PSEUDOXANTHOMA ELASTICUM CONFIRMED BY GENETIC ANALYSIS BUT NOT BY SKIN BIOPSY: A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

In patients with angioid streaks, additional investigations are useful to identify underlying systemic disease, unless age and short peripapillary streaks are indicative of senile streaks as an isolated abnormality. In middle-aged or young adults with angioid streaks and no obvious systemic disease, the possibility of a hemoglobulinopathy or pseudoxanthoma elasticum (PXE) as etiologic entities should be investigated. Hemoglobinopathies can be excluded based on blood screening and the absence of typical ocular fundus changes, such as retinal vessel tortuosity. This allows making a presumed clinical diagnosis of PXE in patients with angioid streaks, based on exclusion of a hemoglobinopathy, and on the presence of extensive angioid streaks, peau d'orange, crystalline bodies and comet tail lesions. For confirmation of PXE, the gold standard was dermatologic examination and skin biopsy, but since the last decade molecular diagnosis is available.

In rare cases, PXE can be diagnosed using molecular techniques in patients with apparently normal skin and negative skin biopsies, as demonstrated in this case and another case published in 2011.

KEY WORDS

ABCC6 gene, Pseudoxanthoma elasticum

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INTRODUCTION

Pseudoxanthoma elasticum (PXE) is a systemic disorder that is characterized by accumulation of mineralized and fragmented elastic fibers in the skin, the Bruch's membrane of the eye and the internal elastic lamina of medium-sized arteries. It is an autosomal recessive inherited disorder which has an estimated prevalence of 1:25,000 to 1:100,000 (1, 2). PXE is most frequently detected when patients seek dermatologic advice for the skin lesions with papules; when angioid streaks are identified incidentally; or upon visual loss due to PXE-associated maculopathy. Other PXE-associated problems include gastrointestinal bleeding, angina pectoralis and claudication.

In this case, a 42-year-old male presented with unilateral visual loss. PXE was suspected based on the typical appearance of the extensive angioid streaks with associated choroidal neovascularization, peau d'orange, and crystalline bodies seen on funduscopy.

Dermatological examination did not reveal PXE-related skin lesions and a skin biopsy from the neck was negative for PXE. However, genetic analysis confirmed the diagnosis of PXE, with a compound heterozygote mutation in the ABCC6 gene.

This is the second case in our department in which we could not confirm the diagnosis of PXE by skin biopsy, but where PXE was confirmed with genetic analysis (3).

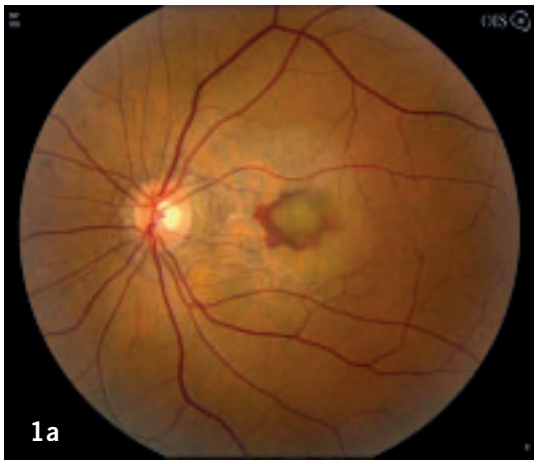
CASE REPORT

A 42-year-old male patient first noticed loss of visual acuity of the left eye upon awaking in the morning. His general ophthalmologist observed a submacular hemorrhage in the left eye and referred the patient to our medical retina department for further investigation.

At presentation, best corrected visual acuity (BCVA) was 20/25 in the right eye and counting fingers in the left eye. Fundus examination showed angioid streaks and peau d'orange lesions bilaterally. In the left eye there was a maculopathy with fibrotic changes and a hemorrhage (*Fig. 1a*). There were no comet tail lesions. However, one crystalline body was present in the midperipheral retina of the right eye (*Fig. 1b*).

Optical coherence tomography (OCT) and fluorescein angiography (FA) revealed an active subfoveal choroidal neovascular membrane that had led to hemorrhage and macular edema.

