

Allergic Fungal Rhinosinusitis

An Attempt to Resolve the Diagnostic Dilemma

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Objective: To resolve the diagnostic dilemma of allergic fungal rhinosinusitis (AFRS), an increasingly recognized type of chronic rhinosinusitis (CRS). In spite of extensive studies, controversy exists regarding the etiologic characteristics, pathogenesis, and diagnosis of this entity.

Design: Prospective, comparative study.

Setting: Department of Otolaryngology–Head and Neck Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Patients: Seventy consecutive patients with CRS, with or without polyps.

Methods: Patients were evaluated by detailed clinical examination, computed tomography (CT), skin test against aspergillin antigen (47 patients), and histopathologic and mycologic monitoring. Based on the presence or absence of allergic mucin (M) and mycelial element (F) in the sinus, the patients were divided into 4 groups: M+F+ (likely AFRS group), M+F– (likely eosinophilic mucin rhinosinusitis), M–F+ (likely sinus myceto-

toma), and M–F– (CRS from other causes). The different parameters were compared in these 4 groups.

Results: Thirty-six patients were categorized in the likely AFRS group, 12 with eosinophilic mucin rhinosinusitis, 4 with sinus mycetoma, and 18 with CRS from other causes. Despite considerable overlap among different groups, the following parameters were significantly more associated with AFRS group: type 1 hypersensitivity ($P<.05$), Charcot-Leyden crystals ($P<.001$), bony erosion ($P<.001$), and heterogeneous opacity with sinus expansion on CT scan ($P<.05$). The above results were further validated in those patients for whom all investigations were conducted ($n=47$). The significance of these 4 parameters with regard to AFRS was reconfirmed in those 47 patients.

Conclusions: To diagnose AFRS, important findings should be considered in addition to the detection of fungal elements and allergic mucin: Charcot-Leyden crystals, type 1 hypersensitivity, bony erosion, and heterogeneous opacity with sinus expansion on CT. The last 3 of these parameters may predict AFRS preoperatively.

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ALLERGIC FUNGAL RHINOSINUSITIS (AFRS) is an increasingly recognized type of chronic rhinosinusitis (CRS). The overall incidence of AFRS is estimated at 5% to 10% of all patients with CRS who undergo surgery.¹⁻³ It is possibly a non-tissue-invasive disease, representing an allergic hypersensitivity response to the presence of extramucosal fungi within the sinus cavity, possibly akin to allergic bronchopulmonary aspergillosis. Patients often have asthma, allergic rhinitis, eosinophilia, and an elevated total and fungus-specific IgE concentration. The involved sinuses contain brown or greenish black material, which has been called *allergic mucin*, and intact and degenerating eosinophils, Charcot-Leyden crystals, cellular debris, and sparse fungal hyphae.⁴

In the diagnosis of AFRS, the detection of fungi in allergic mucin is consid-

ered important, although hyphae are sparse in sinus content. This leads to confusion in categorization of this entity, especially with the description of 2 more closely related entities—eosinophilic fungal rhinosinusitis (EFRS) and eosinophilic mucin rhinosinusitis (EMRS).^{5,6} The confusion is further heightened by the alternate hypothesis of Ponikau et al,⁷ which proposes a different mechanism of AFRS and might be applied universally to encompass CRS as well.⁷ Using detection of fungi in nasal lavage as a method of diagnosis, Ponikau et al demonstrated the presence of fungi in specimens from 93% of patients with CRS and did not find type 1 hypersensitivity to be prevalent in their study group. They offered the hypothesis that CRS is a cell-mediated response to fungal elements and suggested the acceptance of the new term, EFRS. Thus, the question remains whether a separate unrecognized form of nonallergic, fungal eosino-

philic inflammation exists that can lead to a similar clinical presentation. Ferguson⁵ claimed that eosinophilic mucin could be present and cause rhinosinusitis without the presence of fungi. The controversy regarding the definition of AFRS is further intensified with well-documented reports of histologic invasion in possible cases of AFRS.^{8,9} Foci of granulomatous inflammation in a patient of AFRS with orbital apex involvement has also been reported.¹⁰ Thus, in an attempt to resolve this diagnostic dilemma of AFRS, we conducted the present prospective evaluation of patients with CRS.

