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Rhinocerebral aspergillosis

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Abstract

Aspergillosis is increasingly being recognised as a common fungal infection of the paranasal sinuses. Although the disease is almost endemic in neighbouring Sudan, there are few reported cases from the Kingdom of Saudi Arabia. We report four cases of sinus aspergillosis with involvement of the skull bases and/or intracranial spread; a condition we have termed rhinocerebral aspergillosis. Invasive aspergillosis in our subgroup of patients occurs in otherwise healthy patients with normal immune status, quite unlike most reported cases in the western literature. The causative agent in all our patients was identified as *aspergillus flavus*, similar to patients reported from Sudan. This is again at variance with the case reports from other geographical locations, where *aspergillus fumigatus* is the commonest causative agent. Saudi Arabia would appear to represent a distinct geographical enclave, together with Sudan, where rhinocerebral aspergillosis of the sinuses and skull base may be more common than has previously been realised.

Introduction

Aspergillosis is an important fungal disease of the respiratory tract (Romett and Newman, 1982). Air-borne transmission is the principal route of spread. The fungus has been described as the commonest fungal pathogen of the paranasal sinuses (Stammberger *et al.*, 1984). Infections of the paranasal sinuses can assume different forms. Septate hyphae may grow within the sinus and form a mass (aspergilloma) that elicits little reaction. Sometimes, there may be an indolent inflammatory reaction with the disease taking a very slow clinical course. Rarely the clinical course may be fulminant with spread into the anterior cranial fossa and the orbit. This phenomenon is particularly common in immunosuppressed patients. Based on its clinical presentation (Hartwick and Batsakis, 1991), sinus aspergillosis has been classified into four types:

a. Fulminant (invasive) sinusitis,
b. Indolent chronic sinusitis,
c. Aspergilloma and
d. Allergic aspergillosis of the sinuses.

The former two types are also described as invasive forms of sinus aspergillosis.

Invasion of the intracranial cavity by the fungus is an uncommon complication of sinus aspergillosis but is nevertheless, the commonest cause of mortality and morbidity (Quiney *et al.*, 1988). When the fungus invades the intracranial space, the usual route is thought to be haematogenous—from the lung or the intestines (McGill *et al.*, 1980); but intracranial involvement in association with sinus aspergillosis is more likely to be by contiguous spread across the skull base.

Aspergillosis of the paranasal sinuses is reportedly common in Sudan where the disease is almost endemic (Milosev *et al.*, 1969; Mahgoub, 1977). There are however few reports of paranasal sinus aspergillosis from neighbouring Saudi Arabia (Dawlatly *et al.*, 1988). We present here four patients with aspergillus infection of the nose and paranasal sinuses with anterior skull base involvement—a condition better described by the term *rhino-cerebral aspergillosis*. We believe that rhino-cerebral aspergillosis has to be distinguished from aspergillosis of the nose and sinuses without involvement of the skull base or intracranial cavity, as there are major differences in the clinical course, treatment and eventual outcome, between the two entities. Although rhino-cerebral aspergillosis is normally seen in fulminant aspergillus sinusitis in immunosuppressed patients, it may at times, occur in otherwise healthy subjects with a normal immune status especially when the 'non-invasive' forms of the disease are left untreated for prolonged periods (Jahrsdoerfer *et al.*, 1979).

Case reports

Case 1:

A 35-year-old Saudi lady presented to the outpatient department of Asir Central Hospital, with proptosis of the right eye of four weeks duration. Prior to this her only complaints had been nasal irritation, rhinorrhoea and sneezing on and off for a few years. This had been diagnosed as nasal allergy and treated with antihistamines by her family doctor. She had noticed a slight swelling of her right eye about four weeks prior to her first hospital visit. This proptosis had steadily worsened and at the time of her presentation was accompanied by diplopia in some eye

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positions. Clinical examination showed multiple polypoidal lesions in both nasal cavities. Haematological and biochemical investigations including complete blood count, E.S.R., HIV test, blood sugar, renal and liver function tests were all within normal limits. Routine immunological tests such as serum immunoglobulin quantitation, absolute lymphocyte count and serum protein electrophoresis as well as tests of T & B cell function were all normal. Plain X-ray examination of the paranasal sinuses showed complete opacity of the maxillary and ethmoidal sinuses on both sides. C.T. scan of the sinuses showed a mass filling both the nasal cavities, maxillary and ethmoidal sinuses (Fig. 1) with invasion of the orbit and extending intracranially to the anterior skull base.

