

Origin and spread of allergic fungal disease of the nose and paranasal sinuses

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Although expansion of bony walls occurs in allergic fungal disease of the nose and paranasal sinuses by increased mucus secretion and fungal growth, the latter is apparently confined to the lumen and does not invade the tissues. Nevertheless, spread of the disease process from paranasal sinuses to orbit, cheek and intracranial cavity is well described. An imaging and histopathological study was carried out in 16 cases to determine how the disease originates and spreads. The infection starts in the nasal cavity, the lumen of a sinus or in a seromucinous gland or duct. A thin vascular zone of intense allergic inflammation surrounds the infected mucin. Erosion of bone takes place focally, probably by substances produced by the inflammatory tissue, allowing intromission by the thin vascular layer together with its underlying fungus-containing mucus and so extension of the disease process through the eroded bone.

Keywords *allergic fungal sinusitis aspergillosis nasal infection*

Katzstein *et al.*¹ formally described an allergic response to fungi in the paranasal sinuses similar to that of allergic bronchopulmonary aspergillosis in 1981, but the condition had been previously mentioned in the literature on at least two occasions.^{2,3} Assuming that the *Aspergillus* spp. alone were the causative organisms, the condition was first called 'allergic aspergillus sinusitis'. It subsequently became apparent that *Aspergillus* spp. were not the only fungi to be associated with these changes. Black or brown pigmented fungi of a group known as *Dematiaceae*, such as *Curvularia*, *Bipolaris*, *Exserohilum* and *Alternaria* have been shown to be causative organisms and non-aspergillus, non-dematiaceous fungi such as *Fusarium*, *Chrysosporium* and *Rhizomucor* have also been incriminated.⁴ The condition was therefore renamed 'allergic fungal sinusitis', although it is recognized that the nasal cavity is also affected, so that the term 'allergic fungal disease of the nose and paranasal sinuses' may be more appropriate for the condition.

It has been suggested that allergic fungal sinusitis may stem from a fungus ball, in which an immune response to

the fungus subsequently develops, and which then generates an allergic type inflammatory response resulting in mucous exudate, nasal polyps and bone erosion.⁵ Bone erosion has been reported in 19%⁶–80%⁷ of cases. In some patients the bony sinus wall is completely breached and the fungus may even present externally as a soft tissue mass. Despite these well-recognized features, allergic fungal sinusitis has been classified as a non-invasive form of fungal sinus disease since, in contrast to the chronic and acute invasive forms, there is said to be no invasion of the mucosa, submucosa or bone by fungi.⁸

In this paper we describe the results of a study of the imaging and histopathological features of a group of patients with allergic fungal sinusitis to seek evidence as to how the disease originates and how it extends through the soft and bony tissues of the nose and paranasal sinuses at a later stage.

Materials and methods

The study was carried out on 16 consecutive patients diagnosed as having allergic fungal sinusitis which involved the nasal cavity and/or the maxillary, the ethmoid, the sphenoid or the frontal sinuses. Each patient had had symptoms and

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Figure 1. Coronal computerized tomography scan of a case of allergic fungal sinusitis. In the left antrum there are areas of high attenuation centrally, suggesting fungally infected mucin, with a peripheral zone of low attenuation. The right antrum shows an area of high attenuation, suggesting fungally infected mucin, which is invading the upper antral cavity. It is demarcated peripherally with a thin zone of low attenuation (arrow).

signs of nasal and paranasal sinus disease and computerized tomography (CT) and magnetic nuclear imaging (MRI) scans of nose and paranasal sinuses had been carried out, as a result of which pathological changes strongly suggestive of allergic fungal sinusitis were detected. Each patient had then been subjected to an operative procedure on the nose and/or one or more of the paranasal sinuses, and biopsy material had been removed surgically in which the diagnosis was confirmed by the presence of fungal hyphae in an exudate composed of mucin and necrotic eosinophils.

