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# Aspergillosis of the paranasal sinuses*

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SUMMARY

*Aspergillosis of the paranasal sinuses is a well-established clinical entity which has recently been classified into non-invasive and invasive forms with distinct sub-divisions of both types. Two cases are described, both highlighting potential serious complications of the disease as well as the importance of adequate medical and surgical treatment in effecting a favourable outcome. The disease is reviewed and the question as to whether cases necessarily fall into previously-defined clinical and pathological categories is also discussed.*

*Key words: aspergillosis, paranasal sinuses*

## INTRODUCTION

Since an initial report just over a century ago, *Aspergillus* infection of the nose and paranasal sinuses has received increasing attention with the more recent definition of several types of disease process. Two categories are generally recognized: non-invasive and invasive. The former is a relatively benign condition which presents as two distinct entities: the *aspergilloma* and *allergic Aspergillus sinusitis* (AAS). In contrast, invasive disease is classified as either *slowly* or *rapidly progressive* (fulminant), the latter carrying a high mortality rate (Jonathan et al., 1989).

The clinical manifestations and pathology differ significantly between the four types, but more importantly the management is dictated to a great degree by the nature of the infection present. The key, therefore, to a successful outcome lies in the early recognition of the variant of aspergillosis present.

We describe two cases of AAS as defined histologically, but in whom the potential serious complications and relative aggressive behaviour clinically adds fuel to the assertion that not all cases comply with the current classification.

## CASE REPORTS

### *Case 1*

A 30-year-old female presented with a three-month history of impaired vision in her left eye with associated nasal obstruction and post-nasal drip. She had suffered with long-standing myopia of the right eye and therefore visual deterioration in her better eye caused increasing difficulty with her work as a computer visual display unit operator.

Examination confirmed impaired visual acquity in both eyes with a left central scotoma. Basic blood tests, serology and auto-antibody testing were negative. Computerized tomography, however, showed there to be a dense mass in the sphenoid sinus extending to the left posterior ethmoidal sinuses with extradural extension to the pituitary fossa (Figure 1).

At this stage a trans-septal sphenoidotomy and biopsy was undertaken by a neurosurgical team who at operation noted the anterior wall of the sphenoid sinus to be dehiscent and a tenacious waxy yellow-green substance to be filling the sinus. Partial clearance was achieved and microbiology confirmed the presence of *Aspergillus fumigatus*. Histology of the mass showed features consistent with AAS and retrospective blood tests confirmed an eosinophilia with a positive response for *Aspergillus* precipitins. At this juncture the patient's vision remained static and magnetic resonance imaging illustrated a large sphenoid cavity confluent with the nasal fossae. No further action was therefore taken.

Two months later the patient presented with bilateral visual impairment, increasing nasal obstruction and sneezing. Computerized tomography on this occasion showed the sphenoid sinus to be full of a soft-tissue mass extending into the right ethmoidal gallery. An otolaryngologist's opinion was sought and clinical appraisal suggested an active invasive disease. On this basis the patient was admitted for further surgery and commencement of anti-fungal chemotherapy in an attempt to prevent progression of the infection and thus an increased risk of visual impairment in the patient's better eye. An external right transethmoidal sphenoidectomy was undertaken and once again the characteristic sticky green-brown material was encountered filling the sphenoid sinus. This was debrided completely and the sphenoethmoidal cavity was rendered contiguous with the nasal fossae allowing good ventilation. Histology on this occasion merely showed chronic inflammation. As an

