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GUIDELINES

Prurigo chronica multiformis: Expert consensus of the Japanese Dermatological Association

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Abstract

Prurigo chronica multiformis is a commonly used diagnostic designation for a peculiar subtype of prurigo in Japan, although the disease entity might not be well-recognized in other countries. Experts approved by the Japanese Dermatological Association attempted to build a common consensus on prurigo chronica multiformis, agreeing that it is a unique and important disease entity in elderly patients. Skin lesions are characterized by intensely pruritic, edematous, urticarial papules, or small macules, which gradually become solid papules/small nodules. The papules tend to aggregate and occasionally coalesce into polygonal lichenified plaques. The most commonly affected sites are the lower abdomen and lower back, although the chest, thighs, and upper back might also be involved. Common histopathological features of prurigo chronica multiformis include infiltration of lymphocytes and eosinophils in the upper dermis, with minimal epidermal changes. Basophil infiltration is also observed. The epidemiological incidence, differences in clinical manifestations by geographical location, and disease placement among other forms of prurigo and/or related skin diseases need to be further elucidated. Dermatologists should be aware of the clinical characteristics of prurigo chronica multiformis.

KEYWORDS
chronic prurigo, grouping prurigo, prurigo chronica multiformis, prurigo subacuta, urticarial dermatitis

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1 | INTRODUCTION

Prurigo is a pruritic disease with papulonodular skin lesions. Although it is a relatively common skin disease, its pathological causes have not been fully defined. Whether pruritus is a fundamental primary change preceding the formation of pruriginous papules also remains a matter of debate, although scratching seems to be an integral part of the development of skin lesions. In 1808, Robert Willan[1] first described prurigo as one of the types of papular skin diseases. Since then, however, the diagnostic term "prurigo" has long been used without a clear clinical definition.

The common clinical subtypes of prurigo include prurigo simplex acuta (*Strophulus infantum*), prurigo simplex subacuta,[2] prurigo gestationis, and prurigo nodularis of Hyde. However, disease concepts using these terms might differ among countries. In addition, other designations, such as "papular dermatitis" and "itchy red bump disease"[3,4] have been ascribed to prurigo diseases. "Urticarial papulosis"[5] might also belong to the same spectrum. A recent report classified chronic childhood prurigo as perennial prurigo, summer prurigo, and nonsummer prurigo.[6] The European Prurigo Project[7] recently proposed a simple and clear definition for chronic prurigo (CPG), as a disease entity characterized by the presence of chronic pruritus for >6 weeks, history and/or signs of repeated scratching, and multiple localized/generalized pruriginous papules, nodules, and/or plaques. Prurigo nodularis of Hyde is one of the representative forms of CPG. While CPG is a distinct disease entity, according to the definition it can be considered a skin lesion that is preceded by persistent chronic pruritus and scratching. This concept does not, however, cover all previously reported types of prurigo because other prurigo forms, such as prurigo simplex, develop as "primary" pruritic lesions.[8] Moreover, prurigo acuta and papular urticaria are mostly provoked by allergic reactions against insect bites, and are not necessarily or solely preceded by persistent pruritus and scratching.

Certain types of prurigo start as edematous, urticarial, intensely pruritic macules that ultimately develop into persistent papules/nodules. Prurigo chronica multiformis (PCM) is a common and well-known subtype of prurigo in Japan, although it seems to be rare in other countries, considering the limited numbers of related clinical publications in the English literature. Recently, the Japanese Clinical Practice Guideline for Prurigo by the Japanese Dermatological Association defined PCM as one of the representative forms of prurigo.[9] This article provides an expert consensus and presents a review of the historical background, cause, clinical manifestations, diagnosis, and therapy for PCM, a peculiar prurigo subtype, that might occur as a "primary lesion."

2 | MATERIALS AND METHODS

In preparing this position paper, two meetings were held with the core members of the development committee of the Japanese Clinical Practice Guideline for Prurigo. Based on the discussions, one of the authors, Satoh, wrote a draft that was peer-reviewed by the core members, and appropriate revisions were made to the final version.

