

# Angioid Streaks in Psuedoxanthoma Elasticum

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## Abstract

Pseudoxanthoma elasticum (PXE) is a hereditary disorder that affects primarily the elastic tissues of skin, eyes and blood vessels. Its estimated prevalence is thought to be 1:25,000 - 100,000. PXE patients also carry an increased risk for cardiovascular and gastrointestinal diseases. Early diagnosis can play a crucial role in preventing early loss of vision and systemic complications in these patients however despite having characteristic clinical features; it is still to a large extent being under-diagnosed. Here we present two cases of PXE with reduced vision.

## Keywords

Pseudoxanthoma Elasticum (PXE), Angioid Streaks, Drusen

## 1. Introduction

Pseudoxanthoma elasticum (PXE) is a hereditary disorder that affects primarily the elastic tissues of skin, eyes and the blood vessels [1]. In skin, this leads to yellowish papules which can coalesce into plaques. In the course of time the affected skin can lose elasticity, resulting in redundant skin folds. Skin lesions almost always begin at the lateral side of the neck, together with or followed by the flexural sites of the body [2]. In the posterior segment of the eye, Bruch's membrane, an extracellular matrix between the retinal pigment epithelium (RPE) and the choroid, contains elastic fibers. Loss of elasticity and enhanced calcification in Bruch's membrane, leads to cracks in it, which is called angioid streaks. They appear as dark or reddish radial streaks emanating from the optic disc [1]. Angioid streaks are usually asymptomatic, although with increasing age, due to overlying retinal pigment epithelium (RPE) atrophy and weak barrier between choroid and retina, new blood vessels from choroid can grow into the retina

through these cracks, leading to hemorrhages and retinal scarring [3]. Macular degeneration often occurs after age 40 which is in the working age that can lead to significant vision loss [1]. The earliest sign in the fundus is some drusen-like pigmentary changes called peau d'orange. Macular degeneration is associated with disappearance of peau d'orange, atrophy of the RPE and sometimes subretinal fibrosis [4] [5]. PXE patients also carry an increased risk of cardiovascular disease and other internal organ involvement [6]. However, a recent study has shown that between different manifestations of PXE ocular complications have the highest impact on reducing their quality of life. The latter shows the importance of early and serial ophthalmologic examinations in PXE patients [6]. Herein, we present two cases of PXE with typical clinical findings and reduced vision. Morphological and functional ocular changes observed in PXE will be discussed. The patients had given their consents for the case reports to be published.

## 2. Case 1

Case 1 was a 24 years old female, a known case of PXE based on skin lesion biopsy (since 4 years ago), which was referred for evaluation of vision loss in her left eye since 3 months earlier.

On our Examination, the neck skin, showed small asymptomatic soft papules of yellow-ivory color which are among early signs of PXE along with laxity of the skin of the lateral side of her neck (**Figure 1**).

Best corrected visual acuity (BCVA) was 3/10 and 5/10 in the right and left eye respectively. External and anterior segment examination of both eyes, were normal. Relative afferent pupillary defect (RAPD) was negative and intra ocular pressures of both eyes were also normal.

Posterior segment examination of the left eye showed pigmentary changes and gray linear lesions that radiated outward from the peri-papillary area which were compatible with angioid streaks. Peau d'orange like lesions were also visible in the temporal side of macula. Fundus examination of the fellow eye showed angioid streaks with one of the breaks passing through the fovea. In addition chorioretinal atrophic spots in both eyes were visible, which is one of the fundus



**Figure 1.** Case 1, Dermatological examination: Asymptomatic, symmetric and small yellowish papules presenting in a reticular pattern on the lateral side of the neck. The affected skin was lax and wrinkled.

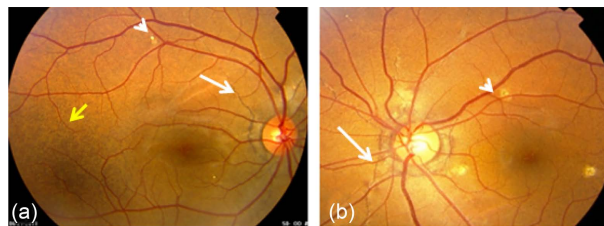
characteristics among PXE patients. Optic discs and retinal vessels were normal (**Figure 2**). Cardiological consult reported normal electrocardiogram and echocardiogram. The patient was followed with serial ophthalmic examinations with no change after one year.

### 3. Case 2

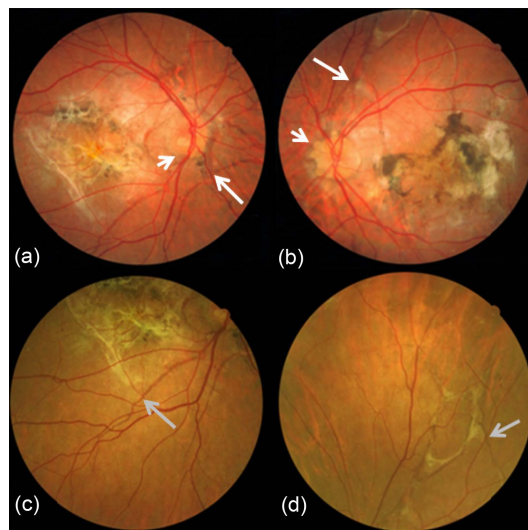
Case 2 was a 29 years old female (biopsy proven PXE 2 years ago) with a chief complaint of long standing decreased vision in both eyes. BCVA was 3/10 and 1/10 in the right and left eye respectively and the intraocular pressures were normal. External and anterior segment examination of both eyes, were unremarkable.

