CASE REPORT

Pseudoxanthoma Elasticum: Case Report.

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Submitted: 02/05/2022. Revised edition: 12/07/2022. Accepted: 10/09/2022. Published online: 01/11/2022

Abstract

Pseudoxanthoma elasticum (PXE) is a rare multisystem genetic disorder with estimated prevalence of 1 in 25,000. It is characterised by calcification of the elastic fibres in the skin, eyes and cardiovascular system which can lead to loss of visual acuity and early cardiovascular complications. This article describes a case of PXE in a 33-year-old female and the role of histopathology and molecular genetic testing in confirming the diagnosis.

Keywords: *Pseudoxanthoma elasticum, molecular genetic.*

Introduction

Pseudoxanthoma elasticum (PXE), also known as Grönblad–Strandberg syndrome, is a rare multisystem genetic disorder with estimated prevalence of 1 in 25,000.[1] It is characterised by calcification of the elastic fibres particularly in the skin, eyes and cardiovascular system. The calcification can lead to loss of visual acuity and early atheromatosis with subsequent cardiovascular complications, hence it is imperative to recognise this rare disorder. PXE is related to mutations in the *ABCC6* (ATP-binding cassette subfamily C member 6) gene, that is located on the short-arm of human chromosome 16. It encodes a transmembrane ATP binding driven anion transporter, which is normally expressed in the liver and the kidney. The particular pathophysiological mechanism of ectopic mineralization is not yet fully explainable [2,3]. As PXE is a form of genodermatoses [4], it is possibly associated with considerable morbidity and mortality as serious cardiovascular complications [5]. Hence, we summarize the recent evidence concerning molecular genetics and pathogenetic mechanisms in a comprehensive overview of treatment perspectives. We describe a case of PXE to highlight its subtle clinical presentation and the role of histopathology in confirming the diagnosis.

Case report

A 33 years old Caucasian patient reported the onset of unusual cluster of papules that had appeared on her neck in her early twenties. She was otherwise well and had no known relevant family history. On clinical examination, the patient had a cobblestone-like cluster of yellow papules distributed symmetrically on the sides of the neck (Fig. 1). There was no lesion present on other areas of skin. She had marked striae gravidarum from two previous pregnancies. The ophthalmologic examination revealed the presence of angioid streaks. Punch skin biopsy was taken and sent for histopathological examination. On elastin stain, the biopsy revealed basophilic, degenerate curly elastin material and early cutaneous calcification (Fig. 2). The changes are mostly seen in the deep papillary dermis and reticular dermis. Based on clinical features and histological findings, she was diagnosed with pseudoxanthoma elasticum. Unfortunately, patient refused for further molecular diagnostic procedures and regular follow up for a full case study.

Discussion

PXE results from mutations in the ABCC6 gene located in chromosome 16p13.1 which codes for transmembrane transport protein. The protein is predominantly expressed in the liver and kidneys; however, its function is currently not well-understood [6]. There is a hypothesis that dysfunction of the transporter protein leads to accumulation of unknown extracellular substances on elastic tissue, subsequently causing calcium deposition and distortion of elastic fibres[7]. Thus, PXE is suggested to be a metabolic disorder, rather than a primary structural disorder of the elastic fibres.

Currently more than 300 different mutations of ABCC6 have been identified [8]. Description of two clinical types of autosomal dominant PXE, initially led to confusion in mode of inheritance of these mutations [9]. However, the recent molecular genetics has demonstrated that the PXE is an exclusively autosomal recessive disease [10]. The mutation can be detected via polymerase chain reaction amplification and direct automated nucleotide sequencing as described previously [11]. The DNA extracted from either peripheral blood leukocytes or formalin-fixed, paraffin-embedded tissues are suitable for the detection.

