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Allergic fungal sinusitis (AFS) – earlier diagnosis and management

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Abstract

Aim: To evaluate the criteria for diagnosing allergic fungal sinusitis and to maintain permanent drainage and ventilation, while preserving the integrity of mucosa. **Methods:** This is a prospective study of 251 patients with chronic rhinosinusitis with or without polyposis, of whom 199 were treated surgically. Mucus sample collection, nasal secretion culture, surgical specimen handling and histological evaluation of surgical specimens are described. The management included wide local endoscopic sinus debridement, adequate sinus aeration, post-operative use of steroids and antifungal therapy. **Results:** Fungal cultures of nasal secretions were positive in 201 (80.01 per cent) of 251 patients. Of the 199 surgical cases, fungal elements were found in 156 histological specimens (62.1 per cent). Allergic mucin was found in 182 patients (91.45 per cent). Nasal obstruction and proptosis were the commonest presentations. All pre-operative versus post-operative changes in AFS-associated complaints reached statistical significance of $p < 0.001$. The ethmoid sinus was commonly involved with adjacent lamina papyracea exhibiting demineralization in 26.6 per cent of cases. Intracranial extension was seen in 15 cases. Recurrence was noted in 11 cases. **Conclusion:** Comprehensive treatment with endoscopic sinus surgery, steroids and antifungal therapy is needed. AFS is readily recurrent. Long-term follow up is important.

Key words: Sinusitis; Fungal Infection; Endoscopic Surgical Procedures; Eosinophils

Introduction

Over the past two decades, allergic fungal sinusitis (AFS) has become increasingly defined. Earlier it was known as paranasal sinus tumor. AFS is now believed to be an allergic reaction to aerosolized environmental fungi, usually of the dematiaceous species, in an immunocompetent host. Several decades ago, fungal disease was managed by extensive surgical debridement. Aspergillus was the only fungus recovered from paranasal sinus, because of limitations of culture techniques and lack of knowledge. The first reported case was by Plaignaud in 1791. An actual detailed clinical description of aspergillus was provided in 1885 by Schubert. In 1983, Katzenstein *et al.*¹ described allergic aspergillus sinusitis as a newly recognized form of sinusitis. In 1989, Robson *et al.*² introduced the term AFS. The incidence of AFS in cases of chronic rhinosinusitis treated surgically has been approximately 6–8 per cent. In 1990, five organisms responsible for AFS were identified by Ence *et al.*³ In 1994, Cody *et al.*⁴ simplified the diagnostic criteria to include only characteristic allergic mucin and non-invasive fungal hyphae within the collected mucin or positive fungal cultures. Other workers

believed that in addition to the above, type I hypersensitivity diagnosed by history, positive skin test or serology was another prerequisite for AFS.^{5,6} Recently, de Shazo and Swain⁷ reported that atopy is not a diagnostic criterion for AFS. Studies have also shown a relationship between AFS and allergic bronchopulmonary fungal disease. In 1991 Allphin and colleagues⁸ described features which differentiated AFS from other forms of sinusitis, including radiographic presence of opacified paranasal sinus, histological findings of allergic mucin and laboratory evidence of allergy.

AFS is relatively a common diagnosis at our centre. This study was a prospective look into the cases. Our aims are:

- (1) To re-evaluate the criteria of diagnosis of AFS via (a) mucus sample collection, (b) nasal secretion culture, (c) surgical specimen handling, (d) histological evaluation of surgical specimens.
- (2) To completely remove surgically the inciting fungal allergic mucin and marsupialization of involved sinuses.
- (3) To maintain permanent drainage and ventilation, while preserving the integrity of the mucosa.

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Materials and methods

The study group constituted 251 cases of chronic rhinosinusitis, including 199 patients who were treated surgically between 1997 and 2004. In this study 137 patients were females (54.58 per cent) and 114 were males (45.41 per cent), aged 15–65 years with an average age of 31.2 years.

The essential criteria for a diagnosis of AFS were: (1) nasal polypi; (2) allergic mucin (grossly it is thick, tenacious, highly viscous; its colour may vary from light tan to brown or dark green with characteristics of peanut butter and axle grease); (3) computed tomographic (CT) scan (paranasal sinus) showing opacification of paranasal sinus with areas of hyperattenuation; (4) positive fungal culture of surgical specimen.

Collections and culture technique

This was a simple non-invasive procedure to obtain as much mucus as possible, because fungi colonize the mucus and this should always be done when sinus infections are present.

