

# Clinical characteristics and prognosis of acquired perforating dermatosis: A case report

MEI-FANG WANG, XUE-LING MEI, LI WANG and LIN-FENG LI

Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, P.R. China

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**Abstract.** Acquired perforating dermatosis (APD) is an uncommon skin disease characterized by umbilicated hyperkeratotic lesions, and involves the transepidermal elimination of dermal components, including collagen and elastic fibers. The disease can affect patients with systemic disorders, especially those with chronic renal failure or diabetes mellitus. The current paper described four cases of patients with APD and investigated the clinical characteristics and prognosis of APD, as well as its possible link with systemic disorders. In each of the four cases, the patient had systemic disorders before the onset of APD, three had concomitant renal and thyroid disorders and one had hepatocirrhosis secondary to chronic hepatitis C. The results of the present study showed that APD occurred after the transient worsening of the original systemic disease. Furthermore, it was revealed that dermatosis symptoms were alleviated upon remission of the original systemic disorder, without specific dermatological treatment. Dermatitis symptoms improved in all four patients, indicating that the management of the associated systematic diseases was essential for the successful clinical outcomes of APD.

## Introduction

Acquired perforating dermatosis (APD) is a rare skin disorder of unknown etiology and pathogenesis, which was first identified by Rapini *et al* (1) in 1989. APD is characterized clinically by umbilicated hyperkeratotic papules or nodules and histologically by the transepidermal elimination (TEE) of basophilic collagen bundles, as well as the onset of skin lesions in patients >18 years old (2,3). Although typical APD cases can be diagnosed at a glance by the characteristic eruptions (4), a skin biopsy is mandatory for definitive diagnosis (1,3,5,6). In some cases, the disease could potentially

be underdiagnosed or misdiagnosed as simple excoriations (5,6). Some researchers suggest that APD is a variant of prurigo nodularis, an umbilicated type of prurigo (7). The substances eliminated during the TEE process of APD include collagen, elastin and keratin (1,8). When collagen is the only eliminated substance, the disease is called acquired reactive perforating collagenosis (ARPC), which was first proposed by Mehregan *et al* in 1967 (5,8,9). There has been some confusion regarding the terminology over the years (1,10) since APD and ARPC are almost identical with regard to their clinical manifestations, pathologies and treatments, but display differences in their TEE substances (5,6,8,10).

APD can occur at any age with no gender predilection, but particularly occurs in the fourth to fifth decade of adult life (9). The common lesions are isolated papules with keratotic plugs, measuring 0.5-2.0 cm in diameter, which can occur on any part of the body but primarily occur on the lower extremities and trunk (3,6). The majority of patients with dermatosis suffer from pruritus with a rare occurrence of pain (2-5,8). In many situations, the lesions self-heal in six to eight weeks without any therapeutic treatment, however, there are cases where the symptoms persist for >8 years (6). APD has been associated with systemic diseases such as diabetes mellitus and renal failure (2). However, the cause of dermatosis remains unknown and the prognosis undesirable, which poses challenges to treatment of the disease.

In the present study, one case of ARPC and three cases of APD were diagnosed in succession within two months. This situation allowed close attention to be paid to the disease and resulted in the discovery that all four patients experienced skin lesions when their original systemic diseases were deteriorating. The severity of the skin lesions and pruritus declined after the patients received basic symptomatic treatment and had healed from their systemic diseases. The present study describes four cases of APD (including a case of ARPC) in patients with various systemic diseases and the clinical characteristics and prognosis of dermatosis are further summarized.

## Case reports

The study protocol was approved by the Beijing Friendship Hospital Ethics Committee for Human Research (approval no. 2019-P2-178-01). Written informed consent was obtained from each patient to have the case details and the accompanying images published.