A biopsy of the lesion was taken from the maxillary sinus through a Caldwell-Luc procedure and diagnosis of fungal granuloma due to *aspergillus flavus* was made. The patient underwent a radical antrostomy of the maxillary sinuses and trans-antral ethmoidectomy through the Caldwell-Luc approach, and anterior cranio-facial resection of anterior skull base. During surgery a fibrous mass containing greenish-black tarry material was seen occupying the sinuses and orbit with destruction of the lamina papyracea. The same material was seen extending through the roof of the ethmoid to the anterior skull base. This was removed and sent for microbiological and histopathological examination. The dura was uninvolved and healthy. Post-operatively the patient was immediately relieved of her proptosis and diplopia and was discharged home after a four week course of amphotericin B (0.8 mg/kg body weight daily to a total dose of 1.5 gms). At follow up, she has been free of recurrence two years after surgery.

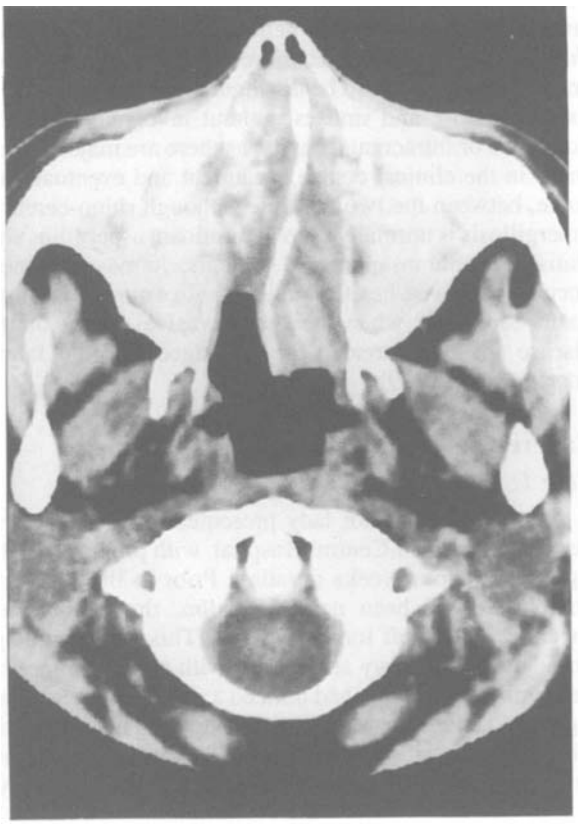

Fig. 1
C.T. scan showing the involvement of the maxillary sinuses and nasal cavities.

Case 2:

A 30-year-old Indian male working as a farm labourer in Saudi Arabia for the past seven years, presented with increasing diplopia of the left eye of three months duration. The patient had rhinorrhoea, nasal obstruction, nasal irritation and sneezing for about six months prior to his presentation. There was no history of headache, vomiting or visual disturbances. Haematological and biochemical tests including complete blood count, E.S.R., HIV test, blood sugar, urea, creatinine and liver function tests were all normal and immunological tests (such as serum immunoglobulin quantitation and serum protein electrophoresis, lymphocyte suppressor and helper subsets) were also reported as normal. Plain x-rays of the sinuses showed opacification of both maxillary and ethmoid sinuses. A C.T. scan showed a mass occupying the entire nasal cavity with involvement of the right maxillary sinus, both ethmoidal sinuses, both orbits and the right frontal sinus with encroachment into the anterior skull base (Fig. 2). The patient underwent anterior craniofacial resection along with clearance of the frontal and ethmoidal sinuses, nasal cavities and the left orbit through a lateral rhinotomy. The maxillary sinus was also cleared simultaneously. The cribriform plate was partially destroyed by the lesion but the dura was uninvolved. The dura was reinforced with a skin graft and the cribriform plate excised. The involved sinuses were filled with a fibrous mass containing greenish-black, sticky, tarry material. This material was sent for histopathology and microbiology and was reported as a fungal granuloma due to *aspergillus flavus*. Post-operatively the patient was relieved of his proptosis and was given a course of amphotericin B (1 mg/kg body weight for six weeks, to a total

