

# Urticarial dermatitis: Clinical features, diagnostic evaluation, and etiologic associations in a series of 146 patients at Mayo Clinic (2006-2012)

Gregory R. Hannon, MD, JD,<sup>c</sup> David A. Wetter, MD,<sup>a</sup> and Lawrence E. Gibson, MD<sup>a,b</sup>  
Rochester, Minnesota

**Background:** Few studies have examined patients initially presenting with clinical features of urticarial dermatitis (UD).

**Objective:** We sought to examine clinical and laboratory evaluations and final diagnoses of patients with clinical features of UD.

**Methods:** This was a retrospective review of patients with UD seen at Mayo Clinic between 2006 and 2012, and formal review of available skin biopsy specimens to identify any patients who also met microscopic criteria for UD.

**Results:** Of 146 patients with clinical features of UD (mean age at onset, 60 years), 88 (60%) were female. The most common final diagnoses were: UD (70 patients [48%]); dermatitis not otherwise specified (24 [16%]); urticaria (14 [10%]); drug reaction (9 [6%]); bullous pemphigoid (6 [4%]); atopic dermatitis (5 [3%]); and contact dermatitis (4 [3%]). Of 40 patients with clinical and microscopic features of UD, 46% (16 of 35) had no response to treatment, whereas 10% (4 of 40) had a newly diagnosed concurrent malignancy (within 4 months of UD onset).

**Limitations:** This was a retrospective study.

**Conclusion:** Clinical features of UD occur in various dermatologic diseases. Some patients with clinical and microscopic features of UD have associated malignancies. Further studies should assess optimal evaluation and management of UD. (J Am Acad Dermatol 2014;70:263-8.)

**Key words:** dermal hypersensitivity; dermatitis; eczema; hypersensitivity; malignancy; urticarial; urticarial dermatitis.

Urticarial dermatitis (UD) was clinically defined by Kossard et al<sup>1</sup> in 2006 as pruritic, erythematous papules and plaques resembling urticaria but that last longer than 24 hours and are sometimes accompanied by eczematous lesions. The features of this subset of the “dermal hypersensitivity reaction pattern”<sup>1,2</sup> have been described as variable even in individual patients, sometimes creating an eczematous dermatitis-like picture, and other times creating a more urticarial picture.<sup>3</sup>

Biopsy specimens from the urticated areas typically reveal a normal stratum corneum, minimal

## Abbreviations used:

BP: bullous pemphigoid  
DIF: direct immunofluorescence  
UD: urticarial dermatitis

spongiosis, and papillary dermal perivascular lymphocytic inflammation with eosinophils (with or without neutrophils).<sup>1</sup> Using these strict parameters, Kossard et al<sup>1</sup> distinguished their newly coined entity, “true UD,” from other reaction patterns

From the Department of Dermatology,<sup>a</sup> and Division of Dermatopathology,<sup>b</sup> Mayo Clinic; and Mayo Medical School, Mayo Clinic College of Medicine.<sup>c</sup>

Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication August 24, 2013.

Reprint requests: David A. Wetter, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: [wetter.david@mayo.edu](mailto:wetter.david@mayo.edu).

Published online November 22, 2013.

0190-9622/\$36.00

© 2013 by the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2013.08.050>

commonly included in the broad differential diagnosis of clinical UD (eg, urticaria, urticarial vasculitis, prodromal bullous pemphigoid [BP]).

Although the clinical presentation of UD encompasses an array of dermatologic diseases, to our knowledge there has not been a large study examining the frequencies of final dermatologic diagnoses in patients initially presenting with clinical features of UD since the original description by Kossard et al<sup>1</sup> in 2006. The proper initial workup of these patients has not yet been fully elucidated in the medical literature.

Our study retrospectively examines the features of UD both as a clinical entity and as biopsy-proven UD per the strict histopathologic definition submitted by Kossard et al,<sup>1</sup> and describes the clinical and laboratory evaluations along with the final diagnoses for a cohort of patients presenting with clinical features of UD at a tertiary care academic referral center.