In addition to a literature review of prior reports on the analyses of PCM, 24 patients who were diagnosed with PCM at the Department of Dermatology, National Defense Medical College (NDMC), in the past 6 years were retrospectively analyzed for their clinical and histopathological manifestations, laboratory findings, and comorbidities. The diagnosis of PCM was principally based on their clinical and histopathological features.

3 | RESULTS AND DISCUSSION

3.1 | Perplexing historical background of the term "prurigo chronica multiformis"

PCM is a subtype of prurigo that is clinically characterized by skin lesions ranging from fresh urticarial papules to solid brown papules. The disease designation became popular during the 1970s to 1980s in Japan. The term prurigo chronica multiformis was originally derived from one of the original descriptions by Lutz[10]: "Polymorphe chronische Prurigo." The clinical characteristics of present-day PCM in Japanese patients somewhat share morphological similarities with the previous entity of polymorphe chronische prurigo (Lutz). However, the two diseases do not appear to be identical, as Polymorphe chronische Prurigo was characterized by widespread lichenification, neurodermatitis-like changes, and/or eczematization with numerous small prurigo papules.

3.2 | Epidemiology

Epidemiological studies of PCM are limited. A recent study evaluated 65 patients with PCM treated at a single center in Japan[11]; among them, 46 were men and 19 were women, and the mean patient age was 69.3 years (range: 40–91 years). A similar male preponderance was observed in the 24 patients with PCM at NDMC (men:women = 19:5), although the patients tended to be older (mean age: 74.7 years, range: 53–83 years).

3.3 | Cutaneous manifestations

Typical characteristics of PCM are summarized in Table 1. The most commonly affected sites in PCM are the lower lateral abdomen and

TABLE 1 Characteristics of prurigo chronica multiformis.

Usually affects elderly patients, with a male predominance
Commonly affected sites are the lower abdomen and lower back
Skin lesions start as intensely pruritic urticarial papules, which gradually become solid papules/small nodules
The papules tend to aggregate and occasionally coalesce into polygonal or lichenified plaques
Histopathological features include dermal infiltration of lymphocytes and eosinophils with minimal epidermal changes

lower back regions, although the chest, thighs, arms, and upper back are also occasionally affected. Involvement of the face, scalp, and flexural surfaces of the extremities is rare, and the palms and soles are not affected. This is in sharp contrast to the preferred skin lesion distribution of atopic dermatitis. Typically, solid papules measuring 2 to 3 mm in diameter appear in crops. Such lesions start as edematous, urticarial, intensely pruritic reddish papules/small macules (Figure 1). They may transiently become serous papules or develop crusts with excoriations, which ultimately develop into persistent solid papules/nodules with brown pigmentation during the disease course. The papules tend to aggregate or sometimes coalesce into polygonal lichenified plaques in some cases (Figure 2). Each papule persists for several weeks to months and resolves with residual pigmentation, although the new appearance of red papules occurs frequently. Consequently, symptoms persist for several months to years with repeated remissions and exacerbations.

3.4 | Histopathological manifestations

The histopathological characteristics of PCM include mild perivascular lymphocytic infiltration that is confined to the upper dermis (Figure 3). Varying numbers of eosinophils are commonly detected in perivascular and intercollagenous spaces. These histopathological features can be referred to as a dermal hypersensitivity reaction pattern.[5,12] In principle, epidermal changes are minimal, but weak acanthosis might be observed. These features are in striking contrast to those of CPG, in particular the nodular type of CPG (prurigo nodularis), in which epidermal proliferation with hyperkeratosis and dermal fibrotic changes are characteristic.[13] Thus, it appears that PCM is not related to CPG.

