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Efficacy of anti-immunoglobulin E therapy in patients with prurigo: A pilot study

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Abstract

Objectives: Chronic prurigo is a reactive skin disease marked by multiple pruriginous lesions such as papules, nodules, and erythema. We previously showed that basophil infiltration into the pruriginous lesions and basophil activation in blood are frequently observed. Therefore, basophils may be involved in the pathogenesis of chronic prurigo. In this study, we examined the efficacy of anti-immunoglobulin E (IgE) therapy with omalizumab, which blocks basophil activation, in patients with prurigo.

Methods: Seven patients with chronic prurigo (prurigo chronica multiformis [PCM]: five patients; prurigo nodularis [PN]: two patients) and one patient with prurigo subacuta (PS) were enrolled. The infiltration of basophils into skin lesions was assessed by immunohistochemical analyses using a monoclonal antibody. All patients were treated three times with 300 mg omalizumab every 4 weeks, regardless of serum levels of total IgE. Skin symptoms were assessed using our unique skin scores before and after treatment with omalizumab. The efficacy of the treatment was determined according to the reduction ratio of skin scores as follows: high (ratio > 70%), moderate (70% ≥ ratio > 40%), mild (40% ≥ ratio > 10%), or none (10% ≥ ratio).

Results: All five patients with PCM were improved: The efficacy was high for three patients, moderate for one patient, and mild for one patient. In addition, the pruriginous lesions were improved mildly in the patient with PS, but not in those with PN.

Conclusions: Anti-IgE antibody therapy with omalizumab may be effective for PCM but not for the other types of chronic prurigo.

KEYWORDS
anti-IgE antibodies, basophils, humans, omalizumab, prurigo

1 | INTRODUCTION

Chronic prurigo is a skin disorder defined by the presence of chronic pruritus with multiple pruriginous inflammatory lesions accompanied by signs of repeated scratching.[1] Different aetiologies such as dermatological, allergic, systemic, neurological, psychiatric/psychosomatic, multifactorial, and unknown origin are considered to trigger chronic itch and then are associated with the development of various skin symptoms.[1,2] In Japan, chronic prurigo is classified into two clinical subtypes: prurigo chronica multiformis (PCM) and prurigo nodularis (PN).[2] PCM is characterized by isolated papules or lichenified plaques of gathered papules, which are spread laterally and mainly over the flank and buttock regions. Each eruption lasts for several weeks. PN presents with isolated, dome-shaped

or verrucous-shaped nodules mainly spread over extremities. Each eruption lasts for several months.[2] The detailed pathological mechanism of each subtype has not been fully elucidated. Patients are generally treated with symptomatic therapies (eg, topical steroids, UV phototherapy, or antihistamines) that reduce inflammation and itch.[2,3] However, many patients are not cured with this conventional therapy and their symptoms are repeatedly exacerbated. Therefore, the elucidation of cell- or molecule-based pathological mechanisms leading to the establishment of a novel therapy is desired.

We previously examined whether basophils infiltrated the lesions of 136 specimens from 24 skin diseases and found that basophils were frequently observed in the lesions of urticaria and chronic prurigo, including PCM and PN.[4] In addition, basophil activation status in peripheral blood, determined by cell surface CD203c expression levels, is higher in patients with chronic prurigo than in healthy donors.[4] In studies using mice, Karasuyama et al demonstrated that basophils initiate immunoglobulin E-mediated chronic allergic inflammation (IgE-CAI) in the skin,[5,6] resembling PCM in clinical presentation. In addition, Satoh et al modified IgE-CAI through repeated challenges with an antigen, leading to the establishment of a mouse model of prurigo.[7] These findings in humans and mice indicate that basophils may be involved in the pathogenesis of prurigo. Moreover, we previously had a patient with PCM associated with papules and erythematous macules on his trunk and extremities who was successfully treated with an anti-IgE agent immediately after the first administration,[8] which supports the involvement of basophils in the pathogenesis of chronic prurigo.

