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Allergic Fungal Sinusitis: A Review of the Literature

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ABSTRACT

Allergic fungal sinusitis was first described in the 1980s. Interest in this disease entity has steadily grown. Several case series have been published describing more than 100 patients. An overview of both typical and unusual clinical presentations, laboratory findings, and radiographic features is provided in this review. Immunologic evaluation of these patients has found some evidence for an IgE-mediated hypersensitivity in the pathogenesis of this eosinophilic reaction. Despite the wealth of literature, controversy exists as to the optimal management of these patients. This review discusses the published outcomes of surgical and medical management, as well as offering some suggestions for monitoring patients for recurrence. In addition, treatment of allergic fungal sinusitis utilizing immunotherapy with fungal extracts is discussed. (Pediatr Asthma Allergy Immunol 2000;14[4]:307–314.)

INTRODUCTION

ALLERGIC FUNGAL SINUSITIS (AFS) in the atopic, immunocompetent individual was initially described in the early 1980s. It was originally associated with allergic bronchopulmonary aspergillosis (ABPA) because patients with ABPA often expectorated plugs from their noses that were similar in consistency to those produced by their lower respiratory tract. In 1983 Katzenstein et al.[1] published the first description of the histopathology of the allergic mucin and named the entity allergic aspergillus sinusitis. Eosinophils, Charcot-Leyden crystals, and fungal hyphae were found in tissue resected from the sinuses of seven adolescents and young adults. These patients ranged in age from 13 to 48 (most were in their teens and early twenties).[1] Interest in fungal sinusitis has increased since that time and many patients with AFS have been described. Several large case series have described the clinical, immunologic, and radiographic features of AFS patients including response to various types of treatment.[2–8] Despite this wealth of literature, optimal choices for the clinical management of these patients remain controversial.

FUNGAL SINUSITIS

Fungal sinusitis is classified by multiple schemas in the literature. The most important differentiation is whether it is invasive or noninvasive. This impacts directly on the aggressiveness of therapy and ultimate

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prognosis. Additionally, the nature of the process can be described as acute or chronic. Noninvasive types of fungal sinusitis include mycetoma and allergic fungal sinusitis. Invasive forms of fungal sinusitis include acute fulminant fungal sinusitis, chronic invasive fungal sinusitis, and granulomatous invasive fungal sinusitis. All forms of fungal sinusitis can be diagnosed accurately only when fungal elements are visualized directly by histopathologic examination of the material removed from a sinus.[9] It is not known whether fungus can exist in a sinus without causing disease. DeShazo et al.[10] have reported that they failed to culture fungus from surgical material in 24 consecutive patients with bacterial sinusitis. In another study, Ponikau et al.[2] utilized nasal saline washings to assay for presence of viable fungus in patients with chronic sinusitis. In the control group of healthy volunteers, 31 different fungal organisms were cultured from the lavage fluid.[2] Therefore, it is clear that nasal washings are not reliable for making the diagnosis of fungal sinusitis and that surgical specimens must be utilized.

A basic understanding of fungal organisms and their interaction with a host is necessary to interpret the meaning of their presence in or on our bodies and to make a causal association with disease. More than 100,000 species of fungi have been described, of which about 100 are known to be human or animal pathogens. Most of these are opportunistic pathogens and require an extraordinary defect of the immune system to become invaders. Only dermatophytes are actually communicable healthy host to healthy host.[11]

The original reports of allergic fungal sinusitis emphasized that the underlying immune pathophysiology seemed most consistent with an immediate hypersensitivity response to fungal antigen in the sinuses. Defining the antigen, the response, and the initiating events leading to AFS have been the subjects of much interest.

