on the right side.

However, she presented four months later with diplopia, blurring, headaches and loss of appetite. The diplopia was due to 'tethering' of the left medial rectus muscle. A computed tomography (CT) scan (coronal and axial) showed complete opacity of the left ethmoid, maxillary antrum and sphenoid sinus (Figures 1a and b). Sinus endoscopy showed a severe inflammatory polypoid reaction in the ethmoid sinus with concretions in the frontal recess. A large inferior meatal antrostomy and sphenoidotomy were created and the sinuses were thoroughly cleaned of all debris. The mucosal lining of the sphenoid and maxillary antrum were polypoid and were biopsied. Histology did not show any fungal elements but a culture grew *Aspergillus* spp. and *Proteus* spp. again. She was treated with oral prednisolone and intravenous fluconazole which was changed a few days later to itraconazole (100 mg daily). The itraconazole was discontinued after six weeks but blood levels had unfortunately not been measured.

Her left eye movements recovered but eight days later she developed a right lateral rectus palsy (Figure 2). A repeat CT scan showed that the left sphenoid and maxillary antrum were both still opaque. The sphenoidotomy was enlarged further and cheesy debris was removed from the left maxillary antrum via a sublabial antrostomy. Endoscopic clearance was performed one month later and on this occasion the sinus lining showed mild inflammation only. A blood test for *Aspergillus* precipitins was positive.

Again, she made an apparently good recovery and eye movements returned but three months later she developed pain behind the right ear. Endoscopy of the left paranasal sinuses showed recurrent infection with pus in the sphenoid, thick mucus in the maxillary antrum and concretions in the ethmoid. Cultures grew scanty *Aspergillus* spp. but histology of the polypoid mucosa from the right maxillary antrum did not show fungal elements although it did show granuloma formation. She was treated with cefuroxime, oral prednisolone and itraconazole (100 mg daily) and she continued to take this dose of itraconazole for five months. During this time she presented with paralysis of the right side of the tongue and palatoglossus which recovered spontaneously within a week (Figure 3). A magnetic resonance (MR) scan at the time did not show any intracranial cause for his. Her sphenoiditis slowly recovered but three months later she had paresis of the left side of the tongue for a few days. She also developed bilateral secretory otitis media for which

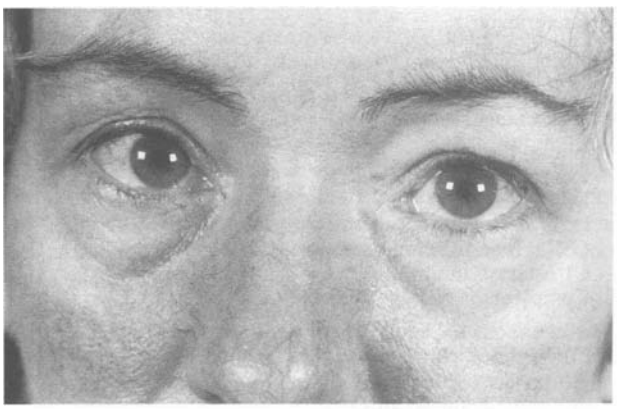

FIG. 2

Diplopia due to right lateral rectus palsy.

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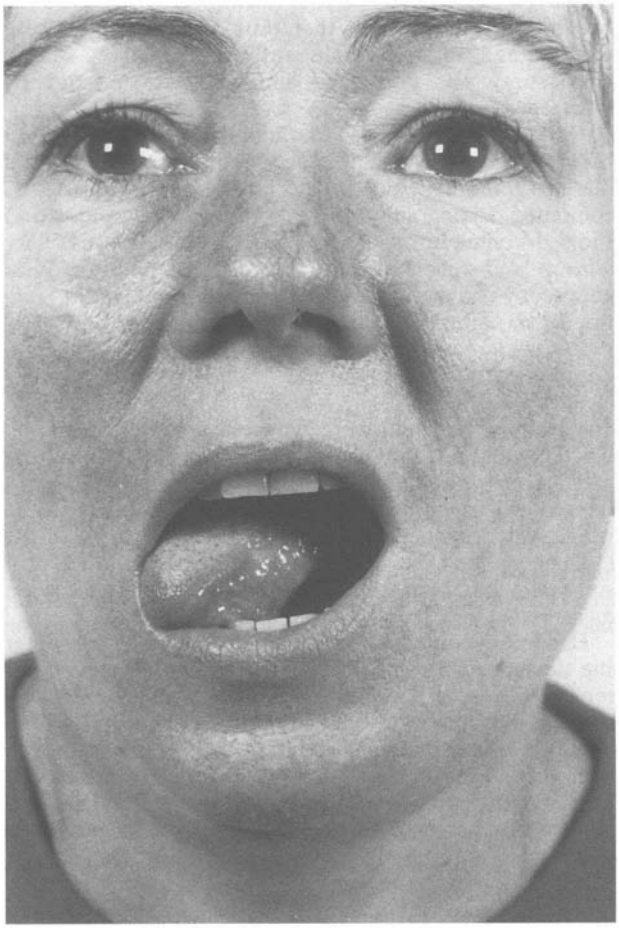