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*Correspondence to:* Dr Lin-Feng Li, Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, 95 Yong'an Road, Xicheng, Beijing 100050, P.R. China  
E-mail: zoonli@sina.com

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*Case 1.* In April 2017, a 54 year old woman was admitted to the Beijing Friendship Hospital outpatient department for a 1 month history of intensely pruritic skin eruptions, which began on the arms and spread over the entire body without any specific cause. The severity of the pruritus and lesions increased over time. The patient received topical corticosteroid treatment, which proved ineffective. A cutaneous examination revealed the diffuse distribution of several well-defined circular umbilicated papules with central keratotic plugs on the trunk and bilateral upper limbs, as well as a few papules on the face and lower limbs (Fig. 1A). A number of papules were identified in a linear arrangement on the back and upper right limb, which were suspected to be Koebner phenomenon (Fig. 1B and C). The patient had a history of type 2 diabetes, hypertension, atrial premature beat, cataracts and hypothyroidism. Laboratory tests confirmed that the patient had albuminuria without creatinine abnormalities two months before the onset of the dermatosis. The patient's laboratory results were as follows: 8.9% glycated hemoglobin level, 0.8 g quantitative 24 h urinary protein and >1,300 U/ml quantitative determination of thyroid peroxidase antibody. A skin biopsy showed a cup-shaped invagination of the epidermis forming a short channel (Fig. 2A), within which there were densely packed degenerated basophilic-staining materials and lymph cells that had accumulated as a result of lymphocytic infiltration, as well as altered collagen bundles. These degenerated fiber bundles were identified as collagen fibers using an elastic fiber stain as Verhoeff-Van Gieson and Masson's trichrome staining. The patient was treated with oral antihistamines and topical corticosteroids, which led to some improvement at the patient's second visit, one month later. However, the improvement was lost by the subsequent follow-up after three months.

*Case 2.* In April 2017, a 54 year old woman was admitted to the Beijing Friendship Hospital outpatient department for a 5 year history of recurrent rash with severe pruritus. Two years prior to admission, the patient sought medical advice for a severe pruritic eruption with a central keratin-filled crater that appeared over her entire body. Despite diagnostic uncertainties, the patient was treated with conservative measures that led to symptomatic relief. At the most recent admission, significant clinical improvements were observed, with a general disappearance of itching and an obvious reduction in skin lesions. For the last 15 years, the patient had been undergoing hemodialysis for chronic renal insufficiency. The patient complained of generalized malaise, body edema and severe itching due to repeated adjustments to hemodialysis parameters during the treatment period. After receiving a subtotal parathyroidectomy to treat parathyroid carcinoma, the patient had a history of hypertension, hyperlipidemia and hyperparathyroidism. Laboratory tests highlighted a sharp rise in urea (19.55 mmol/l) and serum creatinine (805.2  $\mu$ mol/l). The patient's fasting blood sugar level was 11.57 mmol/l and serum phosphate levels were elevated to 2.52 mmol/l. During the present study, hyperpigmented macular patches were identified on the flexor and extensor surface of the legs, while a few rice-sized keratotic papules with central keratinous plugs were found on the back (Fig. 1D). Histopathological examination of a characteristic lesion detected infiltrating inflammatory cells in the cup-shaped invagination of the epidermis, as well as

collagen and elastic fibers in the superficial dermis, with a striking pattern of TEE through the epidermis and into the stratum corneum (Fig. 2B). At the time of the study, the patient was satisfied with the efficacy of hemodialysis. After treatment with topical corticosteroids, the skin lesions improved and other symptoms such as malaise and body edema were relieved.

*Case 3.* In May 2017, a 51 year old male patient who had been hospitalized in the Department of Nephrology (Beijing Friendship Hospital) was referred to the Department of Dermatology for consultation due to a pruritic skin eruption on the back that had continued for one month. The patient had end-stage renal disease (ESRD) and had been undergoing peritoneal dialysis over the previous year. The patient was hospitalized for further adjustment to his therapeutic plan following the development of symptoms such as fatigue, oliguria, lower limb edema and a gradual increase in blood creatinine and urea nitrogen levels. The patient also had a history of metabolic disorders such as hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia and coronary heart disease, as well as other diseases, including hyperparathyroidism and diabetic retinopathy. The examination conducted in the present study revealed a scattered distribution of some well-defined keratotic papules on the back (Fig. 1E). Laboratory tests showed the following: 789.68  $\mu$ mol/l serum creatinine, 51.55 mmol/l blood urea nitrogen, 3.29 mmol/l blood potassium, 1.88 mmol/l blood calcium and 2.47 mmol/l blood phosphorus. A skin biopsy was performed due to clinical suspicion of a TEE disorder. The histopathology examination detected a cup-shaped invagination of the epidermis filled with perforating collagen and elastic fibers (demonstrated using the Verhoeff-Van Gieson staining), as well as some necrotic debris (Fig. 2C). At one month after the concentration and capacity of the peritoneal dialysis fluid had been adjusted, the dermatosis significantly improved, with a disappearance of the rash and an obvious relief of itching, without any dermatological management.

