Lesson of the month

Neuro-ophthalmological presentation of non-invasive aspergillus sinus disease in the non-immunocompromised host

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Abstract
Two cases of non-invasive aspergillosis of the nose and paranasal sinuses are described. The first presented with left proptosis and ophthalmoplegia. Imaging and histology showed a maxillary sinus aspergilloma. The second case presented as a compressive optic neuropathy and histology showed allergic aspergillus sinusitis. The pathological distinction between invasive and non-invasive forms of aspergillus sinusitis is important as in invasive aspergillosis surgical treatment is most effectively combined with systemic antifungal treatment, whereas in aspergilloma of the paranasal sinuses surgical drainage of the sinuses alone is usually sufficient, and in allergic aspergillus sinusitis surgery is best combined with systemic or topical steroids. The distinction between invasive and non-invasive forms is particularly important as both may present with cranial neuropathies.

Aspergillosis of the nose and paranasal sinuses is known to cause ocular pain, proptosis, optic neuropathy, ophthalmoplegia, orbital apex, and cavernous sinus syndromes, but only recently have advances in the understanding of the pathology of aspergillus infections allowed a more rational approach to treatment. It is important that neurologists and ophthalmologists are aware of the distinction between invasive and saprophytic forms of aspergillus sinusitis as treatment differs and both may present with cranial neuropathies. Here we present two cases that represent the two forms of non-invasive aspergillus sinus infection in humans.

Case 1
A 32-year-old man presented with a one-week history of severe left retrobulbar pain and horizontal diplopia. The diplopia was worse on looking to the left. There were no other neurological symptoms. Four years previously he had been successfully treated for tuberculosis affecting the lumbar spine. There was no history of diabetes mellitus and no relevant
family history. He was born in Sierra Leone but had been resident in the United Kingdom for the past four years.

The abnormalities on examination were limited to the left eye. There was 4 mm of axial proptosis and resistance to retropulsion of the left eye. Visual acuity was 6/6, N5 in both eyes. There was no abnormality on colour vision testing or Goldman perimetry in either eye. The left pupil was larger than the right, and this difference in size was more pronounced under bright ambient illumination. The left direct response to light was sluggish but there was no relative afferent pupillary defect. There were no retinal or optic disc abnormalities. There was a small left esodeviation on distance fixation and pronounced limitation of abduction of the left eye. There was also reduced elevation and depression of the left eye but intorsion was present. It was concluded that left III and VI nerve palsies were present. Movements of the right eye were normal. The left maxillary antrum was almost filled with intermediate to high density material on contrast enhanced CT. There was a small central area of low density and also a small haemorrhagic or calcific component (fig 1b). The mass extended upwards and backwards into the left posterior ethmoid and sphenoid sinuses (fig 1d), the left inferior orbital fissure (fig 1c), and through the posterior part of the lateral wall of the antrum into the infratemporal fossa (fig 1a).

An intranasal antrostomy was performed and the contents of the left maxillary antrum biopsied. Culture of biopsied material grew Aspergillus fumigatus. Histological examination of the biopsy specimen showed a ball-like conglomerate of septate branching fungal hyphae (fig 2), partly surrounded by inflammatory exudate. This was lined by respiratory epithelium and was composed of focally hyaline fibrous tissue infiltrated by chronic inflammatory cells. The histological appearances were those of an aspergilloma.

The patient defaulted from further investigation and treatment.

Case 2

A 30-year-old woman presented with a 15-month history of recurrent attacks of nasal discharge and obstruction associated with a feeling of pressure over the cheeks, and a three-month history of slowly progressive painless deterioration of vision in the left eye. She also reported a patch of numbness above the left lip that had lasted for several weeks nine months earlier. She had suffered with poor vision in the right eye as long as she could remember due to myopia. There were no other neurological symptoms or relevant medical history. In particular there was no history of diabetes mellitus or asthma. There was no relevant family history. Although both parents were from South America, the patient had never visited that continent.

General examination was normal. Neurological abnormalities were limited to the visual system. Corrected visual acuity was 6/60, N18, and 6/36, N24 in the right and left eyes respectively. Colour vision with Ishihara plates was normal in the right eye, but she was only able to read the test colour plate with the left eye. There was a left centralerocecal scotoma and left relative pupillary defect. The right visual field and pupillary reflexes were normal. Both optic discs were normal apart from myopic features. Eye movements and corneal reflexes were normal. There was no proptosis.

There was a slight eosinophilia (8%) and Aspergillus fumigatus skin prick test and serum precipitins were positive. On a contrast enhanced CT of the sinuses a mixed intermediate and high density mass was seen in the

Figure 2  Case 1. Grocott's silver preparation showing a dense conglomerate of branching septate fungal hyphae (originally x 400)
sphenoid sinus. The sinus was expanded and there was thinning and erosion of its walls. There was forward extension into the posterior ethmoid air cells on the left side. On axial spin-echo T₁-weighted MRI, the contents of the expanded sinus returned a very low signal. On the spin-echo T₂-weighted images the sinus again appeared hypointense, but with small components of intensity similar to muscle (fig 3, left). After injection of gadolinium-DTPA there was peripheral rim enhancement of the sinus (fig 3, right). There was compression of the intracranial segment of the left optic nerve.

