ORIGINAL ARTICLE

Neutrophilic Urticaria or Urticaria With Predominantly Neutrophilic Inflammatory Infiltrate: Study of Its Clinical and Histopathologic Characteristics and Its Possible Association With Rheumatic Disease

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KEYWORDS
Urticaria;
Neutrophilic urticaria;
Urticaria-vasculitis;
Immune disease

Abstract
Introduction: Neutrophilic urticaria, described by Winkelmann in 1985, has yet to be completely defined and its clinical significance is poorly understood. Nevertheless, recent publications suggest that it could be a marker for rheumatic disease. The primary objective of this study was to compare the prevalence of rheumatic disease in 2 groups of patients with urticaria: those with conventional urticaria (non-neutrophilic inflammatory infiltrate) and those with neutrophilic urticaria.

Material and methods: We retrospectively reviewed all biopsy samples taken from urticarial lesions in our hospital between January 1, 1999 and June 28, 2009. Urticaria was classified according to predefined morphologic and histopathologic patterns. We compared the clinical and histologic characteristics of neutrophilic urticaria with those of conventional urticarias in the 84 patients included.

Results: Of the 84 patients, 57.1% had neutrophilic urticaria. We did not find significant differences between the percentages of patients with rheumatic disease between the neutrophilic and nonneutrophilic urticaria groups. In patients with acute urticaria, we found a significantly higher proportion of samples with histopathologic signs of neutrophilic urticaria as opposed to conventional histopathology. Patients with neutrophilic urticaria also had higher white blood cell counts.


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Conclusions: The percentage of samples with neutrophilic urticaria in this series (57.1%) is higher than the percentages reported in the literature, possibly because we tended to biopsy recent lesions. We highlight that the presence of neutrophils in the biopsies of urticaria is a common finding and does not appear to be associated with other diseases.

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PALABRAS CLAVE
Urticaria; Urticaria neurofilica; Urticaria-vasculitis; Enfermedad inmunológica

Urticaria con infiltrado inflamatorio de predominio neutrofilico o urticaria neurofilica. Estudio de sus características clínicas e histopatológicas y de su posible asociación con enfermedad reumatológica

Resumen
Introducción: La urticaria neurofilica (UN), descrita por Winkelmann en 1985, es una entidad que no está aún completamente definida y de una relevancia clínica desconocida. No obstante, ha sido considerada en la literatura reciente como marcador de enfermedad reumatológica. El objetivo principal de nuestro estudio es comparar la proporción de enfermedad reumatológica en urticarias con infiltrado predominantemente neutrofilico (UN) respecto a la encontrada en urticarias con infiltrado predominantemente no neutrofilico o convencionales.

Material y métodos: De manera retrospectiva hemos revisado todas las urticarias biopsiadas en nuestro centro entre el 1 de enero de 1999 y el 28 de junio de 2009. Las hemos englobado en varios patrones morfológicos histopatológicos definidos. En los 84 pacientes incluidos hemos comparado las características clínicas e histológicas de las UN con las de las urticarias con infiltrados predominantemente no neutrofilicos o convencionales.

Resultados: De nuestros 84 pacientes un 57,1% padecían UN. No hemos encontrado diferencias significativas en cuanto a la proporción de enfermedad reumatológica en las UN respecto a las convencionales. Sí hemos encontrado diferencias estadísticamente significativas respecto a la proporción de urticarias agudas con histopatología de UN en relación con aquellas con histopatología convencional, así como un mayor recuento de leucocitos en la UN.

Conclusiones: En nuestra serie la proporción de UN encontradas (57,1%) es mayor que la descrita en la literatura, dato que puede deberse a nuestra tendencia a biopsiar lesiones recientes. Como conclusión de nuestro estudio cabe resaltar que la presencia de neutrófilos en las biopsias de urticaria es un hecho frecuente que no parece asociarse a otras comorbididades.

