Visual loss and presumed pseudoxanthoma elasticum confirmed with genetic analysis but not with skin examination and biopsies

Abstract

Objective: Case report of a patient with angioid streaks, peau d'orange, comet tail lesions, choroidal neovascularisation and presumed pseudoxanthoma elasticum (PXE). PXE was confirmed by gene analysis but not by skin biopsies.
Methods: Case report of a patient with angioid streaks identified at age 21 and follow-up till age 43 with repeated fluorescein angiography (FA) and optical coherence tomography (OCT). Dermatologic examination, skin biopsies and genetical analysis performed to confirm suspected diagnosis of PXE.
Results: At age 43, no specific skin lesions were identified and 3 biopsies could not confirm PXE. Genetic analysis showed a homozygous mutation in the ABCC6 gene and confirmed the diagnosis of PXE.
Conclusions: This case illustrates that in patients with angioid streaks having strong ocular indicators of PXE, confirmation of PXE can be obtained not only with dermatologic examination and skin biopsies, but also with genetic analysis. PXE associated mutations can be detected occasionally in biopsy negative patients and for this reason are extremely helpful in confirming a suspected diagnosis.

Keywords: pseudoxanthoma elasticum, choroidal neovascularization, skin lesions, scar biopsy, gene analysis, mutation in ABCC6 gene

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Introduction

Pseudoxanthoma elasticum (PXE) is an autosomal recessive systemic disorder characterized by progressive calcification, fragmentation and degeneration of elastic fibers in connective tissue. The disease mainly affects the skin, Bruchs' membrane in the eyes and the internal elastic lamina of mostly medium-sized arteries. In affected patients, there is considerable variation in penetrance of the disorder and phenotypic expression [1], [2], [3], [4]. We report on a 43-year-old patient with bilateral visual loss due to choroidal neovascularization (CNV) associated with angioid streaks and presumed pseudoxanthoma elasticum. He is otherwise healthy, has no PXE associated skin lesions, and 3 skin biopsies from neck and axilla were normal. However, genetic analysis confirmed PXE with a homozygous mutation in the ABCC6 gene.

Case report

In 1989, a 21-year-old male experienced visual loss after diving from a diving board. Ocular examination was performed the same day, and revealed bilateral subretinal hemorrhages and angioid streaks. After clearing of the hemorrhages, more breaks of Bruch's membrane were identified. The macula was not affected and vision returned to normal in both eyes. Twenty years later, in April 2009, he presented again because of recent visual loss in the left eye. Visual acuity (VA) was 20/25 in the right eye (RE) and 20/40 in the left eye (LE). Clinical examination, FA, and OCT revealed active choroidal neovascularisation nasal to the fovea with leakage and edema. One month after a first intravitreal injection of bevacizumab, the edema had resolved and vision improved. Close follow-up with consideration of additional anti-VEGF injections was adviced. Moreover, we observed in both eyes angioid streaks, *peau d'orange* and a few *comet tails*, and made a tentative diagnosis of PXE. We identified the sequellae of diving induced breaks of Bruchs' membrane with linear vertical break formation, different from the irregular course and spiderweb configuration of the angioid streaks. During the following months a total of 8 injections of bevacizumab were administred on the LE and despite this treatment growth of the CNV was observed with further deterioration of vision. In January 2010, active CNV was also identified in the right eye and treatment with bevacizumab intravitreal injections was initiated. At last examination, in April 2011, VA was 20/60 in the right eye and 20/250 in the left eye, with in the left eye a large subfoveal CNV expanding on both sides of the fovea, and in the RE a smaller and mildly active subfoveal CNV requiring further treatment (Figures 1–10).