The patient proceeded to a right transnasal transsphenoidal debulking of the sphenoid sinus mass. At operation the sphenoid and ethmoid sinuses were found to be expanded and occupied by a waxy sticky material, which was removed as far as possible. An artificial ostium was opened between this area and the right nasal cavity. Culture of the sinus contents grew Aspergillus fumigatus. Histological examination of the sinus contents showed clusters of degenerative inflammatory cells surrounded by Schiff and Alcian blue positive acellular material containing Charcot-Leyden crystals. Dichotomous branching septate hyphae were seen on Grocott's silver stain, confirming the presence of Aspergillus (fig 4).

After a brief period of postoperative stabilisation, vision in the left eye began to deteriorate again. Five weeks after the operation corrected visual acuity had fallen to counting fingers in the left eye with enlargement of the left centrocaecal scotoma.

Six weeks after the first operation a right transthooidal sphenoid clearance was performed. Again the sphenoid sinus was found to be full of inspissated waxy debris, and this was widely excised. Histological examination of biopsy specimens showed mucosa with chronic inflammatory changes consisting of numerous plasma cells, lymphocytes, and eosinophils. No fungi were seen in this specimen.

Postoperatively the patient was treated with parenteral amphotericin B (maximum dose 50 mg daily). This led to fevers, nausea, vomiting, anaemia, and renal failure, and oral itraconazole (400 mg daily) was substituted for amphotericin B after 16 days of treatment. The systemic symptoms, anaemia, and renal failure resolved. At the same time treatment was begun with prednisolone (60 mg daily reducing to 30 mg daily two weeks later). There has been a slow but consistent improvement in vision in the left eye since the second sphenoid clearance. The sphenoid sinuses appear healthy at endoscopy.

Discussion
Recent histological advances in the understanding of aspergillus sinus infections have led to the further subclassification of invasive and saprophytic Aspergillus sinus infections into fulminant and chronic invasive aspergillus sinusitis, and aspergilloma and allergic aspergillus sinusitis respectively. The distinction between these forms is important as treatment strategies differ.

Fulminant aspergillosis of the nose and paranasal sinuses was first recognised in 1980. The infection occurs in immuno-suppressed patients, usually with malignant neoplasms of the haemopoietic or lymphoreticular systems. There is prominent mucosal ulceration and destruction of the sinuses, followed by angioinvasion and extension into the orbit and brain. Histologically, there is little tissue reaction and no granulomatous response is seen.

Chronic invasive aspergillus sinusitis occurs in patients without obvious immunodeficiency. It presents as a less aggressive destructive lesion of the nose and paranasal sinuses. Proptosis is often a prominent feature. Extension to the brain and orbit can occur. Histology shows an extensive inflammatory response with granuloma and giant cell formation and fibrosis. Aspergillus hyphae are readily apparent with silver stains.

Management of both fulminant and chronic invasive aspergillosis requires surgical resection and systemic antifungal treatment. Amphotericin B remains the principal antifungal treatment, but its use is complicated (as in case 2) by nausea, fevers, anaemia, and renal failure. Itraconazole is a promising new oral antifungal agent that has been well tolerated, and, in preliminary studies, seems effective against Aspergillus. Despite current treatment regimes, delayed recurrence may occur and the mortality of invasive aspergillosis once intracranial spread has occurred is 80%.

Aspergilloma of the sinuses is a saprophytic extramucosal fungal ball. It is most commonly found in the maxillary antrum and occurs in patients without obvious immunodeficiency. It usually presents as a chronic sinusitis. Case 1, however, presented with left proptosis and ophthalmoplegia. Histology shows a tangled mycelium of Aspergillus with often little or no inflammatory response or mucin production. The condition responds well to drainage of the sinus.

Hartwick and Batsakis have recently
reviewed the clinical features of the 32 patients with allergic aspergillus sinusitis reported up to 1990. The age at presentation varied from eight to 56 years old, although most were young adults. A history of asthma and nasal polyposis was present in over half. Most presented with a history of recurrent or persistent sinusitis involving multiple sinuses for several months or years. Despite its saprophytic nature this infection is not necessarily benign. A quarter of patients with allergic aspergillus sinusitis show radiographic evidence of expansion or bone erosion of involved sinuses. Facial deformities secondary to expansile sinusitis is common in children with allergic aspergillus sinusitis.

Cranial neuropathy in allergic aspergillus sinusitis is rare, but may occur and its presence does not exclude this form of aspergillosis. Case 2 had a compressive optic neuropathy. Dunlop and Billson have also reported optic neuropathy in association with allergic aspergillus sinusitis, although the mechanism underlying the optic neuropathy in their case was unclear.

Pointers to the diagnosis of allergic aspergillus sinusitis are, as in case 2, a blood eosinophilia, positive skin prick test, and aspergillus serum precipitins. The MRIs are unusual, and may be explained by the presence of inspissated dehydrated mucin and the production of haemosiderin by the fungus.

The very low T1 signal, as seen in case 2, should not be mistaken for an aerated sinus. In equivocal cases CT can easily confirm the presence of pathology.

The histological changes in allergic aspergillus sinusitis are typified by those in case 2. In this case a characteristic pale eosinophilic mucin was found. This contained sloughed respiratory epithelium, Charcot-Leyden crystals, and numerous eosinophils. Aspergillus hyphae were present with silver stains but were not numerous. Invasion of tissues by the fungus was not seen. These histological features are similar to those of allergic bronchopulmonary aspergillosis, and the two conditions may coexist.

Treatment of allergic aspergillus sinusitis involves surgical clearance of the sinuses and the restoration of sinus drainage and ventilation. The recurrence rate from surgery alone is high and systemic and topical steroids have proved effective in improving outcome. Antifungal agents are generally not advocated in allergic aspergillus sinusitis as invasion does not occur.

References: