

A Case of Penicillamine-induced Dermopathy

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Abstract

Introduction: We describe an interesting patient with penicillamine-induced dermopathy. **Clinical Picture:** A 49-year-old woman presented with a 1-year history of recurrent haemorrhagic blisters, milia and purpura over both her elbows, while on long-term penicillamine therapy (1.5 g daily) for Wilson's disease. Histologically, dermal elastin fibres were markedly reduced in the affected areas, consistent with penicillamine-induced elastolysis. **Treatment and Outcome:** The patient's lesions improved significantly after reduction of her penicillamine dose to 500 mg daily. **Conclusions:** The cutaneous side effects of long-term penicillamine therapy are important to recognise as they may be associated with significant morbidity and may be markers of more ominous underlying systemic elastic fibre damage.

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Introduction

D-penicillamine is a copper chelator used primarily in Wilson's disease and cystinuria. Other long-term indications include rheumatoid arthritis, scleroderma and primary biliary cirrhosis. Its cutaneous side effects are well-documented,^{1,2} and can be classified into 4 distinct groups, namely, acute sensitivity reactions (e.g., acute urticaria), a toxic-metabolic effect on connective tissue (e.g., penicillamine-induced dermopathy, cutis laxa, elastosis perforans serpiginosa), autoimmune skin manifestations (e.g., pemphigus, lupus erythematosus and dermatomyositis) and those due to unknown mechanisms (e.g., lichen planus, hypertrichosis).

Case Report

A 49-year-old Chinese lady presented in August 2001 with a 1-year history of recurrent haemorrhagic blisters, skin fragility and easy brusability over both her elbows (Fig. 1). She has a known history of Wilson's disease diagnosed in December 1996, when she presented with increased skin pigmentation. Kayser-Fleischer rings were present on slit-lamp examination. Serum ceruloplasmin was low (0.06 O.D.; normal, 0.2 to 0.56) and 24-hour urinary copper was elevated (1.3 umol/day; normal, 0 to

1.1). Computed tomography (CT) of the abdomen showed evidence of liver cirrhosis and portal hypertension. She was started on penicillamine 1.5 g daily upon diagnosis, with good clinical and biochemical response. Her generalised pigmentation reduced significantly after 2 years. Serum albumin improved from 32 to 39 g/L and prothrombin time normalised from an initial 17 seconds (normal, 11 to 14 seconds). An approximate cumulative dose of 3.0 kg had been ingested over the past 5 years.

Clinically, there were multiple tiny white papules with underlying cutaneous atrophy and purpura noted over both elbows. No intact vesicles or bullae were seen. The rest of the cutaneous examination did not reveal any other significant abnormalities.

The initial differential diagnosis considered included penicillamine-induced dermopathy, an autoimmune or drug-induced blistering condition, such as pemphigus vulgaris, bullous pemphigoid or epidermolysis bullosa acquisita. Porphyria cutanea tarda was also considered in view of her underlying liver cirrhosis.

Skin biopsy of the left elbow showed a milium cyst containing laminated keratin, consistent with milia secondary to a healed haemorrhagic blister. Elastin Verhoeff

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van Gieson (EVG) staining showed a prominent paucity of elastic fibres in the dermis, without any calcification (Fig. 2). Periodic Acid-Schiff (PAS) staining did not show any hyaline cuffs around dermal blood vessels to suggest porphyria. Direct and indirect immunofluorescence tests were negative.

Porphyrin was not detected in the urine, stool and blood samples of the patient.

Based on a diagnosis of penicillamine-induced dermatopathy, her dose of penicillamine was reduced to 500 mg daily. A review of the patient 4 months later showed that she had improved significantly with no recurrence of the blisters over both her elbows.

Discussion

Penicillamine is well established as a first-line, life-saving therapy in the management of Wilson's disease. At high doses, penicillamine interferes with elastin and collagen metabolism which can manifest cutaneously in several ways, namely, penicillamine-induced dermatopathy, penicillamine-induced bullous dermatoses, elastosis perforans serpiginosa, excessive wrinkling and cutis laxa.^{1,2}

This case demonstrates a striking example of penicillamine-induced dermatopathy, first described by Sternleib and Scheinberg in 1964 in a patient with Wilson's disease.³ As seen in this case, it is characterised by milia, purpura, skin fragility and wrinkling of the skin, particularly over bony prominences and points of pressure such as the knees, shoulders and elbows. Similar cases of recurrent blister formation with subsequent healing with milia formation have been reported previously as well.^{4,5}

Our patient did not have other associated cutaneous manifestations of penicillamine-induced elastic tissue damage such as elastosis perforans serpiginosa, which presents as pink to red keratotic annular plaques on the neck, axillae and ante-cubital fossae.¹ More extensive skin involvement with pseudoxanthoma elasticum-like skin changes or cutis laxa were absent as well. More significantly, she did not have any signs or symptoms to suggest underlying systemic involvement. This is of crucial importance since elastic fibre damage has been shown to be restricted not only to dermal elastin, but can also affect multiple organ systems such as the upper⁶ and lower⁷ respiratory tract, joint capsules⁸ and blood vessels.⁹ A case of systemic pseudo-pseudoxanthoma elasticum affecting lungs, oesophageal muscle, gum, pharyngeal tissue and cervical connective tissue has been reported with significant associated morbidity in a patient with Wilson's disease on penicillamine 1.5 g daily for 27 years.⁷

