Clinical & Experimental Ophthalmology

RANZCO The Royal Australian and New Zealand College of Ophthalmologists

Clinical and Experimental Ophthalmology 2013; 41: 567–576 doi: 10.1111/ceo.12055

Original Article

Neuro-ophthalmology of invasive fungal sinusitis: 14 consecutive patients and a review of the literature

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Abstract

Background: Invasive fungal sinusitis is a rare condition that usually occurs in immunocompromised patients and often presents as an orbital apex syndrome. It is frequently misdiagnosed on presentation and is almost always lethal without early treatment.

Design: Retrospective case series of 14 consecutive patients with biopsy-proven invasive fungal sinusitis from four tertiary hospitals.

Participants: Fourteen patients (10 men and 4 women; age range 46–82 years).

Methods: Retrospective chart review of all patients presenting with invasive fungal sinusitis between 1994 and 2010 at each hospital, with a close analysis of the tempo of the disease to identify any potential window of opportunity for treatment.

Main Outcome Measures: Demographic data, background medical history (including predisposing factors), symptoms, signs, radiological findings, histopathological findings, treatment approach and subsequent clinical course were recorded and analysed.

Results: Only one patient was correctly diagnosed at presentation. Only two patients were not diabetic or immunocompromised. The tempo was acute in two patients, subacute in nine patients and chronic in three patients. In the subacute and chronic cases, there was about 1 week of opportunity for treatment, from the time there was a complete orbital apex syndrome, and still a chance for saving the patient, to the time there was central nervous system invasion, which was invariably fatal. Only two patients survived – both had orbital exenteration, as well as antifungal drug treatment.

Conclusions: Invasive fungal sinusitis can, rarely, occur in healthy individuals and should be suspected as a possible cause of a progressive orbital apex syndrome.

Key words: aspergillosis, cranial nerve palsy, invasive fungal sinusitis, mucormycosis, orbital apex syndrome.

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Received 7 May 2012; accepted 4 December 2012.

Competing/conflicts of interest: No stated conflict of interest.

Funding sources: No stated funding sources.

Introduction

Few diseases presenting to the ophthalmologist are potentially curable if identified and treated early, but fatal if treated late; invasive fungal sinusitis (IFS) is one. IFS occurs when common saprophytes of the paranasal sinuses[1] invade the paranasal sinus mucosa, usually in diabetic or immunocompromised patients. The fungi spread from the paranasal sinuses directly, or via the pterygo-palatine fossa, to the orbital apex, and then the cavernous sinus and cavernous carotid artery, causing carotid occlusion, cerebral infarction, mycotic aneurysms, subarachnoid haemorrhage, meningitis, cerebral abscess and ultimately death; this is the inexorable sequence of 'rhino-orbito-cerebral' mycosis.[2,3] The problem is that whereas IFS is easy to suspect and diagnose once a complete orbital apex syndrome (OAS) has developed, by then it is usually too late to save the patient's vision and frequently too late to save the patient's eye or life. IFS is difficult to diagnose early when the patient presents with only eye pain followed by diplopia or visual loss. Here, we report our experience with 14 patients who had histopathologically confirmed IFS. Our aim is to develop, based on our cases and a review of the literature, practical criteria to help with early diagnosis of IFS.

Methods

The charts of all patients diagnosed with IFS in our four hospitals between 1994 and 2010 were retrospectively reviewed. Demographic data, background medical history (including predisposing factors), symptoms, signs, radiological findings, histopathological findings, culture results, treatment and subsequent clinical course were reviewed. As each patient had been assessed and followed by at least one author, detailed information was available for every patient.

Results

Age, sex and predisposing factors

There were 10 men and 4 women aged from 46 to 82 years (mean 65 years). Of the 14, 12 had a predisposing factor: 7 were diabetic (2, diabetic ketoacidosis; 2, hyperosmolar non-ketotic acidosis), 4 had leukaemia (3, acute myeloid; 1, chronic lymphocytic and post-bone marrow transplant) and 1 had myelodysplasia. At presentation, five were hospital inpatients: four were receiving chemotherapy, three for acute leukaemia (all were neutropenic) and one for lung cancer (also receiving steroids for presumed brain metastases). Three patients were receiving systemic corticosteroids before symptoms of IFS developed and three were receiving corticosteroids for what were, in hindsight, the initial symptoms of IFS. Only two patients, a 53-year-old woman and an 81-year-old man, had no identified predisposing factor.

