

ORIGINAL ARTICLE

Prurigo pigmentosa: a clinicopathologic study of 16 cases

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Abstract

Background Prurigo pigmentosa is a rare inflammatory disease of unknown origin. It is characterized by the sudden onset of pruritic erythematous papules, usually involving the trunk and neck, which coalesce to form reticulated, mottled patches.

Methods We studied 16 patients with prurigo pigmentosa. The patients were selected from those attending the outpatient Department of Dermatology at the Kyung Hee University Hospital from January 2002 to January 2010. All clinical information was retrospectively collected from medical records. The serum concentrations of ketones (acetoacetic acid, 3-hydroxybutyrate acid [3-OHBA]) were examined in four patients, and a test for ketone in the urine was performed in 10 patients.

Results The age at the time of diagnosis ranged from 18 to 36 years (mean age: 23.5 years), and the female : male ratio was 14 : 2. Skin lesions were almost always characterized by recurrent pruritic erythematous papules that had resolved, leaving a peculiar, reticulate hyperpigmentation. Eight of 16 patients showed a chronological relationship between a prurigo pigmentosa appearance of skin lesions and dieting or fasting. Histopathological findings were either of fully developed lesions (4/16) or late lesions (12/16). Most patients responded well to minocycline treatment. Ketosis was observed in six patients.

Conclusions In conclusion, we propose that ketosis was caused by fasting, and that diet may contribute to the pathogenesis of prurigo pigmentosa. Thus, physicians need to warn that excessive fasting can cause prurigo pigmentosa.

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Conflicts of interest

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Introduction

First described by Nagashima *et al.*¹ in 1971, prurigo pigmentosa is a rare inflammatory dermatosis of unknown aetiology rarely diagnosed outside Japan. It is usually distributed symmetrically over the trunk and neck and presents with recurrent, pruritic erythematous macules, papules and papulovesicles that resolve, leaving behind a net like pigmentation.² Only about 40 cases have been diagnosed outside Japan because clinicians outside Japan are unfamiliar with the criteria.² Herein, we present the clinicopathological aspects of prurigo pigmentosa and evaluate the relationship between prurigo pigmentosa and ketosis.

Methods

Patients with a clinical diagnosis and histopathological confirmation of prurigo pigmentosa were selected from those attending the

outpatient Department of Dermatology at Kyung Hee University Hospital from January 2002 to January 2010. A thorough history was taken from all patients, including age, gender, familial history, underlying disease, previous history of prurigo pigmentosa, characterization and distribution of skin lesions, aggravating factors, dieting or fasting history and response to treatments. Skin biopsies of either erythematous papules or pigmented macules were performed on all enrolled patients, and the histopathological findings were classified according to Boer's criteria.²

The serum concentration of ketones (acetoacetic acid, 3-hydroxybutyrate acid [3-OHBA]) was examined using a direct enzymatic assay method in four patients, and a test for ketone in the urine was performed in 10 patients. Routine laboratory examinations including peripheral blood cell counts, liver function tests, blood glucose levels and urinalysis were completed.

Results

Sixteen patients who fulfilled the diagnostic criteria of prurigo pigmentosa as proposed by Böer *et al.*² were enrolled. The clinical findings were summarized in Table 1.

Demographical findings

The age at the time of diagnosis ranged from 18 to 36 years (mean age: 23.5), and the female : male ratio was 14 : 2.

Family history and past medical history

None of the patients had any relevant family history. There was no history of any skin problems including atopic dermatitis, contact dermatitis, pityriasis versicolour, dermatitis herpetiformis and confluent reticulate papillomatosis in any of the patients. None of the patients had diabetes mellitus. Six patients had a previous history of these skin lesions.

Characterization and distribution of skin lesions

Skin lesions were almost always characterized by recurrent pruritic erythematous papules that had resolved, leaving a peculiar, reticulate hyperpigmentation. Boer *et al.*,² suggested that this disease period could be divided into four stages. According to their description, in early lesions of the disease, urticarial papuloplaques often occur as scratch marks. In fully developed lesions, papules, papulovesicles and rarely papulopustules are observed. Resolving lesions manifest crusted and scaly papules, and then leave reticulated hyperpigmentation in late lesions. Four of our patients had fully developed lesions, and 12 patients had resolving or late lesions (Figs 1a, c and 2a, c).