*Case 4.* In August 2017, a 61 year old male patient was admitted to the Beijing Friendship Hospital outpatient department for a 5 year history of frequent pruritic rash that had been aggravated and spread all over the body over the previous three months. The patient had a 40-year history of hypertension and one month before the present visit was diagnosed with hepatocirrhosis secondary to chronic hepatitis C due to a blood transfusion that occurred 27 years ago. The results of a hepatitis C virus RNA quantification test, conducted a month prior to his visit, identified the replicative state of the virus in the body and thus confirmed hepatocirrhosis. Subsequently, the patient received treatment of subcutaneous injections of pegylated interferon  $\alpha$ -2a (180  $\mu$ g/week) in combination with daily oral intake of ribavirin (900 mg). The cutaneous examination conducted in the present study found a scattered distribution of papules and nodules and a central keratin-filled crater on the trunk and lower limbs of the patient (Fig. 1F). A number of papules on the lower limbs were distributed in a linear arrangement, which was identified as the Koebner phenomenon. A punch biopsy showed cup-shaped plugs in the excavated epidermis, filled with keratin, collagen and



Figure 1. Presentation of acquired perforating dermatosis. The patient in case 1 presented with a large number of skin lesions and severe pruritus. (A) few papules on the face, (B) numerous umbilicated papules with central keratotic plugs on the trunk and (C) bilateral upper limbs with some papules in a linear arrangement, which were confirmed as Koebner phenomenon. (D) The patient in case 2 presented with few papules in the recovery period of APD and displayed several keratotic papules with central keratinous plugs on the back. (E) The patient in case 3 presented with a scattered distribution of well-defined keratotic papules on the back. (F) The patient in case 4 presented with a scattered distribution of papules and nodules with a central keratin-filled crater on the trunk.

