

## Morphea-like reaction to D-penicillamine therapy

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**SUMMARY** We report the case of a 48-year-old woman who developed morphea-like plaques after 1 year of treatment with D-penicillamine at 250 mg daily for a seronegative erosive arthritis of rheumatoid type. The rash began as several red itchy patches on the trunk; these became thickened and shiny over about 3 months. The histological appearance was of increased dermal fibrosis with an inflammatory infiltrate round dermal capillaries. However, epidermal changes were not typical of morphea. New lesions ceased to appear within a few months of stopping penicillamine, and by 1 year all the plaques were pale and symptomless.

Late skin reactions to D-penicillamine are well known as a reason for withdrawing therapy. Some lesions such as increased friability, cutis laxa, and elastosis perforans serpiginosa are probably dose-related<sup>1</sup> and may be due to the lathyrogenic effect of D-penicillamine inhibiting the stabilisation of cross-links in newly formed collagen.<sup>2</sup> Indeed the drug may slow or reverse the early active skin lesions of scleroderma.<sup>3</sup>

Eczematous reactions are the commonest late rashes. Lichenoid eruptions, with dense lymphocytic infiltration in the upper dermis, are seen less often.<sup>4</sup> Bullous pemphigus, with intercellular immunoglobulin in the prickly cell layer, is probably rare, though there are several reports.<sup>5</sup> Drug-induced systemic lupus erythematosus may occur with an erythematosus rash as a feature,<sup>6,7</sup> and there may be a

linear deposit of immunoglobulin in the basement membrane. However, discoid lupus has been described only twice.<sup>8</sup>

Here we describe a patient who developed skin lesions clinically suggestive of morphea (cutaneous scleroderma), though the histology raised the question of a drug reaction. Morphea has not previously been described as a result of penicillamine therapy.

### Case history

In 1972 a 43-year-old woman with a history of mild Raynaud's phenomenon since youth developed a flexor tenosynovitis of the fingers, followed shortly by an arthritis involving wrists, shoulders, neck, metacarpophalangeal, and metatarsophalangeal joints. Rheumatoid factor test was negative with an erythrocyte sedimentation rate (ESR) of 60/h and a haemoglobin of 13 g/dl. In the first year she was treated with aloxiprin and ACTH injections, and subsequently with aloxiprin alone.

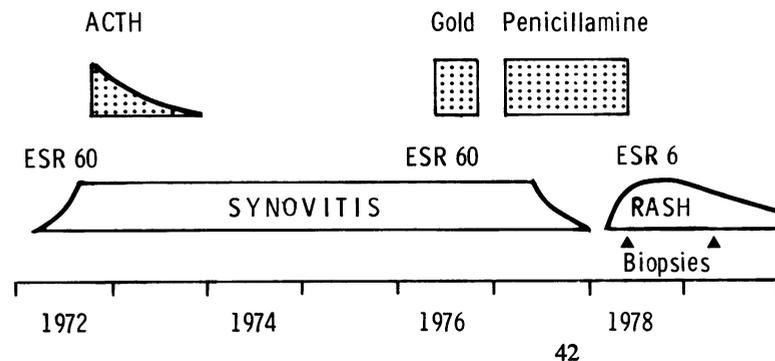


Fig. 1 Course of the arthritis and development of the rash.

Accepted for publication 15 January 1980

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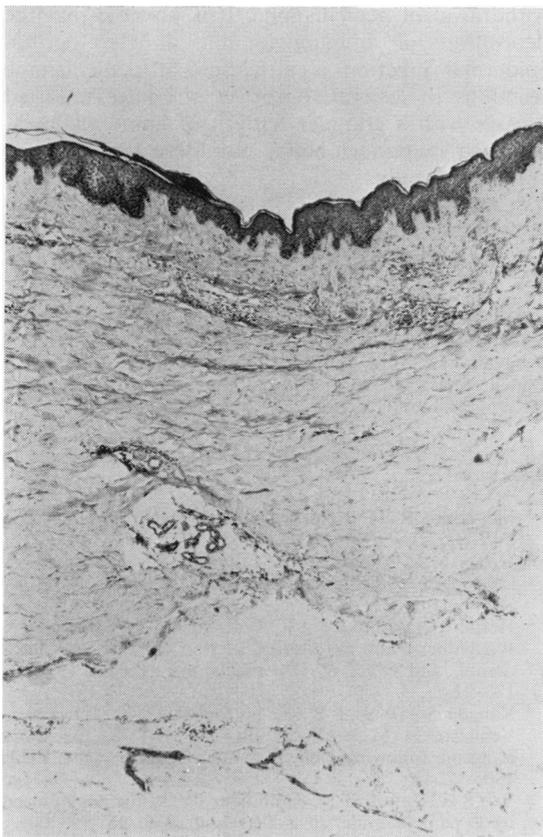


Fig. 2 First biopsy at active stage showing epidermal changes as well as dermal thickening and perivascular inflammatory infiltrate. ( $\times 7$ ).

