

Role of Local Immunoglobulin E Production in the Pathophysiology of Noninvasive Fungal Sinusitis

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Objectives/Hypothesis: Immunoglobulin (Ig)E-mediated hypersensitivity to fungi has been postulated to explain allergic fungal sinusitis (AFS). Not all patients suspected to have AFS demonstrate systemic evidence of allergy. Locally produced IgE might explain those patients with no systemic evidence of allergy but clinical features of AFS. The aim was to determine whether fungal-specific IgE could be demonstrated in sinus mucin in patients with eosinophilic mucin rhinosinusitis. **Study Design:** A prospective study was undertaken in a tertiary rhinology practice in Adelaide, South Australia. **Methods:** Eighty-six consecutive patients with nasal polyposis and thick, colored macroscopically "fungal-like" sinus mucin at time of surgery for chronic sinusitis were entered in the study. The sinus mucin was liquefied and underwent testing for fungal-specific IgE (Pharmacia UniCAP) and fungal culture. Serum fungal-specific and total IgE, eosinophil count, C-reactive protein (CRP), and eosinophilic cationic protein (ECP) were measured. **Results:** Fifty-six (65%) patients were fungal culture positive, and 37% had a detectable fungal-specific IgE in sinus mucin. Data were available to classify 81 patients: AFS = 24 (30%), AFS-like = 6 (7%), nonallergic eosinophilic fungal sinusitis = 32 (40%), nonallergic, nonfungal eosinophilic sinusitis = 19 (23%). Patients with AFS were significantly more likely to have fungal-specific IgE in sinus mucin (17/24, 71%, $P = .02$). In all fungal culture-positive patients, positive mucin fungal-specific IgE was significantly associated with systemic fungal allergy ($P = .005$), but a raised total serum IgE was not. Six (19%) of the 32 patients with positive fungal cultures but negative serum fungal-

specific IgE had a positive mucin fungal-specific IgE, suggesting that they may be reclassified as AFS. The mean ECP and total IgE were raised most significantly in the AFS subgroup. **Conclusions:** This is the first study to show that fungal-specific IgE may be demonstrated in sinus mucin. It was significantly associated with systemic fungal allergy and may play a role in a minority of fungal sinusitis patients in the absence of systemic fungal allergy. **Key Words:** Allergic fungal sinusitis, mucin, IgE, pathophysiology, eosinophilic, eosinophilic mucin rhinosinusitis.

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INTRODUCTION

The pathophysiology of fungal sinusitis in immunocompetent patients is poorly understood. Immunoglobulin (Ig)E-mediated type I hypersensitivity to fungi has been postulated as a pathogenic mechanism in allergic fungal sinusitis (AFS).^{1,2} This condition is characterized by the typical but variably termed "allergic/eosinophilic/fungal" mucin, which is thick and peanut butter-like in color and consistency, infiltrated with eosinophils and their degradation products, and fungal stains or culture of this mucin are positive by definition. In addition, such patients demonstrate systemic evidence of fungal allergy by positive serum fungal-specific IgE or positive skin prick tests (SPT) to fungi.³

Treatment of AFS relies on surgical removal of the mucin, with ventilation of the affected sinuses and suppression of the immune response with oral corticosteroids.⁴ Some evidence exists to support the efficacy of desensitization to fungal allergens to reduce the allergic immune response.⁵

However, a group of patients exists with the clinical features of AFS with positive fungal cultures from their eosinophilic fungal mucin but no systemic evidence of fungal allergy. What then is the role of steroid therapy or desensitization in these patients? What diagnostic label are they given since they do not meet the criteria of AFS, fungal ball, or invasive fungal disease?⁶

Locally produced fungal-specific IgE might explain the pathogenesis of this condition because evidence is emerging that this local mechanism is involved in some patients with

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asthma and eczema and rhinitis.⁷ Alternatively, these patients may genuinely represent another diagnostic group that is not allergic, suggesting that so-called allergic eosinophilic fungal mucin might not always arise from a type 1 immune response.^{8,9} As a corollary to this, we would expect that patients with true AFS who have systemic fungal-specific IgE would have local IgE in the sinus mucin if this condition were truly IgE mediated. The aims of this study were to determine whether fungal-specific IgE could be demonstrated in sinus mucin in patients with eosinophilic mucin rhinosinusitis (EMRS) and whether it always correlated with serum allergen-specific IgE measurements.