METHODS

PATIENTS

Seventy consecutive patients with CRS (of >3 months' duration) with or without nasal polyposis attending the Department of Otolaryngology–Head and Neck Surgery at the Postgraduate Institute of Medical Education and Research, Chandigarh, India, over a period from July 2002 to October 2003 were included in the study group. Patients with apparent immunocompromised status or with histologic documentation of invasive fungal disease were not included. A detailed medical history along with clinical examination including preliminary nasal endoscopy was carried out in all patients. Aspirin sensitivity was considered from history alone. Bronchial asthma was considered in those patients who were under the care of a pulmonologist and were undergoing bronchodilator therapy. Patients were seen for follow-up during the study period.

EVALUATIONS

All patients underwent computed tomography (CT) of the paranasal sinuses and orbit in the axial and coronal planes, total leukocyte count, differential leukocyte count, absolute eosinophil count, and fasting sugar level estimation. An eosinophil count higher than 500 cells/mL was considered to indicate serum eosinophilia.

In 47 patients, an intradermal skin test was performed using 0.1 mL of antigen (1000 protein nitrogen units/mL aspergillin; Hollister Stier, Spokane, Wash). The same volume of sterile phosphate-buffered saline (pH, 7.2) was injected intradermally on the other arm to serve as a control. Type 1 (erythema and wheal of any size within 1 hour) and type 4 (induration of more than 5 mm in diameter after 24 hours) hypersensitivity reactions were considered positive only when there was no reaction in the control arm.

All surgically excised sinus mucosa and intranasal debris (endoscopically removed) were equally divided into halves. One half was used for histopathologic monitoring, and the other half was used for mycologic examination. For histopathologic analysis, the sample was individually fixed in 10% buffered formalin, and 5- μ m-thick sections were cut from paraffin blocks and stained with hematoxylin-eosin, periodic Acid Schiff, and Gomori methanamine silver stains. The histopathologic examination was carried out for the presence (M+) or absence (M-) of extramucosal allergic mucin, eosinophil clusters, Charcot-Leyden crystals, fungal hyphae, and possible mucosal invasion by fungal hyphae. Macroscopically, allergic mucin is chalky gray or sometimes brownish green with gumlike or butterlike consistency interspersed with the nasal polyp. Microscopically, it is extracellular, lamellated eosinophilic mucin, which is paler in the center than at the periphery under hematoxylin-eosin staining. On Grocott staining, it appears as green-gray lamellated aggregations. In addition, allergic mucin consists of clumps of eosinophils, Charcot-Leyden crystals,

and fungal hyphae. The fungal hyphae are found inside the mucin without evidence of tissue invasion, often seen as broken, fragmented hyphae.

The portion of surgically excised specimen used for mycologic examination was collected in sterile normal saline (isotonic sodium chloride). Direct microscopy under 10% potassium hydroxide wet mount was performed on homogenized and nonhomogenized tissue to screen for fungal elements (F+ or F-). The homogenized tissue was cultured by inoculation on Sabouraud dextrose agar for growth of fungi. The different mycelial isolates were identified by microscopic morphologic analysis or slide culture mount, and yeasts were identified by standard biochemical tests.^{11,12}

For univariate analysis, the χ^2 test was used.

RESULTS

The patients ranged in age from 9 to 81 years, with a mean (SD) age of 36.4 (14) years. The male-female ratio was 1.5:1.

On the basis of presence or absence of allergic mucin and fungal elements in the sinus content, the patients were categorized into 4 groups (**Table 1**): M+F+ (likely AFRS) (n=36) (**Figure 1**), M+F- (likely EMRS) (n=12), M-F+ (likely sinus mycetoma) (n=4), M-F- (CRS from other causes) (n=18). On comparison of clinical and laboratory parameters in AFRS and EMRS groups, significantly higher associations of type 1 hypersensitivity ($P<.05$), Charcot-Leyden crystals ($P<.001$) (**Figure 2**), bony erosion, and heterogeneous opacity with sinus expansion on CT scan ($P<.05$) (**Figure 3**) were found in the AFRS group.

