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ORIGINAL ARTICLE

Prurigo pigmentosa: Clinicopathological study and analysis of 50 cases in Korea

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ABSTRACT

Prurigo pigmentosa is a recurrent dermatosis with severe pruritus and several peculiar clinical features. Its exact etiology and pathogenesis are unclear. The aim of this study was to investigate the clinical features and chronological changes in the histopathology of prurigo pigmentosa in Korean patients and to assess the etiology of this condition. We reviewed the medical records, clinical photographs and biopsy specimens from 50 patients diagnosed with prurigo pigmentosa. Mean age at diagnosis was 23.7 years (range, 15–61 years). Prurigo pigmentosa started as urticarial papules or plaques, changing first to papulovesicles and then to reticulated brownish macules. The most frequent sites were the back and chest, especially depressed areas such as the central back and inter-mammary area. Dietary change was suspected as a cause of prurigo pigmentosa in 17 patients. Histopathologically, early-stage lesions had dermatitis herpetiformis-like features; fully-developed lesions displayed impetigo-like or acute, generalized, exanthematous, pustulosis-like features; and late lesions presented with post-inflammatory hyperpigmentation-like features. Oral minocycline, with or without dapsone, was effective in inhibiting the appearance of new lesions, but did not prevent recurrence. Prurigo pigmentosa is not rare in Korea, is apparently associated with dietary modification and preferentially involves the depressed regions of the trunk.

Key words: diet, dietary modification, food, Korea, prurigo pigmentosa.

INTRODUCTION

Prurigo pigmentosa (PP) is a severe pruritic skin disease in young adults and has characteristic clinical features that include recurrent eruptions of pruritic erythematous macules and papules that resolve, leaving reticulate hyperpigmentation. Due to the non-specific histological features of PP, clinicopathological correlation and thorough long-term follow up are necessary to establish a diagnosis. PP was first described in Japan by Nagashima and colleagues,[1] and more than 300 patients with this disease have been reported in Japan to date. However, there have been few reports of PP in countries other than Japan. The exact causes of PP and its pathogenesis are unclear, and in this study, we investigated the clinicopathological features and suspected causes of PP in Korea.

METHODS

The medical records, photographs and histopathological slides of 50 patients diagnosed with PP at three hospitals (Asan Medical Center, Hanyang University Medical Center and Boramae Medical Center) in Korea between May 2003 and December 2011 were retrospectively reviewed. Diagnosis of PP was based on clinicopathological findings from the adapted criteria set by Boer *et al.*[2] Patients without histopathological confirmation of skin lesions were excluded. The duration of follow up ranged 3–9 years.

Data noted from reviewing the medical records included demographics, previous medical history, disease duration, site and extent of disease, signs and symptoms of disease, laboratory examination (including whole blood cell count, serum glucose, serum immunoglobulin E, antinuclear antibodies (ANA), urinary analysis, serum and urinary ketones), histopathology, disease treatment, treatment duration, treatment response and other associated findings.

RESULTS

Clinical findings

Demographics of patients with PP. Of the 50 PP patients included in this study, females were predominant (36/50)

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Table 1. Clinical presentations, associated factors and laboratory findings for the prurigo pigmentosa cases in this study