Previous reports have demonstrated that basophil infiltration is a characteristic feature of PCM,[14,15] as detected using basophil-specific BB1 monoclonal antibodies. In contrast, detailed studies evaluating mast cells are not available to date, except for one report

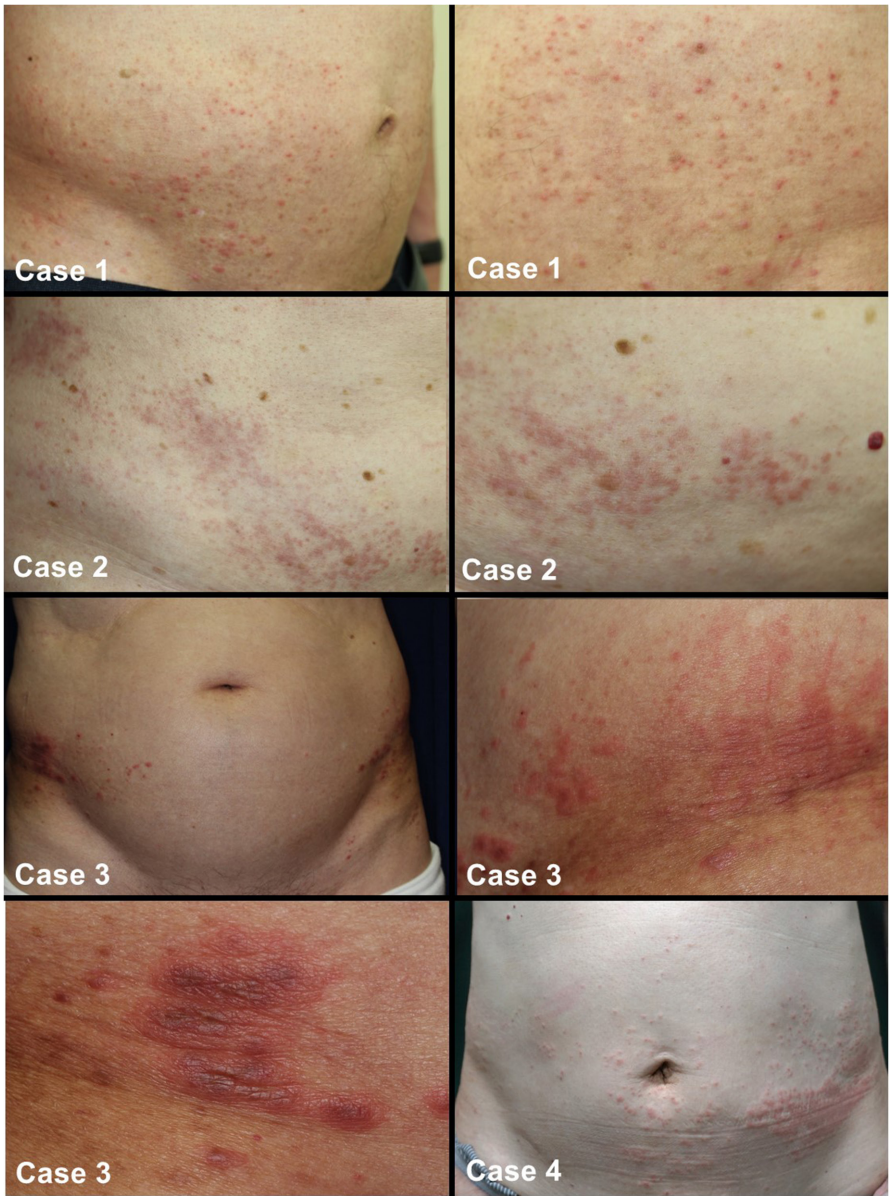

FIGURE 1 Early and intermediate stages of prurigo chronica multiformis. Four cases (cases 1–4) are presented. Small reddish papules and/or urticarial papules were scattered on the trunk. Some lesions were surrounded by urticarial erythema.