A skin test against aspergillin antigen was performed on only 47 patients, and type 1 hypersensitivity was found to be an important criterion to diagnose AFRS. The results were further validated in only those 47 patients who underwent all investigations. Those 47 patients could be characterized into 4 groups (**Table 2**): M+F+ (likely AFRS) (n=24), M+F- (likely EMRS) (n=10), M-F+ (likely sinus mycetoma) (n=2), M-F- (CRS from other causes) (n=11). Similarly, higher associations of type 1 hypersensitivity ($P<.001$), presence of Charcot-Leyden crystals ($P<.001$), bony erosion ($P<.001$), and heterogeneous opacity with sinus expansion on CT scan ($P<.001$) were found in the AFRS group compared with other 2 groups (sinus mycetoma and CRS from other causes). Between the AFRS and EMRS groups, a significantly higher association of asthma ($P<.05$) was observed in the EMRS group, but aspirin sensitivity was detected in only 10% of the same group.

Among the 32 M+F+ patients in the AFRS group, the most common culture isolate was *Aspergillus flavus* (n=26; 81%), followed by *Aspergillus fumigatus* (n=3; 9%). A *Bipolaris* species was isolated in only 2 patients (6%).

COMMENT

Fungal rhinosinusitis, once considered a rare disorder, has been reported with increasing frequency worldwide over the last 2 decades.^{6,13,14} Based on histopathologic findings, 5 possible distinct diagnostic categories are recognized.¹⁵ Three types of fungal rhinosinusitis are tissue in-

Table 1. Clinical Characteristics and Laboratory Data by Category of CRS*

Patient Characteristic	Positive for Allergic Mucin		Negative for Allergic Mucin	
	F+ (n = 36) Likely AFRS	F- (n = 12) Likely EMRS	F+ (n = 4) Likely Sinus Mycetoma	F- (n = 18) CRS From Other Causes
Age, mean $\pm$ SD, y	28 $\pm$ 13	41 $\pm$ 10	44 $\pm$ 11	42 $\pm$ 15
Sex, male	21 (58)	6 (50)	3 (75)	12 (67)
Asthma	5 (14)†	6 (50)†	0	4 (22)
Nasal polyps	34 (94)	12 (100)	3 (75)	18 (100)
Eosinophilia	25 (69)	9 (75)	3 (75)	10 (56)
Type 1 hypersensitivity	22/24 (92)†	2/10 (20)†	1/2 (50)	3/11 (27)
Charcot-Leyden crystals	34 (94)†	4 (33)†	0	0
Aspirin sensitivity	0	2 (17)	0	0
Unilateral involvement	9 (25)	0	1 (25)	1 (6)
Bone erosion on CT	36 (100)†	5 (42)†	0	2 (11)
Heterogeneous opacity with sinus expansion	35 (97)†	8 (67)†	1 (25)	5 (28)
History of recurrence	21 (58)	6 (50)	1 (25)	1 (6)
Culture positive	32 (89) <i>Aspergillus flavus</i> (n = 26) <i>Aspergillus fumigatus</i> (n = 3) <i>Bipolaris</i> species (n = 2) <i>Penicillium</i> species (n = 1)	0	2 (50) <i>A. flavus</i> (n = 1) <i>Candida tropicalis</i> (n = 1)	0

Abbreviations: AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; CT, computed tomography; EMRS, eosinophilic mucin rhinosinusitis; F, fungal hyphae; +, positive finding; -, negative finding.

*Unless otherwise indicated, data are reported as number (percentage) of patients or number of patients with the relevant finding/number of patients tested (percentage of patients).

†Statistically significant finding.

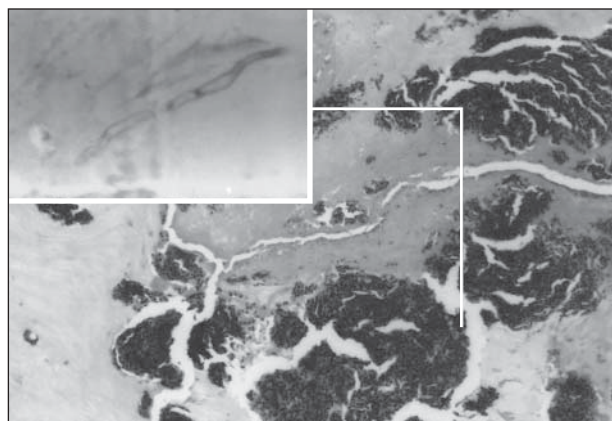


Figure 1. Microscopic sections showing allergic mucin with eosinophilic clusters (main photograph; hematoxylin-eosin, original magnification $\times 33$) and septate hyphae of aspergillus species (inset; periodic Acid Schiff, original magnification $\times 330$).