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Introduction

Urticaria and angioedema affect at least 20% of the population1 and can be classified according to their clinical characteristics, triggers, or associations with various diseases.2-4,7

The characteristic lesion of urticaria is the wheal, an edematous pink to red plaque with a pale center. Wheals vary in size, are evanescent, and can coalesce into larger round or archiform lesions.2

The classic histopathologic descriptions of urticaria note the presence of dermal edema, vasodilation, and a perivascular infiltrate of mononuclear cells. The infiltrate consists mainly of lymphocytes, together with neutrophils and eosinophils in varying numbers, usually arranged between the dermal collagen bundles.1,3 To date, however, histopathologic descriptions have varied considerably, owing to the small number of cases that have included histopathology and to the difficulty of establishing the duration of the biopsied lesions; other confounding factors may be involved as well.6

The presence of neutrophils in biopsy specimens of urticarial lesions was first described in Dermatopathology, a 1967 textbook by Montgomery and coauthors, and later by Jones et al in a 1983 article in the British Journal of Dermatology (cited in Winkelmann and Reizer). As early as 1985 Peters and Winkelmann9 posited the existence of a distinct diagnostic entity they called neutrophilic urticaria, characterized by the appearance of wheals in which histology showed neutrophils in the dermal venules and venular walls and no sign of leukocytoclasia, hemorrhage, or fibrinoid necrosis. In Winkelmann and Reizer’s8 subsequent retrospective study, they found a diffuse dermal neutrophilic infiltrate in 23 (8.7%) cases and the presence of neutrophils lining or invading the venular walls in another 19 (7.1%) cases. Thus, neutrophilic infiltrates were found in as many as 15.8% of the 256 cases of chronic urticaria. As a result, the histopathologic concept of neutrophilic urticaria was broadened.

In later histopathologic studies of urticaria, higher numbers of neutrophils were found in the dermis of patients with acute urticaria compared to other types and in the reticular dermis of those with pressure urticaria.6 Furthermore, there seems to be a direct relationship between neutrophil and eosinophil counts.6

When Winkelmann et al.5 initially studied the clinical characteristics and comorbidities of 8 patients, no conclusive data emerged with respect to abnormalities in complete blood counts or proteins; nor were there patterns with respect to indicators of autoimmune disease. More recent articles have suggested that urticaria with a neutrophilic infiltrate, or neutrophilic urticaria, might be characterized
by shorter flare-ups and by an increase in acute phase reac-
tants. Interleukin-3 and tumor necrosis factor-α seem to be
implicated in the pathogenesis of this condition, although
few studies have focused on how its characteristics differ
from those of urticaria with an infiltrate that is not neu-
rophic.

More recently, in 2009, Kieffer et al. defined a subtype
of neutrophilic urticaria characterized by nodenomatous
lesions lasting up to 48 hours. The distribution of the infla-
trate and the scant evidence of edema, however, led the
authors to consider this subtype to be more similar to acute
neutrophilic dermatosis. The authors identified 9 patients
with this type of urticaria, which they termed neutrophilic
urticarial dermatitis. These patients had interstitial infla-
trates of neutrophils distributed either individually or
arranged linearly; no vascular damage was observed. The
authors concluded that this subtype may be particularly
associated with rheumatic disease.

The histopathologic differential diagnosis of neutrophilic
urticaria requires main consideration of urticarial vas-
culitis. In theory, they can be distinguished because of
the presence of vascular damage in urticarial vasculitis as
evidenced by areas of postcapillary fibrinoid necrosis (in
venules). Nonetheless, rigorous diagnostic criteria have
ever been applied in most studies of urticarial vasculitis,
and in a published series of patients with this disease, fib-
rin deposition was detected in samples from only 9.9% of
patients, many of whom presented a neutrophilic infiltrate
with only slight or no vascular abnormalities. Additionally,
in some published cases of hypocomplementemcent urticar-
ial vasculitis, clinical features and histologic findings in
the urticarial lesions completely overlapped with those of
neutrophilic urticaria. In a prospective study of lesions
clinically suggestive of urticarial vasculitis, it was observed
that there was in fact no vasculitis in the majority of
cases and that a finding of a predominance of polymor-
phonuclear cells on histology was associated with the
presence of fibrin, leukocytoclasia, low complement lev-
els, and anemia. The problem of the overlap between
the 2 diagnoses was pointed out by Winkelmann et al. in
their initial description of neutrophilic urticaria, in which
they stated that its peculiar histopathology might be sug-
gestive of an underlying vasculitis. This hypothesis was
not subsequently explored, however. To complicate mat-
ters further, the true incidence of leukocytoclastic vasculitis
is unknown; nor do we understand its prognostic signifi-
cance in other types of urticaria, such as solar or cold
urticaria.