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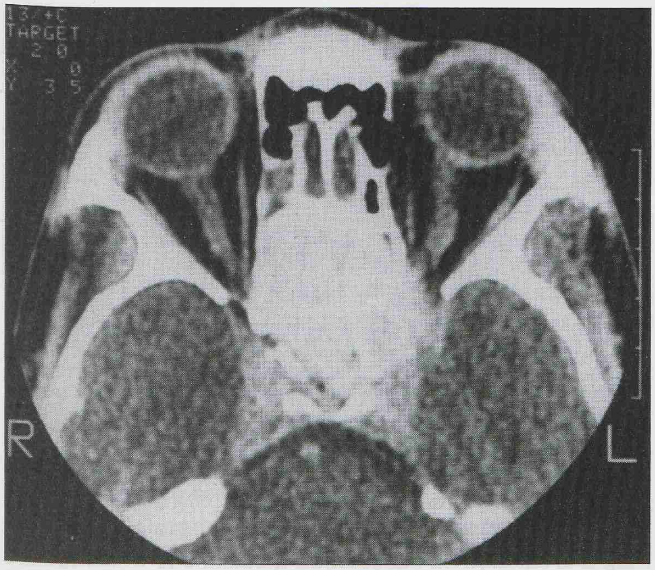


Figure 1. Axial CT-scan (Case 1) showing an enhancing soft-tissue mass in the sphenoid sinus.

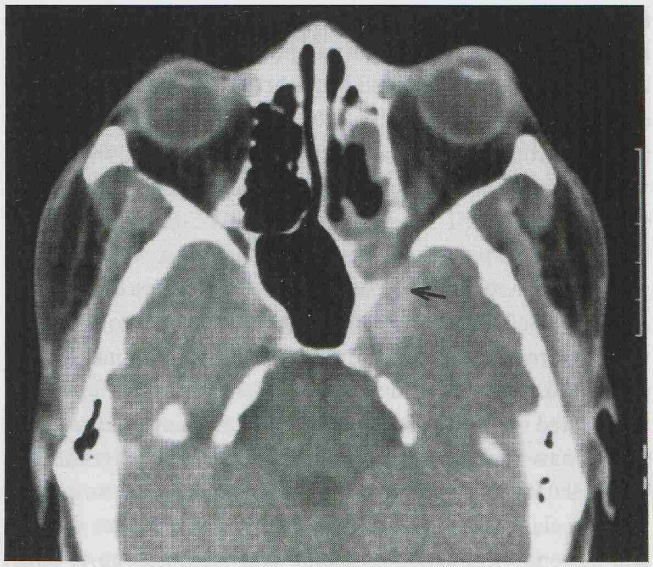

Figure 2. Axial CT-scan (Case 2) illustrating soft-tissue shadowing in the left sphenoid sinus extending to the orbital apex.

adjunct to surgery the patient was commenced on intravenous amphotericin via a central line. The drug was initially tolerated with a commensurate improvement in vision but after ten days the patient developed biochemical signs of renal impairment necessitating changing the regime to lipolysed amphotericin and subsequently to oral itraconazole.

At out-patient review a month later the visual function was continuing to improve, the nasal cavities were clear and endoscopic assessment of the sphenoethmoidal cavity showed a healthy mucosa with no polyposis. Scanning at this stage was satisfactory with no signs of optic canal erosion. Chemotherapy was therefore discontinued. This state of remission was maintained, the patient remained off all medications and was discharged nine months after her initial presentation.

*Case 2*

A 32-year-old West-African male presented to a Neuro-ophthalmology Department with a short history of diplopia preceded by a left frontal headache and post-nasal drip for two months. Examination showed him to have a mild left sided proptosis with lateral displacement of the globe and a degree of vertical diplopia. Investigations were unremarkable apart from computerized tomography which showed a pan-sinus soft-tissue opacification on the left side.

The patient was referred for a rhinological opinion and a left inferior antrostomy and biopsy under general anaesthesia was undertaken. The antrum was found to contain inspissated pus and polypoidal mucosa which histologically consisted of chronic inflammation and scattered *Aspergillus* hyphae. Definitive treatment by way of a left transantral ethmoidectomy with adjunctive intravenous amphotericin followed and operative findings on this occasion revealed the antrum to be full of a thick white fibrous material which was completely excised.