Two puffs of xylocaine 10 per cent were sprayed into each nostril to increase the nasal lumen and the yield from nasal lavage. After two to three minutes, each nostril was flushed with 20 ml of saline using a sterile syringe and needle. The patient was requested to take a deep inspiratory breath and hold it before injection of saline and then forcefully exhale it. The return was collected in a sterile pan. This was sent to the laboratory and inoculated onto inhibitory mould agar containing ciplox or chloramphenicol or brain heart infusion agar. It took 30–40 days for fungi to grow.

Collection of surgical specimens

The principle of maximum mucus preservation was adhered to during the acquisition of surgical specimens. The mucus was manually removed with inflamed tissue and was placed on a sterile saline non-stick sheet. The use of suction devices was limited. Then staining of the specimen was done with haematoxylin and eosin (H&E) and Gomori methenamine silver. The microbiologist was alerted to look out for allergic mucin.

Surgical therapy

Preoperative details. To minimize recurrence of disease, treatment of AFS was directed at removal of the inciting antigenic material via complete surgical removal of allergic mucin and debris and also ameliorating the underlying inflammatory process through the use of oral steroids (i.e. prednisolone at a dose of 0.5–1 mg/kg/day) one week before surgery to decrease intranasal inflammation and nasal polyp volume and intra-operative bleeding. Pre-operative antibiotics were also given to avoid concomitant post-obstructive bacterial sinusitis.

Intra-operative details. At surgery three goals were achieved: (1) complete extirpation of all allergic mucin and fungal debris; (2) permanent drainage

and ventilation of the affected sinuses while preserving the integrity of the mucosa; and (3) post-operative access to the previously diseased areas.

An endoscopic approach was used in all patients. The surgical procedure was tailored to the extent of disease. The disease was evident as hypertrophic mucosa or polypi in the sinonasal cavities surrounding necrotic avascular, caseous, greenish casts. These caseous casts were removed using suction and gentle manipulation.

The ethmoids involved in the caseous process were eroded in 46 per cent of cases. The intersinus septae were thinned and eroded and were seen lying free within the caseous debris. In the maxillary antrum the erosion was limited to the medial wall and the ethmo-maxillary septum.

The expansive behaviour of AFS increased our access to involved paranasal sinuses. Enlargement of the nasal cavity, middle meatus and frontal recess provided us with adequate access to the disease even in the difficult areas such as the lateral area of the frontal sinus. Frontal sinus dehiscence was present in 5.02 per cent of cases.

Orbital extension was seen in 21.10 per cent of cases, which was explored via endoscopic ethmoidectomy. The caseous casts were invariably limited to the extra-periosteal space.

Intracranial extension, which was limited to the anterior cranial fossa (7.53 per cent), was always extradural. Access was obtained by an endoscopic ethmoidectomy along the route taken by the disease. The underlying dura was thickened but displayed no hyperaemia or granulations. no neurosurgical exposure was required.

Once the access was achieved allergic fungal mucin was removed in blunt fashion. Even in cases with significant dissolution of the fovea ethmoidalis, lamina papyracea, clivus and sphenoid planum, wide marsupialization of the diseased area was achieved without causing trauma to the underlying mucosa.

Post-operative details. Post-operative care began immediately after surgery with nasal saline irrigations with antifungal nasal drops (clotrimazole). Antibiotics were given for one week and oral steroids (prednisolone in pre-operative dosage according to the weight of the patient) for two weeks and then on alternate days for the next two weeks.

Follow-up care. The follow-up period ranged from 12.2 to 54.5 months with a mean of 32 months.

- (a) Twice daily irrigation with warm isotonic saline with antifungal drops for a mean period of 28.2 months.
- (b) Full dose intranasal steroidal spray (budesonide nasal spray, two puffs in each nostril once daily 50 µg/100 ml) for a mean period of 31.8 months.
- (c) Antifungal medications [T. fluconazole (oral) 150 mg once daily] for 21 days and liver function tests were done. If liver function tests were normal, then the antifungal medication was continued for seven more days.

