

Atypical Presentation of Pseudoxanthoma Elasticum in Two Siblings from North India

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ABSTRACT

Pseudoxanthoma elasticum (PXE) is a rare hereditary disorder occurring due to metabolic defect in the liver and manifesting predominantly in the skin, eyes and arteries. It shows characteristic yellowish papules on the skin around the nape of neck along with looseness of skin over flexural surfaces. PXE shows marked phenotypic heterogeneity. Complications related to arterial wall and retinal Bruchs' membrane calcification occur later in life; early diagnosis therefore helps keep patient on follow up for development of the same. In Indian patients, classic skin changes may be missed clinically making histopathology pivotal in diagnosis and patient management.

KEYWORDS

pseudoxanthoma elasticum; hereditary; metabolic defect; ectopic calcification

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INTRODUCTION

Pseudoxanthoma elasticum (PXE) is a rare multisystem disorder characterized by progressive calcification and fragmentation of elastic fibers affecting skin, cardiovascular system and retina (1). Its prevalence is estimated to be 1 in 25,000 to 100,000 individuals with slight female preponderance (1). PXE has a highly variable phenotypic spectrum with no particular ethnic or racial predilection (2).

The term PXE was coined by Darrier in 1896 as the characteristic yellowish papular skin lesions give a “plucked chicken” appearance resembling xanthomas seen in hyperlipidemic disorders (3). Mutations in the ATP binding cassette C member 6 (ABCC6) gene are implicated in its etiology (4). We report this rare disorder in two siblings without any systemic complications, thus highlighting that a correct diagnosis in earlier stages of disease allows for timely follow-up of disabling complications.

PRESENTATION OF CASES

A 26-year-old Indian female (case 1) and her 18-year-old younger brother (case 2) (of non-consanguineous parentage) presented with loose skin folds over the anterior abdominal wall and axillary skin since one year which was causing aesthetic concerns (Figure 1). On general physical examination, hair, nails and mucous membranes were normal; no joint hypermobility was appreciated in



Fig. 1 Loose skin over flexural folds (elbow and axilla) and anterior abdominal wall in case 1.

