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Photo Vignette

Penicillamine-associated cutis laxa and milia en plaque - case report and review of cutaneous changes associated with penicillamine

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Abstract

Penicillamine-induced skin changes are rare and include: hypersensitivity reactions, autoimmune reactions, and cutaneous elastoses. We report a case of a 73-year-old man with cystinuria taking penicillamine for over 50 years who presented with penicillamine-induced cutis laxa and milia en plaque. A brief review of penicillamine induced skin changes, specifically cutis laxa and milia en plaque, is presented.

Key Words: penicillamine, elastic tissue, cystinuria, cutis laxa, milia en plaque

Introduction

Penicillamine is a chelating agent commonly used to treat cystinuria and Wilson disease. Cystinuria is a genetic disorder in which patients lack the cysteine amino acid transporter. This leads to increased excretion of cysteine, which causes the formation of kidney stones [1]. Penicillamine is the treatment of choice as it combines with cysteine to form penicillamine-cysteine disulfide, which is significantly more soluble than cysteine and excreted readily. This prevents the formation of cysteine stones in the kidneys, ureter, and bladder. Additionally, penicillamine chelates excess copper, which is used to treat patients with Wilson disease. We report one case of chronic penicillamine usage that led to penicillamine induced skin changes.

Case Synopsis

A 73-year-old man with a history of cystinuria presented with accentuated skin folds on his body and plaques on his bilateral elbows and right knee. The skin laxity had been progressing for years; the plaques occurred intermittently over the past two years and had been worsening owing to trauma from gardening. The patient denied systemic symptoms including shortness of breath. Physical examination revealed thickened, redundant skin folds on his face, neck, chest, back, antecubital fossae, and peri-axillary areas (Figure 1.A and Figure 1.B).

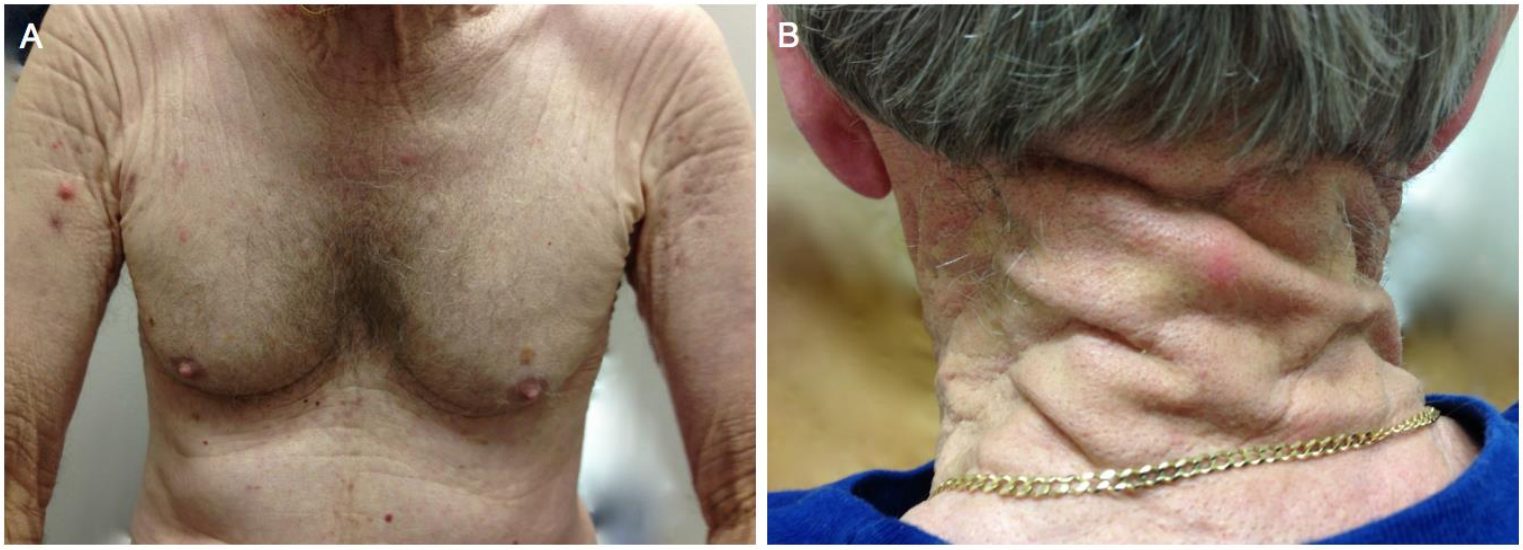


Figure 1.A. Accentuated skin folds on the patient's chest, abdomen, antecubital fossae, and peri-axillary areas. **B.** Thickened, redundant skin folds on posterior neck.