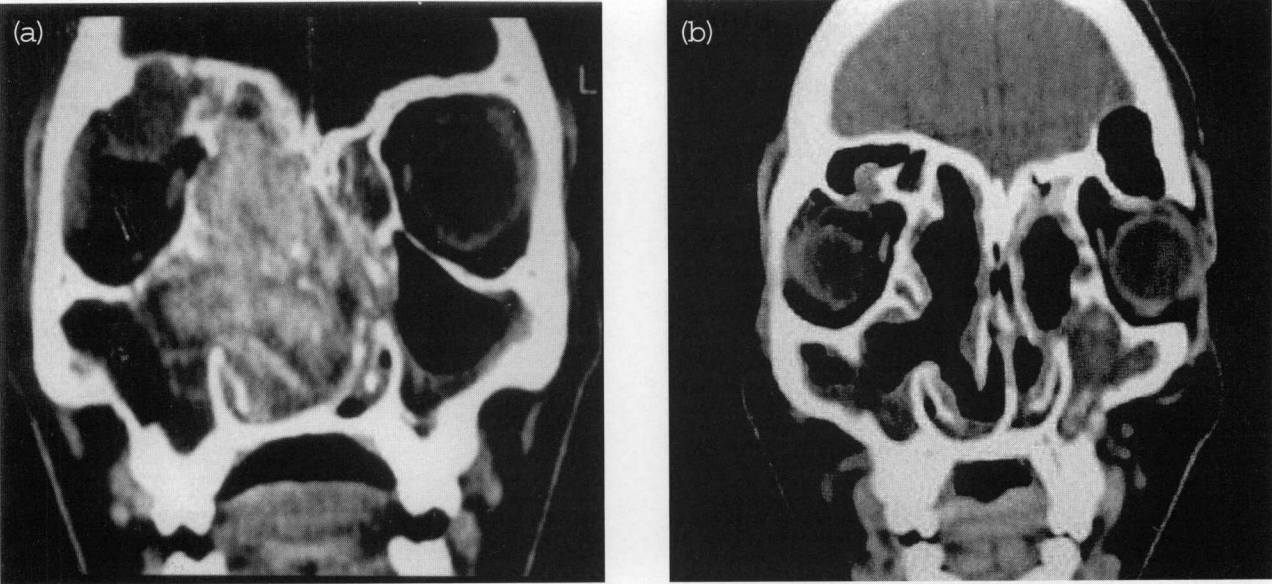


FIG. 1

(a) Coronal computed tomographic (CT) scan showing unilateral opacification of right nasal cavity, maxilla, anterior ethmoid and frontal sinuses with intracranial extension and deflection of septum to left. (b) Post-operative coronal CT scan showing complete resolution of disease.

- (d) Weekly clinic visit for 3 months for debridement of crusts and retained fungal disease.
- (e) Wearing of mask.

At follow up in the first three months we noticed synechiae ($n = 14$), mucosal oedema ($n = 67$), healing granulations ($n = 30$) and fungal debris ($n = 35$), which improved with continuation of follow-up care (Figures 1 and 2).

Results

Demographics

Of the patients who completed the follow up, 54.58 per cent were female and 45.41 per cent were males, with a mean age of 31.2 years. Of these, 38.2 per cent of patients resided in areas of high humidity. Previous sinus surgery had been performed in 100 patients (39.84 per cent) before referral. The study also included our revision cases ($n = 36$; 18.09 per cent).

Fungal culture and staining

There were positive results for fungus in 201 patients (80.01 per cent). A total of 300 positive cultures grew with an average of 1.5 organisms per patient. A total of 14 different genera of fungi were identified (Table I).

Of the 199 surgical cases, fungal elements (hyphae, destroyed hyphae, conidia and spores) were found in 156 histological specimens (62.1 per cent). Allergic mucin containing clusters or sheets of degenerating eosinophils and elongated eosinophilic bodies (Charcot-Leyden crystals), which represent the products of eosinophilic degradation, were found in 182 patients (91.45 per cent). In the remaining four cases allergic mucin and eosinophils were absent. The possibility of pre-operative administration of

steroids could explain the absence of eosinophils.

Symptoms of AFS

In our study the commonest symptom pre-operatively was nasal discharge (88 per cent, $n = 221$), followed by nasal obstruction (78 per cent, $n = 196$). Headaches in 38.2 per cent ($n = 96$) and 58.5 per cent ($n = 147$) were sensitive to aspirin and 23.1 per cent of patients ($n = 58$) had asthma.

Nasal obstruction was improved post-operatively in 96.98 per cent, nasal discharge in 95.47 per cent, headache in 97.98 per cent, asthma in 89.94 per cent and hyposmia in 98.49 per cent of patients. All pre-operative versus post-operative changes in AFS-associated complaints reached statistical significance (all $p < 0.001$, except asthmatic complaints with $p < 0.01$). According to these results, 94.5 per cent of patients had improvement.

