Journal of Pakistan Association of Dermatologists. 2024;**34(2)**:551-555.

Case Report

Unveiling the clinical spectrum of pseudoxanthoma elasticum: A report of two cases

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Abstract Pseudoxanthoma elasticum (PXE) is a rare inherited disorder characterized by progressive disintegration as well as calcification of elastic tissue, resulting in cutaneous, ophthalmic, cardiovascular and other systemic abnormalities. It is an autosomal recessive condition caused by alterations in the ABCC6 gene. We report two cases of pseudoxanthoma elasticum with varying degrees of cutaneous and systemic manifestations of the disease. Both patients had characteristic histopathological changes on skin biopsies and fulfilled the diagnostic criteria for definite PXE. The goal is to demonstrate diverse clinical facets of the disease and to emphasize clinical clues for prompt diagnosis in order to minimize the associated complications.

Key words
Pseudoxanthoma elasticum; Elastic tissue; Autosomal recessive.

Introduction

Pseudoxanthomaelasticum (PXE), additionally referred to as the GronbladStrandberg disease, is genetic disorder inherited in an autosomal recessive pattern caused by mutations in ABCC6 gene localized to chromosome 16p13.[1,2] It is clinically characterized by a triad of cutaneous, ophthalmic and vascular changes. Despite the disease being entirely penetrant, clinical manifestations do not appear at birth. Usually, skin is the first organ to be affected and average age for first appearance of lesions is 13 years but diagnosis is often delayed further by several years. Changes include asymptomatic yellow papules 1-3 mm in size, often coalescing in a reticular pattern to give a cobblestone appearance, symmetrically spread on the neck and flexural regions particularly the axillae. Similar mucosal lesions can be found in the oral, genital and GI mucosae.[3-6] As the disease advances, skin becomes loose with loss of elasticity and hangs down in folds giving the characteristic plucked chicken appearance.[3] Prominent mental creases (horizontal and oblique) is a recently described sign which is much less sensitive but highly specific for the disease in young adults. It is produced by degradation of elastic tissue in the lips and chin causing the mentalis tendon to contract with minimal resistance.[1,7]

The primary ocular observations are a peau'd'orange pattern and angioid streaks on the retina that indicate calcium deposits in the Bruch's membrane covering the retina and can lead to vessel breakage. It results in progressive neovascularization, that leads to retinal hemorrhages and gradual deterioration of visual acuity. Regular monitoring and annual fundoscopy must be performed in patients with ophthalmic involvement.[2,8]

Calcification of small and medium caliber arterial walls occurs resulting in early atheromatosis. It can manifest as gastrointestinal bleeding, elevated blood pressure, sudden

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myocardial infarction (MI), cerebrovascular accident, or peripheral arterial obstruction.[9,10]

There is no particular therapy for this disease, and therapeutic management is centered on evaluation and mitigation of disease-related consequences.[11] A magnesium and vitamin K-enriched diet may slow the advancement of the disease. Calcium intake should not exceed recommended daily allowance particularly in adolescents. Patients should be advised to refrain from activities that include heavy straining, head trauma, sports like football, wrestling, and weight lifting to lessen the risks of retinal hemorrhage.[2] Surgery can be done to improve the appearance of cutaneous lesions.[12]

Case presentation

Case 1 A 30 years old female came to the Dermatology Outpatient Unit, with asymptomatic papules on her neck increasing progressively over the last 8 years. Examination revealed yellow confluent papules and plaques displaying a cobblestone pattern, symmetrically dispersed across the neck extending across and down the clavicles and sternum. There was no involvement of other major flexures of the body. Symmetric widespread reticular pigmentation was found on the abdomen which, according to the patient, appeared progressively over the last decade. The mental creases seemed accentuated **(Figure 1)**.

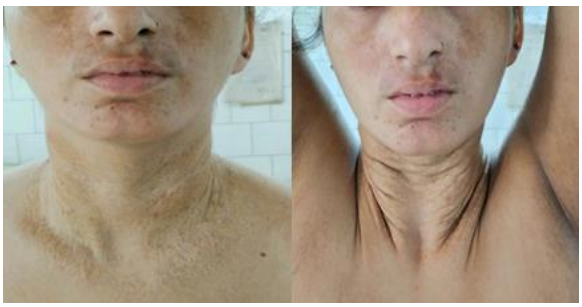

Figure 1 Yellow confluent papules and plaques on neck, exaggerated skin folds and prominent mental crease.

