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Adjuvant itraconazole in the treatment of destructive sphenoid aspergillosis*

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SUMMARY

Paranasal aspergillosis is a potentially progressive continuum of disease, classically described as having four forms: allergic, non-invasive, invasive, and fulminant. The first two have been considered together as extramucosal disease whilst the latter two are both variants of tissue-invasive disease. Sphenoid aspergillosis, given its anatomical location is a more aggressive disease than that found affecting the other paranasal sinuses, even when non-invasive, and may be fatal. This is compounded by the fact that diagnosis is difficult and so may be made late when aspergillosis is consequently more advanced. Intracranial extension may occur via the direct spread of invasive disease or along communicating veins despite intact sinus walls and lack of fungal mucosal penetration. Once this occurs mortality is high. We have successfully treated three cases of destructive sphenoid aspergillosis, two of which had intracranial extension, with surgery and adjuvant anti-fungal chemotherapy including itraconazole. We recommend the use of post-operative itraconazole in all cases of sphenoid sinus aspergillosis. Additionally, when there is evidence of spread to the brain or other adjacent structures we would advocate an initial course of intravenous amphotericin B followed by long-term oral itraconazole.

Key words: sphenoid sinus, paranasal aspergillosis, itraconazole

INTRODUCTION

Aspergillus sinusitis has classically been described in four forms: allergic, non-invasive, invasive, and fulminant (Sarti and Lucente, 1988). They are now covered by two broad histopathological categories, non-invasive and invasive (Hora, 1965; Jonathan et al., 1989; Hartwick and Batsakis, 1991). In the non-invasive group colonization is extramucosal, saprophytic and benign in nature, appearing either as an aspergilloma or as allergic *Aspergillus* sinusitis. In the invasive group infection is destructive and may follow either a slowly progressive course or a rapid, fulminant course (McGill et al., 1980). The organism is found within and deep to the mucosa. A chronic, indolent form of sinusitis has also been described which may result from aspergilloma and have a consequent potential for invasion (Sarti and Lucente, 1988; Hartwick and Batsakis, 1991).

Stammberger (1985) states that chronic sinusitis is due to fungi more often than commonly believed. Failure to recognize this and the confusion of sinus aspergillosis with other diseases (Jahrsdoerfer et al., 1979; Sarti and Blaugrund, 1988) will result in the later diagnosis of more advanced disease. This situation is particularly pertinent in the instance of sphenoid sinusitis which, when isolated, is often misdiagnosed, sometimes for many years (Holt et al., 1984; Brockbank and Brookes, 1991). Sphenoid aspergillosis is also a more aggressive disease because of its anatomical location (Sarti and Lucente, 1988), and may be fatal (Jahrsdoerfer et al., 1979). Invasive aspergillosis, with cerebral extension in particular, carries a high mortality (Jahrsdoerfer et al., 1979) despite combined surgery and amphotericin B therapy (Weber and Lopez-Berestein, 1987; Sarti and Blaugrund, 1988). We therefore report three cases of destructive sphenoid aspergillosis, two of which had intracranial extension, that were successfully treated with surgery and anti-fungal chemotherapy which included the new triazole agent, itraconazole.

PATIENTS

Case 1

A previously fit 68-year-old lady presented with a 6-week history of bitemporal headaches and post-auricular pain. She was nauseated but not vomitting, and had no nasal symptoms.

