Localized immunoglobulin E expression in allergic rhinitis and nasal polyposis

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Current Opinion in Otolaryngology & Head and Neck Surgery 2009, 17:216–222

Purpose of review

This article reviews recent literature on local tissue identification of immunoglobulin E (IgE) in various sinonasal inflammatory conditions. Discussions of local IgE expression in allergic and nonallergic rhinitis, atopic and nonatopic sinonasal polyposis, and allergic fungal rhinosinusitis are included.

Recent findings

Increased levels of IgE and positive reactivity on nasal allergen provocation tests have been demonstrated in nasal lavage fluid of patients with negative systemic allergy testing. In addition, elevated levels of *Alternaria alternata*-specific IgE have been identified in nasal polyp patients; this is hypothesized as a contributory factor in the development of nasal polyposis. Further evidence supports the role of local IgE to *Staphylococcus aureus* superantigens in atopic and nonatopic nasal polyposis. Finally, local IgE specific for a range of antigens has been identified in sinus and inferior turbinate tissue in patients with allergic fungal rhinosinusitis.

Summary

Increased levels of IgE have been identified in sinonasal tissues in allergic and nonallergic rhinitis, atopic and nonatopic sinonasal polyposis, and allergic fungal rhinosinusitis. The ability to identify local tissue IgE in inflammatory sinonasal disease states may have significant diagnostic and therapeutic implications.

Keywords

allergic fungal sinusitis, allergic rhinitis, allergy, atopy, chronic rhinosinusitis, immunoglobulin E, local production, nasal polyps, nonallergic rhinitis, rhinosinusitis

Curr Opin Otolaryngol Head Neck Surg 17:216–222
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1068-9508

Introduction

Research into the inflammatory profile of rhinitis, rhinosinusitis, and nasal polyposis has revealed that numerous cytokines, adhesion molecules, and inflammatory cells contribute to the pathophysiology of these disease processes. Allergy frequently plays a role in sinonasal inflammatory conditions as well. Traditionally, allergy testing is conducted via skin testing or in-vitro assessment of antigen-specific immunoglobulin E (IgE) in serum. However, local IgE production is increasingly recognized as an important factor in sinonasal inflammation. Systemic allergy testing methods may not detect increased levels of IgE produced locally.

In this review, we explore the evidence for local IgE production in sinonasal tissues. Local IgE levels in various inflammatory disorders of the nasal and sinus cavities are evaluated, including allergic and nonallergic rhinitis, atopic and nonatopic nasal polyposis, and allergic fungal rhinosinusitis (AFRS). The potential clinical implications of local IgE in sinonasal disease are addressed and future directions in diagnostic testing are considered.

Evidence for sinonasal tissue immunoglobulin E production

Early descriptions of ragweed-specific IgE in nasal secretions of patients with allergic rhinitis in 1970 by Tse *et al.* [1] brought forth the concept of local IgE production in sinonasal tissues. However, IgE-producing cells have the ability to migrate to various tissue locations, and detection of IgE in nasal secretions does not confirm that the IgE was produced in the sinonasal tissue itself. Various investigators have sought to validate the concept of local tissue IgE production. Gevaert *et al.* [2] demonstrated secondary lymphoid tissue organization associated with plasma cells and follicular structures associated with B and T cells in nasal polyp tissue; IgE was found in conjunction with both of these lymphoid accumulations. In addition to lymphoid organization and follicular structures in nasal mucosa, the mediators required for immunoglobulin heavy-chain class switching are also present in sinonasal tissue. These include interleukin (IL)-4 and IL-13 that target recombination in the ε gene, while CD40 crosslinking on the B-cell membrane activates recombination [3]. It was previously thought that

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immunoglobulin class switching occurred only in the germinal centers of the lymph nodes and spleen. However, recent work has provided convincing evidence that immunoglobulin class switching is possible in sinonasal tissues.

