STUDY

Defining Urticarial Dermatitis

A Subset of Dermal Hypersensitivity Reaction Pattern

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Background: Urticarial dermatitis may represent a useful term for a subset of a reaction pattern designated most commonly as dermal hypersensitivity by pathologists. The term is not commonly used, and requires definition to determine whether it is clinically relevant.

Objectives: To define urticarial dermatitis and distinguish it from other urticarial reaction patterns and to review the frequency with which dermatologists can recognize clinical settings that match the biopsy findings of urticarial dermatitis.

Design: Retrospective analysis of clinical and/or histological diagnosis of urticarial dermatitis, applying strict histological criteria in a center using urticarial dermatitis as a diagnostic term in 190 archived reports.

Setting: Tertiary referral dermatopathology service reporting for dermatological practices in Sydney, Australia.

Main Outcome Measures: The correlation between clinical and histological diagnoses of urticarial dermatitis and alternate diagnoses was analyzed. The frequency of positive immunofluorescence findings for bullous pemphigoid was determined in a subset of patients with urticarial dermatitis in whom this test was ordered to exclude prodromal bullous pemphigoid.

Results: Urticarial dermatitis was the histological diagnosis in at least 1 biopsy result in 148 patients, and matched the provisional clinical diagnosis in 49 (33.1%) patients. Urticarial dermatitis was the only diagnosis provided in 21 patients. The main alternate clinical diagnoses provided were early bullous pemphigoid or dermatitis herpetiformis (47 patients [31.8%]), dermatitis (39 patients [26.4%]), drug reaction (35 patients [23.6%]), urticarial vasculitis (24 patients [16.2%]), and urticaria (12 patients [8.1%]). In 91 patients with a clinical diagnosis of urticarial dermatitis, the histological diagnosis in at least 1 biopsy result was matched in 49 patients (53.8%); other histological diagnoses included dermatitis (21 patients [23.1%]), papular urticaria (12 patients [13.2%]), drug reaction (6 patients [6.6%]), and urticaria (3 patients [3.3%]). Review of 38 direct immunofluorescent results for prodromal bullous pemphigoid and a biopsy finding of urticarial dermatitis revealed only 3 positive results (7.9%).

Conclusions: Urticarial dermatitis seems to be a useful histological and clinical term for a subset of the dermal hypersensitivity reaction pattern. Although the clinical presentation is not restricted to a specific entity, eczema and drug reactions seem to be the most frequent clinical associations; and in a subset of patients, urticarial dermatitis remains as a recognizable reaction pattern. Urticarial dermatitis without eosinophilic spongiosis is not a reliable indicator for bullous pemphigoid, because the findings of immunofluorescence are often negative.

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THERE IS A GROUP OF PATIENTS who present with urticarial plaques and papules that may resemble urticaria, but the individual lesions last longer than 24 hours and often last for days. The lesions are usually intensely pruritic, and there may be a predominant papular element or urticated erythema with excoriations. Biopsy results from the urticated areas typically reveal upper dermal perivascular lymphocytes and eosinophils with or without neutrophils, but no gross epidermal vesication or parakeratosis. This particular combination of histological features has been designated as urticarial dermatitis in our laboratory for at least 5 years. The term dermal hypersensitivity reaction pattern has also been used by pathologists to describe this finding.1 In this study, we review our experience in using urticarial dermatitis as a histological term and examine our archived reports to determine whether the term may be useful for clinicians to help identify a subset of the dermal hypersensitivity reaction pattern.