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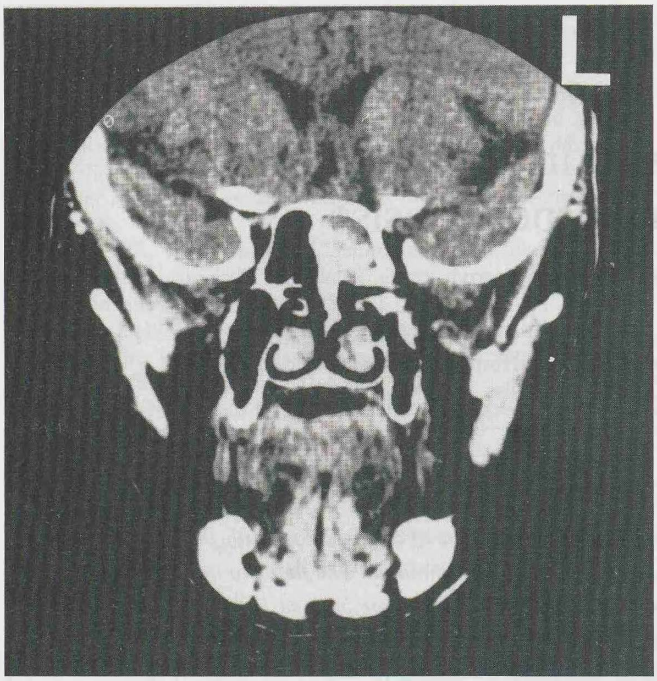

Figure 1. Coronal CT scan revealing complete opacification of the left sphenoid sinus with erosion of the floor. The sinus also contains radiopaque particles characteristic of *Aspergi/lus* concrements.

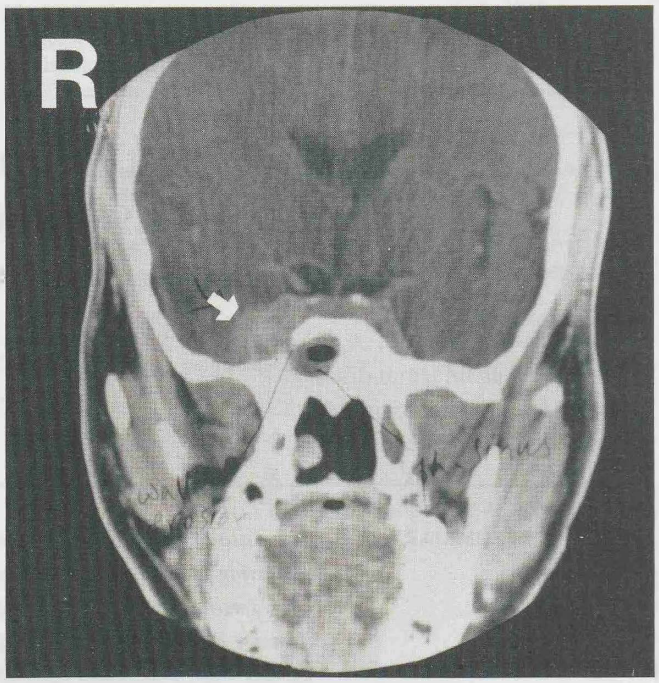

Figure 2. Coronal CT scan demonstrating a mass of invasive aspergillosis which has spread from the right sphenoid sinus to involve the medial side of the right temporal lobe.

Rhinoscopy was normal as was otoscopy and neurological examination. Computerized tomography (CT) scans, however, revealed expansion of the left sphenoid sinus with erosion of the walls. The sinus was completely opaque with radiopaque particles within it (Figure 1). The patient underwent a left external sphenoethmoidectomy at which time the anterior wall of the sphenoid sinus was found to be deficient. Thick pus, yellow concretions and thickened mucosa were removed, from which scanty aspergilli were isolated. Histological examination demonstrated clumps of fungal hyphae separate from the respiratory mucosa and a few non-viable hyphae within the mucosa in some places. A chronic inflammatory cell infiltrate was present but without granulomata or the marked fibrosis, characteristic of slowly invasive disease. This appearance, therefore, was thought unlikely to represent true invasion. However, because of the associated local bony destruction we consider the case to be one of semi-invasive aspergillosis. Following surgery the patient received oral itraconazole (100 mg, once daily) for one month and is free of recurrence 15 months after surgery.

