

Pseudoxanthoma Elasticum: Case Report

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Abstract

Pseudoxanthoma elasticum (PXE) is a hereditary disorder that mainly involves the skin, eyes, and cardiovascular system.

We reported a case of pseudoxanthoma elasticum with involvement of neck, axillae, abdomen and thighs, together with angioid streaking of fundi. Skin biopsy specimen was taken and was stained with hematoxylin and eosin (H and E) that revealed fragmentation of the elastic fibers. These features were suggestive of histopathological diagnosis of PXE.

We have reviewed other published reports to obtain a better understanding of the genetics, histopathology, vascular and ophthalmological manifestations of pseudoxanthoma elasticum.

Keywords: Pseudoxanthoma elasticum; Angioid streaks

Introduction

Pseudoxanthoma elasticum (PXE), also known as the GronbladStrandberg syndrome, is a rare genetic disorder that causes fragmentation and mineralization of the elastic fibers in various tissues, as first described in 1896 by Ferdinand Jean Darrier. It is characterized by elastic fiber degeneration and calcifications, seen in the midlower dermal areas.

The disorder shows a unique triple symptom complex affecting the skin, eyes, and the cardiovascular system. The striking feature of PXE is the skin lesions, which generally institute the first physical sign of the developing disorder [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), and the incidence is about 1/160000 persons, with a female predilection of 2.3:1 ratio [2,3].

Although fully penetrant, clinical findings of PXE are rarely present at birth, and the skin findings usually do not become recognizable until the second or third decade of life.

There is a considerable both intra- and inter-familial heterogeneity, so that in some families the skin manifestations may be predominant with relatively little eye or cardiovascular involvement, while in other families the involvement of the latter organ systems may have severe clinical consequences with limited skin findings [4].

Reasons for this phenotypic heterogeneity are currently not clear [5]. Though there are recent suggestions, however, linking certain types of mutations with pathognomonic alterations of some organs.

Alteration p.R1268Q is associated with early onset of angioid streaks [6, 7], while the stop codon mutation p.R1141X is correlated with cardiovascular involvement independent of hyperlipidemia [8].

Mild forms of the disorder can easily be overlooked and a negative family history does not exclude the diagnosis. It is important to recognize the disease early, in order to minimize the risk of systemic severe complications. Skin lesions are usually noted in the second or third decade and commonly affected sites are the flexures and periumbilical region. Mucous involvement is not rare. Ocular involvement is characterized by angioid streaks, breaks in the Bruch's membrane, with secondary changes of the retinal pigmented epithelium (peau d'orange) and choriocapillaris. While the angioid streaks are asymptomatic at first, they become the sites of choroidal neovascularization and subretinal haemorrhages later in life and central loss of vision may occurs in the case of macular involvement Cardiovascular manifestations usually develop last and result from slowly progressive calcification of elastic arterial walls [9].

Case Report

A 24yearold male patient reported 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 some large cobblestone like yellowish papules, 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. Funduscopy 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 haemorrhagic 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. On hematoxylin and eosin (H and E) staining, elastic fibers in the middermis are seen to be clumped, degenerated, fragmented and swollen (Figure 4).



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.

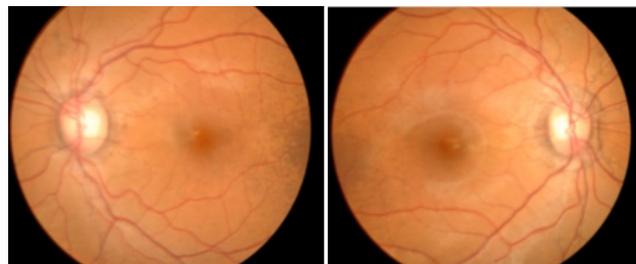


Figure 3: Bilateral angioid streaking of the fundi.

