Pseudoxanthoma elasticum (PXE) is a rare multisystem disorder characterised by progressive calcification and fragmentation of elastic fibres. Recent genetic advances have identified the underlying defect to the ABCC6 gene on chromosome 16p13.1. Patients typically develop cutaneous, ocular, and cardiovascular manifestations but there is considerable phenotypic variability. The skin changes are usually apparent in adulthood, and rarely observed in childhood. Since the prognosis of PXE largely depends on the extent of extracutaneous organ involvement early recognition, intervention and lifestyle adjustments are important to reduce morbidity. First-degree family members should be carefully examined for any cutaneous or ophthalmologic features of PXE.

**AETIOLOGY**

The prevalence is estimated at 1 in 25 000–100 000 with an almost 2:1 female preponderance. The genetic defect has been mapped to the ABCC6 gene on chromosome 16p13.1. ABCC6 encodes multidrug resistance associated protein 6 (MRP6), which belongs to the ABC (ATP binding cassette) transmembrane transporter family of proteins. Its exact biological function is not clear yet but it may play a role in cellular detoxification. Interestingly, MRP6 is highly expressed in the liver and kidneys but only low levels are found in tissues affected in PXE. It has therefore been suggested that PXE is primarily a metabolic disorder with secondary involvement of elastic fibrils. Genetic studies have to date identified about 60 mutations, mainly missense and nonsense mutations, as well as large deletions (for details see OMIM website). The usual mode of inheritance is autosomal recessive, but some families with two generation involvement have been observed in keeping with a pseudodominant pattern.

**PATHOLOGY**

The histology of PXE is characteristic. In skin lesions swollen, clumped, and fragmented elastic fibres and calcium deposits are found in the mid and deep reticular dermis. Similar changes occur in elastic fibres of the blood vessels, Bruch’s membrane of the eye, endocardium, and other organs. Transepidermal elimination of altered calcified elastic fibres may occasionally be seen in PXE.

**CUTANEOUS MANIFESTATIONS**

Most cases of PXE are diagnosed in the age group from 10 to 15 years but cutaneous lesions have been reported in infancy. Because of their subtle and asymptomatic nature there is an average diagnostic delay of nine years. Small, yellowish, flat papules develop typically on the neck, and may coalesce to form plaques giving the skin a “gooseflesh” or “plucked chicken” appearance (fig 1). The antecubital and popliteal fossae, axillae, inguinal, and periumbilical areas are often also involved. The lesions are asymptomatic but often of cosmetic concern. As the disease progresses the affected skin may become lax and wrinkled, hanging in folds. Generalised severe laxity of the skin is rare.

Lesions on the mucous membranes, especially on the inner aspect of the lower lip are common. Occasionally calcium deposits may extrude from the skin in advanced disease, a condition described as “perforating PXE”. Other unusual clinical presentations of PXE include numerous acneiform lesions, chronic granulomatous...
nODULES, AND BROWN MACULES IN A RETICULATE PATTERN.11 BIOPSY OF SCARS AND FLEXURAL SKIN MAY BE HELPFUL WHEN PXE IS SUSPECTED IN THE ABSENCE OF CHARACTERISTIC SKIN LESIONS.14

OCULAR MANIFESTATIONS
The characteristic eye signs of PXE are angiod streaks, which are irregular, reddish-brown, or grey lines that radiate from the optic disc. Angiod streaks appear to be present in at least 85% of patients with PXE and the typical age of onset is between 15 and 25 years.7,13 They result from degeneration and calcification of the elastic fibres of the retina leading to breaks in the Bruch’s membrane. Retinal haemorrhages, neovascularisation, and scarring may occur and can lead to loss of central vision. Some authors estimate the frequency of visual impairment as high as 50–70% of cases.7,15 Major vascular abnormalities at the optic disc such as arteriovenous anastomosis have been found in PXE patients with angiod streaks.16

Angiod streaks are not pathognomonic and have been described in a variety of other systemic disorders including Ehlers–Danlos syndrome, Paget’s disease of the bone, Marfan’s syndrome, sickle cell anaemia, thalassaemia, and lead poisoning.

The first ocular sign is often "peau d’orange" appearance (a yellowish mottled hyperpigmentation of the retina) which may precede angiod streaks by up to 10 years.7 Other less common findings include colloid bodies, macular degeneration, optic nerve head drusen (whitish-yellow irregularities of the optic disc), and “owls eyes” (paired hyperpigmented spots).17,18

CARDIOVASCULAR MANIFESTATIONS
Degeneration of the elastic laminae of medium sized arteries and calcium deposition are the cause of vascular manifestations of PXE.