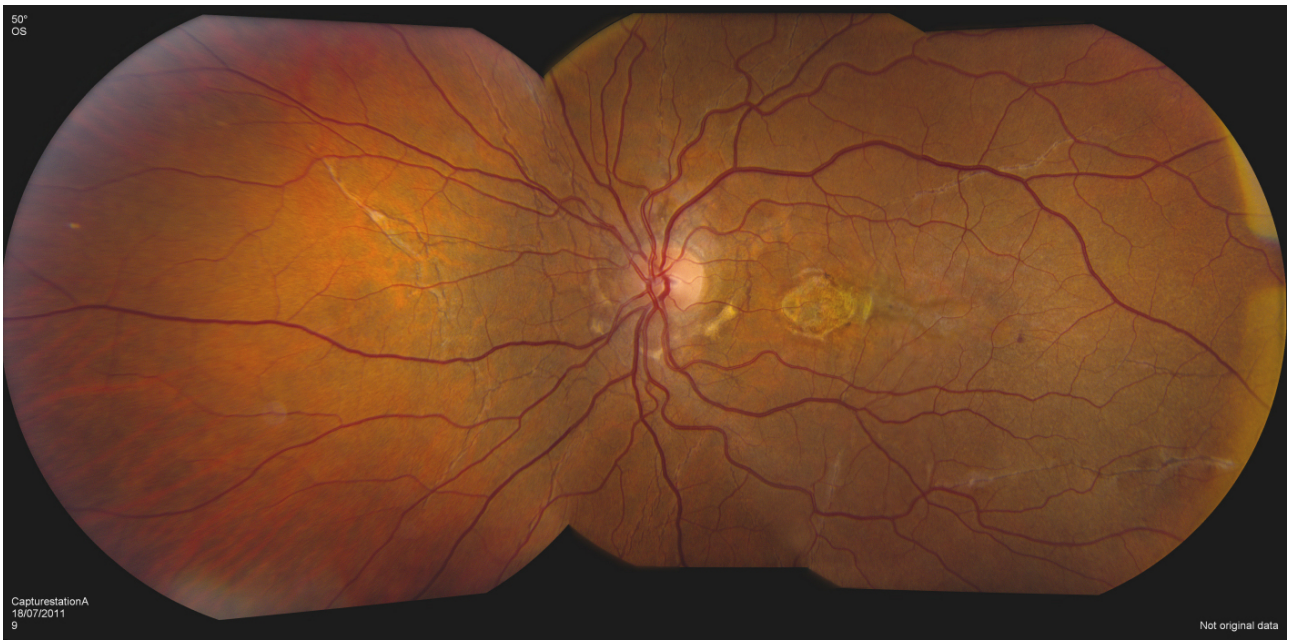

Figure 1: The composite of colour photograph of the left eye shows angioid streaks in a spiderweb configuration centered around the optic nerve head and extending far in all retinal sectors. Note also an atrophic lesion (comet tail) in the nasal periphery. A fibrotic subfoveal membrane is seen with a more recent extension temporal of the macula. Note also temporal of the macula, a vertical traumatic linear break of Bruch's membrane.

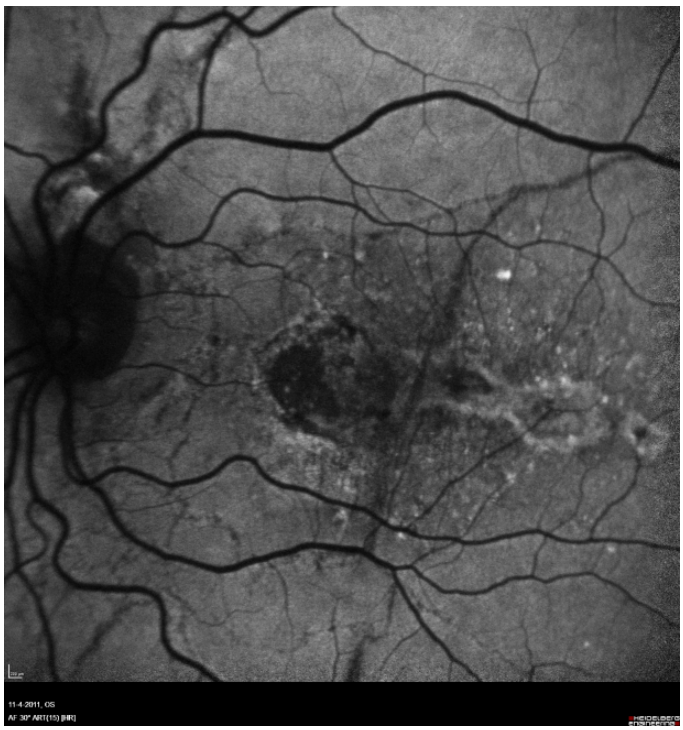

Figure 2: The autofluorescence imaging shows in the left eye hypoautofluorescence of angioid streaks, of the traumatic break, and of the longstanding choroidal neovascular membrane. The hypoautofluorescence suggest irreversible damage to RPE and overlying retina. Hyperfluorescence is noted in the recent extension of the membrane and at the borders of the CNV. Hyperautofluorescence is indicative of diseased RPE and risk for expansion of the lesion.

