Successful Treatment of Acquired Reactive Perforating Collagenosis Induced by Pregnancy with Allopurinol: A Case Report with Review of Literature

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Abstract

Acquired reactive perforating collagenosis (ARPC) is a rare condition caused by transepidermal elimination of collagen, elastin fibers and keratin. To date, the pathogenesis of ARPC remains unknown. Different hypotheses were proposed, including superficial microtrauma due to pruritus and subsequent scratching, diabetes-induced microangiopathy, epidermal and dermal abnormalities in metabolic disorders, dermal microdeposits in patients with chronic renal failure and vasculopathy underlying chronic venous insufficiency and hypertension. In the past two decades, oral allopurinol had been found to be effective in treating ARPC. We report a case of a 36-year-old pregnant woman with itchy skin lesions on the trunk and four limbs since 36 weeks of her gestation. Initially, she was prescribed with oral antihistamine and topical steroid but did not respond well. Skin biopsy was performed and was compatible with ARPC. Normal renal and liver function tests were noted, and the HLA-B5801 test was negative. We treated the patient with allopurinol. Significant improvement was noticed at 1-month follow-up. To the best of our knowledge, this is the first case successfully treating ARPC induced by pregnancy with allopurinol. On careful follow-up of laboratory data and HLA-B5801 test screening, allopurinol may be another effective treatment option for ARPC patients after pregnancy.

Keywords: Acquired reactive perforating collagenosis, allopurinol, pregnancy

INTRODUCTION

Acquired reactive perforating collagenosis (ARPC) is a rare condition caused by collagen, elastin fibers, and keratin elimination through the epidermis.[1] There are four classic types of perforating dermatoses, including elastosis perforans serpiginosa, Kyrle disease, reactive perforating collagenosis, and perforating folliculitis.[1] Among the four types, Reactive perforating collagenosis can be hereditary or acquired. If the disease process starts in childhood, it is called primary or inherent reactive perforating collagenosis. The term “acquired”...
is used when the same disease presents in adulthood. The ARPC is mostly associated with underlying systemic diseases such as diabetes mellitus, chronic renal disease, hypothyroidism, hyperparathyroidism, Hodgkin’s disease, liver disorders, neurodermatitis, IgA nephropathy, obesity, and AIDS.\(^1\) ARPC is a rare condition caused by altered collagen fibers and keratin elimination through the epidermis.\(^2\) Etiology and pathogenesis of ARPC are still not understood very well.\(^3\) ARPC is characterized by chronic, scattered, hyperkeratotic pruritic papules with a central plug. Umbilicated lesions are mainly presented in ARPC. The lesions usually arise on the limbs, but they may also be found on the trunk or face.\(^4\) Skin lesions can be present on the sites which are accessible for scratching. Widening of papillary dermis and necrotic basophilic collagen fibers extruding through the hyperplastic epidermis are common histopathological features of ARPC. Special stains such as Masson trichrome and Verhoeff-van Gieson are very helpful to detect collagen or elastic fibers in the crater respectively. Elastosis perforans serpiginosa can be distinguished from ARPC by the presence of elastic fibers on Verhoeff-van Gieson stain.

Various therapies have been tried in ARPC management.\(^5\) However, no standard treatment is established yet. Results with various treatments are also quite variable. In the past two decades, oral allopurinol has been effective in treating ARPC.\(^6\) We report a case of a 36-year-old pregnant woman diagnosed with ARPC successfully treated with allopurinol after delivery.