In short, neutrophilic urticaria is a clinical entity that
partially overlaps with urticarial vasculitis. Much about the
condition remains poorly understood, including its true inci-
dence and its association with a higher incidence of systemic
conditions, particularly of rheumatic disease.

The primary objective of our study was to compare
the prevalence of rheumatic disease in 2 groups of patients:
those with neutrophilic urticaria (defined as urticaria with a
neutrophilic infiltrate) and those with urticaria with a lymph-
cytic infiltrate that is not predominantly neutrophilic.

Our secondary objectives were to compare the epidemi-
ologic and histopathologic data for neutrophilic urticaria to
all other urticarias that do not fall into that category, as well
as to findings previously described in the literature.

### Material and Methods

We carried out a descriptive, retrospective study using the
database of our hospital’s pathology department for the
period between January 1, 1999 and June 28, 2009 to locate
the cases of urticaria for which the results of skin lesion
biopsies were available.

Our inclusion and exclusion criteria are shown in Table 1.

We studied 84 patients for whom we had complete access
to both clinical and histopathologic data and in whom we
could rule out the possibility of other diseases.

### Histopathology

Biopsy specimens were fixed in 10% buffered formaldehyde
for at least 24 hours and were routinely processed into 5-µm
sections and stained with hematoxylin-eosin. Each specimen
was examined at different magnifications (up to ×400) and
evaluated independently by 2 specialists, a pathologist and
a dermatologist (J.F.F. and M.L.V.). Any disagreements
were settled with the help of another dermatologist (J.S.P.).
The histopathologic aspects analyzed in each case are shown in
Table 2.

The biopsy that was most representative of the findings
for each was classified into one of the following groups:

1. Conventional urticaria with an infiltrate that was not neu-
   trophilic (control group)
2. Urticaria with a neutrophilic inflammatory infiltrate. This
group consists of several subtypes: a) diffuse dermal
   neutrophilia, b) neutrophilic venulitis, c) mixed (diffuse
dermal neutrophilia plus neutrophilic venulitis), and d)
   urticaria in which the neutrophils were mainly intravas-
   cular.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Inclusion and Exclusion Criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>Cases of neutrophilic urticaria, with histopathologic confirmation of a predominantly neutrophilic infiltrate</td>
<td>Cases in which medical history or histopathologic preparations were not available for study</td>
</tr>
<tr>
<td>Cases of urticaria with an infiltrate that was not predominantly neutrophilic, on histopathology</td>
<td>Patients who were pregnant or breastfeeding at the time of biopsy</td>
</tr>
<tr>
<td></td>
<td>Cases with another histopathologic diagnosis other than urticaria</td>
</tr>
<tr>
<td></td>
<td>(Excluded were cases of bullous pemphigoid, papular urticaria, and neutrophilic dermatoses that were diagnosed according to their accepted diagnostic, clinical, and disease progression criteria. We also excluded clear cases of leukocytoclastic vasculitis with fibrinoid necrosis.)</td>
</tr>
</tbody>
</table>
Table 2  Histopathologic Features Analyzed.