With the aim to confirm PXE, the patient was referred for dermatologic examination and biopsy. At age 43, there were no typical plucked-chicken appearance, no papules, macules or other skin lesions. Three biopsies from the flexural skin of the axilla and the neck did not reveal PXE related changes. Subsequently, to further exclude or confirm PXE, a blood sample for genetic analysis was taken. Analysis showed that our patient was homozygous for the R1141X-mutation in the ABCC6-gene. The diagnosis of PXE was withheld, discussed with the patient, and shared with his treating generalist to allow optimal further follow-up of the condition.

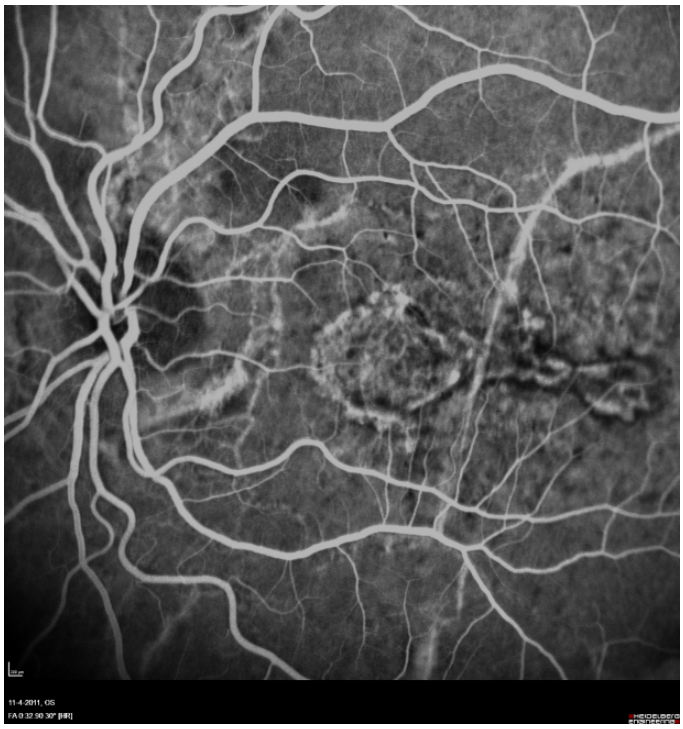

Figure 3: The fluorescein angiography of the left eye shows at 30 seconds hyperfluorescence of the angioid streaks, the traumatic break, and the neovascular membrane.

