

A Clinicopathologic Study of Thirty Cases of Acquired Perforating Dermatoses in Korea

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Background: Acquired perforating dermatosis (APD) is histopathologically characterized by transepidermal elimination of materials from the upper dermis. APD can be divided into four diseases: Kyrle's disease, perforating folliculitis, elastosis perforans serpiginosa, and reactive perforating collagenosis. APD is usually associated with systemic diseases, especially diabetes mellitus or chronic renal failure. So far, there have only been a few Korean studies of APD, which have a limited number of patients.

Objective: The aim of this study is to evaluate the clinical and histopathologic characteristics of 30 cases of APD and to examine the association with systemic diseases. **Methods:** We retrospectively reviewed the medical records and biopsy specimens of 30 patients who were diagnosed with APD.

Results: The mean age was 55.5 years, and the average duration of the lesion was 7.8 months. The lower extremities (73.3%) were the most frequently occurring sites of the lesion. Twenty-five patients (83.3%) had pruritus, and Koebner's phenomenon was present in 11 patients. Patients of 63.3% had at least one systemic disease. Diabetes mellitus (n = 17, 56.7%) and chronic renal failure (n = 10, 33.3%) were the most commonly associated conditions. Most patients received topical steroids (93.3%) and antihistamines (80.0%). The most common histopathologic type was reac-

tive perforating collagenosis (n = 23, 73.3%). **Conclusion:** In this study, most patients had a systemic association to the diseases. Therefore, we suggest that further evaluation is necessary for patients who present with APD. This includes reviewing patient's comprehensive past medical history, clinical exam, and additional diagnostic testing to check for the possibility of associated systemic diseases. (**Ann Dermatol 26(2) 162 ~ 171, 2014**)

-Keywords-

Acquired perforating dermatosis, Elastosis perforans serpiginosa, Kyrle's disease, Perforating folliculitis, Reactive perforating collagenosis

INTRODUCTION

Acquired perforating dermatosis (APD) is histopathologically characterized by transepidermal elimination of various dermal substances. APD can be divided into four diseases, according to the types of epidermal disruption and the natures of the eliminated materials: Kyrle's disease (KD), perforating folliculitis (PF), elastosis perforans serpiginosa (EPS), and reactive perforating collagenosis (RPC)¹. APD is usually associated with diabetes mellitus (DM)² or chronic renal failure (CRF)³. In recent years, it has also been reported to be associated with other systemic diseases, such as non-diabetic hemodialysis⁴, hepatic⁵ and endocrinologic disorders⁵, hepatocellular carcinoma⁶, Hodgkins' lymphoma⁷, acute leukemia⁸, acquired immune deficiency syndrome (AIDS)⁹, tuberculosis¹⁰, pulmonary aspergillosis¹¹, neurodermatitis⁵, atopic dermatitis¹², scabies¹³, and pregnancy¹⁴.

To date, there have been only a few studies of APD, including case reports in Korean literature, which have a

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Table 1. Clinical features of 30 patients

Case No.	Sex/age (yr)	APD duration	Distribution	Symptom	Koebner phenomenon	Clinical appearance	Associated conditions	Treatment	Effectiveness
1	M/50	1 mo	Trunk	Pruritus	-	Hyperkeratotic papules	NIDDM, CRF, CHF	Oral antihistamine, topical steroid	Slightly improved
2	F/44	1 mo	Trunk, LEx	Pruritus	-	Keratotic plugged, umbilicated papules	NIDDM, CRF, hypothyroidism	Oral antihistamine, NB-UVB, topical steroid	Improved
3	M/70	1 yr	LEx	-	-	Hyperkeratotic papules	-	Topical steroid	Slightly improved
4	M/71	2 yr	LEx	-	-	Hyperkeratotic papules	-	Topical steroid	Improved
5	F/61	3 mo	Trunk	Pruritus	-	Hyperkeratotic papules	NIDDM, CRF (HD), xerotic eczema	Cryotherapy, oral antihistamine, topical steroid	Improved
6	F/32	3 mo	Trunk, LEx	Pruritus	-	Keratotic plugged, umbilicated papules	Pregnancy	NB-UVB, oral antihistamine, topical steroid	Improved
7	M/42	2 mo	LEx	Pruritus	+	Keratotic plugged, umbilicated papules	NIDDM, CRF (HD)	NB-UVB, TA ILI, oral antihistamine	Improved
8	F/63	1 yr	Trunk, UEx	Pruritus	-	Serpiginous hyperkeratotic plaques	-	Oral antihistamine, topical steroid	Improved
9	F/78	2 mo	UEx	Pruritus	-	Keratotic plugged, umbilicated papules	NIDDM, HTN, xerotic eczema	Oral antihistamine, topical steroid	Improved
10	F/57	1 yr	Trunk, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	NIDDM	NB-UVB, TA ILI, oral antihistamine, topical steroid	Improved
11	M/83	3 mo	LEx	-	-	Hyperkeratotic papules	CRF, HTN	Topical steroid	Slightly improved
12	M/39	1 yr	UEx, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	IDDM, CRF, HTN, hepatitis	Oral antihistamine, topical steroid	Resistant
13	F/59	2 mo	Trunk	Pruritus	+	Keratotic plugged, umbilicated papules	-	TA ILI, Oral antihistamine, topical steroid	Improved
14	F/40	1 mo	Trunk	Pain	-	Keratotic plugged, umbilicated papules	-	TA ILI	Improved
15	M/68	3 yr	Trunk, UEx, LEx	Pruritus	-	Keratotic plugged, umbilicated papules	NIDDM, CRF (HD), stasis dermatitis	TA ILI, Oral antihistamine, topical steroid	Improved
16	F/48	2 mo	Trunk, UEx	Pruritus	+	Keratotic plugged, umbilicated papules	NIDDM, atopic dermatitis	TA ILI, Oral antihistamine, topical steroid	Improved
17	F/42	4 mo	Trunk, UEx, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	-	Oral antihistamine, topical steroid	Improved
18	F/30	3 mo	Face, scalp, trunk	Pruritus	-	Keratotic plugged, umbilicated papules	IDDM, CRF, atopic dermatitis	Oral antihistamine, topical steroid	Slightly improved
19	F/69	3 mo	Trunk, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	HTN, xerotic eczema	Oral antihistamine, topical steroid	Improved
20	M/81	1 mo	LEx	Pruritus, pain	-	Keratotic plugged, umbilicated papules	NIDDM, HTN, xerotic eczema	Oral antihistamine, TA ILI, topical steroid	Improved