In 1997, Durham *et al.* [4] demonstrated increases in IL-4 RNA and germline ε gene exons (spliced out during immunoglobulin class switching gene recombination) in inferior turbinate biopsies of grass pollen allergic patients following nasal provocation antigen challenge, indicating the potential for induction of local immunoglobulin class switching following antigen exposure. Similar ε gene germline exons have been evaluated by Cameron *et al.* [5] using tissue explants. These authors biopsied inferior turbinates of ragweed-sensitive patients out of season and subsequently exposed the tissue explants to ragweed extract in a tissue culture setting. A dose-dependent increase in ε gene germline exons and induction of DNA switch circles were observed following ragweed extract exposure *ex vivo*, substantiating local production rather than migration of IgE-producing cells from elsewhere. Further, when IL-4 and IL-13 were neutralized with blocking antibodies, the ε gene germline exon measurements were attenuated. Finally, Takhar *et al.* [6] demonstrated the enzyme activation-induced cytidine deaminase (required for immunoglobulin class switching and typically expressed only in germinal centers of B cells in lymphoid tissues), DNA switch circle transcripts, and ε gene germline transcripts in inferior turbinate tissue explants of patients with grass pollen allergic rhinitis. These were seen most frequently when inferior turbinate biopsies were taken in season from patients with allergic rhinitis. Taken together, these studies argue that local production of IgE in sinonasal tissue is feasible and likely occurs.

Localized immunoglobulin E in allergic and nonallergic rhinitis

A number of investigators have identified increased total IgE and antigen-specific IgE in nasal secretions and sinonasal tissues in patients with rhinitis. Classically, the distinction between allergic and nonallergic rhinitis has been determined by systemic allergy testing. However, as indicated by the studies below, elevated local IgE may be seen in the presence or absence of elevated systemic IgE.

Allergic rhinitis

Local tissue production of antigen-specific IgE has been demonstrated in a variety of atopic disease processes, including allergic rhinitis. In one study, inferior turbinate biopsy specimens have revealed grass pollen-specific IgE in patients with documented systemic grass pollen allergy and house dust mite-specific IgE in patients with perennial allergy [7]. Most of the local tissue IgE-positive cells in this study were found to be mast cells. Further investigations utilizing inferior turbinate biopsies from patients with grass pollen and those with house dust mite allergic rhinitis demonstrate increased numbers of IgE-positive B cells and plasma cells in the lamina propria, compared with controls [8]. In addition to the studies identifying local IgE in inferior turbinate biopsies, specific IgE to Japanese cedar pollen has also been isolated from nasal lavage fluid of patients with allergic rhinitis at concentrations higher than serum Japanese cedar pollen IgE from the same patients [9].

Nonallergic rhinitis

Although increased levels of locally produced IgE may be anticipated in the setting of allergic rhinitis, some authors have identified local IgE in nasal specimens from patients with nonallergic rhinitis as well. In 2007, Rondon *et al.* [10•] reported that *Dermatophagoides pteronyssinus*-specific IgE was identified in nasal lavage fluid in 76% of patients with allergic rhinitis and 12% of patients with nonallergic rhinitis, despite negative skin prick test and serum-specific IgE to perennial aeroallergens and negative intradermal test to *D. pteronyssinus* in the patients with nonallergic rhinitis. Further, in the nonallergic rhinitis group, 54% of patients had a positive response to the nasal allergen provocation test with *D. pteronyssinus* [10•]. These recent findings of Rondon *et al.* [10•] are similar to the 1975 findings of Huggins and Brostof [11], in which patients with rhinitis symptoms but negative skin prick and serum radioallergosorbent (RAST) tests to house dust mite underwent house dust mite nasal provocation and were found to have antigen-specific IgE in nasal secretions, along with an increase in symptoms. This evidence of antigen-specific IgE in the nasal secretions of patients with nonallergic rhinitis has led to suggestion of the term 'entopy' by Powe *et al.* [12] to describe local allergen sensitization in the absence of detectable systemic atopy. In 2006, Powe and Jones [13] reviewed the possible mechanisms for this 'entopy' phenomenon or localized allergic responses, suggesting inadequate systemic tests of atopy, covert allergy, tissue-specific immune responses, precursor cell maturation at the site of inflammation, and non-IgE-mediated hypersensitivity.

Localized immunoglobulin E in nasal polyposis

With a high prevalence of eosinophils on histologic examination, nasal polyps have been associated with allergy in the past [14]. However, evidence has shown that nasal polyps are no more common in allergic patients than in nonallergic patients [15,16]. Therefore, two broad categories of atopic and nonatopic sinonasal polyposis are commonly discussed, with the diagnosis of atopy typically based on systemic allergy testing by skin or in-vitro methods.

