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Case Report

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Effects of Histobulin (Immunoglobulin/Histamine Complex) on Depression and Anxiety in Chronic Urticaria: Psychiatric Manifestations or Psychiatric Comorbidities of Chronic Urticaria?: A Case Report

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Abstract

Background: *Psychiatric comorbidities of chronic urticaria (CU) have been reported and examined recently. The prevalence of mental disorders and emotional distress is high in patients with CU. This is a case report in which Histobulin was found to be effective for psychiatric manifestations in chronic spontaneous urticaria (CSU).*

Case Presentation: *Three cases of CSU accompanying psychiatric manifestations (PMs) were treated with Histobulin. One patient with CSU with severe depression showed clinical changes in depressive symptoms in parallel to changes in allergic symptoms during treatment. Histobulin clearly improved not only CSU but also the accompanying PMs in one patient and slightly improved them in another patient. The PMs were not improved by an antihistamine (H1 blocker) in any case. Histobulin is effective not only for allergic manifestations (AMs) but also for PMs of CSU.*

Conclusions: *PMs as well as AMs of CSU were improved by Histobulin therapy. PMs were suspected to be a part of the clinical manifestations in CSU, possibly through histamine-mediated mechanisms. These conditions were suggested to be 'allergic psychiatric manifestations (APMs)' or 'histamine-mediated psychiatric manifestations (HPMs)'. Further study of PMs based on histamine-mediated mechanisms, including allergies, may be necessary. Accordingly, it should be clarified whether the PMs of CSU are a part of the clinical manifestations of CSU or are psychiatric comorbidities of CSU.*

Keywords: Histobulin, Chronic urticaria, Depression, Anxiety, Allergy

List of Abbreviations

CU: Chronic Urticaria;
CSU: Chronic Spontaneous Urticaria;
AMs: Allergic Manifestations;
PMs: Psychiatric Manifestations;
DP: Dermatophagoides Pteronyssinus;
DF: Dermatophagoides Farina

Background

Histobulin (Green Cross PD, Korea) is a histamine-fixed immunoglobulin preparation comprising 0.15 g of histamine dihydrochloride and 12 mg of IgG (immunoglobulin/histamine complex) [1]. Histobulin is known to be effective in chronic urticaria (CU) [2]. The prevalence of mental disorders and emotional distress is high in patients with CU [3]. The improvement of psychiatric manifestations during Histobulin therapy for the treatment of chronic spontaneous urticaria (CSU) in three cases is described in this case report.

Case presentation

Case 1: A 28-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to eosinophilia. In the past, she suffered from atopic dermatitis, allergic rhinitis and chronic urticaria for 24 years and from severe depression with numerous suicide attempts for 14 years. All cases were evaluated by extensive diagnostic interviews at baseline by a psychiatrist. The diagnostic interviews systematically checked for the diagnostic criteria outlined by the DSM-V [4]. She had no family history concerning psychiatric disease. In the past, the diagnosis of major depression disorder was made with

symptoms and signs as described in Table 1A, and fluoxetine was prescribed for 14 years. She took fluoxetine 10 mg once a day at the time of the visit. She showed depressive mood, insomnia, fatigue, feelings of worthlessness, diminished ability to concentrate and the suicidal ideation and attempts many days despite medication. Her being easily fatigued and sleep disturbance did not meet DSM-V criteria for generalized anxiety disorder (Table 1B).

Table 1: Psychiatric symptoms and signs of patients aligned with DSM-V criteria for major depressive disorder (A) and generalized anxiety disorder (B). Regarding the frequency of symptoms and signs, not nearly every day is marked as Δ and nearly every day as O.

Symptoms during the 2 weeks	Case 1	Case 2	Case 3
Depressed most of the day, nearly every day	O		
Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day	O		
Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day		Δ	
Insomnia or hypersomnia nearly every day	O	Δ	Δ
Psychomotor agitation or retardation nearly every day			Δ
Fatigue or loss of energy nearly every day	O		
Feelings of worthlessness or excessive or inappropriate guilt	O	Δ	
Diminished ability to think or concentrate, or indecisiveness, nearly every day	O	Δ	
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	O		

Symptoms during the last 6 months	Case 1	Case 2	Case 3
Restlessness or feeling keyed up or on edge		Δ	
Being easily fatigued	O	O	O
Difficulty concentrating or mind going blank			
Irritability			Δ
Muscle tension			
Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)	O	O	O

In the diagnosis of CU, all patients showed urticaria, skin rash (including urticaria) and itching over 6 weeks. Urticaria developed without any triggering factors, including physical pressure, cold exposure, or exercise. Dermographism was present when urticaria developed. The symptoms and signs of CU, such as skin rash, itching and urticaria, were well controlled by antihistamine (levocetrizine, an H1 receptor blocker) and did not show any positive findings in prior diagnostic examinations in other hospitals. According to the definition of CU, the patients were diagnosed with chronic spontaneous urticaria (CSU) [5].