In the present study, we further examined the efficacy of anti-IgE therapy with omalizumab in seven patients with chronic prurigo (PCM [five patients] and PN [two patients]) and one patient with prurigo subacuta (PS). The infiltration of basophils into skin lesions of each case was assessed by immunohistochemical analyses using a basophil-specific monoclonal antibody.[9] Basophils equally infiltrated into the skin lesions of all the clinical subtypes. All the cases were treated three times with 300 mg omalizumab every 4 weeks, regardless of serum levels of total IgE. Most patients with PCM had good responses to omalizumab, although both PN and PS patients exhibited poor responses to omalizumab. Thus, anti-IgE antibody therapy with omalizumab may be effective for PCM but not PN or PS. From these eight patients and our previous case,[8] we further elucidate how basophils are involved in the pathogenesis of chronic prurigo.

2 | METHODS

2.1 | Cases

This study enrolled eight patients between 32 and 87 years of age who were hospitalized for prurigo at the Department of Dermatology, Tokyo Medical and Dental University. They were divided into clinical subgroups: PCM, five cases (five men and zero women; mean age: 75.6 years); PN, two cases (zero men and two women; mean age: 44 years); and PS, one case (zero men and one woman; mean age: 32 years). The characteristics of these cases are shown in Table 1. This study was approved by the ethics committee of Tokyo Medical and Dental University (Approval number: R2017-0020; M2017-353) and conforms to the Helsinki Declaration of 1975, as amended in 1983.

2.2 | Skin scores

The skin symptoms were evaluated using our original skin-score measurement scale (Table 2). The number of lesions per body, thickness, body area (%), and redness of each skin symptom (papule, nodule, or erythema) was assessed on a 0-3 scale: 0, none; 1, mild; 2, moderate; and 3, severe (Table 2). The papule scale was calculated by (lesion number/body area [%]) × (thickness). The nodule scale was calculated by (lesion number/body area [%]) × (thickness). The erythema scale was calculated by (body area [%]) × (redness). The total skin score was calculated using the total measurements for each skin symptom. We evaluated the skin scores before and after treatment and determined the efficacy of the treatment according to the reduction ratio of the skin scores ([skin scores before treatment−skin scores after treatment]/skin scores before treatment × 100 [%]): ratio > 70%, high; 70% ≥ ratio > 40%, moderate; 40% ≥ ratio > 10%, mild; 10% ≥ ratio, none.

TABLE 1 Characteristics of the eight patients and our previous case

Case	Sex	Age	Subtype	IgE (IU/mL)	Efficacy of omalizumab (onset of effect)
1	F	48	PN	66	None (–)
2	F	32	PS	197	Mild (1 mo)
3	F	40	PN	79	None (–)
4	M	63	PCM	287	High (14 d) ⇒ mild
5	M	70	PCM	12 186	High (3 mo)
6	M	80	PCM	171	High (10 d)
7	M	87	PCM	9076	High (2 mo)
8	M	78	PCM	295	Moderate (3 mo)
9[a]	M	47	PCM	192	High (10 d)

[a]Our previous case.[8]

TABLE 2 Skin-score measurement scale

Symptom	0: None	1: Mild	2: Moderate	3: High
Papule				
Number/body	0	≤15	>15, ≤30	>30
Thickness	None	Mild	Moderate	High
Nodule				
Number/body	0	≤15	>15, ≤30	>30
Thickness	None	Mild	Moderate	High
Erythema				
Body area, %	0	≤10	>10, ≤30	>30
Redness	None	Mild	Moderate	High

Note: Papule scale, (lesion number/body area [%]) × (thickness); nodule scale, (lesion number/body area [%]) × (thickness); erythema scale, (body area [%]) × (redness). The skin score was calculated as a total of each scale measurement.

2.3 | Histology and immunohistochemistry

Skin specimens were obtained from active lesions in all patients after informed consent. Tissue sections of formalin-fixed and paraffin-embedded skin samples were stained with hematoxylin and eosin (HE). Immunohistochemistry was performed as previously described.[4] Briefly, tissue sections of formalin-fixed and paraffin-embedded skin samples were incubated with 0.1% trypsin in 50 mmol/L Tris-HCl (pH 7.5) containing 0.1% $CaCl_2$ at 37°C for 30 minutes, followed by treatment with 0.1% saponin in TBS buffer (pH 7.6) at room temperature for 30 minutes and protein-blocking solution containing 0.25% casein (Dako) at room temperature for 30 minutes to prevent nonspecific binding of antibodies. Samples were subsequently incubated with a mouse monoclonal antibody (mAb) that recognizes basogranulin, the granular component specific for human basophils, (BB1,[9] 1:10 dilution) at 4°C overnight, followed by alkaline phosphatase-conjugated polymers (Nichirei Bioscience). Sections were then incubated in Fuchsin + Substrate-Chromogen solution (Dako) and counter-stained with Mayer's hematoxylin.