During the subsequent two weeks the diplopia settled and ocular alignment became symmetrical. Three weeks post-operatively however the patient noted a sudden impairment of vision on the left with increasing proptosis. At this stage intravenous amphotericin was still being administered and repeat tomography showed pan-sinusitic mucosal thickening extending to the apex of the left orbit (Figure 2). On this basis a trans-septal sphenoidectomy was undertaken as a matter of urgency with histology of the excised polypoidal mucosa showing AAS and microbiology culturing *Aspergillus fumigatus*. The amphotericin was therefore stopped and the patient commenced on oral and topical corticosteroids. There was a concomitant improvement in both visual acquity and diplopia as assessed by the ophthalmologists and the patient was thus discharged on reducing doses of corticosteroids.

The patient unfortunately relapsed four days later and a further scan demonstrated persistent enhancement at the left orbital apex and parasellar region (Figure 3). At this stage it was felt that an open procedure would allow more adequate debride-

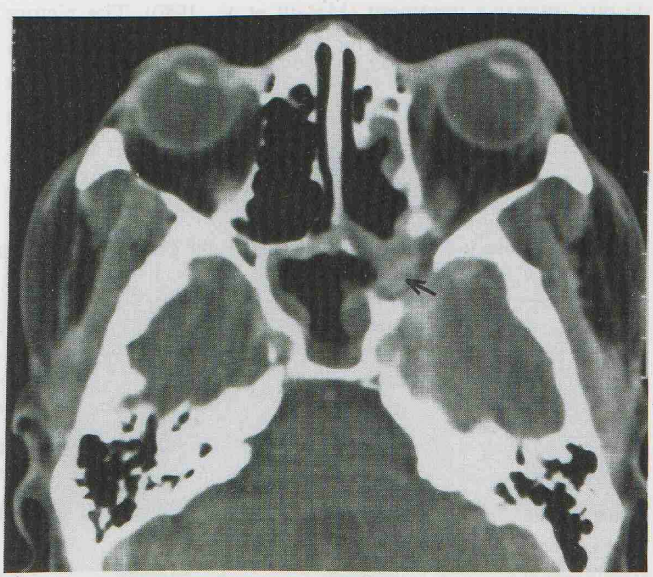

Figure 3. Axial CT-scan (Case 2) showing persistent enhancement at the apex of the left orbit and parasellar region.

ment and ventilation of the spheno-ethmoidal complex and therefore a left external transethmoidal sphenoidectomy was undertaken. Polypoidal material in the posterior ethmoidal cells extending into the lateral aspect of the sphenoid sinus with patchy necrosis was excised to reveal wide bony dehiscence with disease lining the dura of the medial wall of the cavernous sinus.

Following this procedure the patient showed a consistent improvement in vision. Repeated out-patient endoscopic assessment revealed minimal crusting of the sphenoethmoidal cavity with no signs of polyposis or necrosis. Magnetic resonance imaging confirmed resolution of the enhancement at the orbital apex noted on previous scans. On three occasions the corticosteroids have been discontinued with a subsequent deterioration in visual function. The repeated use of high dose corticosteroids over an eight-month period has rendered the patient diabetic and currently the patient is taking oral prednisolone in small doses (5 mg/day). Twenty months after initial presentation the patient's vision is slightly impaired in the left eye and despite the fact that the clinical and radiological appraisal is satisfactory, the visual function deteriorates when the coricosteroids are stopped, necessitating, for the moment the continued use of oral prednisolone.

## DISCUSSION

In 1915, Herbert Tilley reported five cases of aspergillosis of the maxillary antrum, graphically describing the characteristic clinical, operative and pathological findings associated with this type of fungal infection (Tilley, 1915). Over the years it has become increasingly apparent that the disease is not a single entity but exhibits a spectrum of presentation. The exact clinical picture depends on a number of factors including the host response and immunological status.

