

EDITORIAL

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Inflammation in chronic urticaria is not limited to the consequences of mast cell (or basophil) degranulation

This editorial discusses the findings of the paper by A. Tedeschi et al. [9]

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Chronic urticaria is a persisting inflammatory disorder of the skin in which the main manifestation is urticarial lesions that can be accompanied by angioedema in approximately 40% of patients [1]. The cellular infiltrate consists of CD4⁺, T lymphocytes with a mixture of Th1 and Th2 subtypes as well as neutrophils, eosinophils, monocytes, and basophils, in a perivascular distribution [2, 3]. Approximately 75% of patients have a disorder associated with autoimmunity manifest by the presence of IgG antibody to the high-affinity IgE receptor (Fc ϵ RI) in 35–40% of patients and IgG anti-IgE in an additional 5–10% [4, 5]. These antibodies are considered to have pathogenic significance because they are capable of initiating degranulation of cutaneous mast cells [6] and basophils [1, 4, 5]; the latter being used as a diagnostic assay. A prominent association is also seen with anti-thyroid antibodies, although these are not thought to be pathogenic, but indicative of a propensity to B cell activation. B cells are not seen in the cellular infiltrate. Although the cellular infiltrate resembles an allergic late-phase reaction, the T cell subtype distribution is different and the relative numbers of neutrophils and monocytes are more prominent, perhaps related to release of C5a [7], which is chemotactic for neutrophils, eosinophils, monocytes, and basophils.

The cellular infiltrate is present whether autoantibodies are seen or not, and characterizes all chronic urticaria (excluding physical urticarias except delayed pressure urticaria) although the intensity of the infiltrate and severity of symptoms may be increased in the autoimmune subgroup [8]. The article by Tedeschi et al. [9] in this issue of the journal describes important new information regarding the inflammatory response in chronic urticaria with evidence that plasma assays can be employed reflective of changes occurring within the skin. Thus, matrix

metalloproteinase-9 (MMP-9) levels are elevated in the blood of patients with active disease, the quantity found is a rough measure of severity of symptoms, and although the cellular origin of MMP-9 is not addressed, the cutaneous mast cell is one possibility [10]. Levels of TIMP-1, a major inhibitor of MMP-9, are not increased, thus the MMP-9/TIMP-1 ratio is increased in patients. Blood levels of C-reactive protein (CRP), an acute phase reactant usually associated with inflammatory conditions, are also increased in patients with chronic urticaria and the levels correlate with those of MMP-9. However, CRP is an acute-phase reactant produced primarily in the liver that is stimulated by elevated levels of IL-1, TNF- α , and/or IL-6 rather than being produced within the skin, as is likely for MMP-9.

The authors note that the levels of MMP-9 do not correlate with the presence or absence of the autologous skin test or assay of basophil histamine release, tests reflective (particularly histamine release) of the presence of activating autoantibodies. As the inflammatory infiltrate does not relate to the presence or absence of autoantibodies, i.e. chronic 'idiopathic' urticaria vs. chronic 'autoimmune' urticaria, elevated MMP-9 levels in all such patients are not unexpected. Furthermore, the prominent response of all chronic urticaria to corticosteroids, which do not inhibit cutaneous mast cell activation, emphasizes the importance of these infiltrating cells and their secretory products in the physical manifestations of the urticaria. Urticarias such as dermatographism or cold urticaria present with lesions lasting 30 min to 2 h, typical of hives that are solely a consequence of mast cell degranulation, and a significant infiltration of cells is not seen, nor are the symptoms responsive to corticosteroid.

Because the authors employ a low level of basophil histamine release (5%) taken as the upper limit of normal, rather than 15% as has been employed in other studies [5] to control for non-specific histamine release by serum, an analysis of histamine release levels vs.

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MMP-9 levels might have been revealing. Nevertheless, a correlation of histamine release with disease severity was not observed even though such an association has been noted previously [11]. It is important to consider that these data do not relate to the role of autoantibodies as initiators of mast cell and basophil activation; this is analogous to the fact that IgE-mediated allergy is a very important component of childhood asthma, yet intrinsic asthma does exist and it has a cellular infiltrate that is virtually identical to that of allergic asthma but with no role for IgE. Considering pathogenic mechanisms of chronic urticaria, the authors postulate a possible role for the T lymphocyte (or other cells) as activators of cutaneous mast cells, which might explain mast cell activation in all chronic urticaria, and this should be an interesting area of future investigation. Thus, when 'histamine-releasing factors' derived from T lymphocytes [9] were studied to identify the molecular species responsible for the activity, histamine-releasing chemokines such as MCP-1 [12] were described but they acted on basophils rather than mast cells. A T cell product that activates cutaneous mast cells (e.g. stem cell factor, C-kit ligand) [13] in chronic urticaria would be of obvious interest and importance, but would not explain how the T cells got there to start with.

References

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