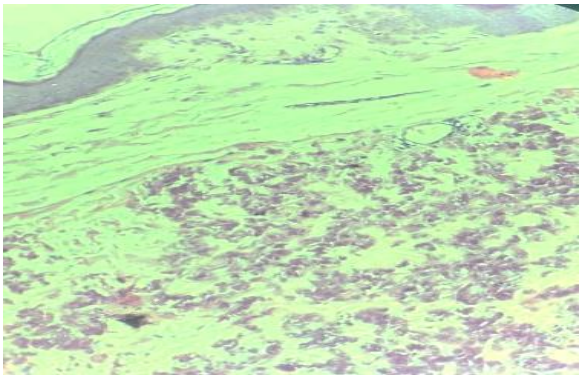

Figure 2 Clumping and fragmentation of elastic fibers in deep dermis on hematoxylin and eosin stain.

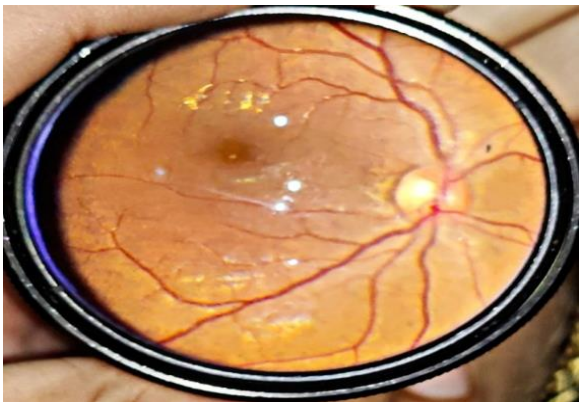

Figure 3 Peau d' orange pattern of retina on Fundoscopy.

She denied any prior experience of pruritus or inflammatory disorder, or significant sunlight exposure on affected area. She also denied using any topical or systemic medications. There had been no previous reports of claudication, elevated blood pressure, or gastrointestinal bleeding. She had a history of one spontaneous abortion in the first trimester, 5 years ago. Her parents were first cousins but none of her 3 other siblings had any comparable dermatosis. Her blood pressure was 110/70 and pulse rate 86 beats/min. ECG and echocardiography were normal. Blood cell counts, renal and hepatic profile, serum calcium, phosphate and parathyroid hormone levels were normal. The histological evaluation of neck lesions revealed swollen, disintegrated and clumped elastic fibers in the reticular dermis **(Figure 2)**. Ophthalmoscopy showed peau d'orange appearance of bilateral fundi **(Figure 3)**.

Case 2 A 40 years old man presented with a 12 years duration of asymptomatic papular lesions on the sides of his neck. There was no previous record of pruritus, trauma or topical medications to the affected area. On cutaneous examination, the patient showed small groups of confluent, smooth, skin coloured papules bilaterally on lower neck **(Figure 4)**. He also had an accentuated mental crease, and few small patches of reticulated pigmentation bilaterally over upper abdomen. For the previous five years, the patient had been hypertensive and was taking antihypertensive drugs. He was diagnosed as having multiple renal stones 3 years ago and got them removed surgically but they were recurrent and he had been experiencing renal colic on and off. There had been no previous claudications, coronary or hemorrhagic crises. His parents were consanguineously married, however no family history of comparable dermatosis was reported. His blood pressure was 150/90. Serum calcium was mildly raised, however serum phosphate and parathyroid hormone levels were normal. Blood cell counts, liver and renal profile, urine analysis, ECG, and echocardiography were all normal. Histopathological analysis with H& E stains revealed clustered and fragmented elastic fibers in the mid-dermis **(Figure 5)**. Angioid streaking of the fundi was discovered during a funduscopic evaluation by ophthalmology department **(Figure 6)**. X-ray KUB showed two radio-opaque calculi in left renal area. Referrals to cardiology, ophthalmology and urology departments were done for proper management of his respective ailments.

