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**Ayman Elgendy, Abdalaziz Altaweel, Eslam Alshawadfy, Eman Ali, Magdy Afify, Morad Abouelela, Karem Khalil, Ahmed M. Elsaidi**

### ABSTRACT

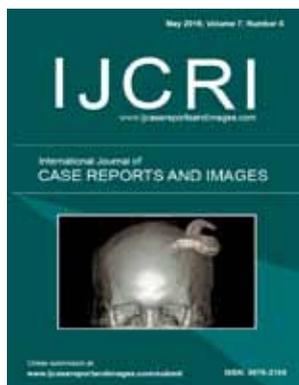
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**Case Report:** We reported a case of pseudoxanthoma elasticum which involves axillae, neck, abdomen and thighs, together with angioid streaks of fundi, but without cardiovascular events. Skin biopsy specimen was taken and was stained with hematoxylin and eosin (H&E) that revealed clumping and fragmentation of elastic fibers.

**Conclusion:** These features confirmed histopathological diagnosis of PXE.



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**Keywords:** Angioid streaks, Elastic fibers, Pseudoxanthoma elasticum

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### INTRODUCTION

Pseudoxanthoma elasticum (PXE) is an inherited systemic disease involves elastic tissue of the skin, eyes and cardiovascular system. Skin and ocular manifestations of pseudoxanthoma elasticum are referred to as Grönblad-Strandberg syndrome. The condition was named by Darier in 1896, who sought to differentiate PXE from common xanthomas. Cutaneous changes are usually the first manifestation of pseudoxanthoma elasticum, but do not become recognizable until the second or third decade of life [1].

Pseudoxanthoma elasticum can be transmitted as an autosomal dominant trait (Type I and Type II) or an autosomal recessive trait (Type I and Type II). PXE has been estimated to have a prevalence ranging from 1 in 70,000 to 1 in 1 million [2, 3].

In some families the cutaneous changes may be predominant with relatively mild eye or cardiovascular involvement, while in other families the involvement of eye and cardiovascular system may be severe with limited skin findings [4]. Pathognomonic alterations of some organs may be attributed to certain types of mutations. Polymorphisms of p.R1268Q is associated with early onset of angioid streaks [5, 6], while the stop codon mutation p.R1141X is correlated with to cardiovascular involvement independent of hyperlipidemia [7]. The first lesions to be noted are on the skin in the lateral part of the neck. Skin lesions begin in childhood but they are not usually noted until adolescence. Small, yellow papules are seen in a linear or reticular pattern and may coalesce to form plaques. Clinically,

patients show characteristic ocular manifestations, including peau d'orange, angioid streaks, and choroidal neovascularizations [8]. Intermittent claudication is the most common cardiovascular symptom (30% of patients) and often represents the first sign of atherosclerosis. Slowly progressive calcification of the elastic media and intima of the blood vessels leads to various cardiovascular manifestations [9].

## CASE REPORT

A 24-year-old male presented with 10-year history of yellow-orange lesions on sides of the neck, axillae and the thighs.

On clinical examination, it was found that the patient had yellowish papular lesions with cobblestone-like appearance, symmetrically distributed on the sides of the neck (Figure 1), the axillae (Figure 2) and abdomen.

These lesions were asymptomatic and rendered no difficulty to the patient. Fundoscopy revealed bilateral angioid streaking of the fundi (Figure 3).

Hair, nails, mucous membranes, and other systemic examinations were normal. The patient was referred to cardiologists and subjected to blood pressure measurement, an electrocardiogram (ECG) and also an examination of arterial stiffness. Furthermore, the patient has been subjected to an abdominal echography. Patient had no cardiovascular or hemorrhagic events. Complete blood cell count and urine analysis were done, which were within the normal limits. There was no family history. Skin biopsy was taken and sent for histopathological examination. Hematoxylin and eosin (H&E) staining demonstrated clumping, degeneration and fragmentation of elastic fibers in the mid-dermis (Figure 4).

## DISCUSSION

Pseudoxanthoma elasticum (PXE) is a rare progressive disorder that affects the elastic tissue of the skin, the eyes and blood vessels. It is also known as Gronblad-Strandberg syndrome. The basic fault in PXE appears to relate to The mutations in the transporter genes MRP6 or ABCC6, which has been mapped to chromosome 16p13. Mutations in the ABCC6 gene cause absence or non-functional MRP6 protein which may cause impairment of release of ATP from cells. As a result calcium and other minerals accumulate in elastic fibers of the skin, blood vessels, eyes, and other tissues affected by PXE [9]. There are two types of autosomal dominant pseudoxanthoma elasticum; type I is characterized by a classic skin lesions, intermittent claudication, severe recurrent angina, and severe chorioretinitis, even blindness, and type II is a much milder form, with a macular rash, mild retinal degeneration and no vascular complications [2]. Autosomal recessive pseudoxanthoma elasticum also has two types: recessive type I has the characteristic



Figure 1: Cobblestone-like yellowish papules, symmetrically distributed on the sides of the neck.



