Seeing through the cracks

Case Report

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Seeing through the cracks

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Abstract

Pseudoxanthoma elasticum (PXE) is an autosomal recessive multisystem disorder showing phenotypic heterogeneity giving rise to complex comorbidities. The most 'visible' signs are dermatological; however, these may be subtle and hidden from the view of an affected individual. Ophthalmic signs can be easily missed, and here we highlight the importance of a multisystem assessment. We report a patient who developed advanced sight loss due to maculopathy whose underlying PXE aetiology went unnoticed until subtle skin signs were noticed on the lateral aspect of his neck. He was aware of the skin changes. Careful review of his previous retinal imaging showed the presence of 'angioid streaks' and anatomic alteration at the outer retina-Bruch membrane associated with his prior history of choroidal neovascularisation. The diagnosis was subsequently confirmed by skin biopsy and genetic testing. This case highlights the subtlety of both dermatological and ophthalmic signs in PXE.

Keywords

pseudoxanthoma elasticum, angioid streaks, choroidal neovascularisation

Introduction

Pseudoxanthoma elasticum (PXE) is a seemingly innocuous disease with mild dermatologic manifestations and rare multi-organ complications. However, over 50% of patients with PXE can progress onto develop irreversible vision loss secondary to choroidal neovascular (CNV) membrane formation if untreated.[1,2] With prompt treatment, vision can be stabilised in over 85% of patients.[1] Despite the frequency of ocular complications, there are no definitive guidelines regarding the management and long-term follow-up of PXE, specifically relating to the eyes. Based on the published evidence, it may be surmised that early diagnosis of PXE, recognition of organ-specific morbidity manifestations, inter-speciality communication and patient information provision collectively enables optimal care and reduces the risk of patients 'falling between the cracks' in service delivery.

Case presentation

A 52-year-old male who worked in IT had received 4 years of treatment for wet age-related macular degeneration at Princess Alexandra Eye Pavilion, Edinburgh. He had declining central vision affecting both eyes despite intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. He had no past medical history and was not taking any medications or supplements. He was otherwise well with no complaints of joint pain, skin concerns, gastrointestinal (GI) upset or cardiovascular disease. Family history was relevant for age-related macular degeneration in his mother; he had no siblings or children.

A second ophthalmic opinion was requested with regard to his bilateral progressive central vision. Incidentally, he was noted to have subtle changes on the dorsolateral aspects of neck (see Figure 1). They were smooth non-tender waxy yellow papules. The patient was unaware of their presence and neither had disclosed this to his friends and family, nor had his barber mentioned the lesions. No other skin changes were identified elsewhere.

In light of the skin findings, fundal examination suggested the presence of subtle subretinal brown, narrow, irregular lines radiating from the optic nerve heads at the posterior poles (see Figures 2 and 3). In conjunction with retinal optical coherence tomography (OCT), a diagnosis of angioid streaks (AS) secondary to PXE was made.

Dermatology confirmed a likely diagnosis of PXE, and further investigation was arranged. Cardiovascular workup included blood pressure, electrocardiogram and echocardiogram, all

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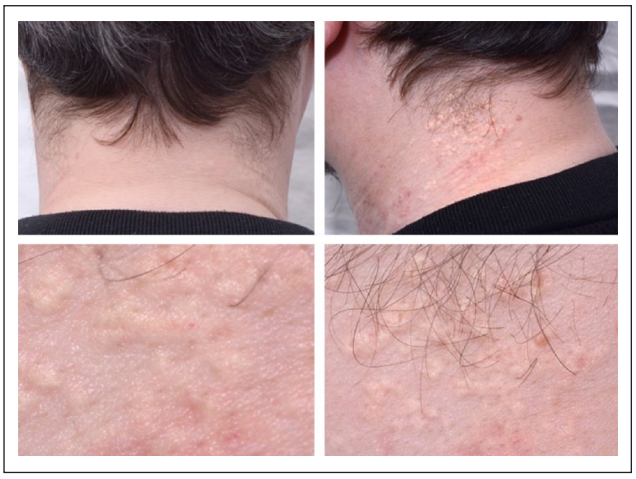

Figure 1. Clinical photograph of dorsolateral aspect of the neck.