Subsequently, anti-VEGF treatment was started and an intravitreal injection of bevacizum-



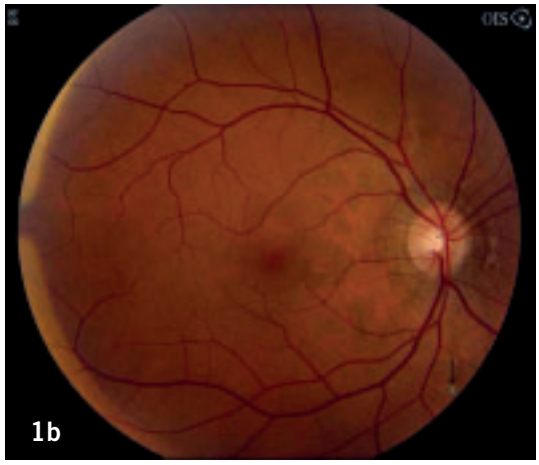


Fig. 1: The colour photographs of the left eye (Fig. 1a) and the right eye (Fig. 1b) show angioid streaks in a spider web configuration around the optic disc and radiating outwards. There is also the typical aspect of peau d'orange temporal of the fovea.
In the left eye (Fig. 1a), a subfoveal fibrotic neovascular membrane is seen, with extensive bleeding and surrounding exudates indicating subretinal fluid.
In the right eye (Fig. 1b) there is a crystalline body in the midperiphery (arrow).

ab was administered to the left eye. Monthly follow-up with evaluation of macular edema and consideration of additional bevacizumab injections were performed. Despite a total of 6 injections of bevacizumab over a 9-month period, the macular edema persisted and visual acuity failed to improve beyond 20/320.

The patient was in good general health except for gastroesphageal reflux disease, for which he used a proton pomp inhibitor, and hypercholesterolemia, which was treated with a statin. Taking into account the identification of angioid streaks, a search for an underlying disease was initiated. Blood examination did not reveal a hemoglobulinopathy, and the cardiovascular investigation was normal.

Dermatologic examination showed a cutaneous rash in the neck suggestive of erythrosis interfollicularis colli and solar elastosis (the patient worked in construction and had had high levels of sun exposure). There were no cutaneous abnormalities in the axillae, the groin or the oral mucosa, any of which might be expected in PXE. A skin biopsy of the neck confirmed solar elastosis without calcifications and without PXE-associated lesions.

Because the ocular lesions were highly suggestive of those associated with PXE, genetic analysis was undertaken. This revealed a heterozygote mutation of the ABCC6 gene, which confirmed the diagnosis of PXE. The patient was found to be the carrier of 2 different mutations: a 3413G>A mutation and a 3389C>T mutation.

The patient and his generalist were informed of the diagnosis and genetic counseling and lifestyle adjustments were advised, in order to minimize the risk of complications.

DISCUSSION

Pseudoxanthoma elasticum is a heritable, multisystem disease associated with ectopic mineralization of connective tissues. It can affect the skin, the eyes and the cardiovascular system (1). PXE is found in all populations, with a higher prevalence in Caucasian settlers of European descent (Afrikaners) from South Africa, who display a founder effect. Women seem to be affected twice as often as men (4). PXE is often a diagnostic challenge because it is usually not present in childhood and there is a considerable intra-and interfamilial variability in terms of penetrance.

Furthermore, angioid streaks can be seen in a number of other conditions without evidence of PXE, such as hemoglobulinopahties and certain connective tissue disorders, while the cutaneous and cardiovascular findings can mimic other conditions, such as solar elastosis and myocardial infarctions (2, 5, 6). The most commonly presenting signs are yellowish papules in the skin and/or angioid streaks identified as an incidental finding during routine eye examination or associated with visual loss and maculopathy.

The primary skin lesions are small, asymptomatic soft, yellowish papules, typically arranged in a reticular pattern on the neck and flexural areas of the axilla, the antecubital fossae, the popliteal fossae and the groin. The papules gradually coalesce to form plaques and eventually the skin loses its elasticity and typical redundant skin folds develop. Biopsy of these lesions usually shows aberrant clumped, fragmented and calcified elastic tissues in the middle and lower dermis (7).

