

Elastosis Perforans Serpiginosa: a D-penicillamine induced dermatoses in a patient with Wilson's disease

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ABSTRACT

Long term use of D-penicillamine for Wilson's disease can be associated with many adverse reactions and systemic side effects. We report the case of a 28-year-old male patient diagnosed with Wilson's disease presenting with a serpiginous raised violaceous skin lesion in the anterior aspect of the neck over the last six months and two small papules with central umbilication during the last month. Histopathological examination of skin lesions demonstrated transepidermal perforating channel, and the Verhoeff's-van Gieson stain showed marked increase number of irregular serrated elastic fibers suggesting the diagnosis of D- penicillamine induced elastosis perforans serpiginosa.

Keywords

Skin Diseases; Biopsy; Elastic tissue.

INTRODUCTION

D-penicillamine (DPA) therapy is the mainstay of chelation therapy for patients of Wilson's disease (WD). Various systemic adverse effects, including many dermatological manifestations, may be observed with prolonged use of this drug. The dermatological side effects of DPA can be of three types; (i) acute hypersensitivity reaction, (ii) bullous and (iii) degenerative dermatoses.¹ DPA induced dermatoses consist mainly of cutis laxa, anetoderma, pseudoxanthoma elasticum (PXE), elastosis perforans serpiginosa (EPS), ecchymoses, and lymphangiectasis.² EPS is a sporadic adverse effect resulted from a long term DPA therapy in WD and is considered as the premonitory sign to a severe systemic complication which warrants a quick diagnosis for appropriate treatment. Here we report a case of WD, which was on long-term medical treatment with DPA and presented with a dermatological lesion, which histopathologic examination confirmed to be EPS.

CASE REPORT

A 28-year-male diagnosed with WD on oral DPA therapy (250 mg thrice daily) for the last 18 years presented with serpiginous raised violaceous skin lesions in the anterior aspect of neck over the last six months and two small papules with central umbilication for one month (Figure 1).

Incisional biopsy was taken from one of the papular lesion for histopathological examination, which showed a curved trans-epidermal channel perforating through the epidermis containing eosinophilic bands and granular basophilic debris mixed with scant mononuclear inflammatory infiltrate. Adjacent epidermis showed acanthosis, mild parakeratosis, and presence of a hair follicle at the base of the channel. (Figure 2A) The surrounding tissue showed mild to moderate chronic inflammatory infiltrate along with very few multinucleated foreign-body type giant cells. (Figure 2B) Verhoeff's-van Gieson stain demonstrates

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coarse and tortuous fibers indicating elastic fibers in the trans-epidermal channel (Figure 2C). On higher magnification, there is the presence of characteristic multiple serrations and buds arising perpendicularly from the elastic fibers, so-called 'bramble-bush' or

'lumpy-bumpy' elastic fibers. (Figure 2D) Based on the history of long-term administration of DPA, clinical and classical histological findings, a diagnosis of EPS was rendered. Local application of 0.1% tretinoin microsphere gel was advised. The lesions are found to be improved after one month of follow-up.



Figure 1. Serpiginous raised violaceous skin lesion in the anterior aspect of the neck.

DISCUSSION

Perforating dermatoses are a group of disorders characterized by the elimination of the dermal connective tissue through the epidermis, resulting in perforation of the skin. They have classically been divided into four types: Elastosis Perforans Serpiginosa, reactive perforating collagenosis, perforating folliculitis, and acquired perforating dermatosis (Kyrle's disease).

EPS is a rare perforating dermatosis due to transdermal elimination of dermal elastic fibers. The lesions of EPS are classically presented as hyperkeratotic papules of 2 to 5 mm sizes, on the