## METHODS

### Data collection

Using the institutional medical index and text retrieval system, we identified adult patients (aged  $\geq 18$  years) who were seen in the dermatology department at Mayo Clinic in Rochester, MN, between January 1, 2006, and May 9, 2012, with a clinical presentation consistent with UD as defined by Kossard et al.<sup>1</sup> We accessed the electronic medical record to abstract information pertaining to patient demographics, disease duration, clinical features, concomitant medical conditions, laboratory tests and results, histopathologic data, and final diagnoses. Finally, we reviewed all available biopsy specimens to determine which patients had biopsy specimens that met the strict histopathologic criteria of Kossard et al<sup>1</sup> for UD.

Our study was approved by the Mayo Clinic Institutional Review Board. Patients who denied research authorization were excluded.

### Definition of UD

Per the requirements for the clinical diagnosis of UD outlined by Kossard et al<sup>1</sup> in 2006, our requirements for a clinical diagnosis of UD included either a diagnosis of UD rendered by the dermatologist or a documented clinical examination by the

dermatologist describing both eczematous and urticarial lesions lasting longer than 24 hours (ie, lacking the transiency seen in true urticaria).

Histopathologic criteria were similarly held to the strict criteria previously published.<sup>1</sup> Slides were reviewed by a senior dermatopathologist (L.E.G.), and values from 0 to 3 were assigned to each specimen for each of the following microscopic parameters: acanthosis, spongiosis, epidermal inflammation (by cell type), dermal inflammation by cell type, dermal edema, and dermal lymphatic dilation. The dermal inflammatory location—papillary, reticular, or both—was also recorded. Only those specimens with mixed inflammation with eosinophils (graded 1, 2, or 3) limited to the papillary dermis with minimal spongiosis (graded either 0 or 1) were deemed consistent with UD as defined by Kossard et al.<sup>1</sup>

## RESULTS

### Clinical UD

From 839 index results, a total of 146 unique patients were identified with a clinical presentation consistent with UD. Of these, 88 (60%) were women and 58 (40%) were men (Table I). The mean age at disease onset was 60 years (range, 19-92 years). The mean duration of disease at diagnosis was 13 months, and the mean length of follow-up was 8 months. Most patients had involvement of the trunk (133 of 146 [91%]), lower extremities (109 of 146 [75%]), and upper extremities (107 of 146 [73%]). Fewer had involvement of the head/neck (17 of 146 [12%]) and groin (9 of 146 [6%]). Fourteen patients (10%) required inpatient dermatologic admission during the course of their treatment. Table I summarizes the characteristics of the 146 patients with clinical UD.

### Laboratory tests and histopathologic analysis

Table II summarizes the initial workup of the 146 patients. Skin biopsy specimens were obtained from 118 patients (81%). Direct immunofluorescence (DIF) was performed in 99 patients (68%). For those 99, results for most (94 [95%]) were negative or nondiagnostic, whereas 3 (3%) had findings consistent with BP, and 1 (1%) each had findings suggestive of either vasculitis or lupus erythematosus. Cutaneous (indirect) immunofluorescence

### CAPSULE SUMMARY

- Urticarial dermatitis is characterized by both urticarial and eczematous lesions.
- Patients with clinical features of urticarial dermatitis can have an array of diagnoses, including various subtypes of dermatitis, drug eruption, bullous pemphigoid, and scabies.
- Further studies are needed to determine the optimal evaluation and management of urticarial dermatitis.