These characteristic pathological features can also be observed in apparently normal skin of affected individuals, the so-called occult PXE, or in biopsies of cutaneous scar tissue (8, 9).

The earliest ocular findings are pigment irregularities temporal of the macula known as peau d'orange. Histological examination of this feature shows calcification and thickening of Bruch's membrane. Subsequent cracks and dehiscences in the mineralized Bruch's membrane result in the formation of angioid streaks. These are greyish, irregular lines which surround the optic disk and radiate outwards.

Angioid streaks generally do not cause visual symptoms unless they are subfoveal or associated with ingrowth of fibrovascular tissue (choroidal neovascularization or CNV) and either subfoveal expansion or scar formation due to hemorrhage and leakage or evolution to atrophy (1). Until recently, the prognosis of PXE-associated CNV was very poor, but intravitreal injections with anti-VEGF have improved the prognosis as in most patients vision can be stabilized or even improved in early disease (10, 11).

Although PXE is the most common systemic disorder associated with angioid streaks, streaks

may be observed in a variety of metabolic and systemic disorders, including Paget's disease, Ehlers-Danlos syndrome, hemoglobulinopathies, acromegaly, diabetes and Marfan syndrome (6). Most of these conditions can be excluded by conducting a thorough medical history and examination.

Hemoglobulinopathy, specifically β-thalassemia, can be suspected in the presence of retinal vessel tortuosity and the absence of comet tail lesions. Occasionally, senile streaks can be observed with advanced age, but these so-called pseudostreaks surrounding the optic disc are short, and characteristically the peripapillary helicoidal choroidal atrophy is more prominent than the streaks themselves (1, 12).

Further ocular findings in PXE include multiple small chorioretinal atrophies, so-called comet tail lesions and optic disc drusen. Comet tails seem to be pathognomonic for PXE, without any effect on visual function (1).

The cardiovascular manifestations of PXE include hypertension, premature atherosclerosis of the medium-caliber arteries, claudication, mitral valve prolapse or stenosis and coronary artery disease resulting in angina pectoris and myocardial infarction. The exact prevalence of cardiovascular events in PXE patients is unknown, but most patients do not experience any problems before the third or fourth decade. Gastrointestinal bleeding with hematemesis and melena occurs in up to 15% of patients (4).

The ABCC6, an ATP-binding cassette transporter gene that encodes a multidrug resistance associated protein 6 (MRP6), has been identified as the defective gene in PXE. It is located on chromosome 16p13.1 and consists of 31 exons with a total genomic size of 75kb (13). The gene is primarily expressed in the human liver and the kidneys, and at very low levels, if at all, in tissues clinically affected by PXE.

These findings suggest that PXE is a metabolic disorder, with a deficiency of yet unknown molecules in the systemic circulation due to a defective ABCC6 transporter, which are required to prevent aberrant mineralization of connective tissue under normal circumstances (14). To date, more than 300 distinct mutations of the ABCC6 gene have been encountered in patients with PXE. The majority of identified mutations are missense or nonsense mutations. Our patient was found to have 2 different mutations: a 3413G>A mutation and a 3389C>T mutation, both of which have been previously described (4).

CONCLUSION

We report a second case of PXE in which there was a strong clinical suspicion based on the ocular findings and in which the diagnosis was confirmed by genetic analysis after negative skin biopsies (3).

When the typical skin lesions are present, the diagnosis of PXE is straightforward and is usually confirmed by skin biopsy. The diagnosis is often more difficult in absence of these lesions, and frequently PXE remains undiagnosed until visual loss occurs and the ophthalmologist identifies angioid streaks.

When there is a strong clinical suspicion of PXE, skin biopsy of possible lesions and of flexural skin of the neck or axillae is recommended. If these investigations appear to be negative, genetic analysis should be considered.

So far, there is no treatment available for PXE, but prophylactic measures, some lifestyle adjustments and careful follow-up, can reduce the risk of complications.

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