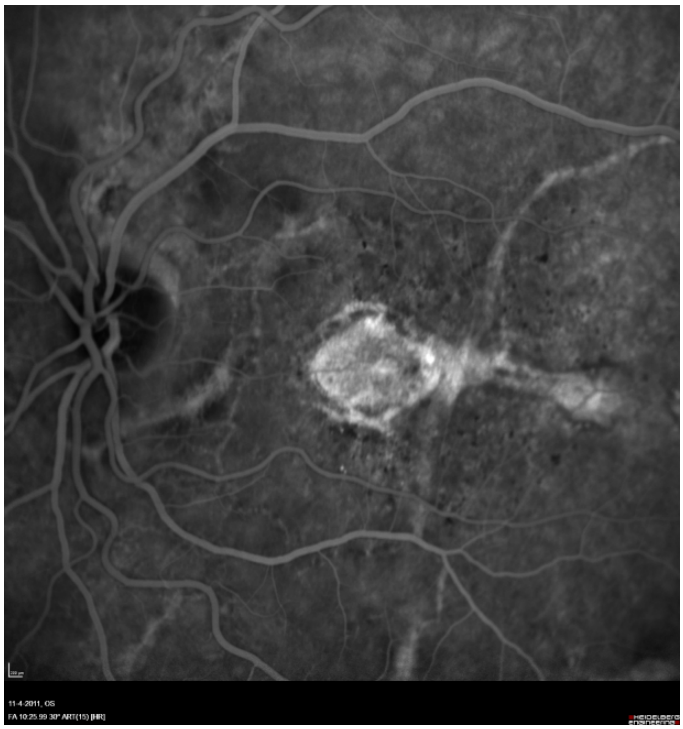

Figure 4: The 10 minutes angiogram of the left eye shows staining of these lesions without leakage and is indicative of low grade activity of the CNV.

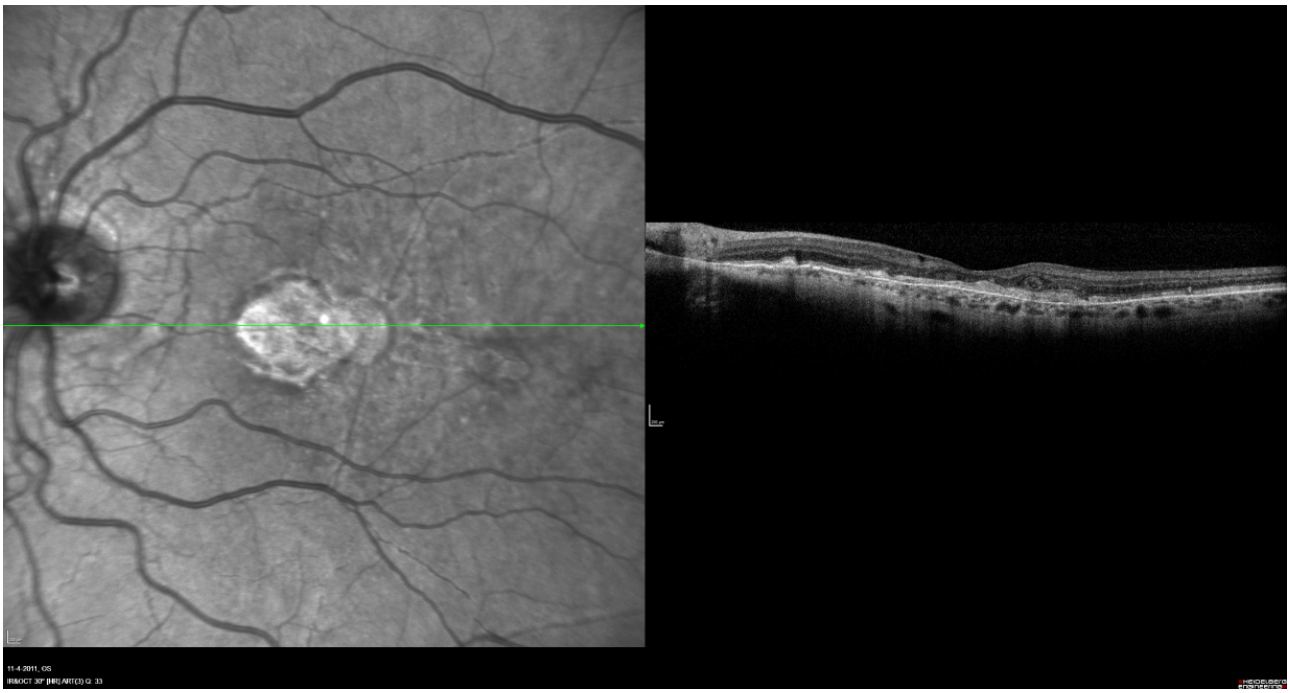

Figure 5: A horizontal section of the Spectralis OCT shows a subretinal neovascular scar and overlying retinal degeneration without obvious oedema or other signs of active CNV.

