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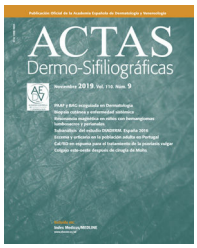

PRACTICAL DERMATOLOGY

# Skin Biopsy in Chronic Urticaria: When and Where and What to Look for?☆

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**KEYWORDS**
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**Abstract** Chronic urticaria is a relatively common condition in dermatology and is usually diagnosed on clinical grounds. Skin biopsy, however, may be indicated in certain cases to confirm diagnosis and rule out other conditions that can cause hive-like rashes. We review histopathologic findings seen in both chronic urticaria and other entities in the differential diagnosis. We then propose an algorithm of indications for skin biopsy in patients with hive-like rashes and suggest possible diagnoses based on the histopathologic findings.


**PALABRAS CLAVE**
Urticaria crónica;
Histopatología;
Algoritmo diagnóstico

## La biopsia cutánea en la urticaria crónica: cuándo realizarla, qué buscar y dónde hacerlo

**Resumen** La urticaria crónica es una entidad relativamente frecuente en la práctica clínica habitual, cuyo diagnóstico se establece de forma clínica. Sin embargo, existen ocasiones en las que está indicado la realización de una biopsia cutánea para confirmar el diagnóstico y diferenciarla de otras patologías que pueden cursar con erupciones urticariformes. En este trabajo revisamos los hallazgos histopatológicos que podemos encontrar tanto en la urticaria crónica como en las patologías que plantean un diagnóstico diferencial. En base a ello, proponemos un algoritmo donde se recogen las indicaciones para realizar una biopsia cutánea y la orientación del diagnóstico en función de los hallazgos histopatológicos que encontremos en la misma.


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## Introduction

Urticaria is an entity defined by the appearance of pruritic wheals, which resolve in less than 24 hours. It is classified as acute or chronic; chronic urticaria is that which lasts more than 6 weeks. The prevalence of chronic urticaria (CU) is estimated to be between 0.5% and 4%.[1,2]

Although diagnosis is usually clinical, disagreement exists among dermatologists. An example of this is the study presented by Ijaz et al at the Global Urticaria Forum held in Berlin in 2016 (results not published). Of 200 patients referred with a diagnosis of CU to a tertiary hospital, a high percentage had a different final diagnosis (eczema, urticarial vasculitis, autoinflammatory syndrome, etc.). Laboratory tests, skin biopsy, or both, may therefore sometimes be indicated. The histologic findings traditionally reported in urticaria are edema in the dermis, vasodilation, and a predominantly mononuclear perivascular dermal infiltrate with a variable number of eosinophils and neutrophils.[3–5] This histologic pattern is very common when urticaria-like lesions are biopsied. It is the presence or absence of other histologic findings that help to establish a correct diagnosis.

## Biopsy Indications. When to Perform a Skin Biopsy

When we encounter a patient with urticaria-like lesions that last more than 6 weeks, the diagnosis is most likely to be chronic urticaria. However, certain clinical and analytical data should alert us to the possibility of other diseases. The clinical data are absence of pruritus, general symptoms, duration of individual lesions of more than 48 hours, and a violaceous halo or residual hyperpigmentation. In blood tests, we should take special note of the erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), proteinogram, and complement factors. The absence of response to supposedly correct treatment is also an alarm sign. In all these situations, we should consider a skin biopsy (Table 1).

The differential diagnosis tends to include drug reactions, bullous pemphigoid (in the urticarial prodromal phase), and urticarial dermatitis. Although less common, neutrophilic urticarial dermatosis (NUD), autoinflammatory syndromes, and urticarial vasculitis should be ruled out.

Table 2 shows the clinical characteristics to consider in the differential diagnosis of chronic urticaria.