<table>
<thead>
<tr>
<th>Histopathologic Variable</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of edema</td>
<td>Mild, mild to moderate, moderate, moderate to severe, very severe</td>
</tr>
<tr>
<td>Intensity of the inflammatory infiltrate</td>
<td>Superficial perivascular, superficial and deep perivascular, interstitial None, vasodilation, infiltration of the vessel wall without structural damage, infiltration of the vessel wall with structural damage</td>
</tr>
<tr>
<td>Leukocytoclasis</td>
<td>Absent or present</td>
</tr>
<tr>
<td>Predominant distribution of the infiltrate</td>
<td>Normal epidermis, severe edema in the dermis, interstitial infiltrate, dilated blood vessels (hematoxylin-eosin, original magnification ×100).</td>
</tr>
<tr>
<td>Vascular findings</td>
<td>Normal epidermis, severe edema in the dermis, interstitial infiltrate, dilated blood vessels (hematoxylin-eosin, original magnification ×100).</td>
</tr>
<tr>
<td>Dermatitis at the dermal-epidermal junction</td>
<td>Normal epidermis, severe edema in the dermis, interstitial infiltrate, dilated blood vessels (hematoxylin-eosin, original magnification ×100).</td>
</tr>
</tbody>
</table>

The definitions used for each of these groups and subgroups are specified in Table 3 and are illustrated with prototypical examples (Figs. 1–4).

Clinical History

The following information was collected from patients’ medical histories: age, sex, personal history, smoking history, long-term medication, date of first visit, time since onset of disease, frequency and site of flare-ups, (type of lesion, duration, presence or absence of residual lesion after resolution, and symptoms), associated systemic symptoms, hemoglobin values, total white blood cell and differential counts, blood sugar, transaminase levels, erythrocyte sedimentation rate, presence of antibodies, complement abnormalities, parasites in stool, and serum levels of IgE. Examples of our patients’ lesions are shown in Fig. 5.

![Image](image1.png)

Figure 1  Conventional urticaria with an infiltrate that was not neutrophilic: normal epidermis, dermis with edema, mild to moderate perivascular lymphocytic infiltrates, vasodilation (hematoxylin-eosin, original magnification ×100).

Statistical analysis of the data was carried out using the SPSS statistical package, version 18. Statistical significance testing was performed using G-Stat software, version 2.0.

Results

Patients

Of the 84 patients studied, 58.3% were women. Mean age at the time of biopsy was 46.49 years (range, 12–79 years).

![Image](image2.png)

Figure 2  Interstitial dermal neutrophilia: normal epidermis, severe edema in the dermis, interstitial infiltrate, dilated blood vessels (hematoxylin-eosin, original magnification ×100).

![Image](image3.png)

Figure 3  Neutrophilic venulitis. A, normal epidermis and dermis, inflammatory infiltrate in the vessel wall (hematoxylin-eosin, original magnification ×40). B, presence of polymorphonuclear neutrophils and eosinophils in a vessel wall (hematoxylin-eosin, original magnification ×200).
Neutrophilic Urticaria: Characteristics and Its Possible Association With Rheumatic Disease

Table 3  Histopathologic Definitions of the Different Types of Urticaria in the Study.

<table>
<thead>
<tr>
<th>Type</th>
<th>Histologic Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria with an infiltrate that is not neutrophilic</td>
<td>Presence of edema and an inflammatory infiltrate of variable intensity, formed mostly by lymphocytes and/or eosinophilic polymorphonuclear leukocytes in varying proportions</td>
</tr>
<tr>
<td>Neutrophilic urticaria (4 subtypes)</td>
<td></td>
</tr>
<tr>
<td>Interstitial or diffuse dermal neutrophilia</td>
<td>Presence of a significant number of neutrophils(^a) in the interstitium</td>
</tr>
<tr>
<td>Neutrophilic venulitis</td>
<td>Presence of neutrophils in vessel walls with or without structural damage</td>
</tr>
<tr>
<td>Mixed</td>
<td>Presence of characteristics of both neutrophilic venulitis and diffuse dermal neutrophilia in a single histologic section</td>
</tr>
<tr>
<td>Predominance of intravascular neutrophils</td>
<td>Presence of a significant proportion (&gt;40%) of vessels with vasodilation and a predominance (&gt;70%) of neutrophils or a finding of 1 or more medium-sized vessels (venule or arteriole or larger) completely occupied by neutrophils</td>
</tr>
</tbody>
</table>

\(^a\)Significant number of neutrophils was defined as the presence of more than 10 to 15 interstitial neutrophils per visual field at a magnification of \(\times200\), in 2 or more fields, whether adjacent or not, provided they are found in a single section.

