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Case Presentation

Pseudoxanthoma Elasticum: report of a case with a novel gene mutation

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Abstract

Pseudoxanthoma Elasticum (PXE) is a rare autosomal recessive disorder characterized by progressive calcification and fragmentation of elastic fibers in the skin, eyes, and cardiovascular system. PXE is caused by mutations in the ABCC6 gene but the specific pathophysiology of this condition remains unknown. We present a case of a patient who was diagnosed with PXE after experiencing vision loss following minor ocular trauma. Our patient had angioid streaks in her right eye, skin laxity of the bilateral dorsal hands, and yellow papules coalescing on the posterior neck. The diagnosis of PXE was confirmed by histopathological examination. PCR amplification of the patient's ABCC6 gene demonstrated a novel gene mutation that is believed to be pathogenic. Patients with PXE are at an increased risk of visual and potentially life-threatening cardiovascular complications. Early diagnosis provides the patient a greater chance of reducing associated morbidity and mortality.

Introduction

Pseudoxanthoma Elasticum (PXE) is a rare autosomal recessive disorder characterized by progressive calcification and fragmentation of elastic fibers in the skin, eyes, and cardiovascular system [1]. The incidence of PXE in the general population is estimated in the range of 1 in 50,000 to 1 in 70,000 [2, 3]. Pseudoxanthoma elasticum is caused by ABCC6 (ATP-binding cassettes subfamily C member 6) gene mutations [4]. The diagnosis is often delayed until the teens or third to fourth decade of life [5, 6]. Patients with PXE are at increased risk for vision loss and cardiovascular complications including early myocardial infarction [2]. We describe a patient who presented with vision loss after sustaining minor ocular trauma. The patient was subsequently diagnosed with PXE and found to have two disease-causing mutations in the ABCC6 gene. The first mutation (p.Arg1314Gln) was previously reported [7]. The second mutation (p.Leu955_Cys956del) has not been reported and is believed to be a novel, pathogenic mutation.

Case synopsis

A woman in her 20s presented to the optometry department with an acute decrease in her right eye vision after being struck by an unknown blunt object while standing outside. The patient had light perception only in her right eye at presentation. She had no significant past medical history and no known family history of genetic disorders. The patient was found to have retinal hemorrhage and sub-foveal blood on exam and was subsequently referred to the ophthalmology department. Foveal sub-retinal hemorrhage was confirmed by ophthalmological examination; hemorrhage was also found to be tracking along probable lines of angioid streaks extending beyond the macula. Skin changes on the neck were also discovered and the patient was referred to the dermatology department. Examination of the left posterior neck was significant for a 3x2 cm plaque of 1-2 mm yellow coalescing papules (Figure 1).

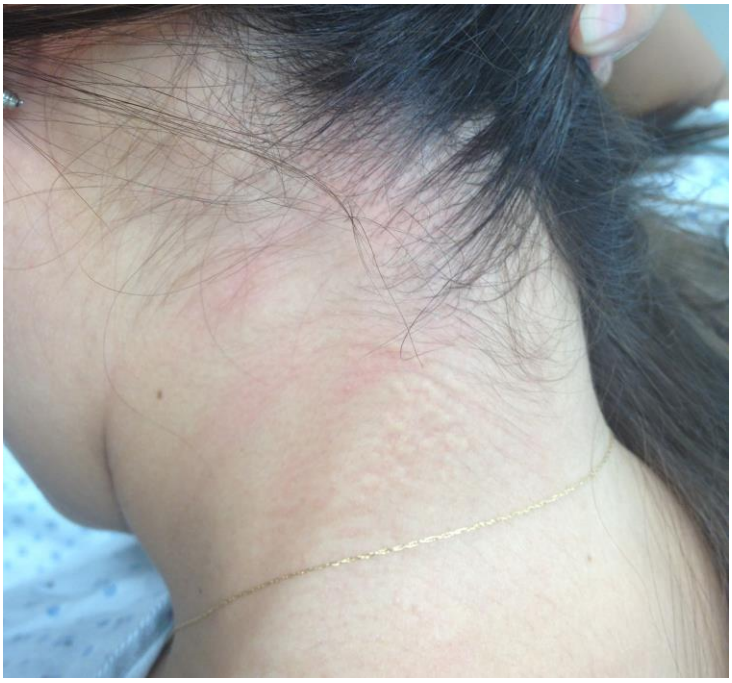

Figure 1. Plaque of coalescing yellow papules on left posterior neck

Skin laxity of the bilateral dorsal hands was also noted (Figure 2).