Clinical presentation	Cases, *n* (%)	Laboratory findings	Cases, *n* (%)
Sex		Whole blood count	29
F:M	2.57:1	Normal	28 (96.6)
Female	36 (72)	Mild leukocytosis	1 (3.5)
Male	14 (28)		
		Eosinophil count	29
Distribution		Normal	29 (100)
Symmetrical	46 (50)		
Asymmetrical	4 (8)	Immunoglobulin E level	6
		Increased	5 (83.3)
Location of skin lesions		Normal	1 (16.7)
Back	35 (70)		
Central	26	Blood urea nitrogen/creatinine	28
Scapular (central sparing)	2	Normal	28 (100)
Chest	32 64)		
Inter-mammary	28	AST/ALT	31
Posterior neck	21 (42)	Normal	31 (100)
Shoulders	5 (10)		
Proximal limbs	4 (8)	ESR	24
		Normal	23 (95.8)
Incidence		increased	1 (4.2)
Spring (Mar–May)	13 (26)		
Summer (Jun–Aug)	18 (36)	Blood ketone	3
Autumn (Sep–Nov)	8 (16)	Normal	3 (100)
Winter (Dec–Feb)	11 (22)		
		Urine ketone†	22
Symptom		Normal	15 (68.2)
Pruritus	48 (96)	increased	7 (31.8)
Severe	11	3+	3
Moderate	11	2+	2
Mild	26	1+	2
No	2 (4)		
		Antinuclear antibody	10
		Normal	10 (100)
Associated factors	Cases, *n* (%)		
Allergic disease*	6 (12)		
Allergic rhinitis	3		
Atopic dermatitis	2		
Metal allergy	2		
Diabetes mellitus	0		
Pregnancy	0		
Aggravating factors			
Dietary modification	17 (34)		
Mechanical irritation	5 (10)		
Emotional stress	2 (4)		
Sweating	3 (6)		

*One patient had both atopic dermatitis and a metal allergy. †Results of urine ketone tests are expressed according to the following semi-quantitative system: –, negative; 1+, <10 mg/dL; 2+, 10–100 mg/dL; 3+, >100 mg/dL. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate.

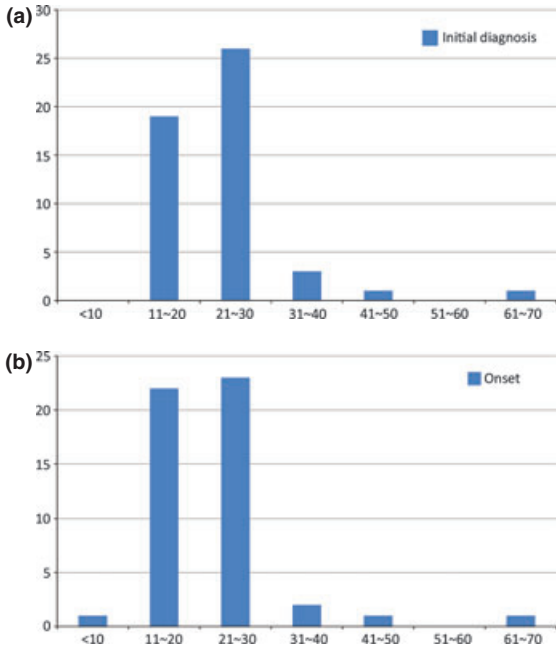

Figure 1. Graph of the age distribution in the current prurigo pigmentosa patients. (a) Age at first onset. (b) Age at initial diagnosis.

(Table 1). Patient ages at initial diagnosis ranged 15–61 years (mean ± standard deviation [SD], 23.7 ± 8.3 years). Patient ages at first onset ranged 7–61 years (mean ± SD, 22.3 ± 8.6 years; Figure 1).

Disease duration and recurrence. The time from first PP onset to diagnosis varied from 3 days to 10 years. The disease occurred more frequently during spring and summer (March–August; $n = 31$ patients) compared with autumn and winter (September–February; $n = 19$ patients). Twenty-seven patients had a previous history of recurrent PP events and 23 patients had their first PP event at the time of diagnosis. During the follow-up period (ranging 3–9 years) after diagnosis, recurrent episodes were noted in 10 patients.

Symptoms of PP. Of the 50 patients, 48 experienced pruritus and two complained very little of this symptom at the initial visit. Twenty-two patients noted moderate to severe itching that caused sleep disturbance every night or impairment of daily life, and the remaining 26 patients reported mild, intermittent itching.