CLINICAL FEATURES

AFS patients are typically young and atopic. The age range reported in the literature is 7 to 62 years with the mean age of all patients reported to date in 1998 was 23.3 years. A slight male predominance exists with a ratio of 1.6 to 1.[4]

Pediatric patients have been described in several series and seem to have no difference in clinical presentation from young adults, although their treatment is complicated by concerns over the side effects of long-term corticosteroids.[5]

In 1998, Schubert and Goetz[6] described the largest cohort of patients with AFS studied and published to date. Sixty-seven patients were identified with a mean age of 33. They were all atopic and had nasal polyps. More than half of the patients also had asthma. Three-quarters had a history of nasal casts, described as rubbery green mucous plugs intermittently expelled from the nose.[6]

Nasal polyps have been found in nearly all reported AFS patients. Allergic rhinitis has been diagnosed in the majority prior to consideration of allergic fungal sinusitis.[4]

Five main features have emerged in the literature as criteria for the diagnosis of AFS: (1) immunoglobulin E (IgE)-mediated hypersensitivity to fungal antigen, (2) nasal polyposis, (3) characteristic computed tomography (CT) scans, (4) histologic evidence of eosinophilic mucus in the sinus cavity without evidence of fungal invasion into sinus mucosa, and (5) positive fungal stain or culture from material obtained from the sinus cavity.[3]

The prevalence of this disease is unknown due to its relative newness as a diagnosis. Two studies have examined the histopathologic findings from patients undergoing surgical procedures for chronic sinusitis and have found 5% to 7% of these patients satisfied the diagnostic criteria.[1]

Occasionally involvement of structures adjacent to the sinuses through bony erosion and extension of the inflammatory material can cause anatomic deformity and nerve dysfunction.[12] Unusual presentations have ranged from destruction of the cribiform plate[13] to an abducens nerve palsy.[14]

The most common ophthalmic manifestation is proptosis. A case series published in 1999 described six patients presenting with proptosis that was subsequently found to be due to AFS. One of the six suffered diplopia and another patient had total visual loss. The mechanism of damage was presumed to be pressure necrosis of the bones of the orbital wall and subsequent mass effect on the other structures in the orbit. The

patient with visual loss in this study recovered his sight following surgery and oral steroids.[15] There have been two cases reported in the literature of permanent visual loss from this phenomena.[16,17] Other ophthalmic presentations include blepheroptsis, epiphora, and ophthalmoplegia.[15]

IMMUNOLOGIC FINDINGS

The original reports describing AFS focused on the fungus aspergillus. Miller et al.[14] described immediate cutaneous reactivity to aspergillus fumigatus antigen in all five patients in their original case series. Katzenstein et al.[1] found specific IgE and immunoglobulin G (IgG) to aspergillus in their series. Other authors described late phase cutaneous reactivity.[18] Nonspecific findings in the 1980s also were notable for the decline in total IgE with treatment using surgery and oral steroids.[4]

As the interest in AFS expanded so also did the number of dematiaceous fungi that have been characterized as being present in the allergic mucin of these patients. Bipolaris, Curvularia, Aspergillus, and other fungi have been shown to induce specific IgE antibody responses and nonspecific eosinophilic inflammation.[2,19,20] Dolen and coworkers[4] observed the expected positive skin test reactivity against fungal antigens in patients with AFS. Immunoblots performed with the patient's allergic mucin and with commercial extracts demonstrated antibody against fungal proteins. All 11 patients' sera recognized an 18-kd protein in all commercial extracts and 4 recognized an 18-kd protein in the allergic mucin.[21] However, 10 of 11 patient's sera recognized a 35–50 kd protein in the allergic mucin that was not found in the commercial fungal extracts.[21] The same size protein was recognized on an immunoblot to an extract of human epithelial cells, suggesting that this presumably nonfungal protein could be the result of nonspecific inflammation and damage to the airway epithelium.[21] This protein could perhaps represent an autoimmune factor in the etiology of AFS. Case series suggesting IgE-mediated specificity include the report by Gourley et al.[22] of specific antibodies to bipolaris in patients with AFS and the finding of specific IgE to bipolaris in only 6% of general allergy patients. In addition Manning and Holman[4] found that all of their AFS patients had a positive radioallergosorbent test (RAST) to a dematiaceous mold (15/15) while only 19% of all patients presenting to their general allergy clinic demonstrated this finding. However, Mabry et al.[23] published a series of 10 patients with AFS who demonstrated some degree of RAST positivity to all of the commonly tested molds. This is reminiscent of the common fungal protein identified by Dolan[24] as previously discussed. Clearly an immunologic reaction to fungal protein is at the heart of allergic fungal sinusitis, but the evidence is mixed regarding IgE-mediated specificity as the sole mechanism of response.

