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

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molecules might be capable of inducing an inappropriate stimulation of the type I IFN response pathway.

In conclusion, our case further expands the clinical spectrum associated with *TRNT1* mutations. TRNT1 deficiency should be considered not only in patients presenting with classical SIFD features but also in patients with B-cell immunodeficiency, prominent gastrointestinal disease, and elevated inflammatory markers (IL-6 and IFN-α) in serum.

We are indebted to the patient and his parents.

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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 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

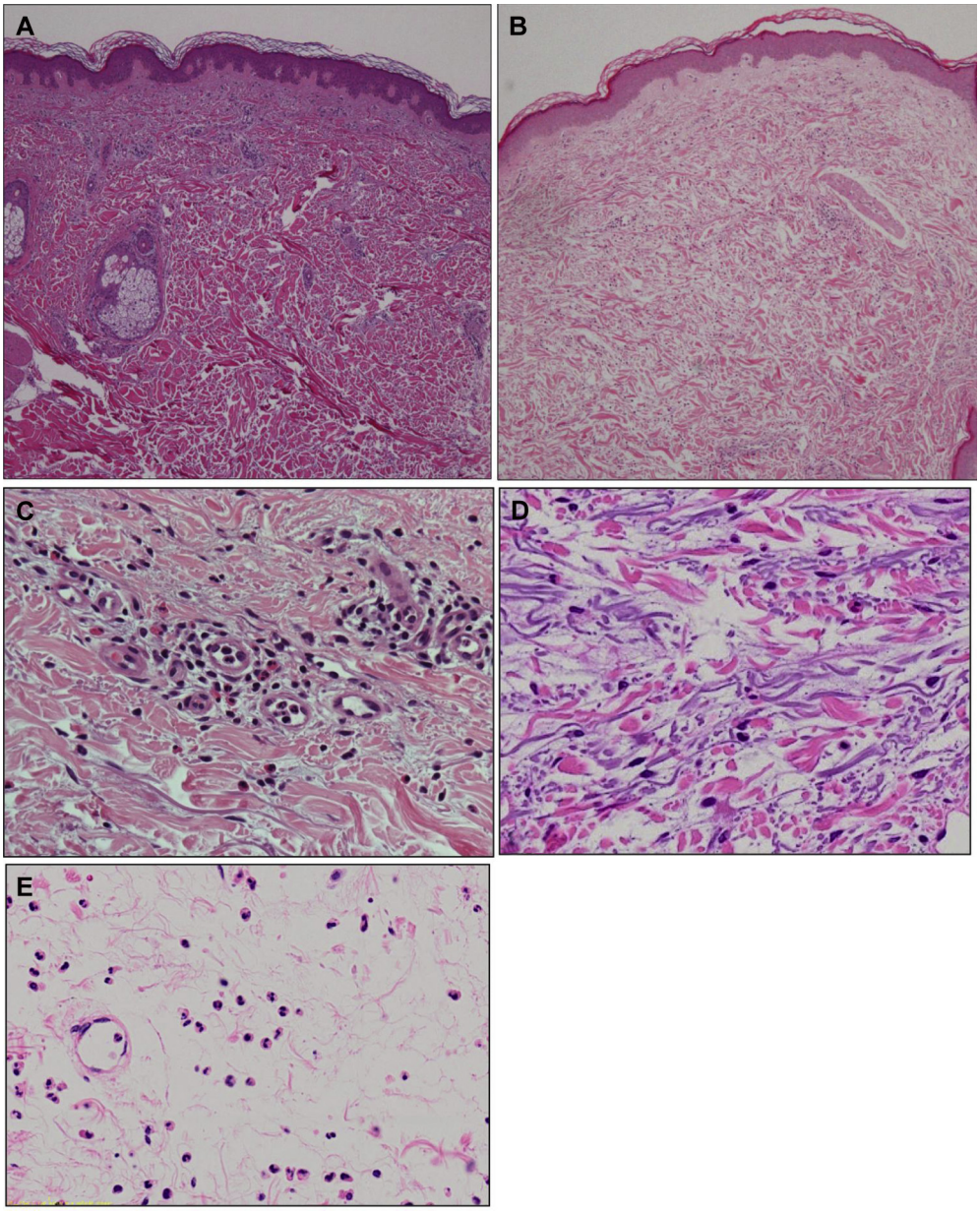

FIG 1. Histopathologic features of CSU. **A,** Mild dermal edema. Original magnification: ×20. **B,** Severe dermal edema. Original magnification: ×20. **C,** Perivascular dermal infiltration. Original magnification: ×100. **D,** Interstitial dermal infiltration. Original magnification: ×100. **E,**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

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

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

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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Exploiting CD22 on antigen-specific B cells to prevent allergy to the major peanut allergen Ara h 2

To the Editor:

Oral, sublingual, and epicutaneous immunotherapies are under clinical study as potential food allergy therapies, yet the side effects, requirement for daily dosing, and lack of prolonged efficacy remain limitations in these human trials.[1,2] Targeting the allergen-specific B cells may limit side effects and promote long-term tolerance.