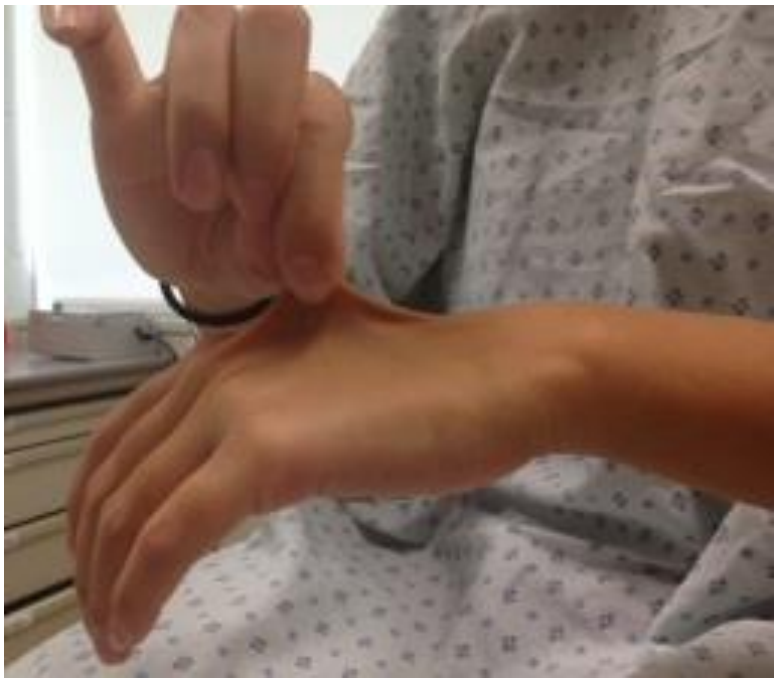

Figure 2. Skin laxity of dorsal hands

There were no skin changes or laxity in the axilla, groin, or other flexural surfaces. A punch biopsy of a neck papule was performed and histological examination demonstrated large, clumped, basophilic elastic fibers in the mid dermis (Figure 3). Stains for both elastin and calcium (von Kossa) highlighted elastic fibers consistent with the diagnosis of PXE.

The patient was subsequently referred for genetic testing. PCR amplification for analysis of exons 1-31 of the ABCC6 gene and the flanking splice sites was performed. Two disease-causing mutations were identified in the ABCC6 gene. The first mutation has been previously reported in association with PXE: p.Arg1314Gln [7]. This mutation is found in the ATP binding domain, where it is thought to affect the gene's protein binding and transport function. The second mutation, p.Leu955_Cys956del, has not been previously reported in the literature as either disease-causing or a benign polymorphism; it is believed to be pathogenic in this case.

The patient continued close clinical follow up with her ophthalmologist and she was screened for further visual complications. The patient's right eye vision improved without intervention to 20/30. She currently has no bleeding and her exam is consistent with resolving hemorrhage and residual scarring characteristic of PXE. The patient was also referred for internal medicine consultation for screening of potential cardiovascular complications. She denied symptoms of obstructive coronary artery disease including dyspnea and chest pain with exertion. The patient was normotensive and her lab work demonstrated normal renal function. Overall there was no evidence of atherosclerosis at an early age to include cerebrovascular accidents, myocardial infarction, and secondary hypertension from renal artery stenosis. The patient was extensively educated on her higher risk for cardiovascular events and gastrointestinal bleeding and instructed to report to the emergency room for chest or abdominal pain. The patient is a smoker and was strongly counseled on the necessity to quit. There have been no additional complications to date.

Discussion

Pseudoxanthoma elasticum is a rare autosomal recessive disorder characterized by the progressive ectopic calcification and fragmentation of elastic fibers in the skin, eyes, and cardiovascular system [1]. Prior claims of autosomal dominant forms appear to be examples of pseudo-dominance owing to familial consanguinity [8]. The cutaneous findings of PXE were first described in 1881 [1]. In 1896, Darier established PXE as a distinct entity from xanthomas that involved elastic tissue fragmentation [9]. Angioid streaks, the principle ophthalmological finding in PXE, were also described in the 19th century, but not connected to the previously identified skin findings until Gronbald and Strandberg reported this association [9]. The potential for early cardiovascular complications in PXE patients was later identified by Carlborg, who described several cases of cardiovascular elastic calcification [10].

Pseudoxanthoma elasticum is caused by mutations in the ABCC6 gene [4]. The ABCC6 protein is an ATP-dependent transporter that is primarily expressed in liver and kidney cell membranes and only sparsely in the tissues that actually exhibit the clinical manifestations of PXE [8, 9]. The physiological substrates exported by and specific role of the ABCC6 gene in the pathological mineralization of elastic fibers remains unknown [5, 11]. More than 300 PXE-associated mutations in the ABCC6 gene have been identified to date [4, 12]. The p.Arg1314Gln mutation found in our patient was previously reported [7]. The second ABCC6 gene mutation found in our patient has never been reported as disease-causing or as a benign polymorphism. This mutation affects a cysteine residue, frequently involved in inter and intra-molecular disulfide bonding that often affects the secondary structure of protein. This mutation specifically affects the 12th transmembrane domain of the ABCC6 protein that is vital to the correct insertion of this protein in the plasma membrane. This mutation is believed to be a novel, pathogenic mutation.