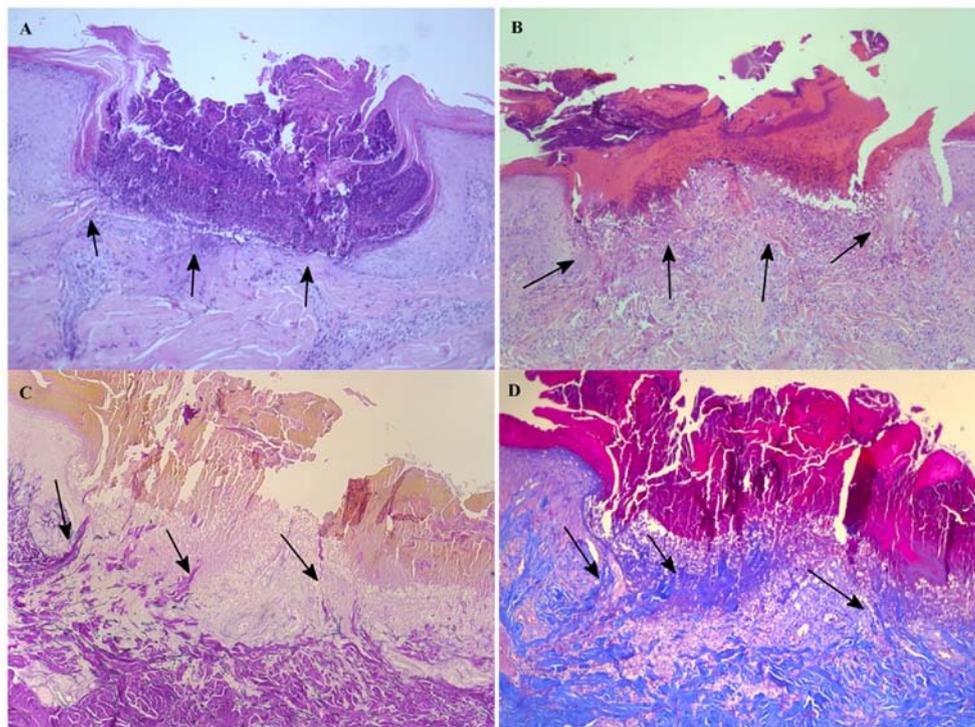


Figure 2. Biopsies displaying cup-shaped invagination of the epidermis and sparse fiber bundles perforating the dermis to the epidermis, as indicated by the black arrows. (A) Several infiltrating inflammatory cells in the patient in case 1, who was in the advanced stage of APD. Sample stained with hematoxylin and eosin and visualized at x100 magnification. (B) Few inflammatory cells in the patient in case 2, who was in the recovery stage. Sample stained with hematoxylin and eosin and visualized at x100 magnification. (C) Transepidermal elimination of collagen (red) and elastic fibers (black) from the patient in case 3. Sample stained with Verhoeff-Van Gieson stain and visualized at x100 magnification. (D) Perforating collagen fibers (blue) from the patient in case 4. Sample stained with Masson's trichrome stain and visualized at x100 magnification.

Table I. Clinical features, associated systemic diseases and abnormal laboratory results of the four patients with APD.

Case no.	Sex	Age	APD duration (months)	Pruritus severity	Koebner phenomenon	Distribution	TEE material	Systemic disorders/number of years with the disorder	Abnormal laboratory results (reference range)
1	F	54	1	Very severe	Positive	Mainly trunk and bilateral upper limbs, few on face and lower limbs	Collagen fibers	Hypertension/2, proteinuria with normal renal function/1, hypothyroidism/1, NIDDM/2, cataract/5, atrial premature beat/2, multiple uterine myoma/5, albuminuria/0.17	HbA1c 8.9% (4.27-6.07), 24-h urinary protein quantitative 0.8 g (0-0.15), ATPO >1,300 U/ml (0-60)
2	F	54	>24	Severe	Negative	Back and extensor surface of legs	Collagen and elastic fibers	Hypertension/20, ESRD requiring hemodialysis/15, hyperparathyroidism and subtotal parathyroidectomy because of parathyroid carcinoma/3, hyperlipidemia/20, generalized malaise and body edema need to adjust hemodialysis parameters	Urea 19.55 mmol/l (2.60-7.50), serum creatinine 805.2 $\mu$ mol/l (53.0-115.0), GLU 11.57 mmol/l (3.92-6.16), serum phosphate 2.52 mmol/l (0.85-1.51)
3	M	51	1	Severe	Negative	Back	Collagen and elastic fibers	Hypertension/10, ESRD requiring peritoneal dialysis/1, hyperparathyroidism/4, NIDDM/2	Serum creatinine 789.68 $\mu$ mol/l (53-115), blood urea nitrogen 51.55 mmol/l (3.6-9.5), blood potassium 3.29 mmol/l (3.5-5.3), blood calcium 1.88 mmol/l (2.11-2.52), blood phosphorus 2.47 mmol/l (0.85-1.51)
4	M	61	3 or maybe 60	Severe	Positive	Trunk and lower limbs	Collagen and elastic fibers	diabetic retinopathy/2, hyperlipidemia/4, hyperuricemia/4, coronary heart disease/4, increase of blood creatinine and urea nitrogen levels for adjustment of the peritoneal dialysis	Quantitative analysis of hepatitis C virus nucleic acid 2.407x10 <sup>3</sup> IU/ml (<1.0x10 <sup>-2</sup> )

F, female; M, male; APD, acquired perforating dermatosis; TEE, transepidermal elimination; NIDDM, non-insulin-dependent diabetes mellitus; HbA1c, glycated hemoglobin level; ATPO, quantitative determination of thyroid peroxidase antibody; ESRD, end-stage renal disease; GLU, blood glucose.

cell debris. The collagen fibers vertically aligned near the epidermis, demonstrated by Masson's trichrome staining (Fig. 2D). The symptoms improved after receiving NB-UVB phototherapy 2-3 times a week for 1 month. When the patient returned for a follow-up two months later, the rash had mostly disappeared.