Basic allergy tests (blood tests and skin prick tests) were conducted on all three patients before and after treatment. They underwent blood tests to determine the complete blood count with the differential count, serum eosinophil cationic protein, serum total IgE and IgE levels for specific allergens using a multiple allergosorbent test (MAST, Green Cross PD, Korea). In the MAST test, the specific IgEs for 41 allergens were evaluated, including Dermatophagoides pteronyssinus (Dp), Dermatophagoides farina (Df), cat, dog, egg white, milk, soybean, crab, shrimp, peach, mackerel, rye pollen, house dust mite, cockroach, Clasporium herbarum, Aspergillus fumigatus, Alternaria alternata, birch-alder mix, white oak, short ragweed, mugwort, Japanese hops, hazelnut, sweet vernal grass, Bermuda grass, orchard grass, timothy grass, reed, Penicillium notatum, sycamore, sallow willow, poplar mix, ash mix, pine, Japanese cedar, acacia, oxeye daisy, dandelion, Russian thistle, goldenrod and pigweed. The test results showed the level of specific IgE for each allergen, and a normal negative range was 0.000-0.349 IU/mL.

A skin prick test was also performed for 53 allergens. The allergens tested were Alternaria alternata, Aspergillus fumigatus, Aspergillus nigre, Candida albicans, Cladosporium, Penicillium chrysogenum, German cockroach, Dp, Df, dog, cat, grey elder/silver birch,

grass mix, mugwort, short ragweed, black willow pollen, orchard grass, Bermuda grass, timothy grass, English plantain, English rye grass, Holm oak, Japanese cedar, cotton flock, milk mix, egg mix, chicken, beef, pork, cod, oyster, salmon, prawn, mackerel, tuna, almond, peanut, bean, carrot, cabbage, walnut, maize, peach, tomato, black pepper, spinach, wheat flour, rabbit, kapok, hops, acacia, pine and poplar. Skin prick tests were performed on the back of the patient. The area to be tested was cleaned with alcohol and coded with a skin marker corresponding to the number of allergens being tested. The marks were 2 cm apart. A drop of allergen solution was placed beside each mark. A small prick was made through the drop into the skin using a Morrow Brown Needle (Morrow Brown Allergy Diagnostics, USA) by holding the needle perpendicular to the test site and punching firmly through the tested extract and into the epidermis. The drop was removed immediately after the skin was pricked, and the needle used was discarded immediately. Histamine hydrochloride (1 mg/ml) was used as a positive control, and physiological saline was used as a negative control. The results were determined according to the wheal size. Reactions were read after 15 min and described as negative (0, no reaction), 1+ (reaction greater than the control reaction but smaller than half the size of the reaction to histamine), 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) and 4+ (equal to or more than twice the size of the histamine reaction). The minimum size of a positive reaction was 3 mm.

In the laboratory tests, the elevation of the eosinophil fraction based on the complete blood counts with differential counts was as high as 11.05% (normal <= 5%), and the blood eosinophil cationic protein level was as high as 54.3 ng/ml (normal <= 24 ng/ml). The serum total IgE level was as high as 3112 IU/ml (normal <= 350). According to the MAST, the positive allergens were Dp (>100), Df (>100), cat (76.75), Clasporium herbarum (0.56), Alternaria alternata (0.35), short ragweed (0.48), mugwort (2.82), hazelnut (1.67), orchard grass (0.54), timothy grass (0.49), Penicillium notatum (0.65), sallow willow (26.85), Japanese cedar (7.60), oxeye daisy (8.14), dandelion (3.63) and goldenrod (11.23). The skin prick test results were positive for allergens of Dp (7/5), Df (10/6), dog (2/3), cat (5/4), mugwort (24/9), short ragweed (4/4), black willow (3/3), Japanese cedar (6/4), almond (3/3), bean (3/3), and histamine (7/5), and the normal control results were 0/0.