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Atopic nasal polyposis

Various studies have identified IgE in nasal polyp tissue from patients with positive systemic allergy testing or allergy symptoms. Hirschberg *et al.* [17] found significantly more total IgE in atopic polyp tissue than in nonatopic polyp or control tissue. Specific IgE to a number of antigens was also detected, and atopic polyp tissue IgE correlated with tissue IL-5 levels [17]. In 2005, Wei and Fang [18] studied specific IgE in serum and nasal polyp tissue from patients with and without allergy symptoms. Among patients with allergy symptoms, 98.3% had positive specific IgE in serum and 36.7% had detectable specific IgE in polyp tissue. However, because all patients with positive specific IgE in polyp tissue exhibited specific IgE in serum and allergy symptoms, the authors concluded that local tissue IgE may be the most specific reflection of the true allergic status of the patient [18].

In an investigation of polyp tissue IgE levels in strongly and weakly atopic patients, Suh *et al.* [19] demonstrated significantly increased total IgE and *D. pteronyssinus*-specific IgE in nasal polyp tissue in patients with both strong and weak systemic hypersensitivity, as compared with controls. The detection of high levels of polyp tissue IgE in patients with weak systemic atopy further supports local IgE production. Finally, in 2007, Sabirov *et al.* [20•] found specific IgE to *Alternaria alternata* in nasal polyp tissue at levels significantly higher than those in nonpolyp tissue from patients with chronic rhinosinusitis and controls. These authors also found that polyp tissue positive for *A. alternata*-specific IgE had increased eosinophil cationic protein, eosinophils, and total IgE. Similar to results found in allergic rhinitis, IgE levels in nasal polyp tissue in some studies were appreciably higher than IgE levels in serum [9,19,20•].

Nonatopic nasal polyposis and *Staphylococcus aureus* superantigens

Investigations into a broader role of local IgE in nasal polyp tissue have found that *Staphylococcus aureus* superantigens may contribute significantly. Superantigens have a potent ability to activate T cells without undergoing traditional processing by antigen-presenting cells. With *S. aureus* commonly found to colonize the nasal cavity, the potential for *S. aureus* superantigens to contribute to nasal polyp formation in both atopic and nonatopic situations is plausible.

Bachert *et al.* [21••] used IgE to *S. aureus* enterotoxin in polyp tissue and serum to characterize patients with current or previous immune reactions to *S. aureus* superantigens. Through various investigations, this group has shown that several patterns of IgE antibodies to *S. aureus* enterotoxin exist in nasal polyp tissue [21••,22]. Approximately 30% of nasal polyp tissue lacks IgE to *S. aureus* enterotoxin, has low total IgE and no IgE to aeroallergens. In approximately 50% of patients, IgE to *S. aureus* enterotoxin is present, along with high total IgE and IgE to inhalant allergens, indicating atopic polyposis in the presence of *S. aureus* superantigen activity. *S. aureus* superantigen positivity may also be present in nonatopic individuals, with the presence of IgE to *S. aureus* enterotoxin, increased total IgE, and absence of IgE to aeroallergens. Finally, a pattern of increased total IgE and IgE to inhalant allergens in the absence of IgE to *S. aureus* enterotoxin indicates that other superantigens or local IgE to inhalants may also play a role in polyp formation. The above scenarios demonstrate that various patterns of local IgE exist in nasal polyp tissue in atopic and nonatopic patients.

In addition to the above classification of atopic and nonatopic nasal polyposis based on association with *S. aureus* superantigens, in patients with IgE to *S. aureus* enterotoxin, total polyp tissue IgE was associated with increased IL-5 and eosinophil cationic protein [22]. Assessments of aspirin-sensitive nasal polyposis also revealed increased IL-5, eosinophil cationic protein, total IgE, and IgE to *S. aureus* enterotoxin compared with aspirin-tolerant nasal polyp samples and controls [23]. However, within the aspirin-sensitive group, there was no association between IgE to *S. aureus* enterotoxin and elevations in inflammatory markers [23]. Gevaert *et al.* [2] have also demonstrated lymphoid organizations with B cells, T cells, plasma cells, and IgE to *S. aureus* enterotoxins in nasal polyp tissue specimens.

Recent findings by Sheahan *et al.* [24] support the presence of local IgE in nonatopic nasal polyposis. These authors report the identification of local antigen-specific IgE in 57% of nasal polyp specimens from patients with negative systemic allergy testing. The identified local tissue IgE represented various classes of antigen, including seasonal and perennial antigens.