Presentation and initial diagnosis

Of the 14 patients, 10 had initially presented to a medical office: 6 to an ophthalmologist, 1 to an internist-physician, 1 to an otorhinolaryngologist and 2 to a general practitioner. Two patients had presented to a hospital emergency department and two were already in hospital for leukaemia treatment. The initial symptom was unilateral eye pain, facial pain or headache in 12 patients; one patient had no pain and another was unconscious at presentation. Five were febrile at the onset of the OAS; two of the five had become neutropenic from chemotherapy for leukaemia. Of the two patients with acute IFS, only one was febrile. Apart from facial pain, only one patient had symptoms (e.g. blocked nostril) to suggest paranasal sinus disease. At initial presentation, the correct diagnosis was made in only one patient (by a haematologist); in the other 13, the following incorrect diagnoses were made: giant cell arteritis (2), bacterial rhino-sinusitis (2), orbital cellulitis (2), uveitis, posterior scleritis, herpes zoster ophthalmicus, Bell's palsy, brain metastasis, sepsis and gastroenteritis.

Tempo of evolution

The evolution of IFS from the onset of the initial symptoms to definitive diagnosis was acute in two patients (measured in days), subacute in nine patients (measured in weeks) and chronic in three patients (measured in months). Of the 12 patients who died, the total duration of the illness from symptom onset to death varied between 6 days and 6 months (date of death not known in one patient who was lost to follow up). The period from the onset of unilateral eye, face or head pain to the initial symptom of cranial neuropathy due to the OAS was 1 and 3 days in the two acute cases, 1 to 22 days in the nine subacute cases and 7, 84, and 167 days (i.e. 1 week to 5 months) in the three chronic cases. The first symptom of cranial neuropathy was exclusively monocular visual loss (due to optic neuropathy) in four patients, exclusively diplopia or ptosis in four patients and a combination of vision loss and ophthalmoplegia in six patients. Thirteen of the 14 patients developed proptosis at some stage. The time to evolve from a partial OAS to a complete OAS was: 1 day in each of the two acute cases; 1, 1, 3, 5, 7, 9 and 10 days in the nine subacute cases; and 7, 9 and 46 in the three chronic cases. Symptoms and signs of

cerebral infarction, subarachnoid haemorrhage or cavernous sinus thrombosis were taken as the onset of central nervous system involvement due to intracranial invasion of the fungus. Data on the time to evolve from a fully developed OAS to the onset of central nervous system involvement were available in seven patients and varied from less than 1 day to 46 days. Chemosis developed in eight patients and involvement of the ophthalmic division of the trigeminal nerve in six patients. There was no evidence of central nervous system involvement in the two patients who survived or in the two patients who died of systemic disease. The period from the onset of pain to the start of antifungal treatment varied from 1 to 170 days. In the two surviving patients, this period was 14 days in one, whereas the other was already receiving voriconazole for fungal pneumonia, which was changed to posaconazole and amphotericin B once IFS was diagnosed.

Imaging

The initial imaging study was computed tomography (CT) of the brain in 13 patients; this revealed no abnormality in five patients, mild sinusitis in two patients, moderate sinusitis in three patients and severe sinusitis in three patients, but no definite extra-sinus extension in any patient. The initial positive imaging study, revealing extra-sinus extension, was CT sinuses in two patients, CT orbits in five patients and magnetic resonance imaging (MRI) of the brain in seven patients. The initial MRI brain showed extra-sinus disease (only when contrast was given) in nine patients (Fig. 1), but did not do so in one patient. MRI brain was normal in the sole patient who had only a non-contrast MRI, and was not done in one patient, who had extra-sinus extension on CT sinuses. The time from onset of symptoms to the first positive diagnostic imaging study was 2–168 days for MRI brain, 7–22 days for CT orbits and 28 days for CT sinuses.

Fungal identification

All patients had, by definition, histological evidence of tissue invasion by fungus on biopsy of the paranasal sinuses or orbital apex. In two patients, sinus biopsy specimens were negative for fungus and the diagnosis was eventually made by orbital apex biopsy directed towards areas where there were imaging abnormalities (e.g. contrast enhancement or fat stranding). Even when many specimens were taken from the sinuses or orbital apex, only a few showed fungal invasion (in one patient, only 2/11). Even in the more extensive specimens taken at debridement or orbital exenteration, fungus was only found in some of the specimens. In nine patients, the fungi were identified on culture of biopsy tissue: *Rhizopus* in four patients, *Aspergillus* in two, *Scedosporium* in one and *Zygomycetes* in two patients. In the other five patients, the culture was negative or the specimen was not sent for culture; in these, the fungi were identified histologically as *Aspergillus* in two and *Zygomycetes* in three patients.