Sections prepared from the material removed from the nose and paranasal sinus were stained with haematoxylin

and eosin and by the methanamine silver (Grocott-Gomori) and/or the periodic acid Schiff stains for fungi. Special attention was paid in this study to the changes in soft tissue which had been removed together with the inspissated mucus. Culture for fungi was not carried out in these cases.

Results

IMAGING CHANGES

In this series the patients presented with either generalized or unilateral loss of translucence in the sinuses and in the nasal cavity due to associated nasal polyps,⁹ accompanied in a typical case by the following triad of appearances produced by inspissated mucus containing necrotic inflammatory cells and fungi:

1. Areas of high attenuation on CT, due to the presence of calcium and/or traces of metallic elements¹⁰ (Fig. 1). These areas were surrounded by a thin zone of low attenuation.¹¹
2. Low signal on MRI from the inspissated mucus, especially on T2 weighted sequences, due to the presence of ferromagnetic elements or tight hydrogen binding in the areas showing high attenuation on CT (Fig. 2).

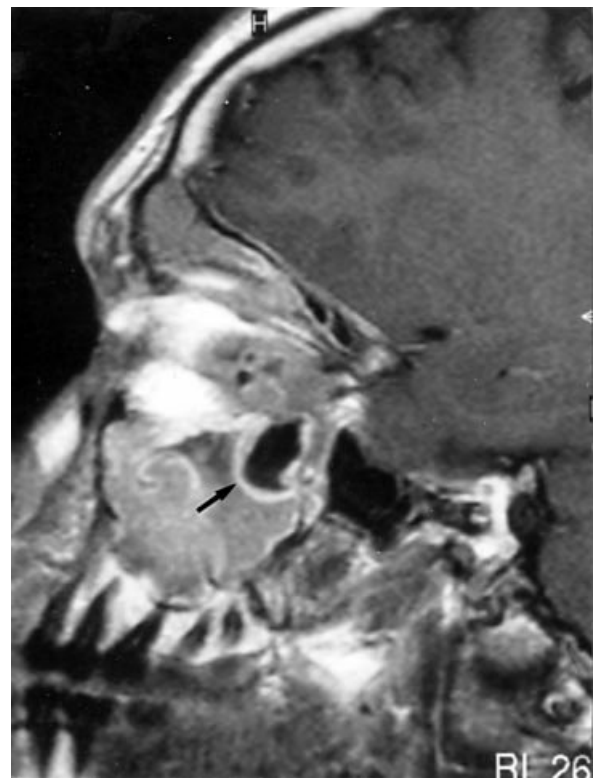


Figure 2. Sagittal magnetic resonance imaging scan of right antrum (T1 weighted with Gadolinium) from the same patient from whom Figure 1 was derived. There is a thin zone of high signal (arrow), indicating hypervascularity, covering a black area of absent signal (suggesting fungally infected mucin) in the upper antrum.

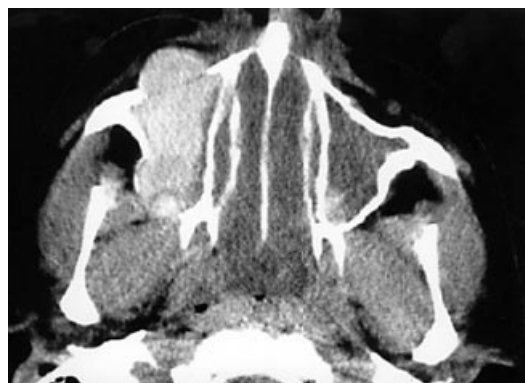


Figure 3. Axial computerized tomography scan showing high attenuation (suggesting fungally infected mucin) in the right antrum, which is eroding the anterior and posterior walls and presenting as a mass in the soft tissues of the cheek.

