Elastosis Perforans Serpiginosa Secondary to D-Penicillamine Therapy With Coexisting Cutis Laxa

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Elastosis perforans serpiginosa (EPS) is a rare complication of D-penicillamine therapy. EPS has been reported in patients with Wilson disease, cystinuria, and rheumatoid arthritis after many years of high-dose therapy. We report a case of D-penicillamine–induced EPS with coexisting acquired cutis laxa in a patient with cystinuria. Although both EPS and acquired cutis laxa can be associated with D-penicillamine therapy, few cases have been reported with overlapping clinical presentations, and previously only in patients with Wilson disease. We review the characteristic clinical and histologic features of EPS and discuss the potential dermatologic manifestations of D-penicillamine therapy.

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Case Report

A 59-year-old white woman with cystinuria diagnosed at 20 years of age who had been on D-penicillamine therapy for more than 25 years, developed acquired cutis laxa a few years after starting therapy (Figure 1). The loose skin folds were asymptomatic over the years, but recently she reported symptoms of dysphagia and was found to have pulmonary fibrosis. She denied a history of joint involvement or cardiac symptoms. The patient developed inoperable kidney stones with worsening renal function (attributed to her cystinuria) and was placed on hemodialysis 6 months prior to presentation.

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The authors report no conflict of interest.

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The patient presented to dermatology with a new onset eruption involving the back, axillae, chest, upper arms, and legs bilaterally. She stated this eruption was sensitive to touch and contact with clothing. Findings from a physical examination showed loose hyperextensible skin on the trunk and extremities with overlying grouped keratotic erythematous papules arranged in a serpiginous pattern (Figure 2). Results of a 3-mm punch biopsy revealed short, thick, eosinophilic fibers with transepidermal elimination of elastin (Figure 3). The Verhoeff-van Gieson stain highlighted elastic fibers with nodular protrusions, giving a "zipperlike" pattern throughout the dermis (Figure 4). Foreign body–type giant cell reaction to the elastic fiber was present.

The patient's history and clinical and histologic findings supported the final diagnosis of elastosis perforans serpiginosa (EPS) secondary to D-penicillamine therapy with coexisting acquired cutis laxa. D-penicillamine therapy was discontinued. At the patient's request, conservative therapy was started with topical corticosteroids and antibiotics with dressings to open wound areas. However, her EPS has continued to progress, with skin breakdown on the hips and thighs leading to chronic ulcerations that currently are being managed by wound care specialists.

Comment

Elastosis Perforans Serpiginosa—EPS, one of 4 essential perforating disorders, including reactive perforating collagenosis, perforating folliculitis, and Kyrle disease, is characterized by extrusion of coarse, fragmented elastic fibers from the papillary dermis through narrow epidermal channels resulting clinically in umbilicated papules arranged in a serpiginous pattern.[1]

The primary lesions of EPS are described as discrete or grouped, flesh- to red-colored papules that form arcuate or serpiginous patterns on the skin. A central plug is seen that, if removed, can result in bleeding. Distribution is primarily on the face,

Figure not available online

Figure 1. Loose skin folding associated with acquired cutis laxa.

