

Elevated total serum IgE in nonatopic patients with aspirin-exacerbated respiratory disease

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ABSTRACT

Background: Aspirin-exacerbated respiratory disease (AERD), also known as Samter's triad, is characterized by asthma, recurrent nasal polyps, and by allergic-like reactions to aspirin and other nonsteroidal anti-inflammatory drugs, although it is not a true immunoglobulin E (IgE)-mediated allergy. Atopy, although common in patients with AERD, is not a characteristic of the disease. Recently, we have observed a subgroup of patients with AERD who have no history of atopy but have abnormally elevated total serum IgE, a phenomenon that has been observed in patients with asthma but has not been further explored. We sought to explore this phenomenon of elevated total serum IgE in the absence of atopy in a subset of patients with AERD.

Methods: Patients were diagnosed with AERD with an oral aspirin challenge at the Brigham and Women's Hospital Allergy and Clinics. Atopy was defined as a positive test result to at least one of the common aeroallergens. Elevated total serum IgE was defined as IgE of >100 IU/mL.

Results: We present six patients with AERD and elevated total serum IgE in the absence of any clear atopy. Total serum IgE in these patients ranged from 110 to 1760 IU/mL. Mean blood eosinophil levels for these patients were not significantly different from those of the entire cohort of patients with AERD included in the study.

Conclusion: In a subset of patients with AERD, we observed elevated total serum IgE even when atopy was not present. To better understand the disease, the cause and clinical relevance of this phenomenon deserves further exploration.

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Aspirin-exacerbated respiratory disease (AERD), also known as Samter's triad, is characterized by sensitivity to aspirin and all nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the cyclooxygenase-1 enzyme and by chronic inflammation of both the upper and the lower respiratory tracts. Clinical manifestations include asthma, recurrent nasal polyps, and rhinitis.^{1–3} Despite the allergic-like reactions to aspirin and NSAIDs that define the disease, AERD is not an immunoglobulin E (IgE)-mediated allergy, because specific IgE antibodies to aspirin have not been identified and all of the structurally different cyclooxygenase-1 inhibitors cause respiratory reactions in these patients.^{4,5} Neither the inciting cause of AERD nor the mechanisms of NSAID-induced reactions in these patients are known. As in patients with asthma, atopy is common in patients with AERD: in a recent cohort study just over one-half had a positive skin-prick test to at least one common aeroallergen and slightly less than one-half had total serum IgE levels ≥ 100 kU/L.⁶ However, atopy is not a defining characteristic of the disease.^{7–9} Recently, we observed a subset of AERD patients with no history of atopy but abnormally elevated total serum IgE levels. This phenomenon of elevated total serum IgE in the absence of atopy has been previously reported in individuals with severe asthma¹⁰; however, its significance remains to be evaluated. This case series presents six patients with AERD who have elevated total serum IgE levels but have no clinical history of environmental allergies and have negative skin and/or blood testing to common aeroallergens.

METHODS

Patients were seen at the Brigham and Women's Hospital Outpatient Allergy Clinics and all subjects gave written consent for participation in the study. The diagnosis of AERD was confirmed with an oral aspirin challenge in all subjects, and atopy was defined by the

presence of a positive skin test or Pharmacia CAP (Pharmacia Diagnostics, Uppsala, Sweden) blood test to any inhalant allergen documented in the medical record. Nonatopic patients had negative skin testing and/or Pharmacia CAP blood testing to a complete panel of environmental allergens, including animal dander, tree pollens, grass pollens, weeds, molds, and dust mites. Specific molds tested included *Aspergillus fumigatus*, *Alternaria alternata*, *Cladosporium herbarum*, and *Penicillium notatum*. Elevated total serum IgE was defined as IgE > 100 IU/mL. The Brigham and Women's Hospital institutional human subjects Institutional Review Board approved the study, and all subjects provided written consent in accordance with the Declaration of Helsinki.

RESULTS

Eighty-two patients with AERD were included in this study. Of those, 60 (73%) were confirmed to be atopic and 22 (27%) were nonatopic by criteria as defined previously. In general, the atopic and the nonatopic patients had similar serum total IgE levels (atopic, geometric mean, 144 ± 8 IU/mL; nonatopic, geometric mean, 86 ± 8 IU/mL; $p = 0.57$). The atopic and nonatopic patients also had similar eosinophil levels (atopic, 736 ± 527 U/ μ L; nonatopic, 853 ± 746 U/ μ L; $p = 0.51$). Of the nonatopic patients, six had elevated total serum IgE levels and are presented here.

