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Acquired Reactive Perforating Collagenosis: Clinicopathologic Analysis of 12 Cases

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Background: Acquired reactive perforating collagenosis (ARPC) is a rare and complex dermatological condition often associated with systemic diseases such as diabetes and chronic kidney disease. It is characterized by the transepidermal elimination of collagen fibers. ARPC presents with diverse clinical manifestations, leading to frequent misdiagnosis. This study provided a comprehensive overview of the clinical pathology and treatment outcomes in 12 confirmed cases of ARPC. The findings aimed to enhance clinicians' understanding of this condition and inform better diagnostic and therapeutic strategies.

Methods: A retrospective analysis was carried out to summarizes the clinical pathology and treatment response of the ARPC.

Results: The patients had a mean age of 60.2 years, with a predominance of female cases. The primary clinical features included papules and nodules predominantly affecting the lower limbs, with central ulceration, necrosis, and severe pruritus. Histopathological examination showing cupped epidermal invagination containing crusts, inflammatory cells, and degenerated collagen; degenerated collagen fibers penetrating vertically through the epidermis. Treatment primarily involved topical therapies, while dupilumab demonstrated efficacy in some refractory cases.

Discussion: Early diagnosis and intervention of ARPC are crucial for improving patients' quality of life. Further research is needed to elucidate the pathological mechanisms and management strategies of ARPC. Exploring its pathogenesis and biological characteristics remains pivotal for advancing diagnostic and therapeutic approaches.

Keywords: reactive perforating collagenosis, acquired, histopathology, Masson staining

Introduction

Acquired reactive perforating collagenosis (ARPC) is a subset of acquired perforating disorders (APD), and many clinical and histological features overlap between these conditions. Due to these similarities, differentiating between the subsets clinically or histologically is often challenging. APDs encompass several subtypes, including Kyrle's disease, perforating folliculitis, and elastosis perforans serpiginosa. Although these disorders share pathognomonic features, clinical differentiation is based on unique patterns of perforation and associated histological changes. ARPC is a relatively rare and complex dermatological disorder characterized by the transepidermal elimination of degenerated collagen fibers. This condition is often associated with various systemic diseases, particularly diabetes and chronic kidney disease.[1,2] The clinical and histological features of ARPC typically include keratotic papules or nodules with central umbilication and the presence of degenerated collagen fibers traversing vertically through the epidermis on pathological examination. The precise mechanisms underlying these phenomena remain under investigation. Limited awareness of ARPC among clinicians often leads to misdiagnosis or missed diagnoses. This study summarizes 12 cases of ARPC confirmed by clinical and pathological evaluation in our department, aiming to elucidate its clinical and pathological characteristics, diagnostic methods, and therapeutic strategies to provide a reference for clinical practice.

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Materials and Methods

A retrospective analysis was conducted on 12 cases of ARPC diagnosed clinically and pathologically at the Dermatology Department of Beijing Hospital between September 1, 2019, and September 1, 2024. Data collected included patient demographics (gender, age at presentation), disease duration, morphological features and distribution of skin lesions, misdiagnosis occurrences, histopathological findings, and treatment modalities.

Results

General Data

Among the 12 patients, there were 4 males and 8 females, with a male-to-female ratio of 1:2. The age at presentation ranged from 47 to 75 years, with a mean age of 60.2 ± 10.3 years. Disease duration varied from 3 weeks to 7 years, with an average of 11.6 ± 25.2 months. None of the patients had a family history of ARPC (Table 1).

Table 1 Clinical Data of 12 Patients With Acquired Reactive Perforating Collagenosis