The lesions were distributed symmetrically over the back (15/16), chest (12/16), nape (11/16), abdomen (7/16), shoulders (3/16), lumbosacral region (2/16), extremities (2/16) and face (1/16).

Relationship between aggravating factors or diet and skin lesions

Aggravating factors were present in two patients, one reported aggravation by rubbing (patient 13) and the other one by sweating (patient 6). Eight patients showed a chronological relationship between the appearance of prurigo pigmentosa and dieting or fasting.

Histopathological findings

Most histopathological findings were nonspecific, and the specimens were classified according to Böer's criteria.² According to their description, in early lesions of the disease, neutrophil infiltration, spongiosis, ballooning degeneration and necrotic keratinocytes were observed. In fully developed lesions, the infiltrate assumed a patchy lichenoid pattern, and eosinophils and lymphocytes in the dermis were more predominant. In late lesions, parakeratosis, epidermal hyperplasia, melanophages and sparse lymphocytes in the upper dermis were observed. Four of our patients had fully developed lesions, and 12 patients had late lesions (Figs. 1b, d and 2b, d).

Response to treatment

Most patients were treated with oral minocycline and topical steroid (13/16). The patients took oral minocycline for 2–7 weeks,

Table 1 Clinical summary of prurigo pigmentosa patients in this study

Pt	Age/Sex	Skin lesion		Aggravating factor	Dieting, fasting	HP stage‡	Treatment	Episodic duration
		Stage‡	Distribution†					
1	22/F	R	A,B,C			L	Minocycline	5 months
2	33/M	L	C,B	(-)	(-)	L	Antihistamine, topical steroid	7 weeks
3	20/F	R	B,C,N	(-)	(-)	L	Topical steroids, minocycline	4 months
4	23/F	F	A,B,C,L,N	(-)	(-)	F	Antihistamine, topical steroid	4 weeks
5	22/F	R	C	(-)	(+)	L	Antihistamine, dapsone	8 weeks
6	24/F	R	A,B,C,N,S	(-)	(-)	L	Topical steroid, minocycline	4 weeks
7	19/F	F	A,B,C,L,N,S	Sweating	(+)	F	Topical steroid, minocycline	6 weeks
8	36/M	L	A,B,C,E	(-)	(+)	L	Minocycline	8 weeks
9	19/F	F	B,C,N	(-)	(-)	F	Minocycline	7 weeks
10	25/F	L	B,N	(-)	(+)	L	Minocycline	5 weeks
11	27/F	F	A,B,C,N,S	(-)	(-)	F	Antihistamine, minocycline	8 weeks
12	26/F	L	A,B,C,E,N	(-)	(+)	L	Topical steroid, minocycline	5 weeks
13	21/F	R	B,N	(-)	(+)	L	Antihistamine, minocycline	8 weeks
14	18/F	R	B,N	Rubbing	(+)	L	Antihistamine, minocycline	7 weeks
15	19/F	R	B,C,F	(-)	(-)	L	Minocycline	5 weeks
16	22/F	R	B,N	(-)	(+)	L	Minocycline	4 weeks

†A: abdomen, B: back, C: chest, E: extremities, F: face, L: lumbosacral, N: nape, S: shoulder.

‡F: fully developed, L: late, R: resolving stage.