MATERIALS AND METHODS

A prospective study was undertaken at the University Hospitals, Adelaide, South Australia, in a tertiary rhinologic practice. Eighty-six consecutive patients with chronic rhinosinusitis and nasal polyposis undergoing functional endoscopic sinus surgery (FESS) with thick, colored "fungal-like/eosinophilic" sinus mucin at the time of surgery were entered into the study. Patients without fungal-like/eosinophilic mucin were excluded (n = 234). Approval for the study was obtained from the Ethics of Human Research Committee.

At the time of surgery, sinus mucin was collected for microbiologic analysis, fungal culture, and histology. Specimens of mucin were centrifuged and liquefied with equal volumes of diluted and buffered Sputolysin Reagent (Calbiochem, San Diego, CA).¹⁰ After this, testing for specific IgE against a fungal antigen mix was carried out using a Pharmacia UniCAP (Sandwich, Kent, UK) system (antigen mix: *Aspergillus*, *Alternaria*, *Cladosporium*, *Penicillium*, *Candida*, and *Helminthosporium*).

Serum was collected for analysis of antifungal IgE using the same system. Serum concentrations of total IgE, eosinophil count, C-reactive protein (CRP), and eosinophilic cationic protein (ECP) were measured. The CRP was measured as an indicator of an active systemic inflammatory response. Positive serum-specific IgE to fungi defined evidence of systemic fungal allergy. Atopic status was confirmed by a positive radioallergosorbent assay test (RAST) to house dust mite, pollens, grasses, or animal dander.

On the basis of the fungal culture results, the histology, and the presence or absence of systemic fungal IgE, the patients were classified into four categories as defined by Bent and Kuhn.³ All the study patients in the categories below had chronic sinusitis with nasal polyposis and (macroscopically characteristic) "eosinophilic fungal" mucin but are separated by the following criteria:

- AFS: positive fungal culture or staining and positive serum IgE to fungi.
- AFS-like sinusitis but no fungus identified: positive serum IgE to fungi but negative fungal culture or staining.
- Nonallergic eosinophilic fungal sinusitis (or chronic noninvasive fungal sinusitis, CFS): positive fungal culture or staining but negative serum IgE to fungi (strictly speaking, no category for these in the Bent and Kuhn classification system but recently described in the literature).^{11,12}
- Nonallergic, nonfungal eosinophilic sinusitis (eosinophilic chronic rhinosinusitis [ECRS]): negative fungal culture or staining and negative serum IgE to fungi.

The refinement of the classification system along these criteria is helpful to clarify the subtle differences between these patients. In an attempt to avoid long-winded names for each of these categories and in accordance with previously published articles, nonallergic eosinophilic fungal sinusitis is shortened to chronic fungal sinusitis (CFS) and nonallergic, nonfungal eosinophilic sinusitis shortened to eosinophilic chronic rhinosinusitis (ECRS).^{11,12} This categorization

allows analysis of the data to determine whether these differences have genuine diagnostic or therapeutic relevance.

Results were entered onto a PC database and analyzed with Statistical Package for Social Sciences (SPSS, Chicago, IL). Analysis was with the chi-square and Mann-Whitney tests for statistical significance.

RESULTS

Eighty-six patients undergoing endoscopic sinus surgery for chronic rhinosinusitis were suspected of fungal disease on the basis of characteristic preoperative and perioperative features (nasal polyps with fungal mucin or double densities on computed tomography scan). This included 50 (58%) men and 36 (42%) women, whose mean age was 48 (range 19–84) years. All patients had visibly characteristic mucin at the time of surgery. If no mucin was visible in any of the sinuses at the time of surgery, then patients were not suspected of having eosinophilic "allergic" (fungal) mucin, and these patients were categorized as simple chronic sinusitis patients and excluded from this study (n = 256). Complete study data were only available on 76 patients with suspected fungal sinusitis at the time of analysis.