Discussion

Pseudoxanthomaelasticum is a multi-system disorder with considerable clinical heterogeneity. Histological examination still remains the gold standard for definite diagnosis.[14] The histopathological evaluation of fully developed skin lesions reveals elastorrhexis, a pattern in reticular dermis showing distortion and calcification of elastic fibers, more prominent with the Verhoeff Van Gieson, and Orcein stains for elastic tissue, and the Von Kossa stain for calcification.[1,2] Differential diagnosis for skin lesions includes white fibrous papulosis of neck, late onset focal dermal elastosis and elastolytic dermatoses such as cutis laxa, postinflammatory elastosis, middermal elastolysis and perifollicular elastolysis. Similar skin changes can also be observed after chronic D-penicillamine therapy. However, none of these entities have characteristic disintegration and mineralisation of elastic tissue.[13,14] So histopathological evaluation is the most important step towards a definite diagnosis after clinical assessment.

The PXE-like skin changes as well as angioid streaks have also been found in as many as 20% of patients with inherited hemoglobinopqthies such as β-thalassemia and sickle cell anaemia, yet no gene defects were observed in ABCC6 in these patients.[3,5]

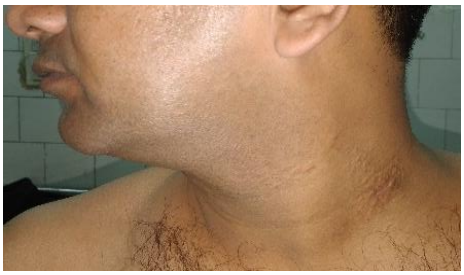

Figure 4 Confluent papules on neck and prominent mental crease.

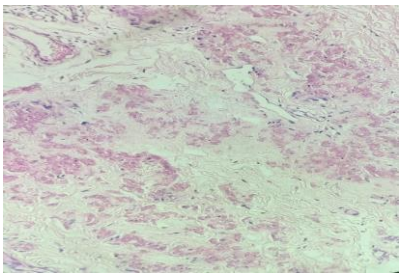

Figure 5 Clumping and fragmentation of elastic fibers in deep dermis on hematoxylin and eosin stain.

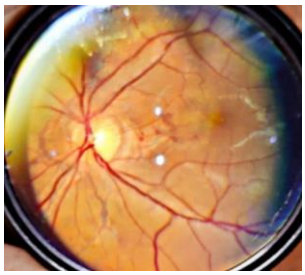

Figure 6 Angioid streaks, peri-papillary hemorrhage and peau d'orange appearance on fundoscopy.

Clinically, the onset of skin changes in these disorders is much later than in PXE, and history of blood dyscrasias since early childhood helps in differentiation. In doubtful cases, hemoglobin electrophoresis can be carried out. Both these cases had characteristic cutaneous and ocular features confirmed on histopathology and fundoscopic examination, respectively, and fulfilled the criteria for definite diagnosis of PXE.[11] Owing to our financial restraints, genetic studies were not carried out because they were essentially not needed.

Studies haves found considerable intra- and inter-familial heterogeneity in PXE so that in some families the skin manifestations may be predominant with relatively little ocular or cardiovascular involvement, while in others the involvement of the latter organ systems have severe clinical consequences with only mild cutaneous involvement.[3] A plenty of factors, genetic as well as environmental, have been proposed to play a role in modifying phenotypic expression of PXE. Diet may also play a role, in particular, high intake of dairy products during childhood and adolescence has been suggested to accelerate the clinical presentation. However, the exact role of individual dietary elements, like calcium and phosphate, as well as phosphate binders merits further investigation.[5] Our male patient had only subtle skin changes but advanced ocular findings as well as systemic involvement in the form of hypertension and renal calculi. Whereas the female patient had prominent skin changes but did not show any systemic involvement.

To summarize, regardless of the rarity of this disease, one should be aware of the protean manifestations of disease, importance of early diagnosis and regular ophthalmologic and cardiovascular evaluation for optimal treatment of the related complications when they occur.

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