Figure 2: Cobblestone-like yellowish papules and comedones, distributed on the axilla.

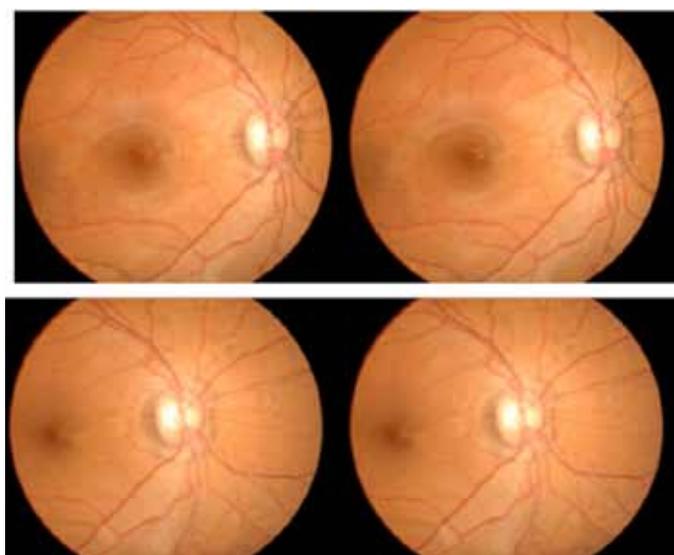


Figure 3 (A, B): Bilateral angioid streaking of the fundi.

flexural distributed skin rash, moderately severe ocular disease, and increased risk to gastrointestinal bleeding, and recessive type II is much rarer and affects the entire skin which is soft, lax and wrinkled. It shows extensive infiltration with degenerated elastic fibers [3].

Cutaneous changes are usually the first manifestation of pseudoxanthoma elasticum. These lesions starts during childhood and progresses sluggishly during adulthood. Small, yellowish papular lesions in a linear or reticular pattern are seen on the neck, axillae, groin, and flexural creases. On advancement of the disease, the skin may become loose, lax and redundant and it hangs down in folds producing the typical plucked chicken appearance [10].

The histology of PXE is characteristic: skin lesions show clumped and fragmented elastic fibers with calcium deposits in the mid and deep reticular dermis. Similar changes occur in elastic fibers of Bruch's membrane of the eye, the blood vessels, endocardium and other organs [11]. Abnormal calcium deposits can be demonstrated with the von Kossa stain in the connective tissue. Initially, mineralization of the elastic fiber has been seen as a central core of electron density on electron microscopy, then core density increases as mineralization continues. Dermal mineralized areas show deposits of thread-like material and collagen fibrils of irregular diameter. Ultrastructurally, extracellular matrix components such as proteoglycans, fibronectin, vitronectin, and have been found to be accumulated in lesional skin. Raised levels of glycosaminoglycans were seen in affected skin and urine of some patients with PXE [12]. It has been found that 87% of patients with pseudoxanthoma elasticum have angioid streaks (AS), seen as irregular radiations from a ring-like area around the disc and extending out into the fundus. Angioid streaks are visible as dark red-to-brown bands and are variable in their pigmentation. Angioid streaks result from crack-like breaks in Bruch's membrane due to its abnormal structural composition, which predisposes to these localized areas of rupture. During fluorescein angiography, angioid streaks reveal

