



Editorial

Immunoglobulin E deficiency . . . is that a thing?



As allergists/immunologists, our work is inextricably tied to immunoglobulin E (IgE). Its presence and function form the foundation of what we treat daily. But rarely do we think about its absence and whether this may be associated with disease. In this issue of the *Annals of Allergy, Asthma & Immunology*, Ferastraoaru and Rosenstreich report their findings on IgE deficiency and its association with malignancy.¹ In their article, the authors report on 47 patients who had absence of detectable IgE in the serum. Each patient had skin prick testing and intradermal testing to common aeroallergens. The authors report that the patients with absent serum IgE who also had negative results of skin prick and intradermal testing had a higher rate of malignancy (6/14, 42.9%) than patients who had absent serum IgE but had positive result of skin testing (2/33, 6.1%). They suggest that even in patients with undetectable serum IgE, tissue-bound IgE can be present and that the skin testing is a proof of this. Furthermore, they suggest that this tissue-bound IgE is functional (even if in low amounts) and plays a role in tumor surveillance.

This is a fascinating concept, and, if true, it would open a much broader idea of the function of IgE beyond its role in the T_H2 immune response. The concept is not entirely new. There are reports on the role of IgE in tumor surveillance, and the authors themselves have published previous reports on the association of IgE deficiency and malignancy.²⁻⁴

However, before one can accept this idea, there are questions to both the data in this current article and the concept in general. Regarding the data presented in this article, there are a few concerns. First, it is debatable how much a positive result of an intradermal test truly represents tissue-bound IgE. Although many allergists use intradermal testing clinically, it is clear that irritant reactions occur. Proving these intradermal tests represent IgE-mediated, type I hypersensitivity reactions vs irritant reactions or mast cell degranulation outside of IgE is difficult, and tissue biopsy would likely be required to prove this one way or the other. Second, of the 8 patients with IgE deficiency who had a malignancy, 5 had testing done after their malignancy diagnosis and treatment. Thus, it is very difficult to prove which is causal. Did the malignancy or even the treatment lead to IgE deficiency or did IgE deficiency lead to the malignancy? Third, given that there were only 8 cases of malignancy in this report, the numbers are quite low to make any

conclusions. Finally, if IgE plays a role in tumor surveillance, it seems plausible that this may be tissue dependent (after all, malignancies are all very different and do not have a single pathophysiology). Perhaps, the role is more evident in lymphoma/leukemia rather than solid tumors, or if in solid tumors, perhaps tissue dependent. However, in their report, the malignancies had no conceptual/pathophysiological similarities.

In addition to these concerns regarding the data in this current article, there are physiological questions with the concept in general. For example, there are human models for IgE deficiency that one can turn to evaluate this phenomenon. The purest model would be X-linked agammaglobulinemia (XLA). There are available data on cohorts of patients with XLA available, and from these reports, malignancy does not seem to be a common finding, with reports of malignancy between 1% and 6% of these patients, which is much lower than the 42.9% in the small number of patients here.^{5,6} Although malignancy rates may increase as these cohorts age and the authors are not suggesting IgE deficiency alone leads to malignancy in every patient, it seems reasonable that if this concept were true, there would at least be a signal of malignancy in the patients with XLA.

In summary, the concept of IgE deficiency and any role this may play in pathology, and specifically malignancy, is fascinating. However, there are clearly many hurdles to overcome to prove this phenomenon more convincingly, and I look forward to future data to convince me one way or the other.

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References

1. Ferastraoaru D., Goodman B., Rosenstreich D. Higher rates of malignancy in IgE deficient patients with negative immediate hypersensitivity skin tests. *Ann Allergy Asthma Immunol*. In press.
2. Ferastraoaru D., Rosenstreich D. IgE deficiency and prior diagnosis of malignancy: results of the 2005-2006 National Health and Nutrition Examination Survey. *Ann Allergy Asthma Immunol*. 2018;121(5):613-618.
3. Ferastraoaru D., Rosenstreich D. IgE deficiency is associated with high rates of new malignancies: results of a longitudinal cohort study. *J Allergy Clin Immunol Pract*. 2020;8(1):413-415.
4. Jensen-Jarolim E, Bax HJ, Bianchini R, et al. AllergoOncology—the impact of allergy in oncology: EAACI position paper. *Allergy*. 2017;72(6):866-887.
5. Shillito B, Gennery A. X-linked agammaglobulinemia: outcomes in the modern era. *Clin Immunol*. 2017;183:54-62.
6. Winkelstein JA, Marino MC, Lederman HM, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. *Medicine (Baltimore)*. 2006;85(4):193-202.

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