Running title:
Allergic Fungal Rhinosinusitis

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REVIEW

Title
An update on the criteria for diagnosing allergic fungal rhinosinusitis: a review of the literature

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SUMMARY

Allergic fungal rhinosinusitis (AFRS) is a type of hypersensitive inflammatory response that causes chronic, recurrent, and non-invasive hypertrophic sinus disease. The aim of this paper is to report the latest research and development in the diagnostic conundrum that allergic fungal rhinosinusitis can present. A literature review was conducted of PubMed English language search of current diagnostic criteria for allergic fungal rhinosinusitis, from 1951 to 2017. In conclusion the diagnosis of allergic fungal rhinosinusitis needs to be considered in all patients with severe chronic rhinosinusitis with nasal polyposis. Patients often have asthma and complain of thick 'wallpaper glue' like nasal secretions that can also often be seen on nasal endoscopy. CT scanning often shows heterogeneity and MRI scanning may also help to identify cases. The diagnostic role of total and fungus-specific IgE in AFRS requires further prospective evaluation. The role of genetic and immunological testing in AFRS requires developing as diagnostic tools. The diagnosis is therefore often a clinical one supported by investigations such as radiology.

Key words: Allergic fungal rhinosinusitis, diagnostic criteria, nasal polyps, Bent and Kuhn criteria

INTRODUCTION

There are a number of causes of chronic rhinosinusitis (CRS) with nasal polyposis (CRSwNP) including allergy, mucociliary disorders, systemic conditions and fungal disease. Fungal rhinosinusitis (FRS) includes a number of conditions which can be broadly divided into 2 main categories; invasive and non-invasive. Invasive FRS includes acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis and chronic invasive granulomatous fungal rhinosinusitis. Non-invasive FRS includes fungus ball and allergic fungal rhinosinusitis (AFRS).

AFRS, a type of hypersensitive inflammatory response, causes chronic, recurrent, and non-invasive hypertrophic sinus disease that affects immunocompetent hosts.[1] AFRS falls into the category of CRSwNP associated with eosinophilic inflammation.[2] The percentage of AFRS in patients with CRS ranges widely from 5 to 10% in some studies[3] to a much higher percentage in others studies, such as in a by Ponikau et al.[4] In the latter study the authors concluded that 93% of patients that underwent endoscopic sinus surgery for CRS met the published criteria for AFRS and speculate that this condition is the principal cause of CRS.

The clinical entity of AFRS was first described by Safirstein et al. in 1976 after noting similar pathological appearances to that of allergic bronchopulmonary aspergillosis.[5] AFRS has characteristic clinical, radiological and histopathological features. The most recognised criteria for AFRS are those presented by Bent and Kuhn in 1994.[6] In this literature review we aim to highlight the latest research in relation to the diagnostic criteria for AFRS.

METHOD

Literature review of PubMed (MEDLINE® and the NLM® database of indexed citations) English language search of current diagnostic criteria for AFRS, from 1951 to 2017.

RESULTS

The Bent and Kuhn diagnostic criteria[6] are historically the standard for diagnosis. The 5 major criteria include: (1) nasal polyposis, (2) presence of fungi on direct microscopy or culture of sinus content, (3) eosinophilic mucin without fungal invasion into sinus tissues, (4) type I (Ig E medicated) hypersensitivity to fungi demonstrated by skin testing or in vitro testing and (5) characteristic CT findings, including sinus expansion or heterogeneous opacification. The Minor criteria include asthma, unilateral disease, bone erosion, fungal cultures, Charcot Leyden crystals and serum eosinophilia.[6] DeShazo et al. proposed to remove type I hypersensitivity as a diagnostic criterion for AFRS given that identical clinical forms of CRS but without type I hypersensitivity to fungi have been described.[3]

The Bent and Kuhn diagnostic criteria for AFRS remain controversial, it may take months to years to establish all 5 of the major criteria. In 2009 the international Society for Human and Animal Mycology convened a working group to attempt to build a consensus on terminology and disease classification of fungal rhinosinusitis. They concluded that they are imprecise and require better definition.[7] The

European position paper on rhinosinusitis and nasal polyps from 2012 acknowledges that of the Bent and Kuhn diagnostic criteria, only type I hypersensitivity combined with characteristic CT findings are unique to AFRS and distinguish it from other forms of inflammatory sinus disease.[8]

Clinical Features

Clinical features of AFRS include a history of sinus disease relatively resistant to medical therapy in an immunocompetent patient. The patient may complain of thick 'wallpaper glue' secretions with more severe sinonasal symptoms than with 'simple' CRSwNP. These patients may well have had multiple nasal polypectomies and endoscopic sinus procedures in the past with only a short lived improvement in symptoms. Two-thirds of patients are atopic and half suffer from Asthma.[9] Patients may well have concurrent Samter's triad (nasal polyposis, asthma, and aspirin sensitivity) which is associated with a more severe form of sinonasal polyposis but part of the severity of the patient's symptoms may be due to the associated AFRS. Therefore, AFRS should be considered and looked for in all patients with Samter's triad and treated appropriately. The condition is more common amongst young adults and in geographical areas of high humidity. AFRS can lead to late complications of proptosis, visual disturbance and facial dysmorphism e.g. telecanthus formation, if not diagnosed and managed appropriately.