TABLE I

NUMBER OF ORGANISMS RECOVERED FROM PATIENTS WITH CHRONIC RHINOSINUSITIS ($n = 251$)

Organism	Per cent
<i>Aspergillus</i>	
<i>A. flavus</i>	6.77
<i>A. fumigatus</i>	13.9
<i>A. niger</i>	8.3
<i>Curvalaria</i>	2.7
<i>Cladosporium</i>	11.5
<i>Candida</i>	5.1
<i>Nigrospora</i>	5.9
<i>Bipolaris</i>	5.5
<i>Phoma</i>	1.19
<i>Trichoderma</i>	1.59
<i>Rhizopus</i>	3.5
<i>Penicillium</i>	18.7
<i>Alternaria</i>	22.3
<i>Fusarium</i>	11.15

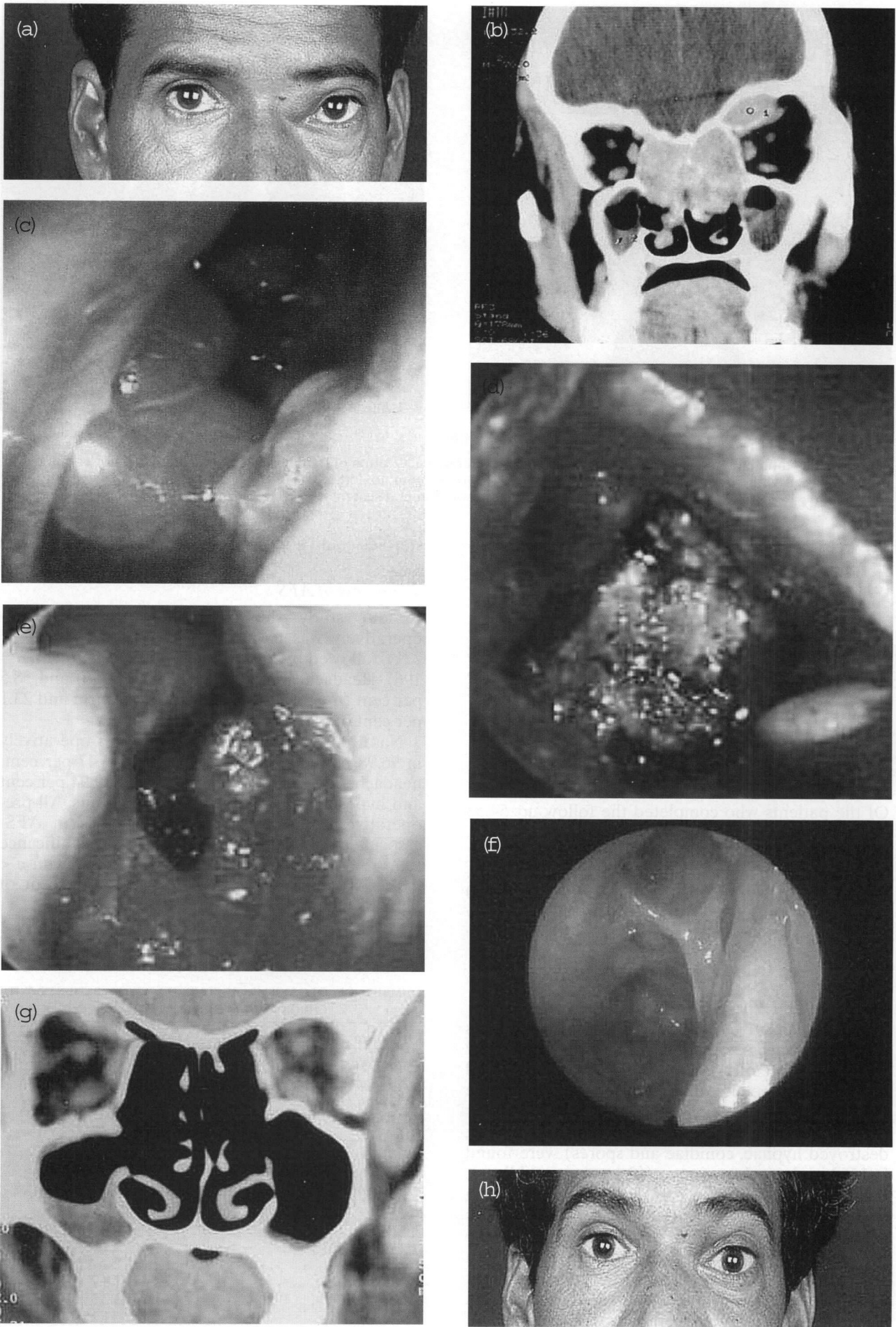


FIG. 2

(a) Proptosis of left eye with displacement laterally and inferiorly. (b) Coronal CT scan shows bilateral ethmoidal involvement with intraorbital extension. (c) Nasal endoscopy showing extensive polyposis. (d) Per-operative nasal endoscopy, light tan to black, greenish brown allergic mucin is shown. (e) Post-operative nasal endoscopy, one week later mucosal oedema with granulation is shown. (f) Six months later on nasal endoscopy, healed cavities can be seen. (g) Post-operative coronal CT scans showing complete resolution of disease. (h) Six months post-operatively patient has no proptosis.

We noted recurrence of disease in 11 of our patients, limited to ethmoids, maxilla or frontal sinus, with no intracranial or orbital extension. We noted that these recurrences were due to: (1) small residua of fungus left *in situ*; (2) discontinuation of steroids; (3) non-compliance with medical and fungal therapy; (4) non-compliance with follow-up visit; (5) non-avoidance of allergens.

Development of nasal airway obstruction was a gradual process such that even the patient was unaware. Seventeen patients had proptosis less than 2 mm and 15 patients had more than 2 mm; 7 patients had telecanthus and 5 patients had glabellar swelling. No diplopia was seen. Visual loss was present in two of our patients due to compression of ophthalmic nerve and atrophy of the optic nerve.

Imaging studies

Radiologically, patients with AFS frequently have areas of high attenuation within soft tissue masses of the affected sinuses on non-contrast CT scan.⁹⁻¹¹ Expansion, remodelling or thinning of involved sinus was commonly noted in our series. Bony erosion of sinus wall and extension of adjacent cavities were found in 34.6% of patients. The ethmoid sinus was a commonly involved sinus, while adjacent lamina papyracea commonly exhibited demineralization (26.6 per cent). Intracranial extension was seen in 15 cases only in the anterior cranial fossa, with no extension into middle or posterior cranial fossa (Table II).

Discussion

