

Histopathology of Urticaria

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Opinion statement

Purpose of review Urticaria is a common skin manifestation with many different causes. It is characterized by local or generalized edematous erythema with itching and increased blood flow and vascular permeability. Individual urticaria lesions typically last less than 24 h (usually less than 12 h), but new lesions may appear and resolve sporadically. Since the diagnosis is usually made based on the history and clinical appearance of the lesions, skin biopsy is not necessarily performed, but it is recommended for evaluating patients with refractory eruptions or suspicion of other diseases exhibiting urticaria-like lesions. The histopathological features of urticaria are dermal edema and perivascular and interstitial inflammatory cell infiltration, and there is only minimal change in the epidermis. Cellular infiltrates are composed of lymphocytes, neutrophils, and eosinophils.

Recent findings In our 64 patients with urticaria, severe edema was found in 48 cases (75%) with mixed cellular infiltration in 45 (70%), lymphocytic infiltration in 17 (27%), and neutrophilic infiltration in 2 cases (3%). Perivascular infiltration was found in 35 cases (55%), and the others were classified into the perivascular and interstitial infiltration type. Subcutaneous cellular infiltration has been shown to be associated with poor treatment response.

Summary In this review, we summarize the histopathological findings of urticaria and its differential diagnosis. Evaluation of the histopathological features may provide further insight into the mechanism of urticaria and potentially provide valuable information to develop more effective treatments.

Introduction

Urticaria is clinically defined as a disease with transient and often pruritic localized dermal edema with wheals or erythematous papules [1•, 2–4]. It is a relatively common disease, with a lifetime prevalence of 8.8 to 20% [5, 6]. Individual lesions of urticaria typically last less than 24 h (mostly less than 12 h), but new lesions may appear and resolve sporadically. The condition is not usually life-threatening, but it has the possibility of impairing the quality of life. If urticaria persists for more than 6 weeks, it is diagnosed as chronic urticaria. Depending on whether the symptoms occur spontaneously or not, it is divided into chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIU). In most patients with CSU, the underlying cause cannot be identified and they often suffer severe impairment in their quality of life [7].

The current guidelines of the European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²-LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) for the management of urticaria recommend the use of second-

generation nonsedating oral H1 antihistamines as first-line therapy. In more than 50% of patients, however, symptoms persist with standard dosing of H1 antihistamines [8]. In these patients, it is recommended to increase the dose of the nonsedating H1 antihistamines up to fourfold [9], followed by third-line options including cyclosporine A and omalizumab.

Since urticaria is often diagnosed from the characteristic clinical symptoms, skin biopsy is not necessarily performed. However, such a biopsy is recommended for evaluating patients with refractory, severe CSU or the suspicion of other diseases exhibiting urticaria-like lesions, such as urticarial vasculitis [10]. In a previous study [11••], we investigated the relationship between clinical outcomes and histopathological findings in CSU and found that subcutaneous inflammatory infiltration was significantly associated with an intractable clinical course of CSU. In this review, we present the histopathological diversity of urticaria and address its differential diagnosis.

Histopathology

Ackerman described the histopathology of urticaria as a sparse mixed cellular infiltrate with dermal edema and suggested that the acute variety is indistinguishable from the chronic form [12]. He also distinguished urticaria from allergic urticarial eruption in that the latter presents prominent edema of the papillary dermis and a moderately dense mixed cellular infiltrate, especially of neutrophils, but also of eosinophils, lymphocytes, histiocytes, and mast cells [12]. Since urticaria occurs due to transient dermal blood vessel hyperpermeability, the extent of dermal edema and inflammatory cell infiltration might differ due to the time course of eruption. Urticaria shows not only clinical diversity but also histological diversity. Two major findings in the histopathology of urticaria, namely dermal edema and cellular infiltrate, are described below.

Dermal edema with minimal epidermal change

Urticaria results from vasodilatation and increased vascular permeability associated with the extravasation of protein and fluids into the dermis [13]. Histopathologically, urticaria shows dermal edema and dermal perivascular and interstitial inflammatory cell infiltration and there is minimal epidermal change (Fig. 1a) [10].

The dermis consists of two layers: the papillary layer, which is thin with loose connective tissue, and the reticular layer, which comprises an irregular, dense connective tissue. Dermal edema, which is recognized by separation of the collagen bundles, is an important feature of urticaria. A mild degree of dermal edema may be difficult to detect. The formation of dermal edema results from increased small-vessel permeability, which occurs primarily in small venules ranging from 20 to 30 μm in diameter. The smallest capillaries (4–7 μm in diameter) are not involved. The majority of the small vessels in the skin are post-capillary venules [10].

