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REFERENCES

- Huang X, Tsilochristou O, Perna S, et al. Evolution of the IgE and IgG repertoire to a comprehensive array of allergen molecules in the first decade of life. *Allergy*. 2018;73:421-430.
- Aalberse RC, Platts-Mills TA. How do we avoid developing allergy: modifications of the TH2 response from a B-cell perspective. *J Allergy Clin Immunol*. 2004;113:983-986.
- Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet*. 2001;357:752-756.
- Akdis M. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol*. 2006;18:738-744.
- Aalberse RC, Platts-Mills TA, Rispens T. The developmental history of IgE and IgG4 antibodies in relation to atopy, eosinophilic esophagitis, and the modified TH2 response. *Curr Allergy Asthma Rep*. 2016;16:45.

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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

help to better understand how urticaria and cancer are linked. This could enhance the guidance given on when and how to look for cancer in CSU patients, to not overwhelm all CSU patients with tests, but to not miss any cancer diagnosis either.

CONFLICTS OF INTEREST

The authors have no conflict of interests to disclose.

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REFERENCES

1. Larenas-Linnemann D, Saini SS, Azamar-Jacome AA, Maurer M. Chronic urticaria can be caused by cancer and resolves with its cure. *Allergy*. 2018;73:1562-1566.
2. Jensen-Jarolim E, Bax HJ, Bianchini R, et al. AllergoOncology - the impact of allergy in oncology: EAACI position paper. *Allergy*. 2017;72:866-887.
3. Jensen-Jarolim E, Bax HJ, Bianchini R, et al. AllergoOncology: opposite outcomes of immune tolerance in allergy and cancer. *Allergy*. 2018;73:328-340.
4. Varricchi G, Galdiero MR, Loffredo S, et al. Are mast cells MASTers in cancer? *Front Immunol*. 2017;8:424.
5. Aponte-Lopez A, Fuentes-Panana EM, Cortes-Munoz D, Munoz-Cruz S. Mast cell, the neglected member of the tumor microenvironment: role in breast cancer. *J Immunol Res*. 2018;2018:2584243.
6. Josephs DH, Bax HJ, Dodev T, et al. Anti-folate receptor-alpha IgE but not IgG recruits macrophages to attack tumors via TNFalpha/MCP-1 signaling. *Can Res*. 2017;77:1127-1141.
7. Valenta R, Natter S, Seiberler S, et al. Molecular characterization of an autoallergen, Hom s 1, identified by serum IgE from atopic dermatitis patients. *J Invest Dermatol*. 1998;111:1178-1183.

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Reply to: "Allergen-specific IgG responses preceding allergic sensitization"

In their comments to Huang et al,¹ Aalberse and Platts-Mills argue that a strong and persistent IgG response is generated by a mature GC, that is the same structure in secondary lymphoid organs that may lead to deletion, rather than to proliferation of IgE+ B cells.² The pre- or coexistence of such an IgG response with IgE to the same allergenic molecule would therefore disagree with their model of a "modified" Th2 response.² Hence, the authors ask for the following information: (i) our definition of a "strong" IgG response and whether a "pre-atopic" IgG response is already "strong" before the appearance of IgE; (ii) our definition of a "persistent" IgG response; (iii) whether there is a "non-allergen-specific" effect of atopic predisposition on the "(pre-)atopic" IgG response. To answer these interesting questions, we will highlight information available in our original papers and present further statistical analyses of our data sets.

In the last years, we have examined the evolution of serum antibodies with a microarray assay (ISAC, ThermoFisher, Uppsala) in the sera of children participating in the Multicenter Allergy Study (MAS),

a German birth cohort born in 1990 and followed until 20 years of age. Three of these papers^{1,3,4} focused on IgG antibodies in their relationship with IgE responses. The results of these can briefly be summarized as follows:

- IgG antibodies against most allergenic molecules are *normally* found in the serum of children already at 2 years of age ("default" IgG response). Prevalence and average concentration of these IgG antibodies are dependent on the extent and route of allergen exposure, being maximal for animal foods, intermediate for vegetable foods and minimal for airborne allergenic molecules.⁴ Moreover, we showed that this default IgG response is characterized by slightly higher prevalence and levels in atopic children⁴ as previously suggested by Aalberse's group.⁵
- The appearance of serum IgE to airborne PR.10 molecules is invariably anticipated or accompanied by an IgG response towards the same molecule.³ Observing the trajectory of its natural evolution at population level, this "(pre-)atopic" IgG response to PR.10