It is noteworthy that our patient had a relatively low cumulative dose of penicillamine at presentation, which may account for her limited cutaneous involvement. The

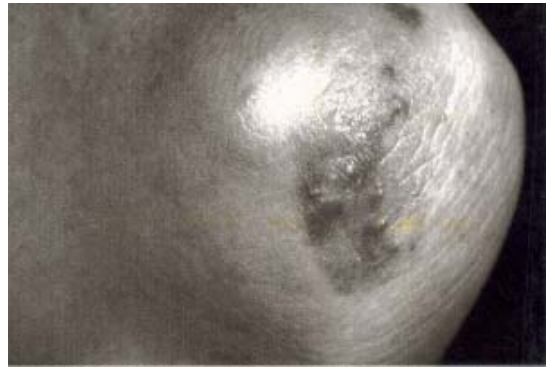


Fig. 1. Purpuric plaque with multiple milia over the patient's elbow.

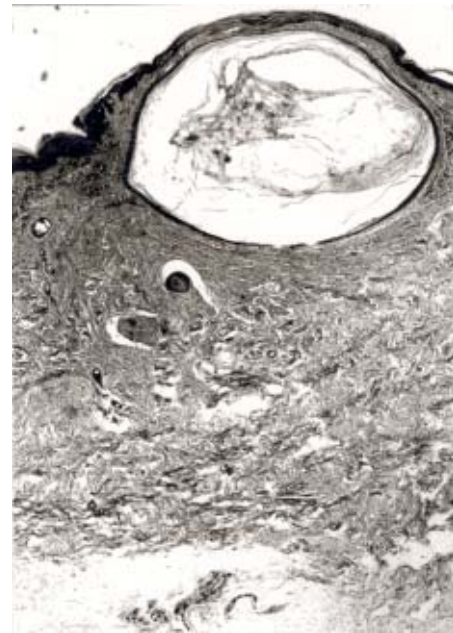


Fig. 2. Skin biopsy specimen showing a milium cyst containing laminated keratin, consistent with previously healed haemorrhagic blisters. Dermis shows a marked paucity of elastic fibres. (elastin Verhoeff van Gieson staining, magnification x100)

precise amount of penicillamine required to produce elastic fibre damage is unknown, but it has been estimated that a minimum of 1 g daily for more than 5 years is necessary to induce these changes.¹⁰ However, a study by Dalziel et al⁸ showed that elastic fibre damage occurred in patients with rheumatoid arthritis receiving low-dose penicillamine therapy (0.25 to 1 g daily), even after as little as 1 year of treatment.

It is postulated that penicillamine interferes with elastin and collagen metabolism in 2 ways. First, it can bind directly with the aldehyde precursors which are essential for elastin and collagen cross-linking and second, it can also inhibit the copper-dependent enzyme lysyl oxidase, that catalyses the cross-linking reaction.¹¹ It, however, has no effect on mature, insoluble collagen,¹² therefore explaining the long period before dermatopathy sets in.

As demonstrated in our patient, the histological findings of penicillamine-induced dermopathy include epidermal inclusions cysts and marked diminution of dermal collagen and elastic fibres.¹³ Haemorrhagic lesions also frequently show dilation of blood vessels and extravasation of erythrocytes.¹³ Another characteristic histological finding is the 'bramble-bush'¹³ or 'lumpy bumpy'¹⁴ appearance of the abnormal elastic fibres, due to small protrusions perpendicular to the long axis of each affected fibre.

Penicillamine-induced pemphigus was excluded in this case based on the negative immunohistochemical findings. Furthermore, in contrast to penicillamine-induced dermopathy, autoimmune blistering caused by penicillamine usually occurs early in the course of therapy (within 6 to 12 months), is not dose-dependent, and has been reported mainly in rheumatoid arthritis patients rather than in Wilson's disease.^{1,2}

As with most cases of penicillamine-induced dermopathy,^{1,2} our patient's lesions improved significantly with reduction of her penicillamine dose. It can be envisaged that this early intervention for our patient will help minimise further widespread penicillamine-induced elastolysis. For Wilson's disease patients with severe penicillamine-induced dermopathy or with systemic involvement, penicillamine may need to be stopped entirely and alternative treatment with agents such as zinc and trientine, will need to be considered.¹⁵

Conclusion

Prolonged use of high-dose penicillamine is associated with elastic tissue damage that can manifest in the skin as skin fragility, milia and purpura, as illustrated in this case. The early recognition of penicillamine-induced skin changes is important since these abnormalities may not be restricted only to the skin, but may be markers of more widespread, multi-systemic involvement.

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