Localized immunoglobulin E in allergic fungal rhinosinusitis

The five classic criteria of AFRS consist of type I hypersensitivity, nasal polyposis, characteristic radiologic findings, eosinophilic mucin without fungal invasion, and positive fungal stain or culture, as described in 1994 by Bent and Kuhn [25]. Clinical and radiologic features of AFRS often include erosion and expansion of bony sinus walls, heterogeneous intrasinus densities on computed tomography (CT) scan, and fungus-specific allergy (Fig. 1). The Bent and Kuhn AFRS criteria characterize a unique group with identifiable clinical, demographic, and immunologic features that differentiate these patients from patients with other forms of atopic nasal polyposis [25–29,30••].

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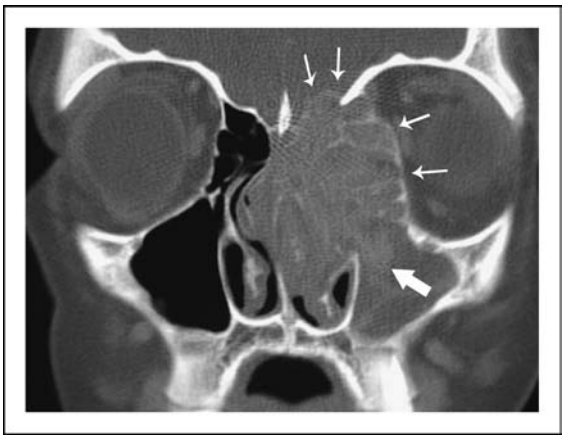
Figure 1 Computed tomography scan of patient with allergic fungal rhinosinusitis