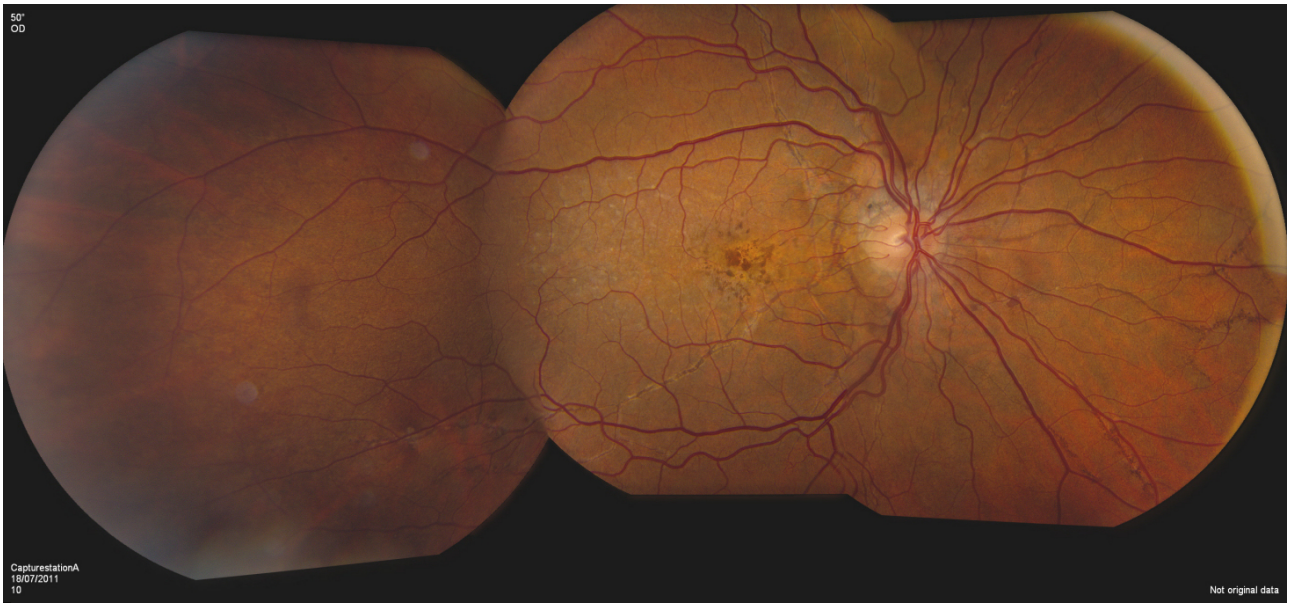

Figure 6: The composite of colour photographs of the right eye shows PXE-associated lesions including angioid streaks centered around the optic nerve and extending in all sectors, peau d'orange temporal of the macula, and a maculopathy with pigment dispersion.

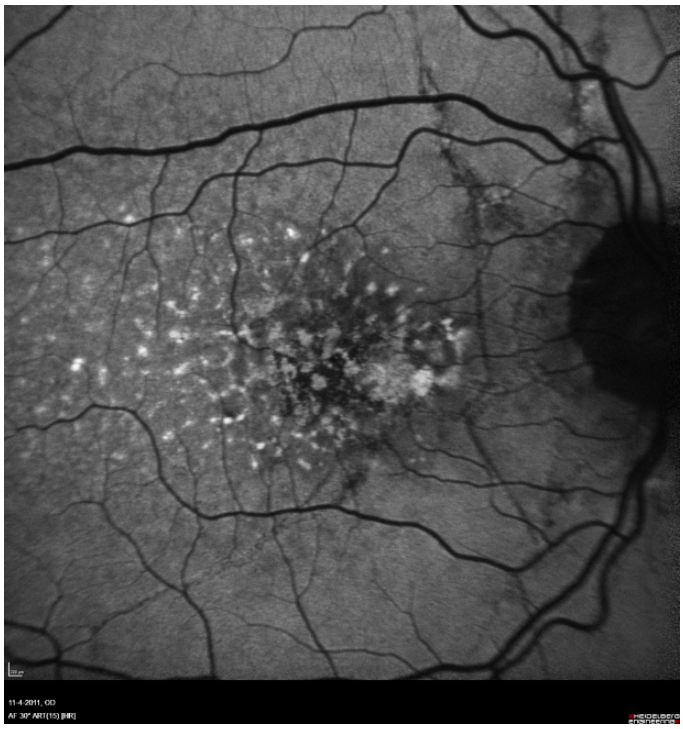

Figure 7: The autofluorescence imaging shows a few hypoautofluorescent spots and numerous hyperautofluorescent lesions.