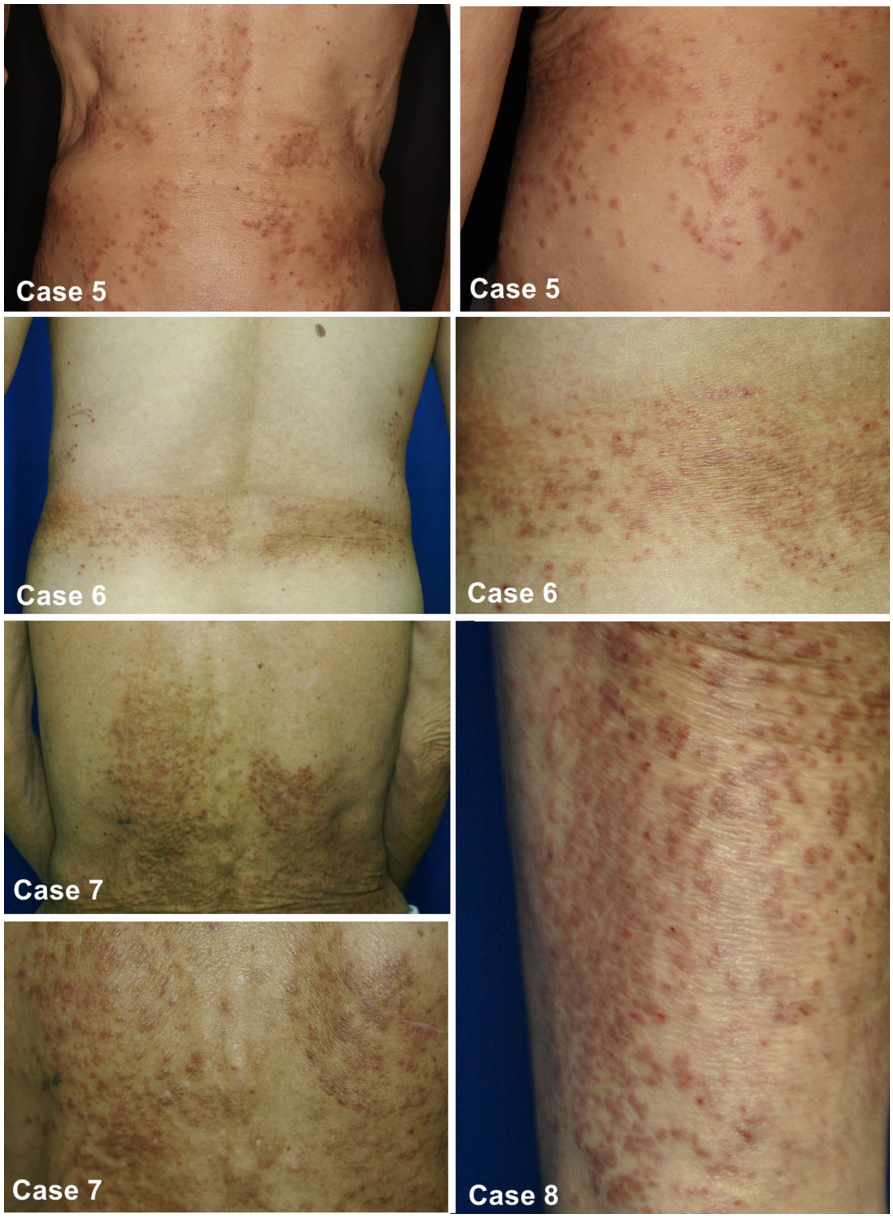

FIGURE 2 Late and chronic stages of prurigo chronica multiformis. Four cases (cases 5–8) are presented. Brown or reddish brown solid papules became persistent and gradually tended to aggregate and coalesce to form polygonal or lichenified plaques.

demonstrating that there was no difference in mast cell numbers between PCM and prurigo nodularis.[11]

3.5 | Laboratory data

Analysis of patients with PCM at NDMC showed mean serum IgE levels of 384.0 U/mL (range: 8.0–1400 U/mL; $n=21$), although 43% of patients with PCM had normal levels of IgE (<170 U/mL). In addition, blood eosinophil counts were 893.1 cells/μL (range: 155–2285 cells/μL; $n=23$). Serum TARC/CCL17 levels were also increased (mean: 1871.0 pg/mL [range: 232–6363 pg/mL]; $n=18$). Another study[11] from a single institute reported elevated mean levels of serum IgE ($n=47$) and blood eosinophils ($n=60$) in patients with PCM. Further, serum TARC/CCL17 levels in that study[11] were extremely high (>10000 pg/mL) ($n=10$).