**Case Report**

A 36-year-old female patient, G4P3A1, came to the outpatient department of dermatology with the complaint of itchy skin lesions on the trunk and four limbs for 2 months. The lesions appeared in the third trimester at 36 weeks of her gestational age. Intense pruritus caused her sleeping disturbance. She had been treated with oral antihistamine and topical steroid in the beginning, but her symptoms did not improve. After delivery, the lesions persisted with severe pruritus. Thus, the patient was referred to our outpatient department for an expert opinion. There was no history of associated renal disease or diabetes mellitus. The patient neither had endocrinal disease nor carcinoma. No other autoimmune disease history was revealed. Physical examination showed multiple, discrete, hyperkeratotic erythematous papules with central plug and excoriations at the trunk and four limbs [Figure 1a]. Few umbilicated lesions were also present. Koebner phenomenon was not observed. Differential diagnoses including prurigo nodularis, other perforating dermatoses, lichen planus, perforating pseudoxanthoma elasticum, hyperkeratosis lenticularis perstans (Flegel’s disease), and perforating granuloma annulare were considered. Our patient met all three components of Faver’s diagnostic criteria for ARPC. The laboratory data revealed normal liver and renal function (serum glutamic-pyruvic transaminases: 12 IU/L, serum creatinine: 0.69 mg/dl, and glomerular filtration rate: 105.47 ml/min/1.73 m\(^2\)). The fasting blood glucose level was 77 mg/dl and the oral glucose tolerance test performed in the third trimester revealed normal results. There was no evidence of gestational diabetes mellitus. Incisional skin biopsy was performed, and histology report showed crater with crust and connective tissue fibers undergoing transepidermal elimination at the ulcer based on hematoxylin and eosin stain [Figure 1b]. The base of crater showed breach in continuity of the epidermis. Adjacent epidermis was thickened with compact hyperkeratosis. On Masson’s trichrome stain, the vertically oriented collagen fibers were evident. Elastic fibers were not present in transepidermal elimination process on Verhoeff-van Gieson stain. The diagnosis of pregnancy-induced acquired perforating reactive collagenosis was confirmed on patient’s history, clinical and histopathological findings. We discussed the treatment options and their outcomes with the patient. The oral allopurinol treatment was chosen by the patient. We performed the HLA-B5801 screening test, and the result was negative. It is important to screen HLA-B5801 before initiating allopurinol treatment. We discontinued the treatment after 1 month. The outpatient department follow-up showed brownish scaling macules and papules at previous lesion sites. Few superficial scar marks were observed on previous umbilicated lesions. Postinflammatory hyperpigmentation was found on flattened lesions. The life quality of the patient was greatly improved. The patient was satisfied with the treatment. Six months after discontinuing the treatment, no recurrence of the disease was documented.

**Discussion**

Mehregan et al. described reactive perforating collagenosis in 1967.\(^7\) The specific term “acquired perforating collagenosis (APC)” was first described in 1988.\(^8\) The year later, Rapini et al. defined the term “acquired perforating dematosis” for perforating skin disorders in adult patients with systemic diseases.\(^9\) ARPC is a rare dermatological condition which is very difficult to treat.

Faver’s diagnostic criteria for ARPC are as follow (a) umbilicated papules or nodules with central keratotic plug, (b) elimination of necrotic basophilic collagen fibers into an epidermal depression, and (c) disease onset after the age of 18 years.\(^10\)

Lesions of ARPC are classified into two groups, early and late, depending on the evolution of the disease process. Early lesions are small pinhead-sized papules, mostly hyperkeratotic and enlarge to become umbilicated and crusted lesions. Ulcerated lesions are seen at the late stage of ARPC. The disease course is often regressing and relapsing for a few weeks. Postinflammatory hyperpigmentation and scar are found in the regressive stage of ARPC. Histologically, early lesions present as basophilic collagen in dermal papilla while late lesions as a keratin plug in dermal depression with hyperkeratosis and inflammatory fragments.\(^11\)

