

Does a strong IgG response precede allergic sensitization?

To the Editor

In their paper on the evolution of the IgE and IgG repertoire,¹ Huang et al analyzed a rich dataset to look for IgG-related clues on the initial phase of allergic sensitization. They conclude that “a strong IgG response almost invariably precedes or accompanies the appearance of IgE to the same molecule in specifically sensitized subjects” and that “a persistent IgG response to an airborne molecule (eg, Der p 1, Fel d 1) is invariably associated with an IgE response to that molecule.”

A strong IgG response requires a Germinal Center (GC) reaction. If sensitization would depend on a full-blown GC reaction, this would argue against our proposal that GC maturation prevents allergic sensitization by a deletion of IgE-switched B cells.² According to this hypothesis, atopic IgE responses to airborne allergens (with pollen and mite as prototypical allergen sources) are characterized by a relatively low IgG/IgE ratio, low B-cell memory, and modest affinity maturation, which fits well with the direct switching pathway. This is in contrast to a nonatopic TH2 immune response (ie, a “modified TH2 response”³). In a modified TH2 response (a “healthy immune response”⁴), the maturation of GCs results in the expansion of IgG-switched B cells and the deletion of IgE-switched B cells. Huang et al propose that the IgE-producing cell in the atopic response is derived from indirect switching to IgE, via an IgG-switched B cells rather than from the nonswitched IgM B cell.

Support in favor of our hypothesis came in 2012 from 3 independent investigative groups, each using their own IgE-reporter mouse model (for a review see 5). They observed a rapid disappearance of IgE-switched B cells from the developing GC coinciding with a rapid expansion of IgG-switched B cells.

Because of these potentially conflicting results, we need some details on the data on which the authors based their conclusions. Firstly, the cut-off value used to classify an IgG response as “strong” is unclear. Secondly, a critical difference between the two hypotheses is the timing of the IgG response relative to that of the IgE response. The IgG and IgE responses are synchronous in the GC hypothesis, whereas in the alternative hypothesis, IgE production depends on the presence of IgG-switched B cells prior to IgE production. The most important missing information is the prevalence (for each of the allergens separately) of a “strong” IgG response in the serum sample preceding the first sample with demonstrable IgE to that same allergen.

Both hypotheses are based on a positive association between IgE and IgG production in an allergen-specific manner. In addition to such an allergen-specific effect, there is evidence supporting a more general

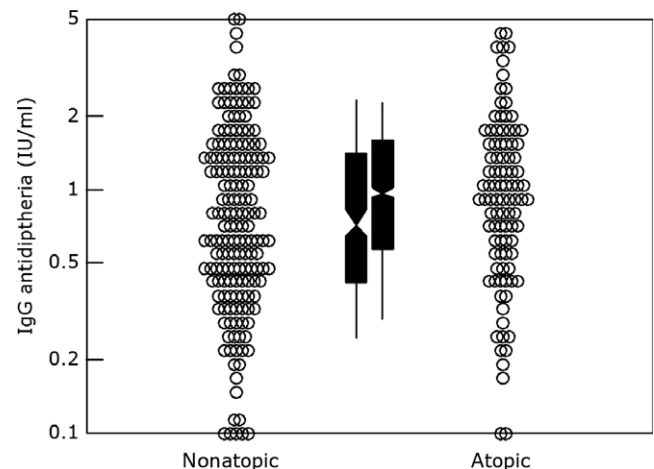


FIGURE 1 The IgG response to diphtheria is higher in atopic children (unpublished observation)

allergen-non-specific effect of atopy, for example a slightly stronger IgG response to diphtheria vaccination in atopic subjects (see Figure 1). As Huang et al based most of the IgG data analysis on the contrast between two groups (sensitized to any allergen vs never sensitized), it would be relevant for the authors to clarify the potential contribution of the non-allergen-specific atopy effect in their results.

The authors mention potentially interesting observations on the persistence of the IgG response in relation to the prediction of an IgE response to the same molecule. However, for the airborne allergens, the IgG patterns shown in the figures look remarkably stable. This suggests persistence in all groups. Our tentative explanation is that we might be misinterpreting the authors' use of the “persistence” terminology. What kind of information (other than a strong and early IgG response) are the authors referring to?

