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Original Article

Diagnosis of Allergic Fungal Rhinosinusitis

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Abstract

Background: Allergic fungal sinusitis is a non-invasive disease, and accounts for approximately 6-8% of all chronic sinusitis requiring surgical intervention. As the treatment and prognosis of these disorders vary significantly, it is extremely important to recognize allergic fugal sinusitis and differentiate it from chronic sinusitis of bacterial and fungal origin. This prospective study evaluates the occurrence of allergic fungal rhinosinusitis in patients with chronic rhinosinusitis with or without polyposis, who were surgically treated in Khalili Hospital during one year.

Methods: The study comprised 38 patients with chronic rhinosinusitis with or without polyposis as case and 10 patients with chronic rhinosinusitis as control. The diagnosis of allergic fungal sinusitis was based on analysis of clinical, radiological, histological, mycological, and immuno allergic criteria.

Results: From a total of 38 patients, 9 were consistent with allergic fungal rhinosinusitis. Twenty-one patients had histological, clinical, and radiological findings suggestive of allergic fungal sinusitis but were negative for fungal culture. Some of these patients had characteristics that recently described as eosinophilic mucin rhinosinusitis. None of the control cases had histological or mycological evidence of allergic fungal sinusitis.

Conclusion: Nine (23.7%) patients had findings consistent with allergic fungal rhinosinusitis. However, more specific diagnostic tests such as skin test and specific IgE should be performed to confirm the diagnosis.
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Keywords ● Chronic bacterial sinusitis ● fungal sinusitis ● eosinophil ● nasal polyp

Introduction

Allergic fungal sinusitis (AFS) is a non-invasive disease which is increasing interest by otolaryngologists and related specialists.[1-3] Although, certain signs and symptoms as well as radiographic, intraoperative, and pathologic findings, may cause the physician to suspect allergic fungal sinusitis, no definitive criteria have been defined for establishing the diagnosis.[4] It is important to recognize AFS and differentiate it from chronic bacterial sinusitis and other forms of fungal sinusitis because the treatments and prognosis of these disorders vary significantly.[4] Unfortunately, misdiagnosis is common, recurrence rates are high and proper treatment remains elusive.[5]

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The incidence of AFS appears to be impacted by geographic factors. Most areas, reporting cases of allergic fungal sinusitis, are located in temperate regions with relative high humidity.[6-8] Also a large number of cases are identified in temperate districts with low humidity such as Arizona, South California and Saudi Arabia.[6,8] A variety of fungal species may be responsible for AFS. *Aspergillus* is the most common species generally encountered in the environment and in fungal sinusitis, and presumably in AFS.[9] The other reported agents belonging to *dematiaceous* family include *Bipolaris, Drechslera, Alternaria, etc*.[8-10] Other agents such as Candida, Penicillium and Geotrichum have also been reported.[9]

Criteria for the diagnosis of allergic fungal sinusitis are not clearly established but elements which may be considered. The "gold standard" is the presence of chronic rhinosinusitis with allergic mucin on pathologic examination and mycelial filament on direct mycological or culture examination. The criteria to be considered for the diagnosis of allergic fungal sinusitis include type 1 hypersensitivity confirmed by history of asthma, intolerance to aspirin, skin test, or detection of specific IgE ,nasal polyposis, characteristic signs of computed tomography, eosinophilic mucus without fungal invasion into sinus tissue and detection of fungal elements in sinus content removed during surgery.[5,11]

The aim of this prospective study is to analyze clinical, radiological, mycological, histological, and immunological criteria for optimizing the diagnosis of true allergic fungal sinusitis.

Patients and Method

This prospective study was conducted from December 2001 to December 2002, in order to determine the frequency of AFS in our region. The study included 38 cases with chronic rhinosinusitis with or without polyposis. All patients underwent surgical treatments in the Khalili Hospital affiliated to Shiraz University of Medical Sciences.

Patients with the following criteria were included in the study: 1) Chronic rhinosinusitis characterized by recurrent upper respiratory tract infections lasting longer than 3 months and refractory to several medical or surgical treatments, 2) inflammatory mucosal thickening found on endoscopic examination and confirmed by coronal computed tomography, and finally 3) the absence of diabetes, previous or subsequent immunodeficiency disease, and treatment with immunosuppressive drugs. Clinical information recorded for each patient comprised age, sex, and history of an allergy, asthma, intolerance to aspirin, nasal polyp, and tomogram finding including non-homogenous opacities, mucoperiosteal thickening and bony erosion. Ten patients with chronic rhinosinusitis without history of asthma, atopy and aspirin sensitivity and characteristic tomogram finding were also selected as controls.