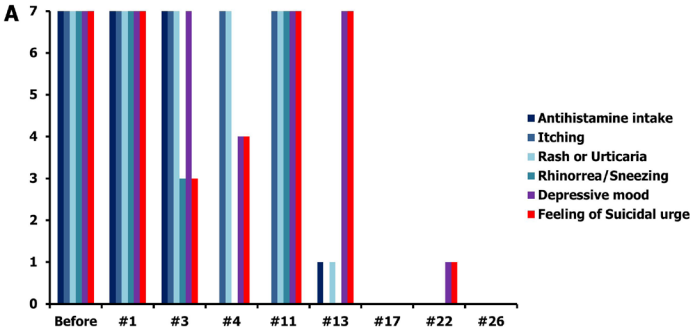
In this case, the clinical progress of CSU was recorded as the frequency of allergic episodes, including the development of urticaria, skin rashes, and/or itching and the frequency of antihistamine intake.

Patients were evaluated before and after treatment to determine their mood using the Beck Depression Inventory (BDI)-2 for depression (normal <= 13, mild 14-19, moderate 20-28, severe 29<=) and the State-Trait Anxiety Inventory (STAI) for anxiety (state: normal <= 51, mild 52-56, moderate 57-61, severe 62<=; trait: normal <= 53, mild 54-58, moderate 59-63, severe 64<=) [6]. The patient in case 1 was the first case who presented symptoms and was the motivation for this study, and the BDI and STAI were not completed. For the patient in the first case, the frequency of suicidal urges with depressive mood for one week was recorded as the first indicator of psychiatric evaluation.

Patients received 2 ml of Histobulin (12 mg human immunoglobulin/0.15 g histamine complex) once a week by subcutaneous injection in the deltoid area of the upper arm. They were instructed to take a tablet of 5 mg levocetrizine every day if necessary when they felt uncomfortable due to urticaria, skin rash or especially itching that prevented them from engaging in activities of normal daily living. Histobulin treatment was well-tolerated, and there were no side effects in any case.

Before Histobulin therapy, allergic symptoms and signs related to CSU and allergic rhinitis occurred nearly every day. Depressive mood changes occurred, and the patient had suicidal urges every day. Using antihistamines, the allergic symptoms and signs were well controlled, but the psychiatric manifestations, such as depressed mood and suicidal urges, were unchanged.

Histobulin therapy was attempted for the treatment of allergic rhinitis and CSU. Allergic rhinitis began to improve after 3 injections of Histobulin. Surprisingly, the frequency of suicidal urges also decreased simultaneously. Thereafter, the severity of the psychiatric manifestations was correlated with the severity of the allergic status (Figure 1A). Consequently, after 26 injections of Histobulin, the allergic rhinitis and CSU remitted, and the concomitant depression and suicidal urges also disappeared.



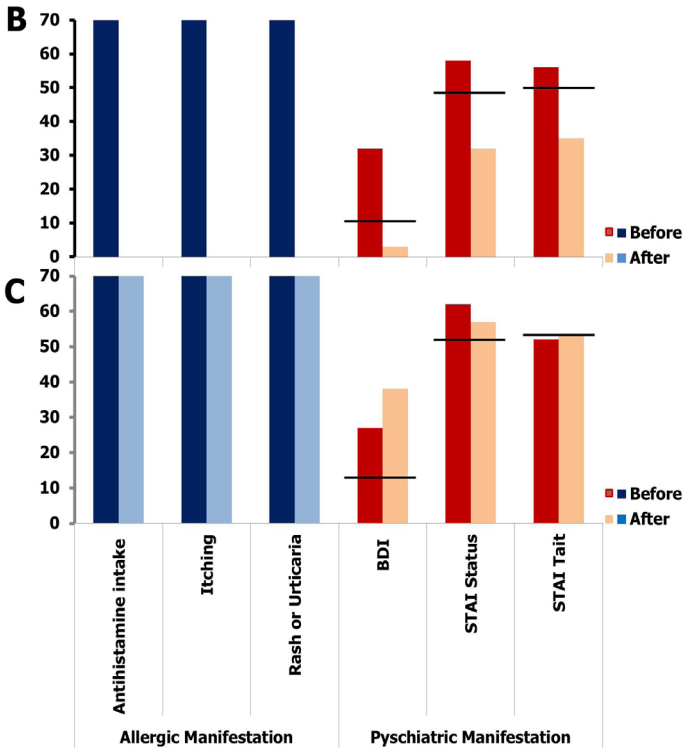


Figure 1. A. Clinical progress of case 1. After the 3rd injection of Histobulin, the patient showed improvement in rhinorrhea with a decrease in suicidal urges. Thereafter, AMs improved with a reduction in depressed mood and suicidal urges. Blue colour, AMs; red colour, PMs. B. Clinical results of case 2. AMs and PMs were all resolved after 12 injections of Histobulin. C. Clinical results of case 3. Only PMs were all resolved without the improvement of AMs after 12 injections of Histobulin. Black line, normal level.