McGill and colleagues defined fulminant aspergillosis of the nose and paranasal sinuses as recently as 1980, in which four patients with an underlying haematological disorder developed a rapidly progressive infection, two succumbing to the sepsis despite intensive treatment (McGill et al., 1980). The picture was further clarified in 1983 by Katzenstein who reported seven cases of aspergillus sinusitis characterized by underlying atopy and an eosinophilic mucosal reaction to the fungus, giving rise to the term *allergic Aspergillus sinusitis* (Katzenstein et al., 1983). The same team reported a further eight cases in 1987 (Waxman et al., 1987), and two cases reported by Philip and Keen (1989) as well as four cases from London in the same year served to highlight the parallels with allergic bronchopulmonary aspergillosis (Jonathan et al., 1989).

The comparative features of the four types of infection encountered are summarized in Table 1.

The species *Aspergillus fumigatus*, *A. flavus* and *A. niger* are prevalent throughout the atmosphere exhibiting a commensal or saprophytic existence in soil and decaying matter. They are true fungi (*Eumycetes*), have septate hyphae with characteristic dichotomous branching at 45 degrees with expanded spore heads on their aerial hyphae (conidiophores). In the absence of any intrinsic keratolytic properties, the fungus can only penetrate skin or mucous membranes if the latter are damaged or debilitated allowing germination and insidious growth over months or even years (Panayiotopoulou et al., 1987). The fungus is cultured on Sabouraud's medium and whilst routine staining with haematoxylin and eosin may demonstrate the hyphae, Grocot's silver methenamine staining will usually allow even scanty hyphae to be demonstrated (Micheals, 1990).

The aspergilloma (fungal ball, mycetoma) is endemic in Sudan and usually presents in otherwise healthy individuals with a unilateral antral infection giving rise to symptoms typical of chronic rhinosinusitis. Plain radiography shows opacification of the affected sinus in 50% of cases with pathognomonic dense lucencies up to 20 mm in length in the antrum. These "metallic opacities" represent calcium phosphate or sulphate and salts of heavy metals such as cadmium (Kopp et al., 1985). Histologically, there is a mass of tangled hyphae with an "onion ring" appearance and an absent or minimal mixed inflammatory response (Figure 4). Surgical debridement such as that afforded by a Caldwell-Luc procedure is effective in precipitating a cure and neither anti-fungal chemotherapy nor corticosteroids are indicated.

AAS tends to involve multiple paranasal sinuses and is usually associated with underlying atopy. Affecting young adults in particular, patients present with a long history of rhinosinusitis and have frequently undergone multiple previous intranasal surgical procedures. At operation, the characteristic finding is thick, inspissated mucoid material termed "allergic mucin" by Katzenstein. This material histologically shows aggregates of necrotic eosinophils, sloughed respiratory epithelium, scanty hyphae and Charcot-Leyden crystals in a mucinous background

Table 1. Summary of features characterizing the four types of paranasal sinus aspergillosis (*: type refers to the classification of hypersensitivity reactions by Coombs and Gell).

| type | host factors | site | immune response | surgery | drugs | outcome |
|---|---|---|---|---|---|---|
| aspergilloma | none (healthy) | antral | none or minimal type 4* | yes | no | good |
| allergic aspergillus sinusitis | atopy | multiple sinuses | type 1 type 3 | yes | +/- corticosteroids | good |
| slowly invasive | none (healthy) | multiple sinuses | type 4 | yes | antifungal chemotherapy | variable |
| rapidly invasive (fulminant) | immune-compromized | multiple sinuses | none or minimal type 4 | yes | antifungal chemotherapy | high mortality |