3.6 | Comorbidities and precipitating factors

A pathogenic association between PCM and underlying disease(s) remains to be clarified. Nevertheless, resolution of PCM after eradication therapy for *Helicobacter pylori* infection[16] has been reported. In a previous study, skin symptoms in a patient with PCM and rectal/esophageal cancer showed improvement after surgical therapy for the cancer.[17] Another study[11] demonstrated a higher incidence of diabetes in patients with PCM than those with prurigo nodularis, but an actual causal association was not determined. In the present study, of the 24 patients with PCM who received treatment at the NDMC, comorbidities included diabetes ($n=6$), hepatic dysfunction ($n=1$), hypertension ($n=7$), dyslipidemia ($n=2$), benign prostatic hypertrophy ($n=3$), arrhythmia ($n=1$), cerebral infarction ($n=2$), bronchial asthma ($n=1$), odontogenic infection ($n=6$), *H. pylori* infection ($n=4$), metal allergy

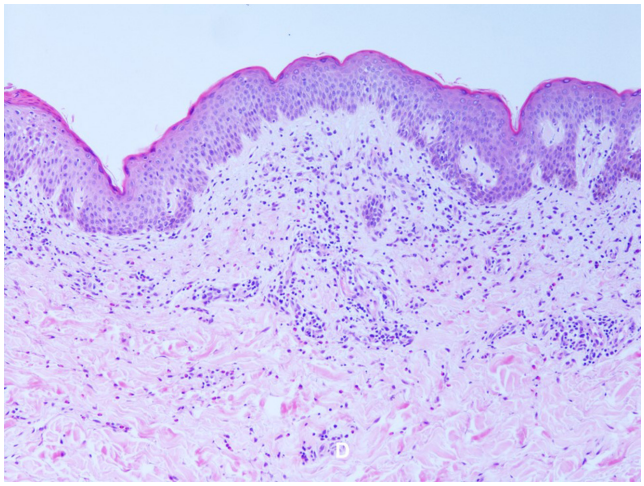

FIGURE 3 Histopathological features of prurigo chronica multiformis. Dermal inflammatory cellular infiltrates comprising lymphocytes and varying numbers of eosinophils (hematoxylin–eosin stain, original magnification: 100×).

($n = 3$), and malignancies ($n = 3$). However, we did not observe a clear association between these conditions and PCM, except for one patient who showed improvement following the eradication of odontogenic infection. None of the patients' condition was confirmed to be provoked by drugs. Moreover, none of them had a history of atopic dermatitis.

3.7 | Immunopathogenesis

Immunological events involving PCM have not been fully studied. Increased dermal infiltration of eosinophils and basophils, in conjunction with a weak or moderate elevation in serum IgE levels, in patients with PCM might suggest immunity skewed toward a type 2 response; this is also the case with other types of subacute and chronic prurigo.[18] In prurigo nodularis, dupilumab, a therapy targeting type 2 immunity through inhibition of interleukin (IL)-4/IL-13 signaling pathways, provided successful therapeutic outcomes.[19–21] Thus, future clinical trials on dupilumab for PCM might reveal whether type 2 immunity functions as the main player in immunological events. However, the immunopathogenesis of PCM likely differs from that of prurigo nodularis because, unlike prurigo nodularis, the histopathological changes principally involve dermal allergic reactions involving lymphocytes, eosinophils, and basophils, without significant epidermal changes. Indeed, a recent human pilot study revealed that anti-IgE therapy with omalizumab exerted therapeutic effects in some patients with PCM, but not those with prurigo nodularis.[15] The successful therapeutic outcome achieved by anti-IgE therapy might have been mediated by inhibition of basophil and/or mast cell function via interference of IgE binding to high-affinity IgE receptors on those cells.[15] In this regard, a mouse model of prurigo, in which antigen-specific IgE induced prurigo-like skin lesions and inflammation, characterized by dermal basophil infiltration with production of type 2 cytokines, has been established.[22] Importantly, this prurigo model is entirely dependent on basophils. Thus, human basophils might participate, at least in part, in the pathogenesis of the immunological process of PCM.