increased fluorescence in the early phase resulting from increased visibility of the choroid due to the local defect in Bruch's membrane and in the later phase due to the leakage from the adjacent choriocapillaris. The frequent clinical association of angioid streaks and disciform degeneration at the macular area and the similarity of the histopathological changes indicate some pathogenetic link between them. Macular involvement with loss of vision usually appears after age 40 years. Angioid streaks may progress slowly or remain stationary for years. Two possibilities are suggested to be the cause of angioid streaks: [1] Degenerative changes in Bruch's membrane which are incidental to several other pathological conditions; [2] Primary degeneration of the Bruch's membrane which is bilateral and inherited with elastic tissue degeneration in other tissues of the body. Bruch membrane defects predispose to choroidal neovascularization, which may cause subretinal hemorrhage and ultimately disciform degeneration. Loss visual field due to optic disk drusen has been reported in some patients with pseudoxanthoma elasticum who have angioid streaks. The prognosis is often very poor because of choroidal ruptures and retinal hemorrhages which may occur in patients with pseudoxanthoma elasticum due to minor ocular trauma [13, 14]. Choroidal neovascularization (CNV) can be treated with surgery, photocoagulation, and photodynamic therapy with varying success [15]. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents should be considered for patients with choroidal neovascularization. Intravitreal injection of aflibercept or ranibizumab or the off-label use of bevacizumab seems to maintain visual acuity [15]. Cardiovascular manifestations include calcifications within the elastic tissue of the intima and media of blood vessels leading to intermittent claudication, coronary and cerebrovascular disease [10]. Valvular changes, mainly mitral valve prolapse, may be present. Early PXE-related coronary artery disease is often severe, most cases presenting as early angina pectoris or myocardial infarction. In some cases, coronary artery disease has led to sudden death [16]. Stroke may also occur as the consequence of ischemic or hemorrhagic cerebrovascular disease. Gastrointestinal hemorrhages are often dramatic and recurrent [17]. Acquired form of PXE has been mentioned in many case reports as an PXE with skin and ocular manifestations, similar to the hereditary PXE but without ABCC6 mutations that do not carry any genetic basis. This form of PXE may be associated with other conditions like autoimmune thyroiditis, and congenital anemia like the sickle-cell disease, and cases of spherocytosis. PXE-like skin lesions in combination with ocular and/or vascular symptoms and calcified elastic fibers were detected in some patient with beta-thalassemia. No disease-causing variant was found in the ABCC6 gene, indicating that this was a phenocopy of PXE. All these conditions related to acquired PXE show degeneration and fragmentation of the elastic fibers infiltrated with calcium and produce clinical and

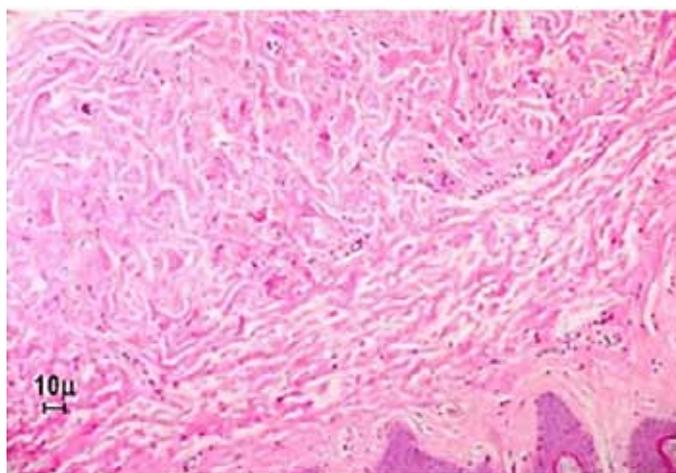


Figure 4: Optical microscope (H&E stain, x100). Elastin fibers are distorted and altered with calcium deposits.

histological changes that become evident. Injury to the elastic fibers in the above conditions may result from the focal, mechanical, and biochemical irritation to the connective tissue inducing a foreign-body reaction and leading to their degeneration [6, 18]. Differential diagnosis includes papillary dermal elastolysis, papular elastorrhexis, perforating periumbilical pseudoxanthoma elasticum, severe actinic damage to the lateral part of the neck long-term, penicillamine therapy and cutis laxa. Severe ocular lesions like those of PXE may occur in some cases. The occurrence angioid streaks in hemochromatosis may be a reflection of iron deposits. Also, angioid streaks were demonstrated in patients with Paget disease of bone and with tumoral calcinosis with hyperphosphatemia due to the deposition of calcium in a relatively normal Bruch membrane [19]. There is no treatment that directly interferes with this multifaceted disorder, although dietary restriction of calcium has been tried with limited results. For excessive areas of skin, plastic surgery may be needed. Avoidance of head trauma and heavy straining is needed to prevent retinal hemorrhage [20].

## CONCLUSION

The early diagnosis of pseudoxanthoma elasticum (PXE) may be important to minimize the serious complications and long-term impact on quality of life. This case report may help the clinicians for the early recognition and minimization of the complications of these rare disorders.

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## Author Contributions

Ayman Elgendy – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Eslam Alshawadfy – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Eman Ali – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Magdy Afify – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Morad Abouelela – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Karem Khalil – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content,

Final approval of the version to be published  
Ahmed Elsaidi – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

## Guarantor

The corresponding author is the guarantor of submission.

## Conflict of Interest

Authors declare no conflict of interest.

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