Microscopic Morphology of Different Types of Urticaria

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Objective: To identify possible special histopathologic features of different types of urticaria.

Design: Hematoxylin-eosin- and toluidine blue-stained sections from biopsy specimens of all patients with urticaria seen from 1990 to 1993.

Setting: Inpatient and outpatient services of the Virchow Klinikum, Humboldt University, Berlin, Germany.

Participants: We studied spontaneous or induced wheals of 108 patients with acute, chronic, and physical urticaria who consented to an additional biopsy from uninvolved skin. The controls were 10 normal volunteers with wheals that tested positive on a prick test and who had contralateral normal skin.

Main Outcome Measure: Mast cell numbers in both lesional and nonlesional skin in the upper and lower dermis of biopsy specimens from patients and controls.

Results: Blind evaluations of microscopic sections showed dermal edema and dilated lymphatic and vascular (P<.001 for all, Fisher exact test) capillaries almost exclusively in involved skin. The same held for inflammatory infiltrates, with significantly increased numbers of neutrophils and eosinophils in specimens from patients with acute urticaria and those with delayed pressure urticaria (P<.01 for each). Mast cell numbers were higher in the upper (P<.01) and lower dermis (P<.05) of lesional and uninvolved skin of all patients with urticaria, with a further increase (P<.01) in patients with disease of more than 10 weeks’ duration. Edema and vascular changes were most prominent in the skin of patients with cold urticaria (P<.005) and mononuclear infiltrates were more pronounced in those with cold urticaria, chronic urticaria, and prick test–positive wheals (P<.05 for each) and in the lower dermis of patients with delayed pressure urticaria (P<.001).

Conclusions: In all types of urticaria, mechanisms must be operative that cause an increase of cutaneous mast cells. Distinctive pathological features can be identified in different types of urticaria, although these are not diagnostic.

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Biopsy specimens were taken from lesional and corresponding contralateral uninvolved skin of 108 consenting patients with diverse types of urticaria referred to the Department of Dermatology, Virchow Klinikum, Free University, Berlin, Germany, from 1991 to 1994. Except for patients with acute urticaria who were seen primarily as outpatients, most other patients were hospitalized because of the severity of their disease. Patients not consenting to a biopsy of nonlesional skin were excluded. Biopsy specimens from skin prick tests (mite antigen) and from corresponding contralateral sites (on the arm) were obtained from 10 clinically healthy volunteers for comparison.

Demographic and clinical data of all subjects are summarized in Table 1. None of the patients suffered clinically from urticarial vasculitis, heat urticaria, or solar urticaria, and 6 of the patients with chronic urticaria had concomitant demographitic (3 patients), cholinergic (1 patient), and delayed-pressure (2 patients) urticaria. None had been treated with antihistamines since 3 days or parenteral corticosteroids since 3 weeks before the biopsy.

Biopsy specimens were taken from spontaneous wheals of patients with acute and chronic urticaria, with lesions as fresh as possible, according to the patients’ recollection, being selected. From patients with physical or cholinergic urticaria, provoked lesions, and prick–positive wheals, biopsy specimens were taken 10 to 20 minutes (2 hours for DPU) after their appearance. Sites were anesthetized by circumferential injection of 1% lidocaine, without vasoconstrictive additives, followed by removal with a 4- to 6-mm-diameter punch or by elliptical excision with a scalpel.

Specimens were fixed immediately in 10% aqueous buffered formalin and were then routinely processed, with 2 to 4 sections of 5-µm thickness being stained with either hematoxylin-eosin, 1% aqueous toluidine blue at a pH of 8.9 for 1 minute, or 0.5% aqueous toluidine blue at a pH of 0.5 for 24 hours, the last to allow for the detection of glycosaminoglycans having fewer sulfate groups. Three to 5 sections from each biopsy specimen were examined with each stain at 400-power magnification (high-power field). Adjacent fields were evaluated separately in the upper and lower dermis for the following features:

1. Edema: absent, weak (separation of collagen bundles), or marked (with flattening of rete ridges);
2. Changes of lymphatic vessels: absent, moderate (slight dilatation), or marked (pronounced dilatation);
3. Vascular changes: none, vasodilatation, vasodilatation plus endothelial swelling, or vasculitis (including vascular necrosis, leukocytoclasia, and erythrocyte extravasation);
4. Mononuclear cell infiltrate, classified as follows: 0 (only a few scattered cells), 1 (mild perivascular infiltrate), or 2 (marked, sleeve-like, perivascular infiltrate); and
5. Extravasal neutrophils and eosinophils, as well as tissue mast cells, counting cells in each high-power field.