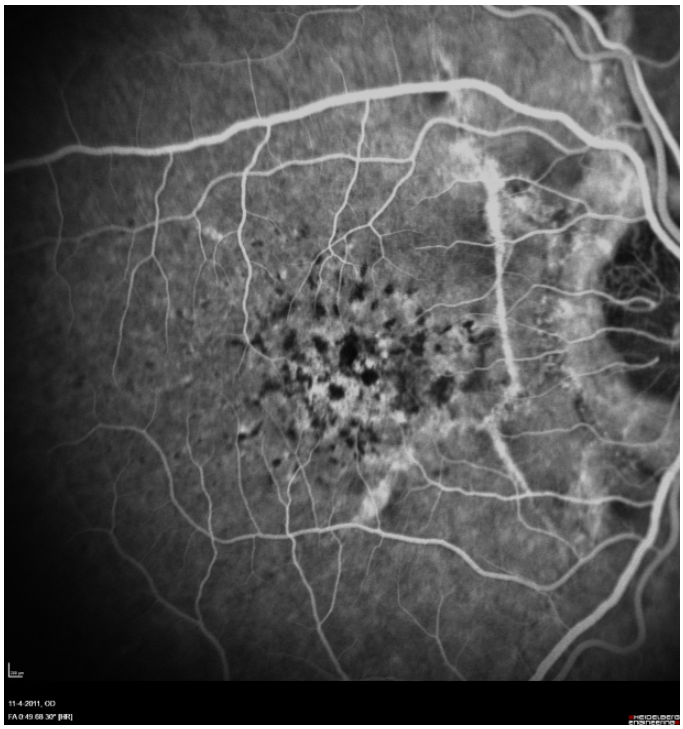

Figure 8: The fluorescein angiography shows at 50 seconds hyperfluorescence of the angioid streaks and of the vertical traumatic rupture in the papillomacular area and macular pigment clumping.

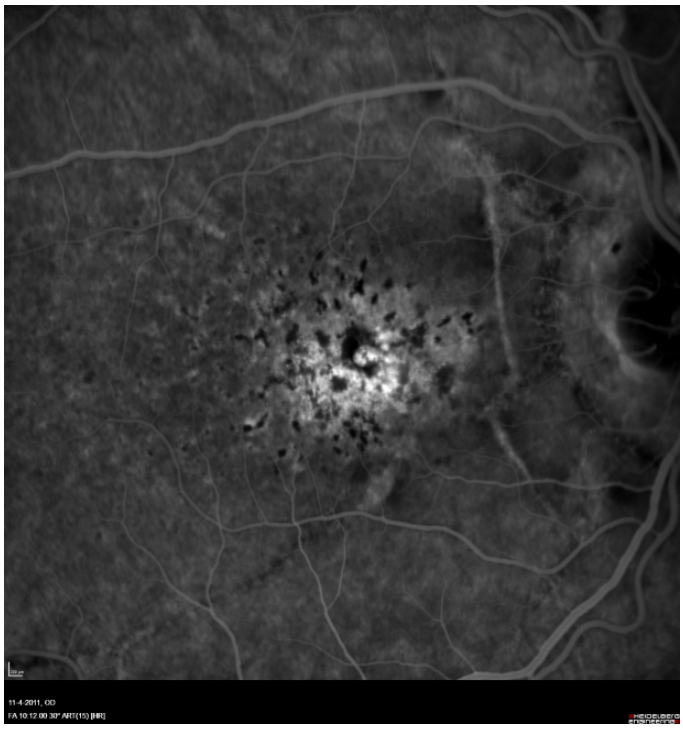

Figure 9: The 10 minute angiogram shows staining of the angioid streaks, and combined staining and leakage in the macular lesion, suggestive for low grade activity of the CNV.

