Prurigo Pigmentosa: Clinicopathologic Study and Expression of ICAM-1

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Background : Prurigo pigmentosa (PP) is a rare inflammatory dermatosis of unknown etiology characterized by recurrent, pruritic erythematous papules and gross reticular pigmentation. Despite the increasing number of patients with PP being brought to attention, the disease is not well understood.

Objective : This study was done to investigate the clinical, histopathological and immunohistochemical characters of PP.

Methods : A retrospective review and study were carried out of the clinical records and histopathological specimens of 11 patients with PP who visited our hospital from 1992 to 2003. Immunohistochemical staining for ICAM-1 from erythematous papules and pigmented lesions were done.

Results : The results of our patients showed distinct clinical and histopathological features, neutrophils observed in the dermis of early lesions. The levels of serum total IgE in the patients with PP were increased notably. Strong focal expression of ICAM-1 by keratinocytes and dermal vessels was observed in the erythematous papules, none or weak in the pigmented lesions. The common condition associated with PP was friction from clothing, and all of the patients showed good responses to dapsone and minocycline.

Conclusion : Prurigo pigmentosa is a peculiar inflammatory disease of the skin and has singular features both clinically and histopathologically. (Ann Dermatol 16(4) 153~162, 2004)

Key Words: Prurigo pigmentosa, ICAM-1

INTRODUCTION

Prurigo pigmentosa (PP), first introduced by Nagashima[1] in 1971, is a distinct and uncommon dermatosis of unknown etiology. More than 300 patients with PP have been reported in Japan, but only several tens of prurigo pigmentosa have been reported in the Western world and Korea[2-9]. Clinically PP shows recurrent, marked pruritic erythematous urticarial papules in reticular pigmented patches which are usually symmetrically distributed on the back, neck and chest. Histopathologic findings of PP are nonspecific but typified by very different findings at each stage of it such as "early", "fully developed", and "late"[10]. Dapsone or minocycline are effective treatments.

We reviewed 11 patients who had been diagnosed as "prurigo pigmentosa" and studied clinical, histopathological and immunohistochemical characteristics of PP.

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MATERIALS AND METHODS

1. Subjects

We studied 11 patients with PP diagnosed in our hospital between 1992 and 2003. Clinical and histopathologic data were reviewed from medical records and 18 biopsy specimens (4 mm) taken from 11 patients. Durations of follow-up were from 1 to 11 years. Of 11 patients, 9 patients could be con-

nected with us in the time of study, but 2 patients were lost to follow-up for reason unrelated to study.

2. Laboratory test and immunohistochemical staining

At the first time examination, CBC, LFT, serum total IgE-RIA and urine analysis were measured in our patients with PP, also an allergen patch test was done with 8 mm Finn chamber (Epitest Ltd Oy, Filland), Scanpor® tape (Alphama AS, Norway) and 20 allergens (Hermal Kurt Herrmanin Germany).

Sections of the paraffin embedded 4 mm biopsy specimens from 8 erythematous papules in 8 patients, and 7 pigmented patches in 7 patients were stained using the anti-intercellular adhesion molecule-1 (ICAM-1), mouse IgG1 monoclonal antibody produced by Novocasta Laboratories Ltd, united Kingdom.

RESULTS

1. Clinical findings

The clinical results in our patients with PP are summarized in Table 1. All of the 11 patients were young women in Busan, Korea, the mean age at the time of diagnosis and first onset from interview were 20.6 years (range; 15 - 29 years) and 18.6 years (range; 13 - 24 years), respectively. None of them had family history of the similar skin disorders.

All of our patients had pruritus (moderate; 2, severe; 9 patients) and erythematous urticarial