Mild to severe itch is common and characteristic in PCM. Itch in PCM is usually resistant to conventional therapies, such as antihistamines, as observed in other types of prurigo. Although studies on the nature and mechanisms of itch in PCM are limited, IL-4/IL-13 and/or a pruritogenic cytokine, IL-31, are potentially strong candidates as contributors to itching. This, however, needs to be further elucidated in the future. The lesional epidermis in PCM expresses high β-endorphin levels. Similarly, expression of autotaxin, an enzyme generating lysophosphatidic acid from lysophosphatidylcholine, increases in the lesional epidermis of PCM.[23] μ-Opioid receptor signals and/or the autotaxin–lysophosphatidic acid axis might, thus, participate in the intractable itch in patients with PCM.

3.8 | Differential diagnosis

Several diseases need to be considered as a differential diagnosis (Table 2).

In 1977, Ofuji et al. reported six cases of pruriginous dermatosis that were characterized by intensely pruritic papules aggregated in localized areas, such as the back and lateral sides of the trunk. They named this condition "grouping prurigo."[24] This report was followed by an additional report of three cases from another Japanese group.[25] Similar cases were also reported by a Korean group as "chronic pruritic papular dermatitis."[26] It appears that grouping prurigo and chronic pruritic papular dermatitis are the same disease as PCM. However, we are not aware of any additional recent reports using these designations in the English literature from other countries.

Kossard et al. defined the clinical entity of "urticarial dermatitis,"[12] which has a dermal hypersensitivity reaction pattern and is clinically characterized by urticarial plaques and papules occasionally accompanied by eczematous lesions. It is still uncertain whether urticarial dermatitis is a type 2–mediated dermal eczematous process or a prurigo reaction.[27] Urticarial dermatitis seems to share clinical and histopathological similarities with PCM, since, even in PCM, urticarial erythema appears occasionally, in particular during the acute exacerbation stage. As noted by Kossard and Hamann, however, urticarial dermatitis can be differentiated from prurigo disease, including prurigo subacuta, in that it is dominated by urticarial

TABLE 2 Differential diagnosis for prurigo chronica multiformis.

Grouping prurigo[24a]
Chronic pruritic papular dermatitis[26a]
Urticarial dermatitis[12]
Atopic dermatitis
Nonbullous type of pemphigoid
Pemphigoid nodularis
Scabies

[a]These appear to be the same disease as prurigo chronica multiformis.

