

REVIEW ARTICLE

Year : 2017 | Volume : 31 | Issue : 2 | Page : 38--44

Diagnostic and treatment challenges in management of allergic fungal rhinosinusitis

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Abstract

Among infections pertaining to head and neck rhinosinusitis holds a significant position both with regard to the prevalence and morbidity. Allergic fungal rhinosinusitis (AFRS) was initially considered a counterpart of allergic bronchopulmonary aspergillosis when first diagnosed by Sa firstein in 1976 due to its clinical presentations and seemingly similar pathogenesis. Initially only *Aspergillus* was known as the causative, but now various other fungal species are known to cause chronic rhinosinusitis; hence, the terminology allergic fungal sinusitis was preferred. Exposure to fungi results in similar as asthma in atopic individuals, but then, some nonatopic individuals may also present with similar symptoms. It has also been studied that the presence of serum immunoglobulin E does not ensure the presence of allergy. Till date, there are several controversies regarding pathogenesis, whether humoral or immune mediated, population at risk, variations in presentations, diagnostic parameters, and treatment protocols. In this review, we try to revisit and learn from past documented experiences to further our attempt toward better understanding of the disease process, its diagnosis, and management.

How to cite this article:

Singh AB, Upadhyay R, Tayal N. Diagnostic and treatment challenges in management of allergic fungal rhinosinusitis. Indian J Allergy Asthma Immunol 2017;31:38-44

How to cite this URL:

Singh AB, Upadhyay R, Tayal N. Diagnostic and treatment challenges in management of allergic fungal rhinosinusitis. Indian J Allergy Asthma Immunol [serial online] 2017 [cited 2017 Oct 19];31:38-44

Available from: <http://www.ijaai.in/text.asp?2017/31/2/38/215838>

Full Text

Introduction

Allergic fungal rhinosinusitis (AFRS) is a commonly occurring pathology with protean manifestations. It is less comprehended among physicians as it simulates many other pathological conditions bacterial being the most common.

Hence, its diagnosis and treatment planning still poses a major challenge. Total estimated fungal species causing diseases existing on the planet is around 1.5 million.[1] Our knowledge regarding pathologies associated with fungus dates back to 9th century. A total of 3%–10% of world's population is allergic to molds.[2] The propensity of fungal spores to spread far and wide and its ability to survive as a saprophyte is an asset for causing infections. Although pollens are 100 times more prevalent than fungal spores, only these spores cause wide array of presentation as they are viable and can cause infections besides causing hypersensitivity.[2] Fungal allergy and its presentation are similar to those of other causes of chronic rhinosinusitis (CRS). AFRS accounts to about 5%–10% of all cases of CRS.[3] Fungal spores are distributed in the ambience both indoors and outdoors, and the susceptible hosts may develop either invasive or noninvasive form of fungal infection. High degree of suspicion is warranted on the basis of presentation so that an early diagnosis is made. Various efforts have been made to know the predisposing factors, susceptible host, pathophysiology, clinical manifestations, and thus planning management of this condition.

With the developing world and increasing population density, environmental factors such as humidity and aerosols have a prominent share in the surroundings favoring the growth of molds and not to forget the global warming adding to the affairs. Fungal rhinosinusitis, earlier an uncommonly seen condition, is being frequently diagnosed these days. Nasal sinuses have been known to occur in 2 forms invasive and noninvasive [Figure 1]. The invasive form being{Figure 1}

Acute necrotizing seen usually in immunosuppressed states [4]Chronic invasive form, andChronic granulomatous.[5]

The noninvasive forms include

Fungal ball like its lower respiratory tract counterpart allergic bronchopulmonary aspergillosis (ABPA)AFRS.[6],[7],[8],[9]

CRS is now finding great attention owing to the great degree of morbidity and the financial burden incurred for the disease where cure is not assured yet.[10] There are several impediments in the way of diagnosis and management of AFRS.

