Penicillamine induced pseudoxanthoma elasticum with elastosis perforans serpiginosa

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ABSTRACT

Long term D-penicillamine therapy, especially when used to treat Wilson’s disease has been shown to cause elastosis perforans serpiginosa, pseudoxanthoma elasticum perforans and other degenerative dermatoses. We report a 23-year-old male patient who presented with multiple firm papules, nodules over the neck, axillae, front of elbows for five years. He was a known case of Wilson’s disease on long-term treatment with penicillamine for the past 12 years. The papulonodular lesions were non-tender and some were discrete while others were arranged in a circinate pattern. There was central scarring of the skin within the circinate lesions. In addition, there were several small yellowish papules on both sides of the neck which eventually became confluent to form plaques. Histopathology confirmed the diagnosis of elastosis perforans serpiginosa and pseudoxanthoma elasticum. He was treated with cryotherapy (using liquid nitrogen through cryojet) for former lesions. The lesions showed remarkable improvement after five sittings. Now the patient is under trientine hydrochloride (750 mg twice daily) for Wilson’s disease.

Key Words: Penicillamine, Elastosis perforans serpiginosa, Pseudoxanthoma elasticum

INTRODUCTION

D-penicillamine induced degenerative dermatoses include cutis laxa, anetoderma, pseudoxanthoma elasticum (PXE), elastosis perforans serpiginosa (EPS), ecchymoses, and lymphangiectasis. We are reporting a case of Wilson’s disease under D-penicillamine therapy for the past 12 years who developed EPS and PXE.

CASE REPORT

A 23-year-old male presented with raised skin lesions on the neck, axillae and front of elbows for five years. He was a known case of Wilson’s disease on penicillamine for the past 12 years. He developed asymptomatic raised skin lesions initially over the neck which gradually involved the axillae and frontal aspect of both elbows with increase in size and shape of the lesions. He was started on penicillamine 250 mg 5 caps daily in 1990. Skin lesions first developed in 1998 which were confirmed as elastosis perforans serpiginosa histopathologically. However, he continued the same medicine for another five years. In Jan 2002, penicillamine was replaced by zinc acetate for a short period of six weeks. Thereafter he has been on trientine hydrochloride 750 mg'day given in two divided doses. This was increased to 750 mg twice daily to bring back
the serum copper to normal level and till date maintained on the same dose. Lesions from the right axilla and left cubital fossa were excised in Aug 2002. There was history of first degree consanguineous marriage of his parents. Out of his three sisters, one died at 6 years of age due to cirrhosis, the second sister died at 2 years of age due to meningitis and the third one is healthy.

All his vitals were stable. Chest and cardiovascular examination were within normal limits. No Kayser Fleischer rings were seen on eye examination. There was no other ocular defect. Central nervous system examination revealed no extrapyramidal signs. No abnormality was present on abdominal and cardiovascular examination.

On cutaneous examination, multiple, skin colored and brownish, firm, non-tender papules and nodules were present over the front, sides and nape of the neck [Figure 1], both axillae and cubital fossae. Some were discrete while others were arranged in a circinate pattern leaving behind hypopigmentation and atrophy in the center [Figure 2]. Some nodules showed perforation with central crater and keratin plug. Postsurgical scarring with atrophy was present in the right axilla and left cubital fossa. In addition, there were a few yellowish, soft papules of size 1 to 2 mm in diameter on both sides and nape of the neck below the discrete brownish nodular lesions. These papules eventually became confluent to form plaques [Figure 1].

Haemogram and renal function tests were normal. Liver function tests showed that the levels of SGOT, SGPT, and alkaline phosphatase were raised. Chest X-ray was normal. Serum ceruloplasmin was 10 mcg/dl (20-55 mcg/dl). Serum copper was 60 mcg/dl (70-140 mcg/dl). Urinary copper (24 hr urine) was 16.2 mcg/dl (2-30 mcg/dl). Prothrombin time was 13.60 sec (11.50 control). Ultrasound of the abdomen showed mild hepatomegaly with dilated portal vein.