No.	Gender	Age	Disease Duration	Affected Areas	Lesion Characteristics	Pruritus	Comorbidities	Initial Diagnosis	Treatment
1	Female	53	3 years	Bilateral lower legs	Papules, crusting	Yes	Endometrial cancer	Eczema?	Compound glycyrrhizin tablets, ebastine tablets orally; 0.1% tacrolimus ointment topically
2	Female	64	3 weeks	Bilateral lower limbs	Erythema, papules, ulceration, crusting	Yes	Lung cancer	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally; 0.1% tacrolimus ointment topically
3	Male	53	2 months	Bilateral lower legs	Papules, nodules, crusting	Yes	None	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally; fluticasone propionate cream topically
4	Female	72	6 months	Trunk, limbs, face	Erythema, papules, crusting	Yes	Chronic renal failure	Eczema?	Compound glycyrrhizin tablets, ebastine tablets orally; fluticasone propionate cream topically. No improvement after 2 weeks. Treated with dupilumab, showing improvement in pruritus within 1 week and gradual resolution of lesions within 2 weeks.
5	Female	48	1 month	Bilateral lower limbs, hands	Papules, crusts	Yes	None	Eczema?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied

(*Continued*)

Table 1 (Continued).

No.	Gender	Age	Disease Duration	Affected Areas	Lesion Characteristics	Pruritus	Comorbidities	Initial Diagnosis	Treatment
6	Female	69	1 month	Bilateral lower limbs, dorsum of feet	Papules, crusts	Yes	None	Allergic cutaneous vasculitis?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied
7	Female	47	7 years	Bilateral lower legs	Papules, ulcerations, crusts	Yes	None	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied
8	Male	75	3 months	Back, limbs	Erythema, papules, crusts	Yes	None	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied
9	Female	72	1 month	Whole body	Nodules, ulcerations, crusts	Yes	None	Nodular prurigo?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied; after 2 weeks, no significant improvement in rash or pruritus. Dupilumab treatment was initiated, with pruritus improving after 1 week and the rash gradually subsiding after 2 weeks.
10	Female	53	1 month	Bilateral lower legs	Nodules, ulcerations, crusts	Yes	None	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied
11	Male	66	3 weeks	Back	Erythema, papules, ulcerations, crusts	Yes	Elevated cancer antigen 72–4	Eczema?	Compound glycyrrhizin tablets, ebastine tablets orally, 0.1% tacrolimus ointment externally applied

(*Continued*)

Table 1 (Continued).

No.	Gender	Age	Disease Duration	Affected Areas	Lesion Characteristics	Pruritus	Comorbidities	Initial Diagnosis	Treatment
12	Male	51	2 months	Bilateral lower limbs	Erythema, papules, ulcerations, crusts	Yes	None	Reactive perforating collagenosis?	Compound glycyrrhizin tablets, ebastine tablets orally, fluticasone propionate cream externally applied

Clinical Manifestations

Lesion Distribution

All 12 patients exhibited symmetrically distributed skin lesions. The most commonly affected site was the bilateral lower limbs, observed in 11 patients. Additionally, 4 patients had lesions involving the trunk, and 1 patient presented with generalized lesions across the body.

Characteristics and Symptoms of Lesions

All patients displayed the characteristic "umbilicated" papules and nodules, with central ulceration, necrosis, and crusting. The central depression of these lesions was covered with keratin plugs. Some patients exhibited accompanying erythema and Koebner phenomenon (isomorphic response), as shown in Figure 1. All 12 patients reported significant pruritus, which severely impacted their quality of life.

Misdiagnoses

Six patients were initially misdiagnosed. Among these, 4 cases were diagnosed as eczema, 1 as nodular prurigo, and 1 as cutaneous allergic vasculitis.

Comorbidities

Among the 12 patients, 3 had comorbid systemic diseases, including malignancies and chronic renal insufficiency. Among the 3 patients with comorbidities, one patient had chronic renal failure, one had endometrial cancer, and one had lung cancer. One patient exhibited elevated serum cancer antigen 72–4 levels; however, further investigations revealed no tumors, and this patient remains under regular follow-up. Eight patients had no other systemic diseases at the time of diagnosis.

Histopathology

Histopathological examination of all patients showed cup- or saucer-shaped depressions in the epidermis, with defects at the base of the epidermis. The depressions contained scabs, neutrophils, and fragmented collagen. The superficial dermis and perivascular areas demonstrated lymphocytic and neutrophilic infiltration. Masson staining revealed blue-stained fragmented and degenerated collagen fibers protruding vertically through the epidermis (Figure 2).