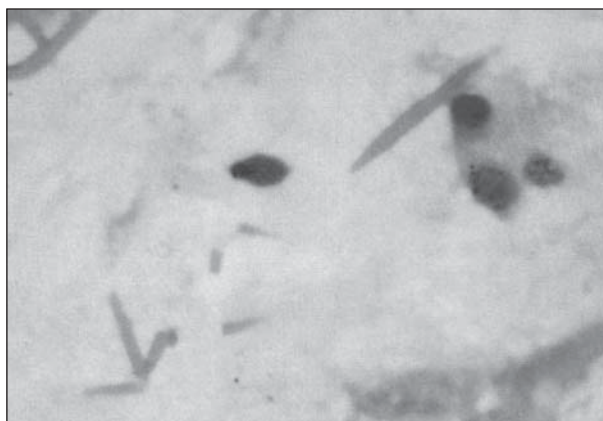


Figure 2. Microscopic section showing allergic mucin with numerous Charcot-Leyden crystals in bipolar shape (hematoxylin-eosin, original magnification $\times 132$).

vasive: acute necrotizing (fulminant), chronic invasive, and granulomatous invasive (indolent). Two types are categorized as noninvasive: fungal ball (sinus mycetoma) and AFRS. However, this categorization is still controversial, especially in defining the AFRS group.

The history of AFRS is somewhat convoluted. Safirstein¹⁶ first noted the combination of nasal polyposis, crust formation, and positive sinus culture for *Aspergillus* species in 1981. In 1981, Miller et al¹⁷ recognized a histologic resemblance between specimens from 5 patients with allergic bronchopulmonary aspergillosis. Two years later, Katzenstein et al¹ independently observed the pathophysiologic resemblance between allergic bronchopulmonary aspergillosis and 7 cases of chronic fungal si-

nusitis. The term *allergic fungal sinusitis* was coined in 1989.¹⁸ Since then, extensive work has been carried out to explain the disease as an immunologically mediated disorder (IgE mediated) rather than a precursor of invasive fungal disease.^{4,8,19-21} It has been estimated that 5% to 10% of patients with CRS carry a diagnosis of AFRS.^{6,22,23} However, in the present series, likely AFRS was diagnosed in 51% of patients (n=36/70) with CRS. This is the largest series reported from a single center. The incidence may depend on location; geographical variation in incidence of AFRS was observed in the United States with most cases found in the southern central region of the country.²⁴ In India, AFRS is increasingly reported in North India.^{9,25-28}

The diagnostic criteria for AFRS vary among authors, but most widely accepted are the 5 criteria described by Bent and Kuhn¹⁹: (1) type 1 hypersensitivity to fungi; (2) nasal polyposis; (3) characteristic radiographic finding of serpiginous areas of high attenuation; (4) eosinophilic mucin; and (5) positive fungal stain. Confusion still prevails in the diagnosis because of difficulty in demonstrating sparse fungal hyphae in allergic mucin. This has led to the description of 2 new entities: EFRS and EMRS.^{5,6} It has been suggested that the traditional classification list should be changed by including EFRS or even substituting EFRS for AFRS. The situation is further complicated by the alternate hypothesis that CRS is a cell-mediated response to fungal elements rather than an IgE-mediated hypersensitivity disorder.⁷ Ferguson,⁵ in her description of EMRS, claimed

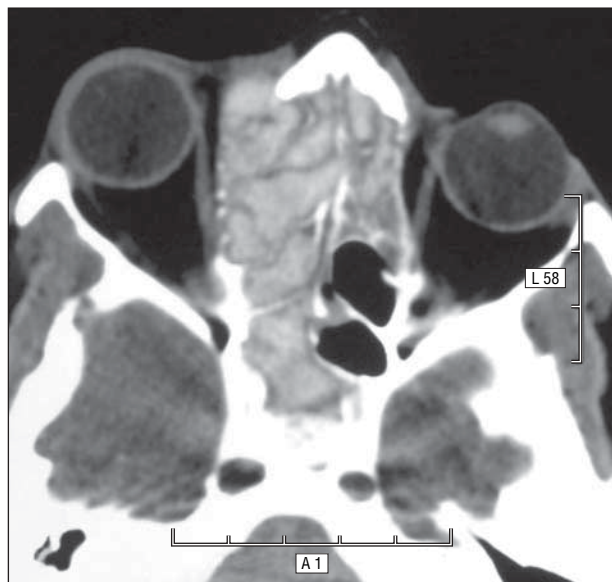


Figure 3. Axial computed tomographic image showing bilateral heterogeneous opacity with hyperattenuation areas in ethmoid and sphenoid sinuses.