Image 1. Endoscopic photograph taken during sinus surgery and shows thick tenacious secretion being removed from the right paranasal sinuses using a sinus sucker.

Radiological features

In AFRS Computer Tomography (CT) findings include pansinus opacification. Due to the deposition of heavy metals, such as iron and manganese, allergic mucin provides the heterogeneous signal intensity that is characteristic of AFRS. However, the heterogeneity may be subtle and missed on bone window setting but may be more apparent on a soft tissue window setting. Local bony involvement such as bone destruction and thinning of bony structures secondary to expansion of accumulated mucus, is 10 times more common in AFRS than in other forms of chronic rhinosinusitis (CRS).[6] This can cause, for example, widening of the nasal bones.

Magnetic resonance imaging (MRI) has been shown to demonstrate a high specificity for AFRS, especially when combined with CT.[10] The high protein concentration of allergic mucin results in crosslinking and slows macromolecular motion, giving rise to T1 central hypointensity and T2 central signal void. Both T1 and T2 series demonstrate peripheral enhancement.[10] Furthermore MRI is an important adjunct when considering dural involvement or intracranial expansion.

Image 2: Non-contrast CT scan of paranasal sinuses in the coronal plane showing opacification of the ethmoid sinuses and maxillary sinuses with heterogeneous areas of hyperattenuation which is often

described as ‘double density’ appearance.

Immunological testing

The total immunoglobulin E (IgE) levels are generally elevated, often to more than 1,000 U/mL. The importance of type I hypersensitivity in AFRS pathophysiology is not clear. Humoral immunity and immunoglobulin pathways may contribute. After in-depth examination of humoral immune response to fungal antigens, Pant et al. found that there was no difference in the levels of total IgE, ratio of mould-mix specific IgE to total IgE and absolute levels of IgE to specific fungi between AFRS patients and patients with allergic rhinitis and fungal allergy (without CRS). This challenges the central pathogenic importance of elevated fungal-specific IgE levels in AFRS, suggesting that immune mechanisms other than fungal allergy are involved and that elevated fungal-specific IgE may simply represent concurrent rhinosinusitis and fungal allergy.[11]

Collins et al. demonstrated that most patients with AFRS had fungal-specific IgE in sinus mucin, and a minority of chronic sinusitis patients with “allergic, eosinophilic fungal-like” sinus mucin and no evidence of systemic fungal allergy also had mucin antifungal IgE.[12] This suggested that a local type I hypersensitivity response against fungal antigens may be present even in those patients without evidence of systemic allergy and irrespective of the identification of fungi in eosinophilic mucin.[11] In the absence of systemically detectable allergen-specific IgE or a positive prick test, the pathogenic importance of locally produced IgE in allergen-specific hypersensitivity responses is yet to be established.[11] The evidence suggests that an IgE-mediated process is involved in the pathogenesis of AFRS, it being a primary factor however is still not clear.[12] A study by Wise et al. in 2008 showed a significant increase in total and fungus-specific IgE staining in AFRS sinus epithelium and subepithelium as compared to controls and to CRSsNP patients.[13] Chang and Fang demonstrated that a group of AFRS patients all had a negative serum IgE response to Aspergillus, but 85.7% of the same patients had maxillary sinus tissue-specific immunoglobulin E (sIgE) to Aspergillus.[14]

In relation to immunology, Ebert et al. found enhanced production of protease-activated receptors (PARs) in AFRS patients as compared to non-diseased controls. PARs cause an increased production of inflammatory cytokines and potentiate Th2 responses, which are characteristic findings in AFRS.[16] Ayers et al. demonstrated that patients with AFRS and CRSwNP have an increased number of local dendritic cells in sinus mucosa samples as compared to controls without CRS.[17] Laury et al. found significantly increased levels of periostin, which is an extracellular matrix protein associated with eosinophil accumulation, in AFRS sinus tissue samples as compared to CRSsNP and control samples by both immunofluorescence ($p < 0.001$) and PCR ($p = 0.011$).[18]

Histopathology

The histopathologic findings in AFRS of mucosal specimens on hematoxylin-eosin (H&E) staining show a typical inflammatory infiltrate composed of eosinophils, lymphocytes, and plasma cells. The

mucosa is hypertrophic and hyperplastic but does not have evidence of necrosis, giant cells, granulomas, or invasion into surrounding structures.[20]

AFRS is associated with a unique allergic fungal mucin that is thick and highly viscous. Microscopically, the mucin often takes on a chondroid appearance with sheets of eosinophils, frequently with the presence of eosinophilic breakdown products or Charcot-Leyden crystals that can be seen with H&E staining.[20] Fungi themselves do not stain with H&E staining. Silver containing stains (e.g. Grocott silver or Gomori methamine silver) are usually needed to appreciate the branching, non-invasive fungal hyphae. Montone et al. in their study observed 74.4% of AFRS patients having histological evidence of fungi.[19]

Microbiological testing

Thick, eosinophilic mucus rich in inflammatory debris should alert the surgeon and pathologist to search for the presence of fungus, although the presence of fungus may not be the defining characteristic to confirm a diagnosis of AFRS. Some experts postulate the first stage of the disease is the allergic reaction which prompts eosinophilic mucus production. The second stage is the antigenic reaction to the fungi trapped by this allergic reaction.