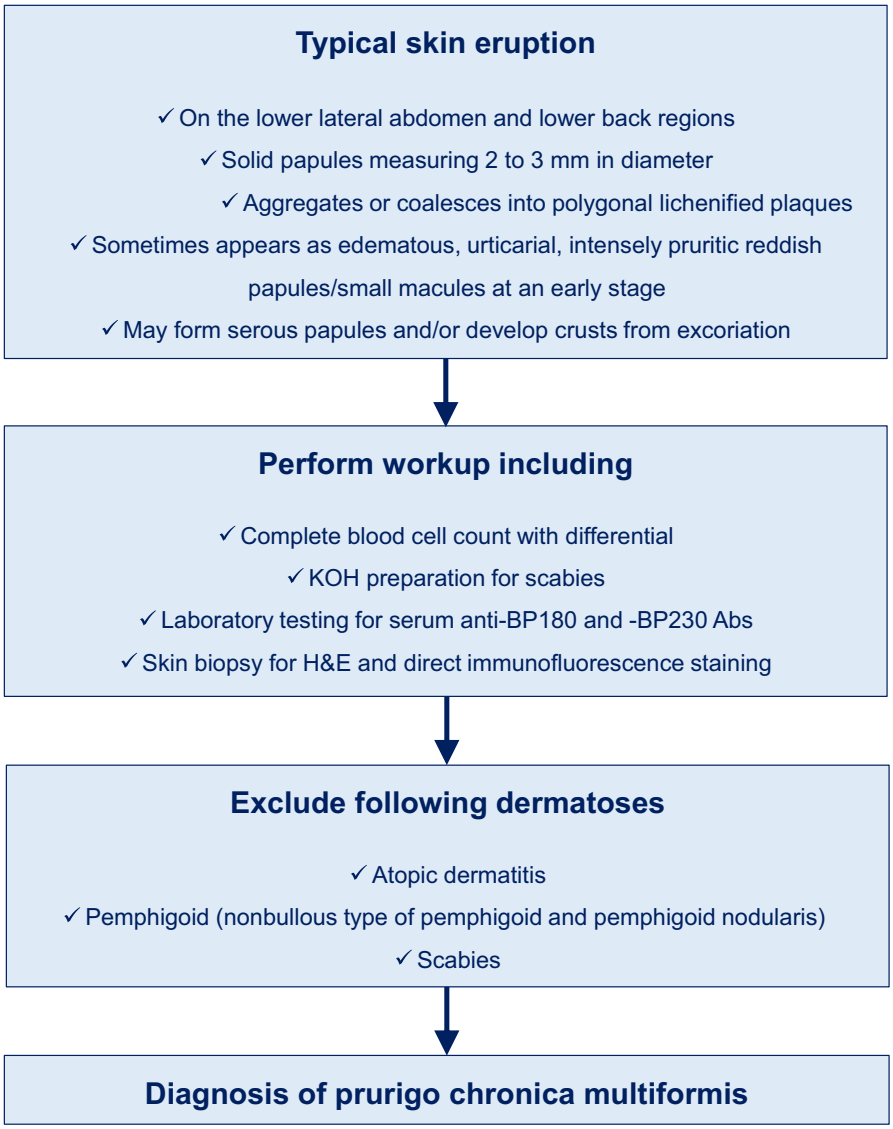

FIGURE 4 Diagnostic flowchart for prurigo chronica multifomis. H&E, hematoxylin–eosin; KOH, potassium hydroxide.

plaques, but not papules.[27] Further detailed study is needed to determine whether the two conditions are the same or different disease entities.

Atopic dermatitis, in particular, atopic dermatitis in elderly patients,[28,29] should be carefully differentiated from PCM, as prurigo lesions occasionally occur in atopic patients. However, the clinical features of prurigo lesions in PCM differ from those of atopic dermatitis. In addition, widespread acute/chronic eczematous skin lesions with eczematous papules or erythroderma-like changes with desquamation are not common in PCM. Weak or moderate elevation of total serum IgE is observed in some patients with PCM, although this finding is not consistent. In addition, preferential production of specific IgE against house dust mites is not necessarily observed.

In the clinical setting, PCM should also be differentiated from the nonbullous type of pemphigoid and pemphigoid nodularis through direct/indirect immunofluorescence studies and serum autoantibodies, such as anti-BP180 and anti-BP230 antibodies. PCM should also be differentiated from scabies by careful clinical observation and detection of *Sarcoptes scabiei* var. *hominis*.

A diagnostic flowchart for PCM is shown in Figure 4.