that eosinophilic mucin could be present and cause sinusitis without the presence of fungi. Thus, the laboratory findings in the possible AFRS groups are quite variable and are a source of controversy. Several studies have reported elevated levels of both total and fungus-specific IgE levels in addition to evidence of type 1 hypersensitivity in patients with AFRS. On the other hand, several investigators have failed to demonstrate these findings.

In an attempt to resolve this problem, we categorized our patients with CRS into 4 groups on the basis of presence of allergic mucin and fungal hyphae and evaluated different clinical features and laboratory findings among those groups. A considerable overlap was observed in findings between likely AFRS and EMRS groups. No significant difference was observed between the 2 groups regarding nasal polyposis and eosinophilia. However, a significantly higher association was observed regarding the presence of type 1 hypersensitivity ($P < .05$ to $P < .001$), Charcot-Leyden crystals ($P < .001$), bony erosion ($P < .001$), and heterogeneous opacity with sinus expansion ($P < .05$ to $P < .001$) in likely AFRS group.

Most studies have shown that AFRS presents frequently as unilateral disease.^{4,5} However, in the present study, only 25% of patients with likely AFRS group had unilateral involvement. Thus, on the basis of the present findings, we propose the following criteria to diagnose AFRS: (1) type 1 hypersensitivity to fungi; (2) CT findings of bone erosion and heterogeneous opacity with sinus expansion; (3) allergic mucin with Charcot-Leyden crystals; and (4) demonstration of fungi on direct microscopy.

The detection of fungal elements in allergic mucin is an important criterion in differentiating the patients with AFRS from those with EMRS. It is sometimes difficult to demonstrate fungal hyphae because of their small numbers. Ponikau et al,⁷ in their initial study using a sensitive detection method (nasal lavage), demonstrated that 93% of patients with CRS had fungi present in tissue speci-

Table 2. Clinical Characteristics and Laboratory Data by Category of CRS in 47 Patients for Whom All Laboratory Investigations Were Performed

Patient Characteristic	Positive for Allergic Mucin		Negative for Allergic Mucin	
	F+ (n = 24) Likely AFRS	F- (n = 10) Likely EMRS	F+ (n = 2) Likely Sinus Mycetoma	F- (n = 11) CRS From Other Causes
Age, mean $\pm$ SD, y	28 $\pm$ 13	41 10	44 $\pm$ 11	42 $\pm$ 15
Sex (male)	14 (58)	5 (50)	1 (50)	6 (55)
Asthma	2 (8)	6 (60)†	0	4 (36)
Nasal polyp	23 (96)	10 (100)	2 (100)	11 (100)
Eosinophilia	16 (67)	8 (80)	1 (50)	6 (55)
Type I hypersensitivity	21 (88)†	2 (20)	1 (50)	3 (27)
Charcot-Leyden Crystal	23 (96)†	3 (30)	0	0
Aspirin sensitivity	0	1 (10)	0	0
Unilateral involvement	3 (13)	0	1 (50)	1 (9)
Bone erosion on CT	24 (100)†	4 (40)	0	2 (18)
Heterogeneous opacity with sinus expansion†	24 (100)	7 (70)	0	5 (45)
History of recurrence	14 (58)	5 (50)	0	2 (18)

Abbreviations: AFRS, allergic fungal rhinosinusitis; CRS, chronic rhinosinusitis; CT, computed tomography; EMRS, eosinophilic mucin rhinosinusitis; F, fungal hyphae; +, positive finding; -, negative finding.

*Unless otherwise indicated, data are reported as number (percentage) of patients.