Characteristics and distribution of skin lesions at the time of diagnosis. In 46 patients, the lesions were distributed symmetrically; the lesions in the other four patients were bilateral but not symmetrical. In 24 patients, urticarial papules and plaques predominated (Fig. 2a), with 14 also showing reticulated brownish macules (Fig. 2b). In 13 patients, papulovesicles predominated (Fig. 2c), with 10 also showing reticulated brownish macules. In two patients, prominent vesicles were the principal

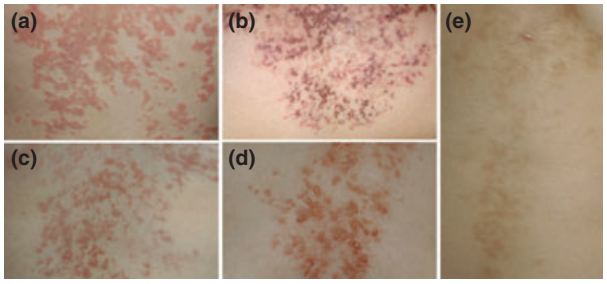

Figure 2. Characteristics of prurigo pigmentosa lesions. (a) Early-stage lesions, showing urticarial papules and plaques. (b) Recurrent lesions, characterized by papules associated with previously reticulated brownish macules. (c) Fully-developed lesions showing the predominance of papulovesicles. (d) Prominent vesicles. (e) Resolving lesions, presenting as reticulated brownish macules only.

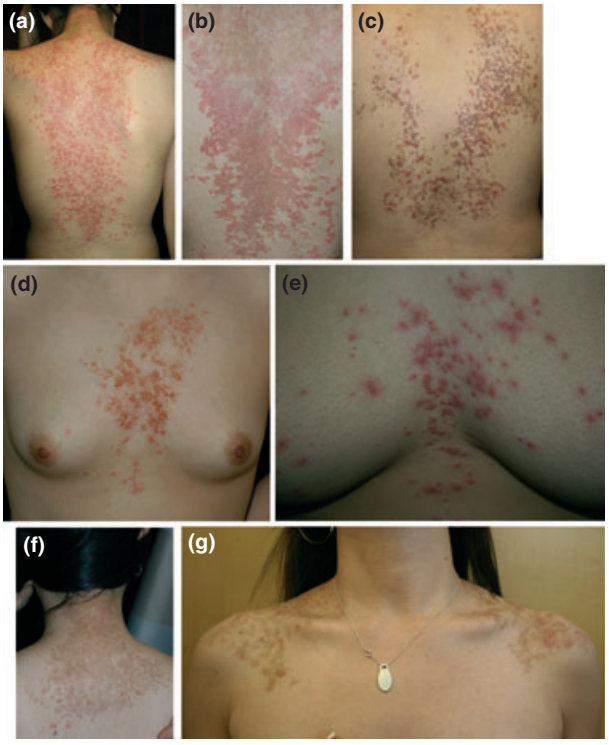

Figure 3. Distribution of prurigo pigmentosa lesions. (a,b) In some patients, prurigo pigmentosa is present on the back in a wedge shape, involving the central portion of the back. (c) In other patients, prurigo pigmentosa is present on the back, but with sparing of the central portion. (d,e) Involvement of the chest. (f) Involvement of the posterior neck. (g) Involvement of the shoulders.

lesions (Fig. 2d), whereas in 11, reticulated brownish macules were the only lesions present (Fig. 2e).

The most common sites for PP were the back and chest. Of 35 patients with back lesions, 26 had lesions in central depressed areas such as the inter-scapular area (Fig. 3a,b). Six patients had lesions distributed over the whole back, but with particularly prominent lesions in the central area. Two patients had lesions on both scapular areas with central sparing (Fig. 3c). One patient had back lesions with an asymmetrical distribution. Of 32 patients with chest lesions, 28 had lesions in depressed areas such as the inter-mammary area (Fig. 3d,e). PP lesions were observed on the posterior neck in 21 patients (Fig. 3f), on the shoulders in five patients (Fig. 3g) and on the proximal extremities in four patients.

Associated conditions. Allergic disease was recorded in six patients, including three patients with allergic rhinitis, two patients with atopic dermatitis and two patients with metal allergy (both atopic dermatitis and metal allergy were noted in one patient). No patient had diabetes mellitus or was pregnant.