**Table 1** Indications for Skin Biopsy in Patients with Urticaria-Like Lesions.

| |
|---|
| Nonpruritic lesions |
| Individual lesions that are not clearly evanescent (lasting more than 24-48 h) |
| Hyperpigmentation or residual violaceous halo |
| Pain or burning sensation rather than pruritus |
| Recurring systemic symptoms: fever, polyarthralgia, etc. |
| Recurring abnormal blood-test results: elevated CRP, ESR, leukocytes, hypocomplementemia, positive ANA, abnormal proteinogram, etc. |
| Lack of response to non-sedating antihistamines at high doses (x4) |

Abbreviations: ANA indicates antinuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

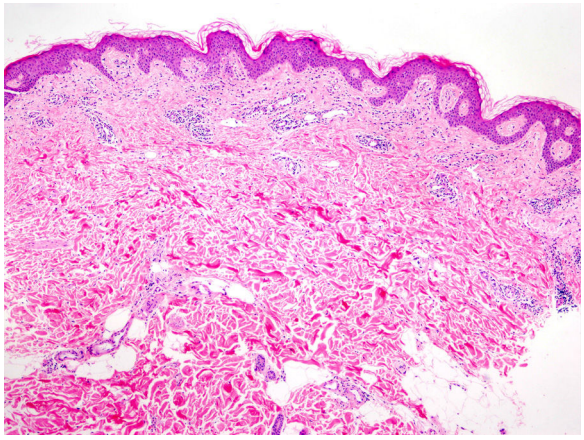

**Figure 1** Spontaneous chronic urticaria (hematoxylin–eosin, ×4). A normal epidermis and a superficial perivascular lymphohistiocytic infiltrate can be seen, together with edema in the papillary dermis.

## Histologic Findings and Diagnostic Guidance

### Histology of Spontaneous Chronic Urticaria

The histology of chronic urticaria (CU) is characterized by mild edema in the papillary dermis with a superficial perivascular infiltrate composed of lymphocytes, eosinophils, and neutrophils (Fig. 1).[6] The infiltrate may sometimes also be interstitial and deep, expanding the classical description, as shown by Barzilai et al.[7]

Attempts have been made to establish the existence of different histologic patterns depending on the predominant cell type in the inflammatory infiltrate and to correlate them to clinical patterns of urticaria. The presence of a predominantly lymphocytic or neutrophilic (*neutrophilic urticaria*) infiltrate has not been shown to affect the clinical presentation.[7]

Barzilai et al[7] analyzed 58 biopsies of patients with urticaria. Lymphocytes were the predominant cell in 26% of biopsies, neutrophils in 21%, and eosinophils in 4%. In the other cases (41%), the infiltrate was mixed. In this study, a predominantly neutrophilic infiltrate was linked to a less easily treatable variant of urticaria.

Marques et al[8] classified the infiltrates of 41 patients with CU into predominantly eosinophilic (46.3%), neutrophilic (24%), and mixed (27%). Those authors found a link between the predominance of eosinophils and higher severity scores, with no effect on treatment response.

Some studies have shown an increase in mast cells.[3,9] However, Smith et al[10] and, more recently, Fujisawa et al[11] found a normal number of masts cells but with increased activity.

Extravasation of red blood cells is a finding in as much as 50% of patients[7] and may manifest clinically with a purplish tone and be confused with urticarial vasculitis.

**Table 2** Differential Diagnosis of Chronic Urticaria.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Associated diseases | No | CAPS, SS, ASD, JIA | CAPS, SS, ASD, SLE | HUVS, SLE, RA, MCTD | AD, CD, CU, BP, DH | No | BP, LIBD, DH, ABE | No |
| Blood-test anomalies | No | Elevated CRP, ESR Neutrophilic leukocytosis | Elevated CRP, ESR Neutrophilic leukocytosis | Low C3, C4; elevated ANA, ESR; anti-CCP, RF Levels of anti-C1q and anti-C1q antibodies | No | Rare | Basement membrane, anti-transglutaminase antibodies | Peripheral eosinophilia (>1500/μL) |
| Systemic signs and symptoms | Rare | Fever, joint pain, general discomfort | Fever, joint pain, myalgia, abdominal pain | Fever, joint pain, abdominal pain | Rare | Rare | Rare | Rare (mild) |
| Angioedema | Possible | Very rare | Rare | Very rare | Rare | No | No | No |
| Residual hyper-pigmentation | No | No | No | Yes Residual purpura | No | Sometimes, with fine desquamation | No | Yes |
| Associated symptoms | Intense pruritus | Burning (pruritus absent or minimal) | Pruritus absent or mild | Pain or burning | Pruritus | Pruritus | Pruritus | Pruritus or burning |

