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CASE REPORT

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A Novel Mutation in ABCC6 Gene found in PXE Patient with Phenotypic Variance

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Abstract

Pseudoxanthoma Elasticum (PXE) is a rare disorder characterized by an accumulation of calcium deposits and mineralization of elastic fibers. The progressive mineralization and fragmentation of elastic fibers can affect a variety of organ systems including the skin, eyes, and heart. The diagnosis of PXE is commonly based on clinical manifestations, histopathological evaluation, and genetic analysis. It is known that PXE is an autosomal recessive multi-organ disorder that has a loss-of-function mutation in the ABCC6 (adenosine triphosphate-binding cassette) gene.

This is a case report of a 48-year-old female who presented with an atypical PXE presentation and was found to have a previously described ABCC6 gene mutation alongside a new gene mutation not previously associated with PXE.

Keywords: Pseudoxanthoma Elasticum; ABCC6; ENPP1; Dermatology; Angioid Streaks; Calcification; Elastic Tissue

Introduction

Pseudoxanthoma elasticum (PXE), known in early literature as Grönblad-Strandberg syndrome, was first separated from a group of related skin disorders by Ferdinand-Jean Darier. [1] PXE is a rare, progressive, systemic, hereditary disorder (autosomal recessive) in which calcium accumulates in the body's elastic tissues. Consequently, PXE can lead to serious health complications for patients; however, some patients may have a milder symptomatic form of the disorder. [2] Due to the mineralization of elastic tissues, changes may occur in the skin, cardiovascular system, eyes, and gastrointestinal tract, manifesting in a myriad of possible symptoms across several organs. [3] In the skin, PXE often results, to varying degrees of severity, in yellow macules, papules, plaques or skin folds. [4] This classic dermatological presentation of PXE includes skin changes such as cobblestone papules and plucked chicken skin that vary from person to person affected by this disorder. PXE ocular manifestations involve the development of angioid streaks, which are calcifications of Bruch's membrane, an elastic tissue containing membrane in the eye, often leading to retinal bleeding, early-onset blindness, and general vision degradation. PXE impacts the cardiovascular system when coronary arteries calcify and narrow, which can lead to myocardial infarction at an early age. Calcification of heart valves, which have elastic tissue, can lead to cardiac valvular abnormalities including mitral valve prolapse. Involvement of carotid and cerebral arteries can lead to strokes. [5] PXE has also been documented as the cause of GI bleeding. PXE causes GI bleeds from the rupture of calcified blood vessels in the GI tract, occurring in 13% of cases according to one study. [6] An autosomal recessive disorder, PXE is primarily caused by mutations in the *ABCC6* gene. These mutations lead to a deficiency of the MRP6 transporter protein responsible for transporting substances across a cellular membrane. PXE has an estimated prevalence of between 1 per 25,000 and 1 per 100,000 people, although females report a higher frequency compared to males. [7] More recently, PXE- like calcification phenotypes have been documented in patients with mutations in the ENPP1gene as a 'second genetic locus'. [8] Compound heterozygotes with ABCC6 and ENPP1 genes have been reported. Formal PXE diagnosis has been delineated as 'two pathogenic mutations in the ABCC6 gene. 'However, clinical criteria for differential diagnosis of PXE was given at a 1994 consensus conference as based upon three primary and two secondary diagnostic criteria. [9] The primary characteristics of PXE are (1) angioid streaks in adults > 20 y.o, (2) calcium in elastic fibers in skin biopsies and Von Kossa stains (calcium stains) and (3) "cobblestone papules" and "plucked chicken skin" – the primary dermatological features of the disease. The secondary criteria for PXE diagnosis are (1) a family history of PXE in close (1st degree) relatives and (2) non-lesioned skin with characteristic histological features [10].

Case Report

A 48-year-old Caucasian female patient, of Greek and Albanian ancestry, presented to dermatology to discuss her possible diagnosis of PXE. She reported no family history of PXE and no pertinent medical history. The patient had previously been seen by cardiology due to repeated myocardial infarctions without clear origin. The patient was further found to have angioid streaks on eye exams by ophthalmology in a visit a few months following her visit to cardiology. Furthermore, the patient had a history of glaucoma. In this visit, the patient's chief complaint was a rash on the bilateral axillae, groin, and abdomen lasting several years. The patient complained of painful itching and burning sensations in those affected regions. A physical exam was performed on the patient which found telangiectasia on the right axilla, but none of the typical features of PXE. Namely, the patient did not have any findings on skin exam suggestive of PXE, i.e. no cobblestone papules nor plucked chicken skin appearance, and there was no redundancy of skin found on neck or axilla (Figure 1). A punch biopsy of normal- appearing skin in the left axilla was taken and revealed fragmented and clumped elastic fibers in the dermis with deposition of von Kossa-stained material in the area of clumped elastic fibers, indicating calcium deposition (Figure 2). The patient further underwent genetic testing with GeneDX. An oral buccal culture was collected and GeneDX performed GGCX and ABCC6 gene sequencing and lesion duplication.