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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Abbreviations: Der p 1, a major mite allergen; Fel d 1, a major cat allergen; GC, germinal center of a lymph node follicle.

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Very rarely chronic urticaria can be caused by cancer and if so, resolves with its cure

To the Editor,

We would like to thank our colleagues for their reply to our letter¹ and for sharing their personal experience with almost 1500 chronic urticaria (CU) patients in Italy (Napolitano Allergy 2018, in press). Their data are in line with our two basic statements: (i) CU can be linked to cancer and disappears after its cure, and (ii) this association is extremely rare. The data reported by Napolitano et al suggest that the frequency of malignancy being linked to CU can be estimated to be 1/1500 or less.

In search of possible mechanisms that might explain the relationship between urticaria and cancer, one should think in both directions: (i) the tumor altering the immune system and/or generating mast cell-activating signals such that urticaria develops or (ii) urticaria causing a chronically altered immune status and failure of effective cancer surveillance. In the cases we presented—including our case—the urticaria resolved upon clearance of the tumor. Thus, (i) seems the most likely explanation. Some authors of the cases we presented commented on possible cancer-derived urticariogenic signals, for example, signals induced by activation of the complement system. However, none of the cases where complement was measured, including ours, reported hypocomplementemia.

Two possible mechanisms may link cancer to mast cell activation and CSU: 1) the production and release of tumor- or stroma-derived signals that promote mast cell accumulation and mast cell activation and 2) the production and release of tumor-derived antigens, detected by IgE, in line with the AllergoOncology concept.^{2,3}

Ad 1) Tumors can produce and release stem cell factor (SCF), vascular endothelial growth factor (VEGF), prostaglandins, leukotrienes, histamine, and other chemoattractants for mast cells that have been linked to the accumulation of mast cell observed in and around many types of tumors.⁴ Some of these signals are also known to induce mast cell degranulation, the key mechanism responsible for the induction of wheals and angioedema in patients with CSU. High-density mast cell infiltration was detected in thyroid,

stomach, pancreas, prostate, melanoma, and breast cancer, and accumulation of mast cells has been correlated with poor prognosis in colorectal tumors.⁵ Half of our cases were diagnosed for one of these cancers, most of the others being of hematopoietic origin.

Ad 2) In some patients with malignancy, IgE directed against tumor-associated antigens is produced and can be found in the peripheral blood. While tumor antigen-specific IgE cannot be cross-linked by the soluble tumor antigens, the same tumor antigens can cause IgE cross-linking when rigidly displayed by a tumor cell.⁶ By this mechanism, IgE-mediated tumor clearance can be stimulated, for instance by macrophages via TNF α /MCP-1 signaling similar to parasitic infections.⁶ The link between cancer and urticaria could very well exist via tumor-specific IgE. This could explain why almost all chronic urticaria linked to cancer is spontaneous and not inducible. Many CSU patients have IgE to thyroid peroxidase (TPO). TPO is not usually detectable in the blood of humans, but one of the conditions that can lead to increased blood levels of TPO might be thyroid cancer, diagnosed in 6 of 25 patients of our series. Another example is the IgE directed against squamous cell carcinoma antigen (SARTi), also known as Hom s 1,⁷ although this has not been studied directly in cancer till now. The questions on how these tumor-derived antigens acquire cross-linking capacity and why actually urticaria symptoms occur exclusively in the skin are likely mechanistically related, but remain to be answered.

We agree with the four features proposed by our Italian colleagues to characterize cancer-associated CSU, that is, (i) antihistamine resistance, (ii) onset before malignancy is diagnosed (mostly 2-8 months), (iii) resolution after effective treatment of cancer, and (iv) recurrence upon relapse of cancer (Napolitano Allergy, 2018 in press). We suggest that these features should be investigated in future studies. As such, we would like to emphasize the importance of the global urticaria registry (Chronic Urticaria Registry, CURE, www.urticaria-registry.com) and the urticarial centers of reference and excellence network (UCARE, www.ga2len-ucare.com), which can