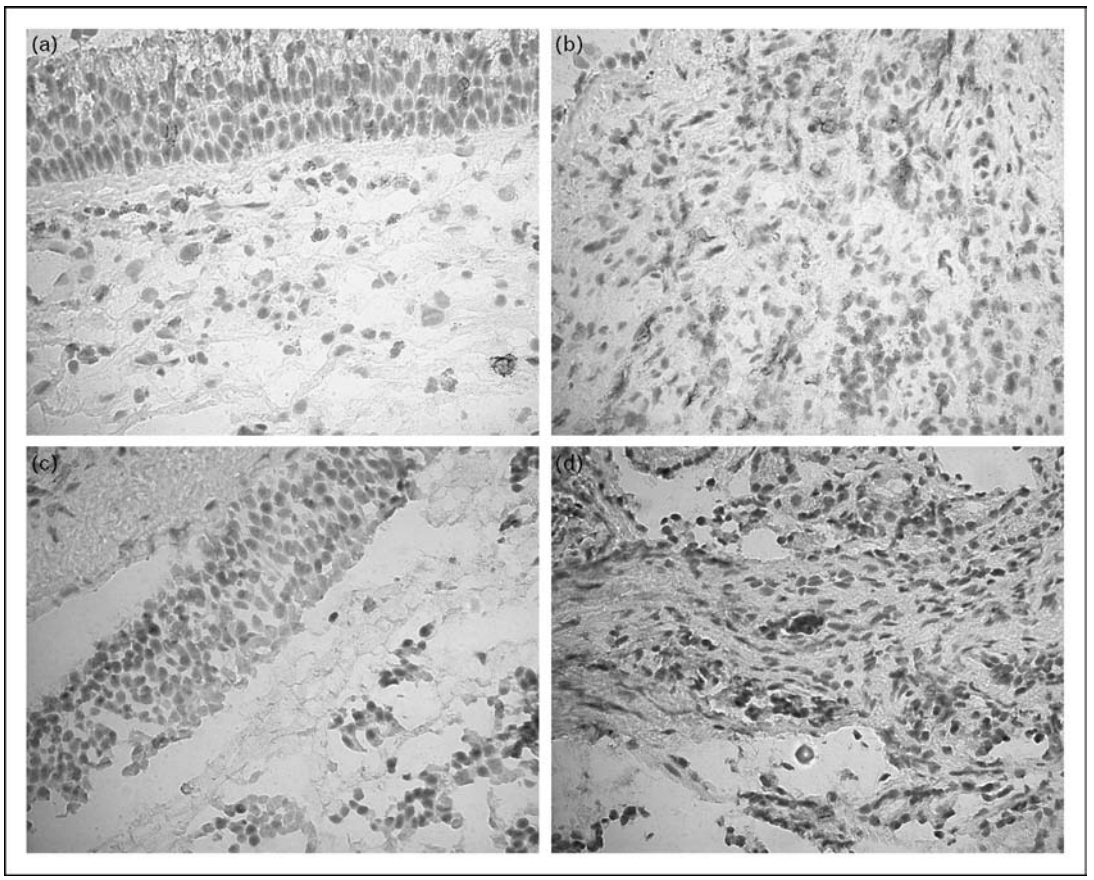


Coronal computed tomography (CT) scan in bone window algorithm of a patient with classic radiographic features of allergic fungal rhinosinusitis (AFRS). Thin arrows indicate expansion and erosion of the bony walls along the ethmoid roof and lamina papyracea. The thick arrow highlights heterogeneous densities in the left maxillary sinus. These heterogeneous densities often show increased contrast on soft-tissue CT windowing.

As part of the diagnosis and treatment of patients with AFRS, systemic allergy testing is frequently performed by skin testing or in-vitro methods. Patients with AFRS often display positive reactions to multiple fungal and nonfungal antigens on systemic allergy testing, indicating increased levels of systemic IgE to these antigens [26,31–34]. Allergen-specific immunotherapy is often instituted in the treatment of patients with AFRS with good clinical results [35–37]. It should also be noted, however, that certain patients with other clinical indicators of AFRS do not exhibit increased levels of serum total IgE [38]. For these patients, as well as those with classic AFRS features, the impact of local IgE production should be considered. The exuberant edema, polyp formation, and eosinophilic mucin seen in the paranasal sinuses of patients with AFRS indicate that increased local tissue levels of IgE likely play a significant role in this disease process.

In 2004, Collins *et al.* [39] identified fungus-specific IgE in paranasal sinus allergic mucin of patients with suspected AFRS undergoing endoscopic sinus surgery. These authors also evaluated systemic fungus-specific IgE

Figure 2 Immunoglobulin E-secreting cells in sinus tissue of patient with allergic fungal rhinosinusitis



Representative tissue sections from immunoglobulin E (IgE) immunohistochemical studies demonstrating multiple stained IgE-positive cells in the epithelium (a) and subepithelium (b) of sinus tissue from patients with allergic fungal rhinosinusitis (AFRS), as compared with epithelial (c) and subepithelial (d) sinus tissue sections from control patients.

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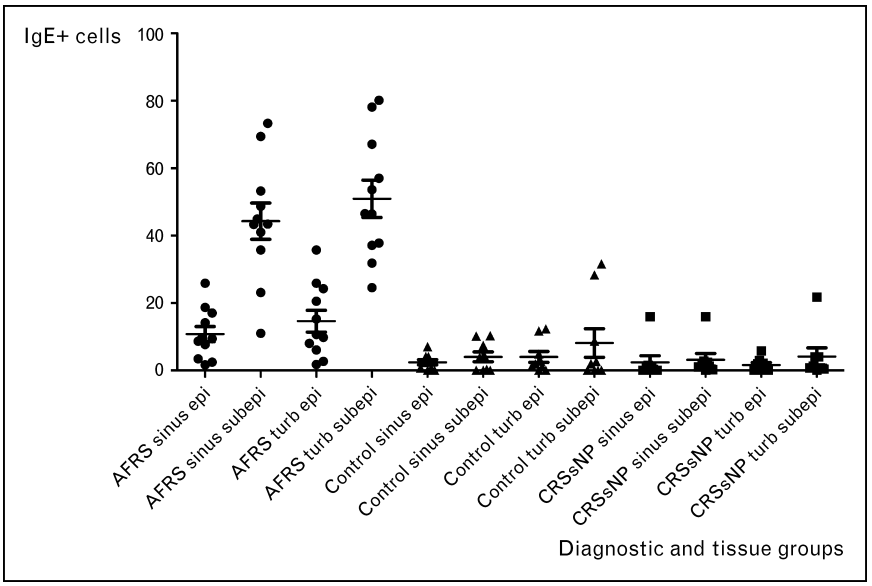
Figure 3 Local immunoglobulin E levels in patients with allergic fungal rhinosinusitis, controls, and patients with chronic rhinosinusitis



Summary graph of local immunoglobulin E (IgE) immunohistochemical staining in allergic fungal rhinosinusitis (AFRS), chronic rhinosinusitis without nasal polyps (CRSsNP), and control patients from Wise *et al.* [30••] and Ahn *et al.* [41] studies. Data from sinus tissue and inferior turbinate (turb) tissue epithelium (epi) and subepithelium (subepi) are included. Significantly more IgE-positive cells were found in AFRS sinus and turbinate epithelium and subepithelium, as compared with similar tissue types and locations from the other patient groups.