3. Bone changes: expansion or erosion. Bone changes are a common feature and in some patients the sinus wall was completely breached, the inflammatory swelling presenting as an external soft tissue mass (Fig. 3). Fourteen patients showed bone changes on CT. In all of these one or more sinuses exhibited a general expansion similar to that seen in a mucocele or pyocele, the inspissated mucus completely filling the sinus cavity and producing an overall enlargement as the bone is remodelled in response to the pressure of the expanding disease process. Six patients showed erosion of bony sinus walls in addition to sinus expansion. Bone erosion is seen as a local bulge in the sinus wall. It may occur in any sinus cavity, but is very characteristic of allergic fungal disease when it breaks through the anterior wall of the maxillary antrum into the soft tissues of the cheek¹² (Fig. 3). All six patients with bone erosion were examined by CT and three of them by MRI, using Gadolinium enhanced T1 weighted sequences and photographic subtraction.¹³

Subtraction studies showed negative or minimal enhancement of the inspissated mucus centrally after intravenous Gadolinium, surrounded by a thin peripheral zone of strong enhancement consistent with tissue of high vascularity (Fig. 4). This corresponded exactly to the zone of low attenuation surrounding the areas of high attenuation found on CT. This thin, vascular zone had a slightly irregular outline. In some cases it could be seen bound to what appeared to be the surface of a mass of mucoid material occupying part of the sinus and crossing the sinus from one wall to another (Fig. 1). The vascular zone could be shown to penetrate the sinus wall at the sites of bone erosion and enter the soft tissues outside the sinus, still covering the inspissated mucus (Figs 4 and 5). The sites of the bone expansion and erosion in the 16 patients are shown in Table 1.

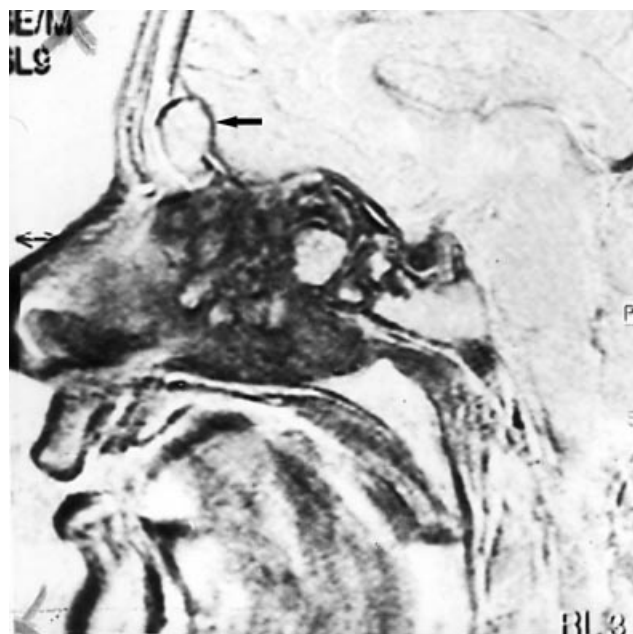


Figure 4. Subtraction Gadolinium-enhanced magnetic resonance scan (T1 weighted) in sagittal section. The arrow points to a hypervascular rim covering a zone of low-signal (suggesting fungally infected mucin) which is eroding the posterior wall of the frontal sinus.

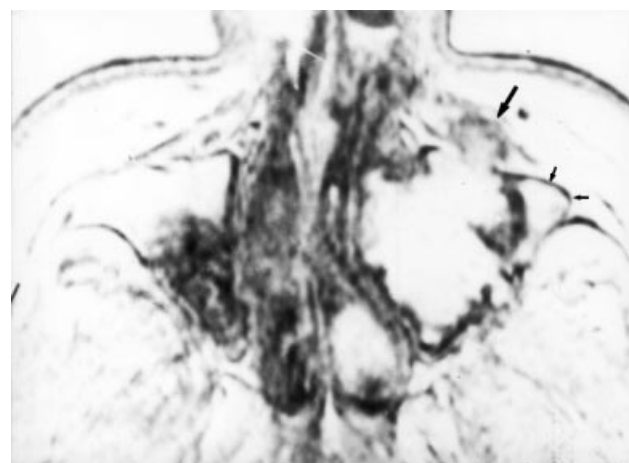


Figure 5. Subtraction Gadolinium-enhanced magnetic resonance scan in axial section showing low signal (suggesting fungally infected mucin) in the left antrum with a surrounding high signal (hypervascular) zone, the forward part of which has eroded the anterior bony wall (large arrow). The small arrows identify the normal mucosa lining the lateral recess of the antral cavity.