**Table I.** Characteristics of 146 patients with clinical urticarial dermatitis

Characteristic	No. (%) <sup>a</sup>
Age at onset, mean (SD), y	60 (18)
Women	57
Men	67
Age at onset, median (range), y	61 (19-92)
Sex	
Female	88 (60)
Male	58 (40)
Site of involvement	
Trunk	133 (91)
Lower extremities	109 (75)
Upper extremities	107 (73)
Head/neck	17 (12)
Groin	9 (6)
Palms/soles	2 (1)
Inpatient dermatologic admission required	14 (10)
Duration of disease at diagnosis, mean, mo	13
Follow-up since diagnosis, mean, mo	8
Follow-up since diagnosis, range, mo	0-73

<sup>a</sup>Values are number (percentage) unless indicated otherwise.

testing of serum was performed for 50 of the 146 patients (34%). This testing was negative in 43 of the 50 patients (86%), whereas 4 (8%) had positive cell surface staining and 3 (6%) had positive basement membrane zone staining. BP antigens 180 (BP180) and 230 (BP230) were measured in 56 of the 146 patients (38%); of these, 43 (77%) were found to have normal levels. Of the 146 patients, 34 (23%) underwent patch testing, and only 1 received a resultant contact dermatitis diagnosis. Ten patients (7%) underwent mineral-oil scabies preparation, yielding 1 positive result.

### Final diagnoses

Of the 146 patients with an initial clinical diagnosis of UD (ie, at the time of initial presentation), 70 patients (48%) received a final diagnosis of UD (biopsy-proven or not) from a dermatologist (Table III). Final diagnoses for the remaining patients were dermatitis (24 of 146 [16%]); urticaria (acute or chronic) (14 of 146 [10%]); drug reactions (9 of 146 [6%]); atopic dermatitis (5 of 146 [3%]); and contact dermatitis (4 of 146 [3%]). Six patients (4%) ultimately received a diagnosis of BP. Other final diagnoses were pruritic urticarial papules and plaques of pregnancy (3 of 146 [2%]); confirmed scabies (2 of 146 [1%]); and other diagnoses (9 of 146 [6%]).

### Histopathologic UD

Of the 70 patients with a final diagnosis of UD, 53 (76%) had biopsy specimens available for review. Of those 53, most (40 [75%]) had biopsy specimen

**Table II.** Workup for 146 patients with clinical urticarial dermatitis

Laboratory test	No. (%)
Skin biopsy specimen (hematoxylin-eosin)	118 (81)
Complete blood cell count	106 (73)
Elevated eosinophil count	35 (33)
Direct immunofluorescence	99 (68)
Negative/nondiagnostic	94 (95)
Consistent with BP	3 (3)
Suggestive of vasculitis	1 (1)
Suggestive of lupus erythematosus	1 (1)
Cutaneous immunofluorescence	50 (34)
Negative	43 (86)
Positive cell surface staining	4 (8)
Positive BM zone staining	3 (6)
BP antigens	56 (38)
Normal	43 (77)
Abnormal BP180 only	6 (11)
Abnormal BP230 only	4 (7)
Both	3 (5)
Immunoglobulin E	29 (20)
Elevated	10 (34)
Normal	19 (66)
Patch testing	34 (23)
Scabies preparation	10 (7)
Positive	1 (10)
Negative	9 (90)
Antinuclear antibody	40 (27)
Elevated	4 (10)
Normal	36 (90)
TTG	33 (23)
Elevated	1 (3)
Normal	32 (97)
Antiendomysial antibody	8 (5)
Elevated	0 (0)
Normal	8 (100)

BM, Basement membrane; BP, bullous pemphigoid; TTG, tissue transglutaminase antibody.

findings consistent with histopathologic UD, confirming the final diagnosis per the criteria of Kossard et al.<sup>1</sup> This group of 40 included 25 (62%) women and 15 (38%) men, with a mean age of onset of 62 years (range, 30-92 years) (Table IV). The mean duration of disease at diagnosis was 22 months (median duration, 4.9 months). Most patients had involvement of the trunk (36 of 40 [90%]), lower extremities (33 of 40 [82%]), and upper extremities (30 of 40 [75%]). Fewer had involvement of the head/neck (7 of 40 [18%]) and groin (3 of 40 [8%]). No patients experienced palm or sole involvement.