With heightened awareness of the disease, an increasing number of reports have been published.^{4,5,12-15} Suggestions regarding the criteria for clinical diagnosis and treatment regimens have appeared in the literature.^{4,6,13-15} The diagnostic criteria^{16,17} for AFS include: (1) chronic rhinosinusitis (confirmed by CT scan); (2) the presence of allergic mucin (predominantly eosinophils) and (3) the presence of a fungal organism within that mucin confirmed by histology or culture. The 92.5 per cent incidence of AFS in chronic rhinosinusitis is considerably higher than the incidence reported in a previous retrospective review.^{18,19} The explanation for the high incidence of fungus isolation in our study may lie in any one of the following. (a) Allergens in our geographical area may be different from allergens identified in other reports. (b) The mechanism resulting in this clinical condition may not be allergic, merely related to sinonasal obstruction. (c) The isolation techniques/histological techniques used in retrospective studies may not have been sufficiently sensitive.

Any patient who we suspected to have sinus

infection underwent mucus culture. Most clinicians concluded from a report of negative culture that fungi were not present in mucus; they probably ignored the possibility that methods might be inadequate to collect mucus, because fungi colonize in nasal mucus. So, the more mucus collected, the greater the chance of obtaining a positive culture. Suction clearance and power microdebrider decreased the amount of recovered mucus. Placing the specimen on absorbent material reduces the collected mucus. For any patient suspected to have fungus, the specimen was stained with Gomori methenamine silver and H&E, and the microbiologist was informed about the nature of disease.

The presence of Charcot-Leyden crystals alone is not specific for AFS and therefore should not be used as a diagnostic criterion. All that the presence of crystals implies is that eosinophils have died. Other markers that are more specific (e.g. major basic protein) may be more useful as histological markers. This concept needs further study.

The histological marker of chronic rhinosinusitis is the striking number of eosinophils.²⁰ Our observation is that eosinophils actually migrate through the epithelium and degranulate within the mucus. It is hypothesized that eosinophils play a role in the general inflammatory response and that their target is located in mucus. In other words the fungal organism in mucus could be the target for the eosinophils, but this needs further validation.