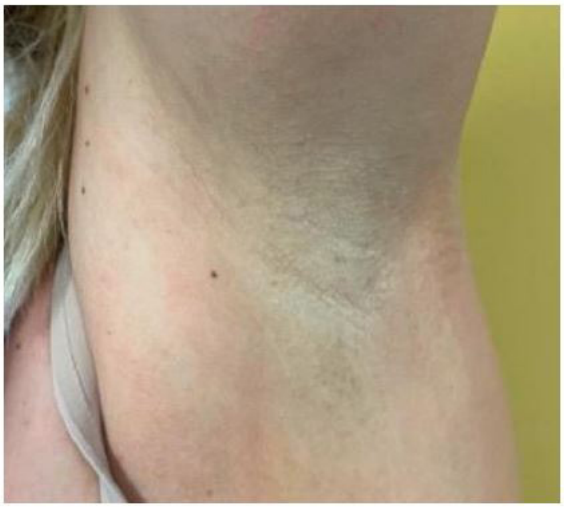

Figure 1: Patient's L axilla displaying no clinical presentation of PXE

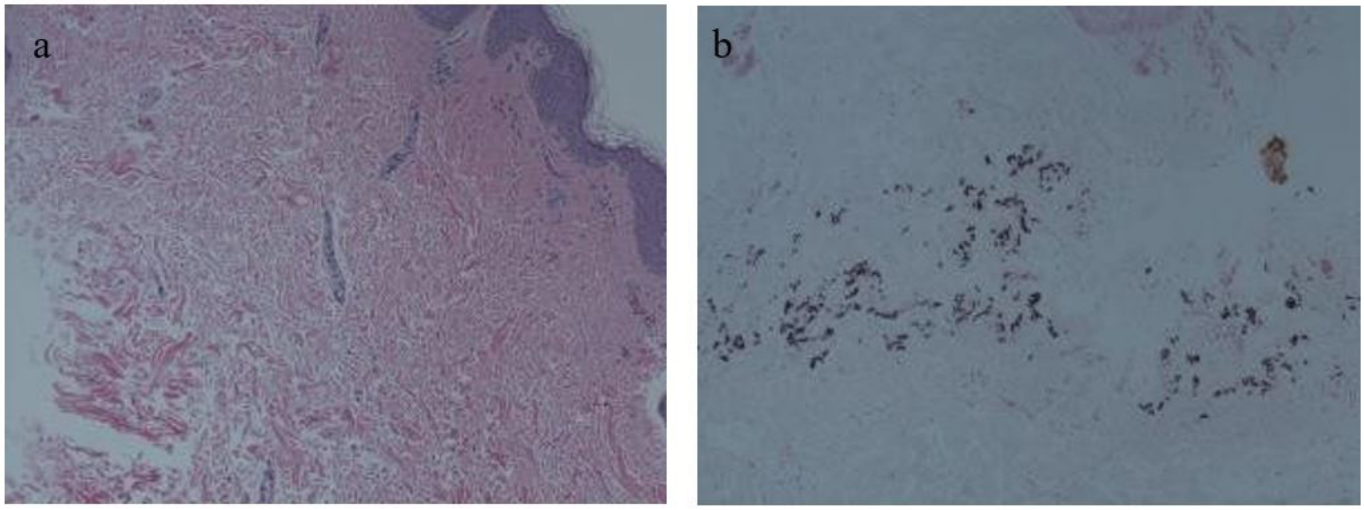

Figure 2: (a) H&E stain and (b) Von Kossa stain

Discussion

Genetic testing from the geneticist revealed a novel heterozygous variant mutation on both ABCC6 genes. The patient presented with a traditional pathogenic ABCC6 gene mutation alongside a novel ABCC6 gene mutation, a combination resulting in PXE. Specifically, this report describes a traditional ABCC6 (known pathogenic) heterozygous variant c.1171A>G (p.R391G) alongside a heterozygous VUS c.1526C>G (p.A509G) mutation of phase unknown.

The first aforementioned mutation is a known pathogenic variant mutation, while the second is also located on the ABCC6 gene but is of uncertain significance. It is difficult to correspond and differentiate specific PXE clinical manifestations/outcomes/complications based on corresponding genetic mutations due to hundreds of distinct ABCC6 mutations causing a gamut of PXE clinical manifestations. [10, 11] Moreover, while the patient did not present with all the classical clinical manifestations of PXE disease, the patient does have a history of ocular and cardiac PXE-typical manifestations including angioid streaks and myocardial infarctions, respectively. Notably absent from the patient's medical history are PXE-associated dermatological symptoms. Specifically, the patient did not present with typical PXE skin lesions. As such, definitive diagnosis of PXE was made through biopsy of normal appearing flexural skin of the left axilla confirming the presence of calcified tissue [12].

Conclusion

This case report describes the first case of PXE resulting from a novel ABCC6 mutation alongside a traditional mutation in the ABCC6 gene. Specifically, this report describes a patient with a traditional ABCC6 (known pathogenic) heterozygous variant c.1171A>G (p.R391G) and a heterozygous VUS c.1526C>G (p.A509G), phase unknown. The patient presented with some typical PXE findings, including ocular and cardiac manifestations, however, noticeably without typical visual skin manifestations. Further research needs to be conducted to see whether this novel mutation necessarily leads to PXE with other pathogenic variants of ABCC6 mutations.

Conflict of Interest

Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica.

Authors Yassky, Mumtaz, Kresch, and Phelps have no conflicts of interest to declare.

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