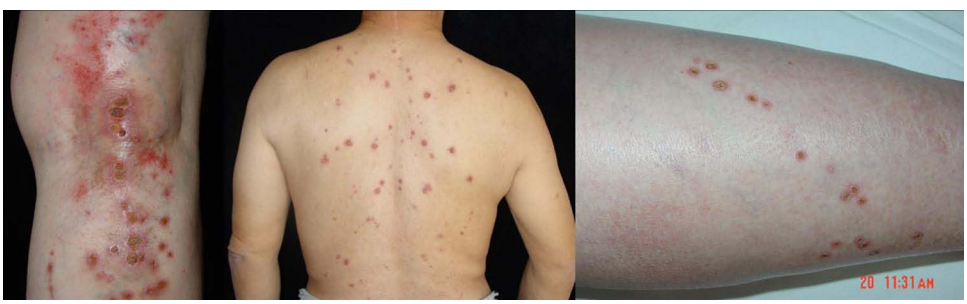

Figure 1 Scattered papules and nodules on the lower limbs and back, showing central necrosis and crusting with an "umbilicated" appearance. Koebner phenomenon observed.

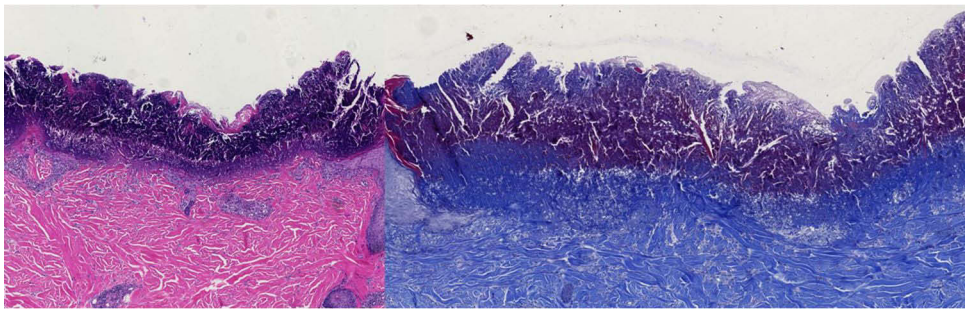

Figure 2 Histopathological examination showing cupped epidermal invagination containing crusts, inflammatory cells, and degenerated collagen; degenerated collagen fibers penetrating vertically through the epidermis (Masson staining).

Treatment and Follow-Up

After diagnosis, patients were instructed to avoid scratching and trauma. Symptomatic treatment for lesions included topical corticosteroids and calcineurin inhibitors. For systemic treatment, patients were initially prescribed oral antihistamines (ebastine) and compound glycyrrhizin tablets. Follow-up at two weeks showed gradual improvement of lesions and pruritus in 10 patients. The remaining 2 patients, who showed no significant response to the above treatment and experienced severe pruritus, were treated with dupilumab (300 mg subcutaneous injection every two weeks). Pruritus relief was observed within one week, followed by gradual resolution of skin lesions. Treatment was maintained for approximately six months until complete resolution of lesions, after which the medication was discontinued. Out of the 12 patients, two experienced lesion recurrence during a six-month follow-up period. Follow-up photographs of lesion resolution were unavailable, which represents a limitation of this retrospective study.

Discussion

ARPC is a perforating dermatosis characterized by the extrusion of degenerated collagen fibers through the epidermis. It was first reported by Mehregan in 1967, and its etiology and pathogenesis remain incompletely understood. Current studies suggest that ARPC may be associated with various intrinsic and extrinsic stimuli, such as skin trauma and tattoos.[3,4]

ARPC is often accompanied by systemic diseases, including diabetes mellitus, chronic renal failure, dermatomyositis, and malignancies.[5–7] Among these, diabetes mellitus and its complications, such as chronic renal failure, are the most commonly observed. Diabetic microangiopathy can lead to hypoxia in the dermis, which in turn induces collagen fiber degeneration and keratinocyte necrosis. In this study, two cases were associated with malignancies, and one case showed elevated serum tumor markers, suggesting that clinicians should remain vigilant for potential malignancies when diagnosing ARPC and perform appropriate tumor screening. Additionally, eight cases in this study had no associated systemic diseases, indicating that the underlying causes of ARPC in such patients require further investigation. The intense pruritus experienced by patients, coupled with scratching-induced microtrauma to the skin, may be an important factor in the disease's onset and progression. This observation aligns with the findings of Kochen et al[8] who reported that trauma might trigger or exacerbate ARPC.

