Elastosis Perforans Serpiginosa

by Dr A. Stevens ©

Wilson's disease itself rarely gives rise to skin problems, although patients with liver involvement may develop spider naevi or, in severe liver disease, some degree of jaundice. Most of the skin problems associated with Wilson's disease arise as a complication of the treatment.

Penicillamine, a highly effective and often life-saving drug used in the treatment of Wilson's (and also used in treating rheumatoid arthritis) is well-known to produce a range of skin rashes as a side-effect. Here I will concentrate on one particular skin disease which is rare but dramatic (and quite a mouthful to pronounce), **elastosis perforans serpiginosa** (**EPS** for short).

EPS occurs in three main circumstances:-

- it can occur spontaneously, with no obvious cause or association with other disease ("idiopathic EPS");
- it can occur in association with other disorders such as Ehlers-Danlos syndrome, Marfan syndrome and Down's syndrome;
- it can occur as a complication of some drug treatments, including penicillamine.

Fig 1 is a picture of a patient with this disorder, located on the neck, a common site. It usually presents as a cluster of small raised, often reddish, nodules about 3 - 5 mm in diameter, arranged either in a line, circle or in a wavy snake-like line. Each nodule eventually develops at its peak a pit filled with brownish crusty material. As in Fig 1, the commonest site is the back of the neck, but it can also occur on the side and front of the neck and elsewhere on the face, and occasionally on the arms. Rarely it occurs on the legs or trunk. The most prominent lesion (***x***) represents a perforated lesion as shown in ***Fig 2c***. The earlier (unperforated) lesion marked (***y***) equates to ***Fig 2b***.

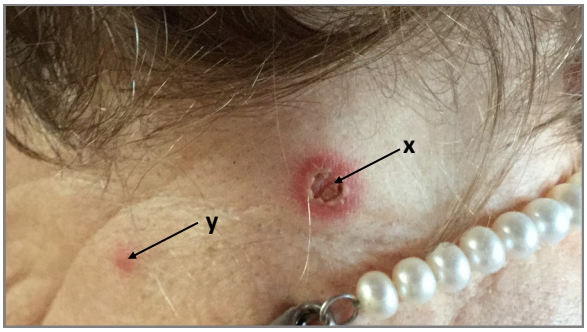

Fig 1

To understand what happens in this skin lesion, it is necessary to know the microscopic structure of the skin (see ***Fig 2a***). The skin has three layers:-

- the **epidermis,** which is the top surface in contact with the air. It is made up of layers of epithelial cells called keratinocytes;
- underneath the epidermis is the **dermis** which contains blood vessels and nerves, and is made up of **collagen** and **elastic** fibres produced by cells called fibroblasts. The dermis is the layer which gives the skin its texture. In youth the skin is taut and smooth, but with ageing it becomes progressively less taut and more wrinkly. This is entirely due to ageing changes in the dermis; and
- underneath the dermis is the **subcutis**, which is mainly composed of fatty tissue which acts as a shock absorber and a thermal insulator.

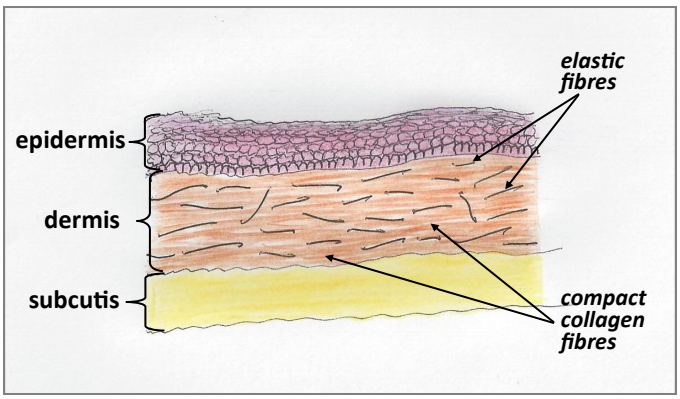

Fig 2a Normal skin with intact straight elastic fibres in dermis

In EPS, the major abnormality occurs in the dermis, and is associated with abnormalities in the **elastic fibres.** Elastic fibres are composed of two fibrous proteins called **elastin** and **fibrillin.** Elastic fibres can be likened to an elastic band in that it is stretchable, and maintains the smooth texture of the skin in youth. However, like an elastic band, as it gets old it can become less stretchable and brittle, and may fragment. This deterioration in the

quality of the elastic fibre is what makes our skin less smooth and more wrinkly in old age (very little to do with the collagen in the dermis which the beauty industry tries to make you believe, with its so-called collagen improving creams!) The main problem lies in the fibrillin component which holds the elastin fibres in stable position, and this fibrillin component is most vulnerable to the effects of ageing, and probably most sensitive to toxic effects. Before I go into the detail of how penicillamine may affect elastic fibre structure and function, let us look at what happens in the skin in elastosis perforans serpiginosa.