The categorization has seen several changes since it was first described from invasive or noninvasive, destructive, or nondestructive, allergic, or nonallergic narrowed to eosinophilic or noneosinophilic and now from serum immunoglobulin E (SIgE) mediated to non-SIgE mediated. Obvious that the identity of the disease has traversed its way from gross appearances to finer levels of humoral responses involved and from the domain of clinicians to the realm of pathologists. The first-ever clinical description of noninvasive fungal sinusitis was given by Mackenzie.[11]

In the earlier days, dematiaceous fungi *Bisporia*, *Curvularia*, and *Alternaria* were considered to be the most common cause of AFRS as much of the literature was based on the prevalent causative in those regions, but studies in Southeast Asia have shown *Aspergillus* to be the most offending species in these areas.[12],[13],[14] After about 10 years of conflicting opinions regarding the diagnosis of AFRS, a common consensus as to the diagnosis of AFRS was reached with the criteria proposed by Bent and Kuhn.[15] The presence of Type 1 hypersensitivity reaction, nasal polyposis, detection of fungal elements on microscopy or culture allergic mucin with or without fungal elements without the invasion of surrounding mucosa and suggestive radiological findings pointed toward the diagnosis of AFRS.[15] Later, it was suggested that Type 1 hypersensitivity need not be included in diagnostic criteria as the mere presence of IgE sensitivity does not ensure the presence of allergy. The role of humoral immunity was also found to be vital as far the causation of AFRS is concerned.

Pathophysiology

AFRS is defined by hypersensitivity reaction [16] against one or more fungal antigens with or without the presence of nasal polyps causing impaired mucus drainage, with the presence of mucin-containing fungal elements without tissue invasion and characteristic findings on computed tomography and magnetic resonance imaging showing inflammatory changes in underlying structures. Initially, only *Aspergillus* was considered as the causative of AFRS in keeping with its relationship with ABPA. But later on, other fungal species were also found to cause the same depending on environmental factors, fungal predominance in the area. The association between environmental conditions and fungal dominance was first confirmed by Ferguson et al.[17] This statement is modified version of the diagnostic criteria proposed by Bent and Kuhn which by far had stood the test of time for AFRS with certain modifications as our understanding of the disease has expanded.[18] AFRS accounts to about 5%–10% of all cases of CRS.[9] Of all cases of hypertrophic sinus diseases, AFS is seen in 5%–10%.[12] Initially, AFRS was considered one of the forms of CRS. However, the differences have been established now shown in [Table 1]. A study conducted by Das et al. concluded that of all cases of CRS, FRS contributed 42.7%,[19] and AFRS contributes 24% of CRS. However, different geographical areas have presented with different statistics pertaining to the environmental conditions and contribution by fungus.[20]{Table 1}

Eosinophilic mucus has historically been linked with fungal allergy and has the appearance of cottage cheese or peanut butter with Charcot Leyden crystals eosinophilic debris or crystals with or without the detection of fungal hyphae. Fungal elements are not always detected in the mucin; hence, a new terminology eosinophilic mucus rhinosinusitis (EMRS).[21] Initially, ARS was associated only with atopic individuals and primarily Type 1 and Type 3 hypersensitivity reactions. AFRS patients present with greater SIgE levels [22] and increased cluster differentiation (CD) 8 +T-cells along with increase in interleukin (IL) 4,5 response.[23],[24] In a landmark study by Ponikau in 1999, the role of SIgE-mediated immune response alone in the pathogenesis of AFRS was reconsidered as fungal antigens were found in >96% of patients with CRS undergoing surgery. Most of the patients who were not known to be atopic and had no specific serum markers against the particular antigen also had fungal antigens in their mucin. Thus, the concept of T-lymphocyte-mediated inflammation and eosinophil activation at the site was propounded, explaining the occurrence of AFRS with eosinophil-rich mucin in nonatopic patients.