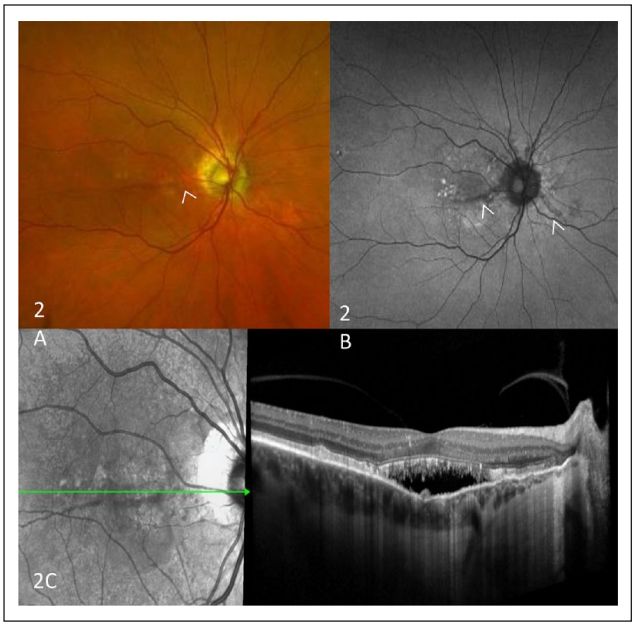

Figure 2. Right eye: (a) Colour fundus picture, (b) Blue autofluorescence. Arrows indicate angioid streaks, and (c) Optical coherence tomography scan right eye demonstrates subretinal fluid and hyperreflective material..

within normal limits. Pseudoxanthoma elasticum was subsequently supported by genetic testing confirming the c.3490C>T p.(Arg1164Ter) mutation, a common cause of PXE in the European population and biopsy showing prominent fragmented elastic fibres.

The patient was given a formal diagnosis of PXE, and he continues to have ongoing monitoring with the macular clinic. Treatment with anti-VEGF injections is as required, determined by CNV activity.

Discussion

Pseudoxanthoma elasticum is a multisystem disorder characterised by the degeneration of elastic fibres. It is a rare autosomal recessive condition predominantly affecting the skin, blood vessels and the eye. A mutation of the *ABCC6* (ATP-binding cassette transporter) gene is commonly seen in PXE.[3] The mutation leads to dysfunctional transmembrane transporter proteins, which impair calcium transport and thus calcification of tissue rich in elastic fibres.

Ectopic calcium mineralisation within the media and intima of blood vessels accelerates atherosclerosis[4] and can impair left ventricular diastolic dysfunction.[5] Gastrointestinal haemorrhage has been observed in PXE and is thought to occur secondary to degeneration of elastic fibres within the vascular wall, resulting in structurally compromised vessels, aneurysmal dilatation and subsequent rupture.[6] Zakko[7] reports 13% of patients experience recurrent acute GI haemorrhage.

Pseudoxanthoma elasticum first demonstrates phenotypic emergence within childhood and is characterised by skin changes primarily within the nape of the neck and axillae. These changes include yellow-coloured papules, which have hence contributed to the title of pseudoxanthoma, and peau d'orange changes on flexural surfaces. It has been suggested that a specific finding for PXE involves horizontal and oblique mental creases before the age of 30.[8]

The slight female predominance in documented cases of PXE may be attributed to aesthetic expectations as females are more likely to seek medical attention for skin changes, particularly for visibly noticeable areas such as the nape of the neck. Our patient was unaware of his cutaneous manifestations and was not noticed by his family, friends and barbers.

The diagnosis of PXE is clinical, although a skin biopsy can be performed to confirm the diagnosis in less obvious presentations.[9] There are suggested diagnostic criteria that require skin findings to be observed together with two mutations in the *ABCC6* gene or display ocular findings.[9] However, despite including ocular findings as a possible diagnostic criterion, long-term ocular management is not included in recommended guidelines.

Ocular manifestations in PXE are often subtle in early disease. Features include AS, peau d'orange, optic nerve head drusen, macular dystrophy and comet lesions. These findings in isolation are relatively benign, although AS can be sight threatening in the presence of CNV. Angioid streaks reflect breaks in the Bruch's membrane.[10] Bruch's membrane acts as the boundary between the vascular choroid and the outermost retinal structures. Angioid streaks occur at points of tension created by the mechanical forces exerted by the extraocular muscles and can easily break if calcified, as in PXE, or from minor trauma. Angioid streaks are often found radiating from the optic nerve and posterior pole as this is the site of greatest tension. They are not specific to PXE and can be seen idiopathically or secondary to other multi-system disorders including, Paget's disease, Ehlers–Danlos syndrome and haemoglobinopathies.[11]

Breaks in the Bruch's membrane predispose to formation of CNV membranes. Eyes are subsequently at risk of subretinal haemorrhage leading to sudden painless loss of vision, which may become irreversible if not managed urgently. Over time the calcification of the retinal pigment epithelium (RPE) contributes towards retinal atrophy and a progressive deterioration in vision. Pattern dystrophy changes may also cause visual deterioration.