Several white and yellow subepidermal papules overlying erythematous plaques were present on his bilateral elbows and right knee (Figure 2.A). His cystinuria was well controlled with penicillamine 2000 mg daily, which he had been taking for over 50 years.

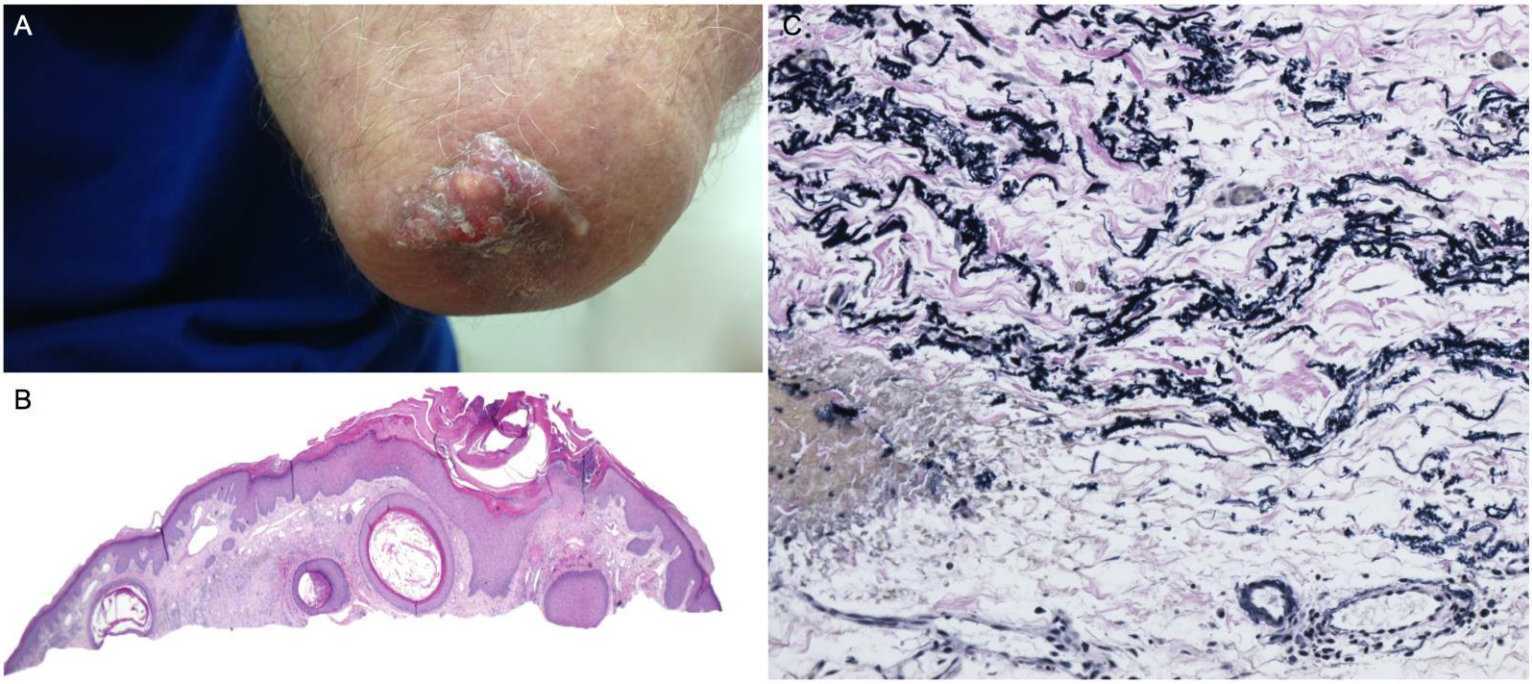
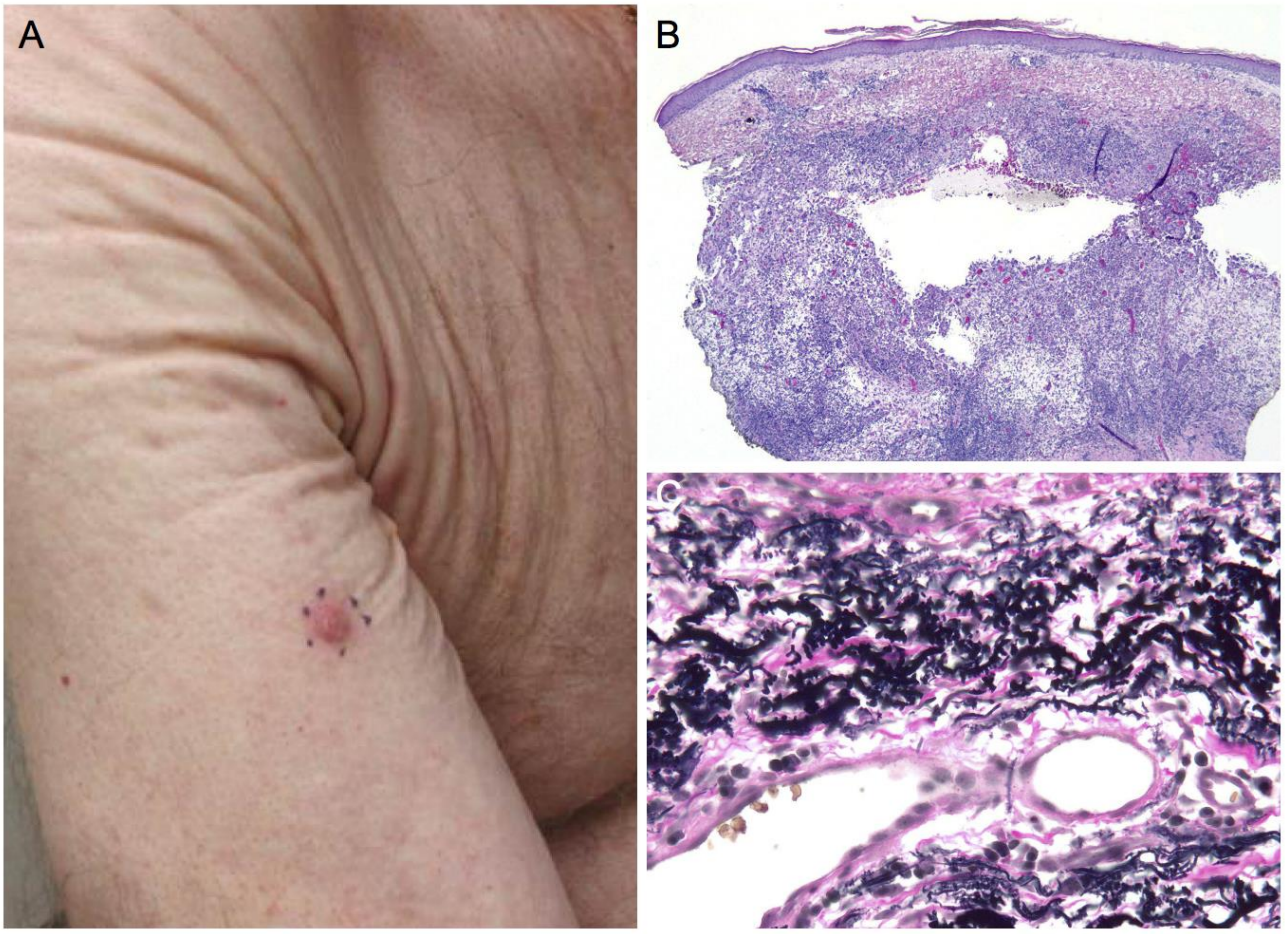