In 1976, when she was first seen at the Canadian Red Cross Memorial Hospital, Taplow, there was synovitis of the metacarpophalangeal, proximal interphalangeal, and wrist joints, X-rays showed widespread erosions.

Gold therapy was begun but was discontinued at 600 mg when mouth ulcers developed. D-penicillamine at a dose of 250 mg daily before food was started in February 1977. At that time antinuclear antibodies were just positive at 25 units in homogeneous pattern. A marked improvement in her synovitis ensued.

After 14 months of therapy she noticed pink, itchy patches on her trunk. When she was examined in May 1978 there were several areas of erythematous, slightly excoriated skin 3–10 cm in diameter in the axillae and groins and on the breasts, abdomen, and pelvis. Some areas were thickened, shiny and pale, having the appearance of morphea (scleroderma). There was no evidence of systemic sclerosis and no joint synovitis. Blood tests showed an ESR of 6/h, antinuclear antibody 25 units as before, DNA binding normal, and antibodies to extractable nuclear antigen (ENA) were negative. Biopsy showed abnormalities in the epidermis and dermis. In the epidermis there was focal hyperkeratosis and parakeratosis, with acanthosis and spongiosis of the Malpighian layer and focal basal cell liquefaction. The papillary dermis was hyalinised and oedematous with prominent thin-walled blood vessels. Around these vessels was a moderate inflammatory infiltrate in which eosinophils were prominent. The reticular dermis showed thickening of the collagen bundles, which extended around and below the sweat glands.

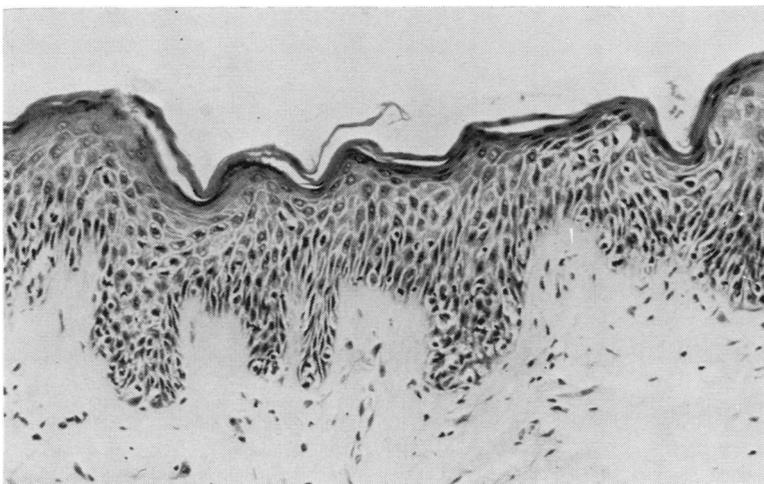


Fig. 3 First biopsy showing focal hyperkeratosis, parakeratosis, and spongiosis in the epidermis. ( $\times 43$ ).

On direct immunofluorescence there was a linear deposit of IgM at the dermoepidermal junction. Serum was negative against normal skin on indirect testing.

Because of the rash penicillamine was discontinued in May 1978. Erythematous itchy areas continued to develop for several months, but after a year all patches were pale, shiny, and thickened. A biopsy at this stage showed an atrophic epidermis with thickening of the dermis and a mild perivascular chronic inflammatory infiltrate. Atrophy of the skin appendages was not seen, and there was no linear deposit of immunoglobulin in the basement membrane.

### Discussion

Although the dose of penicillamine used was low (250 mg/day) it was associated with complete remission of the patient's synovitis. As the initial lesions were itchy, scratching may have contributed to the epidermal changes seen on histological study. The early itching suggested a lichenoid reaction, but the histology did not show the features seen in lichen sclerosis et atrophicans. The dermal changes consistent with morphea were a perivascular cellular infiltrate, hyalinisation of the upper dermis, thickening of collagen bundles in the lower dermis, and the extension of collagen around and below the sweat glands. The features suggesting a drug reaction were the epidermal changes of focal hyperkeratosis and parakeratosis with spongiosis and focal basal cell liquefaction, the predominance of eosinophils in the dermal perivascular infiltrate, the uneven diameter, of collagen bundles in the lower dermis, and the linear immunofluorescence to IgM at the dermoepidermal junction. These features were present on the initial biopsy but not 1 year after

withdrawal of penicillamine. It is possible that the deposition of immunoglobulin at the dermoepidermal junction is a feature of penicillamine reactions in general. Kirby *et al.*<sup>7</sup> have reported 4 cases with a granular pattern of immunofluorescence to immunoglobulin, but there has been no systematic study.

It is concluded that a rash reminiscent of morphea, with increased dermal collagen, may occur as a late skin reaction to D-penicillamine.

We thank Dr B. M. Ansell for advice and for permission to report this case, Dr G. Slavin and Dr A. McQueen for reviewing the histology, Mr K. Ball for immunofluorescent studies, Mrs J. Tyler for photography, and Mrs P. Spencer for typing the manuscript.

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