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METHODS

The archival files for the dermatopathology reports at the Skin & Cancer Foundation Australia were searched for keywords encompassing urticarial dermatitis for 2000 and 2003 (total accessions, 68,484). All reports with these keywords were reviewed, and those with either the clinical or the pathological diagnosis of urticarial dermatitis were further analyzed as to the clinical and pathological correlation of the term. Only reports in which the provisional clinical diagnosis included the term urticarial dermatitis or for which the slides of the biopsy specimen after review revealed that there was an upper dermal perivascular and interstitial lymphocytic inflammatory reaction with eosinophils and an overlying epidermis demonstrating minimal spongiosis and a normal stratum corneum (Figure 1) were included as representing urticarial dermatitis in the study. One hundred thirty-one biopsy results demonstrating parakeratosis, prominent spongiosis, acanthosis, a deep dermal lymphocytic infiltrate with eosinophils (as prominent as the superficial component), prominent neutrophilia, evidence of vascular damage, leukocytoclasis, or dermal fibrosis were eliminated. One hundred ninety patients fulfilled the study criteria, and were referred by 34 dermatologists. There were 123 females (age range, 15–90 years; mean, 59.6 years) and 67 males (age range, 17–87 years; mean, 65.7 years), representing a female-male ratio of 1.8:1. Patients were then stratified into group A, in which the clinical and microscopic description included urticarial dermatitis; group B, in which the clinical diagnosis was other than urticarial dermatitis but the microscopic diagnosis was urticarial dermatitis; and group C, in which the clinical diagnosis included urticarial dermatitis but the biopsy findings revealed an alternate process. All clinical differential diagnoses provided for the 148 patients with a biopsy-proved diagnosis of urticarial dermatitis were extracted, and all histological diagnoses for the 91 patients in whom one of the clinical diagnoses was urticarial dermatitis were included. There were 45 patients in whom multiple biopsy results had been obtained, of which at least 1 result was urticarial dermatitis; the additional biopsy results were collated. Finally, the direct immunofluorescent results for 38 biopsy findings that were reported as urticarial dermatitis with a clinical differential diagnosis including prebullous pemphigoid were reviewed.

RESULTS

One hundred ninety patients with a clinical or histological diagnosis of urticarial dermatitis or both were stratified into 3 groups: group A, in which 49 patients (25.8%) had a clinical and biopsy-proved diagnosis that matched; group B, in which 99 patients (52.1%) had a clinical diagnosis that was other than urticarial dermatitis but in whom the biopsy result showed urticarial dermatitis; and group C, in which 42 patients (22.1%) had a clinical diagnosis that was urticarial dermatitis but in whom the biopsy result was other than urticarial dermatitis.

Urticarial dermatitis was included in the clinical diagnosis in 91 patients (groups A and C) and was the histological diagnosis in 148 patients (groups A and B). Urticarial dermatitis with the defined histological criteria was confirmed in 49 (53.8%) of the 91 patients with a clinical diagnosis of urticarial dermatitis. A further 21 (23.1%) of the patients revealed more advanced changes of dermatitis. The remaining 21 patients had histological findings of papular urticaria (12 patients [13.2%]), drug reaction (6 patients [6.6%]), or urticaria (3 patients [3.3%]). Urticarial dermatitis was the clinical diagnosis in 49 (33.1%) of the 148 patients with biopsy results demonstrating urticarial dermatitis. Urticaria dermatitis was the only clinical diagnosis in 21 patients, but the remainder had additional and, at times, multiple differential diagnoses. In 47 patients (31.8%), early bullous pemphigoid or dermatitis herpetiformis was included in the differential diagnosis. Dermatitis was diagnosed in 39 (26.4%) of the patients, and drug reaction was included in 35 patients (23.6%). Other diagnoses were urticarial vasculitis (24 patients [16.2%]), urticaria (12

Figure 1. Histopathological features of urticarial dermatitis. A, Slight epidermal spongiosis with superficial perivascular lymphocytes and interstitial eosinophils (original magnification ×100). The inset is a scanning view of upper dermal inflammation (original magnification ×25). B, Detail of perivascular eosinophils that spill interstitially into the surrounding dermis (original magnification ×400).
patients [8.1%]), pruritic urticular papules and plaques of pregnancy (PUPPP) or herpes gestationis (7 patients [4.7%]), and bullous urticaria (5 patients [3.4%]).

