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CASE REPORT

# D-Penicillamine induced elastosis perforans serpiginosa with involvement of glans penis

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ABSTRACT

Elastosis perforans serpiginosa (EPS) is an unusual perforating disorder characterized by extrusion of altered elastic fibers through the epidermis. Clinically, it presents as keratotic papules with a tendency for serpiginous or annular distribution that most commonly involves the sides of the neck and the back. However, involvement of the penis has rarely been reported. We present a case of EPS involving the neck, axilla, and glans penis in a 42-year-old man who had received long-term D-penicillamine treatment for Wilson disease. Skin biopsy revealed perforating channels containing numerous altered elastic fibers, with a characteristic "bramble brush" or "lumpy-bumpy" appearance as demonstrated by an elastin stain. The latter is thought to be pathognomonic for penicillamine-induced degenerative elastosis. These degenerative changes occurring in glans penis have rarely been described in the literature. Prompt recognition of the rare presentation could lead to early discontinuation of the offending drug, to prevent further sequelae.



## Introduction

Elastosis perforans serpiginosa (EPS) is recognized as one of the four classical primary perforating disorders, along with reactive perforating collagenosis, perforating folliculitis, and Kyrle disease. It is known to occur in association with other systemic diseases, particularly inherited connective tissue disorders such as Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, or Marfan syndrome.[1] It is also a well-recognized potential complication of long-term D-penicillamine therapy. Here, we present a case illustrating the typical histological findings of D-penicillamine-induced EPS, including characteristic "bramble brush" or "lumpy-bumpy" alterations of elastic fibers, with an extremely rare clinical presentation involving the glans penis. The skin eruptions of our case developed on the glans penis initially without typical annular or serpiginous configuration, which could make it difficult to diagnosis accurately. Our case highlights that EPS should be considered as a differential diagnosis at this site.

## Case report

A 42-year-old male patient presented to our dermatology department with a history of progressive, slightly itchy skin eruptions initially on the glans penis, then spreading to neck and axilla during the previous 2 months. He had been diagnosed with Wilson disease when he was 26 years old and had received long-term treatment with D-penicillamine (600 mg, three-times daily) for more than 16 years. Physical examination revealed erythematous to dusky red keratotic papules, that had a tendency to coalesce into annular and serpiginous plaques, with a central clearing on both sides of the neck and axillary areas (Figure 1A and B). There were also several discrete erythematous papules with central keratotic plugs on the glans penis (Figure 1C and D). Skin biopsy from the axilla and glans penis revealed a localized area of irregular acanthosis with broadened rete ridges and epidermal invagination surrounding basophilic inflammatory debris and eosinophilic material that formed configuring perforating channels (Figure 2A and B). At a higher magnification, degenerated cells, mixed inflammatory cells, and inflammatory debris with an accumulation of eosinophilic fragmented fibers at the base of channels, could be seen in the perforating channels (Figure 2C and D). An elastin stain showed numerous irregular, coarse, and fragmented elastic fibers within the channels (Figure 2E). At a higher magnification, multiple

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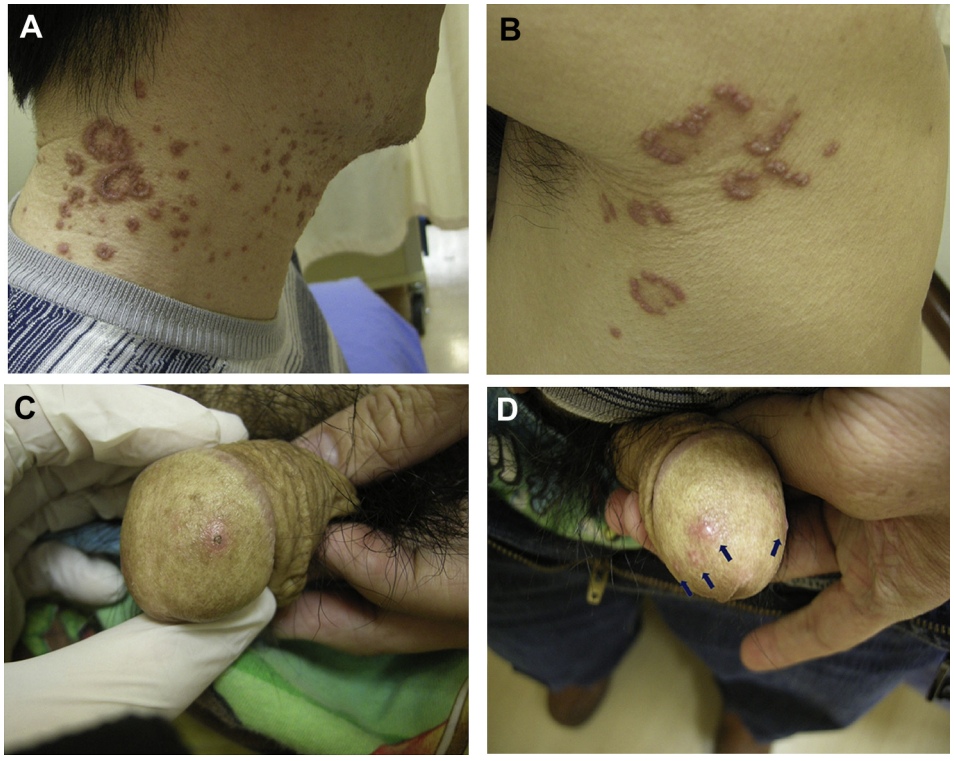