Table 1. Continued

Case No.	Sex/age (yr)	APD duration	Distribution	Symptom	Koebner phenomenon	Clinical appearance	Associated conditions	Treatment	Effectiveness
21	F/55	5 yr	Trunk, UEx, LEx	Pruritus	-	Keratotic plugged, umbilicated papules	-	TA II, Oral antihistamine, topical steroid	Improved
22	F/75	1 mo	Trunk, UEx, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	-	Oral antihistamine, topical steroid	Slightly improved
23	F/55	2 mo	Scalp, trunk, LEx	Pruritus	-	Hyperkeratotic papules	NIDDM, xerotic eczema	NB-UVB, TA II, oral antihistamine, oral acitretin, topical steroid	Improved
24	F/36	1 yr	Upper	Pruritus	+	Keratotic plugged, umbilicated papules	-	Oral antihistamine, topical steroid, topical calcineurin inhibitor	Improved
25	F/39	3 mo	UEx, LEx	Pruritus	-	Follicular infiltrating papules	NIDDM, CRF (PD)	Topical steroid	Slightly improved
26	M/63	3 mo	Trunk, UEx, LEx	Pruritus	+	Keratotic plugged, umbilicated papules	NIDDM	Oral antihistamine, oral acitretin, oral cyclosporine, Topical steroid	Improved
27	M/54	1 mo	LEx	Pruritus	+	Keratotic plugged, umbilicated papules	NIDDM, atopic dermatitis	NB-UVB, TA II, oral antihistamine, oral acitretin, topical steroid	Improved
28	M/57	9 mo	Trunk, UEx, LEx	Pruritus	-	Keratotic plugged, umbilicated papules	NIDDM, CRF (PD), HTN, hepatitis, COPD	NB-UVB, oral antihistamine, topical steroid	Improved
29	M/56	1 mo	LEx	-	-	Keratotic plugged, umbilicated papules	NIDDM	Topical steroid	Slightly improved
30	F/47	3 mo	LEx	Pruritus	-	Hyperkeratotic papules	-	Oral antihistamine, TA II, topical steroid	Improved

APD: acquired perforating dermatosis, M: male, F: female, LEx: lower extremities, UEx: upper extremities, NIDDM: non-insulin-dependent diabetes mellitus, CRF: chronic renal failure, CHF: congestive heart failure, HD: hemodialysis, HTN: hypertension, IDDM: insulin-dependent diabetes mellitus, PD: peritoneal dialysis, COPD: chronic obstructive pulmonary disease, NB-UVB: narrow-band ultraviolet B, TA II: intralosomal triamcinolone injection.

limited number of patients and make it difficult for a literature review. We report the clinical and histopathological features of 30 cases with APD and clarify the association with pathogenesis of APD and comorbidities. To our knowledge, this is the first report of its kind and the largest study on the clinicopathological features of APD, including all classical types of APD performed in Korea.

MATERIALS AND METHODS

We performed a retrospective review of the medical records and biopsy specimens of 30 patients who had been histopathologically diagnosed with APD between January 1997 and October 2012 in the Departments of Dermatology at the Eulji General Hospital and Chung-Ang University Hospital.