Skin biopsy from the nodular lesions showed acanthosis, keratotic plugs and irregular, broadened rete ridges. Keratotic plugs showed eosinophilic bands and granular basophilic debris. Basophilic changes were seen in the collagen in the dermis. Dense inflammatory reaction was seen in the subepithelial zone. Verhoeff’s elastic tissue stain showed coarse, tortuous elastic fibers in the uppermost dermis surrounding a transepidermal channel thereby confirming the
diagnosis of elastosis perforans serpiginosa [Figure 3]. In addition there was fragmentation of elastic fibers in the middle and lower third of dermis. The skin biopsy from the yellowish papular lesion revealed swollen, fragmented, faintly basophilic fibers in the middle and lower third of the dermis in H&E stain and Verhoeff’s elastic tissue stain showed irregularly clumped degenerated black elastic fibers confirming the diagnosis of PXE [Figure 4].

A diagnosis of penicillamine-induced degenerative dermatoses consisting of elastosis perforans serpiginosa, pseudoxanthoma elasticum and secondary skin scarring was made based on the clinical and histopathological findings. Our patient did not have Kayser Fleisher ring and the low serum ceruloplasmin level was due to the fact that the patient was under prolonged therapy with D-penicillamine for Wilson’s disease and now under trientine hydrochloride after receiving zinc acetate for a short period. Like D-penicillamine trientine hydrochloride is a chelating compound for removal of excess copper from the body. EPS lesions were treated with cryospray with liquid nitrogen using a double freeze-thaw cycle. The lesions showed remarkable improvement after five sittings at an interval of three weeks.

DISCUSSION

Long term administration of D-penicillamine has been shown to produce a dermatopathy in 20 to 33% of patients in addition to hematological, immunological and other organ system involvement. Elastosis perforans serpiginosa is an uncommon skin disorder characterized by transepidermal elimination of abnormal elastic fibers. There are a few reports of its familial occurrence and also in association with Down’s syndrome. There have been suggestions that induction of EPS and of localized cutis laxa by D-penicillamine may be due to a similar mechanism. It has been reported after prolonged therapy in Wilson’s disease and cystinuria. It has been also reported in a 10-year-old child with juvenile rheumatoid arthritis who received only 71 grams of the drug over 9 months.

Pseudoxanthoma elasticum is a heritable disorder characterized by progressive mineralization and fragmentation of elastic fibers in various tissues, involving skin (flexural sites), eye (angioid streaks and retinal defects) and cardiovascular system (hypertension, gastrointestinal bleeding, and vascular disease). However, long term D-penicillamine therapy was confirmed to induce biopsy proved acquired systemic PXE with dysphasia, dyspnea and cutaneous signs. Exact mechanism of inducing degenerative dermatoses by D-penicillamine was worked out by several workers. Penicillamine chelates copper and leads to its depletion. Copper is a co-factor for lysyl oxidase which is essential for elastin cross-linking. Penicillamine inhibits lysyl oxidase. It interferes directly with normal tissue maturation by binding to elastin and collagen cross-linked aldehyde precursors, and

Figure 3: Elastic fibers in the uppermost dermis surrounding a transepidermal channel (VVG stain x200)

Figure 4: Fragmented elastic fibers in mid-dermis (VVG stain x200)
forms stable thiazolidone compounds which prohibit the synthesis of sufficient cross-links of collagen and elastin fibres.\textsuperscript{[9,10]}

The pathophysiology of D-penicillamine induced EPS is due to a decrease in rate of synthesis of elastic fibers in papillary dermis but also over-proliferative state of elastic fibers occurring in mid-dermis and has a characteristic appearance similar to bramble bush.\textsuperscript{[11]}

The abnormal elastin is ultimately extruded through the epidermis. Sometimes, a total degenerative dermatoses with collagenosis appears with scar-like skin changes, thickening and wrinkling detected in flexural regions, like axillae and groins.\textsuperscript{[2]} In addition to degenerative dermatoses D-penicillamine can produce several other rare side effects including hypersensitivity reactions and bullous dermatoses.\textsuperscript{[1]} A good knowledge about side effects and their mechanism is helpful in use of this important medicine.

REFERENCES