Table 1. Summary of Clinical and Laboratory Findings

Patient No.	Sex/1st onset age	F/U	Frequency times	Season	Distribution & Pattern	Urine ketone	IgE-RIA KU/L	Patch test
1	F/21	11	7	summer spring	upper back(W), ant. chest(W), post. neck	-	ND	-
2	F/23	8	1	summer	back(P)	-	ND	-
3	F/15	7	6	autumn winter	upper back(W)	-	17.5	-
4	F/21	6	4	spring summer	mid. back,(NW) abdomen, shoulder, neck	-	488	-
5	F/18	6	2	spring winter	upper back(W), ant. chest (W)	-	271	-
6	F/14	4	3	spring winter	back(W), post. arm	-	353	-
7	F/21	4	6	spring chest(W)	back(p),	-	218	nickel sulfate
8	F/21	3	4	summer winter	back(NW), ant. chest(W)	-	80	nickel sulfate
9	F/21	2	1	spring	right neck, right shoulder	-	273	para-phenylenediamine, Nickel sulfate
10	F/11	1	4	spring autumn	back(D), ant. chest(W), abdomen	-	504	-
11	F/14	1	1	summer	back(W), ant. chest(W), abdomen	++	127	-

F/U; follow up duration (year), ND; not done, W; wedge shaped, NW; negative wedge shaped, D; depressed part, P; projecting part, Reference value of serum total IgE-RIA; < 41 (adult), < 85 (child) KU/L.

papules or plaques in reticular pigmented patches, and no scarring. The process of PP in our patients was typified by progression, remission and recurrence. Lesions recurred in 8 of the 11 patients, and the interval between remission and recurrence ranged from weeks to months or even years. The frequencies of recurrence in 8 patients ranged from 2 to 7 times.

The lesions in all of our patients with PP except one (patient No. 9) were distributed symmetrically, the sites of lesions were the back (10/11), chest (7/11), neck (3/11), abdomen (3/11), shoulder (2/11) and upper arm (2/11). The above results showed that the site of preference was the trunk. The pattern of lesions on the back in the 5 patients seemed to be wedge-shaped, the base of the wedge being upper and the apex being caudal (Fig. 1). Also the distribution on the chest in 6 patients was wedge-shaped (Fig. 2).

2. Laboratory findings

Values of eosinophils in the peripheral blood of our patients were within normal limit (reference value; 1 - 4%), but values of serum total IgE-RIA measured in 9 patients with PP ranged from 17.5 to 504 KU/L (Reference value; < 41 (adult), < 85 (child) KU/L) and the mean value was 259 KU/L, it was notable that there was significant difference between the value of serum total IgE-RIA in our patients and the control. One patient on a diet had urine ketone (2+). All of the 11 patients with PP were tested with the patch test, which showed a positive reaction to nickel sulfate in three patients and para-phenylenediamine used as black dye in manufacturing of clothing in one.

3. Associated conditions

The associated conditions in our patients with PP are summarized in Table 2. The lesions in our patients occurred and recurred frequently in the spring and summer, namely the hot seasons, but some lesions occurred and recurred in the autumn and winter. There were associated conditions in 5 patients with PP. Friction from clothing after swimming in the sea was found in No. 2 patient. Friction from clothing after swimming in a pool was found in No. 8 patient who used to be in Japan for a few years, and it was very interesting that the appearance of U-shape lesions was similar to that of the swimming suit (Fig. 3). Friction from clothing, a new uniform in the workplace, was found in No. 9 patient in whom the patch test showed a positive reaction to para-phenylenediamine compound used as black dye in the manufacturing of clothing.

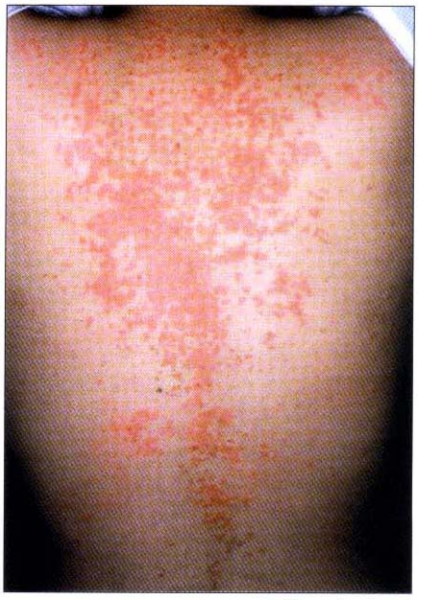

Fig. 1. Pruritic confluent reticulated erythematous urticarial papules and patches distributed symmetrically and in a wedge-shape on the back.