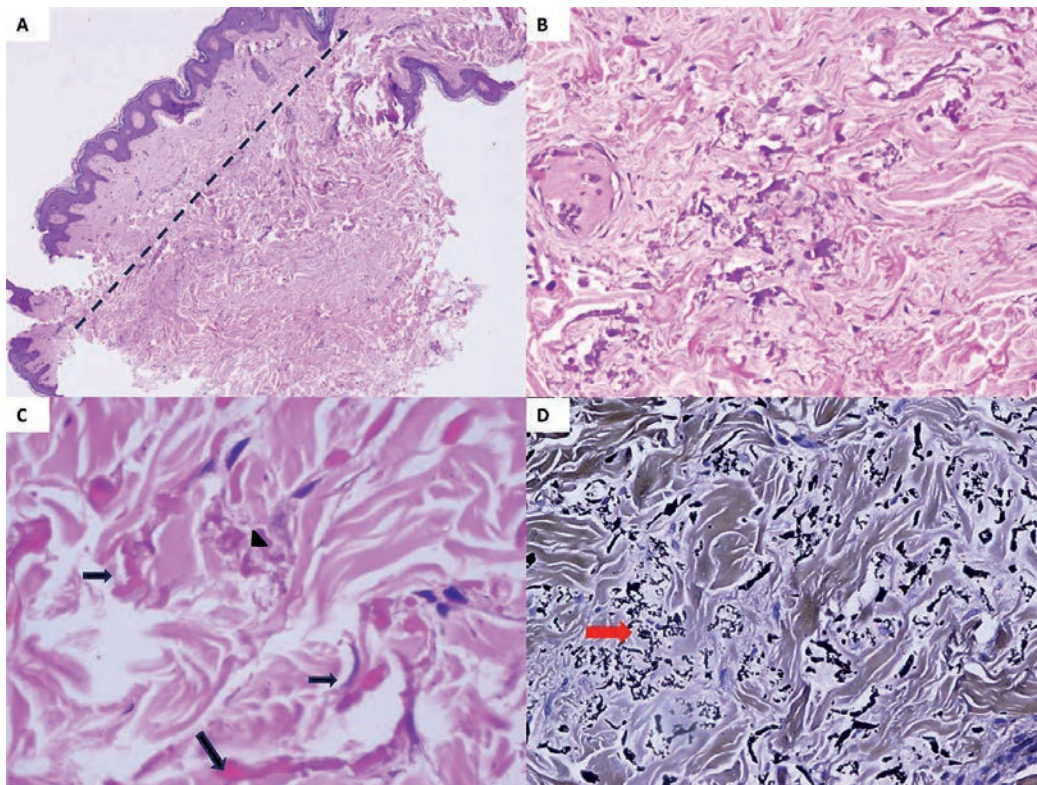


Fig. 2 A: Skin biopsy from anterior abdominal wall shows relatively unremarkable epidermis and superficial dermis while deeper dermis shows irregular, haphazard arrangement of elastic fibers (demarcated by dash line; Haematoxylin and Eosin [HE] stain, 40×), B: Fragmentation of elastic fibers with presence of basophilic deposits on these fibers (HE, 200×), C: eosinophilic, swollen and clumped elastic fibers (arrows) with basophilic granular deposits (arrow head) (HE, 400×), D: Calcium identified as black deposits on the elastic fibers (arrow) (Von Kossa stain, 200×).

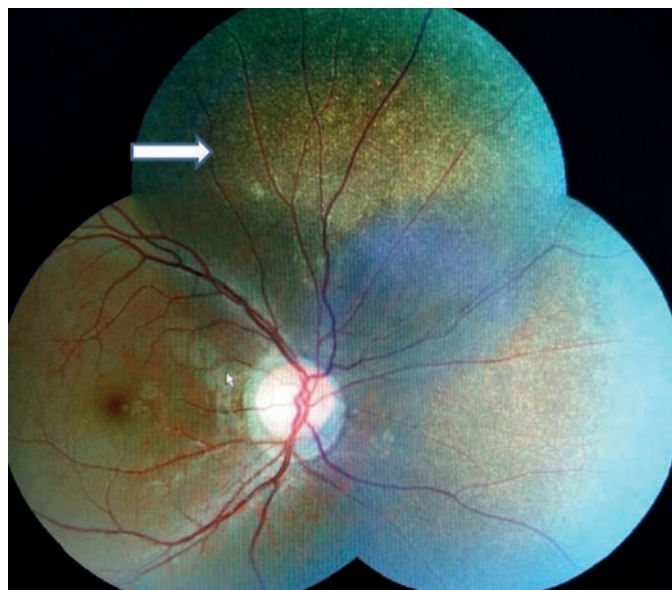


Fig. 3 Funduscopy of case 2 revealed early changes of PXE as pigmentation around optic disc or the peau d' orange appearance of macula (arrow).

either sibling. The peripheral arterial pulses were palpable; though cord like to feel. Cutis laxa and Ehler's Danlos syndrome were kept as the clinical differential diagnoses. Other 3 siblings were unaffected at present.

Skin biopsies were performed from the affected skin over anterior abdominal wall in both cases. They showed similar morphology, though much more marked in case 1 (Figure 2A-D). Epidermis and superficial dermis were unremarkable. The reticular dermis showed fragmented elastic fibers with frayed ends which were swollen, clumped and deeply eosinophilic. Additionally, fine basophilic granular deposits were seen around the fragmented fibers which were strongly positive for Von-Kossa stain indicating them to be calcium phosphate deposits. A diagnosis of PXE was made in both cases, based on characteristic histopathology.

