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Reply to Narra

Esra Ozcan, M.D., Raif S. Geha, M.D.^{*}, and Luigi D. Notarangelo, M.D.

Division of Immunology, Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, 02115.

To the Editor:

In a recent issue of this Journal, Narra and Shearer have reported on a patient with cartilage hair hypoplasia (CHH) who experienced anaphylaxis reaction to insect sting¹. The authors have asked us to comment on the occurrence of atopy in primary immunodeficiencies (PIDs) with increased IgE production, that we covered in a recent review².

The increased IgE production that is observed in patients with hyper-IgE syndrome (HIES), Immune dysregulation-Polyendocrinopathy-Enteropathy-X-linked (IPEX) syndrome, Wiskott-Aldrich syndrome (WAS), Omenn syndrome (OS) and complete atypical DiGeorge syndrome (DGS), reflects immune dysregulation, and is not necessarily accompanied by true allergy manifestations.

In particular, *HIES* patients often present a variable degree of eczema in the first days of life. The eczema is pruritic and of Dten lichenified, but its distribution (back, buttocks and scalp) is not typical for atopic dermatitis. Most HIES patients do not have food allergy. However, true cases of atopic dermatitis (AD) may occur in HIES, as demonstrated by the recent report of three HIES patients who presented with growth retardation, eczema and severe allergy to cow's milk proteins and other food allergens, that responded to elimination of allergens from the diet, in combination with antibiotics and immune suppression³⁻⁵. This contrasts with the inefficacy of diet in most patients with the atypical eczema that is characteristic of HIES, indicating significant pathophysiology differences with AD. A coincidence of HIES and AD will not be unexpected, given the high prevalence of AD in children, currently estimated to be close to 20%.

Mutations of the *FOXP3* gene in the IPEX syndrome prevent the generation of regulatory T (T-reg) cells and result in a systemic multiorgan inflammatory response, loss of oral tolerance and dysregulated T_H1 and T_H2 cytokine production in the absence of overt T_H2 skewing. Skin inflammation, reminiscent of AD, and food allergy are typically observed in IPEX, and may even represent the main clinical feature at diagnosis⁶.

Eczema, indistinguishable from classic AD except for purpuric lesions at sites of excoriation, is a key feature of WAS. Although many patients with WAS manifest specific

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^{*}**Corresponding author:** Raif S. Geha, Division of Immunology, Children's Hospital, One Blackfan Circle, Boston, Massachusetts 02115, USA. Tel. (617) 919 2482; Fax: (617) 730 0528; E-mail: Raif.Geha@childrens.harvard.edu..

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IgE to certain antigens (mostly food allergens), elevated IgE levels can be observed also in the absence of allergen-specific responses ⁷. Impaired function of T-reg cells in WAS may be a key factor in determining the allergic dysregulation of WAS.

Severe skin manifestations, eosinophilia and elevated serum IgE are typical features of Ommen's syndrome (OS). T-cell clones derived from patients with OS have been shown to secrete high levels of IL-4, IL-5 and IL-13, and this T_H2 skewing has been postulated to play a role in the allergic skin inflammation of OS. However, there is little evidence for allergen-specific IgE responses and true clinical features of atopy in OS.

Eczema and wheezing are frequent findings in patients with the partial DiGeorge syndrome, which represents the most common form of the disease ^{8, 9}. Defects in the number of T-reg cells and homeostatic proliferation, leading to a restricted T cell repertoire may play a role in the increased occurrence of allergy. Increased medical attention may lead to a bias in estimating the frequency of allergy among patients with DGS.

Finally, although allergy does not represent a prominent feature of CHH, Rider et al. have recently reported on a cohort of 25 CHH patients from the Amish community, 4 of which (16%) had asthma ¹⁰. CHH is often marked by a variable degree of T-cell immunodeficiency. Whether this results in defects of T-reg cells or increased homeostatic proliferation as in the other forms of PID discussed above, remains to be seen.

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