

Letter to the Editor

Chronic spontaneous urticaria: Implications of subcutaneous inflammatory cell infiltration in an intractable clinical course

To the Editor:

Chronic urticaria is divided into 2 subgroups according to whether symptoms occur spontaneously, which is called chronic spontaneous urticaria (CSU), or are induced by a demonstrable stimulus, called chronic inducible urticaria.¹ CSU is more common than previously thought, with an estimated point prevalence

of 0.5% to 1%.² The duration of CSU is generally 1 to 5 years, but it is likely to be longer in severe cases, despite the use of standard treatments such as antihistamines.² The clinical factors that are associated with a poor response to treatment have not been identified.² We therefore studied the relationship between the clinical outcomes and histopathologic findings of CSU to determine the clinicopathological factors responsible for a poor response to treatment.

For materials and methodology, please see the [Methods](#) section in this article's Online Repository at www.jacionline.org. A flow chart of the patients enrolled in this study is presented in

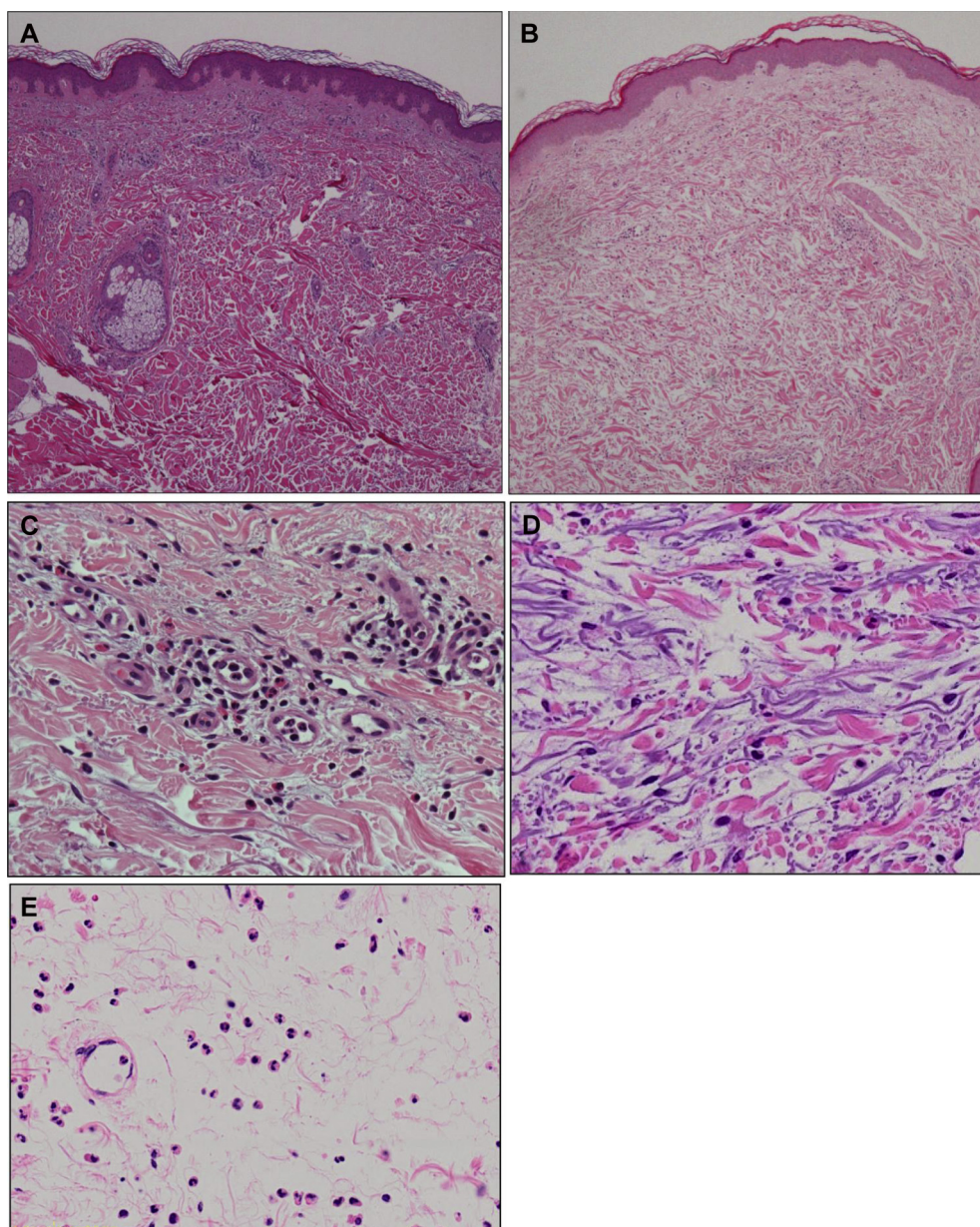


FIG 1. Histopathologic features of CSU. **A**, Mild dermal edema. Original magnification: $\times 20$. **B**, Severe dermal edema. Original magnification: $\times 20$. **C**, Perivascular dermal infiltration. Original magnification: $\times 100$. **D**, Interstitial dermal infiltration. Original magnification: $\times 100$. **E**, Subcutaneous infiltration. Original magnification: $\times 100$.

TABLE I. Clinical and pathological variables of patients regarding good or poor response, and multivariate logistic regression analysis

Characteristics	Good responders (n = 26)	Poor responders (n = 10)	P value
Sex (male/female)	7/19	4/6	.454
Age (y), median (range)	49 (25-70)	47.5 (30-75)	.805
Prior treatment			
H ₁ antihistamine	18	8	.690
Oral steroid	12	4	1.000
None	6	2	1.000
Current treatment in our hospital			
H ₁ antihistamine (standard dose, single)	14	3	.274
H ₁ antihistamine (higher dose or multiple)	10	7	.139
Antileukotrienes	8	8	.011
H ₂ antihistamine	14	9	.060
Oral steroid	16	8	.438