Minimally invasive but complete surgical exenteration of disease, with polypectomy and marsupialization of the involved sinus, is a mandatory component of treatment.²¹⁻²³ Schaefer and co-workers²⁴ reported that when there is bone destruction and extension into orbit and anterior skull base, then an open approach is indicated. However, our approach was completely endoscopic.²⁵

In our experience, distortion of local anatomy and loss of surgical landmarks is potentially disorientating. The involved paranasal sinus acting as a reservoir for allergic fungal mucus was the epicentre of the disease process. The material removed was thick, tenacious, viscous and rubbery,

TABLE II
EXTENSION OF DISEASE

Extension	No. of patients
Pansinusitis	
Unilateral	41
Bilateral	82
Orbital extension	42
Nasopharynx	17
Pterygopalatine	05
Intracranial	15
Frontal sinus dehiscence	10

and the colour varied from light tan to black, greenish-brown with the texture of wet clay. Our cases having extension to the orbit or anterior cranial fossa or frontal sinus were accessed by an endoscopic approach.

Systemic adjuvant steroids have been advocated for AFS to reduce recurrence,²⁶⁻²⁸ but were not used in this study group. Nevertheless, recurrences were infrequent (5.5 per cent). This may be related to the complete exenteration of disease endoscopically, post-operative medical management and close follow up.

Care was taken with the following aspects. (1) The correct technique of irrigation was taught to the patient, which must include adequate amounts of saline. The patients were instructed to add antifungal drops in the irrigator. (2) Excessive crusting or retained secretions was a common problem but regular follow up for debridement and again irrigation was very helpful. (3) Allergy was carefully evaluated and mould and fungal exposures were controlled by continued use of a mask.

We noted that 96 patients lived in coastal areas which were highly humid. In our Indian scenario pollution and dust also played an important role. This shows that fungi survive and multiply in warm and humid climates.

Mabry *et al.*^{29,30} observed that those patients responding to immunotherapy had less need for systemic steroids. We did not give immunotherapy to any of our patients. We believe that long-term follow up is needed to detect recurrence. The follow-up period ranged from 12.2 to 54.5 months. Kupferberg *et al.*^{31,32} observed in their study of 24 patients that 19 developed recurrence after discontinuation of steroids, and endoscopic evidence of disease preceded return of subjective symptoms. Similarly, Bent and Kuhn^{6,12-14} emphasized the importance of long-term follow up. AFS recidivism appears to be influenced by long-term post-operative therapy. Schubert and Goetz^{33,34} reported the clinical outcome of 67 patients following surgical therapy and 35 per cent had recurrent AFS, who did not receive post-operative medical therapy. The study done by Rains *et al.*³⁵ on 139 patients suggested that medical management of recurrent AFS may avoid revision surgery. The endoscopic approach has the following potential advantages over external procedures.

- (a) It avoids facial scars thus avoiding scar complications.
- (b) It can be done under local anaesthesia.
- (c) Endoscopically, by directly accessing the disease area, it limits tissue damage, and surgical trauma, thus preserving the anatomy.
- (d) Immediate mistakes can be revised at surgery.
- (e) Reduced operative time.
- (f) Reduced morbidity.
- (g) Reduced intra-operative bleeding.
- (h) Cost-effective.

With this comprehensive management, 94.5 per cent of patients had symptomatic improvement. All

pre-operative versus post-operative changes in AFS-associated complaints were statistically significant ($p < 0.001$).

In three years of follow up, none of our patients had complications such as diplopia, blindness, haemorrhage, encephalocele or CSF leak.

- **This paper reports the management of 251 patients with chronic rhinosinusitis, with specific attention to possible fungal aetiology**
- **Fungal culture of nasal secretions was positive in 80 per cent of patients, with *Aspergillus* species being most commonly isolated**
- **The authors describe the management of 15 patients presenting with intracranial involvement. Intracranial involvement was always extradural and an endoscopic intranasal approach to surgical treatment is advocated**
- **Renaming of the condition as eosinophilic fungal sinusitis is proposed in recognition of the key role of eosinophils in mediating the inflammatory response**

Conclusion

Diagnosis of AFS required a high index of suspicion. A confirmatory diagnosis was made from the inspissated mucus, clinical and CT findings, along with careful communication with the investigating microbiologist about the possibilities of fungal growth. The term allergic mucin is thus a misnomer and is confusing. We prefer the term eosinophilic mucin, as it is clear and descriptive. Consequently, the term allergic fungal sinusitis is also inaccurate for this disease and should be altered. We propose the term eosinophilic fungal rhinosinusitis to reflect the striking role of the eosinophils in this disease.

A comprehensive management plan with diagnostic criteria, endoscopic sinus surgery, steroids and antifungal therapy is needed, and might provide long-term control of AFS. The long-term follow up is very important. The exact combination continues to be debated strongly.

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