The median duration of urticaria flare-ups prior to biopsy was 45 days and 42.9% of the cases were acute, that is, urticaria that had appeared less than 6 weeks before biopsy. Two patients had physical urticaria triggered by exposure to cold. Most of the biopsied lesions were wheals (64.9%) or plaques (22.1%) in a generalized distribution (34.7%). Lesions lasting more than 24 hours were reported by 55% of patients, although only 14.3% had residual lesions. Histopathology of the lesions that had lasted more than 24 hours \((n = 39)\) showed that 56.4% had an infiltrate that was not neutrophilic. In the remaining 17 patients (43.5%) with a neutrophilic infiltrate, inflammation was mainly perivascular in 10 cases (with marked presence of intravascular neutrophils in 7, neutrophilic venulitis in 2, and mixed in 1 case). The most frequent symptoms were pruritus (80%), pain (5.3%), or both (5.3%).

Systemic symptoms associated with flare-ups were present in 51.2% of patients. Of the 84 patients, 81% had no rheumatic disease; in the others, the following conditions were observed: adult-onset Still disease \((n = 3)\), lupus erythematosus \((n = 3; 2\) cases of systemic lupus erythematosus and 1 of chronic discoid lupus\), rheumatoid arthritis \((n = 2)\), fibromyalgia \((n = 2)\), migratory joint pain of unknown origin \((n = 2)\), and overlap syndrome, polyvmyalgia rheumatica, sjögren disease, seronegative arthropathy, and microscopic polyarteritis nodosa \((1\) case each). One patient was diagnosed simultaneously with systemic lupus erythematosus and rheumatoid arthritis.

Blood tests revealed that 23.2% of patients had a slight increase in acute-phase reactants and only 1 patient \((1.2\%)\) had associated monoclonal hypergammaglobulinemia.

**Comparison Between the Two Groups: Neutrophilic Urticaria Compared to Conventional Urticaria With a Non-neutrophilic Infiltrate**

As age and sex distribution was similar in patients with neutrophilic urticaria and those with an infiltrate that was not neutrophilic, the 2 groups can be considered comparable. With respect to the primary objective of our study, we found no significant differences between the 2 groups in the percentage of patients with rheumatic disease in either the global analysis or the analysis by histopathologic subtypes \((Pearson’s \chi^2\) test; \(P = 0.585)\) \((Table 4)\).

![Figure 4](image)  Predominance of polymorphonuclear cells inside the vessel. Mild to moderate vasodilation with lumen completely occupied by neutrophils (hematoxylin-eosin, original magnification \(\times100\)).
predominance of intravascular neutrophils (19%) and diffuse dermal neutrophilia (17.9%). The distribution of subtypes is shown in Fig. 6.

In the cases with an infiltrate that was not neutrophilic, the perivascular distribution was either superficial (75%) or superficial and deep (25%), generally without leukocytoclasia (97.2%). Furthermore, while 45.8% of the biopsies showed an interstitial distribution of the infiltrate in cases of neutrophilic urticaria, this pattern was not seen cases with an infiltrate that was not neutrophilic. This difference was statistically significant (Table 5).

Vascular abnormalities were observed in 66.7% of the patients with neutrophilic urticaria, with damage to vessel walls but no destruction in 43.8% and with destruction in 6.3%. No fibrinoid necrosis was found in any case. In cases with an infiltrate that was not neutrophilic, there was either no vascular damage (63.9%) or only vasodilation (30.6%). The statistical analysis also showed significant differences between the 2 groups with respect to vascular involvement, which was more frequent and more intense in the neutrophilic urticaria group.