Clinical features

The following clinical data was collected: age, gender, duration, distribution of skin lesions, clinical configuration, associated symptoms, presence of Koebner's phenomenon, associated systemic diseases, and treatment.

Histopathologic features

All of the cutaneous samples were fixed in formalin, and processed and embedded in paraffin. The sections were stained with hematoxylin and eosin. If paraffin blocks were available, new sections were obtained for histochemical staining for all cases; Verhoeff-van Gieson and

Masson trichrome stains were used to evaluate the elimination of elastic or collagen fibers. The samples were classified as KD, PF, EPS and RPC, according to the pathologic features and eliminated materials.

RESULTS

Clinical features (Table 1, 2)

1) Age and gender of patients

Among the 30 patients, 12 were males and 18 were females. Patients ranged from 30 to 83 years of age. The mean age was 55.5 years. The highest frequency of APD was between 50 and 59 years of age (26.7%).

2) Duration, distribution, and associated symptoms

Duration of lesions varied from 1 month to 5 years with the average of 7.8 months. The distribution of the lesions was diffuse and variable. The lower extremities (73.3%) were the most commonly involved site, followed by the trunk (60.0%), and the upper extremities (40.0%). Multi-site involvement was observed in 14 patients (46.7%). There was one case of APD occurring on the face and scalp. However, no APD was observed on the palms and soles. Twenty-five patients (83.3%) had pruritus, and 2 (6.7%) had pain.

3) Clinical configuration and Koebner's phenomenon

Based on the clinical configuration of the lesion, we divided patients into the following four groups: KD-like hyperkeratotic papules, PF-like follicular infiltrating papules, EPS-like serpiginous hyperkeratotic plaques, and RPC-like keratotic plugged, umbilicated papules. The most co-

Table 2. Associated disease of patients with APD

Associated disease	Number of patients (%)
DM	17 (56.7)
NIDDM	15 (50.0)
IDDM	2 (6.7)
CRF	10 (33.3)
HD	3
PD	2
HTN	6 (20.0)
Hepatitis	2 (6.7)
Hypothyroidism	1 (3.3)
Pregnancy	1 (3.3)
COPD	1 (3.3)
Dermatologic diseases	9 (30.0)
Xerotic eczema	5 (16.7)
Atopic dermatitis	3 (10.0)
Stasis dermatitis	1 (3.3)

APD: acquired perforating dermatosis, DM: diabetes mellitus, NIDDM: non-insulin-dependent diabetes mellitus, IDDM: insulin-dependent diabetes mellitus, CRF: chronic renal failure, HD: hemodialysis, PD: peritoneal dialysis, HTN: hypertension, COPD: chronic obstructive pulmonary disease.



Fig. 1. Multiple erythematous linear arranged hyperkeratotic umbilicated papules on the trunk of patient 19. Note Koebner phenomenon from scratching.

Common configuration was RPC-like lesions (n = 21, 66.7%). Koebner's phenomenon was observed in 11 patients (Fig. 1).

4) Associated conditions

Nineteen (63.3%) patients had at least one systemic disease. DM (n=17, 56.7%) was the most commonly associated condition, followed by CRF (n=10, 33.3%), hypertension (n=6, 20.0%), hepatitis (n=2, 6.7%), hypothyroidism (n=1, 3.3%), pregnancy (n=1, 3.3%), and chronic obstructive pulmonary disease (n=1, 3.3%). Of the 17 patients with DM, 2 (11.8%) had insulin-dependent DM (IDDM), and 15 (88.2%) had non-insulin-dependent DM (NIDDM). Among the patients with CRF, 5 (50%) had been treated on dialysis (3 on hemodialysis and 2 on peritoneal dialysis). Eleven patients (36.7%) had no other systemic diseases.

Nine patients had other dermatologic disorders; 5 (16.7%) of which had xerotic eczema, 3 (10.0%) had atopic dermatitis, and 1 (3.3%) had stasis dermatitis. One patient

was a pregnant woman at 29 weeks gestation.

5) Treatment

Twenty-eight patients (93.3%) received topical steroids, and 24 (80.0%) received antihistamines. An intralesional triamcinolone injection was administered to 11 patients (33.3%), narrow-band ultraviolet B (NB-UVB) to 7 patients (23.3%), systemic retinoid therapy to 3 patients, and cryotherapy to 1 patient (3.3%). Almost all patients improved after treatment, but 1 patient (3.3%) had no response to treatment.