### Conditions associated with histopathologic UD

Six of the 40 patients (15%) with a presentation consistent with clinical and histopathologic UD also had a history of malignancy, including 4 patients in

**Table III.** Final diagnoses of 146 patients with clinical urticarial dermatitis

Final diagnosis	No. (%) <sup>*</sup>
Urticarial dermatitis	70 (48)
Dermatitis NOS	24 (16)
Acute/chronic urticaria	14 (10)
Drug reaction	9 (6)
Bullous pemphigoid	6 (4)
Atopic dermatitis	5 (3)
Contact dermatitis	4 (3)
PUPPP	3 (2)
Scabies	2 (1)
Other <sup>†</sup>	9 (6)

NOS, Not otherwise specified; PUPPP, pruritic urticarial papules and plaques of pregnancy.

<sup>\*</sup>Percentages total <100% because of rounding.

<sup>†</sup>Other diagnoses were cutaneous T-cell lymphoma (n = 2), Schnitzler syndrome (n = 1), graft-versus-host disease (n = 1), asteatotic dermatitis (n = 1), hypereosinophilia (n = 1), irritant dermatitis (n = 1), and suspected scabies with response to empiric therapy (n = 2).

**Table IV.** Characteristics of 40 patients with clinical and histopathologic urticarial dermatitis

Characteristic	Value, No. (%) <sup>*</sup>
Age at onset, mean (SD), y	62 (18)
Median (range), y	62 (30-92)
Sex	
Female	25 (62)
Male	15 (38)
Site of involvement	
Trunk	36 (90)
Lower extremities	33 (82)
Upper extremities	30 (75)
Head/neck	7 (18)
Groin	3 (8)
Palms/soles	0 (0)
History of autoimmune conditions <sup>†</sup>	7 (18)
History of malignancy within 4 mo of UD onset <sup>‡</sup>	4 (10)
Inpatient dermatologic admission required	7 (18)
Duration of disease at diagnosis, mean, mo	22
Duration of disease at diagnosis, median, mo	4.9
Follow-up since diagnosis, mean, mo	11

UD, Urticarial dermatitis.

<sup>\*</sup>Values are number (percentage) unless indicated otherwise.

<sup>†</sup>Rheumatoid arthritis (n = 2); primary sclerosing cholangitis (n = 1); autoimmune hepatitis (n = 1); Crohn's disease (n = 1); multiple sclerosis (n = 1); and vitiligo (n = 1).

<sup>‡</sup>Myelodysplastic syndrome (n = 1); colonic tubular adenoma (n = 1); prostate cancer (n = 1); and vulvar cancer (n = 1).

whom UD developed within 4 months of that diagnosis (myelodysplastic syndrome concomitantly diagnosed in 1 patient [this patient also had a remote history of renal cell carcinoma and prostate cancer];

colonic tubular adenoma concomitantly diagnosed in 1 patient; prostate cancer diagnosed 3 months after onset of UD in 1 patient; and stage 4 vulvar cancer diagnosed 4 months before onset of UD in 1 patient). Two other patients had BRCA2-positive metastatic breast cancer (diagnosed 28 months before onset of UD) and infiltrating ductal breast cancer (diagnosed 65 months before UD). Seven of the 40 patients (18%) received a diagnosis of an autoimmune condition (rheumatoid arthritis [n = 2], primary sclerosing cholangitis [n = 1], autoimmune hepatitis [n = 1], Crohn's disease [n = 1], multiple sclerosis [n = 1], and vitiligo [n = 1]).