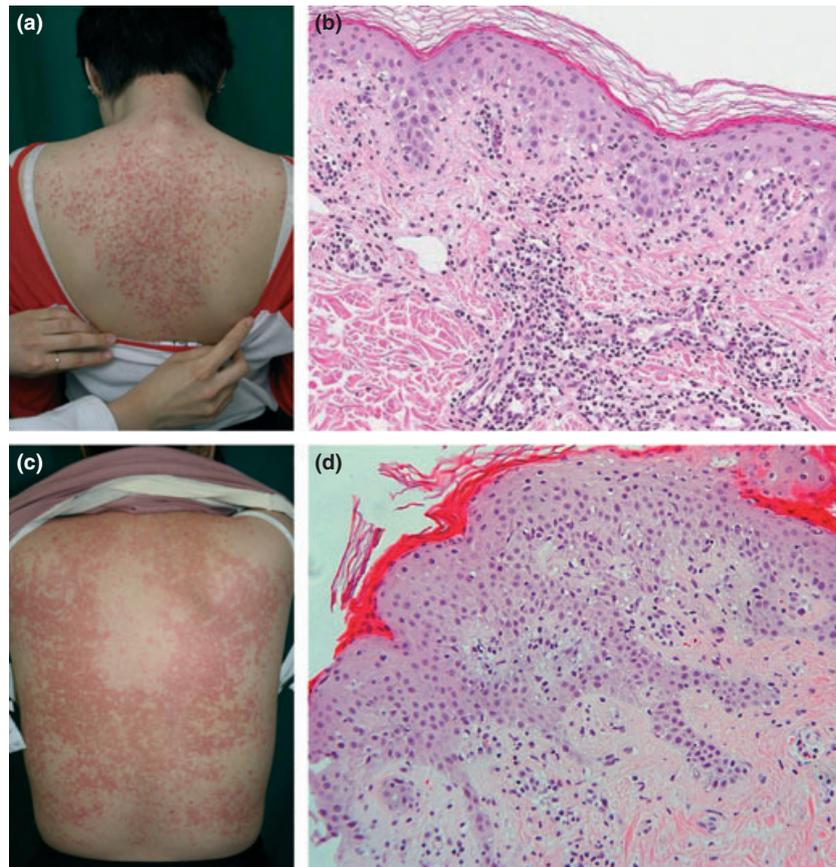


Figure 1 (a), (b) Case 9. A 19-year-old prurigo pigmentosa female in fully developed stage. (a) Erythematous reticulated maculopapules with some crusts on the back. (b) Histopathology of erythematous macule showing some spongiosis, ballooning degeneration of basal layer, perivascular lymphocytic infiltration (HE stain, $\times 100$). (c), (d) Case 11. A 27-year-old prurigo pigmentosa female in fully developed stage. (c) Erythematous reticular maculopatches with vesicles on the back. (d) Histopathology of erythematous macule showing spongiosis, ballooning degeneration of basal layer, lichenoid lymphocytic infiltration (HE stain, $\times 100$).

with an average of 3.7 weeks. Most patients responded well to minocycline.

Associations between ketosis and prurigo pigmentosa (Table 2)

The serum concentration of ketones (acetoacetic acid, 3-hydroxybutyrate acid [3-OHBA]) was elevated in two patients. Urinary ketone tests were positive ($>+1$) in 6 of 10 patients who had undergone the test. Of these, five cases were related to dieting or fasting. Two patients underwent retests after treatment, which were negative in both cases. Routine laboratory test results were normal in all patients.

Discussion

Prurigo pigmentosa is a rare inflammatory dermatosis of unknown aetiology. It was first reported in Japan, where it is found most commonly; less than 40 non-Japanese cases have been reported.² It is still unknown whether those of Japanese origin have a proclivity towards prurigo pigmentosa or whether clinicians outside Japan are simply unaware of the diagnosis, although recently, the number of cases outside Japan has been increasing, leading several reports to argue the latter.³

Table 2 Serum levels of ketones and results of ketone urine tests in patients of this study

Case no.	AA (mmol/L)	3-OHBA (mmol/L)	3-OHBA/AA	UKT†	Associated condition
1	NT	NT	NT	–	(–)
4	NT	NT	NT	3+	fasting
6	NT	NT	NT	–	fasting
7	NT	NT	NT	1+	fasting
8	NT	NT	NT	–	(–)
10	NT	NT	NT	1+	(–)
11	NT	NT	NT	3+	fasting
12	0	0.098	0	NT	fasting
14	0	0.024	0	–	(–)
15	0.044	3.2	72.727	1+	diet
16	0.028	1.657	59.179	3+	(–)

NT, not tested; AA: acetoacetic acid (normal, 0.05–0.15 mmol/L); 3-OHBA, 3-hydroxybutyrate acid (normal, 0.05–0.3 mmol/L); 3-OHBA/AA, 3-hydroxybutyrate acid/acetoacetic acid (normal, ~ 1.0); UKT, urinary ketone test.

†Results of testing for ketones in urine is expressed according to the following semiquantitative system: –, negative; +, <10 mg/dL; 2+, 10–100 mg/dL; 3+, >100 mg/dL.