The results were expressed as the mean±SD in 5 high-power fields (corresponding to 1.41 mm²). In addition, the distribution of the cells was evaluated with regard to adnexal structures. Only cells with an identifiable nucleus were counted. Total mast cell counts include also degranulated cells, which were in turn defined as mast cells with metachromatic granules scattered in the immediate vicinity of the cells. Degranulated cells at the edge of lesions, which are known to be due to a cutting artifact during surgery, were disregarded. Lesions were read in a blind manner by 2 independent observers and yielded at most a 9% deviation of counts.

Several statistical tests were used, as appropriate and indicated in each case, with the advice of mathematicians at the medical statistics department of the Free University, Berlin, and with the help of SPSS (SPSS Inc, Chicago, Ill).

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**Table 1. Demographic and Clinical Data on Patients in Whom Biopsy Specimens of Lesional and Uninvolved Skin Were Studied**

<table>
<thead>
<tr>
<th>Urticaria Diagnosis</th>
<th>No. of Patients</th>
<th>Sex, M/F</th>
<th>Mean Age, y (Range)</th>
<th>Mean Disease Duration, mo (Range)</th>
<th>Associated Atopy, No.†</th>
<th>Increased Serum IgE, No.‡</th>
<th>Mean ESR, mm/h (2 h)</th>
<th>Mean Blood Leukocyte Count, ×10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>20</td>
<td>7/13</td>
<td>44 (18-78)</td>
<td>0.5 (0-1.3)</td>
<td>4</td>
<td>7</td>
<td>48§</td>
<td>9.11</td>
</tr>
<tr>
<td>Chronic</td>
<td>49</td>
<td>19/30</td>
<td>40 (14-72)</td>
<td>48 (2-480)</td>
<td>4</td>
<td>14</td>
<td>22</td>
<td>8.30</td>
</tr>
<tr>
<td>Dermographitic</td>
<td>15</td>
<td>10/5</td>
<td>47 (19-76)</td>
<td>11 (2-24)</td>
<td>2</td>
<td>7</td>
<td>29</td>
<td>8.02</td>
</tr>
<tr>
<td>Cold</td>
<td>10</td>
<td>6/4</td>
<td>39 (14-48)</td>
<td>17 (3-24)</td>
<td>2</td>
<td>1</td>
<td>23</td>
<td>7.54</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>6</td>
<td>4/2</td>
<td>40 (22-68)</td>
<td>59 (2-240)</td>
<td>2</td>
<td>2</td>
<td>17</td>
<td>7.30</td>
</tr>
<tr>
<td>Delayed pressure</td>
<td>8</td>
<td>6/2</td>
<td>38 (21-57)</td>
<td>56 (1-392)</td>
<td>2</td>
<td>2</td>
<td>24</td>
<td>9.14</td>
</tr>
<tr>
<td>All patients</td>
<td>108</td>
<td>52/56</td>
<td>42 (14-78)</td>
<td>30 (0-1-490)</td>
<td>20</td>
<td>33</td>
<td>39</td>
<td>8.64</td>
</tr>
</tbody>
</table>

*§IgE indicates immunoglobulin E; ESR, erythrocyte sedimentation rate; NA, not applicable; and ND, not done.
†Defined by personal and family history and the presence of atopic signs and symptoms.©
‡IgE level higher than 360 µg/L (>150 IU/mL).
§P < .01, χ² test; normal less than 10 mm/h.
¶P < .01, χ² test; normal less than 10 ×10⁹/L.

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To shed further light on the pathological processes involved in different types of urticaria, we analyzed biopsy specimens from wheals and uninvolved skin of a large group of patients with diverse types of urticaria and from prick test–positive wheals of controls for comparison, using conventional histochemistry.
RESULTS

Table 2 summarizes the findings regarding edema and vascular reactions. Changes were almost invariably present in specimens of the upper dermis, but in only 10% of specimens of the lower dermis (not shown). Dilated vascular capillaries were detected in only half of the specimens, primarily in the papillary layer, and in less than 20% of specimens in the lower dermis. When analyzed according to subtypes of urticaria, upper dermal edema and endothelial dilatation were particularly prominent in patients with cold urticaria (Table 3).

<table>
<thead>
<tr>
<th>Biopsy Source</th>
<th>No. of Endothelial Changes</th>
<th>Mast Cell No. per 5 HPF</th>
<th>Mononuclear Cell Infiltrate (No. of Specimens With Grade 1 vs 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper Dermis</td>
<td>Lower Dermis</td>
<td>Upper Dermis</td>
</tr>
<tr>
<td>Acute urticaria</td>
<td>12</td>
<td>6</td>
<td>48.4±16.4</td>
</tr>
<tr>
<td>Chronic urticaria</td>
<td>20</td>
<td>8</td>
<td>59.5±24.8</td>
</tr>
<tr>
<td>Dermograph urticaria</td>
<td>5</td>
<td>0</td>
<td>44.1±17.5</td>
</tr>
<tr>
<td>Cold urticaria</td>
<td>9</td>
<td>3</td>
<td>45.0±10.2</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>3</td>
<td>0</td>
<td>57.5±27.0</td>
</tr>
<tr>
<td>DPU</td>
<td>1</td>
<td>1</td>
<td>52.1±13.9</td>
</tr>
<tr>
<td>Prick test</td>
<td>4</td>
<td>1</td>
<td>27.7±13.1§</td>
</tr>
</tbody>
</table>

*Statistically significant differences occur when compared with all other types of urticaria. HPF indicates high-power fields; DPU, delayed pressure urticaria.