Fundus examination of both eyes showed, angioid streaks which were evident around the optic disc as brownish lines with extension to the periphery of the retinae. The macular area of both eyes also had prominent subretinal fibrous plaques and scar tissue, related to inactive choroidal neovascularization. Optic nerve head drusens were present in both eyes (**Figure 3**).

In autofluorescence imaging, angioid streaks appeared as dark areas due to the



**Figure 2.** Case 1, Fundus Photographs of the right (a) and left (b) eye. Angioid streaks (arrows) and chorioretinal atrophic spots (salmon spots) (arrow heads) are shown. Peau d'orange appearance on the temporal side of the right eye's macula (yellow arrow).



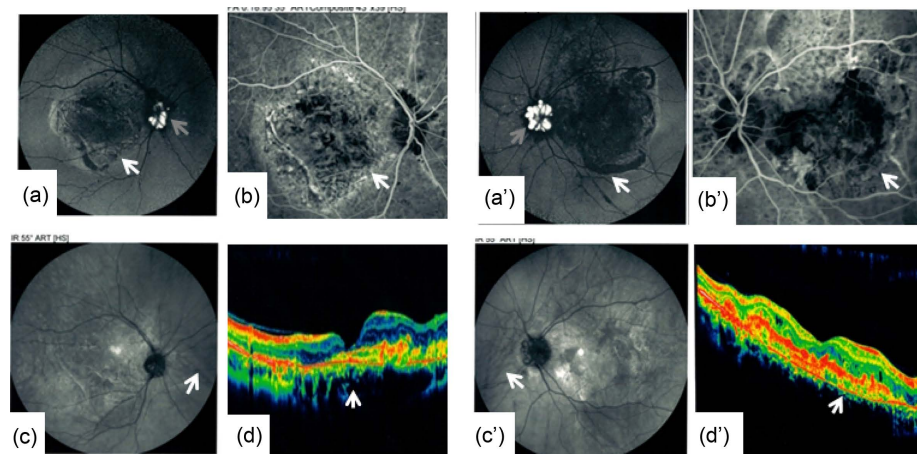
**Figure 3.** Case 2, Fundus photograph of both eyes. (a) and (b): Angioid streaks emanating from optic disc toward periphery (arrow), drusens on optic discs (arrowhead) and macular subretinal fibrosis and pigmentation and scar (grey arrows). (c) and (d): Extension of angioid streaks shown in the right eye.

atrophy of overlying RPE and optic nerve head drusens showed intense hyper autofluorescence. Infrared imaging showed hyporeflective lines in both eyes corresponding to the areas of angioid streaks. Fluorescein angiography, showed a combination of hyperfluorescence and blockage, due to window defect (RPE atrophy), and pigmented scars respectively in the macular area. Angioid streaks were also seen as hyperfluorescence areas in the early phases in fluorescein angiography because of window defect. Spectral domain optical coherence tomography (SD-OCT) showed severe atrophy and fibrosis in the macular areas with undulation of the Bruch's membrane. In the left eye, atrophy progressed to the limit that it seemed some tissue defect in the fovea existed (**Figure 4**). The patient was referred to a cardiologist and had no abnormality in electrocardiogram and echocardiogram. Regular ophthalmic examinations were scheduled for the patient that showed no change after one year of follow-up.

#### 4. Discussion

PXE, also known as Groenblad Strandberg syndrome [7] is an autosomal recessive disease, characterized by systemic mineralization and fragmentation of elastic fibers affecting the skin, eye, cardiovascular system and arterial blood vessels [1] [6] [8]. Its estimated prevalence is a range between 1:25,000 and 1:100,000 [1]. A mutation has been found in the *ABCC6* gene, which encodes for a membrane transport protein involved in the synthesis of the extracellular matrix [2].

Skin is usually the first organ system to be affected by PXE. The mean age for



**Figure 4.** Case 2, Fundus Autofluorescence, Fluorescence angiography, Infrared fundus photography and SD-OCT scans of the right and left eye. ((a), (b), (c), (d)) right eye; ((a'), (b'), (c'), (d')) left eye. ((a) (a')): Autofluorescence imaging of both eyes show intense hyperfluorescent bodies on optic disc which are compatible with optic disc drusens and hypoautofluorescent lines radiating from optic disc that is due to RPE atrophy over angioid streaks. ((b), (b')): Fluorescein angiography of both eyes show window defect in angioid streaks area due to overlying RPE atrophy and blockage of fluorescence in the macular area specially in the left eye with more pigment deposition. ((c), (c')): Infrared imaging of both eyes shows dark lines consistent with angioid streaks. ((d), (d')): SD-OCT imaging showed thickening, fragmentation and undulation of the degenerated Bruch's membrane. Atrophy of RPE and retina and subretinal fibrosis could also be seen which is more severe in the left eye.

the first visible changes at the sides of the neck is 13 years [1]. An early sign in the skin of PXE patients is the appearance of small (1 - 5 mm), asymptomatic, soft papules of yellow ivory color, presenting in a reticular pattern. Skin changes commonly start at the neck, affecting flexural areas such as axillae, inguinal region, antecubital and popliteal fossa later during the course [2].