Case2

A 31-year-old man was referred from Pakistan. He had suffered from rhinitis since adolescence and for the six months prior to consultation had right facial pain with decreased sensation in all three divisions of the right trigeminal nerve. For three months prior he had also had occasional frontal pain and diplopia. CT scan performed in Pakistan one month before his referral revealed mucosa! thickening in the right sphenoid, ethmoidal and maxillary sinuses. This had been treated with bilateral antral wash-outs. A subsequent CT scan demonstrated more extensive changes with a right sphenoidal and tentorial mass spreading into the medial side of the right temporal lobe (Figure 2), and the patient was transferred here for further mamanagement. He subsequently underwent a right frontotemporal craniotomy and removal of a mass which histologically was comprised of chronic gramulomatous inflammation with multinucleated giant cells. Silver stains revealed many fungal hyphae which culture identified as *Aspergillus fiavus.* Twelve days later transsphenoidal removal of the remaining sphenoid mass was undertaken and further fungi were identified. Post-operatively, he received intravenous amphotericin B for six weeks followed by a 6-month course of oral itraconazole (200 mg, once daily). Repeated CT scans, a further six months later, demonstrated no evidence of recurrent disease.

Case3

A 32-year-old man was referred from Saudi Arabia. He had a history of nasal polyposis and eight years of occasional frontal headaches. Three months prior to referral his headache had become constant and was associated with decreased left visual acuity. On examination he was found to have bilateral papilloedema and anosmia. CT scan revealed a large subfrontal mass extending from the sphenoid and ethmoidal sinuses and he, therefore, underwent a bifrontal craniotomy. Histology of the specimen revealed it to be fungal in origin and subsequent culture grew *Aspergillus.* One week later the contents of the sphenoid were evacuated transnasally and the patient received two weeks of intravenous amphotericin **B** and oral flucytosine. **A** magnetic resonance **(MR)** scan, one month later, had shown no recurrent disease, but the patient had developed left proptosis and so received another two weeks of amphotericin **B** and flucytosine. Three months later his frontal pain returned. Repeat **CT** scan showed diffuse opacification of frontal,

ethmoidal and sphenoid sinuses with erosion of the cribriform plate and a small residual mass in the region of the sella extending to the right inferior frontal lobe. The patient was then transferred here for further management. Serology at this time was positive for *Aspergillusfumigatus* antibodies and the patient was commenced on a 6-week course of intravenous amphotericin B and flucytosine followed by long-term oral itraconazole (200 mg, once daily). His symptoms resolved and follow-up CT at six months revealed clearance of his rhinocerebral aspergillosis.

DISCUSSION

Sphenoid aspergillosis is a rare condition, particularly when it occurs as an isolated disease process (Lavelle, 1988).

Up to 1979, 14 cases had been reported (Jahrsdoerfer et al., 1979). Eight of these had sole sphenoid involvement of which foou cases were fatal. The remaining six cases had disease that included the other sinuses or contiguous structures, and four of these died with intracranial spread. The authors reported a further case of their own with isolated sphenoid involvement and bony erosion, as did McGuirt and Harrill (1979). Subsequently, 15 further patients (Table 1) were reported in the English literature (Weinstein et al., 1976; Yu et al., 1980; Stevens, 1981; Nielsen et al., 1983; Holt et al., 1984; Von Haacke, 1984; Fuchs et al., 1985; Comoretto et al., 1986; Weber and Lopez-Berestein, 1987; Lavelle, 1988; Sarti et al., 1988; Wilms et al., 1992). Of these, five cases were of isolated sphenoid disease, three of which were non-invasive aspergilloma. The remaining 10 were destructive and involved other sinuses or adjacent anatomy. Eight of these cases had histological evidence of fungal tissue invasion. Six had intracranial extension, four of which were fatal.