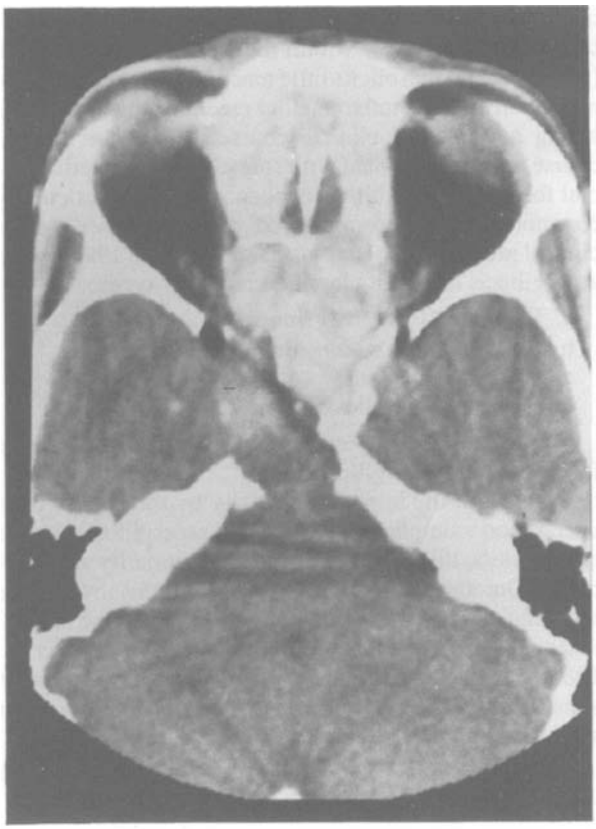

Fig. 2
C.T. scan showing the invasion of the skull base.

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dose of 2.7 gms). The patient has been followed up for over a year now and has been free of recurrence as assessed clinically and radiologically.

Case 3:

A 45-year-old Saudi male presented with bilateral proptosis, anosmia and nasal obstruction of six years duration and increasing headache and diminution of vision of three months duration. On examination, the patient had bilateral proptosis with a full range of eye movement and frank papilloedema of both fundi. Both nasal cavities showed polypoidal masses and the floors of both frontal sinuses and ethmoids were partly deficient and thinned out exhibiting eggshell crackling. A C.T. scan showed an extensive lesion filling the frontal sinuses, both ethmoids and encroaching on to the orbits. The lesion was also filling the upper part of both nasal cavities with intra-cranial extension to the frontal lobes (Fig. 3). Routine biochemical, haematological and immunological tests were all normal. Biopsy of th nasal mass showed a granulomatous lesion containing aspergillus and fungal culture showed the organism to be *aspergillus flavus*. The patient had an anterior craniofacial resection through a bifrontal flap to expose the anterior skull base with removal of the granuloma from the nasal cavities, both ethmoid and frontal sinuses and the sphenoid sinus together with excision of cribriform plate. The dura was extensively involved and the intracranial mass was found to be hard and almost calcific in consistency. The intracranial mass was excised almost completely except for a small area abutting the optic chiasma and infundibulum. The diseased dura was also excised and repaired with facial graft reinforced with a split skin graft. The medial wall of the orbit was destroyed but the orbital periosteum itself was uninvolved. Patient was also given amphotericin B for seven days pre-operatively and 40 days post-operatively amounting to a total dose of 3 grams. The patient improved remarkably after the surgery and had improved sensorium. However four weeks post-operatively the patient had a sudden deterioration in his sensorium and developed urinary and faecal incontinence. A repeat C.T. scan showed a recurrence of the lesion in the intracranial area and skull base and the patient was re-explored. At re-exploration it was found that the intracranial fungal mass had not only recurred but was indeed more extensive than at the first surgery. Excision was however very much easier on this occasion due to the fact that the granuloma was very soft, in contrast to the hard lesion encountered in the first surgery. This was presumably a result of the prolonged course of amphotericin B. The fascial graft used to repair the dura was found to be completely involved by the recurrent fungal granuloma as was the adjoining dura. The entire area was excised and a new repair attempted using fresh fascia. The patient deteriorated inspite of continued amphotericin and 5-flucytosine and died after 15 days.