Clinical manifestations of PXE are present in skin, eyes and cardiovascular system. Cutaneous lesions are the most frequent first physical sign of the disorder and present as multiple yellow papules that form plaques with cobblestone-like appearance. It is usually recognised in the second

or third decade on neck, flexure and periumbilical region [12]. Characteristic ophthalmoscopic examination finding in PXE is angioid streaks caused by small breaks in calcified extracelluar matrix membrane behind the retina (Brush's membrane). Angioid streaks predispose secondary complications such as neovascularisation and subretinal haemorrhage which may impair central visual acuity [13]. In the cardiovascular system, calcification of elastic arterial walls leads to early atheromatosis and subsequent coronary and cerebrovascular disease and peripheral arterial occlusion [14]. Although earlier case reports raised concern of possible obstetric complications in PXE, Bercovitch et al. reviewed 795 pregnancies in women with PXE and concluded that PXE does not adversely affect pregnancy or vice versa [15]. The most commonly reported complications were development of marked striae in multiparous women and increase in area of skin involved by typical lesions during pregnancy.

Histology of PXE in skin classically shows fragmented and/or calcified elastic fibres in reticular and deep dermis. Clumped elastic fibers can be highlighted with elastin stains such as Van Giesson and Orcein stain while calcification can be identified with Von Kossa stain. Similar histopathological changes are present in elastic fibers of Bruch's membrane, blood vessels and endocardium [16].

The most recent diagnostic criteria of PXE was proposed by Uitto et al. which defines the presence of both ocular findings (angioid streaks) and skin finding (classic skin lesion and/or a positive skin biopsy) as diagnostic of definite PXE [11]. The criteria also state that presence of homozygosity or compound heterozygosity of ABCC6 mutations in molecular genetic testing is also diagnostic of PXE. However, the author also described approximately 10% of PXE cases fulfils the phenotypic criteria with no or only one detectable mutation in ABCC6 and emphasised the importance of correlation with clinical features.

Continued progress in understanding the pathogenic mechanisms, genetic and epigenetic factors of the severity of phenotype is required for development of effective, pathophysiology - related therapy of this currently intractable clinical syndrome [17]. There is no effective and specific treatment for the systemic manifestations of PXE until now except for the animal experiments [18].

Theoretically, the easiest way to cure a hereditary disease is to replace the mutated gene (direct gene transfer) with a wild type one. A study investigating the possibility of an adenovirus-mediated delivery of a wild type human ABCC6 to the liver of ABCC6$^{-/-}$ mice resulted in a sustained high expression of human ABCC6 protein for up to four weeks [19].

As such only effective therapies for the ocular complications are currently available [19]. liver transplantation or a partial lobe replacement would be a way to safeguard ABCC6 activity [20]. Future treatment options may include gene therapy/editing and pharmacologic chaperone therapy [21]. Impending ocular manifestations and a progressive loss of vision is often a stressful and frightening situation for patients with PXE. Underlying this pathology is the progressive calcification and friability of Bruch's membrane (BM) [22,23]. Laser Photocoagulation using argon, krypton, or dye laser technology, was the first successful attempt at treating choroidal neovascularization, secondary to age-related macular degeneration (AMD), although there was 77% recurrence in the follow-up cases [24, 25]. Another alternative treatment is photodynamic therapy (PDT. It is based on intravenous injection of a photosensitive dye (Verteporfin), which accumulates in neovascular endothelial cells. After selective activation of the dye via laser light, the emitted light induces local inflammation and vascular occlusion [26,27]. Parolini et al. (2016) reported one case of CNV due to angioid streaks that was successfully treated by using an autologous retinal pigment epithelium (RPE) and choroidal patch [28]. Although the skin alterations are mostly

asymptomatic, there are a few cases of perforating PXE, characterized by chronic or recurrent ulceration of skin lesions [29].

In conclusion, we report a case of a young woman with typical skin lesion, angioid streak and histopathological findings of PXE that fulfils the latest diagnostic criteria. She also developed marked striae gravidarum, most commonly reported adverse effect of PXE on pregnancy. This case highlights the need for correlation between clinical findings and histopathology for an accurate diagnosis of this rare disorder. The only possibility is the direct gene transfer that may hold the best potential of all the therapeutic approaches for PXE.