Mast cell numbers were more easily detectable and always 2 to 3 times higher in the lower pH than in the higher pH toluidine blue–stained sections when sections from the same biopsy specimen were compared (P<.0001, Wilcoxon test, Figure 1). No significant sex- or age-related changes were found, and differences could not be established between mast cell counts in normal vs involved skin or when different types of urticaria were compared. Mast cell counts in all urticarial biopsy specimens were always significantly elevated compared with normal skin and prick-test sites of volunteers, irrespective of the type of toluidine blue staining (Table 3 and Table 4). Sections containing adnexal structures, particularly sebaceous glands, always had higher mast cell counts, particularly in the lower dermis (P<.001, χ² test). The same held for biopsy specimens from the trunk and thigh compared with the arms (P<.01, Student t test), but the increase of mast cell numbers in urticarial biopsy specimens from the arms vs those from control patients remained significant (P<.05, Fisher exact test). Although a linear correlation between disease duration and mast cell counts was not found (Spearman rank correlation), a statistically significant increase of mast cell numbers was detected when patients suffering from urticaria for more than 10 weeks were compared (P<.01, χ² test).

In all specimens, more and smaller mast cells were found in the upper dermis, with increases being more pronounced in this compartment, although mast cell numbers in the lower dermis of these specimens were also significantly increased (P<.001, χ² test). Mast cells in the lower dermis were more frequently degranulated (P=.002, Spearman rank correlation), as were cells in urticarial lesions vs nonlesional skin (P<.001, χ² test), particularly in specimens containing higher mast cell numbers (P<.002, Spearman rank correlation). Associations of degranulated mast cells with special types of urticaria were not found, except for dermographic urticaria, where significantly increased numbers of such cells were found in the lower dermis (P<.01, compared with all other urticarias, χ² test).

Table 2. Percentage of Biopsy Specimens From 108 Patients With Urticaria and 10 With Prick Test Reactions Showing Edema and Vessel Changes in Lesional and Uninvolved Skin

<table>
<thead>
<tr>
<th>Biopsy Source</th>
<th>Skin Involvement</th>
<th>Wheal, %</th>
<th>Uninvolved, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper dermal edema†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>6.8‡</td>
<td>97.7</td>
<td></td>
</tr>
<tr>
<td>Weak</td>
<td>82.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Strong</td>
<td>11.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lower dermal edema§</td>
<td>20.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dilated lymphatics†</td>
<td>12.7</td>
<td></td>
<td>87.0</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>78.8</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>8.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Changes, vascular capillaries, upper dermis¶</td>
<td>54.2</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>44.1</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Endothelial swelling</td>
<td>1.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lower dermis¶</td>
<td>17.8</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant differences occur for involved vs uninvolved skin.
†In 4 patients with delayed pressure urticaria (DPU) and in 1 each with chronic, dermographic, cold, and cholinergic urticaria.
‡P<.001.
§P<.0001.
¶In 7 patients with DPU and in 5 with chronic, 2 with cold, and 1 with cholinergic urticaria.
\*P<.01.

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In normal and uninvolved skin, inflammatory cells were extremely rare, but these cells were greatly increased in most types of urticarial lesions (Figure 2), particularly in acute urticaria, and in the lower dermis in DPU. Even prick-test sites showed mild upper and lower dermal infiltrates (Figure 2). Neutrophilic infiltrates in acute urticaria were primarily arranged around adnexal structures and were significantly higher in the upper ($P<.001$) and lower dermal compartments ($P<.05$; Mann-Whitney U test) than in all other types of urticaria. For DPU, this held only for the lower dermis ($P<.001$, Mann-Whitney U test). Compared with other types of wheals, eosinophils were increased in the upper dermis of acute urticaria in a perivascular distribution ($P<.05$) and, in patients with DPU, only in the lower dermis ($P<.001$, Mann-Whitney U test).