Serum-specific IgE tests to fungi were positive in 30 (37%) of 81 patients, confirming systemic IgE-mediated hypersensitivity to fungi. Fungal cultures were positive in 56 (65%) of 86 patients, with a diverse range of fungi cultured.

Sinus mucin fungal-specific IgE tests were positive in 28 (37%) of 76 patients. Seventeen of these patients were those with the hallmarks of AFS. However, six of these patients had negative serum IgE to fungi with positive fungal cultures, and five of these patients had negative serum IgE to fungi with negative fungal cultures. Therefore, 11 patients with eosinophilic mucin demonstrated specific IgE to fungus in their secretions but not their blood.

Data were available to classify 81 patients: AFS = 24 (30%), AFS-like sinusitis no fungus identified = 6 (7%), nonallergic eosinophilic fungal sinusitis (CFS) = 32 (40%), nonallergic, nonfungal eosinophilic sinusitis (ECRS) = 19 (23%). Total serum IgE was within the normal range in 59% of patients, although the mean serum IgE of the whole group was elevated at 424 (range 5–11,580, SD = 1,450) KU/L.

Serum eosinophil count was normal in 76.6% (mean 0.31×10^9 , range 0–1.94). Mean serum CRP was within the normal range at 5.6 (study range 1–52, normal range < 12) mg/L.

Mean ECP was elevated at 34.6 (study range 5–94, SD 21.2, normal range < 20) $\mu\text{g/L}$. Nonfungal aeroallergen-specific IgE was positive in 29 of 55 patients where results were available, demonstrating atopy in 53%. The results are summarized in Table I.

Fungal Culture-Positive Patients

Fifty-six patients had positive fungal cultures with equal numbers of men and women. Twenty-four (43%) of these patients had a positive serum IgE to fungi and met the criteria to be classified as AFS. Forty-one percent (n = 23) of the fungal culture positive patients had a positive mucin IgE to fungi.

Total serum IgE was within the normal range in 60% of patients, but the mean of the fungal culture positive group was elevated at 484 (range 5–11,580, SD = 1,744) KU/L. Serum eosinophil count was normal in 70% (mean 0.33×10^9 , range 0–1.94).

TABLE I.
Comparison of Data between Subgroups in Study.

	All Patients in Study	Allergic Fungal Sinusitis (AFS)	Nonallergic Eosinophilic Sinusitis (NAEFS, CFS)	AFS-Like Sinusitis	Nonallergic, Nonfungal Eosinophilic Sinusitis (NANFES, ECRS)
No.	86	24 (30%)	32 (40%)	6 (7%)	19 (23%)
+Fungal cultures	65%	All	All	None	None
+Serum fungal IgE	37%	All	None	All	None
+Mucin fungal IgE (%)	37	71	19	16	21
+Serum nonfungal Aeroallergen IgE (%)	53	66	20	66	23
Mean total serum IgE	424*	910*	133		297
Percent total serum IgE normal	59	32	56		55
Mean eosinophil count	0.31×10^9	0.37×10^9	0.3×10^9		0.26×10^9
Mean CRP	5.6 mg/L	4.25 mg/L	5 mg/L		7.3 mg/L
Mean ECP	34.6 μ g/L	46.1 μ g/L	30 μ g/L		31 μ g/L

* Indicates abnormal elevated result.

AFS = allergic fungal sinusitis; AFS-like = AFS-like sinusitis no fungus identified; NAEFS (CFS) = nonallergic eosinophilic fungal sinusitis (chronic fungal sinusitis); NANFES (ECRS) = nonallergic, nonfungal eosinophilic sinusitis (eosinophilic chronic rhinosinusitis); CRP = C-reactive protein (normal range < 12 mg/L); ECP = eosinophilic cationic protein (normal range < 20 μ g/L).

Mean serum CRP was within the normal range at 4.9 (range 1–29) mg/L. Mean ECP was elevated at 36 (range 9–82, SD 19.3) μ g/L. In all patients with eosinophilic fungal-like sinus mucin, negative mucin antifungal IgE was significantly associated with negative serum antifungal IgE ($P = .02$), a normal total serum IgE ($P = .05$), and negative fungal cultures ($P = .04$).