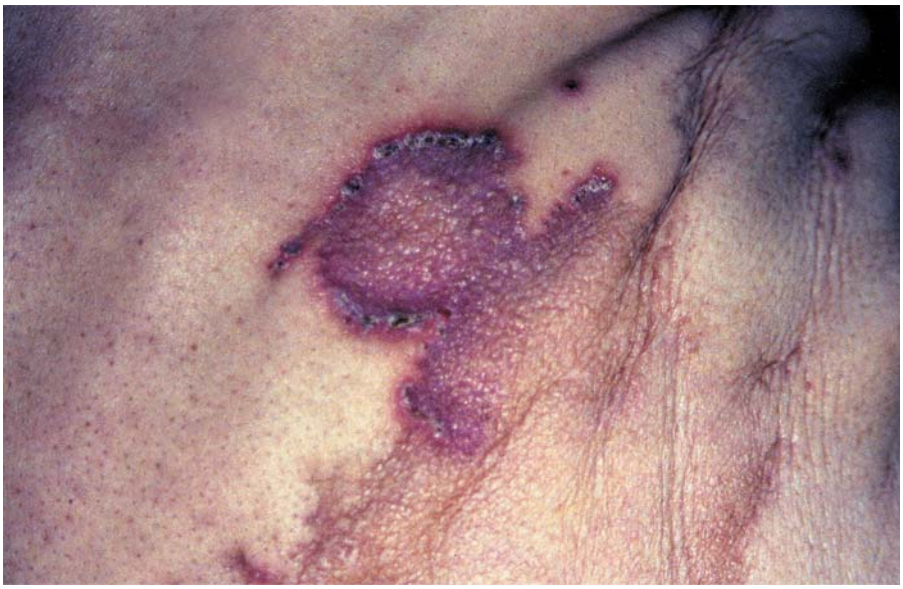

Figure 2. Serpiginous papules of elastosis perforans serpiginosa on the upper back of a patient with acquired cutis laxa.

neck, upper trunk, and extremities and is sometimes strikingly symmetrical. Although the clinical features of EPS are quite distinct, the differential diagnosis includes granuloma annulare, tinea corporis, sarcoidosis, porokeratosis, and the above-mentioned perforating disorders.[1]

The classic histologic changes to elastin associated with D-penicillamine therapy have been described as "lumpy-bumpy," "saw-toothed," or "bramble-bushlike" changes to thickened dermal elastic fibers. These changes, which can be seen with hematoxylin-eosin (H&E) stain, accentuated by Verhoeff-van Gieson elastic stain, or imaged by electron microscopy, are distinctive and specific for the D-penicillamine–induced variety of EPS.[2] Doses of 1 g daily for more than 5 years have been suggested as the likely dose/duration prior to displaying these "classic" histologic changes.[3]

The precise mechanism of D-penicillamine–induced EPS is unclear. The drug has been shown to directly inhibit cross-linking of elastin, resulting in the deposition of abnormal elastin fibers. At higher doses, D-penicillamine also chelates copper, thereby indirectly inhibiting the action of lysyl oxidase, a copper-dependent enzyme required for cross-linking collagen and elastin fibers.[2,4] Supporting this theory, reports show that experimentally induced copper deficiency has led to production of structurally and functionally deranged elastin.[1,5] Excessive buildup of abnormal elastic fiber promotes foreign body–type reaction and transepidermal elimination manifesting clinically as EPS. Considering both the rarity of EPS (even in the presence of long-term D-penicillamine therapy) and the absence of EPS in copper-deficient patients with Menkes syndrome (kinky-hair disease), additional unidentified