Treatment

Two patients, both with leukaemia, were already on antifungal therapy at the time of diagnosis: one was on itraconazole and died of *Scedosporium* infection,

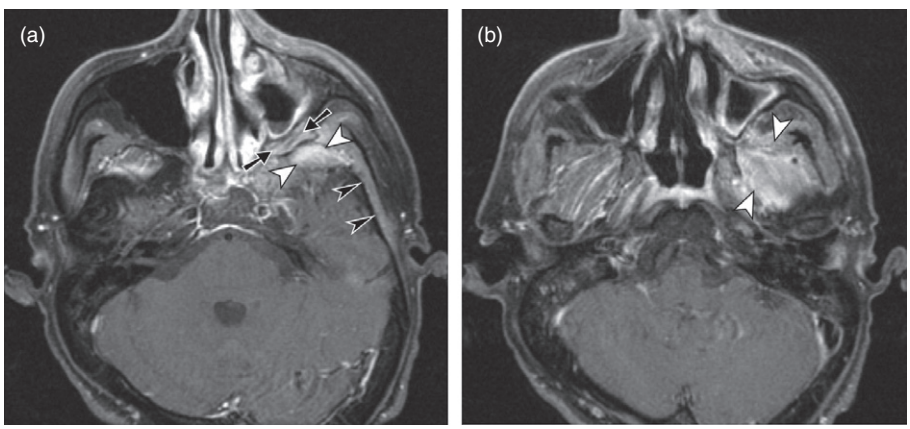

Figure 1. Magnetic resonance imaging (MRI) findings in invasive fungal sinusitis (IFS) (*Zygomycetes*). A 46-year-old male diabetic presented with painful ophthalmoplegia, initially misdiagnosed as herpes zoster ophthalmicus. Paranasal sinus biopsies were negative, but orbital apex biopsies were positive for IFS with *Zygomycetes*, which could not be cultured. He was eventually treated with amphotericin B, voriconazole, hyperbaric oxygen, and orbital exenteration – and survived. Axial T1-weighted fat-suppressed post-contrast MRI shows mucosal thickening in the left maxillary sinus, with avid enhancement in the pterygoid plates (black arrows), left pterygo-palatine fissure (white arrowheads) and supra-zygomatic portion of the left temporalis muscle (black arrowheads).

whereas the other was on voriconazole for presumed *Aspergillus* pneumonia and survived the IFS, but later died of a leukaemic relapse. The other 12 patients were all initially treated with amphotericin B beginning 1, 2, 7, 8, 12, 13, 14, 28, 35, 38, 106 and 168 days after the onset of symptoms. Four patients were subsequently treated with other oral antifungals: posaconazole in two patients and voriconazole in the other two patients (one of these patients also received terbinafine for treatment of *Scedosporium prolificans*). Three patients underwent orbital exenteration – two survived. Six patients had local debridement and three had no debridement – all nine died. Two patients were considered beyond surgical help. A characteristic observation during debridement surgery was that the invaded tissue did not bleed, presumably because all arteries supplying the tissue had thrombosed due to angio-invasion by fungus. Four patients also received hyperbaric oxygen therapy in addition to medical and/or surgical treatment, but only one survived.

Cause of death

Four of the 12 patients who died of IFS had autopsies and, in all, the cause of death was considered to be intracranial fungal arteritis with thrombosis and distal infarction (Fig. 2). Meningitis was also identified in two patients. Clinically identified causes of death were: mycotic aneurysm with subarachnoid haemorrhage (2), cavernous carotid artery occlusion with cerebral infarction (1) and pneumonia (2, fungal in 1). One patient appeared to have been cured of the IFS, but subsequently died of a leukaemic relapse.

Discussion

Neuro-ophthalmic complications of IFS develop due to progressive fungal invasion, first of the orbital apex, then the cavernous sinus and carotid artery and finally the brain, invariably resulting in death if untreated. Fungus invades from the paranasal sinuses to the brain via the orbital apex, so that an OAS is often the first and last warning sign of a lethal intracranial fungal infection. Thus, it is often the ophthalmologist who has the first and last chance for timely diagnosis.