The other entity in the flock to enhance confusion is the EMRS coined by Fergusson and she described it to be an alteration in immunological milieu. This group of patients presented with bilateral disease and IgG1 deficiency.[25] There appears to be a considerable overlap in symptoms of EMRS and AFRS, and it also seems that they may be same as far as the evolution of disease is concerned and only differ due to different stages of diagnosis. Studies using sensitive techniques for diagnosis as chitinase and PCR techniques document fungal antigens as a causative for EMRS.[26]

Pant et al. conducted a study to find out humoral responses in the pathogenesis of EMCRS in patients with or without documented fungal antigens in mucin and irrespective of SIgE status.[27] Eosinophilic mucin is considered pathognomic of the presence of fungi in sinuses.[20],[28]

They concluded that fungal-specific serum IgG3 was present in substantially high concentrations in EMCRS patients irrespective of the presence of fungal antigens. SIgG has been associated with the severity of disease symptoms and activation of complement pathway acting against the fungal antigen, and hence, the destructive features seen in EMCRS. Despite several efforts, the exact pathogenetic process has not been established though several hypothesis have been laid [Figure 2]. According to observations in various studies, SIgE plays a significant role in the process but the role of fungal-specific SIgE still remains controversial as it has not been found in cases of non-AFRS and nonallergic nonfungal rhinosinusitis groups of patients who otherwise have eosinophilic mucin from their sinuses. The role of IgG3 in immunology of EMCRS is well determined, but its role in pathogenesis of the disease per se is yet to be studied. The serum status of SIgG3 in other noninvasive fungal diseases is not yet known.[29],[30]{Figure 2}

Challenges in Diagnosis

Among various causes of rhinosinusitis, AFRS is now considered most common of all forms of fungal rhinosinusitis. The earlier considered pathognomic for AFRS, the allergic mucin is now no more considered a differentiating feature after the recognition of EMRS as a different entity. Allergic or eosinophilic mucin is green to brown or black colored with degenerated eosinophils with peanut butter or cheesy consistency. Microscopic examination shows Charcot Leyden crystals, cellular debris, and sparse hyphae with no tissue invasion.

Later Ponikau's observation changed the theory regarding the pathogenesis of AFRS. The new concept of cell-mediated hypersensitivity response behind the pathogenesis of AFRS has explored a new era for diagnosis. One of the major impediments in the diagnosis of AFRS is the documentation of the presence of fungal elements in the allergic mucin, else the new terminology of EMRS was attributed to the same in the absence of documentation of fungal elements. Similarly, if fungal elements are detected in the mucin, but there is no Type 1 hypersensitivity response the term used for such condition is eosinophilic fungal rhinosinusitis (EFRS). However, this categorization may be false several times as the fungal elements may not be easily procured from the mucin or may not come in contact with the culture media and hence may give false-negative results. The use of mucolytic agents before subjecting the mucous to culture has shown to decrease the false-negative results and increase the diagnostic yield by nearly 96%.[16]

The other reason for diagnostic dilemma lies in the fact that long-standing fungal colonization leads to local inflammatory responses and increased levels of major basic protein (MBP), eosinophil peroxidases, eosinophil-derived neurotoxin, tumor necrosis factor beta, and IL 4, 5, 10, 13 leading to local destruction mimicking invasive, destructive pathologies.[18],[19] Ponikau et al. suggested that the destructive features seen in eosinophilic sinusitis is due to toxic eosinophilic MBP causing damage to the epithelium.[21] Contrary to the conventions that AFRS was found in atopic individuals Ponikau et al. established that <25% of the patients with Type 1 hypersensitivity whereas fungal elements were found in 96% of the

patients. Hence, the terminology eosinophilic mucin and EFRS was coined.[16]

Aspergillus fumigatus is now studied to be the most common pathogen associated with AFRS. CD 4 and CD 8 T-cells proliferate in the peripheral blood in response to fungal-specific antigens. However, the presentation of symptoms depends on the immune status of the individuals and the difference in CD 4 and CD 8 response.[31]

Initially, the immunopathogenesis of allergic fungal sinusitis (AFS) was thought to be similar in nature to ABPA with the similar findings of raised SIgE levels specific to fungal antigens. The culprit fungal elements are easily detected in bronchial mucin than in nasal mucin. On the other hand, fungal antigen-specific SIgG is not raised in AFRS when compared to that in ABPA.[32],[33] AFS cause gross localized destruction which may be attributed to release of MBP from eosinophils which in turn releases cytokines for neutrophil activation resulting in release of elastase protein [34] and release of Th2 cells by peripheral mononuclear cells precipitates further destruction.[24] The simplest way that describes the difference between EMRS than AFRS is that the former is non-IgE-mediated eosinophilic chemotaxis at the localized site of fungal colonization causing altered humoral and cellular responses leading to local destruction. [Table 2] shows differences in various pathological presentations of rhinosinusitis. Simpler depiction of factors posing problems in diagnosis of AFRS is shown in [Figure 3]. Clinical manifestation of chronic Rhinosinusitis is shown in [Figure 4].{Figure 3}{Figure 4}{Table 2}