Duration of disease at biopsy (d), median (range)	176.5 (42-6438)	216 (51-2541)	.297
Comorbid diseases (yes/no)	5/21	6/4	.039
Pathological variables			
Edema (mild/severe)	8/18	4/6	.700
Type of dermal infiltration			
Perivascular type	13	2	.142
Perivascular plus interstitial type	13	8	
Eosinophil count			
≥10/hpf	5	3	.658
<10/hpf	21	7	
Neutrophil count			
≥10/hpf	4	3	.370
<10/hpf	22	7	
Location of infiltration			
Dermal only	18	2	.011
Dermal plus subcutaneous	8	8	
Odds ratio (95% CI)			P value
Age (y)	1.01 (0.93-1.10)		.796
Sex (male)	0.49 (0.02-7.11)		.608
Comorbid disease (yes)	3.64 (0.45-36.33)		.223
Antileukotrienes	33.65 (2.54-1634.08)		.005
Location of infiltration (dermal and subcutaneous)	26.62 (2.62-920.35)		.003

Fig E1 and their demographic findings are summarized in Table E1 in this article's Online Repository at www.jacionline.org. We analyzed 36 cases of CSU and collected clinical information including sex, age, previous and current treatments, duration of disease at biopsy, comorbid diseases, and response to treatment (recurrence interval, ≥3 or <3 months; ie, *poor responders* were defined as those whose recurrence interval was <3 months even though they continued treatments). The histopathological findings were evaluated for 5 variables: edema (mild or severe), type of dermal infiltration (perivascular or perivascular plus interstitial), eosinophil count (≥10/hpf or <10/hpf), neutrophil count (≥10/hpf or <10/hpf), and site of infiltration (dermal only or dermal plus subcutaneous) (Fig 1).

Regarding the histopathologic features, there were no apparent changes in the epidermis. None of the cases showed purpura and vasculitis.³⁻⁵ In most cases (n = 24 [67%]), severe edema was observed in the dermis. The dermal cellular infiltrates were confined to the perivascular area in 15 (42%), whereas there was both perivascular and interstitial dermal infiltration in 21 (58%) specimens. In addition, regarding eosinophils and neutrophils, they had infiltrated at a rate of greater or equal to 10/hpf in 8 (22%) and 7 (19%) cases, respectively. The cellular infiltrate was detected only in the dermis in 20 (56%) cases, but

it extended deep into the subcutaneous tissue in 16 (44%) (Table E1).