First visible changes on the fundus of PXE patients are pigment irregularities called *peau d'orange*, which are most prominently visible temporal to the fovea [4]. These pigment irregularities have a fine, yellow, drusen-like appearance and are assumed to be localized at the level of the RPE [5]. Chorioretinal atrophic spots are seen in the periphery of fundus and are called "Salmon spots" [8].

PXE, affects the Bruch's membrane and leads to breaks in it which may appear clinically as angioid streaks, the most typical and frequent lesions, exhibited by 85% of PXE patients [1] [4] [8] [9] [10]. Angioid streaks are degenerative breaks in elastic tissue of Bruch's membrane [11]. The RPE layer over angioid streaks becomes atrophic so the barrier between choroid and retina becomes weak, facilitating the invasion of new vessels and fibrovascular growth from choroid toward retina and predisposes the patient to development of choroidal neovascularizations (CNVs). This process usually occurs at the third or fourth decade of life [1]. Histopathology demonstrates calcium deposition in the Bruch's membrane which has several well demarcated breaks [12].

Patients with angioid streaks are generally asymptomatic, unless the lesions extend towards the foveola or develop complications such as traumatic Bruch's membrane rupture or macular choroidal neovascularization (CNV) which will then lead to profound loss of vision [7].

Imagings such as autofluorescence, infrared and OCT are informative in angioid streaks, although autofluorescence and fluorescein angiography may poorly detect them unless alteration of the overlying RPE develops which exposes the Bruch's membrane pathology [13]. In other words, autofluorescence and fluorescein angiographic findings depend on the extent of RPE atrophy. Infrared imaging shows angioid streaks as dark fissures. OCT shows early breaks in degenerated, thickened and calcified Bruch's membrane.

The second phundoscopic finding discussed is *peau d'orange*, Autofluorescence imaging shows hypo-autofluorescence due to diffuse RPE alteration [11]. These lesions appear to be much more visible and widespread on infrared imaging, with extension from the posterior pole towards the whole midperiphery [13]. If there is calcification of Bruch's membrane, then they appear as hyperreflective lines [14].

Overall the visual prognosis is usually poor in patients with PXE that is due to development of CNV in 42% - 86% of patients with angioid streaks [3]. The formation of CNVs secondary to angioid streaks can be of any type (type 1, 2 CNV and even polypoidal choroidal vasculopathy) and may lead to the formation of a central disciform scar and fibrosis with subsequent severe central visual loss progressing to legal blindness by 50 years of age [3] [11]. Furthermore, pattern dystrophy like changes located in the macular region may also lead to a loss

of function of the RPE and subsequent visual dysfunction [1].

In our cases decreased visual acuity was due to two different etiologies. It was involvement of fovea by extension of a line of angioid streak (right eye) in the first case which had typical skin lesions however the second case represented an early manifestation of macular degeneration and fibrosis most likely a consequence of a previously active CNV which had not been treated.

Additionally, the rare coincidence of optic nerve drusens and angioid streaks was also seen in the second case. The association of the optic nerve head drusen and angioid streaks has been reported in the literature with a frequency of 5% in PXE patients [11]. It is important to pay attention to this point that the Patients described with angioid streaks here had been diagnosed with PXE before ophthalmologic examination and it should be kept in mind that when a patient is diagnosed with angioid streaks there are numerous other diseases such as Paget's disease, sickle-cell anemia, acromegaly, Ehlers-Danlos syndrome, and diabetes mellitus that these lesions may be associated with, and not only PXE, a thorough systemic evaluation and differentiation between these etiologies is therefore necessary for preventing mismanagement [7].

Systemic manifestations of PXE do not have a definite and effective identified treatment until now but therapies for ophthalmic manifestations have become available [8]. A recent study has shown that Ocular complications have the largest impact on decreasing the quality of life in PXE patients [6], therefore early referral to an ophthalmologist, and serial examinations yield high importance in these patients.

## 5. Conclusions

Although PXE is a rare disease, physicians must be aware of the necessity of the early diagnosis in terms of preventing ophthalmic and systemic complications. All patients with angioid streaks need to be aware of the necessity to see an ophthalmologist on a regular basis with frequency depending on the severity of ocular findings.

Ophthalmologists must also be aware of the need for systemic work-up (Cardiological consult) for patients with angioid streaks and guide the patient for quick anti-VEGF therapy or photodynamic therapy in cases of CNV formation.

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