Based on histopathology diagnosis the cases were reviewed clinically, however classic yellowish papules were not appreciated in either sibling. Following the histopathology diagnosis, complete clinical and biochemical workup for PXE was performed. Serum lipid profile, calcium levels and hemogram were found to be within normal limits in both cases. Two-dimensional echocardiography showed mild left ventricular hypertrophy in case 1. Ejection fraction was within normal limits in both cases; no valvular or arterial calcification was appreciated. Ophthalmic examination revealed "peau d'orange" changes in the macula in case 2 (Figure 3); no ocular abnormality was noted in case 1. Both patients are on routine follow up for disease progression.

DISCUSSION

PXE is inherited in an AR manner, although autosomal dominant (AD) and sporadic forms also occur. Over 350 mutations have been reported in the implicated *ABCC6*

(located on chromosome 16p13.1.2) gene which encodes an efflux transporter primarily expressed in liver, kidney and intestines (6). It is expressed at very low levels in the tissues directly affected by PXE. Based on these lines of evidence, PXE is thought to be a metabolic disorder with primary molecular defect in the liver⁵ and manifestations elsewhere (skin, eyes and blood vessels).

Under physiologic conditions, *ABCC6* protein is expressed at high levels on the baso-lateral surface of liver where it facilitates the transport of anti-mineralization factors from hepatocytes to the circulation. These factors such as Feutrin-A prevent precipitation of calcium/phosphate complexes in peripheral tissues. In the absence of *ABCC6* transporter activity in liver, the concentration of anti-mineralization factors in circulation and peripheral tissues is reduced, allowing mineralization of connective tissues to ensue (5). Additionally, fibroblasts in dermis, retinal Bruch's membrane and blood vessels show enhanced degradation due to elevated levels of matrix metalloproteinases (MMP) (4).

Clinical manifestations occur mainly in the skin, eyes, gastrointestinal (GI) tract and blood vessels (1). Although fully penetrant, clinical findings of PXE are rarely present at birth. Skin changes are the most frequent and also the first to appear; usually manifesting by the second or third decade of life (5, 6); they are characterized by yellowish asymptomatic papules of 1-3 mm in diameter, symmetrically distributed in the neck and flexural areas, especially the axillae with marked loosening of the skin folds. In our cases, classic skin lesions were not identified; only looseness of skin folds was observed leading to other clinical differential diagnoses. Ocular manifestations occur in the form of angioid streaks which represent breaks in the retinal Bruch's membrane due to calcium deposits (7). This may ultimately lead to the rupture of retinal vessels, with subsequent neovascularization, retinal scarring and loss of central vision. Early signs of ophthalmic involvement are seen in the form of "peau d'orange" appearance of the macula on funduscopy (7) (seen in case 2).

Calcification of medium sized arterial wall occurs, predisposing to atheromatosis. When arterial involvement is present, there are an increased propensity to GI hemorrhages, hypertension, acute myocardial infarction, cerebrovascular accident and peripheral arterial occlusion (1, 6). As cardiovascular manifestations are the last to develop, previously diagnosed cases should be on follow up long time period. Renal involvement in PXE has been reported previously (8). Thus, nephrocalcinosis and nephrolithiasis have been found in few instances as the presenting complaint in PXE (9). Of interest, some approaches in the treatment of vascular calcification in renal affected patients may represent a novel therapy in the treatment of the vascular compromise in patients with PXE (10).

Histology of PXE is characteristic. Clumped, fragmented elastic fibers and calcium deposits are found in mid and deep reticular dermis in skin. Similar changes occur in elastic fibers of the blood vessels, Bruch's membrane of the eye, endocardium and other organs. Other dermatological and systemic diseases may have PXE like skin manifestations, clinically and histologically (11) (table 1). The most important clue for diagnosis of PXE is presence of calcium

deposits in fragmented elastic fibers in the deeper layers of dermis. These histological findings should prompt a thorough cardiovascular and ophthalmic examination.

CONCLUSIONS

PXE presents with considerable intra- and inter-familial heterogeneity; varied manifestations maybe seen within same family. Early diagnosis is crucial as it allows for follow-up for subsequent complications. In our cases, classic skin papules were not appreciated leading to clinical misdiagnosis. Hence, histopathology was pivotal in providing correct definitive diagnosis.

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