3 | RESULTS

3.1 | Patient characteristics

Eight patients (five men and three women; mean age: 62.5 years) were enrolled in this study. The patients were divided into clinical subtypes: five cases of PCM (five men), two cases of PN (two women), and one case of PS (one woman) (Table 1). The mean ages for PCM, PN, and PS patients were 75.6, 44, and 32 years, respectively. The mean age of PCM was higher than that of other prurigo types; however, statistical assessment was impossible due to the small number of cases. The serum IgE levels ranged from 66 to 12 186 IU/mL (Table 1). The serum IgE levels of the patients with both PN and PS skin symptoms were within the normal range (≤256 IU/mL). The serum IgE levels of the patients with PCM varied: one patient, normal range; two patients, slightly high (>256 and <1000 IU/mL, respectively); and two patients, considerably high (>9000 IU/mL).

3.2 | Basophil infiltration in the lesions of all clinical subtypes

We first examined the infiltration of basophils into the skin lesions using immunohistochemical analysis with a mAB specific to basophil granular component BB1.[9] The histopathology of the lesions of PCM exhibited subepidermal edema and infiltration of varying levels of lymphocytes with eosinophils around the blood vessels and between collagen fibers of the upper dermis (Figure 1 and data not shown). BB1-positive basophils were observed in perivascular lesions and extended into the collagen fibers of the upper dermis in all five cases of PCM (Figure 1 and data not shown). Dermal basophils numbered 3.7-28.3 cells/high-power field (hpf). The PN lesions showed hyperkeratosis, parakeratosis, acanthosis, and the proliferation of collagen fibers with the infiltration of lymphocytes either with or without eosinophils around blood vessels and between collagen fibers in the dermis. BB1-positive basophils were observed in perivascular lesions and between collagen fibers (Figure 1). Dermal basophils numbered 7.3-17.3 cells/hpf. The PS lesions showed slight subepidermal edema with lymphocyte and eosinophil infiltration around superficial blood vessels and between collagen fibers in the upper dermis. BB1-positive basophils were observed in perivascular lesions (data not shown). Dermal basophils numbered 8.0 cells/hpf. These findings indicate that basophils infiltrate the lesions of all clinical subtypes, and little difference was found in the density of basophils between each subtype.

3.3 | Improvement of skin lesions in PCM, but not in the other types after anti-IgE antibody treatment

Regardless of serum IgE levels, all cases were treated three times with 300 mg omalizumab every 4 weeks. The five patients with PCM showed improved skin symptoms after the treatment (Figure 2, Table 3). The efficacy of the treatment in each patient varied: three patients had high efficacy, one patient had moderate efficacy, and one patient had mild efficacy. The onset time for the efficacy of the treatment ranged from 10 days to 3 months after the first administration of omalizumab (Table 1). The patient that highly responded to treatment within 14 days gradually relapsed, and the efficacy changed to mild (Table 1). With respect to pruritis, as assessed by the visual analogue scale (VAS), three of the patients with a high-efficacy response improved after the treatment, but the others were not changed (Table 3). In cases with PN, the skin symptoms and itch were not improved by the omalizumab treatment (Figure 3, Table 3). In the case with PS, the skin symptoms and itch were improved by the treatment, but the efficacy of the treatment was mild (Table 3). Furthermore, we compared the efficacy of the treatment between PCM and other types of prurigo. The reduction of skin scores was significantly higher in PCM than in other types of prurigo (Figure 4). These findings suggest that anti-IgE antibody therapy is effective for PCM but not the other prurigo types.