In 23 of the 148 patients with a biopsy-proved diagnosis of urticarial dermatitis, 13 underwent an additional biopsy, which showed subacute dermatitis, and there were 7 cases of lichenoid dermatitis, 2 of papular urticaria, and 1 of bullous pemphigoid. In a further 22 patients, multiple biopsy results revealed urticarial dermatitis, including 4 patients with 3 biopsy results and 1 patient with 4 biopsy results, all showing urticarial dermatitis. In 47 patients (31.8%) with a biopsy-proved diagnosis of urticarial dermatitis, early bullous pemphigoid or dermatitis herpetiformis was included in the clinical differential diagnosis. Review of 38 direct immunofluorescent results linked to these patients revealed only 3 (7.9%) demonstrating linear deposits at the basement membrane zone of IgG and C3, confirming bullous pemphigoid.

**COMMENT**

Urticarial papules and plaques individually lasting longer than 24 hours may resemble urticaria, but are more likely to represent a range of other conditions, such as drug reaction, viral exanthem, infestation, prodromal phase of dermatitis herpetiformis, bullous pemphigoid, PUPPP, or urticarial vasculitis. This reaction pattern may also represent part of the eczematous spectrum, given the co-occurrence of lesions histopathologically consistent with urticarial dermatitis and eczema in the same patient. We have used the term urticarial dermatitis to describe this link. The term urticarial dermatitis has not been in common use and probably is a subset of what pathologists have reported as a dermal hypersensitivity reaction. Hypersensitivity urticarial reaction and hypersensitivity dermatitis are additional terms that have been used for dermal hypersensitivity reaction. We prefer urticarial dermatitis, because the key clues to diagnosis for the clinician and pathologist are the urticarial appearance and overlap with an eczematous reaction.

Urticarial dermatitis represents a primary dermal reaction associated with erythema and pruritus that may particularly resemble urticaria or urticarial vasculitis when urticarial plaques rather than papules dominate the clinical presentation. In our study, a range of alternative descriptions was used by clinicians in 33 patients with a biopsy-proved finding of urticarial dermatitis, such as urticated erythema or eruption, fixed urticaria, urticarial rash, erythematous rash with minimal epidermal component, or urticarial plaques and papules. Following the introduction of urticarial dermatitis as a histological diagnosis, this term has been adopted as a clinical term by our referring dermatologists. The number of clinical diagnoses of urticarial dermatitis in our study was underestimated, because alternate descriptions were still used by some clinicians who did not use urticarial dermatitis as a term.

The clinical appearance of urticarial dermatitis in our experience presents as urticarial papules and plaques that are initially urticated erythematous patches with exco-
urticarial reactions that can be associated with systemic symptoms, including anaphylaxis. Contact urticaria to food proteins is often localized and asymmetrical, while the reaction pattern in patients we have observed is more widespread and can resemble a drug reaction. The rebound of dermatitis seen after rapid withdrawal of corticosteroids may be initially urticarial and widespread, and may represent a trigger for urticarial dermatitis. Partially treated spongiotic dermatitis may also appear urticarial. We did not document such cases in this study.

The average age of individuals developing urticarial dermatitis in our study was 60 years, indicating that this reaction is seen mainly in elderly individuals. There was a subset of urticarial dermatitis that was diagnosed in younger women presenting with PUPPP. This raises the issue of whether a counterpart of PUPPP, albeit with differing pathophysiological features, may exist in elderly persons. Our study also indicates that urticarial dermatitis is most frequently linked with an eczematous process, just as in PUPPP. Dermatologists using this term can usually differentiate urticarial dermatitis from urticaria, because only 8.1% of patients had urticaria as a differential clinical diagnosis and only 3.3% of biopsy results revealed urticaria. The most frequent clinical differential diagnosis for urticarial dermatitis other than an eczematous process was an early bullous dermatosis, particularly bullous pemphigoid or a drug reaction. A subset of patients had persistent urticarial dermatitis as a pure reaction pattern.