Table 2 (*Continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Associated diseases | No | CAPS, SS, ASD, JIA | CAPS, SS, ASD, SLE | HUVS, SLE, RA, MCTD | AD, CD, CU, BP, DH | No | BP, LIBD, DH, ABE | No |
| Distribution | Bilateral and asymmetric Anywhere | Bilateral and symmetric Torso and extremities | Torso > extremities | Torso and base of extremities | Bilateral and symmetric Torso > upper extremities > lower extremities | Bilateral and symmetric Torso and base of extremities Axillary/inguinal folds | Symmetric Torso and flexor surface of extremities | More frequent on extremities (also on torso) |
| Types of lesions | Edematous papules/plaques | From flat to infiltrated and stable wheals | Barely palpable macules or plaques | Erythematous-violaceous plaques | Urticarial plaques + eczematous lesions | Convergent papules and plaques | Edematous papules and plaques Blisters | Recurring cellulitis-like or EM-like erythematous urticarial plaques |
| Duration of lesions | Minutes to hours | 12-24 h | 24-48 h | >24 h | >24 h | >48 h | >48 h | >48 h |
| | Urticaria | Autoinflammatory syndromes | Neutrophilic urticarial dermatosis (NUD) | Urticarial vasculitis | Urticarial dermatitis | Drug reactions | Autoimmune blistering disease | Wells syndrome |

Abbreviations: ABE indicates acquired bullous epidermolysis; AD, atopic dermatitis; ANA, antinuclear antibodies; Anti-C1q, anti-C1q antibodies; Anti-CCP, anti-cyclic citrullinated peptides; ASD, adult Still disease; BP, bullous pemphigoid; C1q, complement component 1q; C3, complement factor 3; C4, complement factor 4; CAPS, cryopyrin-associated periodic syndrome; CD, contact dermatitis; CRP, C-reactive protein; CU, chronic urticaria; DH, dermatitis herpetiformis; EM-like, erythema multiforme-like; ESR, erythrocyte sedimentation rate; HUVS, hypocomplementemic urticarial vascular syndrome; JIA, juvenile idiopathic arthritis; LIBD, linear IgA bullous dermatosis; MCTD, mixed connective-tissue disease; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SS, Schnitzler syndrome.

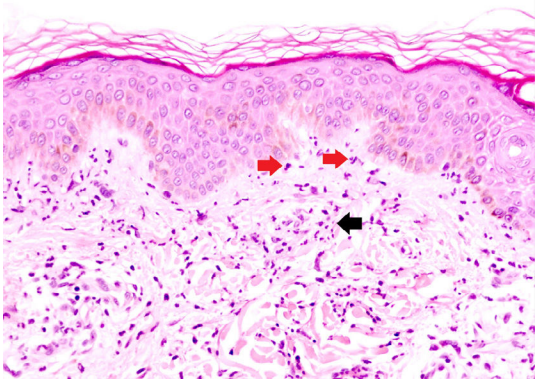

**Figure 2** Neutrophilic urticarial dermatosis (hematoxylin–eosin, ×40) A superficial, perivascular, interstitial infiltrate and infiltrate in the dermoepidermal junction with predominance of neutrophils (red arrows) can be seen. Leukocytoclasia can also be seen (black arrow). No thrombi, necrosis or edema in the vascular walls are observed. The findings were compatible with neutrophilic urticarial dermatosis and the patient was finally diagnosed with Sjögren syndrome.

Direct immunofluorescence in CU is usually negative. Deposits of complement factor 3 (C3) or fibrinogen have occasionally been found on the vessels of the superficial dermis, with no clinical or laboratory findings compatible with vasculitis.[7]

## Key Diagnostic Signs

After performing the biopsy, we should look at the following aspects to guide our diagnosis: the nature of the inflammatory infiltrate, the tissue-reaction pattern, and direct immunofluorescence (DIF). We believe that performing a skin biopsy for DIF is highly recommendable, as it helps us with the diagnosis of many of the entities in the differential diagnosis of CU.