No epidermal abnormalities were observed in any of the cases and only 1 patient with neutrophilic urticaria had interface dermatitis with vacuolar degeneration, with no findings suggestive of connective tissue disease.

Table 5 shows the distribution of other dichotomous variables between the 2 groups (compared with the χ² test) and some of the quantitative variables (compared with the t test).

Discussion

The primary objective of our study was to determine whether or not there was a greater prevalence of rheumatic disease among patients with neutrophilic urticaria. However, we failed to find any such association with neutrophilic urticaria in general or with any of its histologic subtypes. According to the literature, the estimated difference in the prevalence of rheumatic disease between patients with neutrophilic urticaria or another type is at least as high as 30% to 50%. The power of our study, with a total of 84 patients, to detect differences not due to chance was approximately 80%.

In our series 14.6% of patients with neutrophilic urticaria and 22.2% of those with conventional urticaria (without such an infiltrate) had rheumatic disease. In contrast, Kieffer et al.11 found rheumatic disease in up to 77.7% of their patients. In their article they defined neutrophilic urticarial dermatosis as marked by the presence of erythematous non-pruritic lesions lasting less than 48 hours and histologically characterized by considerable interstitial and perivascular involvement, with neutrophils distributed between the collagen bundles either individually or in lines. Curiously, although the presence of edema was one of their exclusion criteria, edema could be seen in their microphotographs. After a critical reading of their article, we have come to the conclusion that the entity that we have included in the category of diffuse dermal neutrophilia overlaps, at least histopathologically, with the one they called neutrophilic urticarial dermatosis. Moreover, in 59% of our patients with diffuse dermal neutrophilia, the clinical lesions were not evanescent. Our results, therefore, are not consistent with those of Kieffer et al. and lend support to the earlier hypothesis that there is no association between neutrophilic urticaria and other diseases.5 However, our study is not directly comparable to theirs, as our criteria did not exclude patients with histopathologically edematous lesions or require the presence of recurrent flare-ups.

Apart from mentioning the overlap between neutrophilic urticaria and urticarial vasculitis that we have referred to above, current reviews do not consider neutrophilic urticaria to be a well defined subtype of urticaria.1 We thus had to define the criteria and histopathologic patterns needed to classify the biopsies of the urticarial lesions in our study. The inflammatory infiltrates found in biopsies of urticarial lesions are indications of an underlying dynamic process. In a study of 22 patients with chronic idiopathic urticaria from whom 2 biopsies were obtained (one of a lesion that appeared less than 4 hours earlier and another of one that appeared more than 12 hours earlier), Sabroe et al.19 demonstrated this dynamic process, observing a predominance of polymorphonuclear cells in blood and in vessel walls in the more recent lesions and a tendency towards interstitial distribution in older lesions. In our study we identified a group of patients with neutrophilic infiltrates both in the dermis and in some vessel walls; these results support the theory of the dynamic nature of the inflammatory infiltrate of urticarial wheals.8

In our series 57.1% of patients had a neutrophilic pattern of urticaria. Of these, 17.9% were cases of diffuse dermal neutrophilia. In the series of Winkelmann and Reizer,8 only 15.8% of cases had neutrophilic urticaria and 8.7% of these showed a dermal infiltrate with a diffuse or interstitial distribution. In 26% of their patients they observed a perivascular concentration of neutrophils,8 as we did in the majority of ours. Toppe et al.10 found a predominantly neutrophilic pattern in more cases of clinically acute urticaria (55%) than in chronic urticaria (18%). Neutrophils were found inside vessels or in vessel walls in 29.1% of their biopsies. As mentioned above, the study of Sabroe et al.19 suggested that the distribution depended on the age of the lesion.19