AFS patients. Twenty-four patients fell into this category, 50% of them men. Total serum IgE was elevated in 68% of patients and the mean elevated at 910 (range 19–11,580, SD = 2,539) KU/L. All patients had positive serum IgE or SPT to fungal allergens, with two thirds of the patients also having IgE to nonfungal aeroallergens. Serum eosinophil count was normal in 74%, with the mean falling within normal limits. Mean ECP was elevated at 46.1 (range 17–94, SD = 22.6) μ g/L. Mean CRP was within normal limits. Seventy-one percent ($n = 17$) of the AFS patients exhibited positive mucin fungal-specific IgE.

Nonallergic eosinophilic fungal sinusitis (CFS) patients. Thirty-two patients had negative serum IgE to fungi in the presence of positive fungal cultures. Mean total serum IgE was not elevated at 133 (range 5–1,032, SD = 223) KU/L. Only 20% of the patients were atopic, with positive RAST to nonfungal aeroallergens. The serum eosinophil count was normal in 68%, with the mean falling into the normal range. Mean ECP was less highly elevated at 30 (range 9–75, SD = 16) μ g/L. Mean CRP was within normal limits. Six (19%) of these patients had a positive mucin IgE to fungi. They could conceivably be reclassified as AFS. There was a significantly higher ECP ($P < .02$) and total serum IgE ($P < .001$) in AFS patients compared with this nonallergic eosinophilic fungal sinusitis (CFS) group but no difference with respect to CRP or serum eosinophil count (Mann-Whitney test).

Comparison of Serum and Mucin Fungal-Specific IgE

The presence of specific IgE to fungi in the serum was significantly associated with IgE to fungi in the sinus mucin, and the absence of serum fungal IgE was significantly associated with negative mucin IgE to fungi ($\chi^2 = 9.7$, $P = .008$). The

total serum IgE was not significantly associated with mucin fungal IgE positivity or fungal culture positivity.

Patients with AFS were significantly more likely to have a positive mucin IgE to fungi ($P = .02$). In all fungal culture-positive patients, positive mucin IgE to fungi was significantly associated with systemic antifungal IgE ($P = .005$), but raised total IgE was not.

Fungal Culture-Negative Patients

Thirty-two patients had negative fungal cultures, of which 70% were men. Six of these patients had positive serum IgE to fungi and met the criteria to be classified as AFS-like sinusitis with no fungus identified. Four (66%) of these AFS-like patients and six (23%) of the nonallergic, nonfungal eosinophilic (ECRS) patients had positive serum IgE to nonfungal aeroallergens. Five (16%) of these 32 patients had positive mucin-specific IgE to fungi.

Total serum IgE was within the normal range in 55% of patients, but the mean of the fungal culture negative group was elevated at 297 (range 44–1,724, SD = 1,744) KU/L. The mean total serum IgE was significantly higher in the positive mucin antifungal IgE group compared with the negative mucin antifungal IgE group even if fungal culture negative ($P < .02$). Serum eosinophil count was normal in 91% (mean 0.26×10^9 , range 0–1.14).

Mean serum CRP was within the normal range at 7.3 (range 1–52) mg/L. Mean ECP was elevated at 31 (range 5–94, SD 25.7) μ g/L.

There were no significant differences between the mucin RAST-positive and -negative patients with respect to any other parameters. If the fungal cultures were negative, then the significant association between serum and mucin IgE to fungi disappeared ($\chi^2 = 7.7$, $P = .1$). Also, there was a significant association between normal serum total IgE and negative-mucin IgE to fungi ($\chi^2 = 12.9$, $P = .01$). Finally, overall, there was no significant difference between the fungal culture-positive and -negative patients with respect to total serum IgE, ECP, CRP, or serum eosinophil count.

Controls

Control subjects were selected to allow validation of the study techniques. Four patients with chronic rhinosinusitis undergoing endoscopic sinus surgery who were not suspected of fungal disease were included. Sinus mucin may be difficult to collect in these patients, but it was sent for fungal culture and mucin-specific antifungal IgE. None of these patients had positive fungal cultures or positive mucin IgE to fungi. All had negative serum IgE to fungi, and none had eosinophilic mucin histologically.