levels in serum and detected fungus-specific IgE in sinus mucin in some patients in the absence of fungus-specific serum IgE [39]. This supports the likelihood of local antigen-specific IgE production at the paranasal sinus tissue level, even when increased levels of systemic antigen-specific IgE are not detected. Further studies by Carney *et al.* [40] demonstrated an increase in IgE-positive cells in sinus tissue biopsies in various groups of patients with chronic rhinosinusitis, including AFRS, as compared with controls.

Recent investigations of local IgE production in paranasal sinus tissue of patients with AFRS by Wise *et al.* [30••] have revealed significantly increased levels of IgE-secreting cells and antigen-specific IgE in the osteomeatal complex sinus tissue of patients with AFRS. Using immunohistochemical staining for identification and localization, IgE-secreting cells were seen in increased numbers in both the sinus tissue epithelium and subepithelium of patients with AFRS, as compared with patients with chronic rhinosinusitis and controls. The greatest numbers of IgE-secreting cells in sinus tissue were seen at the subepithelial level in patients with AFRS (Fig. 2a–d). Similar immunohistochemical techniques were used by Ahn *et al.* [41] to evaluate the inferior turbinate tissue of patients with AFRS for tissue localization of IgE-secreting cells, as compared with patients with chronic rhinosinusitis and controls. These authors found a significant increase in IgE-secreting cells in the inferior turbinate epithelium and subepithelium in patients with AFRS compared with controls and patients with chronic rhinosinusitis. Again, in inferior turbinate tissue, the highest numbers of IgE-secreting cells were seen in patients with AFRS at the subepithelial level (Fig. 3). Evaluations of antigen-specific IgE in sinonasal tissue of patients with AFRS have also revealed increased levels of IgE to fungal and nonfungal antigens in both sinus and inferior turbinate tissues [30••,41]. These findings support local tissue production and secretion of total and antigen-specific IgE at increased levels in patients with AFRS. Further, the local IgE secretion appears to be a diffuse process throughout sinonasal tissues, including the paranasal sinuses and inferior turbinates, rather than restricted to one anatomic site. Given the increased levels of total and antigen-specific IgE in AFRS sinonasal tissues, the authors contend that heightened local IgE levels to a variety of fungal and nonfungal antigens may play a role in the exuberant polyposis in AFRS, but does not account for the anatomic predisposition for polyps to form in the sinus cavity, rather than on the inferior turbinates.

Clinical implications of localized immunoglobulin E in sinonasal tissue

Current practice for systemic allergy testing consists of skin testing or in-vitro assessment of total and antigen-specific IgE. These methods have served clinicians well for many years. However, as many of the studies reviewed in this article indicate, systemic allergy testing may fail to detect relevant levels of local tissue IgE. In

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patients with nasal polyposis or significant symptoms of rhinitis or rhinoconjunctivitis, assessments of local IgE in the shock organ may have a role.

Scenarios in which local IgE assessment may undergo future consideration include patients with classic symptoms of allergic rhinitis or rhinoconjunctivitis but negative systemic allergy testing, patients undergoing sinonasal surgery for polyposis, and pediatric or adult patients with needle apprehension. The methodology for local tissue IgE assessment is currently experimental, however. To our knowledge, laboratory standards for assessment of nasal lavage fluid or sinonasal tissue total and specific IgE levels do not exist. Before the practice of local tissue IgE evaluation could be widely implemented, standard criteria for tissue or lavage fluid collection and processing would need to be developed, along with establishing normal ranges for local versus systemic IgE levels. Nonetheless, the potential for assessment of local IgE in nasal tissue or lavage fluid holds promise for improved diagnosis and treatment of patients with sinonasal inflammatory disorders.

Conclusion

The studies reviewed in this article provide evidence of the presence and local production of IgE in sinonasal tissues. Local IgE appears to play a role in a variety of sinonasal inflammatory disorders, including allergic and nonallergic rhinitis, atopic and nonatopic nasal polyposis, and AFRS. Many investigators have identified locally produced IgE in nasal and sinus tissues in patients with low or absent levels of systemic total or antigen-specific IgE. The potential exists for the future widespread use of diagnostic methods to assess local IgE in patients with sinonasal inflammatory diseases, with promise for improved treatment of this patient group.