Declaration
We declare that there is no financial support and not presented in meeting or organisation. It is also not a clinical trial and there is no conflict of interest among the authors.

Authorship criteria
HJK: Drafting the article or revising it critically for important intellectual content
EM: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
VT: Concept and design of study or acquisition of data or analysis and interpretation of data.
TTH: proofreading related to the references, revision, editing and formatting.
GM: Final approval of the version to be published

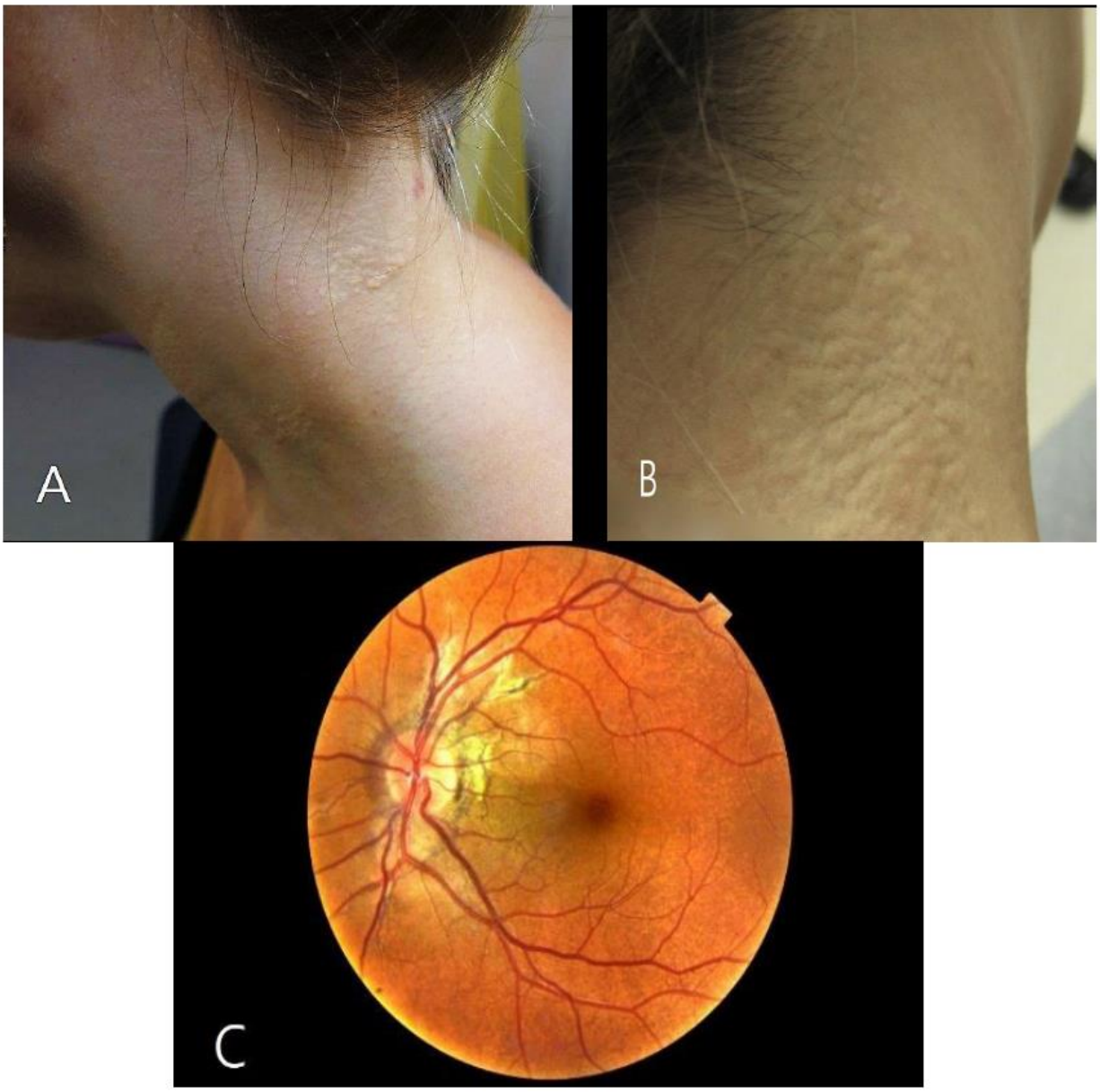

Figure 1. Clinical picture (A&B) Cobblestone-like cluster of yellow papules distributed on the neck; (C) Angioid streaks visualized in retinography.