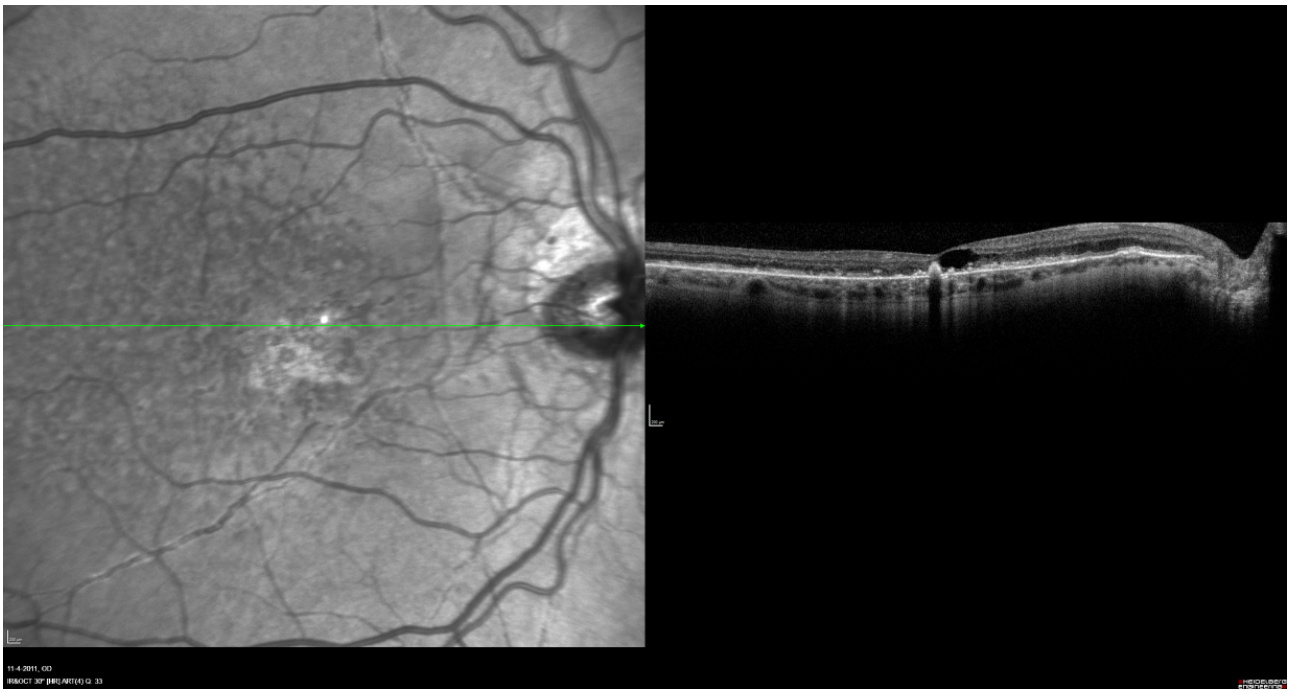

Figure 10: A horizontal section of the spectralis OCT shows in the right eye a subretinal lesion with a large overlying cystic lesion.

Discussion

Pseudoxanthoma elasticum is an autosomal recessive inherited disorder caused by a mutation in the ABCC6 gene on chromosome 16p13.1 which encodes a transmembrane transporter, resulting in progressive mineralization and calcification of the connective tissue [5]. There is a considerable spectrum of genetic mutations, with the most frequent being the R1141X nonsense mutation, accounting for 20–30% of all the mutations [6]. So far, no correlation has been identified between genotype and phenotypic expression, and the expression of PXE is highly variable, even within families.

PXE is a multisystem disease affecting the skin, eyes, cardiovascular and gastrointestinal system. In general, patients with PXE have a normal life span, but the PXE-related morbidity and mortality depend on the extent of systemic involvement. Complications include cosmetic problems, loss of vision, cardiovascular disease with hy-

pertension, premature atherosclerosis, angina pectoris, myocardial infarction and intermittent claudication, and hemorrhagic diathesis with gastrointestinal bleeding.