Table 1. Bone changes demonstrated by imaging

Patient: sex and age	Sinus(es)	Sinus(es) expanded eroded
1. Man aged 35	Ethmoid	Nil
2. Man aged 32	Frontal, ethmoid	Nil
3. Woman aged 34	Nil	Nil
4. Man aged 34	Frontal, ethmoid	Maxillary
5. Man aged 42	Nil	Nil
6. Woman aged 21	Ethmoid	Frontal, sphenoid
7. Woman aged 42	Ethmoid	Nil
8. Woman aged 38	Ethmoid	Nil
9. Man aged 39	Ethmoid, sphenoid	Maxillary, frontal
10. Woman aged 46	Sphenoid	Nil
11. Man aged 26	Frontal	Nil
12. Man aged 19	Frontal, ethmoid	Maxillary, sphenoid
13. Woman aged 24	Ethmoid	Nil
14. Girl aged 9	Ethmoid	Nil
15. Man aged 31	Ethmoid	Ethmoid
16. Man aged 29	Sphenoid	Sphenoid

HISTOPATHOLOGICAL CHANGES

In each case loose-lying masses of inspissated mucus of varying size were present in the surgically removed material. These showed a periphery of darkly staining cellular material comprising necrotic eosinophils, with occasional Charcot-Leyden crystals. Fungal hyphae were demonstrated towards the centre of the mass of mucin by the methanamine silver or periodic acid-Schiff stain. In some cases the fungi were present in large numbers; in others they were sparse. The fungi showed a variety of forms usually comprising branching septate hyphae often with vesicular swelling.¹⁴ Fungi could be observed not only within large collections of inspissated mucus but also within ducts or acini of seromucinous glands. In some of these structures

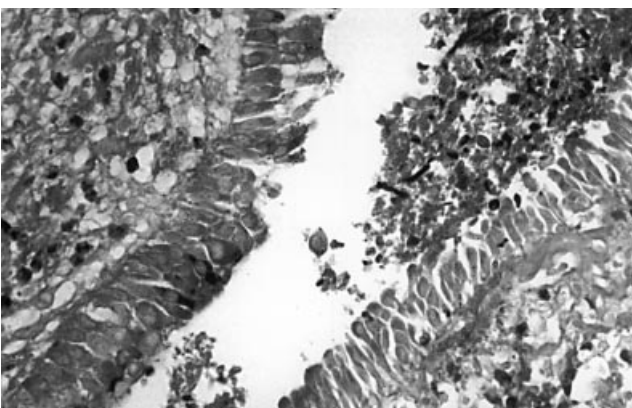


Figure 6. Fungal hyphae, staining black, in duct of seromucinous gland of nasal cavity in a case of allergic fungal sinusitis. There some accompanying, mostly necrotic, inflammatory cells, but no inspissated mucin. Grocott's modification of Gomori's methanamine silver stain, $\times 350$.

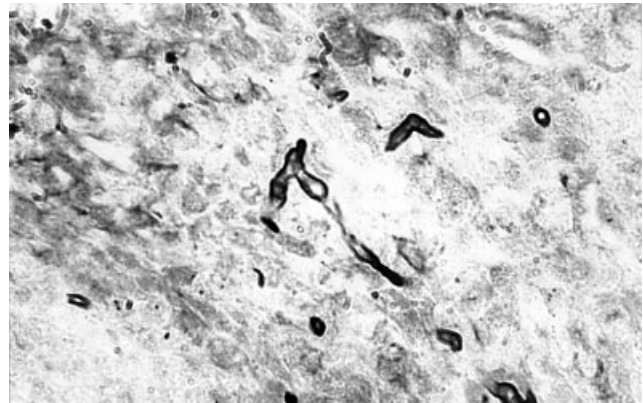


Figure 7. Branching fungal hyphae with vesicular swellings, accompanied by much mucin, from greatly expanded gland of maxillary antral lining in a case of allergic fungal sinusitis. Grocott's modification of Gomori's methanamine silver stain, $\times 400$.