The histological features of urticarial dermatitis may be combined with additional microscopic clues that allow a more specific diagnosis to be made. Gross spongiosis, lymphocytic exocytosis, and perakeratosis may be present on deeper sections, indicating the process is truly eczematous; and we would not use the term urticarial dermatitis as a sole term in this situation. The presence of interstitial dermal fibrosis and irregular epidermal acanthosis may indicate that the process is more long-term and belongs to the pruriginous dermatosis group, including subacute prurigo. Lichenoid features with liquefactive degeneration of the junctional zone and presence of individual necrotic keratinocytes may indicate that the urticarial dermatitis is drug induced or possibly the result of viral exanthem. Eosinophilic spongiosis or eosinophils concentrated at the junctional zone favor prodromal bullous pemphigoid. Urticaria pigmentosa may mimic urticarial dermatitis microscopically on the biopsy, and mast cell stains may be required to reach this diagnosis.

Our definition of the histological features of urticarial dermatitis is identical to those proposed for the dermal hypersensitivity reaction pattern. In the most detailed study of dermal hypersensitivity reaction pattern, the conclusion reached was that this does not represent any particular clinical disorder but could be seen as part of urticaria, drug reaction, or eczema, and is found in a subgroup of patients with persistent excoriated papules on the trunk. The latter has been reported as a variant of papular urticaria, simply as a pruritic papular eruption, and subacute prurigo, or itchy red bump disease, and remains an enigmatic subgroup. Our study differs in that the term urticarial dermatitis has been used to identify a subset of patients with urticarial plaques and papules, providing a link to a group of dermatological conditions with urticarial features that represent a predominantly dermal eczematous reaction. We have restricted the histological definition of urticarial dermatitis to the combination of upper dermal perivascular lymphocytic inflammation with eosinophils with minimal associated epidermal spongiosis. This pattern of histological features can be distinguished from other urticarial reactions, such as urticaria, urticarial vasculitis, early urticarial bullous pemphigoid, or papular urticaria (Figure 3). In urticaria, the lymphocytic inflammation is not restricted to the superficial vessels but extends into the deeper dermis and is more scant and associated with interstitial edema and scattered intact neutrophils and eosinophils. Urticarial vasculitis is associated with leukocytoclasis concentrated around the superficial and middermal vessels, with local vascular necrosis and hemorrhage. The biopsy findings in papular urticaria typically show a prominent superficial and deep lymphocytic inflammation around the blood vessels, with an interstitial infiltrate of lymphocytes and eosinophils and a variable number of neutrophils. There may also be a central focus of epidermal spongiosis and crusting in the case of papular urticaria due to insect bite reactions. In the most detailed study of dermal hypersensitivity reaction patterns, the histological criteria for inclusion were not applied strictly, and many biopsy results were associated with additional features, such as moderate spongiosis, deep perivascular inflammation, significant neutrophilia, and parakeratosis. In our study, such biopsy results were not designated as urticarial dermatitis and were excluded. Although the term dermal hypersensitivity reaction pattern has been used as a descriptive biopsy-proved diagnosis, the term has not been embraced by clinicians because it lacks any specificity. In contrast, urticarial dermatitis in our study has been adopted by dermatologists as a descriptive term, and based on the identical biopsy criteria used, qualifies as a subset of the dermal hypersensitivity reaction. Urticarial dermatitis, like the dermal hypersensitivity reaction pattern, still represents a reaction pattern and embraces a range of possible clinical scenarios, particularly eczematous reaction, but may ultimately represent drug hypersensitivity, infestation, or viral exanthem. There are also patients who have a clinically recognizable morphological reaction pattern that is dominated by urticarial plaques that cannot be further classified, except as an urticarial dermatitis.