Prurigo pigmentosa developed after dietary change in 17 patients and in eight of these patients dietary change was accompanied by weight loss. After 2 or 3 months of dietary modification, average weight loss was 4 kg/month in this subgroup. In eight patients, the dietary change involved predominant intake of a single item (one-food diet) such as boiled egg, sweat potato and cucumber, or a low-carbohydrate diet. All 17 patients in this subgroup stopped their dietary modifications after diagnosis and commenced a well-balanced diet. However, in five of these patients, PP recurred after restarting their dietary modification. Five patients developed PP after mechanical irritation such as bandage, body-scrubbing or friction from clothing. Two patients developed PP after emotional stress, and in three patients, it developed after sweating due to exercise or hot weather. We were unable to identify any cause in the remaining 23 patients.

Laboratory examination. All laboratory findings at the initial visit are summarized in Table 1. A complete blood count was done in 29 patients. The results were within normal limits in 28 patients, and mild leukocytosis was noted in one patient (13 000; reference value, <10 000/mm^3). Eosinophil counts in the peripheral blood were within normal limits in all 29 patients (reference value, 1–7%). The serum total immunoglobulin E level was measured in six patients (reference value, <120 IU/L), and was found to have increased in five of these patients (range, 220–5420 IU/L) and to be within normal limits in the remaining patient. Blood urea nitrogen and creatinine levels were measured in 28 patients and in each case the results were within normal limits. Aspartate aminotransferase and alanine aminotransferase were measured in 31 patients and all results were also within normal limits. The erythrocyte sedimentation rate was measured in 24 patients, and was within normal limits in 23 patients and was increased one patient (24; reference value, <10 mm/h).

Blood ketone levels were measured in three patients, two of whom had early lesions such as urticarial papules and plaques, and one individual who had late lesions only, such as reticulated brownish macules. The results were within normal limits for each of these patients. Urine ketone levels were measured

Table 2. Dietary modifications and urine ketone levels in the prurigo pigmentosa patients

Associated conditions	*n*	Measurement of urine ketone		
		No	Yes	Increased level
Diet	17	9	8	4
Others	33	20	13	3
Total	50	29	21	7

in 21 patients, 17 of whom had early and fully-developed lesions and four who had only late lesions. Of these 21 patients, eight had a history of dietary change before the development of PP and seven showed increased urine ketone levels. Of eight cases with an associated dietary change, four showed increased urine ketone levels, whereas of the 13 cases with no dietary change, only three showed increased urine ketone levels (Table 2). ANA levels were measured in 10 patients and in each case the results were within normal limits.

Treatment and response. Thirty-eight patients were treated with 100–200 mg/day oral minocycline and seven were treated with 100 mg/day oral dapsone. Four patients were treated with both minocycline and dapsone. One patient was treated with 200 mg/day oral doxycycline and one patient was treated with 500 mg/day oral erythromycin. Six patients were treated with oral antihistamines and topical steroids, and three were treated with oral and topical steroids. The remaining three patients received no treatment.

Although oral minocycline, with or without dapsone, was very effective in inhibiting the appearance of new lesions, these drugs did not prevent recurrence. Oral antihistamines, oral steroids and topical steroids were less effective in preventing the appearance of new lesions. Without treatment, lesions tended to resolve spontaneously within weeks.

Histopathology

Lesions were clinically classified as early lesions, including urticarial papules and plaques; fully-developed lesions, including papulovesicles and vesicles; late lesions, which showed reticulated pigmented macules; recurrent early lesions, defined as recurring urticarial papules or plaques over the previous reticulated pigmentation; and recurrent fully-developed lesions, defined as recurring papulovesicles or vesicles over the previous reticulated pigmentation (Table 3).