### Nature of the Inflammatory Infiltrate

When we observe a marked neutrophil presence in the dermis, we should rule out NUD. Key diagnostic signs include leukocytoclastic debris without vasculitis, neutrophilic epitheliotropism, and neutrophils arranged along a line in the papillary dermis.

NUD was described by Kieffer et al in 2008[12] and is characterized clinically by an urticarial eruption and histologically by neutrophilic dermatosis. This entity should not be confused with the histologic term *neutrophilic urticaria*, coined by Peters and Winkelmann in 1985 to describe urticaria with a predominantly neutrophilic infiltrate.[13] In 2016, Broekaert et al defined neutrophilic epitheliotropism to differentiate between the 2 entities histologically; this is important because the former has been shown to be linked to systemic diseases,[12] whereas neutrophilic urticaria has not.[14] Neutrophilic epitheliotropism is defined by the presence of intraepidermal neutrophils, especially inside the epithelium of the eccrine sweat glands, hair follicles, and sebaceous glands. It is also common to find them in the periadnexal dermis and grouped along the dermoepidermal junction (Fig. 2).

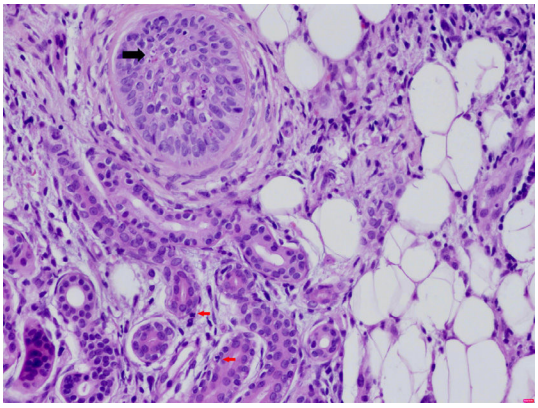

**Figure 3** Neutrophilic urticarial dermatosis (hematoxylin–eosin, ×40). A lymphohistiocytic periadnexal infiltrate can be seen, with neutrophils in the eccrine sweat glands (red arrows) and in the epithelium of the hair follicle (black arrow), together with nuclear debris. The patient was diagnosed with familial Mediterranean fever.

Location on the dermoepidermal junction, however, is less specific and may also occur in neutrophilic urticaria, neutrophilic drug reactions, and systemic lupus erythematosus (SLE) with neutrophil expression.

Systemic diseases associated with NUD include hereditary autoinflammatory syndromes, Schnitzler syndrome, adult Still disease, juvenile idiopathic arthritis, and SLE. The frequent association of NUD with autoinflammatory diseases has given rise to debate regarding whether it is a sign of dysfunction of the innate immune system. Histology of autoinflammatory syndromes typically reveals a dense interstitial and perivascular infiltrate rich in neutrophils (Fig. 3).

In NUD, vasculitis is, by definition, absent. Extravasation of red blood cells or leukocytoclastic debris in dense neutrophilic infiltrates may be observed, but fibrinoid necrosis is never found. Lymphocytes, eosinophils, or both, may also be observed. The epidermis is usually intact and edema in the superficial dermis is absent.[15] Increased mucin may be found in the dermis in cases of NUD associated with SLE.

An infiltrate with eosinophils should lead to including bullous pemphigoid,[16] drug reaction,[17] urticarial dermatitis,[18] and, more rarely, Wells syndrome[19] in the differential diagnosis. Key histologic diagnostic signs include eosinophilic spongiosis, eosinophils in the dermoepidermal junction, and flame figures.

Wells syndrome initially presents as a superficial and deep interstitial dermatitis with a mixed infiltrate of eosinophils and lymphocytes, which may be accompanied by subepidermal edema. If a biopsy is performed at a later stage (between weeks 1 and 3), it is possible to find flame figures, which are characteristic but not definitive of this disease.[19]

## Tissue Reaction Pattern

The presence of other histologic patterns accompanying the superficial perivascular dermatitis characteristic of urticaria may provide us with the key to establishing a diagnosis. The histologic patterns we seek are interface dermatitis, a spongiotic pattern, and a vasculopathic pattern.