Question for consideration

Does the accumulation of eosinophilic mucin itself creates a favorable environment for fungal colonization promoting further activation of humoral responses and hence destruction. This may be hypothesized keeping in view that what remains common to all forms of chronic noninvasive sinusitis is the presence of eosinophilic mucin. We need to further our understanding regarding common bacterial associations with chronic fungal rhinosinusitis which may give us a clue for early diagnosis and also if the destruction is primarily due to changes in immune milieu caused by fungus.

The presentation of AFRS and ARS has overlapping signs and symptoms. Several guidelines have been laid as far as ARS is concerned which facilitates diagnosis. However, the diagnosis of AFRS still does not have a concrete set of guidelines. The flowchart given [Figure 5] shows an approach for the diagnosis of AFRS.{Figure 5}

Molecular diagnostic techniques are now emerging as the promising techniques for diagnosing AFRS. This method entails development of universal oligonucleotide sequence probes for the identification of fungal species [Table 2]. It has been studied that the sequence variation in the genetic component among similar species is very minimal.[35] Identification of specific species by partial sequencing of beta tubulin and calmodulin in some studies has been used for the diagnosis.[36]

Challenges in Treatment

The conflicts regarding the pathogenesis of AFRS leads to differences in the treatment strategies practiced by physicians. It has now been seen that fungus inflection to the sinuses is not limited to AFS but is also responsible for ample number of cases of chronic rhinosinusitis. Owing to the controversies regarding various theories of pathogenesis of AFRS, the management is a big challenge put forth before the treating physicians. Keep aside the controversial issues; there is a common consensus regarding surgical extirpation as the initial step in management. In almost all cases of AFRS, narrowing of the ostia of paranasal sinuses, mucosal edema in various stages interrupting the drainage of the sinuses is a universal finding. Surgical intervention opens up the drainage passages and ensures proper irrigation and availability of the topical medications used locally. It has been seen that the recurrence rates following surgical management are around 35%–75%.[37]

The use of systemic steroids has shown promising results as far as remission of AFRS is concerned. Bent and Kuhn reported recurrences in almost all cases not followed with steroid therapy after surgical debridement.[38] Duration and dose of therapy is not defined but the improvement in disease status can be monitored by Kupferberg staging criteria [39] which is defined as: Stage 0: no edema or allergic mucin, Stage 1: mucosal edema with or without allergic mucin Stage 2: polypoidal mucosa with or without allergic mucin and Stage 4: nasal polyp with fungal debris. The use of steroids postsurgery improves the SIgE levels, and the mucosal odema as reported by Kuhn and Javer.[40] Long-term use of steroids has their own well known adverse effects. Use of topical steroids has been studied as an alternative and budesonide has been shown to have effective results. It can be used in concentrated doses with minimal side effects and least suppression of hypothalamo-pituitary axis. The only reason for not holding this as the prime modality of treatment is inadequacy of doses due to mucous impaction and mucosal edema.[41] Immunotherapy is an emerging promising treatment option which has shown to be neneficial in preventing recurrences with no adverse effects. The only major

concern is the expenses. Marby and Mabry [42] and Folker et al.[43] have studied the use of immunotherapy in small group of subjects and found the results to be beneficial. The main concern refuting the use of immunotherapy in AFS is the possibility of Type 3 hypersensitivity reaction which may be precipitated by the release of SIgG against the fungal antigen load. Studies conducted by Marby and Mabry and Folker et al. did not show any long-term beneficial effects of fungal immunotherapy. In his study by Greenhaw et al.,[44] no beneficial effects were seen with the use of immunotherapy.