the organisms were accompanied by little mucus and few inflammatory cells (Fig. 6). In others the gland/duct involved was expanded by the infective agents together with a large amount of necrotic eosinophils and mucin (Fig. 7).

The tissue covering the infected inspissated mucus, comprising the lining mucosa and submucosa of the nose or paranasal sinus, showed the appearances of allergic inflammatory change with two types of alteration:

1. In many areas the predominant change is loss of seromucinous glands with severe oedema, together with a moderate basement membrane thickening and eosinophil infiltration. These lesions are sufficiently marked in some places to be identified as allergic type nasal polyps.
2. In other areas there are patches of an intense inflammatory change. Such an alteration may be present around the

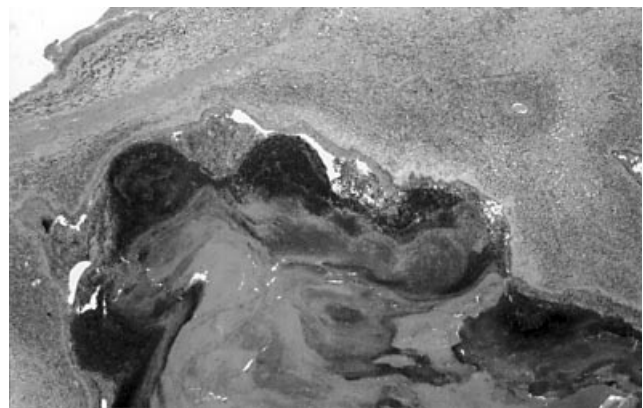


Figure 8. Gland of submucosa of nasal cavity greatly expanded by inspissated mucus in a case of allergic fungal sinusitis. The dark-staining masses at the periphery are composed of necrotic eosinophils. Note the intense inflammation of tissue deep to the epithelium. Haematoxylin and eosin, $\times 10$.

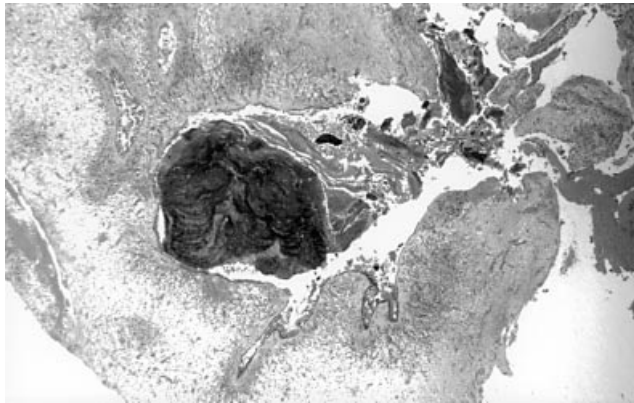


Figure 9. Duct of seromucinous gland of nasal cavity greatly expanded by inspissated mucus and necrotic eosinophils in a case of allergic fungal sinusitis. Note the inflammation of tissue deep to the epithelium. Haematoxylin and eosin, $\times 25$.

periphery of an expanded gland (Fig. 8) or duct (Fig. 9) containing infected mucus or be present in the mucosa or submucosa deep to the lining of the sinus or nasal cavity. The lining epithelium over the inspissated mucus may show areas of severe goblet cell hyperplasia or may be multi-layered with swelling of epithelial cells. Basement membrane thickening is present and the collagen of this process merges with that of newly formed fibrous tissue that may be found in the mucosa or submucosa. There is an intense infiltrate of eosinophils and plasma cells, in some places showing necrosis. This is accompanied by severe congestion of capillaries and the presence of newly formed blood vessels (Fig. 10). In some areas this intense inflammation is present over