Histopathological characteristics (Table 3)

Histopathological features of 23 cases (73.3%) showed cup-shaped invagination of the epidermis plugged with necrotic inflammatory debris. There were vertically oriented collagen bundles at the base of the lesions. Masson-trichrome staining showed transepidermal elimination of the collagen bundles. The overall histological features

Table 3. Histopathological features of 30 patients

Case No.	Masson-trichrome	Verhoeff-van Gieson	Eliminated material	Histopathological features
1	-	-	-	KD
2	+	-	Collagen	RPC
3	-	-	-	KD (Fig. 3)
4	-	-	-	KD
5	-	-	-	KD
6	+	-	Collagen	RPC
7	+	-	Collagen	RPC
8	-	+	Elastic fiber	EPS (Fig. 4)
9	+	-	Collagen	RPC
10	+	-	Collagen	RPC
11	+	-	Collagen	RPC
12	+	-	Collagen	RPC
13	+	-	Collagen	RPC
14	+	-	Collagen	RPC (Fig. 2)
15	+	-	Collagen	RPC
16	+	-	Collagen	RPC
17	+	-	Collagen	RPC
18	+	-	Collagen	RPC
19	+	-	Collagen	RPC
20	+	-	Collagen	RPC
21	+	-	Collagen	RPC
22	+	-	Collagen	RPC
23	+	-	Collagen	RPC
24	+	-	Collagen	RPC
25	-	-	-	PF (Fig. 5)
26	+	-	Collagen	RPC
27	+	-	Collagen	RPC
28	+	-	Collagen	RPC
29	-	-	-	KD
30	+	-	Collagen	RPC

KD: Kyrle's disease, RPC: reactive perforating collagenosis, EPS: elastosis perforans serpiginosa, PF: perforating folliculitis.

were consistent with RPC (Fig. 2). Histopathological features of 5 cases (16.7%) showed a parakeratotic plug containing basophilic debris within a central epidermal invagination, consistent with KD (Fig. 3). In addition, histopathological features of 1 case (3.3%) showed narrow transepidermal channels containing coarse elastic fibers and basophilic debris. Verhoeff-van Gieson staining revealed transepidermal elimination of elastic fibers, consistent with EPS (Fig. 4). One case (3.3%) revealed a dilated follicular infundibulum filled with mixture of keratin, basophilic debris, inflammatory cells, and degenerated collagen fibers- consistent with PF (Fig. 5).

DISCUSSION

Perforating disorders are rare conditions, characterized by transepidermal elimination of dermal substances. In 1989, Rapini et al.¹⁵ reported several cases of perforating dermatosis in patients with DM or renal disease. They noted

that histopathological findings were no difference from the previously defined perforating disorders. They suggested that this process be referred to as 'acquired perforating dermatosis.' Since then, APD has been considered to be an entity that represents perforating disorders, occurring in patients with diabetes or chronic renal failure. However, many literatures still uses other terms such as acquired perforating dermatosis, acquired perforating disorders, and perforating dermatoses.

APD is most often found in middle-aged adults. The lesions are most often developed on the extensor surfaces of the extremities. However, any site on the cutaneous surface can be affected, including the trunk and scalp. There has been a report of KD on the conjunctiva and buccal mucosa¹⁶. In the current study, the lower extremities were the most frequently involved sites, which were consistent with findings from previous reports¹⁷⁻¹⁹. Pruritus was the most frequent symptom in patients with APD¹⁷. In our study, pruritus was presented in the most