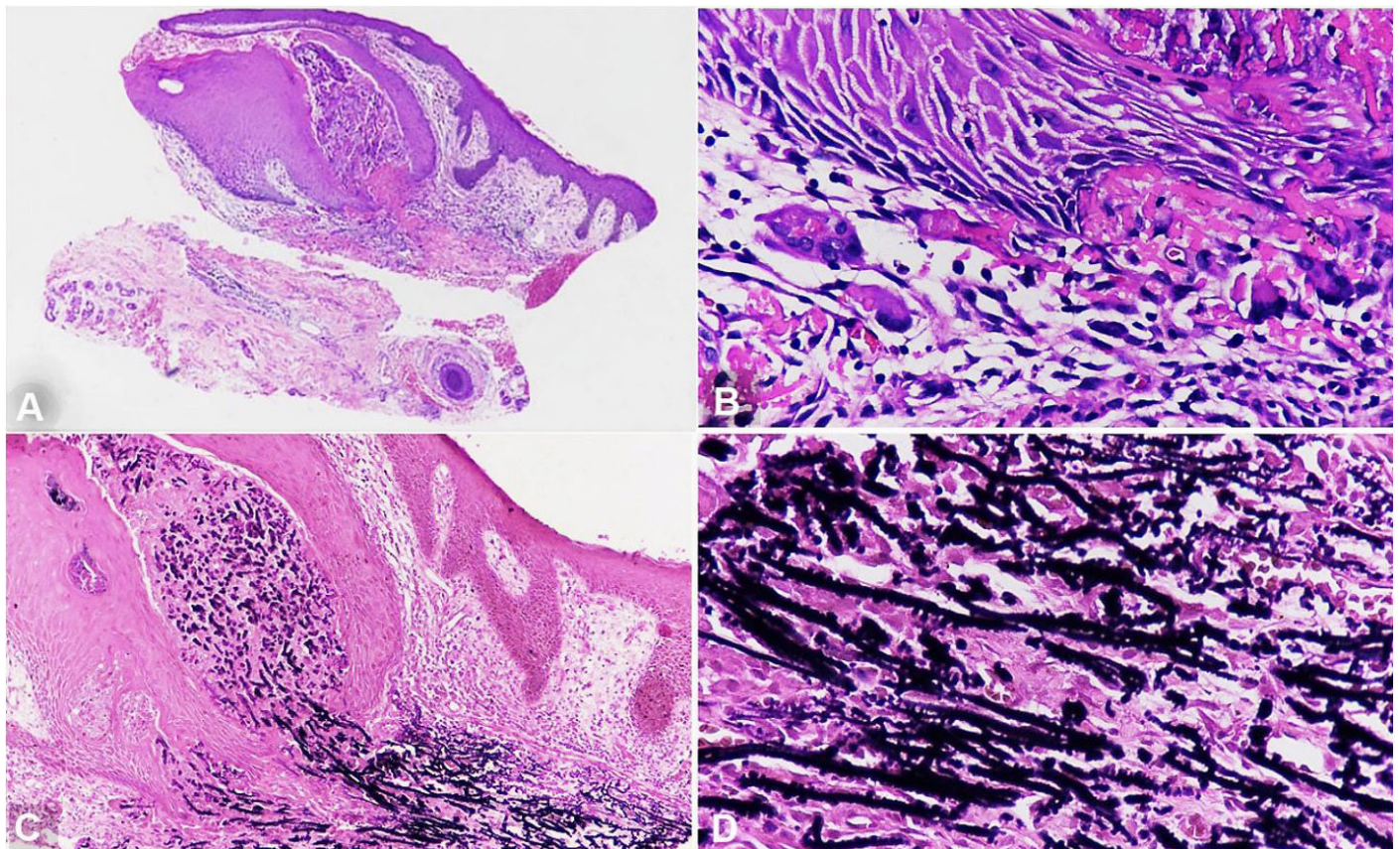


Figure 2. Photomicrographs of the skin. **A** – Curved trans-epidermal channel perforating through epidermis containing eosinophilic bands and granular basophilic debris (H&E, x40); **B** – Mild to moderate chronic inflammation along with very few multinucleated foreign body type giant cells (H&E, x400); **C** – Coarse, tortuous fibers indicating elastic fibers in the trans-epidermal channel (Verhoeff's-van Gieson, x100); **D** – Multiple serrations and buds arising perpendicularly from the elastic fibers; 'bramble-bush' appearance (Verhoeff's-van Gieson, x400).

neck, face, arms, or flexural areas of the body with specific serpiginous or annular pattern. The exact etiopathogenesis of EPS remains enigmatic. EPS are usually associated with various underlying connective tissue disorders - Down's syndrome, osteogenesis imperfecta, scleroderma, acrogeria, Ehlers-Danlos syndrome type IV, Marfan syndrome, Rothmund-Thomson syndrome, cutis laxa, and some systemic conditions like diabetes mellitus and chronic renal failure.^{3,4}

Acquired EPS associated with long term DPA therapy is a rare perforating dermatosis. DPA is a commonly used drug for WD, cystinuria, and rheumatoid arthritis.⁵ Patients of WD mostly remain on long term DPA therapy, and around 20-33% of them are reported to present any dermatopathy.⁶

In the literature, less than twenty cases of EPS have been reported associated with WD treated with DPA with characteristic skin lesions confirmed with histopathology. EPS is mainly seen in male patients, mostly found in the neck, followed by the axilla and the arm. Glans penis involvement was seen in only three cases. The duration of the DPA therapy to initiate the skin lesion ranges from a minimum of five years to a maximum of twenty-nine years. The exact mechanism of penicillamine disrupts the elastin is not well-understood. One of the proposed mechanisms is the inhibition of the copper-dependent enzyme lysyl-oxidase that is required for the elastic and collagen fibers crosslinking. Penicillamine indirectly inhibits this enzyme by removing the copper and causes abnormal elastic fiber accumulation.⁷ Another mechanism is the direct drug inhibition of the deamination of the lysine residues that are necessary for the elastin maturation.⁸ The pathophysiology of penicillamine-induced EPS is due to a decrease in the synthesis of elastic fibers in the upper dermis and an over-proliferative state in the mid dermis with a characteristic appearance described as 'bramble bush'.⁹ These abnormal elastic fibers act as foreign bodies and induce the epidermal response. The epidermis then envelops the irritating material and eliminates it through trans-epidermal channels. Another possible mechanism was proposed by Ramírez-Bellver et al.¹⁰ based on dermoscopy and immunofluorescence findings in EPS, immune-mediated opsonization of the abnormal elastic fibers. Linear and granular deposits of IgG attached to the abnormal elastic fibers in association with typical skin findings support the role of immune-mediated pathogenesis

of EPS. However, a greater number of cases with both dermoscopy and immunofluorescence findings are advised to support the above hypothesis.

Prolonged administration of a high dose of DPA may result in EPS, which can be easily differentiated from that of primary and reactive forms of EPS. In reactive EPS, the elastic fibers are described as clumped, curly, frayed, fragmented, thickened, and granular.¹¹ Besides a rare entity, it is often misdiagnosed in the clinical practice, and the patient may present with scarring and dermatological disfigurement.¹²

EPS can be a premonitory visible side effect if undiagnosed can lead to lethal systemic complications. Therefore, a close follow-up is warranted in the patients on long term DPA therapy, and alternative treatment modalities may be tried for the primary disease.

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