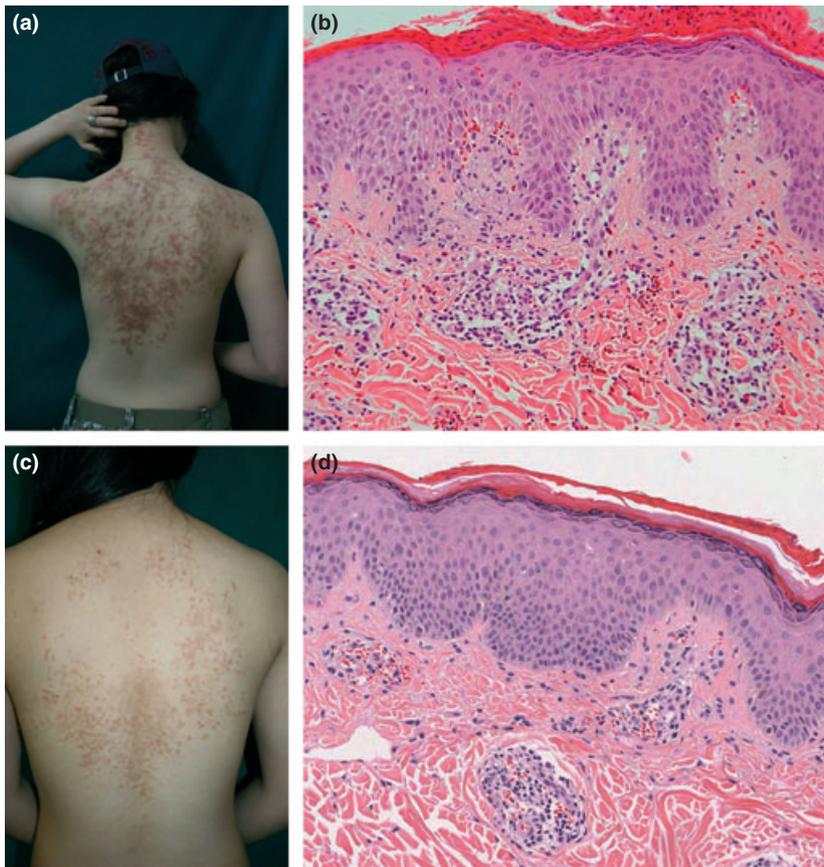


Figure 2 (a), (b) Case 13. A 21-year-old prurigo pigmentosa female in resolving stage. (a) Net like hyperpigmentations with crusted and scaly papules over the back. (b) Histopathology of hyperpigmented macule showing parakatosis, hyperplastic epidermis, RBC extravasation and lichenoid lymphocytic infiltration (HE stain, $\times 100$). (c), (d) Case 10. A 25-year-old prurigo pigmentosa female in late stage. (c) Crusted and scaly papules are mostly disappeared, leaving reticulated hyperpigmentation over the back. (d) Histopathology of hyperpigmented macule showing epidermal hyperplasia, RBC extravasation and perivascular lymphocytic infiltration (HE stain, $\times 100$).

Prurigo pigmentosa is characterized by a rash that consists of very itchy, reddish papules coalescing to form a reticulated pattern. Resolution occurs with hyperpigmentation. Urticarian⁴ or bullous⁵ forms have been reported. The inflammatory stage of the eruption develops rapidly and usually lasts no more than 1 week.⁶ Prior research has claimed a female to male ratio of 4 : 1, with an average age of onset between 23 and 27 years.⁷

The causes and pathogenesis of prurigo pigmentosa are not well understood, but diagnostic criteria have recently been more clearly established. For clinicians unfamiliar with prurigo pigmentosa, Böer *et al.*,² attempted to forge a criteria for diagnosis of the disease both clinically and histopathologically. They reported that the eruption of prurigo pigmentosa distributed symmetrically on the trunk, with predilection for upper part of the back, the sacral area, abdomen and chest. Mucous membranes are rarely affected. Individual lesions were patchy erythematous macules, urticarial papules and plaques at the beginning of eruption (early lesions), evolving to short-lived red papules and vesicles (fully developed lesions). Resolving lesions were crusted and scaly red papules and smooth surfaced pigmented macules. Late lesions tended to be confluent and assume arcuate and reticular shapes.

Comparisons between the largest series reviewed by Böer *et al.*⁴ and this study revealed several similar characteristics, including

gender distribution, absence of family history and good therapeutic response to oral doxycycline.