Urticarial edema differs from mucinoses by the absence of granular, stringy, basophilic material in the widened interstitium. There is also dilatation of small blood vessels and lymphatics, and swelling of their endothelium is often present (Fig. 1b). The histopathological changes in urticaria are most prominent in the upper dermis but may be observed in the deep dermis, particularly in those with complications of angioedema [14].

Cellular infiltrate

The cell type and the intensity of the inflammatory response in urticaria are quite variable [10]. The cellular infiltrate in urticaria is usually mild

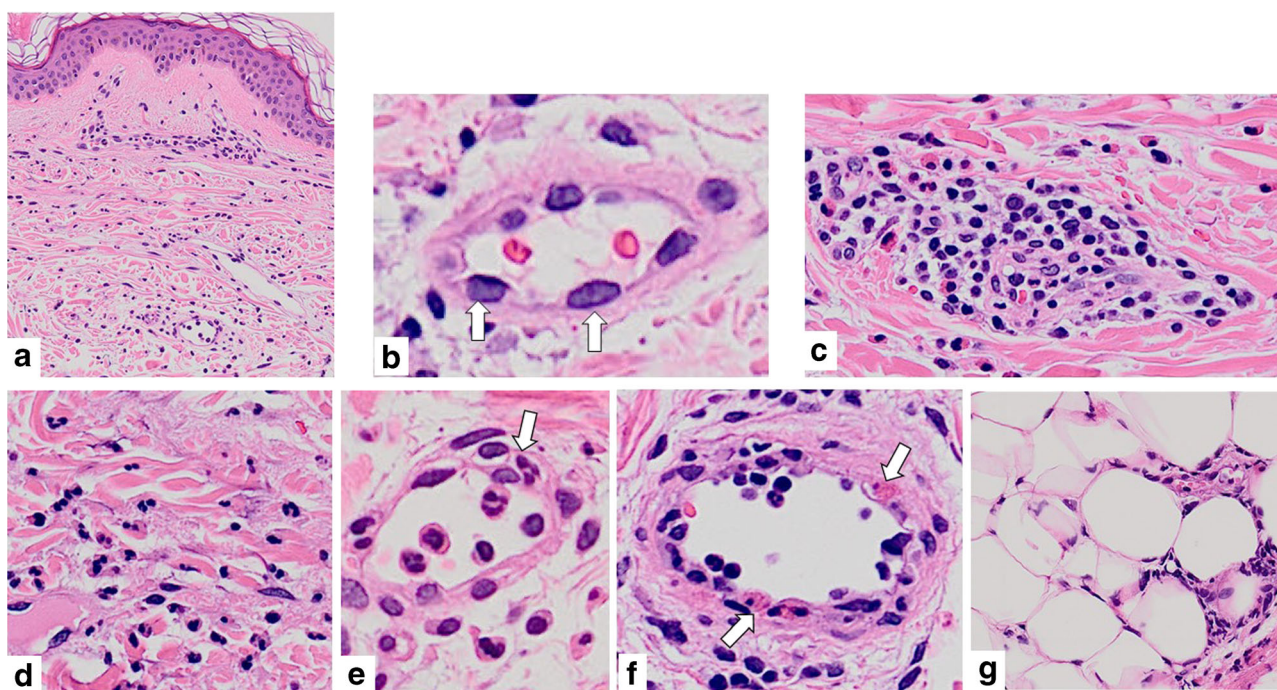


Fig. 1. Histopathological features of urticaria. **a** Dermal edema and perivascular and interstitial inflammatory cell infiltration with minimal epidermal change. Original magnification, $\times 100$. **b** Dilatation of small vessel and swelling of endothelium (arrows). Original magnification, $\times 400$. **c** Perivascular mixed cell infiltrate with lymphocytes, neutrophils, and eosinophils. Original magnification, $\times 200$. **d** Interstitial infiltration. Neutrophils are scattered among the collagen bundles. Original magnification, $\times 200$. **e** Neutrophils are present inside the dilated small vessel. A neutrophil migrates into the vessel wall (arrow). Original magnification, $\times 400$. **f** Some eosinophils are attached to and emigrated from the vessel wall (arrow). Original magnification, $\times 400$. **g** Subcutaneous cellular infiltration. Original magnification, $\times 400$.

and located in the perivascular area. It consists of lymphocytes and, in most cases, a few eosinophils (Fig. 1c) [12]. Occasional interstitial eosinophils and mast cells are also present. Eosinophil granule major basic protein has also been identified in the dermis in urticaria [13]. Neutrophils have been described in urticaria in several different circumstances [15–17]. Intravascular and perivascular neutrophils are a common feature in early urticaria [15], but in most cases, they are relatively sparse; there is some evidence to suggest that they are more prominent in physical urticaria [18–20], particularly in delayed pressure urticaria [21].