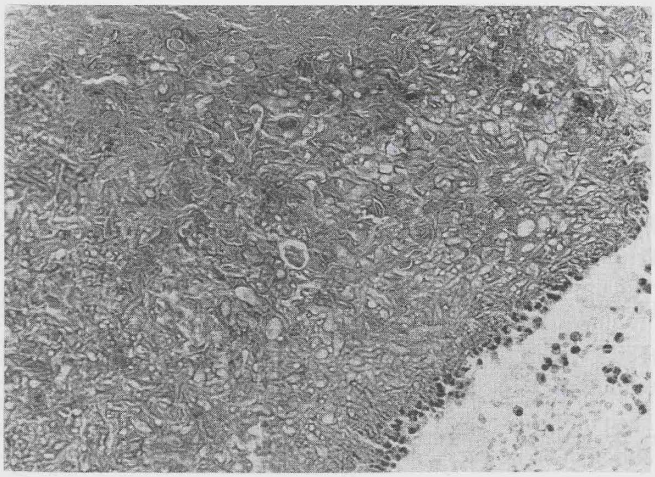

Figure 4. Aspergillus "fungus ball" of maxillary antrum. The aspergillus presents a tangled mass of septate hyphae. Necrotic inflammatory cells are present at the edge (bottom right). Haematoxylin and eosin staining (×400).

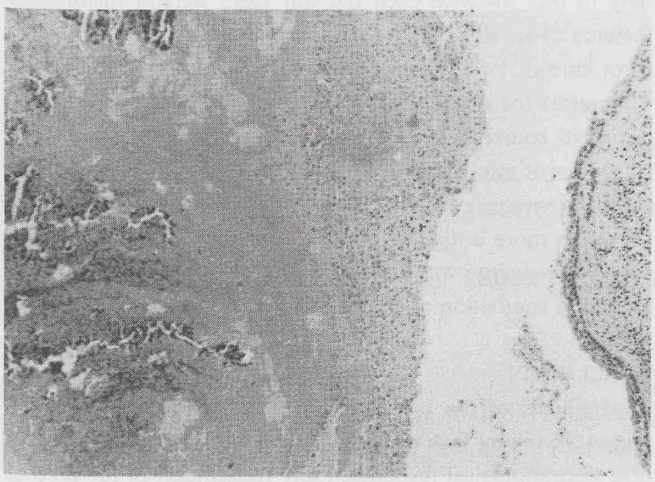

Figure 5. Inspissated mucus from maxillary antrum in a case of AAS. Mucosal tissue at the right edge shows basement membrane thickening and eosinophil infiltration, features of allergic inflammation. Haematoxylin and eosin staining (×100).

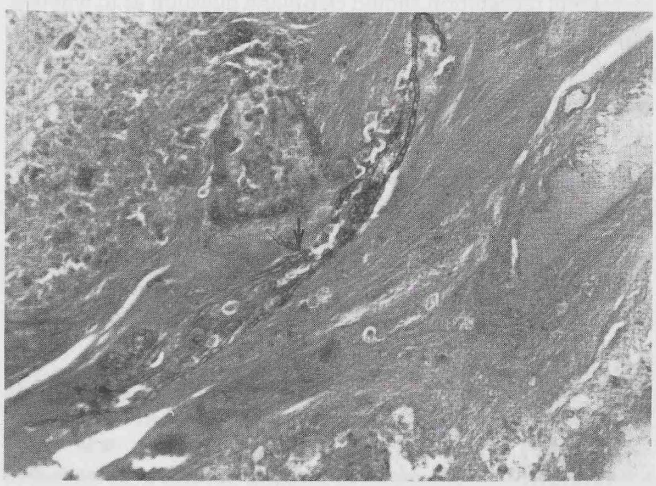

Figure 6. Fungus stain of inspissated mucus from a case of AAS showing septate hyphae of *Aspergillus*, which are branching at 45° (arrow). Grocott's silver methenamine staining (×400).

