



Nociceptive pain as a clinical presentation of chronic urticaria and disappearance with immunoglobulin/histamine complex therapy: a case report

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Itching is a representative manifestation of urticaria. However, under certain conditions, urticaria may be characterized by nociceptive sensations, such as stinging or tingling, either instead of or in addition to itching. Three patients with chronic urticaria (CU) who experienced nociceptive pain accompanied by itching were identified and treated with immunoglobulin/histamine complex (IHC) therapy. Nociceptive pain resolved along with improvement in CU symptoms after 8 injections of IHC in the first patient and after 4 injections in the second and third patients. Nociceptive pain may present as a symptom of CU. The clinical characteristics of the transition from itching to nociceptive pain, together with the observed outcomes of IHC therapy, appear to support the intensity theory explaining this shift, which may be mediated by histamine. Further clinical and basic immunological studies are warranted to clarify the underlying mechanisms.

Keywords: Chronic urticaria; Histamine; Immunoglobulin; Nociceptive pain; Case reports

Introduction

Itching is a characteristic and typical manifestation of urticaria, including chronic urticaria (CU) [1]. However, under certain conditions, urticaria may present with nociceptive pain, such as stinging or tingling, either instead of or in addition to itching [2].

Histamine plays a central role in the pathogenesis of CU [3]. In addition, histamine is a known mediator of pain sensation [4]. Both itching and nociceptive signals are typically transmitted through C-fibers [5].

Histobulin (Green Cross PD) is an immunoglobulin/histamine complex (IHC) preparation comprising 0.15 µg of histamine dihydrochloride and 12 mg of immunoglobulin G [6]. It was developed to regulate serum histamine levels through histaminopexy [7]. IHC is effective in the treatment of allergic rhinitis, bronchial asthma, CU, and atopic dermatitis [8].

IHC therapy has been reported to be effective for the treatment of CU [9,10]. Its therapeutic effects are progressive and gradual, in contrast to those of other treatments, including omalizumab and antihistamines, which typically produce more rapid symptom relief [11,12]. Recent studies have suggested that IHC may induce remission and have proposed IHC therapy as a potentially effective therapeutic modality for CU [8].

The primary mechanism of action of IHC is histaminopexy, which involves regulation of circulating histamine levels through inhibition of histamine release from mast cells and induction of antibodies against histamine [13-15].

Given current understanding of the pathophysiology of histamine-mediated nociceptive signaling [4,5], the clinical presentations of CU—itching and nociceptive pain—may represent closely related manifestations rather than entirely distinct symptoms.

This report describes 3 patients with CU who presented with

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nociceptive pain. The clinical characteristics of itching and nociceptive pain in these patients, as well as their changes during IHC therapy, are detailed.

Case presentation

Ethics statement

Informed consent was obtained from all patients.

Case 1

The first patient was a 39-year-old Korean woman who presented to the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital with urticaria and itching accompanied by a tingling sensation described as nociceptive pain for 1 month (Fig. 1). She reported recurrent episodes of nociceptive pain associated with itching. There was no personal or family history of CU.

Because the patient's symptoms persisted for more than 6 weeks during evaluation, a diagnosis of CU was established according to accepted diagnostic criteria [1]. Following this diagnosis, laboratory evaluations were performed, including a complete blood count with differential and measurements of serum eosinophil cationic protein, total serum immunoglobulin E (IgE), and allergen-specific IgE using a multiple allergosorbent test (MAST; Green Cross PD). Serum immunoglobulin A levels were also measured prior to initiation of IHC therapy (Table 1). In the MAST, specific IgE levels for 41 allergens were assessed, and values < 0.35 IU/mL were considered negative. A skin prick test was also performed for 53 allergens. Histamine hydrochloride (10 mg/mL) served as the positive control, and normal saline served as the negative control. Wheal diameters were measured, and re-



Fig. 1. Urticaria in a patient with chronic urticaria (case 1).