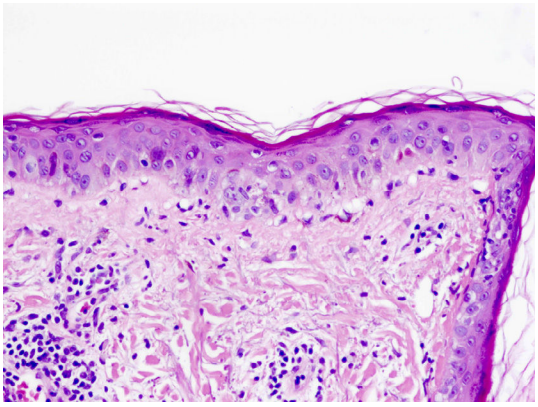

**Figure 4** Interface dermatitis (hematoxylin–eosin, ×40). Epidermal atrophy can be observed, together with vacuolar interface dermatitis with necrotic keratinocytes and a predominantly lymphocytic superficial perivascular infiltrate. This biopsy is from a patient with cutaneous lupus erythematosus.

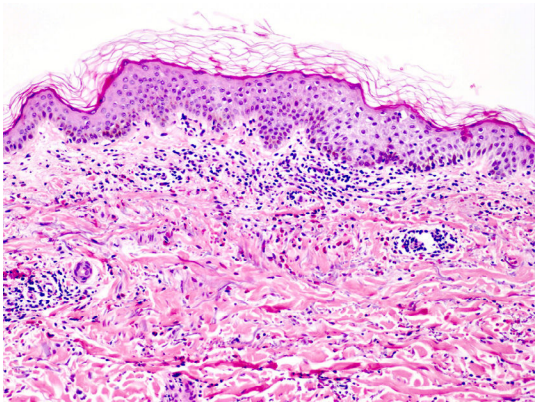

**Figure 5** Urticarial dermatitis (hematoxylin–eosin, ×10). Epidermal spongiosis, discrete exocytosis together with a superficial and interstitial perivascular infiltrate composed principally of lymphocytes with isolated eosinophils. No thrombi, necrosis or edema in the vascular walls are observed.

## Interface Dermatitis

A potential histopathological finding in many diseases in the differential diagnosis with urticaria but not found in urticaria itself is interface dermatitis, which is characterized by vacuolar damage to the basal layer and apoptotic keratinocytes in the epidermis. The entities that can mimic urticaria and present this pattern are drug reactions and cutaneous lupus erythematosus.

Interface dermatitis to a varying degree is typical in drug reactions,[17] together with a superficial perivascular mononuclear infiltrate with some eosinophils. Interface dermatitis is characterized by the accumulation of lymphocytes in the dermoepidermal junction, together with hydropic degeneration of the keratinocytes in the basal layer. Exocytosis may be present.

The histologic spectrum of drug reactions is extremely broad, and several superimposed patterns often appear.[20]

Subacute cutaneous lupus erythematosus reveals vacuolar interface dermatitis together with a superficial and deep perivascular lymphocytic infiltrate (Fig. 4).[21,22] The periadnexal distribution of this infiltrate is also characteristic. Thickening of the basement membrane may appear at a later stage.[23] Increased mucin among the collagen fibers helps with the diagnosis of lupus erythematosus tumidus, a variant of cutaneous lupus erythematosus, in which vacuolar degeneration of the basal layer of the epidermis is usually absent.[24]

## Spongiotic Pattern

Spongiosis is not observed in CU, unless an associated contact dermatitis exists due to the application of topical products. The main characteristic of the spongiotic pattern is intraepidermal intercellular edema (spongiosis). This pattern can be seen in urticarial dermatitis (UD), bullous pemphigoid (BP), and in drug reactions.