FIG. 3
Right hypoglossal paralysis.

grommets were inserted. The lymphoid tissue in the post-nasal space was persistently prominent on the CT scans but a subsequent biopsy was reported as being normal. However, a bone scan showed increased bone turnover extending from the sphenoid to the basi-occiput and the

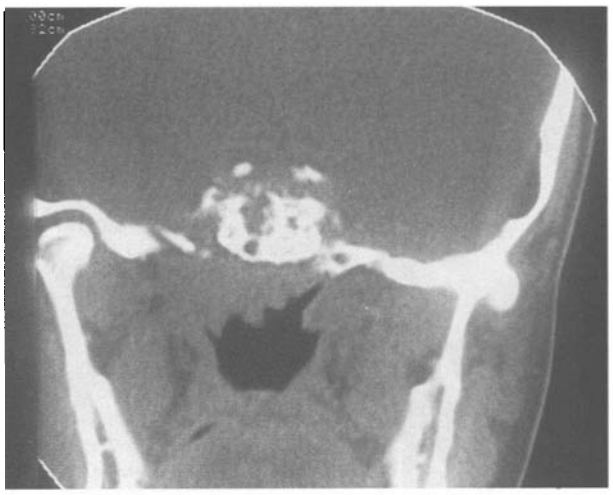

FIG. 4
Coronal CT scan of basisphenoid/clivus showing evidence of bilateral skull base osteitis and prominent right-sided naso-pharyngeal lymphoid tissue.

CT scan showed evidence of osteitis affecting the bone behind the sphenoid and the clivus (Figure 4).

The serum level of itraconazole was measured and found to be very low (0.2 mg/ml; by bioassay (Law *et al.*, 1994)). The dose was therefore increased to 400 mg daily and blood levels were regularly reviewed. Within a week the levels reached the therapeutic range (>6 mg/ml) and gradually accumulated over the next month to >30 mg/ml and later settled to well within the therapeutic range.

Her immunological status was thoroughly evaluated (Table I) and was found to be slightly defective but IgG antibodies to *Aspergillus* continued to be detectable. Repeated CT scans did not show any progression of the disease but her occipital headaches and restricted neck movements persisted and her treatment was therefore changed to a new oral azole (voriconazole; 200 mg b.i.d., Pfizer, Sandwich, UK). She remained on this agent for 14 months and, apart from having an apparent photosensitivity of her face after exposure to strong sunlight, she

TABLE I
SUMMARY OF IMMUNOLOGICAL INVESTIGATIONS

White cell function studies	
Neutrophil function	
Neutrophil *Candida* uptake	Normal
Neutrophil *Candida* killing, autologous plasma	17% (30–70%)
Neutrophil *Candida* killing, control plasma	32% (30–70%)
Chemotaxis	70% (normal >75%)
Bactericidal	0.45 (normal <0.2)
Chemiluminescence	Defective
B cell function	
Response to common viral antigens	Normal
Isohaemagglutinnins	Normal response
Immunology	
Complement C3, C4, CH50	Normal
IgG, IgA, IgM	Normal
IgE	831 iu/mil (normal <100)
CSF screen for complement	Normal
C1 esterase inhibitor	Normal
Complement and complement C1q	Normal
Miscellaneous	
HIV antibody	Negative
Antinuclear antibody	Negative
Antimitochondrial antibody	Negative
Smooth muscle antibody	Negative
Antiphospholipid antibody	4 μ/ml (normal <10)

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responded well. She did develop skin lesions consistent with discoid lupus vulgaris in sun exposed areas, confirmed on biopsy, but these resolved with a factor 30 sunblock. Her neck pain and headaches resolved and her well-being and energy levels improved. The sinuses have remained clean and healthy and repeated CT/MR scans have not shown any suggestion of her skull base disease progressing although the basi-sphenoid still shows patches of sclerosis and lysis.

She has since been seen regularly by both authors. Her facial erythema resolved within three months of discontinuing voriconazole. There has been no clinical endoscopic or radiological evidence of disease progression for over five years and she is now considered to be cured.

Discussion

The lady reported above demonstrates several typical features of chronic invasive fungal sinusitis, such as presentation with symptoms of chronic sinusitis, cranial nerve palsies, potentially serious complications and long-term problems in spite of intensive medical and surgical treatment. The likely course of events was probably infection in a maxillary sinus haematoma, the chronicity of which allowed the proliferation of *Aspergillus*.

