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Comment on: Betrand V et al. Episodic angioedema with eosinophilia (Gleich syndrome) in children: A clinical review

Title: The link between type 2 innate lymphoid cells and eosinophils in Gleich syndrome

To The Editor,

The paper by Bertrand V and colleagues discuss on the roles of cells other eosinophils such as mast cells or lymphocytic-variant hypereosinophilic syndrome (HES_L) cells in episodic angioedema with eosinophilia [1]. There is no consensus on the cut-off values of HES_L cells which could be CD3⁺CD4⁺T cells, CD3⁺CD4⁺CD8⁺TCR^{αβ}⁺ or CD3⁺CD4⁺CD8⁺CD7⁺ T cell subsets during an episode of severe angioedema which makes it difficult to set diagnostic criteria. The obvious question is whether CD3⁺ cells are T cells but HES_L cells have intracellular CD3 demonstrated by flow cytometry and T cell receptor genes by Southern blotting [2]. Group 2 innate lymphoid cells (ILC2) cells appear relevant in this setting as these cells are truly CD3 negative and produce IL-5 and IL-13 [3], that may be consistent with the clinical features and eosinophilia seen in Gleich syndrome. Natural killer (NK) cells negatively regulate ILC2 cells [4], and increased NK cell numbers seen during asymptomatic phases could explain the description as provided by Garcia-Abujeta JL and colleagues in their publication [5].

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Lymphoid cells that reside in tissues and lack T and B markers (lineage negative) are grouped into the ILC family (ILC1, ILC2, ILC3). Conventional NK cells could well be part of this (extended) family and therefore combination of sets of data such as surface receptor expression, transcription factors that control development and cytokine production following activation are required to properly understand their role in physiological states and disease. ILC2 cells secrete type 2 cytokines in response to helminth and viral infection and considered to be factors in allergic inflammation, including eosinophil homeostasis. However, eosinophils themselves can induce and recruits ILC2 cells in the pulmonary tissues, and thus appears dependent on each other in a biofeedback loop. Nussbaum JC and colleagues showed that serum IL-5 levels can be maintained by tissue-resident ILC2 cells, and can be further induced to increase IL-13 production, which results in localized eotaxin production and accumulation of eosinophils [6]. They showed this in the lamina propria of lungs and small intestine of IL-5 reporter mice, and that there was a circadian rhythm linked to caloric intake. Could these provide us with clues as to what happens in our patients with Gleich syndrome, such as the constant hypereosinophilia, and some attacks associated with weight gain? It seems fascinating, but plasticity of cells is likely to be the greatest hindrance to scientists understanding diseases with varied clinical presentations.

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References:

1. Bertrand V, Boccard O, Filhon B, et al. Episodic angioedema with eosinophilia (Gleich syndrome) in children: A clinical review [published online ahead of print, 2019 Nov 14]. *Pediatr Allergy Immunol*. 2019;10.1111/pai.13173. doi:10.1111/pai.13173

2. Simon HU, Plötz SG, Dummer R, Blaser K. Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. *N Engl J Med*. 1999;341:1112-20.
3. Spits H, Cupedo T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. *Annu Rev Immunol*. 2012;30:647–675.
4. Bi J, Cui L, Yu G, Yang X, Chen Y, Wan X. NK Cells Alleviate Lung Inflammation by Negatively Regulating Group 2 Innate Lymphoid Cells. *J Immunol*. 2017;198:3336-3344.
5. García-Abujeta JL, Martín-Gil D, Martín M et al. Impaired type-1 activity and increased NK cells in Gleich's syndrome. *Allergy*. 2001;56:1221-5.
6. Nussbaum JC, Van Dyken SJ, von Moltke J et al. Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature*. 2013;502:245-8.