Figure 2.A. White milia overlying erythematous plaques on left elbow. **B.** Shave biopsy of the left elbow on H&E staining at 60x shows small cystic spaces with a stratified squamous epithelial lining filled with keratin. These histologic findings are consistent with small epidermoid cysts, or milia. **C.** VVG stain with 60x magnification highlights a "bramble bush" pattern of thickened elastic fibers in the dermis.

A shave biopsy of the plaque on the left elbow showed small cystic spaces with a stratified squamous epithelial lining filled with keratin. These histologic findings are consistent with small epidermoid cysts, or milia (Figure 2.B). Together with the clinical picture, these findings were consistent with milia en plaque. A punch biopsy of a pink papule of the right upper arm at an area of lax skin (Figure 3.A) showed a granulomatous infiltrate associated with fragments of keratin in the dermis, consistent with a ruptured cyst or folliculitis (Figure 3.B). The patient declined a subsequent biopsy of otherwise normal lax skin. Examination with a VVG (Verhoeff-Van Gieson) stain, which highlights elastic fibers, showed "bramble bush" elastic fibers - thick elastic fibers with lateral protrusions; these changes were seen in both the biopsy of the left elbow and right upper arm (Figure 2.C & Figure 3.C).



3.A. Erythematous papule on right upper arm in area of accentuated skin folds. B. Punch biopsy of the right upper arm on H&E stain at 4x shows granulomatous infiltrate associated with fragments of keratin in the dermis. C. VVG stain at 60x magnification shows "bramble bush" elastic fibers.

Given the patient's history of penicillamine use, clinical exam findings, and characteristic histologic findings of penicillamine-induced skin changes, the patient was diagnosed with penicillamine-induced cutis laxa and milia en plaque. The findings of folliculitis noted in the right arm biopsy were considered to be unrelated to his generalized skin findings. In collaboration with his nephrologist, the patient's penicillamine dose was reduced to 1500mg daily and his response is being monitored.

Discussion

There are three categories of dermatologic changes seen with penicillamine usage: hypersensitivity reactions, autoimmune reactions, and cutaneous elastoses.

Acute or sub-acute hypersensitivity reactions will often present with dermatological changes including urticaria or morbilliform eruptions. Within a few hours of taking penicillamine, patients can develop urticarial lesions with pruritic, erythematous plaques related to IgE mediated reactions; utricaria may also be a delayed reaction to penicillamine [2]. Within two weeks of taking penicillamine, patients can develop morbilliform cutaneous reactions characterized by erythematous macules or small papules that tend to expand in size over the course of a few days.

Autoimmune reactions including pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid have been related to penicillamine usage for over six months [3, 4]. Other autoimmune conditions including dermatomyositis and systemic lupus erythematosus can also occur secondary to penicillamine use [3, 5, 6]. These autoimmune reactions are infrequent, but their true incidence is unknown.

Chronic treatment with penicillamine, especially with high doses, can lead to dermal adverse effects in about 20% to 33% of patients [7]. Chronically, penicillamine-induced elastic skin changes result from penicillamine's effects on elastin metabolism, both directly and indirectly. Copper is a co-enzyme for lysyl oxidase, an enzyme that catalyzes the cross linking of elastin. Penicillamine prevents the cross-linking of elastin by chelating copper, thereby indirectly inhibiting lysyl oxidase [8]. Penicillamine also directly forms complexes with aldehyde moieties that prevent the cross-linking of collagen and elastin fibers [9]. Therefore, penicillamine prevents tissue maturation. Mature elastin and collagen are unaffected by penicillamine, which

explains why chronic rather than acute use of penicillamine leads to the various dermopathies. Cutaneous elastoses with chronic penicillamine use may include cutis laxa, pseudo-pseudoxanthoma elasticum, elastosis perforans serpiginosa, and anetoderma [3, 9, 10].

On histological examination with a VVG stain, penicillamine-induced dermal changes are seen as thickened elastic bundles with lateral protrusions, which have a “bramble bush” appearance [3].

Patients taking penicillamine can develop cutis laxa-like changes, which is a disorder of elastic tissue. In non-penicillamine-induced cutis laxa, elastic fibers become sparse and fragmented, which manifests as sagging skin. [3]. Drug induced cutis laxa has been reported in patients with long-term penicillamine usage [3, 8, 11]. Although it is more rare, long-term use of penicillamine has also been associated with extra-cutaneous manifestations. The lungs, upper respiratory tract, adventitia, and the aorta may be affected by the elastolytic property of penicillamine [8].

Cases of milia en plaque, purpura, and hemorrhagic vesicles at bony prominences have also been reported with penicillamine use. This is thought to relate to the degeneration of elastin, which leads to trauma-induced skin changes, such as milia, in susceptible areas of skin [10, 12].

Unfortunately, degenerative dermal changes such as cutis laxa are usually irreversible. However, one case report has reported that dosage reduction of penicillamine may improve symptoms of penicillamine-induced milia en plaque [13].

Conclusion

Penicillamine is a chelating agent used to treat cystinuria and Wilson disease. Chronic use of penicillamine affects elastin metabolism, which can lead to the development of cutaneous elastoses, including cutis laxa and milia en plaque. These changes are irreversible in most cases.

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