Important lessons can be learnt from her initial presentation and treatment. Although she had been admitted within a month of being seen in the outpatient department the importance of her underlying pathology had not been appreciated. When she was reviewed in the clinic shortly afterwards she had, unfortunately, not undergone nasal endoscopy and the resolution of her symptoms had given the examining doctor a false sense of security. It is unfortunate that this sequence of events probably happens frequently throughout the country and one cannot over-emphasize the importance of assessing the nose thoroughly with an endoscope and of taking note of the culture report and ensuring that appropriate action is taken when unusual microorganisms or fungi are found. Her condition could have also been more thoroughly appreciated had a CT scan of the sinuses been performed shortly after her initial presentation. There is therefore a need to emphasize the clinical importance of fungal sinusitis to trainees so that they acquire an increased awareness of the consequences.

In a case of *Aspergillus* infection of the sphenoid with intracranial extension into the frontal cranial fossa and right middle fossa, the typical presentation was very similar to ours. Tsuboi *et al.* (1988) reviewed 16 cases of intracranial aspergillosis secondary to sinus infection and noted that visual disturbance, followed by headache and ophthalmoparesis are common. Cheek swelling predominated in the early stages of the disease; however, advanced disease led to raised intracranial pressure, and rupture or thrombosis of the internal carotid arteries. The outlook of this disease is poor and 12 of these 17 patients died.

Fungal sinusitis can masquerade as chronic bacterial sinusitis, malignancy or a granulomatous disease and a high index of suspicion is required to make the correct diagnosis in the early stages of the disease. However, once diagnosed the most important clinical decision is to differentiate non-invasive from invasive disease. It has recently been suggested that invasive disease probably follows an apparently innocuous non-invasive disease state and that there is probably an intermediate stage of destructive 'non-invasive' disease (Rowe-Jones and Moore-Gillon, 1994). In non-invasive aspergillus infection there is no mucosal invasion. An aspergilloma may exist in a single sinus, usually the maxillary sinus, with very few symptoms or there may be a localized infection of the affected sinus leading to a presentation with recurrent acute bouts of chronic sinusitis. In contrast, invasive disease insidiously erodes bony barriers leading to infection in adjacent sinuses and eventually there is spread beyond the confines of the sinuses into the orbit, skull base, pterygopalatine fossa or hard palate. Examples of such invasion are eruditely described by Washburn *et al.* (1988) in seven such patients.

The distinction between non-invasive and invasive disease may not be clearly apparent. Brown *et al.* (1994) have described cranial neuropathies in two non-immunocompromised patients whom they considered to have either invasive or saprophytic *Aspergillus fumigatus* sinusitis. The patient with invasive disease had left optic nerve compression due to expansion of the sphenoid sinus and posterior ethmoid air cells. However, their other patient presented with severe retro-orbital pain, diplopia and proptosis and CT showed disease in the left maxillary, posterior ethmoid and sphenoid sinuses which was extending into the infratemporal fossa and the inferior orbital fissure. A biopsy taken via an intranasal antrostomy had the histological appearances of an aspergilloma. Unfortunately, this patient was lost to follow-up but it does seem from their description that he had invasive rather than saprophytic disease. In another recent report, a frontal lobe abscess was described in a 32-year-old man with a right frontal mucopyocele, proptosis, bilateral nasal polyps, bronchiectasis and an endobronchial mass (Tsimikas *et al.*, 1994). *Aspergillus fumigatus* was identified from the cerebral abscess, the mucopyocele and the chest and the authors considered the patient to have allergic aspergillus sinusitis and allergic bronchopulmonary sinusitis.

Once fungal sinusitis is suspected tissue samples and purulent debris should be sent for both histology and microbiology. Cultures will take several days to complete and fungal growth may be scanty and of doubtful significance, particularly if there is a coexisting bacterial sinusitis. Histological examination will however clearly demonstrate fungal hyphae in surgically removed material, as long as the sample is large enough. Hyphae may be missed if only routine stains such as haematoxylin and eosin are used and specialized fungal stains are appropriate. Hyphal fragments in the submucosa or bone of tissue samples confirms that the disease is invasive but a careful thorough search of the tissue is usually necessary to find these fragments (Washburn *et al.*, 1988). Sometimes granulomata only are found, but this does not rule out chronic invasive aspergillosis. Our case demonstrates how infrequent such hyphae may be even with multiple tissue samples in spite of there being unequivocal disease radiologically, supported by repeated positive cultures and serology.