UD is a term initially used in histopathology, defined in 2006 by Kossard et al,[25] and later adopted as a clinical entity to describe patients with urticarial lesions lasting more than 24 hours, in association with eczematous lesions. Of the patients who present with a clinical picture compatible with UD, between 53.8% and 75% present histologic findings consistent with UD.[18,25] On the other hand, only 33.8% of patients with histologic criteria for UD have a prior clinical diagnosis of UD.[25] Of the patients who present initially compatible clinical signs and symptoms, many end up with a definitive diagnosis of dermatitis (16%-26.4%), urticaria (8.1%-10%), drug reactions (6%-23.6%), atopic dermatitis (3%), contact dermatitis (3%), BP or dermatitis herpetiformis (4%-31.8%), or urticarial vasculitis (16.2%).[18,25] UD appears to represent a reaction pattern that can be seen in several skin conditions and a diagnostic evaluation is required to establish a clinical-pathologic correlation. A biopsy of an urticaria-like lesion of a patient with UD will reveal spongiosis in the epidermis with a normal stratum corneum and a lymphocytic infiltrate with a variable number of eosinophils in the papillary dermis (Fig. 5).[18,25] Subepidermal edema may also be present, as occurs in urticaria.

The spongiotic pattern may also appear in drug reactions (less characteristically than interface dermatitis) and in BP. The presence of eosinophils is also characteristic of both entities.

The histologic findings of BP are not definitive but are highly suggestive. In early pre-bullous phases (urticarial phase), subepidermal clefts, eosinophilic spongiosis, and/or an eosinophilic infiltrate in the superficial dermis, covering the dermoepidermal junction are characteristic observations (Fig. 6).[26] Subepidermal blistering disorders may have an urticarial prodromal phase that precedes the typical blisters by days or weeks; in cases where the urticarial phase lasts longer, it should not be included in the differential diagnosis.[27]

## Vasculopathic Pattern

Urticarial vasculitis (UV) is one of the main diagnoses to consider in a patient with an urticaria-like rash.

It has traditionally been described as a leukocytoclastic vasculitis with swollen endothelial cells, edema in the dermis, extravasation of red blood cells, and fibrinoid necrosis of the vessel walls,[28,29] with a variable dermal infiltrate of

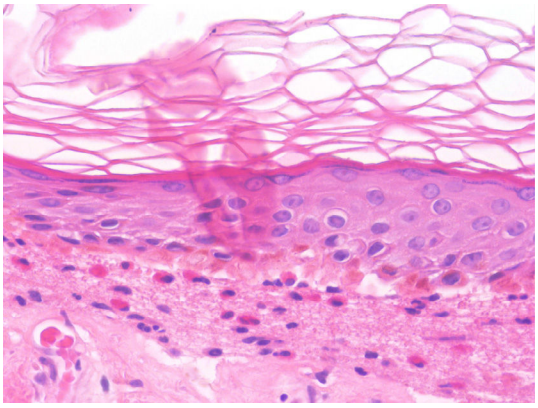

**Figure 6** Bullous pemphigoid in the urticarial phase (hematoxylin–eosin, ×100). Spongiosis can be seen in the dermis, together with an infiltrate with abundant eosinophils arrayed in the superficial dermis and in the dermoepidermal junction. The start of formation of a subepidermal vesicle can be observed, a finding compatible with the diagnosis of bullous pemphigoid.

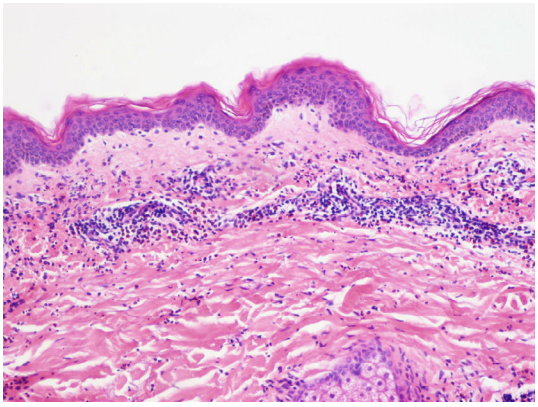

**Figure 7** Urticarial vasculitis (hematoxylin–eosin, ×10). A normal epidermis, with predominantly lymphohistiocytic superficial perivascular inflammation, together with isolate perivascular eosinophils and neutrophils. Also of note is the edema and damage to the vascular walls of the small vessels in the superficial dermis. These findings were accompanied by extravasation of red blood cells, interstitial leukocytoclasia, and edema in the superficial dermis. Fibrinoid necrosis was not observed in this case. A clinical-histologic correlation was required to establish the definitive diagnosis.

neutrophils, eosinophils, or both (Fig. 7).[30] In CU, we may occasionally find both extravasation of red blood cells and leukocytoclasia[7]; leukocytoclasia is also common in NUD.[15] According to the classical description of UV, however, the absence of fibrinoid necrosis rules out that entity in both cases.