Table 1. Results of basic allergy laboratory tests

	Case 1	Case 2	Case 3
Laboratory tests (normal range, unit)			
Blood eosinophil fraction (0%–5%)	1.7	0.2	3
Blood basophil fraction (0.0%–1.0%)	0.9	0.1	0.5
Serum eosinophil cationic protein (0–24 ng/mL)	48.9	16	104
Serum total IgE (≤ 350 IU/mL)	52	179	726
Serum IgA (70–400 mg/dL)	271	232	240
MAST allergens (IU/mL)			
<i>Alternaria alternata</i>	< 0.35	< 0.35	< 0.35
<i>Aspergillus fumigatus</i>	< 0.35	< 0.35	< 0.35
<i>Penicillium notatum</i>	< 0.35	< 0.35	< 0.35
<i>Cladosporium herbarum</i>	< 0.35	< 0.35	< 0.35
Cockroach	< 0.35	< 0.35	< 0.35
House dust mites	< 0.35	< 0.35	< 0.35
<i>Dermatophagoides pteronyssinus</i>	< 0.35	1.54	19.79
<i>D. farinae</i>	< 0.35	0.65	5.37
Dog	< 0.35	< 0.35	< 0.35
Cat	< 0.35	< 0.35	< 0.35
Birch-Alder mix	< 0.35	< 0.35	9.05
Mugwort	< 0.35	< 0.35	0.97
Short Ragweed	< 0.35	< 0.35	0.98
Sallow willow	< 0.35	< 0.35	< 0.35
Orchard grass	< 0.35	< 0.35	46.56
Bermuda grass	< 0.35	< 0.35	0.47
Timothy grass	< 0.35	< 0.35	97.76
Sweet vernal grass	< 0.35	< 0.35	19.71
Rye pollen	< 0.35	< 0.35	29.37
White oak	< 0.35	< 0.35	< 0.35
Japanese cedar	< 0.35	< 0.35	0.38
Reed	< 0.35	< 0.35	< 0.35
Japanese hop	< 0.35	< 0.35	< 0.35
Acacia	< 0.35	< 0.35	< 0.35
Pine	< 0.35	< 0.35	< 0.35
Poplar mix	< 0.35	< 0.35	< 0.35
Sycamore	< 0.35	< 0.35	< 0.35
Ash mix	< 0.35	< 0.35	0.35
Oxeye daisy	< 0.35	< 0.35	< 0.35
Dandelion	< 0.35	< 0.35	< 0.35
Russian thistle	< 0.35	< 0.35	< 0.35
Goldenrod	< 0.35	< 0.35	0.95
Pigweed	< 0.35	< 0.35	0.38
Crab	< 0.35	< 0.35	< 0.35
Shrimp	< 0.35	< 0.35	< 0.35
Mackerel	< 0.35	< 0.35	< 0.35
Soybean	< 0.35	< 0.35	< 0.35
Hazelnut	< 0.35	< 0.35	0.98
Peach	< 0.35	< 0.35	< 0.35
Milk	< 0.35	< 0.35	< 0.35

(Continued on the next page)

Table 1. Continued

	Case 1	Case 2	Case 3
Egg white	< 0.35	< 0.35	< 0.35
Skin prick test (grade) allergens			
<i>Alternaria alternata</i>	-	-	-
<i>Aspergillus fumigatus</i>	-	-	-
<i>Aspergillus niger</i>	-	-	-
<i>Candida albicans</i>	-	-	-
<i>Cladosporium</i>	-	-	2
<i>Penicillium chrysogenum</i>	-	-	-
German cockroach	-	2	-
<i>D. pteronyssinus</i>	-	3	3
<i>D. farinae</i>	-	3	3
Dog	-	-	-
Cat	-	-	-
Grey alder, silver birch	-	-	2
Grass mix	-	-	4
Mugwort	-	-	4
Short ragweed	-	-	-
Black willow pollen	-	-	-
Orchard	-	-	4
Bermuda grass	-	-	-
Timothy	-	-	-
English plantain	-	-	-
English ryegrass	-	-	4
Holm oak	-	-	-
Japanese cedar	-	-	2
Latex	-	-	-
Milk	-	-	-
Egg	-	-	-
Chicken	-	-	-
Beef	-	-	-
Pork	-	-	-
Cod	-	-	-
Oyster	-	-	-
Salmon	-	-	-
Prawn	-	-	-
Mackerel	-	-	-
Tuna	-	-	-
Almond	-	-	-
Peanut	-	-	-
Bean	-	-	-
Carrot	-	-	-
Cabbage	-	-	-
Walnut	-	-	-
Maize	-	-	-
Peach	-	-	-
Tomato	-	-	-
Black pepper	-	-	-
Spinach	-	-	-