Acknowledgements

Dr Wise currently receives grant support from Arthrocare and has previously received grant support from XoranTech. Dr Ahn has no financial conflicts of interest to declare. Dr Schlosser receives grant support from the Flight Attendant Medical Research Institute, the American Academy of Otolaryngology, Greer, NeilMed, and XoranTech. Dr Schlosser is a consultant for BrainLAB, Medtronic, Gyrus, and Greer and serves on the speaker's bureau for GlaxoSmithKline.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 246–247).

1 Tse K, Wicher K, Arbesman C. IgE antibodies in nasal secretions of ragweed-allergic subjects. J Allergy 1970; 46:352.

2 Gevaert P, Holtappels G, Johannson S, *et al.* Organization of secondary lymphoid tissue and local IgE formation to *Staphylococcus aureus* enterotoxins in nasal polyp tissue. Allergy 2005; 60:71–79.

3 Agresti A, Vercelli D. Molecular mechanisms of IgE regulation. Vercelli D, editor. New York: Wiley; 1997.

4 Durham S, Gould H, Thienes C, *et al.* Expression of the ε germ-line gene transcripts and mRNA for ε heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. Eur J Immunol 1997; 27:2899–2906.

5 Cameron L, Gounni A, Frenkiel S, *et al.* SεSμ and SεSγ switch circles in human nasal mucosa following ex vivo allergen challenge: evidence for direct as well as sequential class switch recombination. J Immunol 2003; 171: 3816–3822.

6 Takhar P, Smurthwaite L, Coker H, *et al.* Allergen drives class switching to IgE in the nasal mucosa of allergic rhinitis. J Immunol 2005; 174:5024–5032.

7 KleinJan A, Godthelp T, van Toornenenbergen A, *et al.* Allergen binding to specific IgE in nasal mucosa of allergic patients. J Allergy Clin Immunol 1997; 99:515–521.

8 KleinJan A, Vinke J, Severijnen L, *et al.* Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. Eur Respir J 2000; 15:491–497.

9 Yoshida T, Usui A, Kusumi T, *et al.* A quantitative analysis of cedar pollen specific immunoglobulins in nasal lavage supported the local production of specific IgE, not of specific IgG. Microbiol Immunol 2005; 49:529–534.

10 • Rondon C, Romero J, Lopez S, *et al.* Local IgE production and positive nasal provocation test in patients with nonallergic rhinitis. J Allergy Clin Immunol 2007; 119:899–905.
This article reports increased levels of local IgE in nasal secretions and increased symptoms following nasal provocation testing in patients with nonallergic rhinitis, despite absence of systemic allergy.

11 Huggins K, Brostoff J. Local production of specific IgE antibodies in allergic rhinitis patients with negative skin tests. Lancet 1975; 2:148.

12 Powe D, Mason M, Jagger C, *et al.* 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. Clin Exp Allergy 2003; 33:1374–1379.

13 Powe D, Jones N. Local mucosal immunoglobulin E production: does allergy exist in nonallergic rhinitis? Clin Exp Allergy 2006; 36:1367–1372.

14 Batemen N, Fahy C, Woolford T. Nasal polyps: still more questions than answers. J Laryngol Otol 2003; 117:1–9.

15 Caplin I, Haynes T, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy 1971; 29:63–68.

16 Settipane G, Chaffe F. Nasal polyps in asthma and rhinitis: a review of 6037 patients. J Allergy Clin Immunol 1976; 59:17–21.

17 Hirschberg A, Jokuti A, Darvas Z, *et al.* The pathogenesis of nasal polyposis by immunoglobulin E and interleukin-5 is completed by transforming growth factor beta-1. Laryngoscope 2003; 113:120–124.

18 Wei C, Fang S. Tissue-specific immunoglobulin E in human nasal polyps. Ann Otol Rhinol Laryngol 2005; 114:386–389.

19 Suh K, Park H, Nahm D, *et al.* Role of IgG, IgA, and IgE antibodies in nasal polyp tissue: their relationships with eosinophilic infiltration and degranulation. J Korean Med Sci 2002; 17:375–380.