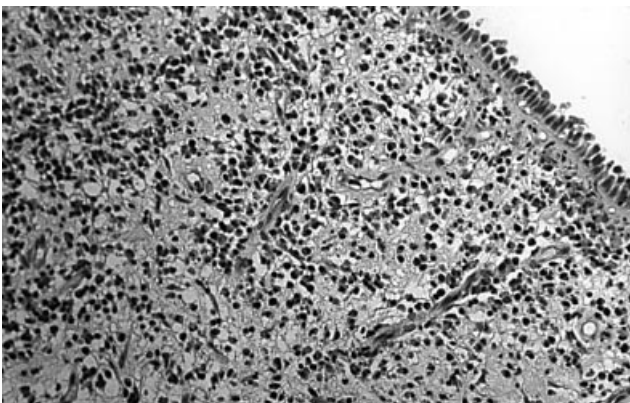


Figure 10. Severe inflammation of mucosa surrounding inspissated infected mucus in a case of allergic fungal sinusitis. The inflammatory cells are mainly eosinophils. Note prominent blood vessels. Haematoxylin and eosin, $\times 250$.

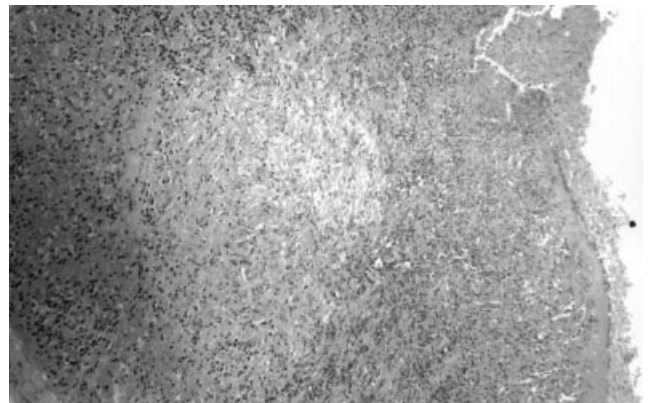


Figure 11. Fibrous nodule in submucosa of tissue surrounding inspissated infected mucus in a case of allergic fungal sinusitis. Haematoxylin and eosin, $\times 250$.

a wide area of subepithelial tissue. Areas of fibrosis are present; these sometimes take the form of a large submucosal fibrous nodule (Figs 11 and 12).

Bony trabeculae may be present in the biopsy material. When they are adjacent to the severe inflammatory change, evidence of new bone formation and/or bone erosion can be identified. Appearances suggesting penetration of an attenuated bony septum by vascular inflammatory tissue, fibrous tissue and infected mucus may occasionally be seen.

Discussion

In this study we were able to utilize the imaging characteristics of the allergic fungal lesions as indications of the gross *in-situ* pathological changes stimulated by the disease process within the tissues of the nose and paranasal sinus. By

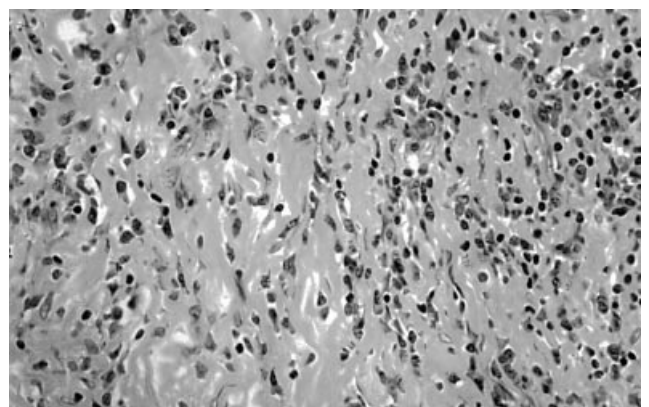


Figure 12. Higher power of part of Figure 11 showing plasma cells, fibroblasts and collagen bundles. Haematoxylin and eosin, $\times 400$.