Because fungi usually colonize the mucus, a simple novel and non-invasive procedure was performed to obtain sufficient mucus. This was done by immersing a mesh in 0.5% phenylephrine hydrochloride and placing it into each nostril to produce vasoconstriction. The phenylephrine also dilated the nasal lumen and consequently increased the yield from nasal lavage. After approximately 2 minutes each nostril was flashed with 20 ml of sterile saline using a sterile syringe with a curved blunt needle under aseptic condition.

The patient took a deep inspiratory breath and held it before saline injection. The patient then forcefully exhaled through the nose during the flushing. The return was collected in a sterile pan. The collected fluid was directly sent to mycology laboratory.

The tube was centrifuged at 3000 g for 10 minutes. The supernatant was discarded and the sediment was vortexes for 30 seconds, 0.5 ml of the sediment was inoculated onto a Sabouraud agar medium, incubated at 30^{o}C and allowed to grow for 10 days. The plates were examined at 2-day intervals.

A direct microscopic examination with KOH was performed before culture. All the surgical procedures were performed without a power microdebrider to ensure maximal mucin collection. In addition, use of suction devices was limited. The mucus was manually removed together with inflamed tissue. The specimens were stained with hematoxylin and eosin, PAS, and also Gomori-methenamine-silver stains.

In all specimens, we looked for the degree and nature of the inflammatory cells, especially eosinophils, the presence of Charcot-Leyden crystals, and mycelial filaments. Allergic mucin is a sheet of mucin, often layered with a pale center and Charcot-Leyden crystal and groups of more or less necrotic eosinophils. The Charcot-Leyden crystals were formed from aggregates of eosinophil granules and appeared hexagonal in cross-section or bi pyramidal in longitudinal sections. Gomori-methenamine silver slides were used for the detection of mycelial filaments. Positive fungal cultures were subjected to Prick skin test, an immediate hypersensitivity skin test.

Results

Clinical and radiological findings of 38 patients with chronic rhinosinusitis are presented in

Table 1. Atopy and nasal polyp were present 81.6% and 94.7% of the patients respectively. One-third had bilateral polyp and 32 (84.2%) had more than three sinus involvements. Asthma and aspirin sensitivity were found in one third, and atopy and asthma in 8, and aspirin sensitivity in 4 patients. Tomgram findings were non-homogenous opacities in all nine cases and mucoperiosteal thickening in two cases.

Table 1: Clinical and radiological findings in 38 patients with chronic rhinosinusitis.

Clinical Findings	n.(%)
Atopy	31 (81.6)
Asthma	15 (39.5)
Aspirin sensitivity	12 (31.6)
Polyp Unilateral	22 (57.9)
Polyp Bilateral	14 (36.9)
> 3 Sinus Involvement	32 (84.2)
Radiological findings	
Non homogenous Opacities	38 (100)
Mucoperiosteal Thickening	17 (44.7)
Bony Erosion	2 (5.3)

Histologic sections showed fragments of edematous respiratory mucosa containing different degrees of eosinophilic infiltration and varying amounts of mucin some of witch had characteristic of allergic mucin.

Most patients (78.9%) showed moderate to severe infiltration, and mixed inflammatory infiltration observed in 21.1%. PAS and Gomori-methenamine silver stain for fungus were negative for all cases. Fungal culture was positive in nine cases with direct examination positive in three patients.

Clinical, histological, and culture positive mycological findings are presented in Table 2. All patients with positive culture had nasal polyp, of which eight (88.8%) cases had asthma and atopy and of these four patients (66.6%) had aspirin sensitivity. In respect of fungal culture, candida albicans, aspergillus flavus and aspergillus fumigatus were found in six, two and one patients respectively.

Direct examination showed pseudohypha and blastospore in two patients and septate hyphae in one patient. Both negative direct and culture examinations showed moderate to severe eosinophilic infiltration with mucin and by-product of eosinophils in 21 (72.4%) of 29 cases. Of these 19 (65.5%) patients had history of atopy. Nasal polyps were found in 82.6% of which only 24.1% had bilateral polyps (Table 3).