Case 2: A 30-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to itching and urticaria for 5 months. She was taking levocetrizine 5 mg daily and suffered from allergy symptoms and signs every day. There was no specific medical history, including a history of allergy or psychiatric problems. Angioedema occurred every week. Dermographism was present when urticaria developed. Urticaria and itching developed without any triggering factors. According to the definition, her final diagnosis was CSU.

There was no past history or family history concerning psychiatric disorders or medication. At the time of the visit, she had significant weight loss with insomnia, feeling worthlessness and diminished ability to concentrate many days but not nearly every day (Table 1A). She was interviewed by a psychiatrist intensively. However, she did not meet the DSM-V criteria for major depressive disorder. She showed restlessness, was easily fatigued and experienced sleep disturbances, but these symptoms did not meet DSM-V criteria for generalized anxiety disorder (Table 1B). She also indicated that the development of depression and anxiety coincided with the beginning of the AMs.

Her basophil fraction was as high as 1.1% (normal range: 0-1%). The levels of serum eosinophil cationic protein and total IgE were normal. There were no positive results for the MAST and skin prick tests. The BDI score was 32 (severe), the STAI state score was 58 (moderate) and the STAI trait score was 56 (mild).

Histobulin therapy began. After the third injection, the patient's allergic symptoms and signs improved along with the improvement of the PMs. Twelve weeks after injection, there were symptoms and signs, including urticaria and itching, as well as angioedema without antihistamine medication (Figure 1B). According to the allergic laboratory test, the blood basophil fraction had become normal. PMs were also absent after 12 weeks of treatment. The BDI score was 3 (normal). The STAI status score was 32 (normal), and the STAI trait score was 35 (normal).

Case 3: A 50-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to suffering from itching and urticaria for 8 years. She was taking levocetrizine 5 mg daily and was affected by allergy symptoms and signs every day. Urticaria and itching developed spontaneously without any triggering factors, and the diagnosis of CSU was made. When urticaria developed, dermographism was positive. She also experienced chest tightness with respiratory difficulty sometimes when AMs appeared. She complained of both depression and anxiety at the time of the visit.

There was no specific medical history, including a history of allergy. She had the history taking alprazolam 0.25 mg due to anxiety two times 3 years and 4 years ago. In her family history, her female

cousin was treated for anorexia nervosa. At the time of the visit, she suffered from insomnia and psychomotor retardation (Table 1A). A psychiatrist intensively interviewed her. However, she also did not fulfil the DSM-V criteria for major depressive disorder. She also was easily fatigued, and irritable and experienced sleep disturbances, but these symptoms did not meet the DSM-V criteria for generalized anxiety disorder (Table 1B).

Her laboratory tests were normal, except for positive results for the MAST for Dp (4.27), Df (21.18) and shrimp (0.72). Additionally, there were no positive results for the skin prick test. The BDI score was 27 (moderate), STAI state score was 62 (severe) and STAI trait score was 52 (normal)..

Histobulin therapy began, and after the sixth injection of Histobulin, the patient's psychological state was enhanced with the improvement in depressive mood and anxiety. Twelve weeks after Histobulin injection, the CSU had not improved objectively (Figure 1C). However, anxiety improved slightly despite the aggravation of depression. The patient's BDI score was 38 (severe). The STAI status score was slightly improved at 57 (moderate) from severe, and the STAI trait score was 53 (normal) after treatment.