Classification of fungal sinusitis

Fungal sinusitis has two basic forms: invasive and non-invasive.[4,5] Based on the tempo of evolution, IFS can be classified as acute, subacute or chronic. Allergic fungal sinusitis (AFS), although non-invasive, can also cause an OAS by compression or local hyperimmunity.[6]

Types of fungi

IFS is usually caused by *Zygomycetes* of the order Mucorales (9/14 of our cases), *Aspergillus* (4/14), or rarely, but increasingly, by *Scedosporium* (1/14).[7,8] An OAS is more likely to be due to invasion by *Zygomycetes* than by *Aspergillus*.[9]

Host factors

IFS rarely affects healthy individuals;[10–12] only 2 of our 14 patients had no identified predisposing factor. Most affected patients are immunocompromised,

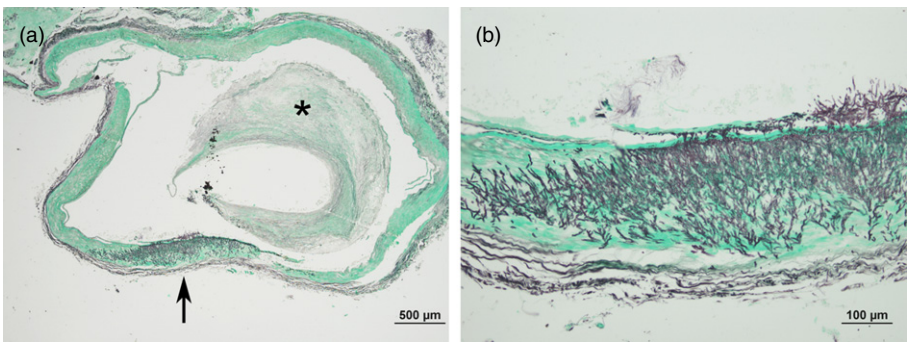

Figure 2. Pathology of the carotid artery in invasive fungal sinusitis (*Aspergillus*). Autopsy specimen from a previously healthy 81-year-old man, who presented with isolated eye pain. He had been treated with steroids and cyclosporin for presumed posterior scleritis. After 3 months, he developed sudden visual loss and then a progressive orbital apex syndrome. Magnetic resonance imaging showed normal paranasal sinuses and subtle orbital apex enhancement. Paranasal sinus biopsy showed invasive aspergillosis. He was treated with amphotericin, but 3 weeks later had a fatal cerebral infarct. Autopsy showed widespread fungal invasion of the brain arteries and meninges. Low-power (a) and high-power (b) photomicrographs of the intradural segment of the right internal carotid artery, stained with methenamine silver, show transmural invasion by fungal hyphae (*Aspergillus*; arrow). The artery also shows moderate atheroma with artifactual separation of the thickened intima from the media (*).

immunosuppressed, neutropenic or diabetic.[13] Diabetics (7 of our 14), particularly those with ketoacidosis (1 of our 14), are particularly at risk for mucormycosis. Patients with haematological malignancies (5 of our 14) are at risk, especially when neutropenic.[14–17] Other reported risk factors for mucormycosis include iron overload states and use of desferrioxamine.[11] Risk factors for invasive aspergillosis include neutrophil defects and corticosteroid use (3 of our 14 patients),[18] whereas there is a predilection for *Scedosporium* infection in patients with haematological malignancies and in transplant recipients (1/14 patients).[19,20]

Mechanism

Once fungus invades the paranasal sinus mucosa, it spreads to adjacent structures by invading bones, nerves and blood vessels, first in the pterygopalatine fossa,[21] then the orbit, orbital apex, mouth, palate and face. Arterial invasion produces thrombosis, ischaemia/infarction[22] or mycotic aneurysm formation,[23] with intracranial haemorrhage.[24] Perineural spread of fungus[25] might, as with skin cancer, cause face and eye pain. Once through the paranasal sinus, fungus invades the cavernous sinus via the orbital apex, so that the OAS may be considered a sign heralding central nervous system involvement. Once the fungus reaches the cavernous sinus, the patient is in mortal danger, not from the sinus thrombosis itself, but from fungal invasion of the cavernous segment of the carotid artery, with subsequent thrombosis or mycotic aneurysm formation with subarachnoid haemorrhage. From the carotid, the fungus can spread to other arteries of the circle of Willis, causing cerebral and brainstem infarction. There was clinical or imaging evidence of cerebral infarction in 5 of our 14 patients and of subarachnoid haemorrhage in 2. All four patients who had autopsies showed evidence of fungus invading the large arteries at the base of the brain (Fig. 2) and cerebral infarction (based on imaging in three). Two also showed evidence of meningeal invasion.