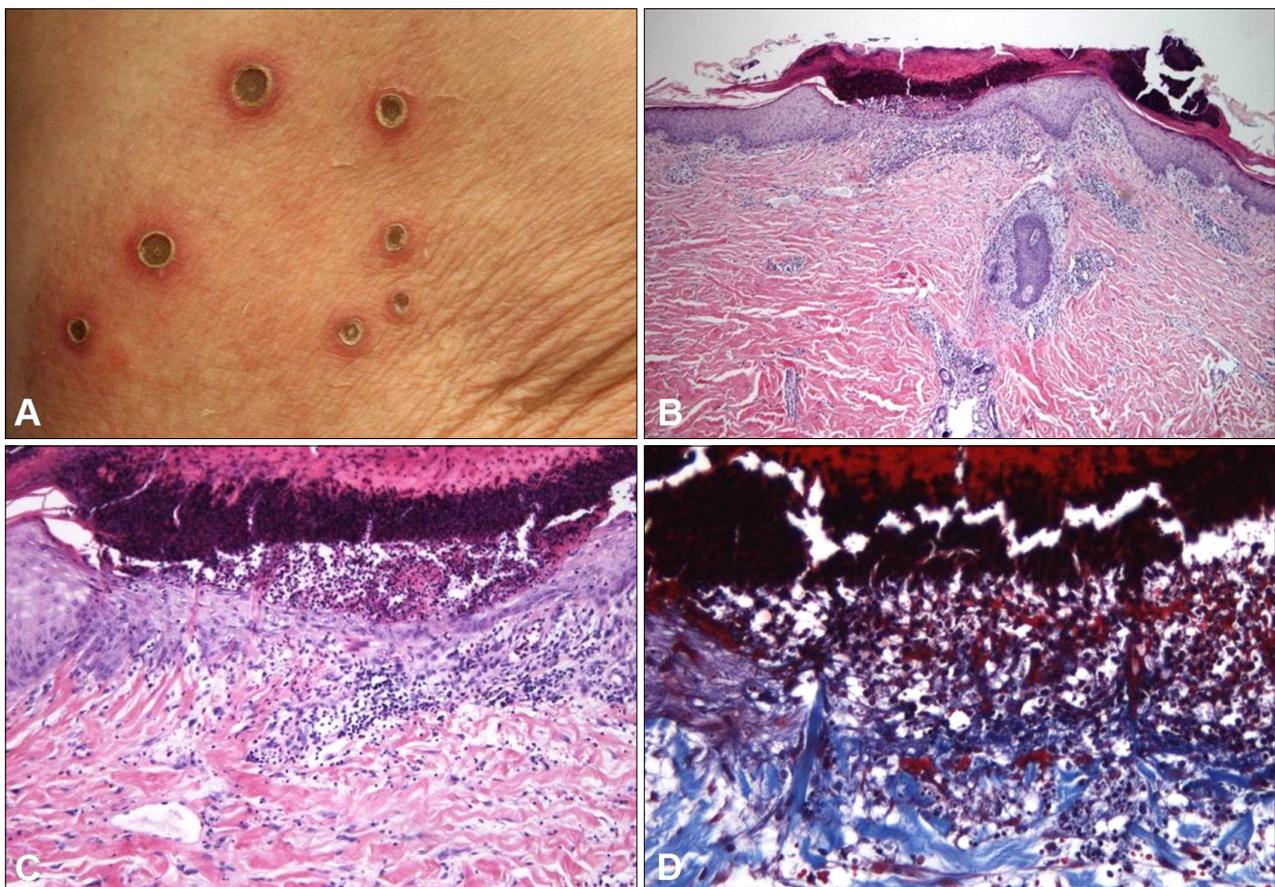


Fig. 2. (A) Reactive perforating collagenosis-like keratotic plugged, umbilicated papules on the lower extremities of patient 14. (B) Cup-shaped invagination of the epidermis plugged with necrotic inflammatory debris (H&E, $\times 40$). (C) There were vertically oriented collagen bundles at the base of the lesions (H&E, $\times 100$). (D) Transepidermal elimination of the collagen bundles (Masson-trichrome stain, $\times 200$).