Out of 36 patients who were followed up (mean, 18 months; range, 4-267 months), 26 were free of urticaria for more than 3 months (good responders), whereas the outcome in 10 cases remained poor (poor responders). Table I presents a comparison of the clinical and pathological variables of patients for good and poor responders. Fisher exact test demonstrated (1) that comorbid diseases and antileukotrienes were significantly more common in poor responders than in good ones ($P = .039$ and $.011$, respectively) and (2) that, in the biopsy specimens from poor responders, deep-seated dermal plus subcutaneous infiltration was significantly more common than in good responders ($P = .011$). Multivariate logistic regression analysis with 5 variables (age, sex, comorbid disease, antileukotrienes, and location of infiltration) revealed that antileukotrienes and subcutaneous inflammatory infiltration were significantly associated with a poor response in CSU (antileukotriene odds ratio, 33.65; 95% CI, 2.54-1634.08; subcutaneous inflammatory infiltration odds ratio, 26.62; 95% CI, 2.62-920.35) (see later part of Table I).

In this study, poor clinical response in CSU was significantly associated with the presence of comorbid diseases, antileukotrienes,

and subcutaneous inflammatory cell infiltration. Other clinical factors unrelated to the treatment outcome were age, sex, prior therapeutic drugs, and disease duration at biopsy. In multivariate logistic regression analysis, antileukotrienes and subcutaneous inflammatory cell infiltration remained as significant factors that predicted intractability to therapy. Regarding antileukotrienes, the present data led us to confirm that physicians tend to prescribe these drugs to patients with CSU with a more intractable clinical course.

The histopathological features of urticaria were previously characterized as dermal edema and dermal perivascular and interstitial inflammatory cell infiltration with minimal epidermal change.⁵ Edema of the dermis is evaluated by the extent of disintegration of dermal connective tissue, while the cellular infiltrates are composed of neutrophils and eosinophils, as well as lymphoid cells.⁵ These studies prompted us to examine the correlation of histopathological findings with the clinical response to therapeutic modalities in CSU. The present study revealed that the intensity of edema, type of dermal cell infiltration (perivascular or perivascular plus interstitial), and number of infiltrated eosinophils or neutrophils were not related to the responsiveness to standard treatments. We found that 44% of CSU specimens exhibited subcutaneous inflammatory cell infiltration together with dermal infiltration. Subcutaneous inflammatory cell infiltration in CSU was not discussed in previous reports,³⁻⁶ whereas subcutaneous eosinophilic infiltration was noted in delayed pressure urticaria.⁷ In our cases, the subcutaneous inflammatory cells were composed of neutrophils, eosinophils, and lymphoid cells, consistent with those infiltrating the dermis, but at lower levels.

Our multivariate analysis identified a significant association between subcutaneous inflammatory cell infiltration and a poor treatment response. CSU is well known to be significantly associated with autoimmune diseases such as thyroiditis, rheumatoid arthritis, and Sjögren syndrome, as shown by a large population study.⁸ In our 36 cases with CSU, 4 comorbid autoimmune diseases (Basedow disease, rheumatoid arthritis, Sjögren syndrome, and ulcerative colitis) were found. Among the autoimmune diseases, thyroid diseases show conspicuously frequent comorbidity, although the pathomechanisms behind this remain unclear.⁹ Interestingly, all 4 of our patients with autoimmune diseases had subcutaneous inflammatory cell infiltration. Such infiltration might also be indicative of an association of CSU with autoimmune diseases.

There were many limitations in this study, such as a small number of eligible cases, retrospective clinical evaluation,

variable histological and clinical features, and different treatment regimens. The timing and location of biopsy may also affect the histopathological findings of CSU. Further large-scale studies are thus required to confirm the validity of the present results. In conclusion, subcutaneous inflammatory cell infiltration is an integral part of the histopathological features of CSU and is potentially predictive of the failure of CSU to respond to standard therapies.