The clinical features, associated systemic diseases and abnormal laboratory results of the four patients are illustrated in Table I. All of the four patients' skin specimen was stained with three dying methods, including hematoxylin and eosin, Verhoeff-Van Gieson and Masson's trichrome staining. The specimen was firstly stained using hematoxylin and eosin staining, which was fixed by 10% neutral buffered formalin for 4-12 h at room temperature, and dyed using hematoxylin solution for 3-5 min and eosin solution for 30-60 seconds at room temperature. The specimen was secondly stained via Verhoeff-Van Gieson staining, which was fixed with 10% neutral buffered formalin for 2-4 h at room temperature, dyed with elastin for 8-24 h and Van Gieson for 1 min at room temperature. The specimen was thirdly stained via Masson's trichrome staining, which was fixed with 10% neutral buffered formalin for 2-4 h at room temperature, stained with Weigert hematoxylin for 5-10 min, acid Fuchsin for 5-10 min and aniline blue for 3-5 min at room temperature. All of the above reagents were supplied by Baso Diagnostics Inc. The thickness of pathological section of skin was 4  $\mu$ m, which was observed under ordinary light microscope and analyzed using Leica camera software (LAS V4.5; Leica Microsystems Ltd).

## Discussion

Diagnosis of APD is based on the patient's medical history, the clinical appearance of lesions and the results of histopathological examinations. In the present study, the patients involved were middle-aged, without a family history of related diseases. All patients displayed lesions with severe pruritus, primarily on their trunk. One of the patients had lesions on the face, while two demonstrated the Koebner phenomenon. In addition to these clinical features, the skin lesions of the four patients were in the form of isolated round or oval papules that were uniform in size and shape, with keratotic plugs that were difficult to scratch off. In all four cases, the histological features of the dermatosis were cup-shaped invaginations of the epidermis, which formed a short channel. The channel was densely packed with degenerated basophilic staining materials, neutrophils, infiltrating lymph cells and altered connective tissue. These typical pathological findings are one of the important diagnostic parameters for APD (1,3,5,8). The substances in the cup-shaped plugs may, to some extent, affect the clinical manifestation of the disease. For instance, neutrophils and infiltrating lymphocytic cells were identified in the patient in case 1, who had advanced stage dermatosis, while few infiltrating inflammatory cells were observed in the epidermal invagination of the patient in case 2, who was in the recovery stage.

It is widely recognized that this dermatosis occurs most commonly among those with systemic disorders, especially diabetes mellitus and renal failure (1-12). It is worth noting that despite its rarity, a 2-11% incidence of APD onset has been reported in patients receiving maintenance dialysis for

end stage renal disease (13). Some diseases, such as hypertension, hepatitis, hypothyroidism and chronic obstructive pulmonary disease, are frequently mentioned as being related to the dermatosis (10,14,15). Similarly, certain malignancies, including lymphoma and thyroid, prostate and breast carcinoma, were found in 9.1% of patients with APD (16-18). In addition, the possibility of APD onset in the presence of certain autoimmune diseases, such as systemic lupus erythematosus, vasculitis, dermatomyositis and Mikulicz disease, has been confirmed (19,20). Moreover, APD has also been identified among patients with various infections, such as scabies, herpes zoster and insect stings (8). However, few cases of APD were reported in patients using biologics, such as infliximab, natalizumab and gefitinib (6). Although the pathogenesis of the dermatosis remains unclear, some reports suggest that trauma and microvasculopathy may trigger TEE and degeneration of the collagen fibers (8,18).