(Figures 5 and 6) and is indistinguishable from the mucoid impaction found in allergic bronchopulmonary aspergillosis (Katzenstein et al., 1983). Charcot-Leyden crystals are hexagonal in cross-section and are believed to represent eosinophilic granules. The usual causative organism is *Aspergillus fumigatus*, although *Aspergillus flavus* is occasionally isolated, particularly in cases from Sudan (Jonathan et al., 1989). The pathogenesis of AAS is a combination of Type 1 and Type 3 hypersensitivity to the fungus resulting in a focal microvasculitis, thrombosis, ischaemia and subsequent necrosis (Waxman et al., 1987). This evidence, coupled with the presence of precipitins to the fungus and an eosinophilia in the serum has allowed close parallels to be drawn between AAS and its bronchopulmonary equivalent. Interestingly though, only one case of concomitant disease in a single individual has been reported (Safistein, 1979). Management of AAS involves thorough surgical excision of diseased tissue with the additional option of topical corticosteroids, systemic steroids being reserved for refractory cases. In the absence of histological evidence of fungal invasion, antifungal agents are not indicated and the overall prognosis is favourable as long as the initial index of clinical suspicion remains high (Jonathan et al., 1989).

In marked contrast, invasive aspergillosis displays a different pathophysiology and clinical course. The slowly progressive variant is rare and tends to affect otherwise healthy individuals. With its propensity to destruction clinical presentation is one of an enlarging mass giving rise to cheek, nasal or orbital swelling with proptosis being a prominent feature. It is insidious and characterized by a granulomatous (Type 4) reaction with cellular infiltration typical of chronic inflammation (Figure 7). Fungal hyphae are scant but silver staining allows identification particularly since malignant neoplastic disease is high on the differential diagnosis (Milroy et al., 1989). Computerized tomography is the radiological investigation of choice allowing assessment of the extent of sinus involvement as well as giving indication of bone destruction and intracranial extension, features which characterize the lesion (Centeno et al., 1981). Treat-

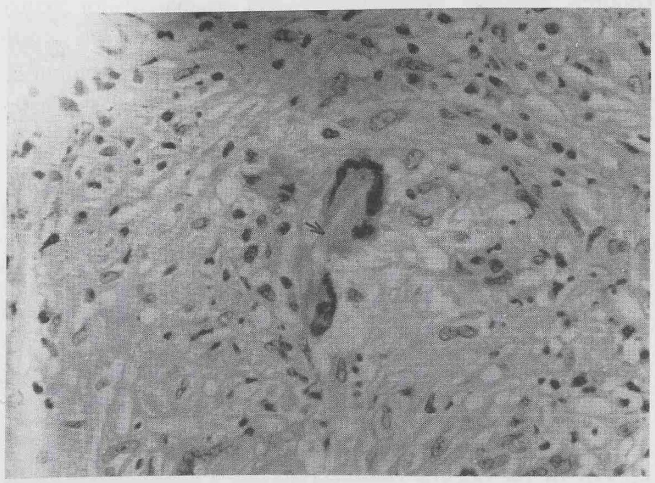

Figure 7. Invasive aspergillosis showing giant-cell granulomatous reaction. Note septate hyphae of *Aspergillus* which has been phagocytosed into the cytoplasm of the giant cell (arrow). Haematoxylin and eosin staining (×400).

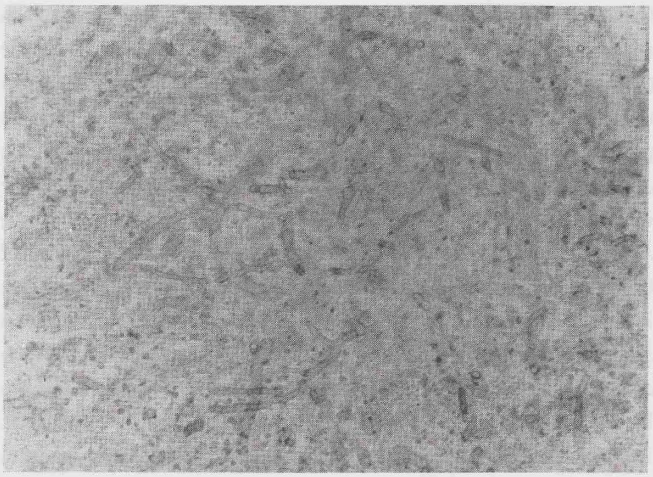

Figure 8. Fulminant aspergillosis. There is complete tissue necrosis and large numbers of *Aspergillus* hyphae. Haematoxylin and eosin staining (×400).

ment necessitates both surgery and chemotherapy. Extensive and complete debridement is essential with the adjunctive use of anti-fungal agents such as amphotericin, although itraconazole, available on a named-patient basis is currently being assessed as it is neither nephro- nor haematotoxic and can be given orally (Hay, 1991). If diagnosed and treated promptly, then a favourable outcome is expected but the overall prognosis is variable (Bahadur et al., 1983).