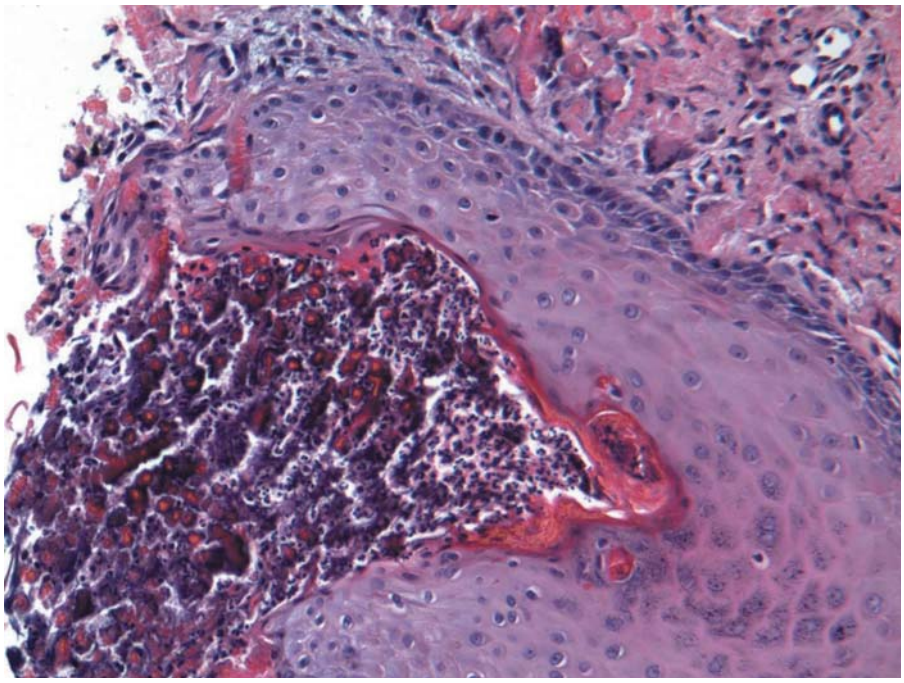

Figure 3. Lesional biopsy of elastosis perforans serpiginosa showing epidermal hyperplasia with transepidermal elimination of elastin (H&E, original magnification ×100).

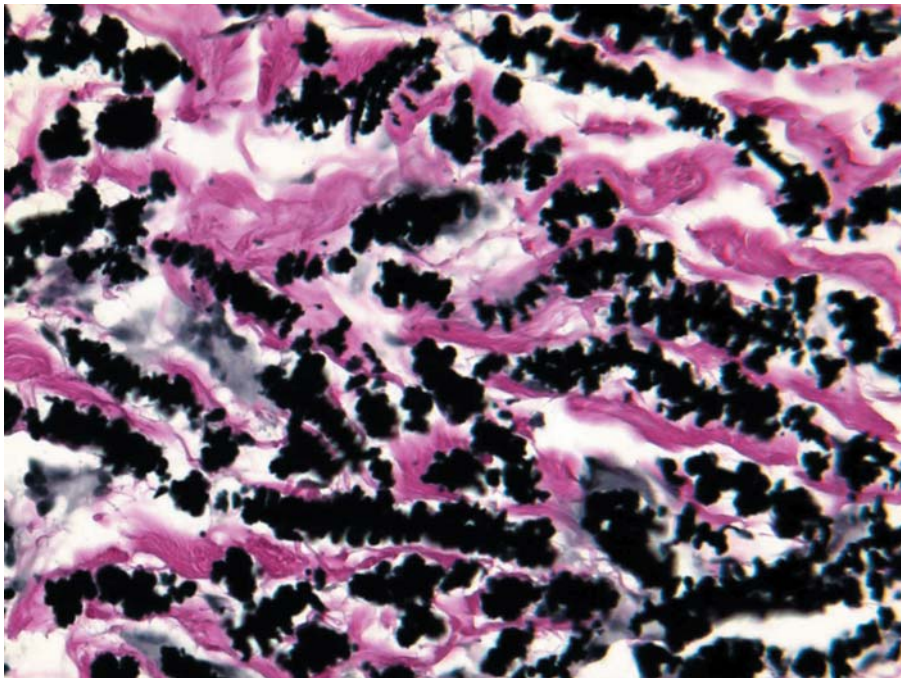

Figure 4. Elastic fibers exhibiting the classic "lumpy-bumpy" or "zipperlike" nodular protrusions associated with penicillamine-induced elastosis perforans serpiginosa (Verhoeff-van Gieson stain, original magnification ×400).

factors besides the effects of D-penicillamine are likely needed to cause EPS to manifest.[1]

Development of EPS, though rare, is well described in cases of Wilson disease and is presumably due to the longer treatment courses and the higher doses of D-penicillamine required. Even fewer reports exist documenting the coexistence of EPS and acquired cutis laxa, with both cases occurring in patients receiving treatment for Wilson disease.[6,7] To our knowledge, we report the first case of D-penicillamine–induced cutis laxa and EPS in a patient with cystinuria.

Therapeutic management of EPS can be challenging; only a few treatment options are reported in the literature. Successes with isotretinoin and pulsed dye laser have been reported, as well as

spontaneous resolution 36 months after cessation of D-penicillamine therapy.[8] In our case, outside of stopping D-penicillamine, the patient opted to forego systemic treatment because of existing comorbidities.