the use of the MRI subtraction method before and after Gadolinium we were able to observe the mode of penetration of the bony wall by the disease. We have also studied the histopathological changes in the cellular tissues of these regions, in addition to and unlike all other studies of this type which have described only the histological appearances of the inspissated mucus in this disease. By correlating imaging with histopathology we have been able to develop a concept of the early stages of allergic fungal disease in the nose and paranasal sinuses and its subsequent mode of spread.

Aspergillus fungal species are known to be present in indoor as well as outdoor air and can colonise the mucosa of the respiratory tract.¹⁵ Little is known in this regard about the dematiaceous and non-dematiaceous fungi that can also give rise to allergic fungal sinusitis, but it is likely that they too can colonise the respiratory tract. In this study we have observed that fungi may be present in large numbers in the lumina of the paranasal sinuses or nasal cavity and we have also observed them in the acini and ducts of seromucinous glands. In the latter situation the early stages of the disease process may be identified. These early stages do not suggest the genesis of a fungal ball, unlike what has been suggested previously,⁵ in that in allergic fungal sinusitis the fungi are not fused together like a colony, and they soon become intimately associated with mucous secretion and are surrounded by eosinophils, not by neutrophils.

We have demonstrated fungi in allergic fungal sinusitis to be present only within the lumina of seromucinous glands or ducts or within those of the nasal cavity or paranasal sinuses. The organisms are never seen in the tissues. This observation enhances the strong evidence that is already available by systemic immunological tests that this is a hypersensitivity response which is triggered by antigen from the infecting fungus.¹⁶ The local immunological mechanism for the pathogenesis has not yet been studied, but it is pre-

sumably based on alterations similar to those that are known to take place in allergic rhinitis. A soluble fungal allergen, it may be suggested, passes through the epithelium and is processed by antigen-presenting cells in the mucosa and then T helper which stimulate B cells to produce high levels of specific antifungal IgE and IgG. Degranulation of mast cells or basophils then occurs from the combination on their surfaces of specific IgE and IgG with fungal antigen. This produces the release of histamine and other spasmogens, the main effect of which is to increase mucous secretion and also to release cytokines, which amplify the inflammatory response in the tissues and activate and accumulate eosinophils¹⁷ (Fig. 13).

The mucous secretion in allergic fungal sinusitis is a conspicuous part of the pathological process and gives rise to a diagnostic appearance on CT of high attenuation, and to a low signal on MRI especially on T2 weighted sequences. The cells that produce the mucin, presumably under stimulation from the spasmogens released by degranulation of mast cells and basophils, are the hyperplastic goblet cells lining the nasal cavity, paranasal sinuses and ducts and submucosal glands, in which the fungi are harboured. It is likely, because in some cases we observed large numbers of fungi in the mucus, that this material provides ample nutrients for the growth of the fungi, so enhancing the cycle of hyper-immune reactivity.

The other major change, probably stimulated by cytokines released by the degranulation of mast cells, is the inflammatory change that takes place in the subepithelial tissues around the inspissated mucus. Although the degree of this change ranges from the mild one found in allergic nasal polyps to one of great intensity, the predominant inflammatory cell is everywhere the eosinophil. Our finding of a vascular zone of strong enhancement after intravenous Gadolinium in this region in six patients is explained by severe congestion in local blood vessels and in the large

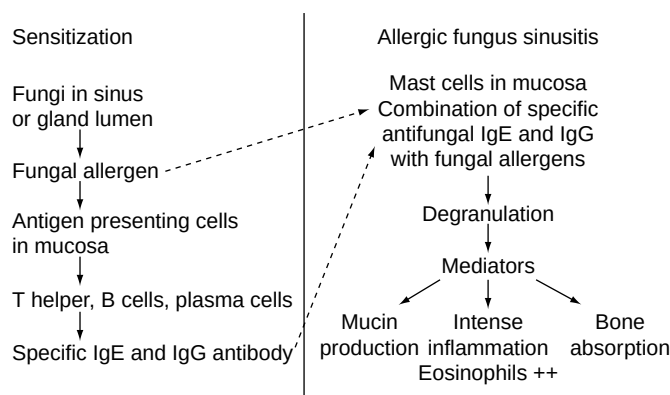


Figure 13. The proposed mechanism for allergic fungal sinusitis.