Skin biopsy specimens of early lesions revealed dermal perivascular neutrophilic infiltration and scattered neutrophils in the dermal papillae (Fig. 4a–b). Fully-developed lesions showed dermal neutrophilic infiltration, intraepidermal neutrophils and spongiosis with some intraepidermal vesiculation (Fig. 4c–f). In late lesions, the dermal infiltrates consisted mainly of lymphocytes rather than neutrophils (Fig. 4g), with some specimens showing lichenoid changes. Epidermal hyperplasia, epidermal hyperpigmentation and dermal melanophages were frequently observed (Fig. 4h–j). Recurrent early lesions showed histopathological characteristics of both early and late lesions, whereas recurrent fully-developed lesions showed features of both fully-developed and late lesions.

DISCUSSION

Prurigo pigmentosa was first described in 1971 as a peculiar pruriginous dermatosis with gross reticular pigmentation and non-specific, non-diagnostic histopathological findings.[1] Recent findings, however, suggest that PP is a histopathologically distinct inflammatory disease of the skin.[3] The diagnosis of PP requires clinicopathological correlation and diagnostic criteria based on the typical features of PP that have been established.[2] Although most early cases were reported in Japan, PP has also now been reported in other countries. This disease usually occurs in patients in their late teens and early twenties, and most often appears in the spring and summer.

Prurigo pigmentosa lesions are distributed symmetrically, preferentially on the trunk, with most lesions appearing on the back, chest and neck. Individual lesions show rapid changes. Early lesions appear as urticarial papules and plaques, later becoming fully-developed lesions, such as papules, papulovesicles and vesicles. These lesions subside within 1 week,

Table 3. Histopathological features of prurigo pigmentosa at each stage in the prurigo pigmentosa patients

	Early (*n* = 10)	Fully-developed (*n* = 5)	Late (*n* = 11)	Recurrent early (*n* = 14)	Recurrent fully-developed (*n* = 10)
Perivascular neutrophilic infiltration in dermis	6	2	2	4	7
Intraepidermal neutrophils	4	2	0	5	3
Spongiosis	6	3	2	3	4
Intraepidermal vesiculation	1	1	0	0	1
Predominance of lymphocytes over neutrophils in a dermal infiltrate	4	3	8	8	4
Patchy lichenoid infiltration of lymphocytes	1	0	1	2	0
Vacuolar alteration of dermoepidermal junction	1	0	2	3	3
Extravasated erythrocytes	1	1	0	1	0
Epidermal hyperplasia	1	1	5	7	2
Epidermal hyperpigmentation	1	0	3	4	1
Dermal melanophages	0	0	6	3	2