### Table 4 Contingency Table of Presence or Absence of Rheumatic Disease in the Various Histologic Subtypes.

<table>
<thead>
<tr>
<th></th>
<th>Urticaria Without a Neutrophil Infiltrate</th>
<th>Interstitial Dermal Neutrophilia</th>
<th>Neutrophilic Venulitis</th>
<th>Mixed</th>
<th>Predominance of Intravascular Neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without rheumatic disease</td>
<td>28</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>With rheumatic disease</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*The χ² test showed no significant differences between the groups (P = .585).*
Table 5  Comparison of Clinical, Analytical, and Histopathologic Data Between Cases With and Without Neutrophilic Urticaria.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neutrophilic Urticaria</th>
<th>No.</th>
<th>Non-neutrophilic Urticaria</th>
<th>No.</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, women/men</td>
<td>64.6%/35.5%</td>
<td>48</td>
<td>50%/50%</td>
<td>36</td>
<td>.0674</td>
</tr>
<tr>
<td>Type of biopsy: punch/incisional</td>
<td>56.3%/53.7%</td>
<td>48</td>
<td>36.1%/36.9%</td>
<td>36</td>
<td>.1797</td>
</tr>
<tr>
<td>Frequencies of acute urticaria/chronic urticaria</td>
<td>66.5%/41%</td>
<td>40</td>
<td>33.3%/59%</td>
<td>35</td>
<td>.0262(^a)</td>
</tr>
<tr>
<td>Lesion site</td>
<td>Lower limbs, 51.5%</td>
<td>48</td>
<td>Upper limbs, 27.3%</td>
<td>36</td>
<td>.3268</td>
</tr>
<tr>
<td>Age of lesion &gt; 24 hours</td>
<td>31.3%</td>
<td>36</td>
<td>18.2%</td>
<td>28</td>
<td>.0184(^a)</td>
</tr>
<tr>
<td>Residual hyperpigmentation</td>
<td>14.5%</td>
<td>46</td>
<td>13.9%</td>
<td>36</td>
<td>.4225</td>
</tr>
<tr>
<td>Hemoglobin, g/dL(^b)</td>
<td>13.8 (1.97)</td>
<td>40</td>
<td>14.3 (1.23)</td>
<td>27</td>
<td>.8706</td>
</tr>
<tr>
<td>White blood cell count, (\times 10^3/\mu)L(^b)</td>
<td>9998 (3846.2)</td>
<td>40</td>
<td>8231 (2567)</td>
<td>28</td>
<td>.0184(^a)</td>
</tr>
<tr>
<td>Neutrophils, %(^b)</td>
<td>63.48 (16.33)</td>
<td>40</td>
<td>59.32 (12.04)</td>
<td>28</td>
<td>.2624</td>
</tr>
<tr>
<td>Lymphocytes, %(^b)</td>
<td>27.87 (14.08)</td>
<td>40</td>
<td>30.17 (11.63)</td>
<td>28</td>
<td>.4801</td>
</tr>
<tr>
<td>Eosinophils, %(^b)</td>
<td>2.03 (1.67)</td>
<td>40</td>
<td>2.86 (2.06)</td>
<td>28</td>
<td>.0750</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h(^b)</td>
<td>22 (27.8)</td>
<td>21</td>
<td>16.7 (12)</td>
<td>20</td>
<td>.5018</td>
</tr>
<tr>
<td>Signs of autoimmune disease</td>
<td>Present</td>
<td>25</td>
<td>36.4%</td>
<td>13</td>
<td>.7654</td>
</tr>
<tr>
<td></td>
<td>IgE level, μg/mL(^b)</td>
<td>222.8 (272.3)</td>
<td>31</td>
<td>115.32 (117)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Distribution of the infiltrate</td>
<td>Perivascular, superficial, 43.8%</td>
<td>48</td>
<td>75%</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perivascular, superficial + deep, 10.4%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial, 45.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular damage</td>
<td>Absent, 33.3%</td>
<td>48</td>
<td>63.9%</td>
<td>36</td>
<td>.0013(^a)</td>
</tr>
<tr>
<td></td>
<td>Vasodilatation, 22.9%</td>
<td>30.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vessel wall damage, 37.5%</td>
<td>5.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vascular destruction without fibrinoid necrosis, 6.3%</td>
<td>0%</td>
<td></td>
<td></td>
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</tbody>
</table>

\(^a\)For a 95% CI, values of \( P < 0.05 \) were considered to be statistically significant.