Another diagnostic category has been proposed in the non-invasive group of diseases – 'allergic aspergillus sinusitis' (Waxman *et al.*, 1987; Corey *et al.*, 1990). These patients have polyposis, sinusitis and asthma and histology of the mucin shows fungal hyphae, eosinophils and Charcot-Leyden crystals. However, whether these hyphae grow as saprophytes or induce an allergic inflammatory response is not known. Complications are unlikely but a unilateral temporary visual loss has been reported (Dunlop and Billson, 1988).

The evaluation of fungal sinusitis has been greatly enhanced by CT scanning. Both bone destruction and adjacent sinus infection will be clearly demonstrated. Characteristic bone-dense areas may be seen within the soft tissue mass and these have been shown to be due to calcium phosphate deposition (Stammberger, 1991). Furnace atomic absorption spectrometry of concretions has

shown a high manganese and iron content (Denning, 1997). Other features are sclerosis of the lateral wall of the involved maxillary sinus, gas bubbles and erosion of the adjacent osteomeatal complex (Chang *et al.*, 1992). MR scans are a useful adjunct to CT scans, particularly where there is suspected invasion of the orbit or skull base. They are also useful in limiting the dose of irradiation in patients who require repeated scanning during follow-up. Lesions in the sphenoid have been reported to appear as an isointense mass (Tsuboi *et al.*, 1988) although low signals with rim enhancement after gadolinium have also been described (Demaerel *et al.*, 1993). Osteomyelitis has been described in the vertebra but radiological features are nonspecific (Denning, 1997). Slight lucency of the disc plate has been noted and an extradural abscess is often seen. A CT scan is not only essential in assessing the extent of sinus disease, thus facilitating a management plan prior to surgery, but it is also a useful means of monitoring the disease in the long term. However, there is a cumulative radiation dose with each CT scan and MR scans were therefore done on several occasions on our patient to limit potential complications from excess radiation.

Cranial neuropathies secondary to sinus disease are uncommon but they have been recognized to occur after fungal sinusitis for many years. They may be permanent or temporary and arise from either direct intracranial extension of the disease or local inflammation. It has also been hypothesized that remote palsies are due to the local production of neurotoxins by the fungus (Stammberger, 1991). However, there are no data to support this. The temporary paralysis described in our case infers that the neuropathies were caused by local inflammation rather than true invasion. We consider that the bilateral nature of these cranial neuropathies to be due to fungal disease affecting both sides of the clivus and most of the sphenoid since the sphenoid septum was primarily on the right (Figures 1b and 4). In a recent review, cranial neuropathies were present in 12 per cent of 207 patients admitted with sinus disease (Weisberger and Dedo, 1977). Neuropathies were secondary to neoplastic disease (32 per cent), acute inflammation (eight per cent) and chronic inflammatory disease (four per cent). There were two patients with mucormycosis and both had cranial neuropathies, but none of the patients had *Aspergillus* sinusitis.

Why infection with *Aspergillus* becomes invasive in 'non-immunocompromised' patients is not fully understood but it is plausible that there is an altered host-fungus response. However, no specific immunological deficiencies have been identified (Washburn *et al.*, 1988). It is therefore of great interest that our patient had neutrophils with a reduced ability to kill *Candida in vitro*. This finding has not been previously reported in this condition, to our knowledge.

A high index of suspicion is necessary for the diagnosis to be made in the early stages of the disease and a useful algorithm for the clinical management has been suggested by de Carpentier *et al.* (1994). The clinical differentiation between non-invasive and invasive disease is important for both the management and for predicting the likely outcome. Non-invasive disease should be treated by surgical clearance and drainage of the affected sinus. Antifungal agents are unnecessary and the long-term outlook is good (Washburn *et al.*, 1988). Invasive disease needs much more aggressive management and the affected area should be thoroughly cleared. However, the disease may relapse even after wide excision and antifungal therapy and it has therefore been suggested that this group of patients should be treated by amphotericin B (total dose 2 gm) after surgical extirpation (Washburn *et al.*, 1988). The other choice is oral itraconazole, in a dose of at least 400 mg daily (Denning *et al.*, 1994). It is pertinent at this stage to note that the initial dose of itraconazole which this patient received was too low. Low serum concentrations are associated with therapeutic failure (Denning *et al.*, 1994). Ketoconazole and fluconazole have no clinical activity against *Aspergillus*. The new azole, voriconazole, is active against *Aspergillus*, and is presently undergoing clinical evaluation. It appears to have been efficacious in this patient.

In conclusion, fungi are ubiquitous organisms throughout the environment and will often be inhaled through the nasal airway. However, they can then set up an inflammatory reaction and on rare occasions this can invade natural tissue barriers with potentially disastrous consequences. Management of established invasive disease needs to combine radical, aggressive surgery with intensive antifungal therapy for long periods but even after this relapse may occur.

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