The early changes (lesion ***y*** in *Fig 1* opposite) are shown in ***Fig 2b***. The elastin fibres, instead of being long and straight, are fragmented and a bit knobbly, an appearance (under the microscope) fancifully likened to blackberries on a branch of a bramble bush. These abnormal fragmented elastic fibres accumulate in clumps in the upper dermis, producing a raised lump in the skin. Because the fibres are abnormal they produce inflammation around the clumps, and this makes the raised skin lumps red.

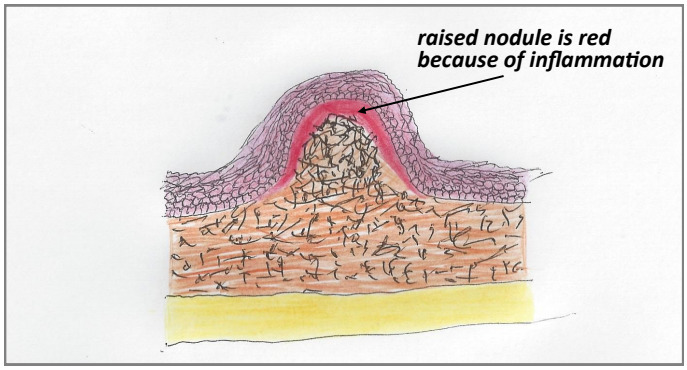

Fig.2b Early lesion of EPS with degenerate elastin forming raised nodule

In the fully developed lesion shown in ***Fig 2c***, the clump of abnormal and fragmented elastic fibres is being extruded on to the surface of the skin by perforating through the overlying epidermis. The brownish crusty material in the pit at the tip of each nodule is made up of this extruded degenerate elastin. Again there is inflammation in the raised skin lump, producing reddening. This stage can be seen in the clinical photograph *Fig 1*, as the main lesion identified as ***x***.

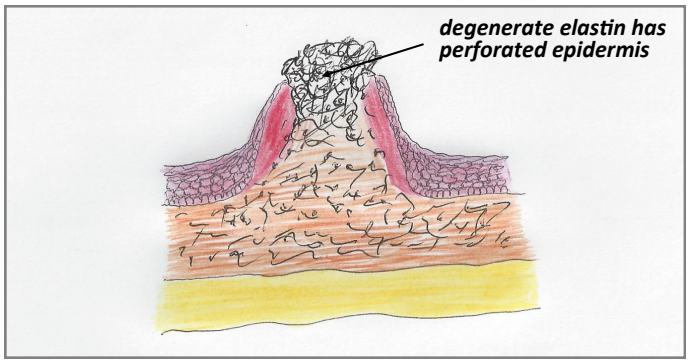

Fig. 2c Late lesion in EPS. Nodule of degenerate elastin has broken through epidermis and formed brown plug

EPS can occur as a complication of treatment by penicillamine for Wilson's disease, rheumatoid arthritis and a rare genetic disease called cystinuria; its incidence is thought to be related to the dose of penicillamine (more common if the dose is greater than 1 gram per day), although cases have been described in rheumatoid arthritis patients on lower doses. Only 1 in a 100 Wilson's patients on penicillamine will develop EPS.

EPS is but one of a group of skin diseases in which the underlying abnormality is damage to, and disruption of, the elastic fibres (*elastolysis*); other diseases in this group include **cutis laxa** (in which the skin is lax and forms folds) and **pseudoxanthoma elasticum** (in which yellowish lumps appear in the skin of the neck, armpits and other areas). Patients who develop EPS after penicillamine sometimes have associated cutis laxa, and skin changes which mimic pseudoxanthoma elasticum in clinical appearance but with slight differences in the appearances under the microscope.

It is interesting that genetic abnormalities have been discovered in idiopathic EPS, in cutis laxa, and in pseudoxanthoma elasticum, a point I will come to below.

It is known that the formation and maintenance of elastic fibres is partly dependent on the activity of an enzyme called lysyl oxidase, and that the functioning of this enzyme is dependent on the presence of copper ions. It is proposed that high doses of penicillamine clears the skin of copper, and that this leads to malfunctioning of lysyl oxidase and hence damage to elastic fibres. It is unlikely that this is the sole reason for EPS developing since, if it were so, every patient on high-dose penicillamine would develop it, instead of only 1 in a 100. Furthermore, patients on other copper-chelating drugs, such as trientene, would probably also develop it, although trientine may be less efficient at chelating copper from the skin than penicillamine. Taking into account the known genetic basis of idiopathic EPS and the other skin lesions based on abnormal elastic fibres, it may be that there is a genetic predisposition, whereby only certain patients develop EPS when treated with penicillamine.