In our experience, viral exanthemas can have identical histological features to urticarial dermatitis but are usually distinguished by the clinical features, including lack of marked pruritus and a self-limited course, and a biopsy is often not performed. Urticarial dermatitis associated with scabies is usually polymorphous but may provide difficulties in diagnosis in persistent and unrecognized cases. Most patients in our series were elderly persons, and in our experience, urticarial dermatitis is frequently chronic and resistant to simple topical therapy, prompting consideration of prodromal bullous pemphigoid or a drug reaction as a diagnosis. Confirmation of bullous pemphigoid by biopsy results in the absence of additional features of eosinophilic spongiosis, dermal eo-
sinophilia, or accumulation of eosinophils at the junctional zone was low. In our study, using the strict histological criteria of urticarial dermatitis without these additional features revealed only 3 of 38 such cases to have confirmatory immunofluorescence for bullous pemphigoid.

Drug reactions have been linked clinically with the dermal hypersensitivity syndrome in 20% of cases, and were provided in the clinical diagnoses in 23.6% of patients with a biopsy result of urticarial dermatitis in our study. In a clinical follow-up of 74 patients with dermal hypersensitivity reactions, 13 had a final clinical diagnosis of

Figure 3. Histological reaction patterns in the differential diagnosis of urticarial dermatitis. A, Urticarial dermatitis with lymphocytes and eosinophils around the superficial vessels. B, Urticaria with lymphocytes, eosinophils, and scattered neutrophils around superficial and deep vessels, with an interstitial component. C, Papular urticaria with central epidermal inflammation and superficial, deep perivascular, and interstitial lymphocytic inflammation, with eosinophils and neutrophils. D, Urticarial vasculitis with leukocytoclasis and vascular damage. E, Urticarial bullous pemphigoid with eosinophilic spongiosis and eosinophils at the dermoepidermal junction. Black circles indicate lymphocytes; blue circles, neutrophils; and red circles, eosinophils.
drug reaction to various drugs, including antibiotics, analgesics, and anti-inflammatory agents. Subtle lichenoid features on biopsy result may be a clue to particularly consider a drug reaction.

Although the term urticarial dermatitis may be a better term for clinicians for what has been reported as dermal hypersensitivity reaction, the term does not encompass all the settings of dermal hypersensitivity syndrome, particularly the form associated with predominantly excoriated papules. This is reflected in our study, because the clinical correlation of urticarial dermatitis in 53.8% of patients with the histological features was greater than the histological correlation in 33.1% of patients with the clinical diagnosis. From a histological point of view, the finding of urticarial dermatitis should prompt close examination for a more definitive diagnosis by checking for subtle clues, sectioning the tissue more thoroughly, or obtaining further biopsy specimens of nonurticatated lesions. In our experience, urticarial dermatitis can be persistent and difficult to treat, because the reaction may not settle readily with topical corticosteroids or oral antihistamines. Oral corticosteroids and narrowband UV-B may be useful, but a relapsing course is not uncommon and careful review for evidence of eczema, unrecognized infection, or drug reaction is warranted.

The primary aim of our study was to explore the use of urticarial dermatitis as a term for the clinician and the pathologist. The term urticarial dermatitis seems to be useful clinically and histologically, as the descriptive term highlights recognizable features. Although the clinical presentation is not restricted to a specific entity, eczema and drug reaction seem to be the most frequent clinical associations. In a subset, urticarial dermatitis remains as a sole reaction pattern. The pathophysiological features of urticarial dermatitis remain to be explored, but may represent a persistent T helper cell 2 reaction that is usually transitory and precedes the dominant T helper cell 1 cytokine profile, particularly in atopic dermatitis. In many patients with the clinical diagnosis of urticarial dermatitis, clinicopathological correlation can be achieved, and these form a subset that is mixed within the larger group classified as having a dermal hypersensitivity reaction pattern.

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REFERENCES