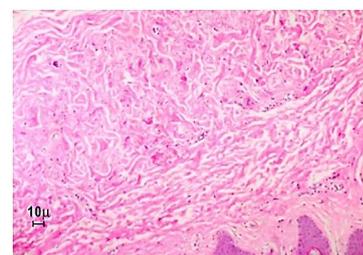


Figure 4: Optical microscope (haematoxylin-eosin staining). Elastin fibers are distorted and altered with calcium deposits.

Discussion

PXE is a rare disorder characterized by unusual fragmentation and calcification of the elastic fibers that leads to a characteristic triad of cutaneous, ocular, and vascular manifestations constituting the GronbladStrandberg syndrome. The mutations in the adenosine triphosphate (ATP) binding cassette transporter gene multidrug resistance-associated protein 6/ATP-binding cassette subfamily C member 6 (MRP6/ ABCC6), which has been mapped to chromosome 16p13; it is believed to be the leading cause of this disorder. The concept of PXE as a systemic metabolic disorder, rather than a purely structural disorder of the connective tissue, comes from the fact that the ABCC6 gene encodes for the cellular transport protein [10].

There are two types of autosomal dominant pseudoxanthoma elasticum; type I is characterized by a classic flexurally distributed rash, severe and frequent angina of effort, intermittent claudication, hypertension, and severe choroidoretinitis, even blindness, and type II is a much milder form, with a macular rash, no vascular changes, and mild retinal degeneration [2]. Autosomal recessive pseudoxanthoma elasticum also has two types: recessive type I has a flexurally distributed rash, moderately severe retinal disease, and a particular predisposition to gastrointestinal bleeding, and recessive type II is much rarer and affects the entire skin which is loose-fitting, lax, and extensively infiltrated with degenerated elastic fibers [3].

The first manifestation of the disorder starts during childhood as very pronounced cutaneous lesions and progresses sluggishly and arbitrarily during adulthood. Yellow papules are seen on the skin in a linear or reticular pattern, giving rise to a cobblestone like appearance and forming plaques. These lesions are generally seen on the lateral part of the neck, axilla, popliteal fossa, inguinal, and periumbilical

region. On advancement of the disease, the skin becomes loose and soft, laxity is seen with the loss of elasticity, and it hangs down in folds producing the typical plucked chicken appearance [11].

The histology of PXE is characteristic: in skin lesions swollen, clumped, and fragmented elastic fibers and calcium deposits are found in the mid and deep reticular dermis. Similar changes occur in elastic fibers of the blood vessels, Bruch's membrane of the eye, endocardium and other organs. Transepidermal elimination of altered calcified elastic fibers may occasionally be seen in PXE [12]. The use of elastic stains (for example, Verhoeff-van Gieson or Orcein) and stains for calcium deposits (for example, von Kossa) are recommended. Electron microscopy may be used to show the characteristic abnormalities. Initially the mineralization of elastic fiber occurs in the core. As the disease progresses the outer rim becomes increasingly dense and eventually when maximum calcification is reached fragmentation occurs. Ultrastructurally, extracellular matrix components such as fibronectin, vitronectin, and proteoglycans associated with altered elastic fibers in PXE accumulate in lesional skin. It has been suggested that these matrix proteins which are not present in normal fibers have a high affinity to calcium ions or induce mineral precipitation. Raised levels of glycosaminoglycans have been found in affected skin and urine of some patients with PXE [13].