In a review of the AFS literature published in 1996, Morpeth et al.[24] noted the following immunologic findings in the published AFS patient population: 48% with positive skin tests to fungi, 44% with elevated total IgE (range not given), 40% with peripheral eosinophilia, 33% with elevated specific IgG, and 28% with serum precipitins to fungal antigens. Schubert and Goetz[6] found that 67% of their patients had an elevated total IgE (greater than 199 IU/mL). The mean total IgE for their patients was 668 IU/mL.[6] All of their patients had positive skin tests for aeroallergens with specific IgE to their presumably causal mold.[6] They found normal peripheral eosinophil counts.[6] Two-thirds of their patients also had elevated specific IgG to molds.[6]

Nonspecific inflammatory findings in the surgical debris removed from AFS patients include elevated levels of eosinophilic cationic protein and major basic protein. This indicates eosinophilic degranulation. In contrast, neutrophil elastase and mast cell tryptase have been found to be at much lower levels than specimens from other chronic sinusitis patients.[25]

Ponikau et al.[2] from the Mayo Clinic published a study in 1999 challenging some of these findings of IgE-mediated hypersensitivity to fungal antigens. They collected nasal secretions by lavage from 210 patients with chronic sinusitis but not AFS and were able to culture fungus from 96%. Of 101 of the cases who had sinus surgery, they identified fungal elements in 81% and found allergic mucin in 96%. Their immunologic evaluation included skin tests for molds, which found 25% or their patients with positive prick testing and an additional 17% with a positive intradermal test. Twenty-eight percent had an elevated serum specific IgE for at least one fungal species. They postulate a nonspecific eosinophilic response in these pa-

tients to the presence of fungal elements in the nose and sinuses.[2] If other studies confirm these findings, this concept will have important implications on the role of specific immunotherapy in the treatment of AFS. If the inflammatory process in AFS is actually driven mostly by a nonspecific eosinophilic reaction and not by specific IgE, then steroids will continue to be the primary medical therapy and immunotherapy with fungal antigen extracts will have no role. If the etiology of AFS is a specific IgE-mediated immunologic response then appropriate immunotherapy may be initiated and would be efficacious.

RADIOLOGIC FINDINGS

Reports in the literature have been remarkably consistent in the description of radiographic findings in this disease process. CT and magnetic resonance imaging (MRI) results in AFS patients were first described in 1988. CT remains the main diagnostic tool and MRI is used principally to assist when questions arise following CT.[26] MRI can assist in differentiating AFS from neoplasm as the cause of bony erosion around the sinuses and orbits. The most typical and nearly pathognomonic CT finding in AFS is an irregular area of high attenuation in an opacified sinus.[7,26]

Mukherji et al.[7] published a retrospective review of the radiographic findings in 45 patients with AFS. Mucosal thickening and increased intrasinus attenuation was noted in 100%.[7] Complete opacification and expansion of the opacified sinus was noted in 98%.[7] Multiple sinuses were involved in 96%. Thinning of the involved sinus walls was found in 93%.[7] Adjacent soft tissue structures were affected in 20% of the cases.[7]

In summary, CT findings of sinus expansion with central areas of irregular high attenuation should prompt suspicion for AFS. Bony erosion noted is likely due to pressure resorption but may be due to the effect of inflammatory mediators.