20 • Sabirov A, Hamilton R, Jacobs J, *et al.* Role of local immunoglobulin E specific for *Alternaria alternata* in the pathogenesis of nasal polyposis. Laryngoscope 2008; 118:4–9.
This study discusses the identification of specific IgE to *A. alternata* in nasal polyp tissue and the potential role of *A. alternata* in the pathogenesis of nasal polyposis.

21 •• Bachert C, van Zele T, Gevaert P, *et al.* Superantigens and nasal polyposis. Curr Allergy Asthma Rep 2007; 3:523–531.
This is a recent and thorough review of the research supporting *S. aureus* superantigens in the development of nasal polyposis.

22 Bachert C, Gevaert P, Holtappels G, *et al.* Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol 2001; 101:607–614.

23 Perez-Novo C, Kowalski M, Kuna P, *et al.* Aspirin sensitivity and IgE antibodies to *Staphylococcus aureus* enterotoxins in nasal polyposis: studies on the relationship. Int Arch Allergy Immunol 2004; 133:255–260.

24 Sheahan P, Ahn C, Harvey R, *et al.* Local IgE production in nonatopic nasal polyposis. Paper presented at the fall meeting of the American Rhinologic Society. Chicago, IL; September 2008.

25 Bent J, Kuhn F. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994; 111:580–588.

26 Manning S, Mabry R, Schaefer S, *et al.* Evidence of IgE-mediated hypersensitivity in allergic fungal sinusitis. Laryngoscope 1993; 103:717–721.

27 Wise S, Venkatraman G, Wise J, *et al.* Ethnic and gender differences in bone erosion in allergic fungal sinusitis. Am J Rhinol 2004; 18:397–404.

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28 Ghegan M, Lee F, Schlosser R. Incidence of skull base and orbital erosion in allergic fungal rhinosinusitis (AFRS) and non-AFRS. Otolaryngol Head Neck Surg 2006; 134:592–595.

29 Ghegan M, Wise S, Gorham E, *et al.* Socioeconomic factors in allergic fungal rhinosinusitis with bone erosion. Am J Rhinol 2007; 21:560–563.

30 •• Wise S, Ahn C, Lathers D, *et al.* Antigen-specific IgE in the sinus mucosa of allergic fungal rhinosinusitis patients. Am J Rhinol 2008; 22:451–456.
This article reports significantly increased total and specific IgE in sinus tissue of patients with AFRS, as compared with controls and patients with chronic rhinosinusitis.

31 Braun J, Pauli G, Schultz P, *et al.* Allergic fungal sinusitis associated with allergic bronchopulmonary aspergillosis: an uncommon sinobronchial allergic mycosis. Am J Rhinol 2007; 21:412–416.

32 Bartynski J, McCaffrey T, Frigas E. Allergic fungal sinusitis secondary to dematiaceous fungi: Curvularia lunata and Alternaria. Otolaryngol Head Neck Surg 1990; 103:32–39.

33 Gourley D, Whisman B, Jorgensen N, *et al.* Allergic Bipolaris sinusitis: clinical and immunopathologic characteristics. J Allergy Clin Immunol 1990; 85: 583–591.

34 Stewart A, Hunsaker D. Fungus-specific IgG and IgE in allergic fungal rhinosinusitis. Otolaryngol Head Neck Surg 2002; 127:324–332.

35 Mabry R, Manning S, Mabry C. Immunotherapy in the treatment of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1997; 116:31–35.

36 Mabry R, Marple B, Folker R, *et al.* Immunotherapy for allergic fungal sinusitis: three years' experience. Otolaryngol Head Neck Surg 1998; 119:648–651.

37 Folker R, Marple B, Mabry R, *et al.* Treatment of allergic fungal sinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. Laryngoscope 1998; 108:1623–1627.

38 Kuhn F, Swain R. Allergic fungal sinusitis: diagnosis and treatment. Curr Opin Otolaryngol Head Neck Surg 2003; 11:1–5.

39 Collins M, Nair S, Smith W, *et al.* Role of local immunoglobulin E production in the pathophysiology of noninvasive fungal sinusitis. Laryngoscope 2004; 114:1242–1246.

40 Carney A, Tan L, Adams D, *et al.* Th2 immunological inflammation in allergic fungal sinusitis, nonallergic eosinophilic fungal sinusitis, and chronic rhinosinusitis. Am J Rhinol 2006; 20:145–149.

41 Ahn C, Wise S, Lathers D, *et al.* Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. Paper presented at the annual meeting of the American Academy of Otolaryngic Allergy. Chicago, IL; September 2008.

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