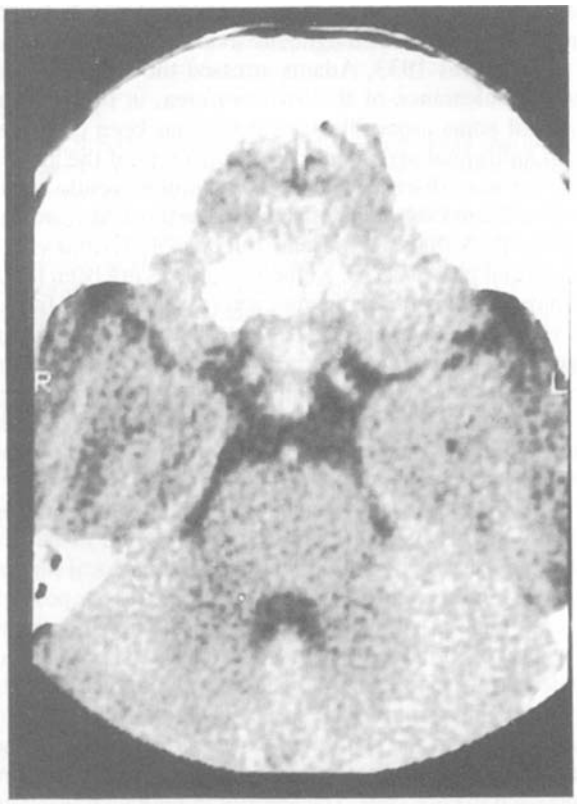

Fig. 3
C.T. scan showing the lesion in the frontal lobe.

Case 4:

A 60-year-old Saudi lady presented to the E.N.T. outpatients with a history of increasing proptosis, headache, anosmia and recurrent nasal polypi. She had had a nasal polypectomy on three previous occasions at various other hospitals. A C.T. scan of the patient revealed an extensive mass occupying the maxillary, ethmoidal and frontal sinuses and nasal cavities of both sides. Biopsy of the nasal lesion was reported as a granuloma caused by aspergillus species and culture grew *aspergillus flavus*. A complete blood picture, HIV test, blood chemistry including L.F.T. and random blood sugar were normal. Immunological studies were normal. The patient underwent an anterior skull base exploration with lateral rhinotomy. At exploration, the cribriform plate and roof of the ethmoids was found to be destroyed by a granuloma containing greenish, tarry material. The dura was however healthy-looking and there was no intracerebral pathology. The involved part of the skull base was excised and the dura reinforced with a split skin graft. In addition the orbit was decompressed by removing the lamina papyracea. The orbital periosteum was however uninvolved. The maxillary sinuses were also cleared of the granuloma. Patient was given a course of amphotericin B post-operatively (1.5 grams given over a course of 30 days) and was discharged home after completion of the chemotherapy in good health. She has now been followed up for 14 months with no clinical evidence of recurrence. A C.T. scan performed four months post-operatively has shown no recurrence.

Discussion

Aspergillosis or infection with aspergillus species is the commonest fungal infection of the paranasal sinuses (Stammberger *et al.*, 1984). The causative agent is a filamentous fungus (Fig. 4) which occurs as a saprophyte in soil and decaying matter and is probably spread by airborne transmission. Transmission between humans is unknown. The fungus has septate hyphae and reproduces as asexual conidia.