3.9 | Therapies

Topical corticosteroids are the first line of local therapy for PCM.[9] For patients resistant to topical corticosteroids, which is common, and/or patients with widespread skin lesions, UV phototherapy, including narrow-band UV-B therapy, should be effective. Since dry skin in elderly patients can also predispose to the development of PCM, moisturizers in sufficient quantities to ameliorate skin dryness is also recommended. Oral reserpine and etretinate might also lead to improvement in some patients.[9,30,31] While systemic corticosteroids and immunosuppressive agents, such as oral cyclosporine, are typically effective, long-term use of these therapies should be avoided. Antihistamines can be used as supportive therapy for severe itch, although their effectiveness is limited. Alternative therapeutic options include serotonin-noradrenaline reuptake inhibitors,[32] selective serotonin reuptake inhibitors, gabapentin, pregabalin, and Chinese

herbal medicines.[9] Omalizumab might be another useful option for treatment-resistant cases of PCM.[15] In addition, a recent pilot study revealed improvements of skin and visual analog scale scores in two cases with PCM,[33] and, thus, the actual clinical benefits of dupilumab in PCM need to be further evaluated in the future.

4 | CONCLUSIONS

The core members of the Japanese Clinical Practice Guideline Development Committee for Prurigo determined that PCM is a subtype of prurigo with peculiar clinical manifestations that is distinct from prurigo acuta, prurigo simplex subacute, and CPG, with potential variations in clinical phenotype based on geographical location and racial differences. It may be an East Asian–specific phenotype of prurigo reactions. Further investigation of these clinical phenotypes, the pathological mechanisms underlying PCM, and detailed clinical observation are necessary.

CONFLICT OF INTEREST STATEMENT

Satoh T: AbbVie, Asahi Kasei, Bristol Myers Squibb, Eli Lilly, Hisamitsu Pharmaceutical, Kracie, Kyorin Pharmaceutical, Maruho, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Pfizer, Sanofi, Torii Pharmaceutical, Kissei Pharmaetical, Leo Pharma, Amgen Inc., UCB Japan, Nippon Zoki Pharmaceutical, Kaken Pharmaceutical – speaker honorarium; AbbVie, Daiichi Sankyo, Eli Lilly Japan K. K., Kaken Pharmaceutical, Kyowa Kirin, Nippon Zoki Pharmaceutical, Otsuka Pharmaceutical, Sato Pharmaceutical, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Maruho – research grants; Nankodo – other fees; Sanofi, Maruho – investigator. **Murota H:** AbbVie, Eli Lilly, Hisamitsu Pharmaceutical, Kyorin Pharmaceutical, Maruho, Pfizer, Sanofi, Torii Pharmaceutical – speaker honorarium; AbbVie, Hoyu, Kaken Pharmaceutical, Mandom, Sanofi – investigator; AbbVie, Kaken Pharmaceutical, Sanofi- Consultancy fee or commissioned fee. **Aoyama M:** Maruho, Sanfi, Abbvie, Eli Lilly, Japan Blood Products Organization – speaker honorarium. **Hashimoto T:** Sanofi, AbbVie, Torii Pharmaceutical, Mitsubishi Tanabe Pharma, Taiho Pharmaceutical, Kissei Pharmaceutical, Kracie, Galderma– speaker honorarium. **Ishiuji Y:** Maruho, Sanofi, Eli Lilly, Otsuka Pharmaceutical, AbbVie – speaker honorarium; Hoshi Pharmaceutical- scholarship donation. **Hatano Y:** Sanofi. Maruho, Taiho Pharmaceutical– research grants; Sanofi, Nippon Boehringer Ingelheim, AbbVie, Maruho, Torii Pharmaceutical, Eli Lilly, Kyowa Kirin– speaker honorarium. **Nakahara T:** AbbVie, Eli Lilly, Pfizer, Otsuka, Maruho, Leo pharma, Sanofi – speaker honorarium. **Kabashima K:** P&G, Toray, Janssen, Maruho, Astellas, Shiseido, Cose, JT, Lion– research grants; Maruho, Eli Lilly- Consultancy fee or commissioned fee. **Takamori K:** Kao, FANCL, Kirin HD, Torii Pharmaceutical, Oji Pharma, Eternam-Followship grant. **Katayama I:** Sanofi, Maruho – speaker honorarium.

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