Fungal cultures in AFRS should be interpreted with caution because of their variable yield (64%–100%).[21] A diagnosis of AFRS is possible in the context of negative cultures. Furthermore, Ponikau et al. showed that 100% of normal and healthy volunteers were positive for fungi on culture, with an average of 2.3 different organisms per volunteer.[16] Therefore, fungal culture is unlikely to be helpful in the diagnosis of AFRS and a fungal smear should instead be used.

The role of staphylococcus aureus cultures from patients with AFRS should also be considered. Clark et al. cultured significantly higher levels of Staphylococcus aureus from AFRS patients versus non-AFRS patients (63.2 and 24.1%, respectively).[12] Dutra et al. hypothesize that staphylococcus aureus may play a crucial role in AFRS on the basis of their findings of staphylococcus aureus co-existing with Aspergillus species within the sinuses of AFRS patients, and the presence of specific IgE antibodies to the classical staphylococcus aureus superantigens in the serum of nearly all subjects with AFRS.[22] This study suggested that staphylococcus aureus synergizes with or makes use of Aspergillus species preferentially amplifying inflammatory reactions, and adds its superantigenic activities to the disease, resulting in the high total IgE concentrations typically found in AFRS. In this way, Aspergillus species and staphylococcus aureus benefit from each other's potential to overcome the mucosal barrier, bias the immune system, and cause the fulminant characteristics of AFRS.[22]

Genetic and proteomics blood testing

In relation to genetic testing, Orlandi et al. performed a DNA microarray analysis on sinus mucosa

samples in AFRS and non-diseased patients and found 38 genes or potential genes expressed in the AFRS patient samples that were not expressed in the non-diseased patient samples.[23] Schubert et al. performed HLA DNA genotyping on a group of AFRS patients and found that 66% of patients with AFS carried at least one HLA-DQB1 *03 allele.[24]

Proteomics blood testing is a progressing field. Das et al. through surface-enhanced laser desorption/ionization time-of- flight mass spectrometry (SELDI-TOF-MS) proteomic profiling of serum samples was able to identify patients with AFRS out of a group of patients with chronic sinusitis, with 84% sensitivity and 90% specificity.[25] In 2013, Den Beste et al. compared epithelial cell samples from AFRS patients and non-in inflammatory control patients and demonstrated a 41% mean decrease in transepithelial resistance in AFRS cells, a finding that was also associated with decreased expression of 2 tight junction proteins and increased expression of a leaky tight junction protein.[26]

Management of AFRS patients

The mainstay of surgical treatment is extensive endoscopic debridement and establishment of effective drainage pathway of all affected sinuses. This may well include radical sphenoethmoidectomies as well as frontal sinus 'drill out' procedures to remove all the tenacious thick secretions and fungal debris that often require large suckers and even microdebrider and forcep removal. This is followed by medical treatment in the form of a prolonged oral course of Corticosteroid treatment ideally extending for two to three months, on a gradually reducing dose regime. There is no consensus regarding corticosteroid dosage or duration. Topical corticosteroid treatment is usually continued indefinitely. Nasal douching is also helpful. During follow up of patients with AFRS, it may be useful to monitor blood levels of IgE (specific to the relevant fungal type) as a marker of recurrence. No anti-fungal treatments have been proven to change the course of the disease. A 2011 Cochrane database review concluded that there were no data to support the use of anti-fungal treatments.[27]

DISCUSSION

Patients with AFRS represent a subgroup of chronic rhinosinusitis with nasal polyposis that are more difficult to manage, therefore identifying these individuals is important. The diagnosis needs to be considered in all patients with severe chronic rhinosinusitis with nasal polyposis. Patients often have asthma and complain of thick 'wallpaper glue' like nasal secretions that can also often be seen on nasal endoscopy. CT scanning often shows heterogeneity and MRI scanning may also help to identify cases. The diagnostic role of total and fungus-specific IgE in AFRS requires further evaluation. The role of genetic and immunological testing in AFRS requires developing as diagnostic tools. The diagnosis is therefore often a clinical one supported by investigations such as radiology.

Table 1. Diagnostic and management protocol for AFRS

AUTHORSHIP CONTRIBUTION

Faisal Arshad - Principle author and researcher
Showkat Mirza – Author of clinical aspects, supervisor and proof reader

CONFLICT OF INTEREST

No conflict of interest exists.

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