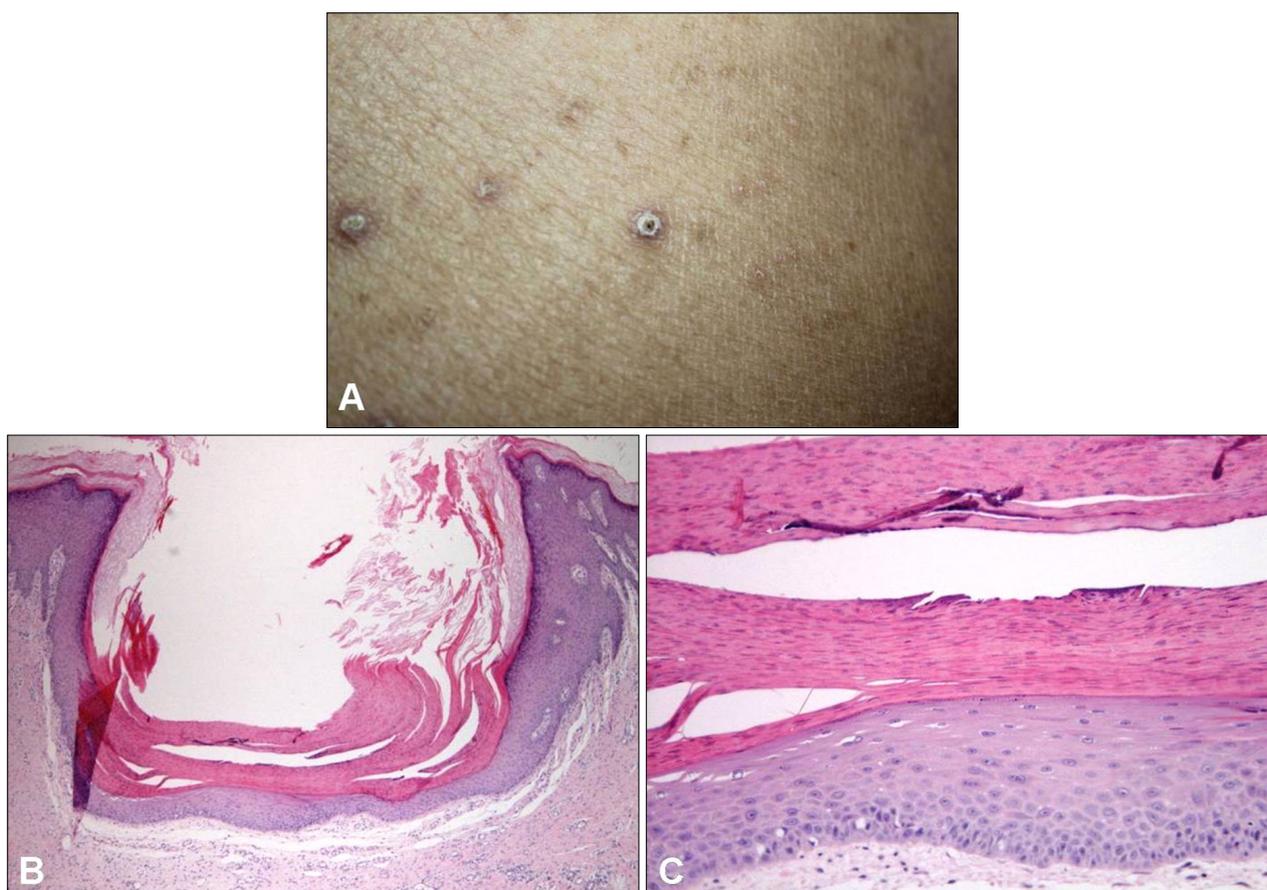


Fig. 3. (A) Kyrle's disease-like hyperkeratotic papules on the lower extremities of patient 3. (B) Central epidermal invagination containing parakeratotic debris (H&E, ×40). (C) Parakeratotic plug containing basophilic debris (H&E, ×200).

patients (83.3%). Two patients were presented with pain, which was a rare symptom for APD. Similarly, Saray et al.¹⁷ reported 22 cases with APD, 2 of which presented with pain. In APD patients, Koebner's phenomenon may occur after scratching, rubbing or trauma to the lesion¹⁸. Koebner's phenomenon was observed in 11 patients from our study.

The pathogenesis of APD remains unknown. Trauma from scratching, as a major trigger of perforating disorders, may induce damage of the epidermis or dermal collagen, leading to transepidermal elimination of collagen or elastic fibers²⁰. This hypothesis is supported by the predilection of the lesions to the previous areas of trauma, and the presence of Koebner's phenomenon¹⁷. Another hypothesis is the alteration in collagen or elastic fibers due to metabolic disturbances or microdeposition of substances, such as calcium salts²¹. Underlying dermal microvasculopathy related to DM is another suggested predisposing factor of APD. Diabetic vasculopathy induces a hypoxic state, in which the trauma from scratching causes dermal necrosis. This hypothesis has been supported by the

findings of a positive stain with periodic acid-Schiff, and thickening of the vessel walls in the upper dermis of diabetic patients with APD¹⁸.

APD is classified into 4 diseases, according to the type of epidermal disruption and the nature of the eliminated material: KD, PF, EPS and RPC¹. Classically, KD, PF and RPC present similar clinical features, characterized by umbilicated papules with central white, keratotic crusts. However, EPS presents with hyperkeratotic papules in a serpiginous distribution²². In our study, we observed one case that presented with serpiginous hyperkeratotic plaques, which was EPS confirmed by histopathology. Histopathologically in RPC, collagen bundles perforate through the epidermis. In EPS, elastic fibers are eliminated through the epidermis. In PF, degenerated follicular units with or without collagen and elastic fibers are eliminated, and in KD, amorphous dermal materials without collagen or elastic fibers perforate through the epidermis¹⁷. We classified the 30 cases of APD into the above-mentioned 4 diseases according to the histopathologic features, and observed all classic types of perforating dermatosis. The