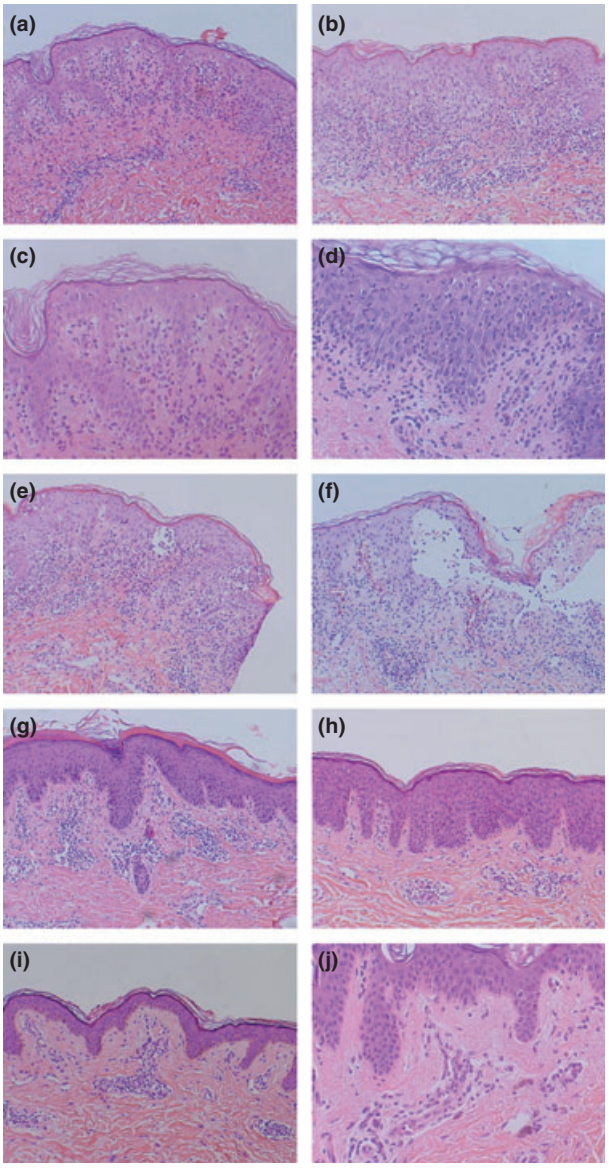

Figure 4. Histopathological findings of prurigo pigmentosa. (a,b) In the early stage, many neutrophils infiltrate the dermis perivascularly, becoming scattered in the dermal papillae (hematoxylin–eosin [HE], original magnification ×100). (c–e) In the fully-developed stage, neutrophils are swept into the epidermis, causing intraepidermal neutrophils to become prominent and leading to the formation of intraepidermal abscesses (HE, [c,d] ×200, [e] ×100). (f) Spongiosis may be prominent at this stage, along with intraepidermal vesiculation (HE, ×100). (g–j) In the late stage, lymphocytes predominate over neutrophils in the dermis, and epidermal hyperplasia, hyperpigmentation and dermal melanophages are observed (HE, [g–i] ×100, [j] ×200).

leaving reticulated pigmented macules. Lesions at different stages of development are often present together. Recurring lesions are usually located at the same sites as the primary lesions. Pruritus is usually severe in early lesions, but resolving lesions may be devoid of symptoms. Indeed, in our 11 patients with reticulated, hyperpigmented resolving lesions, none complained of severe itching. Although bullous PP is rarely reported,[4–6] two of our 50 patients had prominent intact vesicles, indicating that bullous PP may not be as rare as commonly thought.

The etiology of PP remains to be elucidated. Several endogenous and exogenous factors have been suspected as causes of PP. Endogenous factors include ketosis,[7] diet,[8] fasting (anorexia nervosa),[9] diabetes mellitus,[10] pregnancy,[11] *Helicobacter pylori* infection[12,13] and atopic diathesis.[14,15] Exogenous factors include sweating,[16] friction from clothing,[17] and contact with allergens such as *para*-amino compounds, trichlorophenol, chromium and nickel [18–20] In addition, ethnic predisposition[21,22] or environmental factors have been suspected as contributing factors.

Of these potential etiological factors, many studies have focused on dietary modification and ketosis.[7–10,23–26] Recently, Oh *et al.*[23] studied 16 patients with PP and a chronological relationship between PP and dieting or fasting was observed in eight patients, while ketosis was observed in six patients. Seventeen patients in our present study underwent dietary changes prior to the development of PP; this high rate is similar to the results obtained by Oh *et al.*,[23] but contrasts with another study, which found a much weaker link between dietary change and PP.[3] After resolution of an initial PP event, five patients in our present study experienced recurrence after restarting their dietary modification.

Ketosis is a transient condition characterized by elevated serum levels of ketone bodies.[27] When blood glucose levels are low (during fasting) or when insulin is lacking (poorly controlled diabetes), ketogenic metabolic processes are initiated. Ketone bodies pass from the circulating blood into the tissues, enter the cells and modify processes in the cytoplasm. The ketone bodies may also remain around the blood vessels and cause perivascular inflammation.[27] Some case reports have suggested a relationship between PP and ketosis,[7,28] while other reports have suggested that ketone production may be responsible for the association between fasting (anorexia nervosa)[9] or diabetes mellitus[24,25] and PP. Dietary modification is a common approach to weight loss in young Korean females. Many studies note the ketogenic effect of a low-carbohydrate diet,[29] and this may explain the reported high frequency of PP in Korean patients. In our present study, urine ketones were measured in eight of the patients with dietary modification, with positive results in four of these patients.