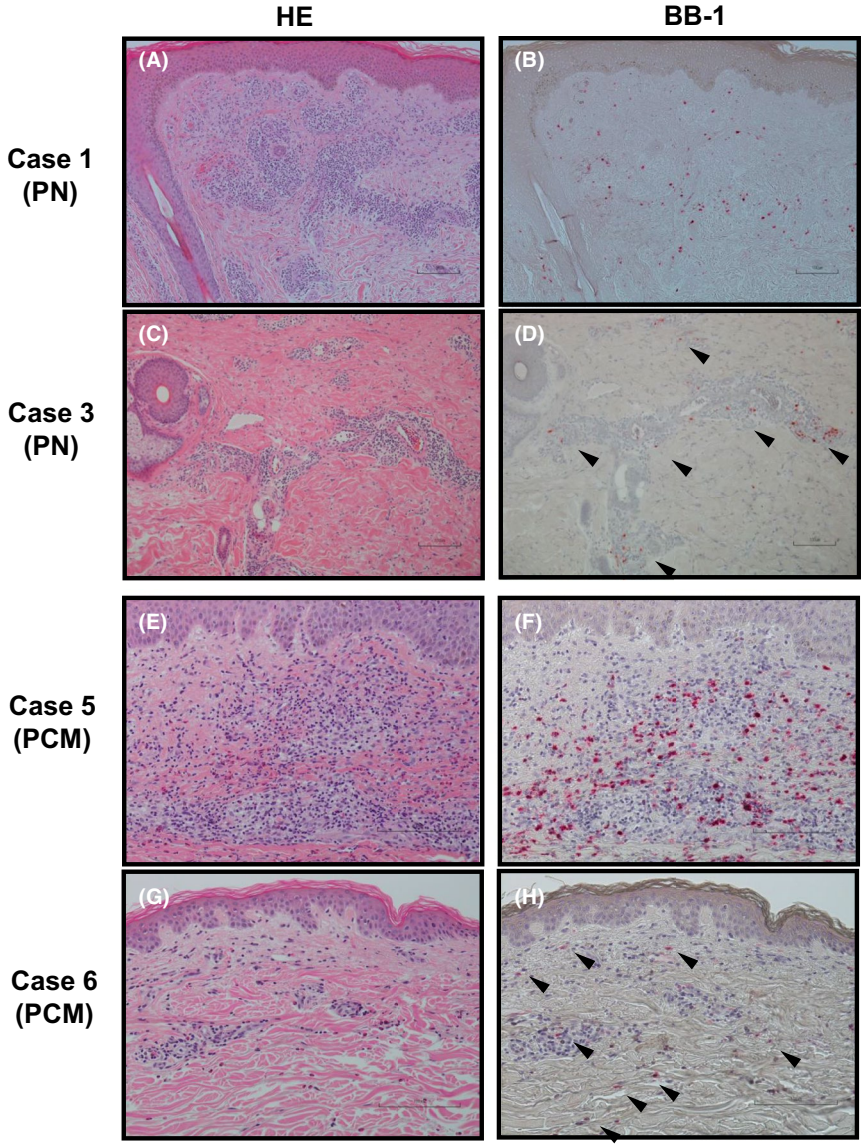

FIGURE 1 Histological features of prurigo cases. A, Hyperkeratosis and acanthosis with lymphocyte and eosinophil infiltration around superficial blood vessels and between collagen fibers (hematoxylin and eosin [HE], ×100). B, Red-stained basophils were observed around superficial blood vessels and between collagen fibers (reaction products visualized using Fuchsin, ×100). C, Fibrosis with lymphocyte and eosinophil infiltration around dermal blood vessels (HE, ×100). D, Basophils (arrowheads) around the dermal blood vessels and between collagen fibers (reaction products visualized using Fuchsin, ×100). E, Hyperkeratosis, parakeratosis, and acanthosis with infiltration of many lymphocytes and eosinophils around blood vessels and between collagen fibers in the dermis (HE, ×200). F, Many red-stained basophils are around blood vessels between collagen fibers (reaction products visualized using Fuchsin, ×200). G, Dermal edema with lymphocyte and eosinophil infiltration around superficial blood vessels and between collagen fibers (HE, ×200). H, Basophils (arrowheads) around the dermal capillaries and between collagen fibers (reaction products visualized using Fuchsin, ×200). Scale bar, 100 μm

4 | DISCUSSION

Chronic prurigo is difficult to treat using conventional therapies such as topical steroids, antihistamine agents, and phototherapy.[2,3] Recently, several reports[4,7,8] showed that basophils are involved in the pathogenesis of prurigo-like reactions in mice or prurigo in humans, suggesting that basophil-targeted drugs may be a novel therapy for prurigo. Omalizumab selectively binds to free-serum IgE and interferes with IgE binding to the high-affinity IgE receptor, FcεRI on basophils as well as mast cells.[10] The reduction in free IgE downregulates FcεRI on basophils and mast cells and suppresses their activation and function.[10–12] In the present study, we examined the efficacy of omalizumab in patients with prurigo and demonstrated that most of the cases with PCM showed a good response to omalizumab.