Most studies have shown that there is no underlying disease in patients with prurigo pigmentosa. However, some researchers have postulated an association between prurigo pigmentosa and diabetic mellitus, ketonemia, fasting, dieting, pregnancy or atopy.^{8–12} We found relationships with diet in 8 of our 16 patients. As the lesions are mainly restricted to covered areas of the body, the occurrence of prurigo pigmentosa has been considered to be triggered by rubbing. Clothing friction acting as a mechanical stimulus has also been suspected as a possible triggering factor.¹³ However, we found no such aggravating factors apart from two patients whose symptoms were aggravated by rubbing (patient 13) or sweating (patient 6).

According to Nagashima *et al.*,¹⁴ the duration of the disease from the first attack ranges from 6 months to 7 years. Our result was similar to their study, with total durations ranging from 1 month to 7 years (mean duration: 11 months). Six patients experienced attacks intermittently for several years, and three of these reported that the attacks were associated with changes in their diet.

Early reports of histopathological findings were described as non-specific.¹⁴ In agreement with Nagashima *et al.*'s interpretation,

most authors who have studied biopsied tissues report non-specific findings that are not diagnostic. However, Böer *et al.*¹⁵ proposed that the histopathological changes of prurigo pigmentosa may be specific and transpire rapidly. Böer *et al.*⁴ propose initial histopathological findings of neutrophils infiltrate over superficial perivascular, interstitial and epidermis associated with spongiosis, ballooning and necrotic keratocytes in the epidermis (early lesions). Subsequently, eosinophils and lymphocytes predominate in the dermis (fully developed lesions). Finally, the epidermis experienced hyperplastic, parakeratotic alterations and hyperpigmentation along with melanophages in the upper dermis (late lesions). However, it should be noted that the changes also transpire rapidly (in most cases, within 1 week), and histopathological features are diagnosable with specificity much more easily at the beginning and at the eruption peak (which lasts less than 2 days), rather than at a time after the lesions have resolved.²

Lesions may resemble dermatitis herpetiformis, linear IgA disease or acute lupus erythematosus. Lesions gradually involute, leaving reticulate postinflammatory hyperpigmentation, which can resemble confluent and reticulated papillomatosis of Gougerot and Carteaud or macular amyloid.⁶ However, ketosis is not observed in these diseases. Following histopathological analysis, in a comparison of confluent and reticulated papillomatosis with chronic prurigo pigmentosa, the presence of papillomatosis was not frequently noted. Thus, it is necessary to combine both clinical and histopathological findings to differentiate prurigo pigmentosa from eczema or other inflammatory diseases.

Previous cases of prurigo pigmentosa that were associated with fasting, dieting^{10,16} or insulin-dependent diabetes mellitus (IDDM)¹¹ may also have been related to ketosis. Teraki *et al.*¹⁰ found that the serum concentrations of 3-hydroxybutyric acid were elevated in 7 of 10 cases of prurigo pigmentosa, and urinary ketosis was present in 8 of 10 cases.

Ketosis was observed in six patients in our study. Of these, we detected an associated diet episode in five patients. Although this study can suggest that ketosis may play a role in the pathogenesis of prurigo pigmentosa, the interpretation of result is limited due to the small number of patients. Larger samples will be needed to clarify the relationship between ketosis and pathogenesis of prurigo pigmentosa.

Oral minocycline (200 mg) taken daily is usually considered as the first-line therapy for prurigo pigmentosa.^{17,18} Doxycycline, dapsone, potassium iodide and macrolide antibiotics have also been reported to be effective.^{2,19,20} Two cases of prurigo pigmentosa treated with isotretinoin has also been recently reported.^{21,22} In our experience, most patients showed a good response to oral minocycline.

In conclusion, the epidemiologic and clinical aspects of our study were similar to those of previous reports. The histopathol-

ogy were nonspecific in our cases, but histopathological features are diagnosable with specificity much more easily at the beginning of an eruption or at its peak (which lasts less than two days), rather than at the resolved state.² Therefore, a biopsy is recommended during the early phase.

Our findings also support the argument that ketosis produced by fasting or dieting may play a role in the pathogenesis of prurigo pigmentosa. Therefore, physicians need to warn that excessive fasting can cause prurigo pigmentosa.

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