

Mast-cell phenotype in urticaria

E. Nettis*, P. Dambra, M. P. Loria, L. Cenci,
G. A. Vena, A. Ferrannini, A. Tursi

Key words: chymase; immunohistochemistry; skin biopsies; tryptase.

● CHRONIC idiopathic urticaria (CIU), a reactive skin and mucosa syndrome of unknown cause, is characterized by the persistence of lesions for more than 6 weeks (1). Mast cells (MC) play an important role in the determination of urticaria, as confirmed by many studies

(2). There are two distinct MC subpopulations (3): tryptase-positive, chymase-negative (tMC), and tryptase-positive, chymase-positive (tcMC). Their differentiation occurs as a result of microenvironmental influences.

Ten CIU patients aged 19–52 years (six women and four men) underwent punch-biopsy of the lesioned skin (LS). The control samples consisted of biopsies of the healthy skin (HS) of the patients and of 10 healthy subjects (HP: two men and eight women; age range, 20–58 years). The patients discontinued antihistamines 48 h before the biopsy.

Tissue sections of 4 µm were immunohistochemically stained with antichymase and antitryptase monoclonal antibodies (Chemicon, USA). Individual stainings were carried out to identify chymase or tryptase alone, as well as serial stainings of the same tissue sections with both monoclonal antibodies. Hematoxylin-eosin staining was used to evaluate the inflammatory infiltrate, and toluidine blue to measure the total number of MCs.

Total MC were counted under light microscopy at $\times 100$. The percentages of tcMC and tMC were also calculated. The data were compared and analyzed by the

Wilcoxon test for independent and paired samples.

When we compared the biopsies of LS of patients with CIU and biopsies of healthy subjects, the differences between the mean values of total MC/mm² (LS: 126.74 ± 28.7 ; HP: 90.33 ± 7.39 ; $P=0.0004$) and tMC/mm² (LS: 30.33 ± 8.54 ; HP: 4.9 ± 1.05 ; $P=0.0001$) were statistically significant, but not those between the values of tcMC/mm² (LS: 96.31 ± 20.52 ; HP: 85.32 ± 7.36 ; $P=0.06$). The differences between the mean values of total MC/mm² and tMC/mm² in comparing the LS and HS biopsies (total MC/mm²: 89.74 ± 7.19 ; tMC/mm²: 5.4 ± 1.08) were also statistically significant ($P=0.003$ and $P=0.002$, respectively), but not those between HP and HS.

The inflammatory infiltrate contained lymphomonocytic elements, granulocytes, neutrophils, and eosinophils in varying amounts and was compatible with that of a late-phase cutaneous reaction.

Although the pathogenesis of urticaria is still unknown, the present study shows that the lesioned skin of IU patients contains an increased number of total MC (particularly tMC) in comparison with the lesion-free skin of the same patients and healthy controls. The recent observations indicating that MCs can produce a considerable number of cytokines suggest that the activation of MC may initiate and sustain the development of the late-phase allergic reaction that we observed, and could influence the chronic inflammatory response. Furthermore, some authors have shown that cytokine products, like proteases, are different in two MC subsets: tcMCs mainly produce IL-4 and in a greater amount than tMCs, whereas only the latter produce IL-5 and IL-6 (4). Our finding that the skin of CIU patients has increased tMC levels leads us to suppose that an increase in the IL-5 and IL-6 proinflammatory cytokines would explain the recruitment and activation of eosinophils, basophils, and T cells and the maintenance of phlogosis.

We think that an underlying factor in CIU is the alteration in MC homeostasis leading to an imbalance in the normal mechanisms of MC inhibition and activation. The difference between our findings and those of Smith et al. (5) could be due to the differences in our patient selection criteria.

In conclusion, on the basis of our own and others' results, the fundamental role of MC in the pathogenesis of CIU has been clearly demonstrated. Further in-depth studies of skin MC and their subpopulations should provide insights into the possibility of using drugs directed against MC subtypes and mediators.

Acknowledgment We thank Dr Fiorenza Zotti for her cooperation.

*Cattedra di Allergologia e Immunologia
Clinica
Padiglione Chini – Policlinico
Piazza Giulio Cesare
70124 Bari
Italy
Tel. 0039 080 5592281
Fax: 0039 080 5478780
E-mail: e.nettis@allergy.uniba.it

Accepted for publication 28 May 2001
Allergy 2001; 56:915
Copyright © Munksgaard 2001
ISSN 0105-4538

References

1. GREAVES MW. Chronic urticaria. *N Engl J Med* 1995;**332**:1767–1772.
2. ROSENSTREICH DL. Chronic urticaria, activated T cells, and mast cell releasability. *J Allergy Clin Immunol* 1986;**78**:1098.
3. IRANI AA, SCHWARTZ LB. Neutral proteases as indicators of human mast cell heterogeneity. In: SCHWARTZ LB, editor. *Neutral proteases of mast cells*. Basel: Karger, 1990:146.
4. BRADDDING P, OKAYAMA Y, CHURCH MK, HOLGATE ST. Heterogeneity of human mast cells based on their cytokine content. *J Immunol* 1995;**155**:297–307.
5. SMITH CH, KEPLY C, SCHWARTZ LB, LEE TH. Mast cell number and phenotype in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1995;**96**:360.