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METHODS

Patients and histopathological findings

Among the archival biopsy specimens ($n = 16,595$) obtained at the Department of Dermatology, Kyushu University, between January 1, 2002, and December 31, 2014, 82 biopsy specimens were diagnosed as urticaria in concert with the clinical findings. Among these 82 cases, 27 were acute urticaria and the remaining 55 were clinically proven CSU. Among these 55 cases of CSU, we excluded 19 cases because of missing data on clinical follow-up. We thus finally analyzed 36 cases of CSU in this study (Fig E1). None of these 36 cases showed the features of urticarial vasculitis and angioedema. We collected clinical information including sex, age, previous and current treatments, duration of disease at biopsy, and comorbid diseases. Data on clinical responses to treatment were also retrieved from the patients' files. The histopathological findings were evaluated for 5 variables: edema

(mild or severe, Fig 1, A and B), type of infiltration (perivascular or perivascular plus interstitial, Fig 1, C and D), eosinophil count ($\geq 10/\text{hpf}$ or $< 10/\text{hpf}$), neutrophil count ($\geq 10/\text{hpf}$ or $< 10/\text{hpf}$), and location of infiltration (dermal only or dermal plus subcutaneous, Fig 1, E). This study was approved by the ethics committee of Kyushu University Hospital (approval no. 27-157).

Statistical analysis

Continuous variables are presented as the median (range) and were compared using the Mann-Whitney U test. Categorical variables were compared using Fisher exact test. Logistic regression analysis was performed to identify variables associated with a poor response. Values of P less than .05 were considered statistically significant. Data are expressed as median and range. All statistical analyses were performed using JMP 11 (SAS Institute, Inc, Cary, NC).

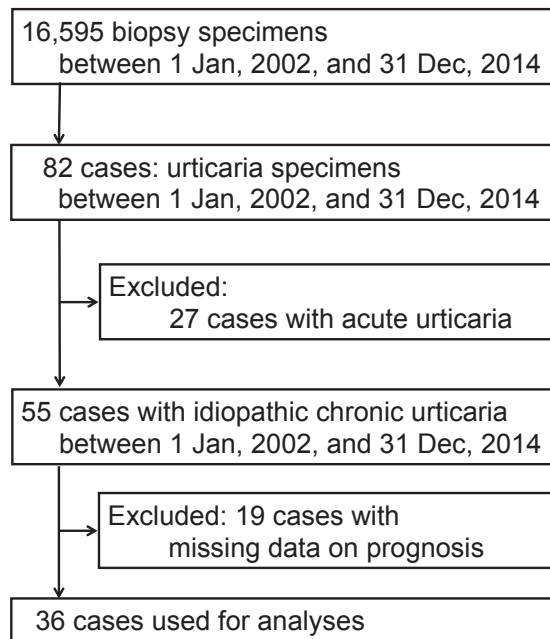


FIG E1. A flow chart of patients enrolled in this study.

TABLE E1. Characteristics of 36 patients with CSU

Characteristic	n (%)
Sex	
Male/female	11/25 (31%/69%)
Age (y), median (range)	49 (25-75)
Prior treatment	
H ₁ antihistamine	26 (72%)
Oral steroid	16 (44%)
None	8 (22%)
Current treatment in our hospital	
H ₁ antihistamine (standard dose, single)	17 (47%)
H ₁ antihistamine (higher dose or multiple)	17 (47%)
Antileukotrienes	16 (44%)
H ₂ antihistamine	23 (64%)
Oral steroid	24 (67%)
Duration of disease at biopsy (d), median (range)	184 (42-6438)
Comorbid diseases	
Yes/no	11/25 (31%/69%)
Pathological variables	
Edema	
Mild	12 (33%)
Severe	24 (67%)
Type of dermal infiltration	
Perivascular type	15 (42%)
Perivascular plus interstitial type	21 (58%)
Eosinophil count	
≥10/hpf	8 (22%)
<10/hpf	28 (78%)
Neutrophil count	
≥10/hpf	7 (19%)
<10/hpf	29 (81%)
Location of infiltration	
Dermal only	20 (56%)
Dermal plus subcutaneous	16 (44%)