Clinically, intermittent claudication is often the first sign of accelerated atherosclerosis and the most common cardiovascular symptom, occurring in 30% of patients. Coronary artery disease and renovascular hypertension may occur at a much younger age in PXE patients and can result in angina pectoris, myocardial infarction, congestive cardiac failure, renal failure, or stroke. Although cardiovascular disease rarely presents before the third or fourth decade it has been reported in children as young as 9 years of age.7,10,19

MANAGEMENT AND PROPHYLAXIS
Patients with PXE typically have a normal life span but morbidity and mortality depend on the extent of systemic involvement. Many of the pathological changes are irreversible. However, prophylactic measures and lifestyle adjustments can be used to minimise the risk of complications (box 2). Early diagnosis of PXE is therefore paramount.

If the appearance of skin lesions becomes a cosmetic problem plastic surgery has been used successfully.26 However, wound healing appears to be slower than usual.

Box 1 Criteria for the diagnosis of PXE (adapted from Lebwohl et al14)

**Major criteria**
- Characteristic skin signs (yellow cobblestone lesions in flexural areas)
- Characteristic ophthalmologic features (angiod streaks, peau d’orange, maculopathy)
- Characteristic histological features of lesional skin (elastic tissue and calcium or von Kossa stains)

**Minor criteria**
- Characteristic histological features of non-lesional skin (elastic tissue and calcium or von Kossa stains)
- Family history of PXE in first-degree relatives

Category I patients fulfill all three major criteria and definitely have PXE. However, in children ocular changes are not required to establish the diagnosis as they often do not develop until early adulthood. Category II patients do not have typical skin lesions but have either angiod streaks with at least one minor criterion, or two minor criteria.

Echocardiography may show marked calcification of the atrial and ventricular endocardium, valves, and calcified thrombi, which can result in mitral valve prolapse, mitral valve stenosis, or restrictive cardiomyopathy.20 On renal ultrasonography a characteristic hyperechogenicity with dotted pattern has been reported in patients with PXE, possibly reflecting the calcified elastic layers of the arteries.21 Similar sonographic findings were seen in spleen and pancreas.

About 10% of PXE patients experience bleeding complications, especially gastrointestinal haemorrhage, due to fragility of calcified submucosal vessels. Bleeding may occur without warning and has been described in children and teenagers.18,22 Bleeding may also affect other organs such as the cerebrovascular system, uterus, urinary tract, or joints.10,22

PXE-LIKE CONDITIONS
A PXE-like syndrome with cutaneous, ocular, and vascular manifestations has been described in patients with thalassaemia and sickle cell disease.23 It is an acquired condition and age dependent with generally late onset.

Localised acquired PXE is a disorder occurring predominantly in black women with recurring abdominal distension, for example pregnancies or ascites.24 Typical skin lesions develop predominantly in the periumbilical area but without systemic features and negative family history.

Papillary dermal elastolysis is an acquired cutaneous disorder, which mainly affects women aged 60–80 years.25 It is characterised by white-yellow papules resembling PXE; histologically there is loss of elastin in the papillary dermis. In contrast, actinic elastosis shows thickening, yellow discoloration, and marked wrinkling of sun exposed skin areas. Histologically there is an increase in dermal elastosis.

PXE-like skin lesions have also been observed in longstanding end-stage renal disease, L-tryptophan induced eosinophilia myalgia syndrome, and amyloid elastosis as well as with D-penicillamine, cutaneous exposure to calcium salts, and salpeter.13,17,24

Figure 1 Characteristic yellow papules on the neck. Parental consent was obtained for publication of this figure.

If the appearance of skin lesions becomes a cosmetic problem plastic surgery has been used successfully.26 However, wound healing appears to be slower than usual.
Box 2 Suggested management of patients with PXE

**Eye examination**
- 6–12 monthly check by ophthalmologist
- Regular use of Amsler grid by patients to monitor central vision (chart consisting of evenly spaced horizontal and vertical lines with a small dot in the centre of the grid)

**Cardiology assessment**
- Yearly check of blood pressure, peripheral pulses, and for heart murmurs
- If abnormal findings, refer to cardiologist for further investigations, e.g. echocardiogram

**Laboratory tests**
- In children low threshold/in adults 6–12 monthly
- Blood count, ferritin, serum lipids, urinalysis

**Medicaments**
- Avoidance of non-steroidal anti-inflammatory analgesics and warfarin
- Selective use of aspirin for prevention of thromboembolic events in high risk patients
- Avoidance of oestrogens, e.g. oral contraceptive pill, HRT

**Diet**
- Avoid high cholesterol
- Moderate calorie intake

**Lifestyle**
- Regular exercise but avoid contact sports and straining
- Weight control
- Avoidance of smoking

**Genetic counselling**
- Be necessary. Fundoscopy is recommended as eye changes may precede cutaneous signs. Patients and their families should also receive genetic counselling. All the current evidence suggests that the inheritance pattern in PXE is usually autosomal recessive. Recurrence risks in sporadic cases are therefore generally low. Molecular genetic testing is available only on a research basis.

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Consent was obtained for publication of figure 1

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Pseudoxanthoma elasticum

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