A more diffuse dermal neutrophilia has also been described in nearly 10% of urticaria cases [16, 22]. The term “neutrophilic urticaria” is used in these circumstances. In these cases, neutrophils are scattered among the collagen bundles, usually in the upper dermis but sometimes throughout its thickness (Fig. 1d). The infiltrate is usually mild in intensity [16], and nuclear dust is rarely present. In many early urticaria cases, an important diagnostic feature is the presence of neutrophils and sometimes eosinophils in the lumen of small vessels in the upper dermis [19]. Neutrophils and eosinophils occasionally adhere to the vascular endothelium (Fig. 1e and f). Although mast cells are often increased in early lesions and even in unstimulated skin of patients with chronic urticaria [23], they appear to be decreased in late lesions, plausibly due to the failure of histochemical methods to detect degranulated mast cells [24, 25].

Histopathological diversity of urticaria

To elucidate the histological diversity of urticaria, we examined 64 biopsy specimens of urticaria obtained at the Department of Dermatology, Kyushu University, between January 1, 2011, and May 31, 2017. None of these 64 cases showed features of urticarial vasculitis and angioedema. The histopathological findings consisted of the following six variables: edema (mild or severe), type of infiltration (perivascular type or perivascular plus interstitial type), type of infiltrating cell (mixed cellular type: mainly composed of lymphocytes, eosinophils, and a few neutrophils; lymphocytic type: infiltrating cells are mainly lymphocytes; neutrophilic type: mainly neutrophils), eosinophil count [≥ 10 /high-power field (HPF) or < 10 /HPF], neutrophil count (≥ 10 /HPF or < 10 /HPF), and location of infiltration (dermal only or dermal plus subcutaneous [Fig. 1g]).

The demographic data are summarized in Table 1. There were no obvious changes in the epidermis in all specimens. In the majority of cases (48/64, 75%), dermal edema was severe in the dermis. The cellular infiltrations of the dermis were confined to the perivascular area in 35 (55%) cases, while 29 (45%) specimens showed both perivascular and interstitial infiltration. Mixed cell type was found in 45 (70%), lymphocytic type in 17 (27%), and neutrophilic type in 2 (3%) cases. Regarding the numbers of infiltrated eosinophils and neutrophils, their infiltration at ≥ 10 /HPF was observed in 5 (8%) and 3 (5%) cases, respectively. In 47 (73%) cases, the cellular infiltration was

detected only in the dermis, but it expanded deeply into the subcutaneous tissue in 17 (27%) cases (Table 1). The present results stress the histological diversity of urticaria, which may underpin its clinical diversity.

Subcutaneous cellular infiltration correlates with poor treatment response in chronic spontaneous urticaria

Chronic spontaneous urticaria is more common than previously thought. In terms of point prevalence, 0.5 to 1% of the population suffers from this disease [8]. Although the duration of CSU is generally 1 to 5 years, it is likely to be longer in severe cases, despite the use of standard treatments [8]. The clinicopathological factors that are associated with a poor response to treatment are still not fully understood. Our recent study confirmed that there is a significant association between subcutaneous inflammatory cell infiltration and a poor response to treatment [11••]. However, further studies are warranted to explore

Table 1. Pathological characteristics of 64 patients with urticaria

	Number (%) <i>n</i> = 120
Pathological variables	
Edema	
Mild	16 (25%)
Severe	48 (75%)
Dermal infiltration	
Perivascular type	35 (55%)
Perivascular plus interstitial type	29 (45%)
Cell infiltration	
Mixed cellular type	45 (70%)
Lymphocytic type	17 (27%)
Neutrophilic type	2 (3%)
Eosinophil count	
≥ 10/HPF	5 (8%)
< 10/HPF	59 (92%)
Neutrophil count	
≥ 10/HPF	3 (5%)
< 10/HPF	61 (95%)
Location of infiltration	
Dermal only	47 (73%)
Dermal plus subcutaneous	17 (27%)
The demographic data	

the endogenous regulators that facilitate or inhibit urticarial inflammation.