(Continued on the next column)

Table 1. Continued

	Case 1	Case 2	Case 3
Wheat	-	-	-
Rabbit	-	-	-
Kapok	-	-	-
Hop	-	-	-
F acacia	-	-	-
Pine	-	-	-
Poplar	-	-	-

IgE, immunoglobulin E; IgA, immunoglobulin A; MAST, multiple allergosorbent test.

actions were read after 15 minutes. Responses were graded as follows: negative (0, no reaction); 1+ (reaction greater than the control but less than half the size of the histamine reaction); 2+ (equal to or more than half the size of the histamine reaction); 3+ (equal to or more than the size of the histamine reaction); or 4+ (equal to or more than twice the size of the histamine reaction). A wheal size of ≥ 3 mm was considered positive. The patient was instructed to discontinue antihistamines for at least 5 days before testing.

All allergy laboratory tests yielded results within normal ranges, including the eosinophil fraction on complete blood count, serum eosinophil cationic protein, and total serum IgE levels (Table 1). No allergen-specific IgE levels were elevated on MAST, and no positive reactions were observed on skin prick testing.

The clinical severity of CU was assessed using the Urticaria Severity Scale described by Jariwala et al. [16], which has a maximum possible score of 93 points. Pain severity was evaluated using a numerical rating scale with a maximum score of 10 [2].

Histobulin (Green Cross) was used as the IHC preparation. Each 2-mL ampule contains 12 mg of human immunoglobulin and 0.15 μ g of histamine [6]. IHC was administered by weekly subcutaneous injection into the deltoid region of the upper arm until remission was achieved. During therapy, the patient was instructed to take levocetirizine 5 mg once daily as needed if symptoms interfered with activities of daily living, work, or sleep. Nociceptive pain resolved as CU symptoms improved following 8 IHC injections (Fig. 2A).

During symptomatic episodes, itching developed first and was followed shortly thereafter by nociceptive pain (Fig. 3). In all 3 patients, administration of levocetirizine led to resolution of nociceptive pain; itching subsequently reappeared briefly before gradually subsiding during each episode.

Case 2

The second patient was a 42-year-old Korean woman who presented to the Department of Allergy and Clinical Immunology at