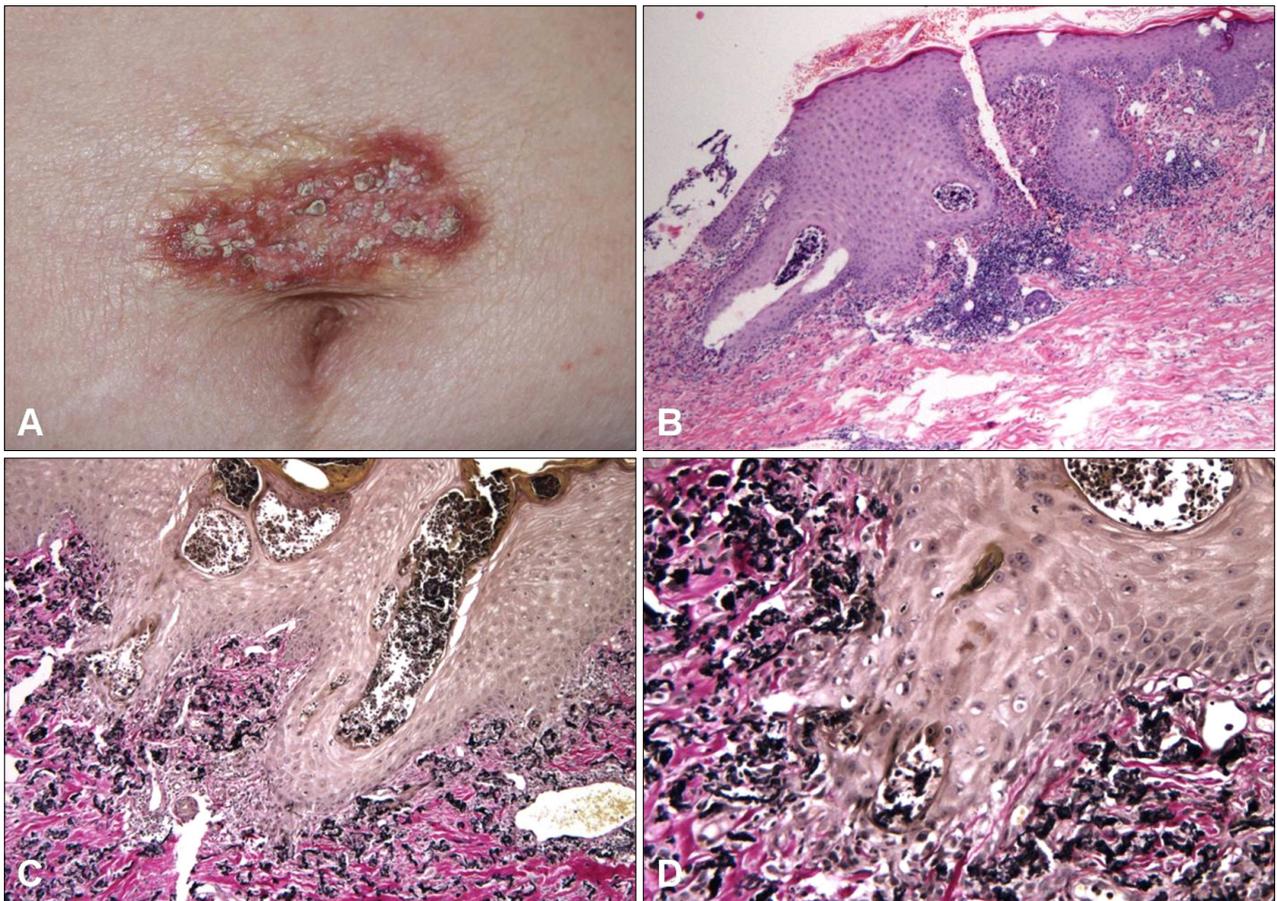


Fig. 4. (A) Elastosis perforans serpiginosa-like serpiginous hyperkeratotic plaques on the abdomen of patient 8. (B) Narrow transepidermal channels containing coarse elastic fibers and basophilic debris (H&E, $\times 40$). (C, D) Transepidermal elimination of elastic fibers (Verhoeff-van Gieson stain; C: $\times 100$, D: $\times 200$).

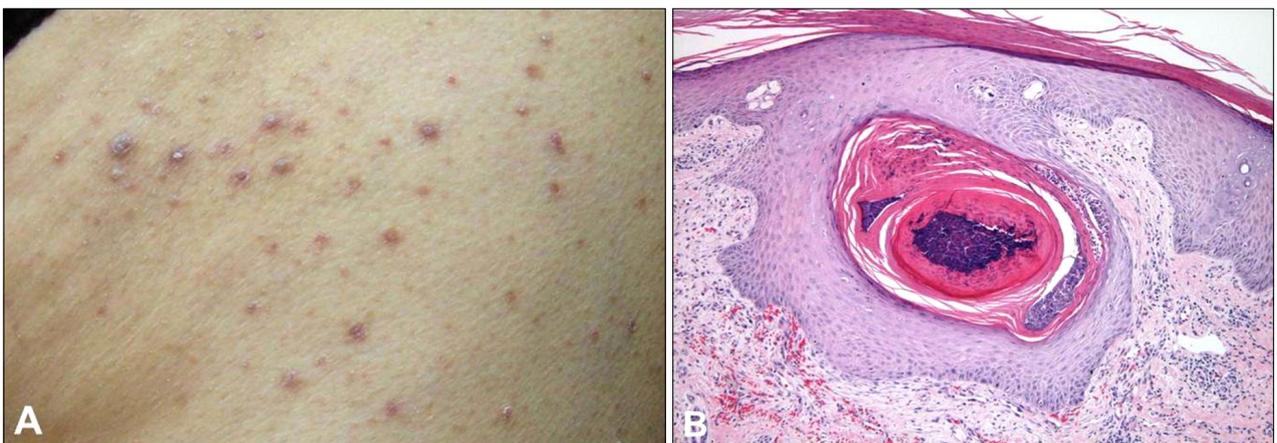


Fig. 5. (A) Perforating folliculitis-like follicular infiltrating papules on the thigh of patient 25. (B) Dilated follicular infundibulum filled with mixture of keratin, basophilic debris, inflammatory cells and degenerated collagen fibers (H&E, $\times 100$).