In this study, we enrolled seven patients with chronic prurigo (five patients with PCM and two patients with PN) and one patient with PS. We first evaluated the infiltration of basophils into the lesions of each subtype. The infiltration of basophils was observed around perivascular regions and/or intra-collagenous areas in the lesions of all subtypes. The densities of basophils in the lesions varied even when clinical subtypes were the same. There was little difference in densities of basophils between the subtypes. These findings suggest that basophils may be involved in the pathogenesis of each prurigo subtype in a similar way.

Contrary to our expectation, the efficacy of omalizumab varied based on the clinical subtype. All five patients with PCM improved following the treatment, and the efficacy of the treatment was high in three of the patients, which coincides with our previous case (Table 1).[8] In addition, the patient with PS also improved after the treatment, but the efficacy was mild. However, neither patient with PN improved after the treatment. The efficacy of the anti-IgE antibody treatment, determined using the reduction ratio, was higher in the patients with PCM than in the other prurigo types (Figure 4). These findings suggest that basophils may be more closely associated with the pathogenesis of PCM than with the other prurigo types.

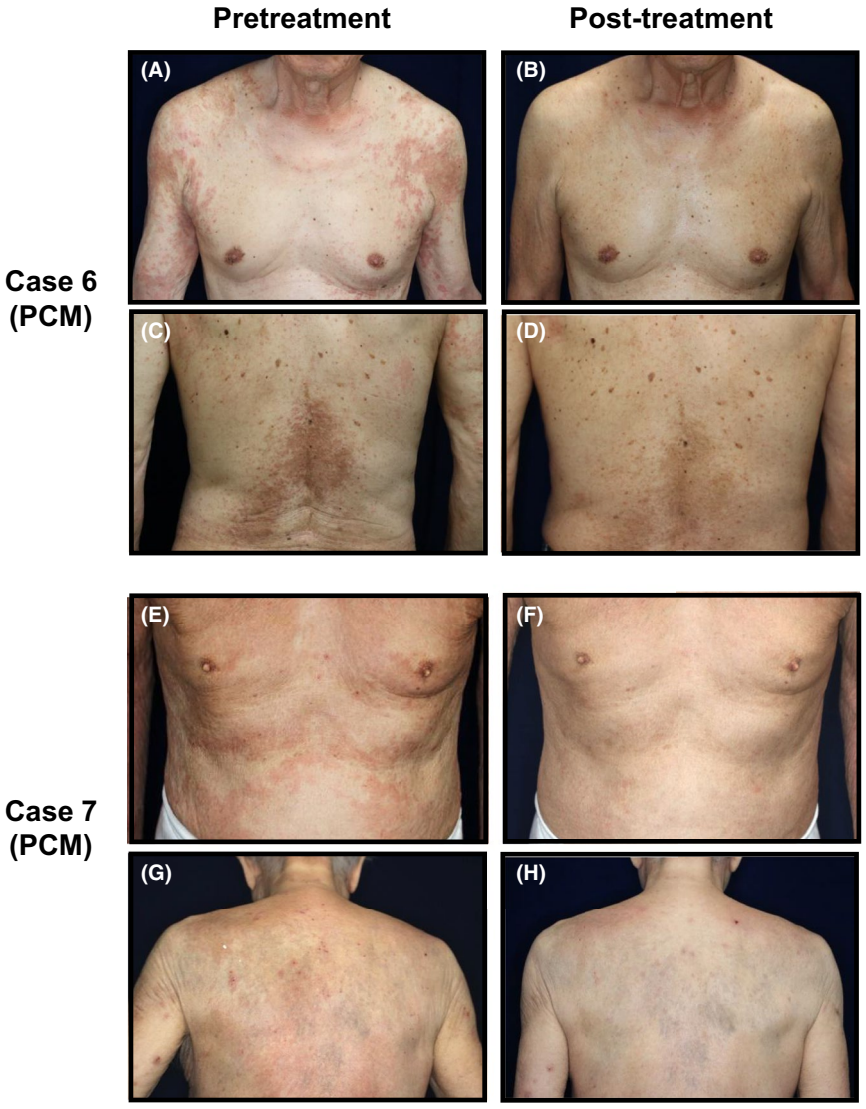

FIGURE 2 Clinical features of the PCM cases. A, C, E, G, Clinical manifestations before the administration of omalizumab. A, C, Case 6, papules and erythematous macules were spread over the trunk and upper extremities. E, G, Case 7, erythematous macules and a few nodules were spread over the trunk. B, D, F, H, Clinical manifestations after administration of omalizumab three times. B, D, Case 6, papules and erythematous macules on the trunk and upper extremities were highly improved after the treatment. F, H, Case 7, erythematous macules and nodules on the trunk were highly improved after the treatment

TABLE 3 Skin scores and VAS scores of prurigo cases

	Skin score		VAS (%)	
	Pretreatment	Post-treatment	Pretreatment	Post-treatment
Case 1 (PN)	9	9	70	75
Case 2 (PS)	11	9	60	25
Case 3 (PN)	9	9	70	50
Case 4 (PCM)	9	6	75	60
Case 5 (PCM)	6	1	55	35
Case 6 (PCM)	9	1	60	0
Case 7 (PCM)	15	3	100	50
Case 8 (PCM)	9	4	85	85
Case 9* (PCM)	8	0	80	5

Note: Skin scores and VAS scores of the eight patients and our previous case[8] before and after the administration of omalizumab.
*Our previous case. [8]

The onset time of the efficacy varied. Two patients with PCM promptly improved within 10-14 days after the first administration of omalizumab, similar to the finding in our previous case (Table 1).[8] The three residual patients with PCM required 2-3 months for improvement after the first administration of omalizumab (Table 1). Omalizumab inhibits the activation and function of basophils and mast cells by lowering free IgE in serum and decreasing expression of FcεRI.[10] FcεRI expression on basophils is decreased approximately

