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Semi-invasive allergic aspergillosis of the paranasal sinuses

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Abstract
Aspergillosis of the nose and paranasal sinuses has classically been divided into four types: allergic, non-invasive, invasive and fulminant. Recent reports have suggested that a semi-invasive form with bone destruction and erosion, but without fungal tissue invasion, may occur. We present a case of allergic non-invasive aspergillosis of the paranasal sinuses with associated bone destruction extending into the orbit and anterior cranial fossa, in a non-immunocompromised patient. Surgical debridement combined with a prolonged course of oral itraconazole has resulted in long-term resolution with no evidence of recurrence of disease five years later.

Key words: Aspergillosis; Paranasal sinuses

Introduction

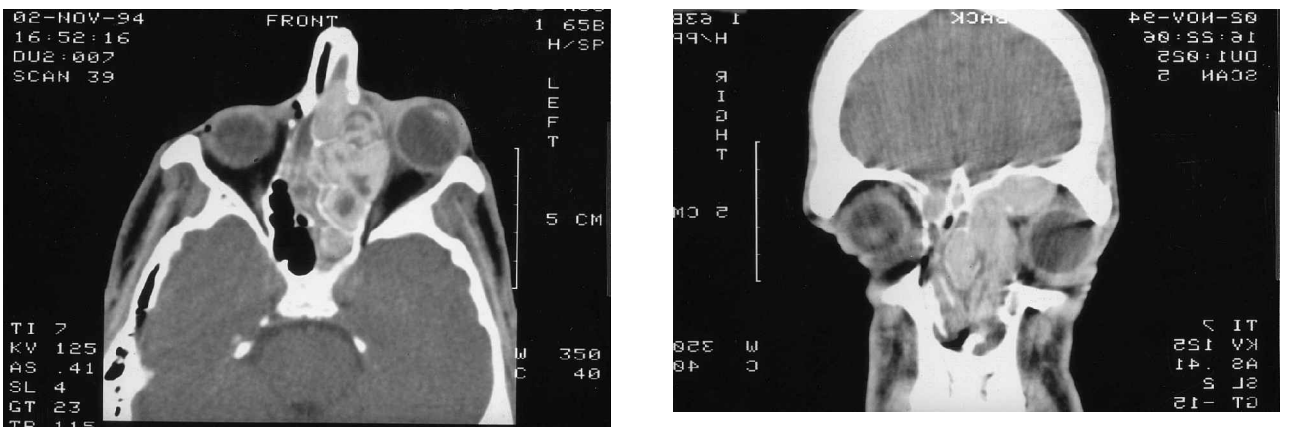
Schubert[1] first reported aspergillosis of the nose and paranasal sinuses in 1885. The initial classification into invasive and non-invasive forms by Hora[2] in 1965 was further modified by McGill *et al.*[3] in 1980. He used the term 'fulminant aspergillosis' to describe a rapidly progressive and, often fatal, invasive form presenting in immunocompromised patients. Non-invasive aspergillosis was also further subdivided by Katzenstein *et al.*[4] in 1983 who first recognized allergic aspergillus sinusitis (AAS). Since then it has been traditionally accepted that aspergillosis of the nose and paranasal sinuses occurs in four different forms: allergic, non-invasive, invasive and fulminant.[5]

A detailed analysis of previously reported cases by Rowe-Jones[6] in 1993 showed that *Aspergillus* infection may produce marked destruction and erosion of the sinuses without fungal tissue invasion and suggested that paranasal aspergillosis should be considered as a spectrum of disease. His proposed classification includes a semi-invasive form that may represent a progression from a non-invasive to an invasive form.

The following case report discusses the presentation and management of a patient with AAS. The association of extensive bone destruction and the histological features of AAS would support the theory that this condition may present as a locally destructive semi-invasive form without tissue invasion.

Case report

A 41-year-old single Caucasian male librarian was referred by the ophthalmologists with a six-month history of epiphora and displacement of the left eye, a two-year history of nasal obstruction and an abnormal computed tomogram (CT) of his orbits. Clinical examination revealed non-axial left proptosis with lateral and downward displacement of the eye together with a soft tissue



(a) (b)

Fig. 1

Axial (a) and coronal (b) CT images of the nose and sinuses showing mottled calcification within the mass with lateral nasal wall destruction and orbital invasion.