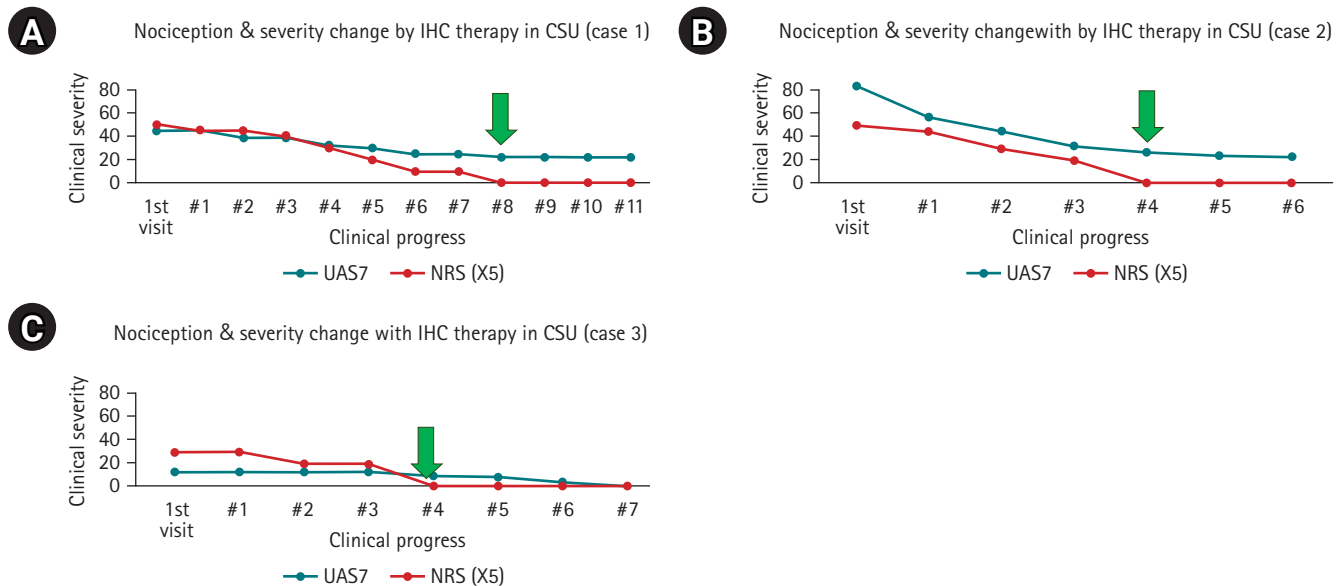


Fig. 2. Changes in nociceptive pain and clinical severity during immunoglobulin/histamine complex (IHC) therapy. (A) Case 1. (B) Case 2. (C) Case 3. Nociceptive pain resolved with decreasing clinical severity of chronic urticaria during IHC therapy. The green arrows in (A), (B), and (C) indicate the points at which nociceptive pain resolved. CSU, chronic spontaneous urticaria; UAS7, urticaria activity score for 7 days; NRS, numeric rating scale.

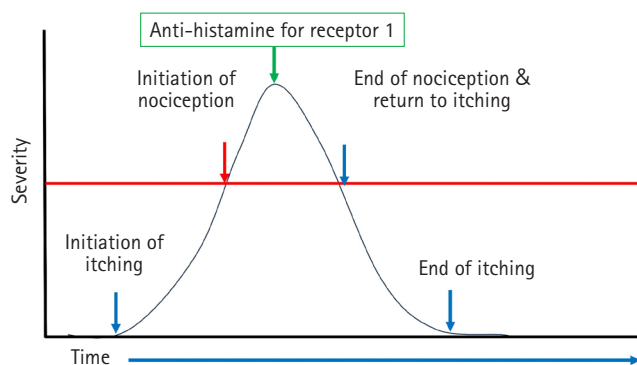


Fig. 3. Schematic of changes during an episode of itching and nociceptive pain symptoms in a representative case (case 1). Severity on the y-axis is shown schematically based on patient descriptions. Nociceptive pain and itching resolved after administration of an antihistamine (histamine receptor 1 blocker).

Cheju Halla General Hospital with urticaria, combined itching and stinging described as a nociceptive sensation, and frequent angioedema of the lips for 4 months. She had no personal history of CU; however, her brother had previously experienced urticaria and itching. She underwent the same basic allergy evaluation as described in case 1, including MAST and skin prick testing.

No abnormal laboratory findings were identified except for elevated allergen-specific IgE levels to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and cockroach on MAST and posi-

tive skin reactivity on skin prick testing (Table 1). IHC therapy was initiated, and nociceptive pain resolved as CU symptoms improved after 4 IHC injections (Fig. 2B).

Case 3

The third patient was a 57-year-old Japanese woman who presented to the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital with urticaria and combined itching and a tingling sensation described as a nociceptive symptom. Her history included several prior episodes of urticaria. She also reported a family history of urticaria in both parents, and her grandmother had atopic dermatitis. Basic allergy testing with MAST and skin prick tests was performed as described in case 1.

Laboratory testing showed allergen-specific IgE to multiple allergens, including *D. pteronyssinus*, *D. farinae*, and pollens, on MAST, along with positive skin reactivity on skin prick testing (Table 1). IHC therapy was administered, and CU symptoms improved. After 4 IHC injections, the patient's nociceptive pain resolved as her CU presentation improved (Fig. 2C).

Discussion

As shown in this report, some patients with CU may experience nociceptive pain in addition to itching. In all 3 patients, nociceptive pain resolved as CU symptoms improved following IHC therapy (Fig. 2).