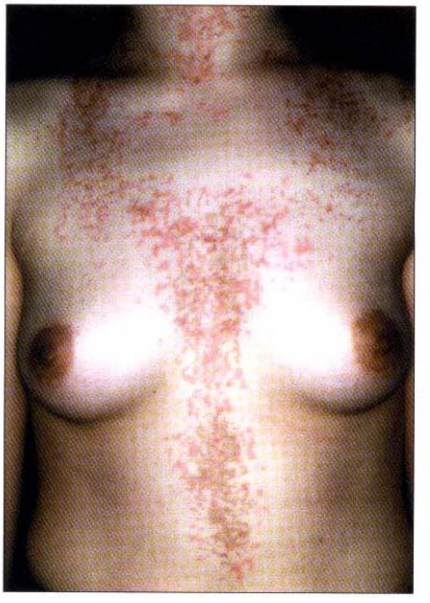

Fig. 2. Pink to dusky red colored papules and pigmented patches in a reticulated pattern on the anterior neck, chest and abdomen.

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Table 2. Associated Conditions Found in the Patients with Prurigo Pigmentosa

Patient No.	Associated condition
2	friction from clothing after swimming in the sea
8	friction from clothing after swimming in a pool
9	friction from new clothing
10	sweating, fatigue
11	diet and work-out

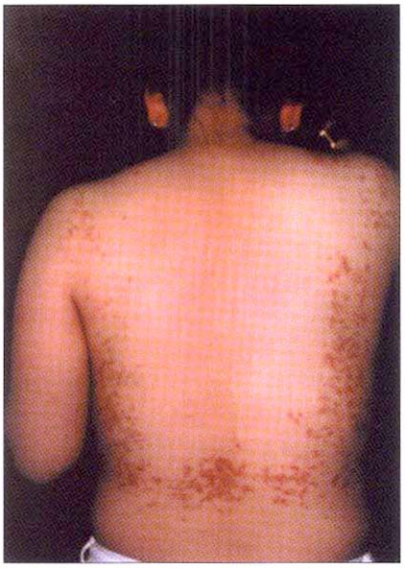

Fig. 3. The appearance of lesions, U-shaped, is similar to that of a swimming suit and shows confluent reticulated erythematous to hyperpigmented papules and macules.

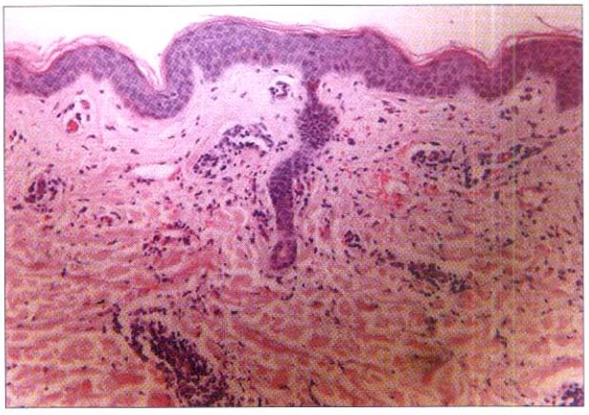

Fig. 4. Early lesion. Histopathologic findings of urticarial papule revealed that neutrophils, nuclear dusts, lymphocytes and extravasated red cells were situated around vessels of the superficial plexus and in the edematous upper dermis. The cornified layer had a normal basket-woven pattern that is showed in the recent lesion (H&E, × 100).

Excessive sweating was found in No. 10 patient. Therefore we suggested that friction from clothing or sweating could be claimed to worsen the matter in 4 patients. Lastly, diet and work-out were found in No. 11 patient who had ketonuria.

4. Histopathology

The findings from biopsy specimens of erythematous macules, papules or plagues in our patients showed that there were "intercelluar and intracellular edema of the epidermis (10/11)", "exocytosis of inflammatory cell into the epidermis (9/11)", "liquefaction degeneration of the basal layer (10/11)", "necrotic keratinocyte in the epidermis (4/11)", "neutrophils or nuclear dusts in the epidermis or dermis (8/11)", "eosinophils in the epidermis or dermis (5/11)", and "in the dermis, superficial perivascular infiltrate (10/11)". In the early lesion in the 3 patients, erythematous macules and urticarial papules, the biopsy specimens showed that the infiltrate consisted of neutrophils and sparse infiltrate of inflammatory cells in the epidermis and upper dermis (Fig. 4). In the fully developed lesions in the 8 patients , dusky red colored papules, the biopsy specimens showed that spongiosis, necrotic keratinocytes, exocytosis, vacuolar alteration of epidermal basal cells and lichenoid infiltrate of lymphocytes in the upper dermis (Fig. 5). Also the findings from biopsy specimens of pigmented lesions, that is old lesions, showed that there were "pigmentary incontinence (8/8)" and "perivascular lymphocytic infiltrate (4/8)" (Fig. 6).