These cases and our own illustrate well that a spectrum of disease severity may be encountered with paranasal aspergillosis. The condition has already been described as a continuum of change from non-invasive to invasive and subsequently fulminant forms by Sarti and Lucente (1988). Other authors have also suggested that the distinction between non-invasive and slowly invasive forms is unclear (Jahrsdoerfer et al., 1979), whilst Hartwick and Batsakis (1991) have proposed that chronic, indolent sinusitis with aspergillosis has potential for invasion. Horn's (1965) initial description of invasive disease was based on the clinical findings of destructive lesions that behaved locally like malignant neoplasms, but did not include histological evidence of tissue invasion by *Aspergillus*. Similar erosive cases have subsequently been reported that do include true sinus mucosa! fungal invasion (Veress et al., 1973; Miglets et al., 1978; Colman et al., 1985; Robb, 1986). However, cases of

Table 1. Fifteen cases reported in the English literature since 1979 with sphenoid sinus aspergillosis. Only case B described by Weber and Lopez-Berestein (1987) and the case presented by Wilms et al. (1992) were immunocompromized (*: intracranial extension; L: liposomal).

authors	site	nature	treatment	outcome
Comoretto et al. (1986)	sphenoid	non-invasive	surgery	clear at 4 months
Nielsen et al. (1983)	sphenoid	non-invasive	surgery	clear at 2.5 years
Stevens (1981)	sphenoid	non-invasive	surgery	clear at 4 months
Von Haacke (1984)	sphenoid + pan-sinusitis with erosion of lamina papyracea	semi-invasive	surgery	clear at 3 months
Weinstein et al. (1976)	sphenoid	semi-invasive	surgery and amphotericin B	clear at 3 months
Lavelle (1988)	sphenoid	superficial invasion	surgery	clear at 4 days
Holt et al. (1984) (3 cases)	sphenoid and contiguous sinuses (incl. orbit in 2 cases)	invasive	surgery and amphotericin B	survived. No follow-up period given
Fuchs et al. (1985)*	sphenoid and sella erosion	invasive	surgery, rifampin, amphotericin B	a-symptomatic at 1 month
Sarti et al. (1988)*	sphenoid + pan-sinusitis, sella, orbit, and cribriform plate	invasive	surgery and amphotericin B	died
Weber and Lopez-Berestein (1987) (2 cases)*	sphenoid + pan-sinusitis	invasive	case A: surgery, amphotericin B, L-amphotericin B case B: amphotericin B, L-ampbotericin B	died died
Wilms et al. (1992)*	sphenoid, orbit and optic canal	invasive	radiotherapy	died
Yu et al. (1980)*	sphenoid, sella, and orbit	invasive	surgery, rifampin, amphotericin B and flucytosine	clear at one year

erosive disease have also been reported in which Aspergillus is extramucosal (Warder et al., 1975; Weinstein et al., 1976; Stevens, 1981; Romett and Newman, 1982; Von Haacke, 1984). We have termed those in the latter group "semi-invasive" in Table 1. Probably more of these types occur, but frequently the reported histological findings associated with erosive lesions are inadequate to confirm or deny submucosal fungal invasion (Jahrsdoerfer et al., 1979; McGuirt and Harrill, 1979; Holt et al., 1984). The semi-invasive but destructive cases support the concept that non-invasive disease may become invasive.

Early diagnosis to prevent progression is especially important in the case of sphenoid aspergillosis as the disease behaves in a more aggressive fashion, even when non-invasive (Nielsen et al., 1983). The sinus is in intimate anatomical relationship with other structures of the skull base and intracranial spread may also occur despite intact bony walls, via septic thrombophlebitis involving communicating veins. Often, however, diagnosis is difficult and made late due to the masquerading of sphenoiditis as other conditions. Initially, sphenoid disease may not be considered and when it is aspergillosis may be confused with a neoplasm (Fuchs et al., 1985; Gupta et al., 1990). Fungal disease may also not be considered in the differential, resulting in failure to use appropriate stains and cultures (Holt et al., 1984; Sarti et al., 1988).