### Treatment of patients with histopathologic UD

The most commonly used treatments (in descending order of frequency) were oral antihistamines; topical corticosteroids; wet dressings with topical corticosteroids (at home or on the inpatient dermatology service); narrowband ultraviolet-B phototherapy; prednisone; and topical calcineurin inhibitors. Treatment responses to individual therapies could not be ascertained because multiple therapies were used simultaneously in many patients and there was no long-term follow-up in some patients after starting treatment. Overall, of the 35 patients who had more than 15 days of follow-up after treatment initiation, 7 (20%) had a complete response to treatment (ie, resolution of old lesions without incidence of new lesions); 12 (34%) had a partial response (ie, decreased extent and severity of lesions); and 16 (46%) experienced no response to treatment (ie, development of new lesions and persistence of old lesions). The patient with colonic tubular adenoma had complete resolution of UD after tumor resection and a tapering course of prednisone, but the eruption recurred shortly after prednisone was discontinued.

## DISCUSSION

### Comparisons with previous reports

We present a large case series of 146 patients with clinical features of UD seen at Mayo Clinic, and we describe the clinical characteristics, diagnostic evaluations, and etiologic associations of these patients. To our knowledge, this cohort represents one of the largest retrospective case series of patients presenting with clinical features of UD in the English-language medical literature since the original description of Kossard et al.<sup>1</sup> The demographics of our study population were fairly consistent with those of Kossard et al,<sup>1</sup> but with some slight differences. The female-to-male ratio was less pronounced in our study (1.5:1 vs 1.8:1), whereas the male-to-female difference in mean age of onset was

more pronounced (10 vs 6 years). Both studies suggest that UD primarily affects older patients (mean age of approximately 60 years), few if any under the age of 18 years, and women more frequently than men.

We found clinical UD to be less frequently associated with histopathologic UD than did Kossard et al.<sup>1</sup> The group of 91 patients with clinical UD in their study had histopathologic UD confirmed in 49 (53.8%) compared with our 27%. Other diagnosis frequencies were more similar; Kossard et al<sup>1</sup> diagnosed dermatitis in 23.1% (21 of 91) (vs 24% of our patients), urticaria/papular urticaria in 16.5% (15 of 91) (vs 10% of our patients), and drug reactions in 6.6% (6 of 91) (vs 6% of our patients). Despite these similarities, we found clinical UD to encompass a wider range of final diagnoses. Unlike the group of patients we studied, the clinical UD group examined by Kossard et al<sup>1</sup> did not have any ultimate diagnoses of scabies, BP, or pruritic urticarial papules and plaques of pregnancy. This difference may reflect methodology used in the current study; whereas the study of Kossard et al<sup>1</sup> searched archived dermatopathology reports containing UD (either within the clinical or pathologic diagnosis), we searched clinical medical records to identify our patient cohort. Dermatitis herpetiformis, urticarial vasculitis, and herpes gestationis—although commonly included as differential diagnoses in the subgroup of Kossard et al<sup>1</sup> of patients with histologic UD—were not seen as final diagnoses in our study.

### Clinical UD

Nearly half of the patients who presented with clinical features of UD (70 of 146; 48%) received a final diagnosis of UD upon completion of their evaluation. An additional 35 patients (24%) received a final diagnosis of another type of dermatitis based on the results of their diagnostic evaluation for UD (Table III). However, 41 patients (28%) who initially presented with clinical features of UD had other diagnoses (eg, drug reaction, BP, pruritic urticarial papules and plaques of pregnancy) to explain their cutaneous findings (Table III), strongly suggesting that clinical UD represents a reaction pattern seen in various dermatologic entities, and warrants further evaluation for a final diagnosis, as noted by Kossard et al<sup>1</sup> and Tharp.<sup>4</sup>

Fourteen of the 146 patients (10%) who received an initial diagnosis of UD received a final diagnosis of urticaria, despite the 24-hour requirement for distinguishing the former from the latter. This could be owing to an unclear history that was clarified over subsequent visits, or less likely, to lesions lasting

approximately 24 hours that made the distinction difficult. Nevertheless, our finding is fairly consistent with that of Kossard et al,<sup>1</sup> who found that 16.5% of patients with an initial clinical diagnosis of UD had a final diagnosis of urticaria or papular urticaria.