DISCUSSION

Patients were selected for study on the basis of the presence of visible characteristic (referred to in this text as “eosinophilic fungal”) mucin within the sinuses. Histologically, this mucin is defined by the presence of significant eosinophils, Charcot-Leyden crystals, and fungal elements.¹³ However, we have not found the histologic detection of fungal elements to be reliable, even in patients who have fungal elements on microbiologic microscopy and positive fungal culture. The absence of mucin indicated that no specimen could be collected for analysis, and the patient was excluded from the study. Previous work has indicated that eosinophilic mucin in the sinuses may be associated with fungal disease.¹⁴ We believe that fungus found in mucin collected from the sinuses is more likely to be associated with the disease process than fungus found in washing the nasal cavity. As seen in previous work, such douching techniques were positive in all patients, including normal controls.¹⁴ It is recognized that conventional fungal culture techniques lack sensitivity, adding to the diagnostic difficulties in EMRS.¹⁵ Reported positive culture rates range from 6% to 93% in patients with chronic rhinosinusitis.^{3,14} The group of patients included in this study was that in whom fungal disease could be suspected from their clinical presentation and operative findings. Fungal cultures or microscopy were positive in 56 (65%) of these patients (n = 86).

This is a noninvasive disease in immunocompetent patients, and current classification systems cannot discriminate between subgroups. The clinical presentation is not that of a fungal ball (mycetoma) or of saprophytic, incidental overgrowth of fungal organisms. The main diagnostic category in most classifications is AFS. But this raises the question of how we label the patients who do not fulfil all the diagnostic criteria for AFS. We are interested specifically in the group that has eosinophilic mucin with demonstrable fungus but has no specific systemic IgE to fungus. If these patients could be shown to have locally produced specific IgE, this may be a variant of AFS with a similar immunopathogenesis.

A body of evidence is emerging that target–organ-specific or locally produced IgE may play a role in asthma, allergic rhinitis, and eczema.^{7,16,17} Evidence in the literature also supports the possibility of B-cell switching in the nasal mucosa and that the resulting locally produced IgE may account for local disease expression in allergic patients.⁷ Thus, patients without serum fungal-specific IgE or positive SPT to fungi, who would otherwise be classified as AFS, may still be exhibiting a local allergic response to fungi to explain their clinical findings.

This study did confirm, for the first time, that fungal-specific IgE could be demonstrated in the mucin of patients with chronic rhinosinusitis that may be fungal in

origin. Where fungi are cultured, it is significantly more likely that fungal-specific IgE will be detected in sinus mucin. If systemic IgE to fungi is also present (i.e., AFS is diagnosed), then the sinus mucin is also significantly more likely to be positive for specific IgE (71% vs. 19%).

In addition, there were six patients with positive mucin IgE in the absence of systemic IgE to fungi in the culture-positive group and four in the culture-negative group. This may provide evidence for the pathogenic mechanism of locally produced fungal-specific IgE. It is intriguing that apparently “local” IgE without systemic IgE could be demonstrated in at least some cases, and this raises the question as to whether more sensitive testing might detect it in a higher proportion. It may be justifiable to reclassify the six patients in the culture-positive group on the basis of the positive mucin IgE to fungi as AFS even in the absence of systemic antifungal IgE. Given the difficulties with fungal cultures, what is the significance of the four fungal culture-negative patients with “local” IgE? The cultures may be insensitive, the local IgE demonstrated is suggestive of a locally active immunologic mechanism, and these patients may be more closely allied to AFS than previously judged.

The clinical dilemma that arises is where AFS is suspected by the presentation, surgical findings, and computed tomography scans, and fungal cultures are positive, but there is no demonstrable systemic IgE to fungi. These patients may indeed have AFS on the basis of local IgE production.

Another postulated mechanism is that of a non-IgE-mediated cytokine-driven eosinophilic inflammatory mechanism akin to that of nonallergic asthma.⁶ The fungi isolated from the mucin may be epiphenomena or contaminants rather than the precipitants of an allergic process.