RPC (n = 23) was the most common type, followed by KD (n = 4), EPS (n = 1) and PF (n = 1). Rapini et al.¹⁵ reported combined transepidermal elimination of both collagen

and elastic fibers in four patients with APD. They proposed that varying histological findings in APD may represent the different stages or different types of lesions

in the same pathological process. However, Saray et al.¹⁷ suggested that APD represents the broad spectrum of perforating disorders rather than the variants of the same pathological process. We also could not observe the overlapping histologic features in the same lesion. Therefore, our study findings support a suggestion that APD is the spectrum of perforating disorders.

APD is usually associated with systemic diseases, especially DM, CRF or both. In our patients, DM was also the most commonly associated disease (56.7%). Two of our patients had IDDM, and 15 had NIDDM. A lot of studies have debated which type of DM is more strongly associated with APD. Similar to our result, some authors found that NIDDM is more frequent in patients with APD^{5,23}. However, Morton et al.²¹ reported that APD is more often in IDDM, compared with NIDDM. Consequently, Hong et al.¹⁸ suggested that the DM type does not appear to be a predisposing factor in APD.

In majority (90%) of our patients with CRF, the underlying cause of CRF was DM. Morton et al.²¹ reported that DM is the most frequent cause of CRF in APD patients. However, some authors have reported cases of renal impairment, not due to diabetes, including obstructive nephropathy, hypertensive nephrosclerosis, acquired immune deficiency syndrome, chronic nephritis, and anuria^{4,5,9,24,25}. In our study, we also found one patient with non-diabetic CRF. Thus, based on the present findings, as well as the previous reports, CRF itself might be an important predisposing factor in development of APD. In patients with CRF, APD often developed, following dialysis, but also occurred before dialysis⁵. Among our patients with CRF, 5 patients had undergone either hemodialysis or peritoneal dialysis. In all of these patients, the lesions had developed after the initiation of dialysis.

In recent years, there have been many reported cases of APD associated with other various diseases, such as malignancy, hepatic and endocrinologic disorders, AIDS, tuberculosis, pulmonary aspergillosis, atopic dermatitis, scabies, and pregnancy^{17,19}. In the current study, congestive heart failure, hypothyroidism, pregnancy, hypertension, hepatitis, chronic obstructive pulmonary disease, xerotic eczema, atopic dermatitis, and stasis dermatitis were observed in APD patients. However, these associated diseases, except pregnancy, were accompanied with DM, CRF, or both. Therefore, it could not be explained that these diseases contribute to the occurrence of APD by itself.

We observed a case with APD occurring in pregnancy, which was an unusual associated condition. Healy et al.¹⁴ described a case with APD occurring in pregnancy. She had undergone polymorphic eruption of pregnancy before

the development of APD. Thus, they proposed that persistent scratching might be a contributing factor. However, our patients had no other previous cutaneous problems and had no dermatologic diseases during pregnancy, such as pruritic urticarial papules and plaques in pregnancy. It remains unknown why APD develops in pregnant woman without an underlying disease.

In this study, there were 9 patients with other dermatologic diseases, such as xerotic eczema, atopic dermatitis and stasis dermatitis. Although all of these patients had underlying DM or CRF, we suggested that associated dermatologic problems might contribute to development of APD because those associated dermatologic diseases commonly presented with itching and scratching.

Treatment of APD can be difficult and various therapies have been reported. The most commonly described are topical and intralesional steroids, oral antihistamines and topical retinoids. Others include NB-UVB, psoralen plus ultraviolet A, oral retinoid, allopurinol, doxycycline and methotrexate^{14,19}. Most of our patients were treated with topical steroids, oral antihistamine and intralesional triamcinolone injection. The key point of treatment in APD is relief of pruritus. If the patient is protected then it is probable that APD has improved.

In the current study, RPC is the most common observed type of APD, followed by KD, EPS and PF. The results of the current study were consistent with previous studies of APD performed in other countries, including age, duration, distribution of skin lesion, clinical configuration, associated symptom, presence of Koebner's phenomenon, and associated systemic diseases. In this study, most patients had systemic association to the diseases. Therefore, we suggest that further evaluation including comprehensive past medical history, clinical exam and additional diagnostic testing for possibility of associated systemic diseases is necessary for patients who present with APD. On the other hand, the interesting fact was that there were 11 patients who had no other systemic diseases in our study. For those reasons, we propose further studies to identify the mechanisms of development of APD in healthy individuals. Additionally it is necessary to certify the mechanism of itching in APD patients.

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