Moreover, Lee et al[31] have shown that some patients meet the clinical criteria for UV but histologically present a predominantly lymphocytic perivascular infiltrate and inside the vessels of the dermis. This group of patients show indirect evidence of vascular damage, such as extravasation of red blood cells and swelling of the endothelial cells but without extravasation of fibrin or nuclear debris. No consensus currently exists regarding whether a fibrin deposit is required to establish the diagnosis of lymphocytic vasculitis, nor is lymphocytic vasculitis widely accepted as a pathogenic mechanism.[32]

## Direct Immunofluorescence

Immunofluorescence in CU is normally negative. Nevertheless, we may encounter pathologic findings in subepidermal blistering disease, in cutaneous lupus erythematosus, and in UV; we therefore believe that immunofluorescence should be performed, if available, on all patients with chronic urticaria who are candidates for a skin biopsy.

Direct immunofluorescence (DIF) of BP reveals linear deposits of immunoglobulin G (IgG) and C3 in the basement membrane, although deposits of immunoglobulins M or A may be present, though always at lower levels. Deposits of C3 are typically greater than those of IgG. A small percentage of patients with BP present only deposits of C3, without IgG. IgG deposits form a serrated N pattern.[16,26]

In UV, DIF can reveal immunoglobulins, complement, and fibrinogen in the basement membrane, perivascular region, or both,[30] especially in the context of systemic diseases such as SLE and mixed connective-tissue disease.[33]

Cutaneous lupus erythematosus reveals granular or fibrillar deposits of immunoglobulins IgG, IgM, and sometimes IgA, and deposits of complement factor C3 in the dermoepi-

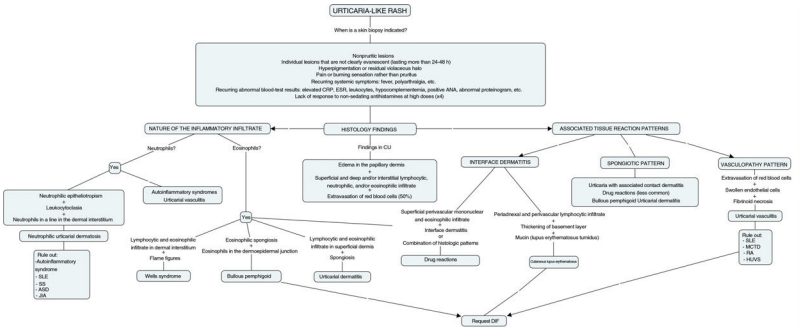


**Figure 8** Histologic diagnosis algorithm for rashes that mimic chronic urticaria.
Abbreviations: ASD indicates adult Still disease; CRP, C-reactive protein; DIF, direct immunofluorescence; ESR, erythrocyte sedimentation rate; HUVS, hypocomplementemic urticarial vascular syndrome; JIA, juvenile idiopathic arthritis; MCTD, mixed connective-tissue disease; RA, rheumatoid arthritis; SCU, spontaneous chronic urticaria; SLE, systemic lupus erythematosus.

dermal junction of the lesional skin.[23] Some authors use the term *lupus band* to refer to these findings.[34]

We propose an algorithm for guiding the histopathologic diagnosis in Fig. 8.

## Conclusions

Chronic urticaria is an entity whose diagnosis is essentially clinical, although clinical symptoms are sometimes insufficient for establishing a definitive diagnosis. A skin biopsy is necessary in patients with clinical warning signs or recurrent abnormal blood-test results, as it makes it possible to distinguish between chronic urticaria and other urticaria-like signs and symptoms.

The nature of the inflammatory infiltrate and the tissue reaction pattern found in the biopsy, together with direct immunofluorescence, interpreted in the clinical context of the patient, are key to establishing the diagnosis.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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