Our review of the patients' workup (Table II) revealed a few findings that were somewhat discordant with results that might be expected on the basis of the final diagnoses. One patient with DIF microscopy results suggestive of vasculitis ultimately had a diagnosis of chronic urticaria after an extensive workup (including routine histopathology and additional negative DIF studies). Another whose DIF result was suggestive of lupus ultimately had a diagnosis of an adverse reaction to ramipril based on clinical history and routine histopathologic findings. Although 1 patient was found to have a weakly positive tissue transglutaminase antibody (immunoglobulin G), further evaluation was negative for gluten-sensitive enteropathy. In addition, only 1 of 4 patients with contact dermatitis had clinically relevant positive patch test results, whereas 3 had a diagnosis based on history and examination (2 of whom did not undergo patch testing). Finally, 8 patients had mild and clinically insignificant elevations of BP180 and/or BP230 antigens, with negative additional workup for BP; whereas 1 patient with a final diagnosis of BP (based on clinical and routine histopathologic findings) had normal BP180 and/or BP230 values.

Our study found several final diagnoses not commonly associated with clinical UD, including cutaneous T-cell lymphoma, Schnitzler syndrome, and graft-versus-host disease. Another patient experienced hypereosinophilia for many years before onset of UD. After extensive workup, her cutaneous symptoms were attributed to hypereosinophilia, similar presentations of which have been described previously.<sup>3,5</sup>

### Clinical and histopathologic UD

Forty of the 70 patients with a final diagnosis of UD in our study had skin biopsy specimens compatible with UD (Table IV). Although our study design did not allow us to assess treatment responses to individual therapies, nearly half of the patients with at least 15 days of follow-up after treatment initiation had no response to therapy, which underscores the assertion of Kossard et al<sup>1</sup> that UD can often be persistent and difficult to treat.

Interestingly, 4 of the 40 patients with UD (10%) described above had a cancer diagnosis within 4 months of the onset of their cutaneous findings. Whether UD also represents a paraneoplastic phenomenon in a small subset of patients is unclear,



but perhaps a malignancy workup should be considered in patients with recalcitrant UD and/or in those with a concerning review of systems.

### Limitations

Given the retrospective design of this study, diagnostic evaluations and treatment protocols were not standardized for patients who presented with UD. Our study design precluded us from describing the spectrum of clinical entities that can present with histopathologic findings of UD. However, one strength of the current study is that it identified the eventual dermatologic diagnoses and outcomes in a large cohort of patients who initially presented with clinical features of UD.

### CONCLUSION

Our study delineates a broad array of ultimate dermatologic diagnoses in a large cohort of patients presenting initially with UD, which suggests that the clinical features of UD represent a reaction pattern that may be seen in various dermatologic conditions

and that diagnostic evaluation is necessary to correlate clinical findings in a given patient. We also found a minority of patients (10%) whose onset of clinical and histopathologic features of UD was temporally associated with a malignancy diagnosis. Future studies should prospectively assess patients with UD to determine the optimal evaluation and management of UD.

### REFERENCES

1. Kossard S, Hamann I, Wilkinson B. Defining urticarial dermatitis: a subset of dermal hypersensitivity reaction pattern. *Arch Dermatol* 2006;142:29-34.
2. Fung MA. The clinical and histopathologic spectrum of "dermal hypersensitivity reactions," a nonspecific histologic diagnosis that is not very useful in clinical practice, and the concept of a "dermal hypersensitivity reaction pattern." *J Am Acad Dermatol* 2002;47:898-907.
3. Rietschel RL. A clinician's view of urticarial dermatitis. *Arch Dermatol* 2006;142:932.
4. Tharp MD. Top-accessed article: defining urticarial dermatitis. *Arch Dermatol* 2011;147:1436.
5. Kazmierowski JA, Chusid MJ, Parrillo JE, Fauci AS, Wolff SM. Dermatologic manifestations of the hypereosinophilic syndrome. *Arch Dermatol* 1978;114:531-5.