Discussion and Conclusions

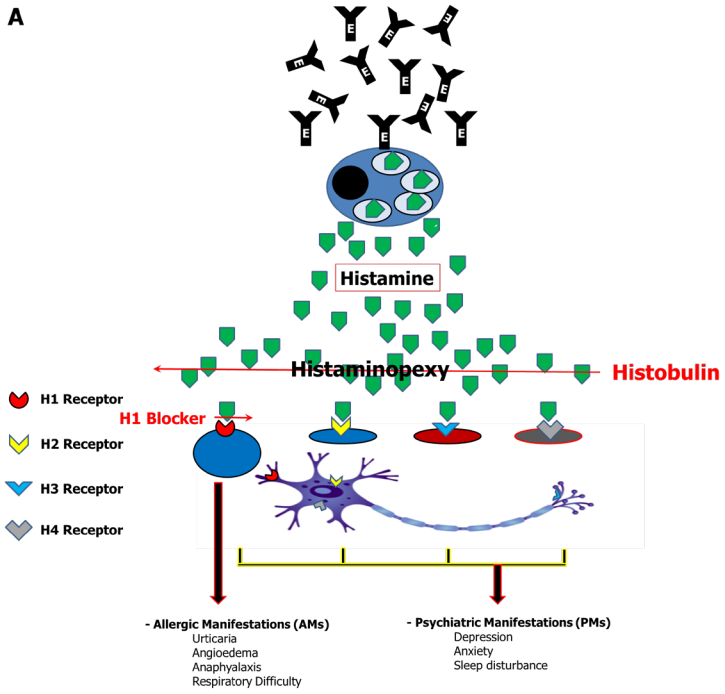
Histobulin improved psychological status in CSU. The clinical results of this case report are as follows: 1) PMs were improved by Histobulin therapy in all three cases, regardless of the improvement AMs and 2) interestingly, Histobulin therapy resulted in different results in each case. AMs and PMs were improved simultaneously in cases 1 and 2. However, some PMs were improved slightly by Histobulin therapy without the improvement of AMs in case 3. The clinical responses in this report provide many important clues for better understanding the pathogenesis of PMs that are related to allergies and for new concepts for treatment modalities for psychiatric symptoms and signs.

Mechanisms of the effect of Histobulin on psychiatric manifestations in chronic urticaria

In all three cases, AMs were well controlled with an antihistamine (H1 blocker) without the improvement of PMs before Histobulin therapy. However, psychological status was improved by Histobulin therapy in this report.

Histobulin treatment is a non-allergen-specific immunotherapy [7]. It inhibits mast cell degranulation and histamine release in rats [8, 9]. One of the most important mechanisms of Histobulin is histaminopexy and the production of antibodies against histamine [10]. Consequently, histaminopexy reduced the level of histamine. PMs in CSU are suspected to be histamine-mediated symptoms and signs. Hereby, the use of the term 'histamine-mediated psychiatric manifestation (HmPM)' or 'allergic psychiatric manifestation (APM)' is suggested.

There are four kinds of histamine receptors [11]. H1 plays a well-known role in allergies. In general, antihistamines bind to the H1 receptor and resolve the AMs of CSU as well as other allergic diseases, including allergic rhinitis. Antihistamine H1 blocks the H1 receptor and interferes with the action of histamine through the H1 receptor [12]. However, histaminopexy and the reduction of the systemic histamine level by Histobulin had the same effect on interfering with the action of histamine, regardless of the type of receptor (Figure 2A). Therefore, PMs did not seem to be improved by blocking only the H1 receptor and instead might be resolved by Histobulin, which might reduce the levels of histamines that affect all 4 histamine receptors on neurons (Figure 2A). Through the effects of Histobulin on PMs in CSU, the effects of histamine on PMs in CSU seemed to be demonstrated in this case report.



B

Theory	Case 1	Case 2	Case 3	Possible Thesis
Chronic Disease -> PM	Possible	Possible	N/A	No
Chronic Disease-> Stress Factor	Possible	Possible	N/A	No
Comorbidity & Histobulin Effects on PMs	Possible	Possible	Possible	Yes
PMs as Histamine-mediated disease	Possible	Possible	Possible	Yes

Figure 2: A. The presumptive mechanisms of action of Histobulin. PMs were not changed by an antihistamine H1 blocker but were resolved by histamine. B. Investigation of the different responses of AMs and PMs in the 3 cases to Histobulin to rule out causes. Based on the different responses to Histobulin, 5 statuses are possible. 1) PMs may be induced by chronic diseases, including CSU. 2) Stressors, such as allergy provocation in CSU, also possibly induce PMs. 3) PMs are comorbidities of CSU. 4) PMs are the clinical manifestations of CSU. The last two mechanisms, 3) and 4), are applicable to all 3 cases. Histobulin is effective in treating PMs in chronic urticaria, regardless of whether they are PMs or psychiatric comorbidities of CSU

Are histamine-mediated responses comorbidities or psychiatric manifestations of chronic urticaria?