Presentation

Of our 14 patients, 12 presented with a painful OAS, but only 1 had symptoms suggesting rhino-sinusitis. The absence of rhino-sinusitis in a patient with an OAS does not exclude IFS, any more than does the absence of an OAS in a patient with nasal obstruction or discharge, facial pain and swelling, or pale ischemic nasal mucosa with eschar.[26] Half of our patients had no clinical or imaging evidence of significant rhino-sinusitis at the time of presentation. When nasendoscopy was essentially normal in two of our patients, our otorhinolaryngologists required persuasion to take biopsies, which nonetheless showed fungal invasion. In two patients with negative paranasal sinus biopsies, an orbital apex biopsy was needed to make the diagnosis. Thus, multiple biopsies from multiple sites may be needed to make the diagnosis.

Differential diagnosis

The three elements of the OAS are: (i) visual loss due to optic neuropathy; (ii) ophthalmoplegia due to third, fourth and sixth cranial neuropathy; and (iii) ocular-orbital pain and/or anaesthesia due to involvement of the ophthalmic division of the trigeminal nerve. Typically, the OAS in IFS presents with constant pain in or around the eye, followed by visual loss and ophthalmoplegia, which can occur simultaneously or sequentially.[27] The sequence in which the cranial neuropathies develop is critically important for early diagnosis. If visual loss and ophthalmoplegia occur simultaneously, it is obvious that the patient has an OAS and IFS should be considered a possibility. If, however, there is only pain followed by visual loss, the differential diagnosis is that of an acute painful optic neuropathy; IFS is unlikely to be suspected. Similarly, if there is only pain followed by ophthalmoplegia, IFS is also lower on the list of possible diagnoses. Therefore, if IFS presents as painful optic neuropathy or ophthalmoplegia, diagnosis and treatment will be delayed, increasing the likelihood of a poor outcome. There might be proptosis,[28] but there might be no chemosis initially. There is a broad differential diagnosis for a painful OAS, including infectious, inflammatory, vascular and neoplastic conditions (Box 1).[29] Patients with eye or facial pain due to unsuspected IFS are occasionally treated empirically with steroids for presumed orbital inflammatory disease or giant cell arteritis (two of our patients). Because steroids will contribute to the demise of the patient with IFS, a painful eye in a diabetic or immunocompromised patient, even without ophthalmoplegia or visual loss, should raise the suspicion of IFS. Both paranasal sinus mucocoele and non-invasive AFS can also cause an OAS by compression.[30–32] AFS can also cause an OAS by local hyperimmune effects.[6] Although there can be intracranial involvement with both mucocoele[33] and AFS,[34] it is by extension and compression rather than invasion. Imaging and tissue biopsy will distinguish IFS from AFS and mucocoele.[35,36]

Tempo

IFS causes a relentlessly progressive painful OAS and its tempo from symptom onset to death can be measured in days in acute cases (2 of our 14), weeks

Box 1. Differential diagnosis of orbital apex syndrome[29]

Inflammatory conditions:
- Sarcoid
- Vasculitis (e.g. Churg–Strauss syndrome, Wegener's vasculitis, giant cell arteritis)
- Thyroid eye disease
- Idiopathic inflammation (e.g. idiopathic orbital inflammation, Tolosa–Hunt syndrome)

Infectious conditions:
- Fungus (e.g. invasive fungal sinusitis, allergic fungal sinusitis)
- Bacteria (e.g. *Mycobacterium tuberculosis*)
- Viruses (e.g. Herpes zoster ophthalmicus)

Vascular conditions:
- Carotid-cavernous fistula
- Cavernous sinus thrombosis

Neoplastic conditions:
- Primary tumours (e.g. meningioma, perineural invasion by cutaneous neoplasm)
- Secondary tumours (e.g. metastatic lesion, lymphomatous deposit)

Other conditions:
- Mucocoele
- Trauma
- Iatrogenic

in subacute cases (9 of our 14) and months in chronic cases (3 of our 14). An opportunity for curative treatment exists, we suggest, before the complete OAS develops. The findings of our series suggest that there is about a week from the time the patient develops optic neuropathy or ophthalmoplegia to the time there is a complete OAS. Once the diagnosis is suspected, it is mandatory to obtain a high-quality contrast-enhanced and fat-suppressed MRI of the orbits looking for extra-sinus extension of disease or loss of contrast enhancement of the sino-nasal mucosa.[36] If the patient is deteriorating, immediate paranasal sinus or orbital apex biopsy is mandatory, as is empiric antifungal treatment. In our view, IFS is an even greater neuro-ophthalmic emergency than giant cell arteritis; IFS not only blinds, but kills.