This study shows that where eosinophilic fungal sinusitis (CFS) occurs in those who are atopic, fungal-specific IgE is more likely to be present, but it is absent in the nonatopic patients. Considering that 40% of the population is atopic, we see that these data are also consistent with the hypothesis that EMRS is a disease with a common eosinophil-associated inflammatory pathogenesis, with superimposed IgE-driven pathogenic mechanisms in the atopic subset. If this were the case, we might expect that immunotherapy would only partially address the pathophysiology of the disease.

It has to be acknowledged that there are limitations to the approach used in this study. The sensitivity of UniCAP IgE studies on liquefied mucin has not been established, but specific IgE studies have been performed on nasal secretions and nasal polyp and turbinate homogenate.¹⁸ There were six fungi screened for in a mix (*Aspergillus*, *Alternaria*, *Cladosporium*, *Penicillium*, *Candida*, *Helminthosporium*), and it is possible that there were IgE to other fungi that were not detected, although fungal cross-reactivity would lead us to expect that this test may detect IgE to some other species. In fact, the test fungal mix included the majority of the fungi subsequently cultured from the mucin samples. We did not attempt in this study to determine the specificity of the mucin IgE to the fungi that were cultured in the sinuses, and although this is a highly problematic area (for example, different fungi may be cultured at different times or from different sinuses in the same individual), we will attempt to address this in future work. Immunoblotting

procedures may be required to confirm specificity of IgE. However, this report has the advantage of a relatively large number of subjects, which is often not the case in more detailed immunologic studies.

Answering these questions is not simply an academic exercise. Therapeutic interventions that suppress the IgE-mediated response in AFS are increasingly recognized to play a useful role.^{4,5} It is unclear whether these therapies might be applicable to patients who do not have systemic fungal allergy. There may be an underlying immunologic problem to be addressed, and systemic or topical antifungal agents might be useful. There may be another pathologic process involved where the end result is mucin that we describe as “allergic,” “fungal-like,” or “eosinophilic,” where the fungi are present but not provoking an immune response.^{8,9}

A body of evidence has accrued to support the hypothesis that IgE-mediated hypersensitivity to fungal antigens is an important pathogenic mechanism in AFS. AFS patients have been shown to have specific serum IgE to the fungal antigens in the family of their cultured organism,² and eosinophilic inflammatory markers have been demonstrated in the sinus mucosa of AFS patients.¹⁹ The serum total IgE was found to be significantly elevated in AFS patients compared with controls, and their mucin ECP levels were found to be elevated, although the serum ECP levels were not.²⁰ ECP is a granule protein located within the matrix of the eosinophil, which indicates eosinophil degranulation and activation when present. Serum ECP levels have been used to monitor eosinophilic inflammation as well as disease activity in asthma and dermatitis, although its usefulness in AFS has yet to be determined.

This study did not find significant differences between the fungal culture-positive and -negative patients with respect to serum IgE, ECP, CRP, or eosinophil count, although, over the whole group and the fungal culture-positive patients, the mean serum IgE level was elevated and outside the normal range in 40%. The eosinophil count and CRP measures were not discriminating and in the normal range in the great majority of patients. This study found that the mean serum ECP was elevated in all the patient groups but most significantly in the AFS group compared with the nonallergic eosinophilic fungal sinusitis (CFS) group. The AFS group was also significantly more likely to be aeroallergen atopic (62% vs. 36%).

This study provides further information on the contribution of fungal-specific IgE to the pathophysiology of AFS, but there remains a clinically similar IgE-negative eosinophilic fungal sinusitis group. It may be that there is another pathophysiologic mechanism in these patients, or that specific IgE tests are too insensitive to detect locally produced antifungal IgE antibodies. It seems premature to extend the recommended management of AFS to other patients with similar clinical features but without demonstrable systemic IgE to fungi.

CONCLUSION

This is the first study to show that fungal-specific IgE may be demonstrated in sinus mucin. Most patients with AFS 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. This provides some support for the hypothesis that locally produced fungal-specific IgE plays a role in disease pathogenesis. However, 30% to 40% of the Australian population is atopic, and it is possible that the presence of fungal-specific IgE is a reflection of this underlying genetic predisposition superimposed on an eosinophilic inflammatory disease process, which may or may not be driven by fungi. Further studies will be required to determine the role of specific immunologic mechanisms in the EMRS spectrum of disorders, and the detection of local IgE is likely to play an important part.

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