Acquired Cutis Laxa—Acquired cutis laxa is also a well-described complication of long-term D-penicillamine therapy. Defined by loose sagging skin with decreased elasticity, acquired cutis laxa occurs as a localized or generalized eruption. Inflammatory conditions (eg, urticaria, Sweet syndrome, erythema multiforme, nephrotic syndrome), hematologic disorders (eg, myeloma), Borrelia infections, and long-term D-penicillamine therapy are a few conditions associated with disease onset.[9] Proposed mechanisms include the release of activated elastases from inflammatory cells into the extracellular compartment, leading to proteolytic degradation of elastic fibers.[10] In D-penicillamine–induced cutis laxa, the drug is thought to directly and indirectly interfere with elastin cross-linking, as described with EPS, resulting in poorly stable elastic fibers and the clinical manifestations of loose sagging skin.[9]

D-Penicillamine—D-penicillamine has been used in the treatment of Wilson disease, cystinuria, and juvenile rheumatoid arthritis. Cutaneous side effects include immediate hypersensitivity reaction, pemphigus, and morphea; at higher doses, side effects include drug-induced dermatopathy, EPS, cutis laxa, and pseudoxanthoma elasticum. A comprehensive listing of adverse events associated with D-penicillamine therapy is noted in Tables 1 and 2.[11,12]

Although extracutaneous manifestations of D-penicillamine include visceral disruption of elastic fibers in the lung, aorta, and joint capsules, these reports are far outnumbered by EPS as a sole entity. Hill et al[6] reported a 36-year-old woman with EPS and acquired cutis laxa from long-term D-penicillamine therapy for Wilson disease. She also had pharyngeal and tongue weakness with ineffective cough reflex, which the authors believed represented upper respiratory involvement of D-penicillamine–induced elastolytic change.[6]

Price and Prentice[2] reported another patient with Wilson disease who received D-penicillamine

Table 1.

Adverse Reactions Associated With D-Penicillamine Therapy[11,12]

Adverse Reactions	Incidence, %
Cutaneous reactions	25–50
Gastrointestinal symptoms (anorexia, epigastric pain, nausea, vomiting, diarrhea)	17
Dysgeusia	12
Proteinuria/hematuria	6
Thrombocytopenia	4
Leukopenia	2

Table 2.

Cutaneous Adverse Reactions of D-Penicillamine Therapy Based on Induction Mechanism[12]

Induction Mechanisms	Cutaneous Manifestations
Interference with collagen and elastin	Penicillamine dermatopathy, elastosis perforans serpiginosa, excessive wrinkling, acquired cutis laxa, pseudoxanthoma elasticum
Acute sensitivity reactions	Urticaria or macular and papular eruptions
Autoimmune mechanisms	Pemphigus group, bullous pemphigoid, systemic lupus erythematosus, dermatomyositis
Unknown mechanisms	Lichen planus, psoriasiform dermatitis, seborrheic dermatitis–like eruption, alopecia, hypertrichosis, nail changes

therapy for 14 years who was found to have not only EPS but also elastolytic changes to nonlesional skin and an artery. The changes found in the artery predated the development of EPS, which they argue may suggest potential serious systemic effects from D-penicillamine prior to any attributable disease.[2] Some advocate regular histologic evaluation of normal skin to monitor for elastolytic skin changes, though these changes have not been shown to be predictable or expected.[3]

Not all patients treated with D-penicillamine develop EPS nor do all those who develop EPS have visceral involvement. It may be that risk is increased with higher doses because both reported cases with visceral change had Wilson disease—historically requiring high-dose, long-term D-penicillamine therapy. Difficulty remains in making a clear correlation due to the uncommon nature of this disease and the even less common occurrence of visceral involvement.

Conclusion

Although D-penicillamine–induced EPS is a well-known consequence of long-term therapy, the clinical presentation is considered rare. With few preexisting reports, our case of D-penicillamine–induced EPS with coexisting acquired cutis laxa in a patient with cystinuria is both notable and previously unreported. Additionally, this case highlights the multiple cutaneous manifestations associated with D-penicillamine therapy.

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