When to suspect IFS

IFS should be suspected in any patient with an OAS, especially if painful in a diabetic or immunocompromised patient. Urgent otorhinolaryngology consultation should be requested for paranasal sinus biopsy. If the patient is immunocompetent and the OAS is partial rather than complete, the appropriate course of action is less clear, because idiopathic optic neuritis and microvascular cranial neuropathy are much more common than IFS. Furthermore, few cases of presumed idiopathic optic neuritis or microvascular cranial neuropathy turn out to be due to IFS, which will always declare itself without treatment.

Imaging

In a patient with an OAS, even if complete, a normal *brain* CT cannot exclude IFS and false positives abound, because sinus mucosal thickening, often asymmetric, is common. A *paranasal sinus* or *orbit* CT can show bony erosion in IFS, but this can also occur with non-invasive AFS[35] and with paranasal sinus mucocoele.[37] Nonetheless, obvious sinusitis on CT, especially with bony erosion, requires urgent nasendoscopy, although in most cases it will turn out to be due to bacterial or allergic sinusitis. MRI with contrast and fat suppression will usually show soft tissue abnormalities at the orbital apex and skull base by the time the OAS is complete and perhaps even before then. These soft tissue changes typically show a markedly decreased signal on T2-weighted imaging.[35] Orbital and perimaxillary fat stranding (Fig. 1) can be an early indication that the inflammatory process is no longer confined to the paranasal sinuses. Loss of mucosal contrast enhancement on MRI is a sign that is specific for IFS, indicating mucosal infarction.[36] Does a normal MRI with contrast in a patient with a painful OAS exclude IFS and obviate the need for biopsy? The findings of our series suggest that it does, but this decision calls for clinical judgment, especially if the patient has predisposing factors for IFS.

Biopsy

IFS requires a tissue diagnosis that can only be made by showing fungus, histologically, invading the paranasal sinus mucosa.[38] If a patient with a partial OAS has evidence of extra-sinus disease on CT or, more likely, on MRI, the paranasal sinuses must be biopsied, even when there is no significant macroscopic abnormality. Multiple biopsies need to be taken from various sinuses, as fungal invasion is patchy and the biopsy will need to be repeated if the initial biopsy is negative. If the sinus biopsy is negative, it might be necessary to biopsy the orbital apex – a diagnostic procedure with acceptable risk in a patient with a blind eye who is at risk of death. The orbital apex biopsy should be directed towards areas of imaging change (e.g. contrast enhancement or fat stranding) using either an anterior approach (e.g. medial orbital apex biopsy via medial lid crease incision and lateral orbital apex biopsy via lateral canthotomy) or via the sinuses if the imaging change is medial. On histology, there may be features that suggest that the fungus is a *Zygomycete* or *Aspergillus*, but definitive identification can only be made if the fungus is cultured. Detection of the *Aspergillus* galactomannan cell-wall antigen in serum can support a diagnosis of invasive aspergillosis.[39]

Invasive versus non-invasive fungal sinusitis

Non-invasive (allergic) fungal sinusitis (AFS) can also cause an OAS, but the risk of intracranial involvement is much lower; if it does occur, there is a fungal mass lesion without angio-invasion. The CT and MRI changes in AFS are usually dramatic and obvious (Fig. 3): the sinuses are impacted with solid material that might show what appears to be calcification and there will be bony erosion, from compression, into the orbit and through the skull base. Critically, there will not be any evidence on MRI of extra-sinus contrast enhancement or of loss of mucosal enhancement.[35,36] Paradoxically, the worse the imaging looks, the more likely that the diagnosis is AFS, rather than IFS, and the better the prognosis. In these cases, the sinus contents will show profuse fungus, usually *Aspergillus*, but the mucosal biopsies will not show invasion. Sinus surgery is usually curative and the patient does not need antifungal drug treatment. The diagnosis of IFS is made, as the name implies, by demonstrating mucosal invasion by fungal hyphae on tissue biopsy.[38] In contrast, the diagnosis of AFS is made by finding eosinophils infiltrating both the sinus mucosa and contents ('allergic mucin'), with fungi only in the mucin and not invading the mucosa.