Previous case studies have reported that ARPC predominantly occurs on the lower extremities and trunk, with the lower extremities being the most commonly affected sites. The average age of onset is around 50 years, and the condition is more frequently observed in females than in males.[1] The clinical manifestations are diverse, typically presenting as papules or nodules. These lesions often exhibit central umbilicated depressions filled with keratotic plugs and are accompanied by scratch marks and crusting. Intense pruritus is a common symptom, potentially leading to repeated scratching, which exacerbates skin damage and disease progression.[9] In this study, 11 cases involved bilateral lower extremities, and all patients experienced severe pruritus. The average age of onset was 60.2 years, with a predominance of female patients, consistent with previous literature. The characteristic histopathological features of ARPC include focal epidermal defects containing keratotic plugs, inflammatory cells, and degenerated collagen. Degenerated collagen

fibers can be observed protruding vertically through the epidermis. In the superficial dermis, inflammatory cell infiltration is often seen around small blood vessels.[1] Masson's trichrome staining highlights the degenerated collagen fibers in blue, demonstrating their vertical extrusion through the epidermis.

The clinical manifestations of ARPC are diverse, often accompanied by scratch marks and crusting, which make misdiagnosis and missed diagnosis common. It is frequently misdiagnosed as eczema, nodular prurigo, allergic vasculitis, or acute varioliform lichenoid pityriasis. Histopathological examination remains the cornerstone for diagnosis and differential diagnosis. Analyzing the patient's history and the characteristics of the skin lesions can improve the recognition of ARPC.

Currently, there are no standardized treatment strategies or guidelines for ARPC. Effectively managing associated systemic diseases or malignancies is essential for controlling ARPC-related skin symptoms. Given the association of ARPC with systemic conditions, a multidisciplinary approach involving dermatology, oncology, and internal medicine specialists was utilized, ensuring comprehensive care. The challenge in treating ARPC lies in its diverse etiologies and clinical manifestations, making individualized therapy particularly important. Topical therapy is usually the first-line treatment for ARPC, primarily involving corticosteroids and calcineurin inhibitors.[10] Maintaining regular skin care is equally critical; minimizing scratching and reducing friction on the lesions can alleviate symptoms and promote healing. Traditional antihistamines are commonly used to control the pruritus associated with ARPC. Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, has been approved for the treatment of moderate-to-severe atopic dermatitis and has shown efficacy in managing nodular prurigo, cutaneous amyloidosis, lichen planus, and other pruritic conditions. Yang Ying[9] reported two cases of ARPC combined with senile atopic dermatitis (AD), where the patients exhibited poor responses to conventional treatments but responded well to monotherapy with dupilumab. Similarly, in our study, two patients showed inadequate responses to standard therapies but responded positively to dupilumab treatment. This suggests that dupilumab may serve as an alternative for controlling pruritus in ARPC and managing coexisting AD. Other systemic treatments, including oral corticosteroids and immunosuppressants, are typically reserved for refractory cases that do not respond to topical therapy. However, the potential side effects of these medications must be carefully considered. Additionally, UVB phototherapy and surgical debridement have been used in specific cases requiring specialized interventions.

Although current knowledge of ARPC remains limited, early diagnosis and intervention are critical to improving patients' quality of life. Further exploration of the disease's pathological mechanisms and biomarkers could pave the way for developing novel therapeutic strategies.

Conclusion

The management of ARPC requires a multidisciplinary approach and individualized treatment strategies. Ongoing clinical research and the accumulation of experience are essential for gradually enhancing our understanding and handling of this complex disease. ARPC is often misdiagnosed so clinicopathologic examination is very important and Dupilumab may be a promising therapy, but further research is needed.

Ethics Approval and Informed Consent Statement

The study was approved by the Ethics Committee of Beijing Hospital (2022BJYYEC-208-02). Informed consent was obtained from each patient. Written informed consents were obtained from all the patients for the publication of case details and images included in this article. This study was conducted in accordance with the principles of the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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