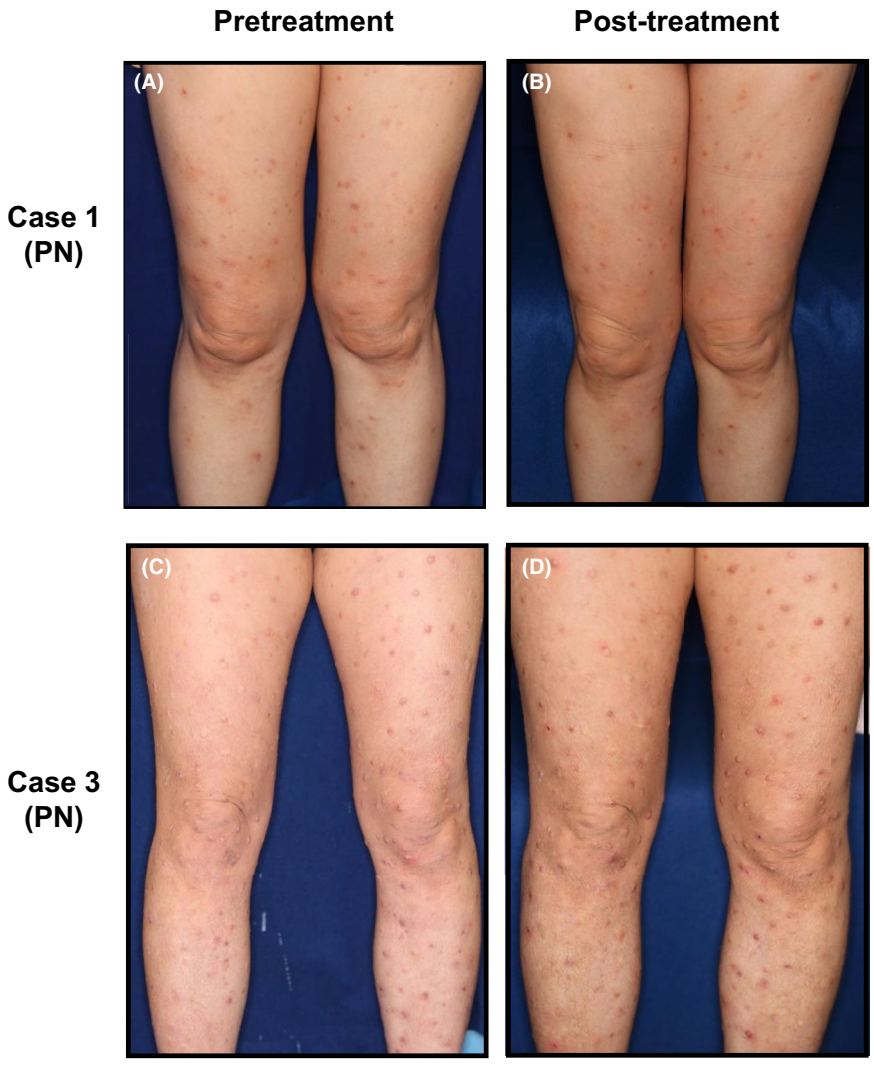

FIGURE 3 Clinical features of the PN cases. A, C, Clinical manifestations before the administration of omalizumab. Case 1 (A), Case 3 (C), nodules were spread over lower extremities. B, D, Clinical manifestations after the administration of omalizumab. Case 1 (B), Case 3 (D), nodules on lower extremities were not improved

90% 7 days after the administration.[12] However, FcεRI expression on mast cells is not changed 7 days after administration, but is reduced approximately 80% after 70 days.[12] The prompt, successful effect of omalizumab observed in our three cases, including our previous case,[8] corresponds to the timing of the reduction in FcεRI expression on basophils. In these cases, basophils may be closely related to the pathogenesis of prurigo. On the other hand, the other cases with PCM required 2-3 months for improvement, indicating that mast cells, not basophils, may be more closely related to the pathogenesis in these cases. However, the serum IgE levels of these cases tended to be higher than those of the early responders (Table 1). In asthma, there is a dose range for omalizumab from 75-600 mg, according to serum IgE levels as well as patient body weight. In our cases with high serum IgE levels, a fixed dose of 300 mg may be insufficient for neutralization of free-serum IgE.[13] Consequently, the cases with high IgE serum levels may take more time to achieve the therapeutic effect. If so, it remains a possibility that basophils are also associated with the pathogenesis in these cases.

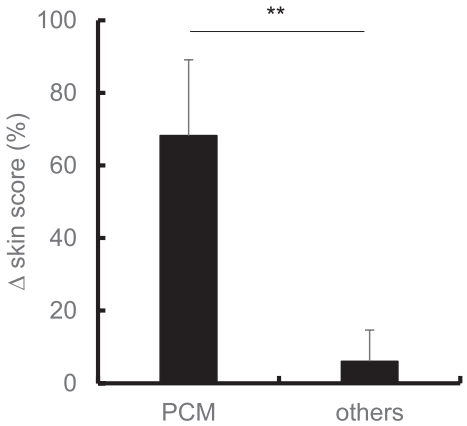