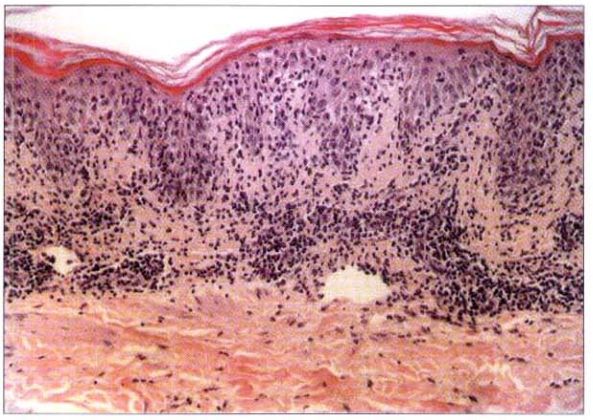

Fig. 5. Fully developed lesion. Histopathologic findings of a dusky red colored papule showed that spongiosis, ballooning, necrotic keratinocytes and vacuolar alteration of the basal layer were seen in the slightly hyperplastic epidermis. A lichenoid infiltrate of lymphohistiocytes in the papillay dermis and the infiltrate of lymphocytes along the dermo-epidermal junction and within epidermis were observed. Eosinophils were seen in the lichenoid infiltrate, too (H&E, × 100).

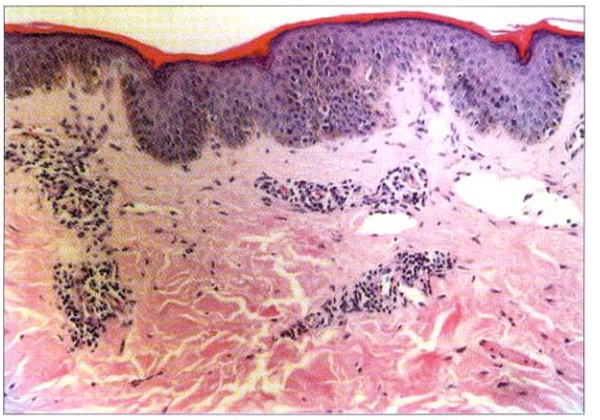

Fig. 6. Late lesion. Histopathologic findings of a pigmented macule showing increased melanin of lower epidermis and melanophage, mild lymphohistiocytic infiltrate in the upper dermis (H&E, × 100).

5. Immunohistochemical study

The result of immunohistochemical staining for ICAM-1 in our patients are summarized in Table 3. Immunohistochemical staining from all of erythematous and pigmented lesions revealed positive reactivity for anti-ICAM-1 in the endothelial cells of papillary microvessels. In the erythematous papules in 5 of the 8 patients, there was intensive expression of ICAM-1 by keratinocytes in the lower part of the epidermis (Fig. 7). In the pigmented lesion in all of the 7 patients, there was no or very weak expression of ICAM-1 by keratinocytes (Fig. 8).

Table 3. Expression of ICAM-1 by Keratinocytes and Vascular Endothelial Cells in Erythematous and Pigmented Lesion of Prurigo Pigmentosa

patient No.	Erythematous lesion		Pigmented lesion	
	Keratinocytes	Dermal vessels	Keratinocytes	Dermal vessels
2	++	++	+	+
3	ND	ND	+	++
4	++	++	-	+
5	++	++	-	+
6	++	++	ND	ND
7	+	+	ND	ND
8	-	+	-	+
10	++	++	+	+
11	+	++	-	+

dermal vessel; superficial dermal microvessel, ND; not done, -; no positive, +; weak to moderate positive, ++; strong positive