SURGICAL TREATMENTS

In the past, otolaryngologists operated on the sinuses through an open approach. This necessitated the removal of bone and frequently distorted the natural flow of mucus. The Caldwell Luc procedure, for example, removes a large portion of bone from the anterior wall of the maxillary sinuses. This dramatically distorts the sinus anatomy and alters drainage. It also precludes the regrowth of cilia. The Lynch procedure or external ethmoidectomy removes the medial orbital wall and distorts the frontal sinus drainage pathway. The advantage of these procedures is their exposure and ease of approach, which nearly guarantees adequate debridement.[27]

Today the otolaryngologist typically utilizes the functional endoscopic sinus surgery (FESS) technique. Endoscopic sinus surgery (ESS) was the older approach that removed large amounts of bone, but utilized endoscopic visualization. The functional part was added to delineate the new approach to preserve normal anatomy and drainage routes as much as possible.[27]

Quraishi and Ramadan[28] reported a case series of six patients successfully treated for their AFS with FESS procedures. Two of the six patients needed revision within months of the initial surgery.[28] Mirante et al.[29] published a case series of 11 patients with AFS in whom they utilized newer powered endoscopic surgical instruments (that included irrigation and suction). All 11 were successfully treated without need for revision in the year following, and fewer complications were reported.[29]

Another issue in the surgical treatment of AFS is the timing of oral steroids. Many otolaryngologists prescribe steroids to shrink polyps prior to surgical removal. Graham and Ballas[30] report the case of a patient with polyps and chronic sinusitis who was given 5 days of prednisone prior to surgery. During the procedure, aspergillus was identified by the pathologist in the biopsy specimen, but allergic mucin and eosinophils were not noted. The patient was given the errant diagnosis of mycetoma. As a result, he received a more limited procedure and no postoperative steroids. Because he actually had AFS, his symptoms recurred within weeks and he required another surgical procedure during which the correct diagnosis was made. Steroids

should probably be withheld when a diagnosis of AFS is suspected from the clinical data at hand until the diagnostic surgery is performed.[30]

In 1997, Bent and Kuhn[3] published their retrospective review of 26 patients who had undergone FESS for AFS. Only 5 of 24 who underwent surveillance endoscopy demonstrated normal findings.[3] The rest had recurrence within 14 months. They noticed that the patients who had taken steroids the longest had the lowest level of recurrence and the fewest symptoms.[3] They argued strongly for endoscopic surveillance as the best way to detect early disease and to guide steroid therapy.[3] This is necessary given the absence of a serum marker and the late onset of symptoms in recurrence.[3]

Schubert and Goetz[8] note the change in surgical technique during the 1980s and 1990s from open procedures to ESS and FESS. They postulate that this change has led to recurrent disease in AFS. Leaving the sinus mucosal layer intact may predispose to early recurrence as opposed to the older surgical technique of completely removing this layer.[8]

In summary, surgical debridement is the most important diagnostic and therapeutic modality in the management of allergic fungal sinusitis. Unfortunately, recurrence is the rule and surgical cure is the exception.

MEDICAL THERAPY

Given that surgery alone is not enough to cure patients with AFS additional treatment is required. Steroid treatment of patients with noninvasive fungal disease was originally noted to be efficacious in the care of allergic bronchopulmonary aspergillosis patients. In the 1970s, it became known that this population experiences a rate of clinical remission of 80% when given long-term oral steroids.[31] Oral corticosteroids have been recognized as an effective treatment for the symptoms of AFS. But questions remain as to the optimal dose, and the duration of steroid therapy for AFS. Considerable debate also exists as to the markers of AFS that should be monitored.

Schubert and Goetz[8] published their therapeutic findings in a population of 67 AFS patients and addressed these questions. After surgical debridement, their patients were placed on oral steroids on a modified ABPA protocol.[8] The total duration of therapy was individually determined.[8] They found a difference in clinical severity by 2 months from surgery with one-half of the currently treated patients being symptom-free and only a one-fourth of the patients who had stopped steriods early being symptom-free.[8] The most important finding was the improved survival time to recurrent surgical intervention.[8] In addition, they noted that total IgE not only correlated with disease severity at onset but may be a useful marker for early recurrence.[8] An increase of 10% in total IgE was predictive of the need for more surgery.[8]