Studies have established a significant role of immune system in the pathology.[45] We have already discussed the ubiquitous nature of fungi in our surroundings, and some studies have also shown the presence of fungal elements in the nasal mucin in people who do not have CRS.[46] Thus, it can be derived that inadvertent use of antifungals may not be required in the treatment of AFRS. Initially, the disease was primarily linked to atopic group and hence management primarily dealt with steroids and antihistaminics. Recurrent nasal polyposis was managed surgically but was not very effective. The use of systemic steroids caused relief of symptoms by suppressing the immune response but also had a potential risk of paving grounds for invasive rhinosinusitis.[47]

The controversies regarding use of topical or systemic antifungals for AFRS have been addressed by Sacks et al. in his meta-analysis [45] and concluded that the routine use of topical antifungals in 5 studies did not show any beneficial effect as far as symptom control, disease-specific quality of life scores, endoscopic, or radiological findings were concerned. Systemic antifungal therapy was given only in one trial where oral terbinafine was used, but it showed no improvement in symptoms. No significant changes were observed in the radiological picture.[48] Patients in both the groups presented with adverse events, sometimes even precipitating the disease which led to the discontinuation of trials. The common side effects observed were increased congestion,[49],[50],[51],[52],[53] nasal irritation acute exacerbation of CRS.[53] Ponikau et al. have shown beneficial effects of topical antifungal in one of his study, but the use of therapy did not show any improvement in symptoms.[52] The use of immunotherapy was questioned initially for several years for the fear of inciting a Type 3 immune complex-mediated hypersensitivity reaction.[51]

These studies differed pertaining to the drug dosage, prior surgery functional endoscopic sinus surgery before starting topical antifungal therapy hence differed in their opinions regarding the same. With the new concept of EMRS, use of antifungals has no role as the possibility of eosinophil-derived factors MBP and other cytokines may cause destruction of fungal elements along with the destruction of local tissues hence mucin obtained may not even contain fungal elements, and thus, the long-standing concept regarding pathogenesis of AFRS is being questioned. Based on several studies and discussions related to the pathogenesis of the disease, the common consensus is reached for surgical debridement followed by the use of steroids.[37]

Topical and systemic antifungal therapy have been found ineffective. The role of immunotherapy for the treatment of AFRS is shielded by various concerns, i.e., rise in antigen load, treatment failure. Although in a small group population, Mabry's study showed improvement in symptoms, decrease in use of steroids, and decreased recurrences.

In one of the cases described by Martin Oman Evans II,[54] a patient with sinobronchial allergic mycosis syndrome-specific immune therapy, anti-IgE omalizumab was considered due to the persistence of symptoms. The symptoms gradually improved and the levels of SIgE were found to gradually decrease with remission of polyps and improvement in airway functions as measured by spirometry. Hence, immunotherapy can be considered in resistant cases with recurrences, and this has shown to have good results.

Conclusion

New concepts have come to light regarding pathogenesis, and the hypersensitivity responses that besides the Type 1 IgE-mediated response IgG-mediated responses also have a key role. SIg G 3 is found to be specific for the diagnosis of EMRS. Studies are been done to find out a specific marker for AFRS. Although eosinophilic cationic protein shows some association, it does not explain its elevation in nonallergic EMRS.[28] AFRS has also been seen in some cases of SIgE-negative patients. Pathogenesis in these conditions can be explained by the fact that locally produced SIgE may be a major factor responsible. Controversy regarding the etiology of disease has been clarified in the studies by Manning and Holman where patients of AFS were found to have positive skin tests along with positive radioallergosorbent test and positive ELISA inhibition for fungal-specific IgE and IgG.[55] In a similar study, sinus mucosal specimens in patients with AFS when compared for eosinophilic mediators and neutrophilic mediators were found to have predominant eosinophilic mediators thus establishing an immunological response. They also identified the common fungal antigens responsible for the pathogenesis of AFRS and brought to light that dematiaceous fungi were the most common culprits for AFRS rather than *Aspergillus*. A study by Feger et al. suggested some locally mediated pathogenesis when he documented increase in

eosinophilic cationic protein in patients of AFS when compared to controls.[56] With a better understanding of the pathogenesis of the disease, the newer molecular tests hold promise for more accurate diagnosis of AFRS and hence timely treatment and less destruction of the sinuses.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Thursday, October 19, 2017

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