It was recently reported that autoimmunity may contribute to the pathogenesis of PP. Park *et al.*[30] presented three cases of PP with elevated ANA levels, suggesting that PP might be a sign of dormant autoimmune disease. In our study, however, ANA levels were found to be within normal limits in the 10 patients in whom they were measured. Elevated ANA levels can sometimes occur in healthy people[31] and may be an incidental finding in PP patients.

It has been generally considered that the histopathological features of PP are non-specific and non-diagnostic.[1,32] Recent findings, however, suggest that PP is a histopathologically dis-

tinct inflammatory disease of the skin.[3] PP displays stage-specific histopathological features,[3] with an initial superficial perivascular neutrophil infiltrate, followed by scattering of neutrophils in the dermal papillae. The neutrophils sweep rapidly through the epidermis, leading to spongiosis and ballooning, which are accompanied by keratinocyte necrosis. Abscesses may form in the epithelium. Over time, lymphocytes and eosinophils come to predominate over neutrophils in the dermis and may form patchy lichenoid patterns. The epidermis subsequently becomes hyperplastic and hyperpigmented, and melanophages appear in the dermis. In general, our present results corresponded to these findings: early-stage PP showed dermatitis herpetiformis-like histopathological features; fully-developed PP presented with impetigo-like or acute, generalized, exanthematous, pustulosis-like features; and late-stage PP were characterized by post-inflammatory hyperpigmentation-like features. Interestingly, as PP frequently becomes exacerbated and recurs, usually at the same sites as previous lesions, early PP lesions may also show hyperplastic and hyperpigmented epidermis and melanophages in the dermis.

The differential diagnosis of PP includes confluent reticulated papillomatosis, dyschromicum perstans and pigmented contact dermatitis. Nagashima[33] noted that clinical features of PP included a predominant incidence in young females, a preferential occurrence in spring and summer, and the distribution of skin lesions and severe pruritus. Yamasaki *et al.*[34] noted that, in contrast to pigmented contact dermatitis, oral and topical corticosteroids are not effective in treating PP, and that oral antihistamines do not effectively reduce pruritus in affected patients. In our present study, however, cases of PP associated with old age, male sex, autumn and winter incidence, and the absence of pruritus were noted. Clinicopathological correlations in PP showing these atypical features should be examined in a long-term follow up.

A variety of agents are used in the treatment of PP, the most effective of which are oral antibiotics such as minocycline, doxycycline and sulfonamides such as dapsone.[35–38] Recently, minocycline has been preferred to dapsone because it has fewer side-effects and results in a longer remission.[36] The therapeutic effects of minocycline and doxycycline are thought to be due to their anti-inflammatory effects. These drugs inhibit mitogen-induced human lymphocyte proliferation, neutrophil migration and chemotaxis, and phospholipase A2.[39] Minocycline and doxycycline also inhibit the expression of cytokines and chemokines, which regulate leukocyte differentiation and activation and the local tissue inflammatory response.[20,40] Leukocyte activation and inflammation are key pathological features in PP, suggesting that these mechanisms may contribute to the therapeutic effects of minocycline and doxycycline.

Lesions frequently recur in patients with PP. Indeed, 10 of our patients experienced recurrence at follow up ranging 3–9 years. Neither oral minocycline nor dapsone prevented further recurrences after the discontinuation of medication.

In summary, we show in our present study that PP is not rare in Korea; 50 patients were diagnosed with this condition over a 9-year period at three hospitals. This is likely to be an underestimate because we retrospectively assessed only those patients who underwent skin biopsies. PP was found to be frequently associated with dietary modifications. The mechanism by which dietary modifications provoke PP is not yet clear, but there are several previous reports of an association between ketosis and inflammation. Further investigations are needed to fully understand the pathogenesis of PP and to prevent this disease in patients at high risk.

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