When diagnosis has been made before local destruction has occurred, most authors have advocated treatment with surgery alone (Table 1). However, despite a lack of local bony erosion, superficial mucosal invasion may still be present (Lavelle, 1988) and may not be detected given that hyphae are only scantily found in the slowly invasive form of aspergillosis (Milroy et al., 1989). Reported follow-up has also been short in the surgically treated non-invasive cases. If disease has progressed to become destructive and/or invasive, surgery combined with anti-fungal chemotherapy is usually advocated (Table 1). Aspergillosis, though, may still not be eradicated or may recur (Hora, 1965; Yu et al., 1980; Fuchs et al, 1985).

Once progression with intracranial or orbital extension has occurred, mortality is high (Jahrsdoerfer et al., 1979; Yaulai et al., 1985; Yumoto et al., 1985; Lowe and Bradley, 1986; Jinkins et al., 1987; Weber and Lopez-Berestein, 1987; Sarti et al., 1988; Wilms et al., 1992). In some such instances even surgical exenteration with adjuvant, multiple chemotherapeutic combinations of amphotericin B, liposomal amphotericin B, flucytosine and rifampin has failed (Yanai et al., 1985; Yumto et al., 1985; Weber and Lopez-Berestein, 1987; Gupta et al., 1990).

The treatment of deep-seated fungal infections has, in the past, depended largely on the use of amphotericin B, often in combination with flucytosine. Amphotericin B is a broad-spectrum polyene antibiotic, active against most yeasts and fungi. However, it has several disadvantages which include: (1) poor gastrointestinal absorption necessitating intravenous administration; (2) relatively poor penetration into body fluids such as cerebrospinal fluid; and (3) major, often dose-limiting toxicity. The latter includes dose-related nephrotoxicity which makes it unsuitable for long-term use. Anaphylactic reactions, fevers and nausea are also associated with infusion of the drug. Flucytosine, which may be given orally or intravenously, is synergistic with amphotericin B for yeasts, but many isolates of *Aspergillus* are resistent. It, too, has serious side effects including bone marrow and renal toxicity (Speller and Warnock, 1992).

The newer azoles offer significant advantages; they are active orally, have good tissue and fluid penetration and are relatively non-toxic. Whereas both ketoconazole and fluconazole are only weakly active against *Aspe1gillus* species, the triazole agent itraconazole is considerably more active. It has good bio-availability after oral administration and is well tolerated at daily doses of 400 mg or less (Hay et al., 1987). Its efficacy in the treatment of invasive *Aspergillus* infections, particulary in the immunocompromized, has been reported previously (Dening et al., 1989).

There are few reports to date of itraconazole in the treatment of invasive paranasal sinus aspergillosis. A recent study of post-operative therapy with itraconazole (200-300 mg daily) given for a mean of 19.7 weeks to 22 patients with this condition in Sudan reported 62% in complete remission at a mean of 17.2 months after completion of treatment (Gumaa et al., 1992). However, although many of their patients had evidence of bony erosion on plain X-ray, no **CT** or **MR** scans were performed to assess cerebral invasion and none of their patients had involvement of the sphenoid sinus. Gresenguet et al. (1989) reported a single patient with invasive aspergillosis involving the sphenoid sinus, optic canal and base of skull, who was treated initially with surgery and conventional, short course anti-fungal therapy. His disease relapsed after 14 months and he then received itraconazole (200 mg daily). This produced a marked clinical improvement which was sustained during one year of continuous treatment with the drug.

We advocate surgical clearance, combined with itraconazole for non-invasive and destructive semi-invasive sphenoid aspergillosis, due to the aggressive nature of disease in this location and the potental for progression. Once true mucosal fungal invasion has occurred or the organism has spread into contiguous structures, then surgical exenteration should be accompanied by chemotherapy with intravenous amphotericin B, with or without flucytosine, and subsequent long-term itraconazole.

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