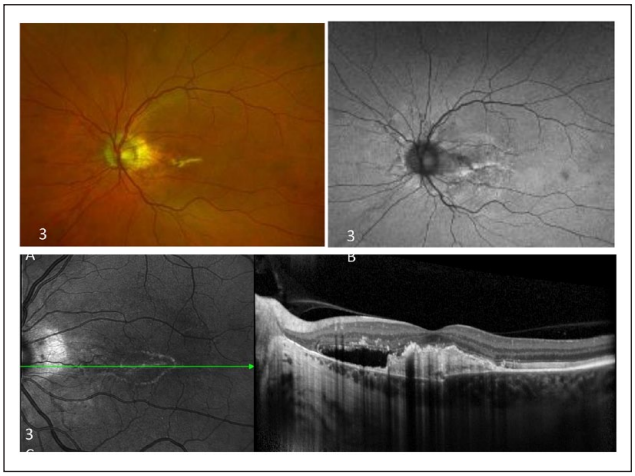

Figure 3. Left eye. (a) Colour fundus picture. (b) Blue autofluorescence. Arrows indicate angioid streaks. (c) Optical coherence tomography scan left eye demonstrates subretinal fluid adjacent to hyperreflective material suggesting fibrovascular scarring at the site of the Bruch's membrane complex discontinuity.

Choroidal neovascularisation associated with AS occurs in 72%–86% of eyes.[12] And if initially unilateral, the time to bilateralisation is 1.5–2.4 years.[1,13] Choroidal neovascular is not specific to PXE and can be seen in multiple ocular pathologies including age-related macular degeneration. A finding of CNV in a young patient should warrant further history and multi-system examination. Pseudoxanthoma elasticum-related CNV affects the younger working population, significantly impacting on quality of life if suboptimally treated.[14] A diagnosis of CNV secondary to PXE is important with respect to determining prognosis and identification of at risk family members.

Choroidal neovascularisation secondary to PXE is rare, and the published evidence is confined to small retrospective studies with limited follow-up.[15] For this reason, injection protocols vary widely across centres, and treatment remains at the ophthalmologist's discretion. Generally, patients receive anti-VEGF loading with three monthly injections and subsequently receive as required injections dependent on CNV activity, as determined by ophthalmic assessment and OCT imaging.

The PIXEL study,[1] a 72-patient multicentred trial, is the largest to explore the efficacy and safety of ranibizumab for CNV related to PXE in a real-world setting. Over a 4-year follow-up with a mean number of 4.1 injections per year, 52.6% of patients had stable vision and 26.3% had a deterioration of vision of greater than 15 letters. One patient suffered endophthalmitis and another suffered an ischaemic stroke, both of which were thought to be attributed to the intravitreal injection.

Ramakrishnan et al.[16] also demonstrated a 70% recurrence of CNV within 5 years, highlighting the need for close follow-up despite CNV regression. Such patients are difficult to discharge and may benefit from education, regular OCT in the community and clear instructions when to re-present.

Blindness may result without administration of intravitreal injections of anti-VEGF in the presence of active CNV. This case should encourage dermatologists to review any visual changes in patients diagnosed with PXE in addition to referring to ophthalmology to prevent patients from falling through the cracks.

Learning points

- Dermatologists should ask about ocular manifestations in diagnosed PXE patients at every visit and should refer on to ophthalmology.
- Ophthalmologists should be cautious when assessing PXE patients as signs, such as AS may be very subtle and precede CNV in young patients.
- Current guidelines do not include long-term ophthalmic follow-up despite the frequency of ocular complications; patients should have yearly ophthalmic review.
- This report highlights the subtlety in dermatological signs of PXE lurking in hidden locations, requires awareness of the association, vigilance in detection and astuteness in the observer. Seeing something at the back of one's neck is the privilege of an intimate partner, the local barber and occasionally an interested clinician who we hope might be representative of readers of this article.

Informed consent

Informed patient consent signed and completed.

Declaration of conflicting interests

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