The skin lesions are usually the first lesions indicative of PXE. The earliest sign is the appearance of small, asymptomatic soft, yellowish papules in a reticular pattern on large flexor surfaces. The diagnosis of PXE is occasionally made in children [7], [8]. However, the typical PXE patient presents around the age of 20, with yellowish papules or macules which give the skin a plucked-chicken appearance. These lesions most frequently occur in the flexural areas as the neck and axillary folds, antecubital and popliteal fossae [4]. Sometimes the dermal anomalies are extremely mild, and in our case apparently absent. Lebwohl et al. described so-called 'occult-PXE' in several patients with premature coronary artery disease [9]. The diagnosis of PXE was made with identification of angioid streaks and with biopsies from non-lesional flexural skin showing fragmented and clustered calcified elastic tissues in the dermis.

The cardiovascular manifestations include hypertension, premature atherosclerosis intermittent claudication and coronary artery disease with angina pectoris and myocardial infarction. The prevalence of cardiovascular events in PXE patients is unknown. Most patients do not have problems before their third or fourth decade, but PXE associated cardiac failure has been reported in children. Gastrointestinal bleeding occurs in up to 15% of patients, resulting in hematemesis and melena, and can be pronounced and lethal [10].

The characteristic ocular findings are *peau d'orange*, angioid streaks, and *comet tail* atrophic lesions. In the eyes, the first visible changes are pigment irregularities giving the fundus a peau d'orange-aspect, most visible temporal to the fovea. This typically precedes the appearance of angioid streaks by several years [11]. *Comet tails* are pathognomonic PXE-related lesions, without functional repercussion, appearing later in the disease [2]. Angioid streaks are not pathognomonic for PXE, although PXE is the most common associated systemic disorder. Angioid streaks have been described in a variety of other systemic disorders including Ehlers-Danlos syndrome, Paget's disease, Marfan's syndrome, sickle cell anaemia, thalassaemia and acromegaly and in these systemic diseases other characteristic findings may lead to identification of the angioid streaks-associated disease. On the other hand, angioid streaks are observed in at least 85% of PXE patients. They are disease-induced breaks of Bruchs' membrane and remain asymptomatic, unless the macula is affected. In patients with skin lesions, fundus screening usually reveals angioid streaks as early as at age 15 and occasionally earlier [1]. Vision loss occurs in the majority of patients with PXE by the age of 50 because of macular or paramacular angioid streaks-associated ruptures in Bruchs' membrane and choroidal neovascularization causing retinal oedema, hemorrhages and scar formation. Till recently, the prognosis of PXE-associated CNV was extremely poor, but intravitreal injections with bevacizumab and ranibizumab have improved the prognosis and are able to stabilize or even improve vision in patients with recent loss of vision due to CNV [12], [13]. Other causes of visual loss in PXE are macular atrophy, generalized retinal dysfunction and optic nerve head drusen with associated nerve fiber loss [14].

When there are typical skin lesions the diagnosis of PXE is usually straightforward, but diagnosis is more difficult and often delayed for an extensive period when these are absent or atypical. Relatively frequently PXE is diagnosed when vision loss occurs and angioid streaks are identified by the ophthalmologist. In some patients the diagnosis of PXE remains overlooked due to non specific symptoms or lack of complaints. When PXE is suspected, biopsy of flexural skin of the neck or axillae and/or genetic analysis are useful to confirm the diagnosis [9].

Patients with confirmed PXE should be informed on the hereditary character of their disease and on the associated risks of complications. So far, there is no treatment available for PXE, but prophylactic measures and lifestyle adjustments should be discussed to minimize the risk of complications.

Conclusions

The patient described in this report had identification of angioid streaks at age 21, was otherwise healthy, and had at age 43 other signs of PXE, including *peau d'orange* and *comet tail*s making him very suspect for PXE. In the absence of typical skin lesions, it was mandatory to have biopsies of the neck and axillary region and to perform genetic analysis to confirm PXE. The skin biopsies could not confirm PXE, but the genetic analysis confirmed PXE resulting in genetic counseling and advise to minimize risk of PXE-associated complications. This case illustrates that strong ocular indicators of PXE, should urge the ophthalmologist to additional prove, and even in the absence of skin lesions, take opportunity to confirm PXE with skin biopsies and genetic analysis.

Notes

Competing interests

The authors have no notes/conflicts of interest concerning the report of this case.

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