**Figure 1** (A) Erythematous to dusky red keratotic papules coalescing to form annular or serpiginous plaques with a central clearing on both sides of the neck occurred in this 42-year-old man. The patient had been on long-term treatment with D-penicillamine for Wilson disease; (B) serpiginous plaques with a central clearing and atrophy near the axilla were observed in the same patient; and (C, D) several erythematous papules with central keratotic plugs were seen on the glans penis of the same patient (arrow).

serrations and buds arising perpendicularly from the surface of the irregular elastic fibers, producing a characteristic "bramble brush" or "lumpy-bumpy" appearance, were observed (Figure 2F).

According to the clinical observations and histological findings, a diagnosis of D-penicillamine-induced EPS was made. We initially administered topical tazarotene gel, but the patient could not tolerate the side effects that included peeling and irritation. He was further treated with cryotherapy. Although some of the previous lesions showed partial regression after treatment, some continued to progress. After consulting with the patient's neurologist, we substituted trientine dihydrochloride for D-penicillamine to control the symptoms of Wilson disease. The skin lesions stopped progressing, leaving central atrophic scars during a 1-year follow-up (Figure 3A and B).

## Discussion

EPS is a rare perforating dermatosis characterized by transepidermal elimination of altered elastic fibers. These conditions are characterized by the clinical presentation of hyperkeratotic papules that occur in a serpiginous arrangement, with the microscopic characteristic of transepidermal elimination of abnormal elastic fibers. It is a rare disorder that mainly affects adolescents or young adults, with a 4:1 male predominance.[2] It has traditionally been classified into the following three subtypes: idiopathic; secondary to treatment with D-penicillamine; or associated with other systemic, inherited, fibrous tissue abnormalities such as Down syndrome, Marfan syndrome, acrogeria, pseudoxanthoma elasticum, osteogenesis imperfecta, Rothmund-Thomson syndrome, Ehlers-Danlos syndrome, or scleroderma. Once the diagnosis of EPS is made, the clinician should investigate the possibility of comorbid states or penicillamine therapy. Some experts recommend ophthalmologic examination and cardiac echocardiography, whereas others defer such investigations beyond a thorough patient history and physical examination.[1]

The exact cause of EPS is unknown, but it has been suggested that the primary abnormality is possibly in the dermal elastin, which provokes a cellular response leading to the extrusion of abnormal elastic tissue.[3] Fujimoto et al demonstrated that elastin could be a potent inducer of migration and terminal differentiation of cultured keratinocytes, mediated by the 67 kDa elastin receptor.[4] The receptor is abundantly expressed in the active peripheral keratotic area of EPS and appears to be related to the elastic fiber content in the dermal material.[5] It has been postulated that the elastin-keratinocyte interaction, mediated by the elastin receptors, plays an important role in the transepidermal elimination of elastin, inducing EPS.

D-Penicillamine has been used as one of chelating agents and disease modifying antirheumatic drugs in the treatment of Wilson disease, cystinuria, rheumatoid arthritis, and scleroderma.[6] The most common adverse effects of D-penicillamine are cutaneous, occurring in approximately 25–50% of patients. These adverse effects can be classified into four groups based on the induction mechanism, including: (1) interference with collagen and elastin such as pseudoxanthoma elasticum, cutis laxa, and mucosal elastosis; (2) acute sensitivity reactions such as urticaria and exanthematous drug-induced eruption; (3) autoimmune mechanisms such as bullous and lupus-like reactions; and (4) miscellaneous dermatoses that result from undefined mechanisms.[7,8] The postulated mechanisms relevant to collagen and elastic fibers include: (1) direct inhibition of collagen synthesis, a well-known effect of D-penicillamine for the treatment of scleroderma that further interferes with elastic fiber cross-linking; and (2) copper deficiency secondary to D-penicillamine treatment at higher doses, that impairs the lysyl oxidase activity on elastic fiber desmosine cross-linking, a crucial process in fiber stabilization.[7,9] Accordingly, the