Psychiatric comorbidities have been the focus of recent reports, and there have been many reports concerning the relationship between allergic diseases and the manifestations and comorbidities of psychiatric disease [13]. Depression scores were positively correlated with changes in allergy symptoms in recurrent mood disorders after exposure to seasonal peaks in aeroallergens [14]. The relationship of high pollen counts and the seasonality of mood worsening was also reported [15]. Allergic rhinitis induced anxiety-like behaviour and altered social interactions in rodents [16]. In the first case, the frequency of suicidal urges was evaluated according to a report that described allergy as a risk factor for suicide [17]. Based on the clinical progression of case 1, the PMs occurred in parallel to those of CSU during treatment, and PMs were affected by allergic provocation. This patient served as the initial motivation for this report.

The presence of psychiatric comorbidities is very important for determining the quality of life in CU [18]. The treatment of psychiatric comorbidities as well as CU is important. It is significant to note that both AMs and PMs were controlled by Histobulin. The presence of histaminergic neurons that have H1, H2, H3, and H4 receptors have strongly suggested the possibility of histamine-mediated neuropsychiatric responses without direct evidence. To date, it has not been confirmed whether PMs are independent of psychiatric comorbidities or are the clinical manifestations of CU.

Histobulin therapy showed different results in the three cases. AMs and PMs were improved simultaneously in cases 1 and 2. However, only anxiety was improved slightly by Histobulintherapy without the improvement of AMs in case 3. In spites of the slight improve, the authors focused on the clinical results of case 3. The relationship between AMs and PMs that are PMs mediated by histamine has not been proven directly due to the absence of H3 and H4 blockers for therapeutic use, as described above. Four possibilities may be suggested based on the results of this case report. 1) PMs may be induced by chronic diseases, including CU. This possibility could not be excluded in cases 1 and 2. However, it is not applicable in case 3 (Figure 2B). 2) Stressors, such as allergy provocation in CU, also possibly induce PMs. This is also not applicable in case 3. However, many factors affect psychological status, and the clinical situations in these three cases were complex and variable concerning PMs. Therefore, the possibility that only the attenuation of physical distress with improvement of CU improves psychiatric symptoms should be considered. 3) PMs are comorbidities of CU. Although they could be comorbidities of CUS in these cases, it is suspected that the PMs occurred through histamine-mediated mechanisms, at least based on the fact that PMs in all these cases were resolved by Histobulin. 4) PMs are the clinical manifestations of CU. It is reasonable to explain the effects of Histobulin on PMs in CU based on the results of this report. The last two mechanisms, 3) and 4), are applicable to all 3 cases. The PMs in CU were suspected to occur through histamine receptors in neurons.

In similar allergic conditions, not only the kinds of allergic diseases but also the relevant symptoms and signs vary according to individual differences. PMs may develop despite allergic provocations. Therefore, not all allergic patients show PMs, but some patients may possibly develop PMs due to histamine-mediated allergic conditions, including CU. Adult- onset asthma due to mental disorders has been reported [19]. It is not clear whether any of the PMs or AMs developed earlier or independently. According to the sensitivity of organs or individual differences, only histamine-mediated PMs potentially appeared without AMs. Therefore, it may be possible that psychiatric conditions occur due to allergic causes. Further clinical and experimental investigations are urgently needed on the mental health of humans to understand the causative role of allergies for PMs.

Histobulin is not the first line of treatment for CU. However, if patients wanted to cease taking antihistamines or escape from suffering from CSU, Histobulin therapy was considered, even in the clinical conditions in which the symptoms and signs were well controlled by antihistamines.

In conclusion, psychological status was improved by Histobulin. The results of this report suggest that PMs may be histamine-mediated clinical manifestations rather than comorbidities in CSU and that Histobulin seems to be an effective treatment for PMs in CSU. This is the first report that Histobulin is possibly effective in

psychological manifestations including anxiety and depression of which histamine may be related with the development. Histobulin may be the first drug that is effective in the treatment of histamine-related psychological manifestations and histamine-related psychiatric disorders possibly by affecting the histamine effects through H3 and H4 histamine receptors as well as H1 and H2 histamine receptors simultaneously although Histobulin was approved in human only for the treatment of allergy, officially.

Declaration

Ethics approval and consent to participate: Histobulin therapy in this report was approved by the IRB of Cheju Halla General Hospital (IRB No. 2020-M07-01).

Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author's contributions: GN did major work for this report. HSK managed the aspects of basic immunoloci theory. All authors have read and approved the manuscript.

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