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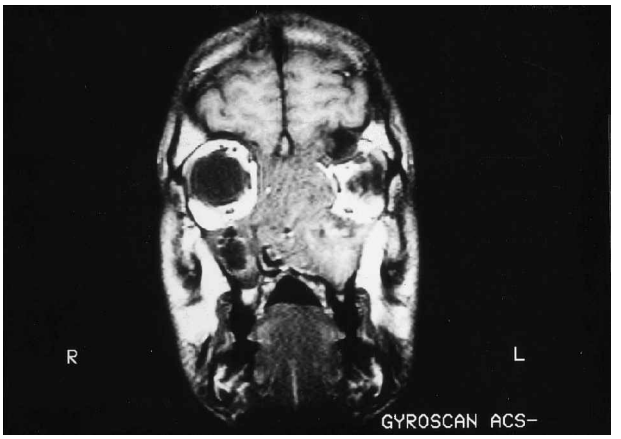

FIG. 2

T_1-weighted coronal MRI scan showing similar features to Figure 1 and, in addition, the nasal mass abutting on the inferior surface of the frontal lobe without dural transgression.

swelling at the inner canthus. The nose was completely obstructed by a large, friable polypoidal mass filling the left nasal cavity and displacing the nasal septum.

A CT scan of the nose and paranasal sinuses showed a large soft tissue mass with mottled calcification occupying the left nasal cavity. There was associated opacification of the left maxillary, ethmoidal, frontal and sphenoid sinuses together with bone destruction of the left lateral nasal wall, lamina papyracea and cribriform plate (Figure 1). The mass extended into the left orbit and further expansion into the anterior cranial fossa was suspected. Magnetic resonance imaging (MRI) showed similar features to the CT scan with abutment of the mass onto the inferior surface of the left frontal lobe, but without evidence of dural transgression (Figure 2). The T_2-weighted images showed a hypointense signal in the affected areas (Figure 3).

Haematological indices were within normal limits, including immunoglobulin electrophoresis. An autoimmune profile was negative to all common autoantibodies. The CD4/CD8 ratio was normal with a marginally low CD8 count. A test for human immunodeficiency virus (HIV) was negative. Both angiotensin-I-converting enzyme (ACE) and antibodies to neutrophil cytoplasmic antigens (ANCA) were normal.

Examination under anaesthesia confirmed the presence of a large polypoidal mass obstructing the left nostril from which piecemeal biopsies were taken. The left maxillary

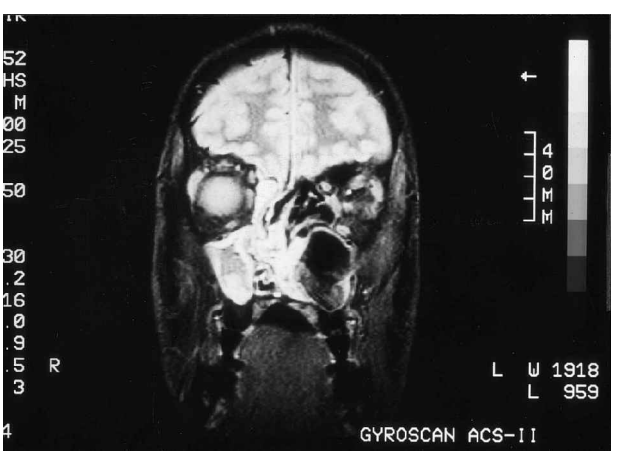

FIG. 3

T_2-weighted coronal MRI scan showing a hypointense signal in the affected area.

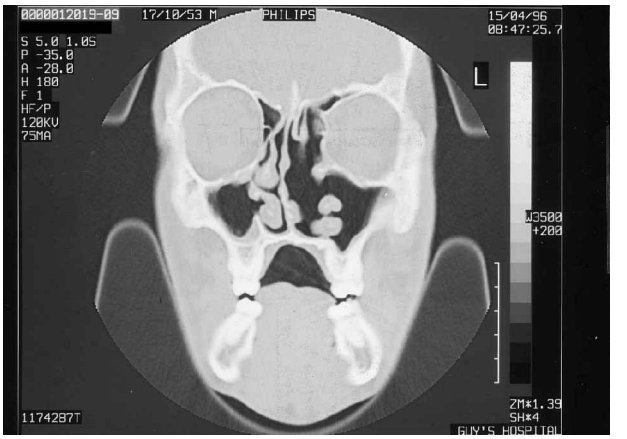

FIG. 4

Post-operative coronal CT scan showing absence of disease in a well-ventilated nose and sinuses.

antrum was full of thick, brownish-green inspisated mucus. Histological examination revealed allergic-type nasal mucosa, large masses of laminated mucus with heavy eosinophil infiltration and Charcot-Leyden crystals. Occasional septate hyphae were noted within the mucus but there was no evidence of tissue invasion or neoplasia. These results were consistent with an *Aspergillus* infection and treatment with oral itraconazole was commenced at a dose of 600 mg daily.