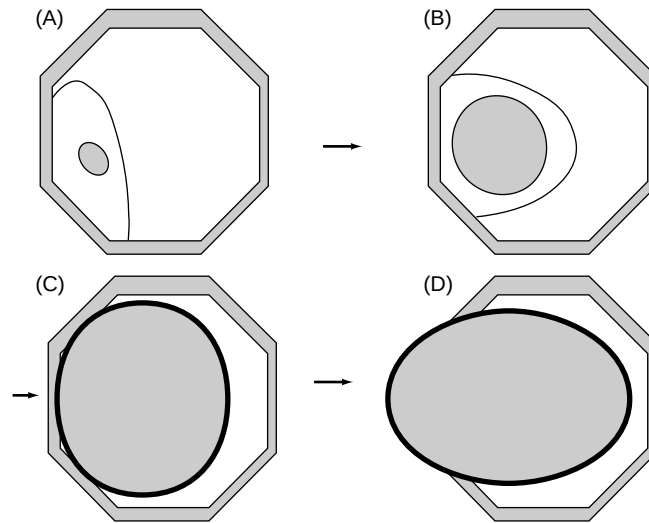


Figure 14. Diagrams of origin and spread of allergic fungal sinusitis from a focus commencing in a gland of a paranasal sinus (A) and leading to protrusion of the inflammatory mass through the bony wall of the sinus. The diagrams are described in the text.

number of newly formed ones that is a manifestation of the intense inflammation in these cases. The appearance of such a thin vascular zone actually passing across the lumen of a sinus that was seen on imaging studies (Figs 1 and 2) may be explained on the basis that the infection in that region was present in a dilated gland, the enhanced region being congested inflammatory change on the mucosal side of the gland and so appearing to cross the lumen of the sinus (Fig. 14).

Bone erosion was found on imaging studies of six of the 16 patients in our series. In each case the vascular zone penetrates the sinus wall. It seems likely that the erosion of bone is the result of the secretion of substances from the vascular inflammatory tissue in a similar fashion to that of the erosion of ossicular and middle ear wall bone that frequently takes place in cholesteatoma. In this condition, substances including proteases,¹⁸ cytokines such as $\text{TNF-}\alpha$ ¹⁹ and metalloproteinases²⁰ are derived from the inflammatory tissue that accompanies the cholesteatoma and account for erosion of bone taking place there; similar substances may be present in allergic fungal sinusitis.

Figure 14 summarizes diagrammatically the origin and spread of allergic fungal sinusitis. In (A) and (B) the infection is depicted as an enlarging grey area representing a seromucinous gland acinus distended by fungi, eosinophils and mucin within a swollen region of the submucosa and mucosa of a paranasal sinus, the bony walls of which are shown as a hexagonal boundary of each figure. The condition probably commences very frequently also in the lumen of the nose or paranasal sinuses, but the mode of progression of the allergic reaction and its effect on the surrounding

bony walls would be the same. In (C) the infected mucus now becomes surrounded by a thin, dark, certainly vascular layer, as seen on MRI subtraction before and after Gadolinium. The vascular layer may cross the lumen of the sinus. Distension with the fungal-eosinophil-mucin mixture may cause expansion of the bony periphery of the sinus. In (D) erosion of the bony wall of the sinus as a result of the underlying intense inflammatory change is depicted as taking place at one point and the vascular rim with underlying infected mucus have herniated through the eroded bone.

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