Another feature of this multifaceted disorder includes the characteristic eye manifestations comprising angioid streaks of the retina, seen as shadowing network branching around the disc and extending out into the fundus. This network was situated more deeply than the retinal vessels and tapered as they extended with white lines on each side of the grey streaks. The colour of the streaks may be brown or black and may vary from point to point or may not have a white border or be white throughout. Streaks may also resemble pre-formed or new built vessels, coloured by a perivascular deposit of haematogenous pigment. Sometimes the streaks appear frankly red like actual vessels, although without visible connections with the retinal and choroidal vessels. Sometimes it may resemble the vessels either in the form or in colour and occasionally crossed by red-lines which appears to be underlying choroidal vessels resembling minor varieties of traumatic choroidal rupture or the fissures of the membrane of Bruch's and the retinal pigment layer of the highly myopic eye. Angioid streaks show fluorescence on photography during the arterial phase which increases during the venous phase. This is ascribed to increased visibility of the choroid as a result of the local defect in the pigment epithelium and Bruch's membrane and in the later phase to the leakage from the adjacent choriocapillaries. Reference has been made to the frequent clinical association of angioid streaks and disc form degeneration at the macular area and the similarity of the histological changes suggest some pathogenetic link between them. As a rule the angioid streaks are slow in progress and completely static while the macular lesions are apt to pass through several phases in relatively quick succession. Sometimes the angioid streaks appear before the macular changes or become visible only after the absorption of haemorrhages or exudates. 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. The degenerated membrane shows staining changes, thinned out in places and gaps which appear as cracks, erosion and perforation. Coincidentally with the alteration in Bruch's membrane and integral to the diseases are vascular changes in the choroid which lead to transudation haemorrhages and

neovascularization. The frequent appearance of the streaks long before there are signs of exudation or neovascularization suggests a primary degeneration of Bruch's membrane. The prognosis is often very poor because of the haemorrhagic exudative changes which may affect the macula [14,15].

Therapeutic approaches to treat subfoveal choroidal neovascularization (CNV) have included surgery, photocoagulation, and photodynamic therapy with varying success [15]. More recently, vascular endothelial growth factor inhibitors such as bevacizumab have led to the slowing of CNV growth and the concomitant deterioration of visual function [16].

Cardiovascular manifestations include calcifications within the elastic tissue of the intima and media of blood vessels leading to intermittent claudication, coronary and cerebrovascular disease [11].

Cases of renovascular hypertension have also been reported. 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 [17].

Stroke may also occur as the consequence of ischaemic or haemorrhagic cerebrovascular disease. Gastrointestinal haemorrhages are often dramatic and recurrent [18].

Another form of PXE has been mentioned at many instances as an acquired PXE with skin and ocular manifestations, similar to the hereditary PXE but not related to ABCC6 mutations that do not carry any genetic basis. This form of PXE is also known as pseudoPXElite syndrome and perforating calcific elastosis. Acquired PXE has been described in association with many other conditions like rheumatoid arthritis, autoimmune thyroiditis, and congenital anemia like the sickle cell disease, thalassemia, and cases of spherocytosis. All these conditions related to acquired PXE show degeneration and fragmentation of the elastic fibers infiltrated with calcium and produce clinical and 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 [7].

It was shown by Baccarani Contri et al., that elastic fibers have enhanced expression of normal constitutive proteins and are found to accumulate aberrant matrix proteins known for their high affinity for calcium and involvement in mineralization processes like alkaline phosphatase, bone sialoprotein, and osteonectin [7,19].

Differential diagnosis includes actinic elastic and elastolytic dermatitis, such as cutis laxa, middermal elastolysis, postinflammatory elastosis, and perifollicular elastolysis. However, these entities are all characterized by the loss of elastic fibers in the dermis [20].

Presently, there is no treatment of this multifaceted disorder but severity of the disease can be minimized to a greater extent. The ingestion of calcium in the affected individuals should not exceed the recommended daily allowance, particularly during childhood and adolescence. Avoidance of head trauma and heavy straining is needed to prevent retinal hemorrhage. Plastic surgery may be helpful in improving the cosmetic appearance [21]. Unless a major breakthrough in gene therapy occurs, an effective treatment for PXE lies in the basic research aimed at the defective cellular transportation mechanism of this disorder.

Conclusion

Here, we report a case of PXE with typical skin and involvement, confirming the diagnosis of PXE. Current studies suggest that PXE may be a primary metabolic disorder, with a secondary involvement of the elastic fibers. The limitation in our understanding of this disorder is due to its rarity and very minimal number of case reports in the literature.

This case report is a contribution to the readers and clinicians for the early recognition and minimization of the complications of these rare disorders.

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