The primary mechanism of action of IHC is thought to involve

histaminopexy, including histamine-fixing effects that promote the production of antihistamine antibodies [13]. Nociceptive pain has been reported as a symptom of cholinergic urticaria [2]. Histamine plays a central role in the pathogenesis of CU [3] and is also a known mediator of pain sensation [4]. Accordingly, some patients with CU may experience nociceptive symptoms, including pain, either instead of or in addition to itching. In these cases, the resolution of nociceptive pain following IHC therapy suggests that histamine may contribute to nociceptive pain in CU (Fig. 2). Levocetirizine also improved both itching and nociceptive pain (Fig. 3), suggesting involvement of histamine receptor 1. Histamine receptor 1 activation increases intracellular Ca^{2+} , which activates protein kinase C-dependent phosphorylation and promotes formation of calmodulin complexes; these processes suppress potassium voltage-gated type 7 (Kv7) channels, leading to depolarization and increased nociceptive pain [17]. In animal models, venom-induced hyperalgesia in rats was reduced by histamine receptor 1 and 2 antagonists [18,19]. Collectively, these observations suggest that nociceptive symptoms, as well as itching, should be considered in CU.

Itching and nociceptive signals are typically transmitted through C-fibers [5]. Several theories have been proposed to explain the relationship between itching and nociceptive pain; one is the intensity theory, which posits that the transition from itch to pain occurs because of increased nociceptor discharge frequency [4,20]. In the 3 cases described here, itching consistently preceded nociceptive pain. After nociceptive pain resolved, itching was alleviated but then returned (Fig. 3) before ultimately resolving. These clinical observations appear consistent with the intensity theory. In addition, the disappearance of nociceptive pain alongside decreasing CU severity during IHC therapy also seems to support this explanation (Fig. 2).

In a previous report, CU symptoms were schematically classified according to disease severity [8]. After IHC therapy, symptoms reportedly resolved in parallel with decreasing clinical severity, beginning with angioedema, followed by urticaria, and ultimately itching as severity continued to decline. This pattern of resolution may be related to the intensity of allergic effects. Systemic manifestations, including angioedema, respiratory difficulty, and nociceptive pain, may represent the most severe symptoms, followed by urticaria and then itching as the least severe symptom.

In these patients, nociceptive pain was the first symptom to resolve as CU improved. More broadly, symptom severity may be related to the emergence of nociceptive pain during episodes and as the disease progresses. Thus, these findings suggest that nociceptive pain may reflect a more severe manifestation of CU than urticaria and itching.

To our knowledge, formal reports emphasizing the transition and coexistence of itching and pain in CU have been limited. In addition, the clinical transition between itching and nociceptive pain has not been described in detail. Although this report includes only 3 cases, it describes clinical characteristics of itching and nociceptive pain during symptomatic episodes and the resolution of nociceptive pain as CU severity decreased during IHC therapy. The clinical changes observed during IHC therapy also appear to support the intensity theory regarding the transition from itching to nociceptive pain. Histamine may mediate the resolution of nociceptive pain, based on the effects of histamine receptor 1 blockade and IHC therapy, which has histaminopexy effects.

The primary limitation of this analysis is that, as a descriptive case series involving only 3 patients, the findings cannot be conclusive. In addition, the absence of a control group represents a clear methodological limitation.

In conclusion, nociceptive pain occurred in association with typical urticaria manifestations in 3 patients with CU. Based on the clinical findings reported in this case series, nociceptive pain may represent a more severe manifestation than urticaria and itching. The observed clinical characteristics and response to IHC therapy appear to support the intensity theory regarding the transition from itching to nociceptive pain, which may be mediated by histamine. Pain may represent a type of histamine-mediated syndrome. Further clinical and basic immunological studies are needed.

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Authors' contribution

Conceptualization: GN, HK. Data curation: JS. Methodology/formal analysis/validation: YN. Project administration: GN. Funding acquisition: none. Writing—original draft: YN. Writing—review & editing: HK, JS, YN, GN.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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