In the present study, three patients with APD had various systemic disorders, whilst the dermatosis in the fourth patient was associated with hepatocirrhosis secondary to hepatitis C virus infection. The patient in case 1 had seven different types of systemic disorder, including diabetes mellitus, hypothyroidism, hypertension, atrial premature beat, proteinuria, cataracts and multiple uterine myoma. The patient in case 2 had four systemic diseases including ESRD, parathyroid carcinoma, hypertension and hyperlipidemia. The patient in case 3 had eight systemic diseases, including ESRD, diabetes mellitus, diabetic retinopathy, coronary heart disease, hyperparathyroidism, hypertension, hyperlipidemia and hyperuricemia. Two of the patients had been undergoing dialysis for kidney problems, such as ESRD, while one had been receiving hemodialysis for 15 years and another had been receiving peritoneal dialysis for one year. In the available literature, few cases reported as many concomitant diseases in one patient as was found in the patients in the present study (1,5,6,10,16-22). At the same time, the patients in the present study did not pay enough attention to the dermatosis. The prevalence of this condition may be underestimated because the patients with multiple systemic disorders were not aware of the severity of the skin rash and were reluctant to undergo a pathological examination.

In the four cases described in the present study, the dermatosis occurred with the progression of systemic disease, three of which were kidney problems and one of which was liver cirrhosis. The patient in case 1 was diagnosed with albuminuria with no creatinine abnormalities two months before the onset of the skin disease. The eruption of the rash in case 2 may have been associated with the repeated adjustments of the hemodialysis that the patient had been receiving, however, the symptoms were relieved without specific treatment by a dermatologist. The patient in case 3 was hospitalized for the adjustment of peritoneal dialysis, which he had been undergoing to alleviate the discomfort of the symptoms inflicted by the dialysis before the onset of APD. Likewise, the dermatosis symptoms subsided without any dermatological interventions. The patient in case 4 was diagnosed with hepatocirrhosis before the skin pruritus was exacerbated. After systematic antiviral therapy and NB-UVB phototherapy for about one month, the skin symptoms disappeared almost entirely. These four cases demonstrated that the occurrence and remission of APD symptoms were synchronized with the occurrence

and remission of the patients' systemic diseases. In other words, APD associated with systemic diseases occurred when systemic disorders worsened or had not been well-controlled for a long period, while its symptoms may have lessened with the successful treatment of the associated systemic diseases (21). As such, the occurrence or exacerbation of the systemic diseases that a patient has should be taken into consideration regarding APD diagnosis.

Currently, there is no definitive or efficient treatment for APD (5,8,22,23). Topical steroids and oral antihistamines are the most commonly prescribed drugs, which primarily aim to control the symptoms (5,8,22,23). Other effective therapies include topical agents such as emollients, keratolytics, retinoids, steroids, doxycycline, imiquimod, maxacalcitol and allopurinol; oral agents such as retinoids, systemic antibiotics and amitriptyline, and medical treatments such as cryotherapy, curettage, electrocautery, excision and phototherapy such as NB-UVB and 308 nm excimer laser (6,8,19,20). In the present study, clinical symptoms of APD improved gradually even though the treatment was primarily aimed at relieving the symptoms of pruritus. The effective control of the associated systemic diseases was essential for the successful therapeutic result of the dermatological treatment.

In conclusion, APD skin lesions are characterized by isolated circular papules with uniformity in size and shape. Accompanied by severe pruritus, APD is often associated with a variety of systemic disease (3,5,14). The substances generated via TEE may include collagen, elastin and keratin, whilst the materials in the cup-shaped plugs are related to the clinical manifestation of the dermatosis. There is a high association between APD and the systemic disorders in regard to their occurrence and development. Desirable prognoses were obtained in the four APD cases described in the present study and the management of the associated systemic diseases was important for the APD treatment outcomes.

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### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Authors' contributions

MFW was responsible for the clinical management of patient, the evaluation and analysis of data, and was a major contributor in writing the manuscript. XLM and LW was responsible for the preparation of biopsy, analyzed and interpreted the patient data regarding the hematological disease. LFL was involved in making substantial contributions to conception and design, drafting and revising the manuscript for important intellectual content, and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part

of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The Ethics approval was obtained from the Beijing Friendship Hospital Ethics Committee for Human Research (approval no. 2019-P2-178-01). Written informed consent was obtained from each patient to have the case details and the accompanying images published.

### Patient consent for publication

Written informed consent of the patient were obtained for publication.

### Competing interests

The authors declare that they have no competing interests.

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