The role of steroids seems clear. But the role for antifungal therapy is less clear. Because the pathogenesis of AFS is thought to be immunologic and not infectious, the burden of organisms is thought to be low. Bent and Kuhn[32] published a review of 32 cultures of fungi from 15 patients with AFS. They studied the *in vitro* susceptibility to various common antifungal drugs.[32] All fungi were susceptible to ketoconazole, and nearly all were susceptible to amphotericin B and itraconazole.[32] A high degree of resistence to nystatin and fluconazole was noted.[32] Topical treatment with a solution of ketoconazole in acetic acid (1 mg/mL) could be used as an irrigation therapy.[32] Any role for antifungal drugs would only be as an adjunct to other immunomodulating therapy.[32]

Kupferberg et al.[3] studied 26 patients with AFS. Five of these patients received itraconazole as an adjunct to corticosteroids.[3] All showed signs of recurrence with monitoring through endoscopic surveillance.[3]

Rains[33] reported in 1997 that 68 AFS patients underwent ESS, postoperative itraconazole, and systemic steroids. They experienced 100% improvement in symptoms but had a 50% rate of recurrence.[33] Rains[33] reported a 4% adverse drug reaction rate to itraconazole, and the cost of his 3-month antifungal regimen was about $1,500.[33]

In summary, systemic steroids delay the need for further surgery in patients with AFS. Antifungals have no clear useful role in the treatment of this disease.

IMMUNOTHERAPY

If the IgE-mediated hypersensitivity hypothesis is true, then specific immunotherapy should be effective in reducing symptoms, recurrences, and repeat surgeries.[34] Ferguson[34] presented a paper in 1993 detailing a retrospective review of seven patients who received mold immunotherapy for treatment of AFS.[34] Five of seven seemed to worsen while on therapy.[34] The other two clearly improved.[34]

Quinn et al.[35] published a case report in 1995 of a patient who improved with Bipolaris immunotherapy over a period of 18 months. Prior to immunotherapy, the patient needed frequent antibiotics, nasal and oral steroids, and had had several surgical procedures.[35] After immunotherapy her nasal polyps did not recur, she needed no further surgery, and her CT scan improved.[35]

Mabry et al.[36] began a study in 1994 to follow a group of AFS patients prospectively utilizing immunotherapy as an adjunct. Twenty-three patients were enrolled.[36] After sinus surgery and perioperative oral steroids the patients were skin tested for molds and had RAST performed for other aeroallergens.[36] They then began immunotherapy.[36] Their average maintenance dose was 0.05 mL of a 1:100 wt/vol concentration given every 2 weeks.[36] This dose is lower than that typically used by most allergists for effective immunotherapy. Despite this, 11 patients who continued the immunotherapy and had received at least 1 year of treatment had no recurrence of disease at the time of publication.[36] Only 3 patients needed additional oral steroids, and only another 3 received nasal steroids.[36]

In summary, immunotherapy may have a place in controlling AFS.

CONCLUSIONS

The weight of the evidence to date implies a role for IgE-mediated hypersensitivity in the pathogenesis of the eosinophilic reaction in many if not all patients with AFS. Whether other pathways of inflammation can lead to the same common end point is not yet clear.

General diagnostic criteria are agreed on and include nasal polyposis, characteristic CT scans, allergic mucin, and presence of fungal elements in the debrided tissue. The final criteria of the presence of specific IgE for fungal antigens is agreed on by most researchers.

Surgical debridement, usually by endoscopic techniques, is the standard of care in the initial phase of treatment. Oral corticosteroids are effective in controlling symptoms and increasing the time to recurrence and need for further surgery when used for at least 2 months. Topical corticosteroids have not been studied. Oral antifungals have no clear role. Unfortunately, recurrence is common. Endoscopic surveillance with a rhinoscope is the best modality to detect early recurrence, although in some patients a change of greater than 10% in serum total IgE may be useful. Immunotherapy is possibly effective in reducing recurrence over a 3-year period. Double-blind placebo-controlled trials would add weight to the promise of this therapy.

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