Demographic information, total IgE and eosinophil levels, and the development of upper and/or lower respiratory reactions to aspirin during the oral aspirin challenge are presented in Table 1 for each of the six subjects. Serum total IgE levels ranged from 110 to 1760 IU/mL. All subjects with the exception of subject 3 had negative Pharmacia CAP blood tests to four molds, including *A. fumigatus*, *Alternaria*, *C. herbarum*, and *P. notatum*. Subject 3 had negative skin testing to *A. fumigatus*, *A. alternata*, and *C. herbarum*. Although none of the patients were current smokers, four of the six patients had significant lifetime tobacco exposure, with one reporting environmental exposure in the home during childhood and three reporting smoking histories of 5–13.5 pack-years. Mean blood eosinophil level was similar to the mean blood eosinophil level of the entire cohort of patients with AERD (subset, 865 ± 715 U/ μ L; entire cohort, 772 ± 594 U/ μ L; $p = 0.77$).

DISCUSSION

We have presented a series of six nonatopic patients with AERD and elevated IgE, observed in a clinical setting that serves a large

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Table 1 Characteristics of six patients with AERD and elevated total serum IgE in the absence of atopy

Patient	Gender	Age (yr)	Total IgE (IU/mL)	Eosinophils (per μ L)	Molds Tested	Tobacco Exposure
1	F	46	1760	1900	<i>Aspergillus fumigatus</i> <i>Alternaria alternata</i> <i>Cladosporium herbarum</i> <i>Penicillium notatum</i>	5 pack-yr
2	F	40	479	1620	<i>A. fumigatus</i> <i>A. alternata</i> <i>C. herbarum</i> <i>P. notatum</i>	Environmental exposure as a child
3	M	67	110	200	<i>A. fumigatus</i> <i>A. alternata</i> <i>C. herbarum</i>	13.5 pack-yr
4	F	33	342	590	<i>A. fumigatus</i> <i>A. alternata</i> <i>C. herbarum</i> <i>P. notatum</i> <i>C. albicans</i>	7–8 pack-yr
5	M	49	113	580	<i>A. fumigatus</i> <i>A. alternata</i> <i>C. herbarum</i> <i>P. notatum</i>	Never
6	M	39	300	302	<i>A. fumigatus</i> <i>A. alternata</i> <i>C. herbarum</i> <i>P. notatum</i>	Never

AERD = aspirin-exacerbated respiratory disease; IgE = immunoglobulin E.

population of AERD patients. Although the mechanism behind this phenomenon is unclear, recognizing its existence may be helpful for clinicians diagnosing AERD and deserves further exploration.

The high IgE levels detected in this cohort of patients could be specific IgE to aeroallergens that were not tested, although given that each patient underwent testing to a large panel of the most common aeroallergens, we believe that this is unlikely. Although production of specific IgE to molds and fungus is common in patients with chronic rhinosinusitis and nasal polyps,¹¹ all of the patients in this subset had negative test results to the most common fungal aeroallergens (see Table 1). However, there remains the possibility that these patients have developed specific IgE to an unknown allergen that is not routinely tested. Because IgE that specifically recognizes bacterial components¹² and respiratory viruses¹³ is known to be produced *in vivo* under some circumstances, it is plausible that the IgE identified in this subset of patients with AERD is directed toward a microbial epitope. In particular, specific IgE to *Staphylococcus aureus* endotoxin is common in subjects with nasal polyps and aspirin sensitivity¹⁴; however, microbial IgE is not routinely clinically tested at Brigham and Women's Hospital, so it is possible that some of these patients do have specific IgE to *S. aureus* or another microbial epitope. Another possibility is that these patients are, in fact, atopic, but that the allergen-specific IgE exists only in local tissues and is not present in systemic circulation. This locally produced specific IgE has been reported in allergic rhinitis patients^{15,16} and in nonatopic asthmatic patients, although this local manifestation of atopy would not be expected to lead to an increase in circulating total IgE.¹⁷

Although significant lifetime tobacco smoke exposure may be relevant, because exposure to environmental tobacco smoke during both childhood and adulthood is associated with increased odds of developing AERD,¹⁸ it is not likely causative of elevated total IgE levels because two of the six patients in this subset did not have any tobacco exposure. Furthermore, although current smokers are known to have significantly higher IgE than never smokers, exsmokers have not been found to have higher IgE than never smokers.¹⁹

Additional research is necessary to determine both the cause and the clinical relevance of the elevated IgE levels observed in this subset of nonatopic patients with AERD, which, hopefully, will shed light on this mysterious disorder.

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