Rapidly progressive or fulminant aspergillosis of the nose and paranasal sinuses (Figure 8), described by McGill and colleagues in 1980 is primarily a disease affecting immunocompromised patients. This includes primary diseases such as uncontrolled diabetes mellitus, solid and haematological tumours as well as patients on immunosuppressive chemotherapy and radiotherapy (McGill et al., 1980). More recently, aggressive aspergillus sinusitis has been described in patients with established Acquired Immunodeficiency Syndrome (AIDS), occurring either with pulmonary aspergillosis (Minamoto et al., 1992) or as basal meningitis secondary to invasive sinusitis (Carrazana et al., 1991). The most susceptible individuals, however, are children receiving chemotherapy and irradiation for acute leukaemias (Baydala et al., 1988).

The initial characteristic lesion indicating nasal involvement is crusting of the anterior end of the inferior turbinate beneath which is insensitive gangrenous tissue due to ischaemic necrosis. Progression to the nasal septum and paranasal sinuses with subsequent orbital extension is rapid, the patient at this stage usually having disseminated disease with particular involvement of the lungs, liver and spleen. The pathological hallmark in fulminant disease is arterial wall invasion in the absence of a host immune response (Centeno et al., 1981). Experimental work in canines demonstrates that embolic occlusion of the vasa-vasorum allows mycotic growth into the vessel (Fernando and Lauer, 1982). Extension into the anterior cranial fossa either directly or via vascular channels heralds a fatal outcome with post-mortem studies showing involvement of the anterior cerebral artery or branches thereof (McGill et al., 1980). This type of rhinocerebral aspergillosis is clinically similar to the so-called mucormycosis, though the two should not be confused as the latter is caused by the mucorales group of non-septate *Phycomycetes,* particularly in acidotic diabetics.

Surgical exenteration in fulminant disease may require repeated procedures with the aggressive use of anti-fungal agents, haemodynamic and renal support and consideration of bone marrow transplants or granulocyte transfusions if the underlying condition dictates it. Despite such measures the mortality remains high, no doubt partly related to the initial factors leading to immuno-incompetence.

The cases we describe in this paper both have pathological features consistent with AAS. The clinical course however has been more in keeping with the slowly invasive type of infection, although on no occasion was fungal invasion demonstrated histologically. Milroy and co-workers (1989) describe the co-existence of aspergilloma with fulminant disease, and there is at least one report of synchronous antral carcinoma and aspergillosis, although this relationship is better documented with primary bronchial tumours (Tanaka et al., 1985). Interestingly, only in one instance each did our cases exhibit histological features of an allergic basis and remaining biopsies tended to show chronic inflammation as seen in slowly invasive disease. This raises the question as to whether the infection can alter during its course or if cases transcending the currently defined categories of infection will appear as further cases are reported. One fact emerges without doubt and that is that both patients showed a more lasting response to treatment when an "open" surgical procedure was undertaken allowing extensive debridement and ventilation of the sinuses involved.

## CONCLUSION

Aspergillosis of the paranasal sinuses is a disease that may present in one of four ways depending to a great degree on the host immunological response. Early recognition of the type of infection present is vital in planning appropriate treatment as the management differs between sub-types. To this end a high index of clinical suspicion is required whilst close collaboration with microbiologists and histopathologists is mandatory. Increasing recognition should clarify the question as to whether clinical sub-types that transcend the defined categories exist.

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