Treatment

Early empiric systemic antifungal treatment is essential, as well as treatment of the underlying medical condition or metabolic state, such as reversal of ketoacidosis or neutropenia and cessation of immunosuppression.[15] Most patients will need radical surgical debridement, but the timing and extent of surgery is a matter of debate that will depend on the extent of the disease, the condition of the patient and the enthusiasm of the surgeon.[40,41] In general, early

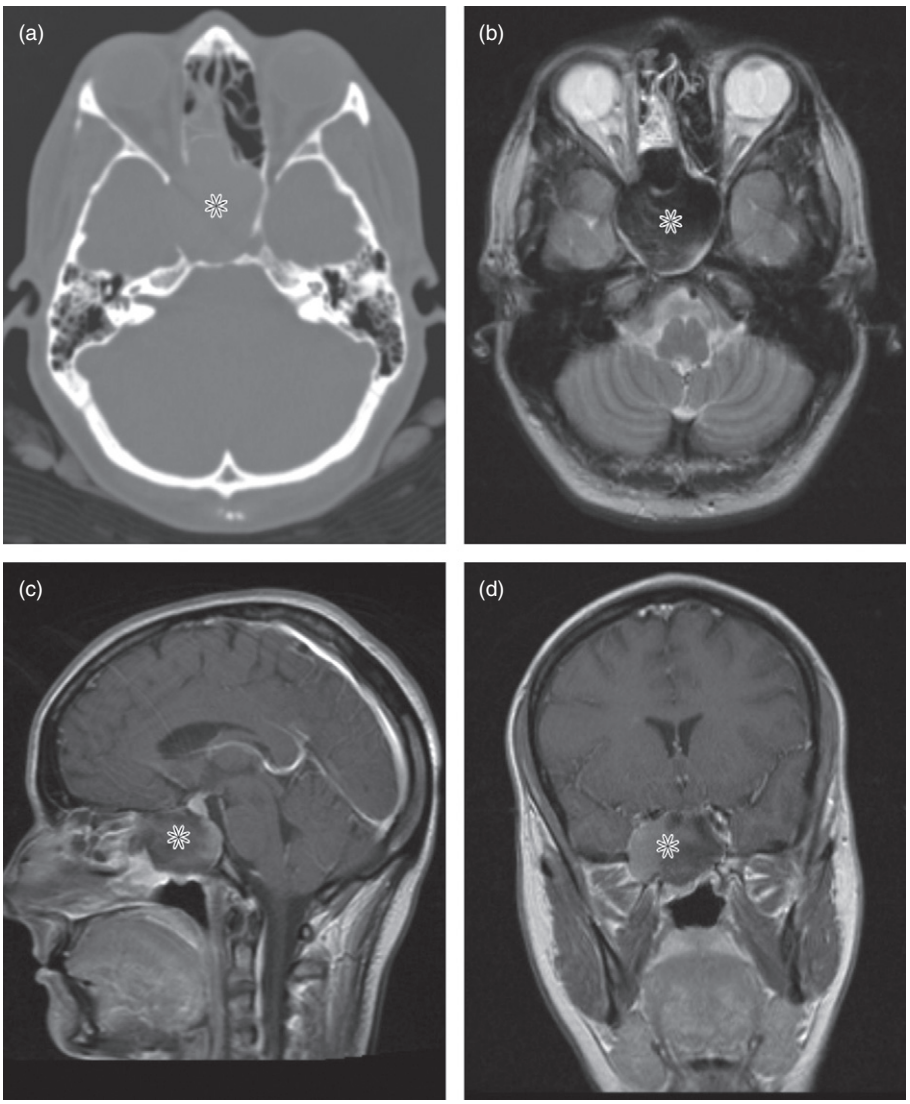

Figure 3. Computed tomography (CT) and magnetic resonance imaging (MRI) findings in allergic fungal sinusitis (*Aspergillus*). A 34-year-old woman presented with a 1-week history of severe frontal and right orbital headache, followed by diplopia, right-sided ptosis and right-sided monocular visual loss. Examination showed a right optic neuropathy, a partial right oculomotor nerve palsy and ophthalmic division trigeminal sensory loss. Axial CT scan (a) demonstrates extensive bone destruction involving the sphenoid sinus with extension to the right orbital apex. The bony destruction extends to the posterior ethmoid air cells on the right. Axial T2-weighted MRI (b) demonstrates laminated low signal material centred on the sphenoid sinus (*), with extension into the posterior ethmoid air cells on the right. Sagittal and coronal post-contrast T1-weighted MRI (c, d) demonstrates expansion of the sphenoid sinus, which is filled with heterogeneous material (*). The lesion disrupts the posterior cortical margin of the clivus and extends laterally into the right middle cranial fossa. Following urgent decompression, for what was shown to be allergic rhinosinusitis due to *Aspergillus*, she made a near-complete recovery.

aggressive surgical debridement with wide local excision is the mainstay of treatment of established disease – orbital exenteration may be, but is not always,[40] required. The two patients from our series who survived both had orbital exenteration. Rarely has medical therapy alone been successful.[27,42] Intravenous amphotericin B was previously the agent of choice for both *Zygomycetes* and *Aspergillus*,[43] but oral voriconazole is now considered as effective for *Aspergillus*.[44,45] Combination therapy, along with aggressive surgical debridement, has been successful in controlling disseminated infection.[46] Amphotericin B therapy alone, or in combination with flucytosine, fluconazole, itraconazole or micafungin, has been employed.[44] Posaconazole alone has been reported to be effective against *Rhizopus oryzae*.[47] Management of *Scedosporium prolificans* infection is complex and rarely successful,[46,48] due to its inherent resistance to antifungal agents. Antifungal prophylaxis is commonly given to patients receiving chemotherapy for haematological malignancies, especially those receiving stem cell transplant; in the two patients receiving antifungal prophylaxis in this series, itraconazole failed to prevent IFS due to *Scedosporium* in one patient and voriconazole failed to prevent IFS due to *Aspergillus* in the other. In neutropenic patients, it is essential to improve neutrophil count as quickly as possible once IFS is diagnosed.[49]