Discussion

In our study, nine patients suffered from nasal polyp and chronic rhinosinusitis according to AFS criteria. Deshazo and Swain described seven patients with AFS diagnostic criteria excluding atopy for the reasons that literature review had indicated that two-third of the culture positive patients had positive skin test to the fungal culture.[12]

In a study on 210 patients with CRS with or without polyposis, Ponikau et al. found that 93% of them had suffered from allergic fungal sinusitis. Their diagnostic criteria included chronic rhinosinusitis, confirmed by compute tomography, the presence of allergic mucin, predominantly eosinophils with degenerated byproducts, as well as fungal elements within mucin.[4] Therefore, instead of acute fungal rhinosinusitis eosinophilic fungal rhinosinusitis was used.[4,13] We believe that positive skin test, or specific fungal IgE, in combination with positive fungal culture are essential for the diagnosis of AFS. In our study, all nine cases with positive culture had positive skin test.

Table 2: Clinical, histopathological, and mycological findings of nine patients with positive culture.

Patient #	Age Yr	Clinical features				histopathology	Mycology
		Asthma	Polyp	AS	Atopy		
1	20	+	+	+	+	MEI	Ca-albicans
2	50	-	+	-	-	MEI	Ca-albicans
3	52	+	+	-	+	MEI	Ca-albicans
4	19	+	+	-	+	MEI	Ca-albicans
5	30	+	+	-	+	MEI	Ca-albicans
6	45	+	+	+	+	MEI	Ca-albicans
7	47	+	+	+	+	MEI	Ca-albicans
8	43	+	+	-	+	MEI	Ca-albicans
9	45	+	+	+	+	MEI	Aspergillus Flavus

AS= Aspirin sensitivity; MEI= Moderate Eosinophilic Infiltration

Table 3: Significant clinical and histological features in 29 patients with negative direct and culture examination.

Age (yr)	Sex		Atopy	Asthma	Polyp		Aspirin sensitivity	Histology	
	F	M			Unilateral	Bi lateral		Moderate to severe eosinophilic infiltrate with mucin	Mixed inflammation without mucin
13-62	12	17	19	9	17	7	7		
Mean 31	41%	58.5%	65.5%	31%	58.5%	24.1%	24.1%	21	8
Total	29		19	9	24		7	72.4%	27.6%

The histologic markers are increasing number of eosinophils and their by-products in AFS. In our study we found high numbers of eosinophils, mostly in the form of cell clusters, within the tissue and the mucus. Serrano et al in their study on 165 patients with chronic rhinosinusitis on their histological examination they found that 14 cases with allergic fungal sinusitis had allergic mucin.[11]

In our study, of nine (23.7%) culture positive patients, two had Aspergillus flavus, one Aspergillus fumigatus, and six candida albicans. In the study of Ponikau and colleagues, from a total 210 patients who had chronic rhinosinusitis, Alternaria, aspergillus, and candida were present in 44%, 29%, and 21% respectively.[4]

Torres et al. believed that in some of the AFS cases, the lack of fungal hyphae may have been resulted from inadequate sampling in the presence of sparse or degenerated fungal hyphae.[14] Because of the colonization of fungi in the mucus we think adequate mucus is necessary for the evaluation of allergic mucin and fungi. Although, 21 patients of our study had clinical and histopathologic findings of allergic mucin suggestive of AFS, we believe the scanty mucin was the culprit.

Ferguson observed a form of histopathological sinusitis similar to allergic fungal sinusitis with the absence of fungal hyphae and coined eosinophilic mucin rhinosinusitis (EMRS) for this cases.[15] It is postulated that AFS is an allergic response to fungi in predisposed individuals, whereas EMRS is possibly due to dysregulation of immunologic system.

Because EMRS was a systemic disease the unilateral variant was not seen. Whereas, AFS is an allergic response to fungi, depending on the antigenic stimulation it might occur unilaterally or bilaterally.[15] In our study 21 of the 38 patients had some recently described clinical and histopathological features consistent with EMRS. However, more diagnostic tests such as IgG_1 are needed to confirm the diagnosis.

Conclusion

According to various sets of criteria for the diagnosis of AFS, a more specific diagnostic test such as specific IgE to fungal antigen is needed to confirm allergic fungal sinusitis.

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