\(^b\)Data are means (SD) unless otherwise indicated.

While in our study the exact age of the wheal before biopsy was unknown, our hospital tends to select recent lesions for biopsy and this could account for the higher percentage of neutrophilic urticaria in our series. Furthermore, although our inclusion criteria did not take clinical data into account, the urticarial lesions biopsied in our hospital were those with clinical findings suggestive of neutrophilic vasculitis and, to a lesser extent, clinically atypical cases that raised doubts as to diagnosis or that responded poorly to treatment. Our finding that a neutrophilic pattern was more frequent in patients with chronic urticaria is consistent with the increase in dermal neutrophils found in acute urticaria compared to other types described by Toppe et al.\(^6\)

Winkelmann et al.\(^7\) considered that the rare presence of leukocytoclasia, the absence of fibrinoid necrosis, and the scant presence or total absence of red blood cell extravasation in the histologic sections they reviewed could serve to differentiate cases of neutrophilic urticaria from those of leukocytoclastic vasculitis or urticarial vasculitis. In the light of our histologic findings, however, this possibility seems somewhat doubtful, as we found varying degrees of vascular damage. Dense perivascular infiltrates with leukocytoclasia and, more rarely, small points of fibrinoid necrosis can be found in the biopsies of up to 52% of patients with urticaria.\(^{20}\) Clear vascular damage, with destruction of the vessel walls but without fibrinoid necrosis, was found in only 6.3% of our patients with neutrophilic urticaria. With less rigid criteria for vascular damage, up to 60.4% of those cases could have been considered urticarial vasculitis. In contrast, no vascular abnormalities were found when the infiltrate was not neutrophilic. Our study suggests that the disparity in the frequency of vascular damage found in the various series described in the literature might be due to the inclusion of differing percentages of patients with neutrophilic urticaria.

Blood tests showed only 1 significant difference between the 2 groups: white blood cell counts in peripheral blood were higher in patients with neutrophilic urticaria, a finding described previously.
Figure 5  A, multiple partially confluent wheals with a circinate configuration on the back of a woman with acute urticaria. B, erythematous, edematous plaques that are well-defined, oval in shape, somewhat infiltrated, with no epidermal involvement.

The main limitation of our study, resulting from its retrospective design, was the lack of homogeneity in the clinical and laboratory data and in the duration of follow-up. Consequently, we were unable to analyze some of the data. Moreover, in the absence of reliable information concerning the age of the wheals, we were unable to study possible differences in the composition of the inflammatory infiltrates and their development over time. The lack of this information and of generally accepted criteria for neutrophilic urticaria may explain why we could not rule out the possibility that in some of the cases included in our study the differences found between the 2 groups might be attributable to having biopsied lesions at different points in their development, making it more difficult to interpret the data.

Conclusions

The frequency of a neutrophilic inflammatory infiltrate in biopsy specimens of urticarial lesions is high (57.1%), especially in patients with acute urticaria. None of the different histologic patterns found in neutrophilic urticaria seems to be associated with a greater prevalence of rheumatic disease compared to urticaria with infiltrates that are not neutrophilic.

Neutrophilic urticaria could be a reaction pattern that is intermediate between urticaria with an infiltrate that is not neutrophilic and urticarial vasculitis with fibrinoid necrosis. To determine whether neutrophilic urticaria and urticarial vasculitis are 2 different entities, however, would require a prospective study, given the frequent presence of vascular damage in patients with neutrophilic urticaria and its overlap with urticarial vasculitis.

Conflicts of Interest

The authors declare that they have no conflicts of interests.
References