Differential diagnosis

Table 2 shows the histopathological differential diagnosis of urticaria. When urticarial lesions show prominent edema of the papillary dermis and perivascular cell infiltrate, the differential diagnosis may include the initial urticarial stage of bullous pemphigoid, polymorphic light eruption, drug eruption, arthropod reaction, viral eruption, and id reaction [1•]. In drug eruption and arthropod reaction, the presence of eosinophils is often more pronounced than in urticaria. Diffuse neutrophilic infiltration in the dermis raises the possibility of cellulitis or erysipelas [1•]. In contrast to these infectious lesions, the infiltrating neutrophils in urticaria have no nuclear dust and exhibit sparse invasion between collagen fibers of the dermis. In the case of adult-onset Still's disease, neutrophilic infiltration is observed in the dermis, but is also found in the epidermis. In addition, numerous dyskeratotic cells, singly or in aggregates, are seen in the upper epidermis and the stratum corneum [26, 27]. Although neutrophilic urticaria shows diffuse neutrophils in the dermal infiltrate, it usually lacks the other features with true vasculitis, namely leukocytoclasia, extravasated erythrocytes, and fibrin deposition. If those features are found, we should suspect urticarial vasculitis [28, 29•]. The term urticarial dermatitis was introduced by Kossard et al. [30], in which urticarial and eczematous features are combined. As

Table 2. Histopathological differential diagnosis of urticaria

Histopathological findings	Differential diagnosis
Urticaria-like lesions plus	
1. Prominent edema of the papillary dermis and perivascular mixed cell infiltrate	1 Bullous pemphigoid 2 Polymorphic light eruption 3 Drug-induced exanthema ^a 4 Arthropod reaction ^a 5 Viral exanthema 6 Id reaction
2. The presence of neutrophils in the dermal infiltrate	1 Still's disease ^b 2 Neutrophilic urticarial dermatosis ^c 3 Cellulitis 4 Erysipelas
3. Presence of vasculitis	Urticarial vasculitis
4. Eczematous features	Urticarial dermatitis
^a Perivascular lymphocytic infiltrate plus the presence of eosinophils	
^b Occasionally, there are multiple dyskeratotic cells located in the upper epidermis. Neutrophilic infiltration is frequently observed in the epidermis	
^c Mild dermal edema, leukocytoclasia	

spongiotic changes never occur in urticaria, urticarial dermatitis may represent a secondary eczematization of an urticarial lesion.

Current and future therapies

The international EAACI/GA2LEN/EDF/WAO consensus guidelines recommend aiming for complete symptom control by the safest approach possible in urticaria [9]. Therapeutic options include treatment and elimination of the causes, inhibition of mediator release by mast cells, and inhibition of the effect of mediators on target organs [31•]. In the international guidelines, a stepwise treatment algorithm for CSU management is recommended [9]. The first-line treatment is modern second-generation H1 antihistamines, and if symptoms persist after 2 weeks, the second step is to increase the dosage of modern second-generation antihistamines up to fourfold. If symptoms persist after 1 to 4 further weeks, the guidelines recommend the addition of omalizumab, cyclosporin A, or montelukast. A short course of systemic corticosteroids may also be used at all times if exacerbations demand this. Although many alternative treatments have been evaluated, the evidence levels of such treatments are low. In the future, treatment options may include inhibitors of cutaneous mast cells and antagonists of mast cell activation signals associated with the induction of CSU signs and symptoms [32•].

Conclusions

Urticaria is defined by the occurrence of transient pruritic wheals caused by increased vascular permeability associated with the extravasation of protein and fluids into the dermis. Although skin biopsy is not mandatory in such cases, it is useful for evaluating patients with severe refractory cases or other diseases exhibiting urticarial lesions. The histopathological features of urticaria are characterized by various degrees of dermal edema and dermal perivascular and interstitial inflammatory cell infiltration with minimal epidermal change. The histopathological features of urticaria are diverse and still not well-defined. The age of the lesion and the nature of the evoking stimulus may influence the type and intensity of the inflammatory response. Evaluation of the histopathological features may provide further insight into the mechanism of urticaria and potentially provide valuable information to develop more effective treatments.

Compliance with ethical standards

Conflict of interest

Dr. Eriko Itoh, Dr. Minao Furumura, and Dr. Masutaka Furue declare that they have no conflicts of interest.

Human and animal rights and informed consent

With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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