Subsequent surgical debridement was performed through an extended lateral rhinotomy incision. The friable soft tissue mass which had eroded the lateral nasal wall and lamina papyracea back to the orbital apex was removed from the left nasal cavity together with bony remnants from the affected sinuses. A large bony defect was found communicating between the orbital roof, the frontal sinus floor and anterior cranial fossa but the dura was intact. Histological examination of the operative specimen showed similar features to the previous sample in keeping with AAS but without any evidence of tissue invasion. Fungal stains demonstrated fungal spores and hyphae with appearances consistent with *Aspergillus*. The patient made an uneventful post-operative recovery with gradual improvement of the proptosis. He was discharged on 400 mg of itraconazole daily for three months. Regular follow-up and repeat CT and MRI scans have failed to demonstrate any recurrence of disease to date, five years later (Figure 4).

Discussion

Aspergillosis of the nose and paranasal sinuses has been recognized for over a century, but the exact pathogenesis of this condition remains poorly understood. Immunosuppression plays an important role in the pathogenesis of invasive aspergillosis[5,7] with an increasing number of reports in patients with the acquired immunodeficiency syndrome (AIDS).[8,9] In the immuno-competent host invasive aspergillosis has a more indolent progressive course with bone destruction and tissue invasion and may prove fatal.

The terms fungal ball, mycetoma and aspergilloma have all been used in the literature to describe the saprophytic, extramucosal, non-invasive form of the disease. Usually they involve a single sinus although multiple sinuses can be affected and bone destruction may be present.[10]

The description of AAS by Katzenstein and her colleagues[4] in 1983 was based on the histological similarities with allergic bronchopulmonary aspergillosis (ABPA). An association between AAS and ABPA has

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been described in four patients to date.[11–14] It has been suggested that AAS rather than a true infection is the result of a combination of type I (IgE) and type III (immune complex) immune reactions to *Aspergillus* antigens.[15] Patients with AAS usually present with chronic sinusitis, nasal polyps and a history of atopy. Multiple sinus involvement is the norm and bone erosion is not infrequent.[16,17] Although primarily classified as a non-invasive form it would appear that AAS has a potential for local destruction. It has yet to be demonstrated whether this erosive effect represents a direct manifestation of the progression of the disease or a different pathological entity within AAS.

It has been postulated that the severity of paranasal aspergillosis is related to the duration of the disease and given time a non-invasive form may become invasive.[5] An alternative explanation is that the diagnostic features of the subtypes of paranasal aspergillosis are not sufficiently robust to allow classification at presentation.

The non-invasive cases, with obvious bone destruction and spread into adjacent structures, together with those where progression from a non-invasive to an invasive form occur, or where both forms co-exist in the same patient, can not be easily accommodated in the traditional classification. This problem was addressed in 1993 by Rowe-Jones[6] when he suggested that paranasal aspergillosis should be considered as a 'spectrum of disease' with the following classification:

(1) non-invasive, either aspergilloma or allergic in type;
(2) semi-invasive, being locally destructive without tissue invasion;
(3) invasive, representing true fungal invasion either non-fulminant or fulminant in course.

The term 'semi-invasive' has already been adopted by some authors[18] and it would seem appropriate to do so until a better understanding of the pathophysiology of paranasal aspergillosis is developed.

A diagnosis of paranasal aspergillosis should be based on a high index of suspicion. Areas of increased attenuation in paranasal soft-tissue masses on unenhanced CT scans are strongly suggestive of fungal involvement. A decreased signal intensity on T_1 and very decreased intensity on T_2 weighted MR images is even more characteristic of fungal sinusitis than CT.[19] Definite diagnosis should however be based on histological findings.

Surgical treatment is always indicated in all forms of fungal sinusitis in order to aerate the affected sinuses and obtain specimens for histological studies. The surgical approach will depend on the sinuses involved and the extent of the disease. Klossek *et al.*,[20] have successfully treated 109 mycetomas of the paranasal sinuses by functional endoscopic sinus surgery (FESS) with only four recurrences.

Most authors support the use of adjuvant antifungal chemotherapy in invasive disease following surgical treatment. Systemic amphotericin B has been widely used but carries considerable morbidity. Oral itraconazole is an alternative to amphotericin B therapy, being relatively non-toxic and effective against *Aspergillus*.[7] Systemic corticosteroid therapy has been used in AAS following surgical treatment due to its allergic nature and similarity with ABPA.[15] Surgical treatment alone may not be able to prevent progression to an invasive form in semi-invasive disease and therefore the use of adjuvant itraconazole has been suggested.[6] This treatment protocol was used in the case presented with good result.

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