Mononuclear cell infiltrates were present in all types of urticaria (Table 3), with significant differences between involved and normal skin ($P<.001$, Wilcoxon test for paired differences). In 20 biopsy specimens from patients with chronic urticaria, the infiltrate consisted of mononuclear cells only. In patients with acute urticaria, mononuclear cells were most prominent, but in the perivascular region, they were always intermingled with infiltrating granulocytes. Mononuclear infiltrates were significantly less intense and frequent at prick test sites ($P<.03$, Mann-Whitney U test). A looser infiltrate was also invariably present in most lesions of DPU and in the upper dermis of those with cold urticaria, except in 1 patient who had massive lesional neutrophilia.

When the different types of infiltrating cells were viewed together (Spearman rank correlation test), significant correlations could be found between the numbers of neutrophils and eosinophils ($P<.0001$) (although no eosinophils were detected in 24 and no neutrophils in 6 biopsy specimens), neutrophils and mononuclear infiltrates ($P=.005$ for the upper and $P=.001$ for the lower dermis), and eosinophils and mononuclear cells in the lower dermis ($P=.001$). Such correlations, however, could not be established between numbers of mast cells and infiltrating cells. Furthermore, correlations between special types of urticaria, the causes of urticaria, clinical features, and laboratory values could not be made, except for a relative leukocytosis and an increased erythrocyte sedimentation rate in patients with acute urticaria (Table 1).
COMMENT

The most striking finding of the present study is the increased number of mast cells in both lesional and uninvolved skin of all types of urticaria studied, including even acute urticaria, with a further significantly increased number of these cells in biopsy specimens of patients with a disease duration of longer than 10 weeks. The low mast cell numbers at prick-test sites and in normal skin are in agreement with almost identical mast cell numbers (25.4 cells per 5 high-power fields) in normal skin in another study done with the same staining technique by independent observers at our clinic.2-3

A 2-fold increase of mast cells in nonlesional skin has been observed before in a study of chronic urticaria using Alcian blue-safranin staining4 and in lesional but not in nonlesional skin of diverse inflammatory dermatoses like atopic eczema, psoriasis, and lichen planus.5-7 In accordance with our findings, more mast cells are found in the upper dermis where the cells are smaller and more numerous and in normal skin.8-10 The 10-fold increase in mast cell counts reported in 1 study of chronic urticaria lesions using Giemsa staining5 is probably due to the additional staining of neutrophils with this method.

The pathomechanisms underlying the increases in mast cells in different types of urticaria are unclear. So far, stem cell factor and nerve growth factor are the only mast cell growth factors unequivocally identified in humans.11,12 These factors, which are produced by resident skin cells, might induce the accumulation and local differentiation of mast cell precursors in the skin, an increased mast cell survival, or an immigration of mast cells from other organs, also with the help of mast cell chemoattractant anaphylatoxins.13-15

In contrast to the increase in mast cells in the entire skin of patients with urticaria, changes such as edema, lymphatic and blood capillary dilatation, and endothelial swelling are almost exclusively confined to lesional skin. The same holds for the infiltration of blood leukocytes, although deposits of the eosinophil proteins (major basic protein and eosinophil cationic protein) have been identified also in uninvolved skin of patients with delayed pressure, chronic, or cholinergic urticaria.16-18 Infiltrates of neutrophils, eosinophils or eosinophil products, activated macrophages, and T-helper lymphocytes have been described before in lesions of chronic and cholinergic urticaria and in DPU, with the last involving primarily the lower dermis.19-22 In about half of our patients with chronic urticaria and also those of Monroe et al.,1 mono-nuclear cells were predominant. It remains to be clarified whether this is due to an increased duration of these lesions before biopsy or to specific pathological features. The scanty infiltrates observed in dermographic, cold, and cholinergic urticaria and in prick-test wheals (Figure 2) may be explained in part by the more fleeting nature of these lesions. A loose and scanty leukocytic and lymphocytic infiltrate has been observed by most other investigators in patients with cholinergic urticaria2 and those with cold urticaria,23-26 although pronounced individual variations seem to prevail, in agreement with our observation of massive neutrophil infiltrates in 1 of our patients with cold urticaria.

Thus, the aim of this study—to identify distinct histopathological features in different types of urticaria—has been only partly achieved. This holds particularly for DPU, with its characteristic deep dermal pathological changes, for the prominent dermal edema, the vascular changes, and the previously reported platelet infiltrates27 in cold urticaria and for the scanty upper dermal infiltrate in cholinergic and dermographic urticaria. Acute urticaria differs from all other types of urticaria by the more intense leukocytic infiltrate and the associated increased erythrocyte sedimentation rate and leukocytosis. Because of the wide variations of these features in the individual lesions, none of them can be viewed as diagnostic for any type of urticaria. The increased number of mast cells in lesional and nonlesional skin in all types of urticaria suggests, however, that factors enhancing mast cell development and chemotaxis are a common feature of all these disorders.

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