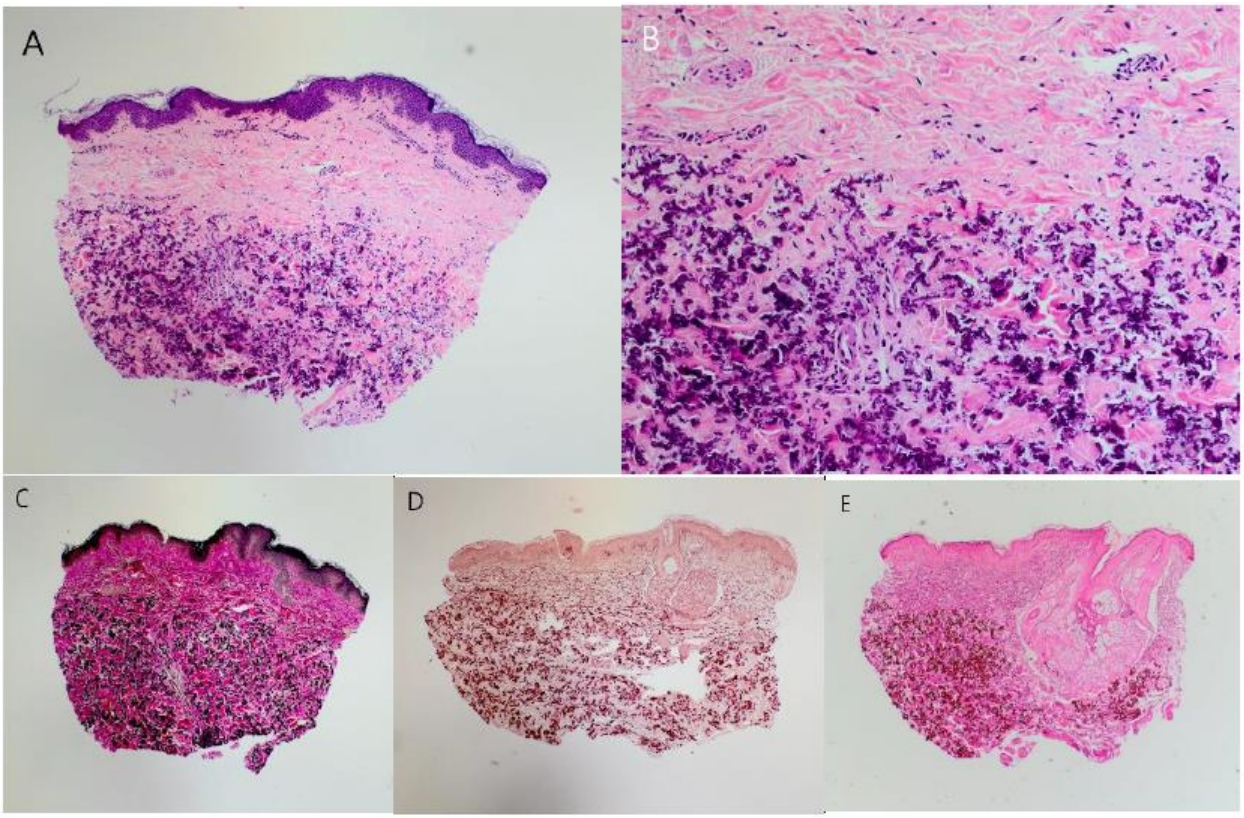

Figure 2. Fragmented and calcified elastic fibers in the deep dermis, visible under hematoxylin-eosin staining (A and B); made evident after Van Giesson (C); Orcean stain (D); and Von Kossa stain (E).

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