FIGURE 4 The reduction ratio of skin scores was higher in patients with PCM than in those with the other types of prurigo. The reduction ratio of skin scores ([skin scores before treatment–skin scores after treatment]/skin scores before treatment × 100 [%]) was compared between PCM and the other types of lesions. Data represent the mean ± standard deviation; $^{**}P < 0.01$ by Student's *t* tests.

Recent murine studies demonstrated that basophils could act as an initiator in IgE-CAI.[5] IgE-CAI resembles PCM in clinical features.[5] These findings, together with our observations, indicate that basophils are likely to initiate inflammation directly or indirectly via IgE in PCM. Like mast cells, basophils release various mediators, such as histamines, proteases, arachidonic acids, and cytokines, upon stimulation.[14] In mice, basophil-derived proteases induce microvascular permeability and infiltration of leukocytes, such as basophils, eosinophils, and macrophages into the skin.[15] Basophils also release IL-4, which acts on fibroblasts[16] and endothelial cells,[17] thus leading to eosinophilic skin inflammation in mice, which is also frequently observed in PCM. In humans, mediators derived from basophils may contribute to the initiation of skin inflammation like prurigo. However, further study is required to elucidate the molecular mechanisms underlying the initiation of PCM.

In summary, omalizumab exerted a therapeutic effect on PCM. Thus, omalizumab may be a good option for the treatment of chronic prurigo.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

This study was approved by the ethics committee of Tokyo Medical and Dental University (Approval number: R2017-0020; M2017-353) and conforms to the Helsinki Declaration of 1975, as amended in 1983.

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