Prognosis

Even with aggressive medical and surgical therapy, the prognosis of IFS is poor, perhaps because of delays in diagnosis and initiation of treatment. The ophthalmologist can play a critical role, by suspecting the diagnosis and arranging an immediate contrast-enhanced and fat-suppressed MRI of the orbits. If the MRI shows abnormalities consistent with IFS with extra-sinus extension, urgent paranasal sinus or orbital apex biopsy should be arranged. Survival rates for rhino-cerebral mucormycosis range from 13% to 70%.[50] In immunocompetent patients with invasive aspergillosis, only 6 of 21 cases survived in one series.[12] Prognosis is largely dependent on early diagnosis, extent of invasion, feasibility of surgical debridement and the host's immune status.[15]

Summary

1 IFS is a rare cause of OAS that it is potentially curable if treated early and lethal if treated late. The IFS patient is often diabetic or immunocompromised, which is the reason why saprophytic fungi are able to invade the orbit from the paranasal sinuses.

2 Although the tempo of the disease can be acute, subacute or chronic, the outcome is always fatal if untreated.

3 At the orbital apex, the fungi invade nerves, arteries and veins, producing a typically painful OAS, so that the ophthalmologist will often have the first (and perhaps last) chance to save the patient's life.

4 From the orbital apex, the fungi can invade the meninges, cavernous sinus and cavernous carotid artery, causing carotid occlusion with cerebral infarction or mycotic aneurysm with subarachnoid haemorrhage.

5 Once a complete OAS has developed, the chance of losing vision permanently is 100% and the chance of losing life is at least 60%, even with treatment.

6 There is often little or no clinical or CT evidence of paranasal sinus disease at the time of presentation. MRI enhancement at the orbital apex or skull base is, if present, an important finding. If MRI with contrast shows no evidence of extra-sinus disease in a patient with an OAS, IFS can probably be excluded.

7 IFS is a tissue diagnosis. A painful complete or partial OAS in a diabetic or immunocompromised patient is an ophthalmic emergency; the diagnosis of IFS should be suspected, and immediate imaging followed by paranasal sinus or orbital apex biopsy is required to confirm the diagnosis.

8 Empiric antifungal treatment should be initiated in patients where the diagnosis is likely and continued at least until the biopsy results are available.

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