Sialic acid–binding immunoglobulin-type lectins (Siglecs) are a family of immunomodulatory receptors with cell-specific expression.[3] Inhibitory Siglecs, including CD22 expressed on B cells, use immunoreceptor tyrosine-based inhibitory motifs to suppress activatory receptors, such as the B-cell receptor (BCR). Enforcing colocalization of CD22 with the BCR, with liposomes that codisplay an antigen and high-affinity CD22 ligand, not only prevents B-cell activation but also induces apoptosis of the antigen-reactive B cells, resulting in robust immunological tolerance due to depletion of the antigen-specific B cells from the B-cell repertoire.[4] These Siglec-engaging tolerance-inducing antigenic liposomes (STALs) can be formulated with any antigen of choice. STALs displaying factor VIII (FVIII) inhibit antibody responses to exogenous FVIII, preventing bleeding in FVIII$^{-/-}$ mice.[4] Accordingly, STALs have the potential to prevent undesired B-cell responses and we were motivated to examine their potential for inducing immunological tolerance to a food allergen.

Peanut allergies are dominated by undesired IgE antibody responses to the 2S albumin Ara h 2 (Ah2),[5,6] which induce degranulation of effector cells on exposure to the antigen. We hypothesized that STALs displaying both a high-affinity and selective CD22 ligand and Ah2 (Fig 1, *A*) could be an attractive strategy to prevent sensitization and subsequent anaphylaxis to Ah2 and potentially whole peanut extract (WPE).

A schematic representing the experimental design is shown in Fig 1, *B*. All animal studies were approved by the University of North Carolina Institutional Animal Care and Use Committee and investigated under protocol number 13-216.0. Four-week-old female BALB/cJ mice (Jackson Laboratories, Bar Harbor, Me) were injected intravenously with 200 μL of 100 μM Ah2 STALs (n = 8), 300 μM Ah2 STALs (n = 8), 100 μM immunogenic Ah2 liposomes (n = 8), or 300 μM immunogenic Ah2 liposomes (n = 7). All liposomes consisted of 0.03 mol% Ah2, which amounted to a dose of 0.12 μg of Ah2 in the 100-μM group. STALs also consisted of 1% BPA-Neu5Gc, the high-affinity and selective CD22 ligand.[4] Two weeks following infusion of STALs, a time frame previously determined to maximize tolerance induction through STALs,[4] the mice were orally sensitized, with 2 mg WPE and 10 μg cholera toxin (CT) weekly for 3 weeks followed by a boost dose of 5 mg WPE and 10 μg CT. A group of naive mice (n = 8) underwent the same protocol and were injected with PBS to determine baseline titers. Serum was collected 1 week later to quantify specific IgE (sIgE) and sIgG$_1$ levels to Ah2, WPE, Ah1, and CT by ELISA.[6] Mice were initially challenged with 200 μg Ah2 via an intraperitoneal injection. One week later, mice were challenged intraperitoneally with 750 μg WPE. To assess anaphylaxis during challenge, rectal temperatures were recorded for 30 minutes, and symptom scores were documented at 30 minutes using a 0- to 5-point scale, where 0 represents no symptoms and 5 represents death, as described previously.[6] All methods are described in detail in this article's Online Repository at www.jacionline.org.

On day 42, before the challenge, Ah2 sIgE levels were significantly lower in animals injected with either 100 μM or 300 μM Ah2 STALs compared with those injected with the same dose of immunogenic controls (100 μM, $P = .0002$; 300 μM, $P = .0006$) (Fig 1, *C*). Pretreatment with Ah2 STALs also inhibited production of Ah2 sIgG$_1$ compared with controls (100 μM, $P = .0047$; 300 μM, $P = .0006$) (Fig 1, *D*). Upon challenge with 200 μg Ah2, mice pretreated with either 100 μM or 300 μM Ah2 STALs were protected from hypothermia, an objective feature of anaphylaxis in mice, compared with mice pretreated with immunogenic control that

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 (≥10/hpf or <10/hpf), neutrophil count (≥10/hpf or <10/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).

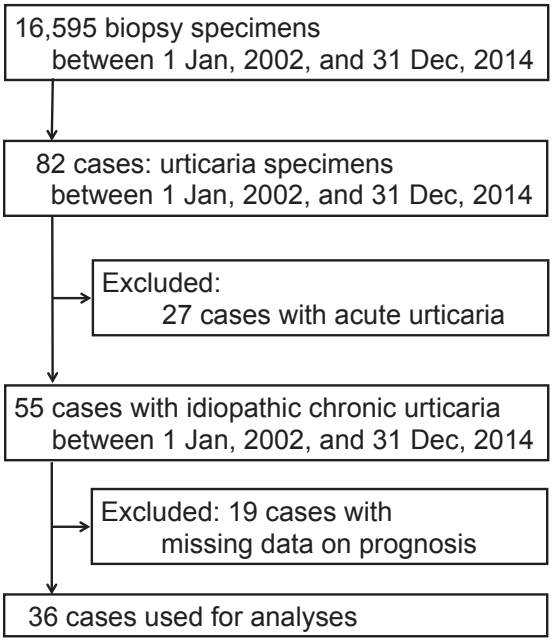

FIG E1. A flow chart of patients enrolled in this study.

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%)