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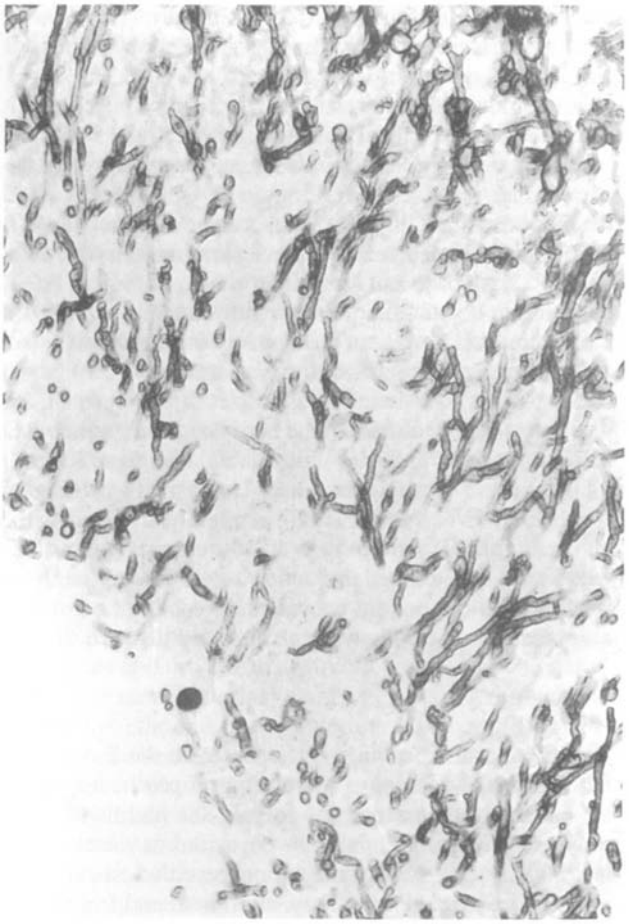

Fig. 4
Low power view showing the numerous organisms. The septate nature of the hyphae can be discerned.

Three species, *A. fumigatus, A. niger* and *A. flavus* have been most commonly associated with human pathogenecity. While *A. fumigatus* is perhaps the commonest species associated with sinus disease in most geographical areas, *A. flavus* is the commonest organism isolated from patients in Sudan (Milosev *et al.*, 1969; Mahgoub, 1977). The isolation of *Aspergillus flavus* from all four of our patients points to a remarkable similarity of our cases to the cases reported from Sudan.

Sinus aspergillosis has been classified into two broad categories: invasive aspergillosis and non-invasive aspergillosis based on the presence or absence of tissue invasion in histopathological studies. Invasive aspergillosis has been further categorised into fulminant (invasive) aspergillosis predominantly occuring in immunosuppressed patients and indolent chronic sinusitis occuring in normal subjects. This categorization is however too simplistic, as there is little doubt that the disease can present in its invasive and aggressive form in non-immunologically compromised patients. It is quite possible that when non-invasive forms are left untreated for prolonged periods they may eventually assume an aggressive clinical course. Alternately the behaviour of the disease in patients from Sudan and the Middle East may be different from other geographical areas, in as much as, normal immune status in patients with invasive aspergillosis seems to be the rule rather than the exception (Milosev *et al.*, 1969; Quiney, *et al.*, 1988). Differences in pathogenecity has also been associated with differences in the ability of the strain to produce aflatoxin (Mahgoub, 1971) and may perhaps explain the sporadic occurence of invasive aspergillosis in immunologically normal patients in other geographical areas (Robb, 1986).

Clinical symptomatology of rhinocerebral aspergillosis is at best non-specific and patients may present with proptosis or polypoid lesions in the nose. Two of our patients had symptoms of vasomotor/allergic rhinitis and one patient had had multiple procedures in the nose for nasal polyps. Blood stained nasal discharge, nasal congestion, ozaena, mild discomfort over the nasal bridge and headache are the other symptoms reported by other authors (Quiney *et al.*, 1988). In Sudan, sinus aspergillosis has been implicated as the commonest cause of non-congenital unilateral proptosis (Milosev *et al.*, 1969). Zinemann (1972) contrasted the slowly progressive proptosis of sinus aspergillosis with the more fulminant type of proptosis seen in mucormycosis. In an authorative review of the literature, Jahrsdoerfer *et al.* (1979) noted the remarkable increase in the incidence of the disease not least from an increased awareness of the condition. The authors also noted the remarkable similarity in the clinical presentation of the disease with sinus tumours.