As ARPC is associated with underlying systemic diseases, different hypotheses regarding pathogenesis have been mentioned. The pathogenesis of ARPC is still under...
investigation. Etiology varies from infectious focus to several underlying diseases including malignancy. Hepatitis C virus infection is also mentioned as one of the etiological factors in ARPC. In inherited form, trauma-induced dermal collagen damage in genetically susceptible patients can be the proposed mechanism. In acquired form, an underlying disease may be initiating an altered collagen response leading to its transepidermal elimination. Metabolic changes occurring in diseases such as diabetes mellitus, renal failure, and liver disease may be responsible for the presentation of an acquired form of ARPC. Recent study using immunofluorescence stains revealed the presence of collagens Type IV and Type VII within the keratin plug. Immunohistochemical and ultrastructural studies have shown that the extruded collagen is normal. Collagen Type IV elicits an immune response, leading to its elimination through the epidermis once the epidermis reaches to normal maturation stage. Transforming growth factor beta 3 (TGFβ3) plays a crucial role in connective tissue metabolism and wound healing. Overexpression of TGFβ3 is noted in cup-shaped invagination of ARPC histopathological lesion sites. Leukocyte infiltration found in lesions secretes interleukin-1 which stimulates synthesis of metalloproteinases and thus degrading the components of extracellular matrix including collagen fibers.

Confusing terms for acquired perforating dermatoses have been used in the past. The clinical and histopathological features sometimes may overlap between two diseases of the main spectrum of perforating dermatoses. In this article, we have used more specific term “ARPC” to describe the disease process. In English literature, only two cases of APC in pregnancy have been reported to date [Table 1]. The onset of APC in the previously reported cases was both in the third trimester, same as our case. Healy et al. reported the APC case in pregnancy which coexisted with polymorphic eruption of pregnancy. The second case reported in 2014 was a case of ARPC in pregnancy with urticarial vasculitis. Treatment with allopurinol was not described in any of these previous reports. Our case is unique for its presentation in pregnancy without any associated systemic or dermatological diseases and successful treatment with allopurinol. Our case had no other pruritic disease or any kind of vasculitis. There was no overlap with other perforating disorders. As there was no previous stimulus for scratching or diabetes-induced microangiopathy, the mechanism of pregnancy inducing ARPC in our case remains unclear. Perhaps by collecting more similar cases in the future would give us a better view of the disease process.

Several treatments for APC have been mentioned in the literature. No standard treatment is available due to the rarity of the dermatosis. The most commonly used treatment options are topical and intralesional steroids, topical retinoids, and antihistamines. Other treatments include oral retinoids, doxycycline, rifampicin, ultraviolet B phototherapy, psoralen ultraviolet A (PUVA), allopurinol, liquid nitrogen cryotherapy, keratolytics, methotrexate, and transcutaneous electrical nerve stimulation. PUVA therapy works by directly acting on fibroblast and damaged collagen. Retinoids are effective in treating hyperkeratosis, and it acts on dermal fibroblast and collagen as well. These might be the mechanisms making PUVA and retinoids effective in some cases of ARPC. The outcome of the treatment usually depends on treating the underlying systemic disorder. In the past two decades, oral allopurinol has proven its efficacy in treating ARPC. Allopurinol inhibits xanthine oxidase enzyme and thereby reducing oxygen free radicals which cause collagen damage. This drug may also have an antioxidative effect by inhibiting collagen cross-linking through advanced glycation end products formed in diabetes mellitus patients. The different treatment regimen had been applied in previous cases, ranging from 50 mg/day to 300 mg/day. In our case, the mechanism responsible for positive response to allopurinol is not understood clearly. However, therapeutic effectiveness of allopurinol should be balanced against potential adverse drug reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Therefore, screening with HLA-B5801 is important to minimize the risk of adverse effects. To the best of our knowledge, this is the first case treating ARPC with allopurinol after pregnancy. The US Food and Drug Administration pregnancy category of allopurinol is class C, the same as the steroid or oral retinoid. By carefully following the laboratory data and HLA-B5801 test screening, allopurinol...
may be an effective treatment option for ARPC induced by pregnancy when conventional treatment is ineffective.

**Ethical statement**
This study was exempted from Institutional Review Board at our institution (China Medical University Hospital, Taichung, Taiwan).

**Declaration of patient consent**
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**
There are no conflicts of interest.

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