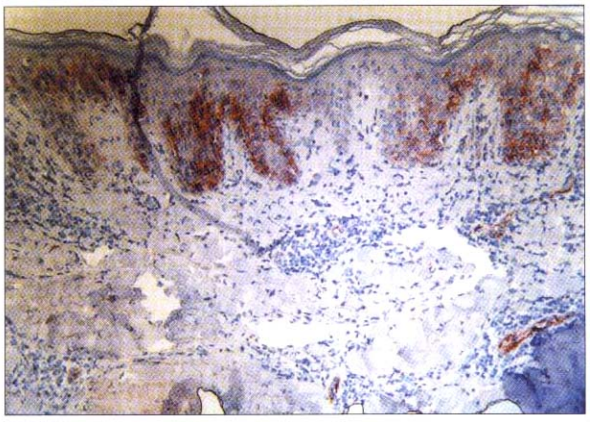

Fig. 7. Immunochistohemical staining for ICAM-1 of a fully developed lesion. Intense expression of ICAM-1 by keratinocytes in the lower epidermis and endothelial cells in the upper dermal vessel was observed (immunoperoxidase, × 100).

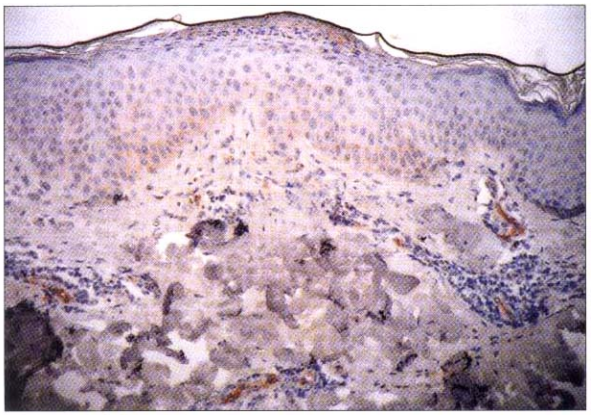

Fig. 8. Immunohistochemical staining for ICAM-1 of a pigmented lesion. Weak expression of ICAM-1 by keratinocytes in the lower epidermis was observed (immunoperoxidase, × 100).

6. Treatment

In short, all of our patients were very well treated with dapsone (100 to 200 mg/day for 2 to 3 weeks) and minocycline (100 mg/day for 2 to 3 weeks), alone or in combination. Adminstration of dapsone or minocycline could not stop the recurrence of the eruption. We could not find the relation between the duration of therapy and relapse. Because there were the adverse effects of dapsone, consisting of cyanosis and anemia in two patients, we prescribed minocycline alone in these cases and minocycline showed a good response, like dapsone.

DISCUSSION

Prurigo pigmentosa (PP) is a distinct type of dermatosis that would be typified clinically and histopathologically. Clinically, the lesions are characterized by recurrent, pruritic, symmetric corps of erythematous papules that resolve, leaving a peculiar, reticular pigmentation. It is more preponderant in young woman and occurs more frequently in spring and summer, commonly in Japan. The sites most commonly affected are the back, chest and neck, although there have been other reports in which the eruptions of PP occurred in the clavicular regions, antecubital fossa, lumbosacral region, limbs and forehead. The individual lesion, lasting less than a week from beginning to end, of PP shows the chronological sequence[10]. Individual lesion shows chronological changes that consist of "early, a smooth reddish macule or an urticarial papule", "fully developed, a crusted red papule, a smooth-surfaced papulovesicle", and "late, pigmented macule". Our results were alike to previous literatures[10]. Since all of our patients had pruritus (moderate; 2, severe; 9 patients), we thought that pruritus was one of the features in PP. All of our 11 patients were young women. It was a question why occurrence of PP has a preponderance in young women. It may be suggested that unknown hormonal or genetic factors contribute to the etiology of it. PP cases were reported commonly in Japan, not in the Western world. To our knowledge until now, 18 cases (including our 3 cases[4,9]) of PP were literatured in Korea[2-9], and several tens of PP cases in the Western world. Our 11 cases of PP are thought to be many, in comparison. The fact that our hospital in Busan, Korea is just a short distance from Japan, could account for the reason why we had the chance to meet many patients with PP, compared with the Western world or other cities of Korea. So unknown environmental or genetic factors are suggested to contribute to the etiology of PP.

From comments about histopatholgic findings in articles, Nagashima et al.[11] noted only nonspecific findings and lichenoid tissue reaction. In 1994 Fugita et al.[12] wrote of their findings histopathologically in 23 patients with PP. Early lesions were described by them as displaying slight spongiosis, an

infiltrate of neutrophils in the epidermis and upper dermis. Fully developed lesions showed that there were epidermal hyperplasia, microabscess, spongiosis, vesicles, dyskeratotic cell, liquefaction degeneration of the epidermal basal cell, elongated rete ridge, dilation of vessel, and an infiltrate in the dermis that consisted of lymphocytes and eosinophils. In late lesions, they mentioned dyskeratotic cells in the epidermis, dilated blood vessels, and a slight infiltrate of lymphocytes and melnophages in the dermis. Arial et al.[13] called attention to neutrophils in the epidermis as being typical of a lesion at the earliest stage of PP. Sakamoto et al.[14] wrote that marked infiltrate of neutrophils into the epidermis seemed to be a feature of early PP. Also Böer et al.[10] stated that "PP begins with a superficial perivascular infiltrate of neutrophils.", and the findings of "fully developed" and "late" are the resolving process. Dapsone[15] and minocycline[16,17] are effective treatments; both of these drugs inhibit migration and/or function of neutrophils. At an early stage of PP when neutrophils are preponderant, administration of these drugs may abort the pathologic process. So they concluded that histopathology of PP was not nonspecific, but distinctive. The cause and pathogenesis are not determined, but Böer et al.[10] gave emphasis on neutrophils in PP.

On light microscopic examination of 11 biopsy specimens from erythematous papules in 11 patients, there were nonspecific, but consistent histopathologic findings that were lichenoid tissue reactions in which epidermal change consisted of liquefaction of basal cell, exocytosis of inflammatory cell, and intercellular and intracellular edema. Dermis showed perivascular lymphocytic infiltrate, and edema. Also histologically individual lesions in our patients showed chronological changes that consisted of "early" (Fig. 4), "fully developed" (Fig. 5), and "late" (Fig. 6) as Fugita[12] and Böer et al.[10] described. Also 3 biopsy specimens from our patients showed the feature of early lesion which was characterized by neutrophils in the upper dermis. Chronological changes were suggested to make this histological difference. We agree with the statement that neutrophils are important in the pathogenesis of PP.

Intercellular adhesion molecule-1 (ICAM-1) mediates the adhesion and trafficking of circulating activated skin-seeking CD45RO+ memory CD4+ T lymphocytes from the vessel into the dermis and epidermis by ligand lymphocyte function-associated antigen-1 (LFA-1) expressed on membranes of lymphocyte. Teraki et al.[18] carried out immunohistochemical studies on the skin lesions of PP in 2 patients. There was a predominance of CD4+ cells in the dermal infiltrate, whereas those lymphocytes in the epidermis were mainly CD8+ cells. The majority of dermal and epidermotropic lymphocytes showed intense expression of lymphocyte function-associated antigen-1 (LFA-1). The number of CD1+ cells was increased in the epidermis. There was intense expression of ICAM-1 by keratinocytes in the erythematous papules. Teraki et al.[18] said that focal expression of ICAM-1 (CD54), still observed in the residual pigmented areas, could explain the recurrent rash that was localized to these sites. A similar persistence of expression of ICAM-1 in lesional keratinocytes has been reported in fixed- drug eruptions and this could explain the site-specific nature of the eruption.[19]

In the pigmented area from all of our 7 patients, there was no or very weak expression of ICAM-1 by keratinocyes in the epidermis. Our results were different from the literature of Teraki et al..[18] Our results suggested that the role of ICAM-1 in the residual pigmented lesions did not contribute to the recurrence of the lesion. But ICAM-1 expression on endothelial cells of superficial microvessel and keratinocytes of the epidermis may play an important role in the migration of lymphocytes from the vessel into the dermis and epidermis in the erythematous lesions of PP.

The etiopathogenesis of PP remains unknown. As it occurred most commonly in Japan, Nagashima[1] suggested that environmental contaminant and ethnic preponderance might be a factor, and friction from clothing might act as a nonspecific mechanical stimulus. Yamasaki et al.[22] also suggested a contact allergic reaction to clothing or other related materials. Since the eruptions primarily involve a covered area of the body, the contact allergy may be the trigger by the friction of clothing and break out commonly during adolescence, with a seasonal preference for spring-summer, when increased sweating occurs. Contact allergy to trichlorophenol[21], para-amino compounds[22], chrome in detergent[23] and the chronium component of an acupuncture needle[24] were considered as the pathogenesis of PP. In other cases, PP associated with helicobacter pylori infection[25] and administration of bismuth-

subsalicylated-containing antacid[20] were reported. In addition to these exogenous factors, systemic conditions such as pregnancy[7], insulin-dependant diabetes mellitus[26,27], fasting (anorexia nervosa)[28], and diet[29] have been associated with PP. Because ketosis was found in these conditions, the eruptions in these patients seemed to be correlated with blood and/or urine ketone level. Ketone bodies pass from the circulating blood into the tissue, enter into the cell, and reach the cytoplasm to be utilized directly in lipogenesis, and mitochondria is oxidized and injured[30]. Surplus ketone bodies may remain around blood vessels and give arise to perivascular inflammation. That is, ketosis may contribute to the pathogenensis of PP[26].

The known associated conditions were found in 5 patients. Friction from clothing seemed to be the cause in 3 patients, excessive sweating in one, and diet and work-out were associated with ketonuria in one. Friction from clothing after swimming in the sea was found in No. 2 patient and the lesion was located in the projected part of the back. In No. 8 patient, the appearance of lesions, U-shape, was similar to that of a swimming suit, so friction from clothing seemed to be the cause in this patient. Friction from clothing, a new uniform in the workplace, was found in No. 9 patient whose lesions were on the arm and shoulder which are the projecting parts of the body. Excessive sweating was found in No. 10 patient whose eruption was in the depressed area of the back. So it was suggested that the lesion on the neck, shoulder, upper arm and lateral side of the back, which are the projecting parts of the body, seemed to be associated with friction from clothing. Also the wedge-shaped or depressed lesions on the back and chest, where excessive sweating is concentrated, seemed to be associated with sweating. Since the wedge-shaped lesions in the chest and back were common in our patients, sweating seemed to be related to unknown associated conditions in our patients.

It was very interesting that the levels of serum total IgE-RIA in our patients with PP were frequently increased. The mean level of serum total IgE-RIA, measured in 9 patients with PP, was 259 KU/L (reference value: < 41 (adult), < 85 (child) KU/L). The increased level of serum total IgE-RIA might suggest that some process of allergic response to unknown materials contribute to the pathogenesis. Because our patients with PP have lived in Busan, Korea close to Japan where PP have been reported commonly, there is a possibility that injured skin by friction from clothing is permitted to invasion of causative unknown contact allergens which may be environmental contaminants other than clothing materials.

The administration of antihistamine and steroid, systemically or topically, cannot make an effect on eruptions or pruritus of PP. At first we misdiagnosed PP as allergic contact dermatitis, and we prescribed steroid and antihistamine. But these drugs did not reduce any eruption and symptom. Later the patient was diagnosed as PP typical of clinical pictures and supportive biopsy. Administration of dapsone showed the dramatic efficacy, reducing eruptions and pruritus, and stopping new lesion evolving. We prescribed dapsone or minocycline alone or in combination. All our patients showed the dramatic effect of these drugs, but these drugs could not prevent recurrence of PP in all patients. Miyachi et al.[15,31] showed that dapsone had an inhibitory effect on the generation of oxygen intermediates (OIs) from polymorphonuclear leukocytes, and they also suggested the possibility that OIs produced by infiltrated cells were involved in the inflammatory process of PP, and that sulfonamide exerted their anti-inflammatory effect by affecting OIs generation which resulted in the protection against lichenoid tissue reaction. Minocycline, a semi-synthetic tetracycline, is safer than dapsone and other sulfonamides. Even though the exact action of minocycline is not clear, the therapeutic effects include inhibition of OIs, neutrophil chemotaxis, and the mitogenic response of lymphocyte.[32]

In conclusion, our results and review of literatures indicate that prurigo pigmentosa is a distinctive disease that we should elucidate clinically, histopathologically.

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