†Statistically significant finding.

mens. However, they also identified fungus in the nasal lavage from 100% of healthy volunteers, demonstrating the ubiquitous nature of these saprophytic fungi. Lebowitz et al²⁹ proposed that using standard laboratory methods (specimens were treated with sputolysin as in the processing of sputum), fungi can be readily identified in the surgical specimens of patients undergoing endoscopic sinus surgery for CRS. Schubert⁴ proposed that for diagnosis of AFRS, the allergic mucin must be positive for fungal hyphae, or fungal cultures must be positive in properly obtained surgical sinus content in an otherwise characteristic patient. However, transnasal acquisition of specimens invariably shows culture positive for many normal nasal organisms, including fungi. Moreover, the saprophytic fungi may also be laboratory contaminant if the sample is not processed under strict conditions. Thus, it would be better to include demonstration of fungal element in tissue histopathologic samples in diagnostic criteria rather than culture isolation.

Dhiwakar et al²⁸ suggest that the combination of nasal polyposis, CT scan, and specific IgE titer has high preoperative AFRS diagnostic value. In the present study, no significant difference was observed regarding the presence of nasal polyposis in the likely AFRS and EMRS groups; rather, nasal polyposis was seen in all patients with likely EMRS. Therefore, it would be logical to include only the combination of hyperattenuation and bony erosion on CT scan and type 1 hypersensitivity as preoperative predictors of AFRS.

To define the EMRS group, Ferguson⁵ claimed that these patients have a significantly higher association with asthma, an increased incidence of aspirin sensitivity, and an increased incidence of IgG1 deficiency. In the present study, though a significantly higher association with asthma was observed ($P < .05$), a small percentage of patients (17%; 2/12) had increased incidence of aspirin sensitivity. The level of IgG1 was not measured in this study. Thus, the overlapping entities require further study in more patients to resolve the diagnostic dilemma.

To diagnose AFRS, the presence of allergic mucin in histopathologic specimens is important in addition to the demonstration of fungal elements. However, allergic mucin is not uniformly distributed throughout sinus content. An inadequate sampling may thus pose problems in proper categorization of cases. Hence, a detailed examination of all the fragments is mandatory. In the present series, 4 patients were categorized as having sinus mycetoma owing to absence of allergic mucin, although type 1 hypersensitivity was positive in 1 of 2 patients tested, and eosinophilia was seen in 75% of patients ($n = 3$ of 4). Earlier, in a large series of patients with sinus mycetoma, members of our research group observed type 1 hypersensitivity in over 90% cases.²⁵ These observations further emphasize the need of a detailed histopathologic workup and long-term follow-up studies.

The noninvasive and invasive forms of fungal rhinosinusitis are not necessarily discrete and may coexist in the same patient. There are well-documented reports of histologic invasion in cases of AFRS.^{8,9} Klapper et al¹⁰ reported foci of granulomatous inflammation in a patient of AFRS with orbital apex involvement. Thakar et al⁹ recommended that fungal sinusitis be considered a poten-

tially progressive continuum, wherein noninvasive disease may convert to or coexist with an invasive form. Although we did not observe noninvasive CRS turning into invasive disease in our patients during this short follow-up period of 16 months, a longer follow-up of such patients is required to understand the behavior of the lesion in fungal rhinosinusitis. Of course, the recurrence of the disease was significantly more associated with AFRS and EMRS groups.

In the initial studies, *Aspergillus fumigatus* was considered the primary etiologic agent of AFRS cases, but later, pigment-producing dematiaceous fungi—*Bipolaris spicifera*, *Exserohilum roibatum*, *Curvularia lunata*, and *Alternaria* species—were found as predominant etiologic agents in Western literature.^{1,4,15} However, in contrast *A flavus* is the predominant etiologic agent causing AFRS on the Indian subcontinent along with other form of fungal rhinosinusitis.²⁵⁻²⁸ This contrasting feature may be due to a higher load of conidia of *A flavus* in the environment of tropical countries, and that can be evaluated in future studies.

In conclusion, a considerable overlap exists between AFRS, EMRS, and CRS from other causes regarding the clinical features and radiologic and immunologic parameters. However, the definite diagnosis of AFRS is desirable to choose a required management protocol. The present study found that in addition to detection of fungal elements and allergic mucin in the sinus content, determining the presence of type 1 hypersensitivity, Charcot-Leyden crystal, bony erosion, and heterogeneous opacity with sinus expansion on CT scan may be considered important criteria to define this entity. The combination of hyperattenuation and bony erosion on CT scan and type 1 hypersensitivity may be considered as preoperative predictors of AFRS. The existence of the geographical diversity of fungus being implicated in AFRS is further confirmed.

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Announcement

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