Stammberger *et al.* (1984) noted the occurence of radio-opaque concretions in sinus aspergillosis which may be detectable in plain x-rays of the sinuses. Notwithstanding this observation, the mainstay in the diagnosis of rhino-cerebral aspergillosis continues to be C.T, scan and tissue diagnosis. A C.T. scan helps to delineate the extent of the disease and may demonstrate diagnostic features such as heterogenous opacification with radio-opaque concretions probably due to heavy metal content. M.R.I. scans in both axial and coronal planes have been employed usefully in diagnosing the condition by some authors (Quiney *et al.*, 1988) although we have no experience with this newer diagnostic modality.

As early as 1933, Adams stressed the importance of surgical clearance of the involved area, in the management of sinus aspergillosis. Surgery has been combined with antifungal agents in the management of the aggressive invasive disease. The main chemotherapeutic agents used in the management of sinus aspergillosis are, amphotericin B, 5 flucystosine and fluconazole (Arora *et al.*, 1978) and itraconazole. Ketoconazole has not been found to have significant therapeutic activity against the fungus in vitro (Clissold, 1987). The use of systemic anti-fungal agents in the treatment of the allergic form of fungal sinusitis is considered questionable both in terms of their value as an adjuvant to surgery and the possible serious and sometimes fatal side effects (Zinneman, 1972; Titche, 1978; Katzenstein *et al.*, 1983; Waxman *et al.*, 1987).

The most logical approach to the management of these locally aggressive 'tumours' in our subgroup of healthy patients seems to be a combination of radical local surgery with an aim to eradicate as much of the disease as possible in combination with antifungal chemotherapeutic agents. Surgery of rhinocerebral aspergillosis can be a major undertaking necessitating surgical clearance of the involved areas of the skull base and sinuses. The extent of involvement of the skull base can vary from case to case, requiring the surgeon to modify his technique and approach in each case. The anterior craniofacial resection for fulminant aspergillosis has been employed earlier (Cheeseman *et al.*, 1986; Quiney *et al.*, 1988) and affords

an excellent approach to the involved area. The procedure was combined with lateral rhinotomy in our patients to gain access to the other sinuses and the orbit. Surgery was combined with antifungal chemotherapy in all our patients.

The prognosis in our series of four patients, all of whom enjoyed normal immune status, seemed to be related to the extent of dural involvement. In the one patient in whom the dural barrier was completely breached with intracerbral extension, the disease had a fulminant course inspite of meticulous surgical clearance and aggressive chemotherapy. Excision of the involved dura along with the intracerebral granuloma and repair of the dura with a fascial graft did not succeed in limiting the spread of the disease, as the graft and adjoining dura were found to be involved in the recurrent fungal granuloma when the patient was re-explored four weeks after the first exploration. In patients with extensive intracerebral spread of the disease, it is clear that our present management strategies are inadequate and only the arrival of newer, more effective fungicidal agents could substantially alter the outcome in these patients. It is therefore incumbent on clinicians to diagnose rhinocerebral aspergillosis at a relatively earlier stage before extensive intracranial involvement has occured. A high index of suspicion on the part of clinicians (especially in geographical areas where the disease seems to have a high prevalence rate) and C.T. evaluation of all suspicious cases are pivotal for achieving this goal.

Although reports of sinus aspergillosis from the Kingdom of Saudi-Arabia are few, our cases bear a striking resemblance to the cases reported from neighbouring Sudan, both in the pattern of clinical presentation as well as causative agent, and it seems likely that the Kingdom of Saudi-Arabia may also have a higher incidence of sinus aspergillosis than has previously been suspected.

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