The diagnosis of PXE is often delayed owing to significant clinical heterogeneity and typically occurs in the teens or third to fourth decade of life [5, 6]. Skin changes tend to be the earliest clinical sign [1]. The primary lesions are yellow papules that gradually coalesce into plaques with a cobblestone appearance. These papules are most commonly located on the neck and flexural areas [9, 13]. The axilla is often involved, in addition to the antecubital fossa, popliteal fossa, and groin. The skin in affected areas can eventually lose its elasticity and develop redundant skin folds. In our patient, skin laxity was noted to the bilateral dorsal hands, which is atypical in classic PXE. There have been only a few case reports of PXE with generalized cutaneous laxity [14, 15]. A PXE-like syndrome with cutis laxa beyond the flexural areas has also been described, but is associated with mutations in the GGCX gene [16]. Horizontal and oblique mental creases have also been shown to have high specificity for the diagnosis of PXE before the age of 30 [14].

Histopathological evaluation of the skin reveals clumped and fragmented elastic fibers in the mid dermis demonstrated by hematoxylin-eosin stain or by specific elastic stains (orcein or Verhoeff's). Characteristically these elastic structures become progressively mineralized with calcium and phosphorous deposits that are highlighted with the von Kossa stain [2, 9].

Visual complications in PXE can be difficult to treat and often have the most significant impact on quality of life. The hallmark ophthalmological findings are angioid streaks, which result from the fragmentation and calcification of the elastic component of Bruch's membrane [18]. Other ocular manifestations of PXE include disc drusen, peau d'orange changes, and focal chorioretinal comettial lesions. Choroidal neovascularization arising from angioid streaks or choroidal rupture following minor trauma can lead to vision loss [12]. Cardiovascular complications can also have a major impact on the morbidity and mortality of PXE patients. Hypertension, intermittent claudication, gastrointestinal bleeding, and early myocardial infarction are among the complications resulting from arterial blood vessel mineralization and subsequent progressive segmental arterial narrowing [2,4].

There is no specific treatment for PXE. Patients with cosmetic concerns owing to high laxity of skin and redundant skin folds may pursue plastic surgery treatments. However, potential complications including tissue fragility and slow wound healing should be considered [15]. More recently, a case report described the use of a fractional CO2 laser on cutaneous lesions of the neck [19]. Sustained improvement in surface irregularities and distensibility of the cervical region was reported two years following treatment [19]. General management includes regular cardiovascular and ophthalmological screening examinations. Specific standards for the timing and frequency of these screening exams has not been established.

Conclusion

Pseudoxanthoma elasticum is a rare, autosomal recessive disorder characterized by ectopic calcification in the skin, eyes, and cardiovascular system. Our patient was diagnosed after sustaining a minor ocular trauma. She had angioid streaks along with classic skin and histological findings. Genetic testing revealed a novel ABCC6 gene mutation. It is important to identify individuals affected by PXE at an early age as they are at an increased risk for visual and potentially life-threatening cardiovascular complications. Our patient was extensively educated on her diagnosis and instructed to follow up annually with both the ophthalmology and internal medicine clinics for close monitoring and screening.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. Drs. Meunier and Zaleski are military service members. This work was prepared as part of their official duties. Title 17, USC, § 105 provides that 'Copyright protection under this title is not available for any work of the United States Government.' Title 17, USC, § 101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person's official duties. Dr. Meunier and Dr. Zaleski had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Ohtani T, Furukawa F. Pseudoxanthoma elasticum. J Dermatol. 2002 Oct; 29(10): 615-20. [PMID: 12432991]
2. Li Q, Jiang Q, Pfendner E, Varadi A, Uitto J. Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanims. Exp Dermatol. 2009 Jan; 18(1): 1-11. [PMID: 19054062]
3. Uitto J, Li Q, Jiang Q. Pseudoxanthoma Elasticum: molecular genetics and putative pathomechanisms. J Invest Dermatol. 2010 Mar; 130(3): 661-70. [PMID: 20032990]
4. Hendig D, Knabbe C, Gotting C. New insights into the pathogenesis of pseudoxanthoma elasticum and related soft tissue calcification disorders by identifying genetic interactions and modifiers. Front Genet. 2013 Jun 19; 4:114. [PMID: 23802012]
5. Li Q, Sadowski S, Uitto J. Angioid Streaks in Pseudoxanthoma Elasticum: role of the p.R1268Q Mutation in the ABCC6 Gene. J Invest Dermatol. 2011 Mar; 131(3): 782-5. [PMID: 21179111]
6. Li Q, Schumacher W, Jablonski D, Siegel D, Uitto J. Cutaneous features of pseudoxanthoma elasticum in a patient with generalized arterial calcification of infancy due to a homozygous missense mutation in the ENPP1 gene. Br J Dermatol. 2012 May; 166(5): 1107-11. [PMID: 22229486]
7. Le Saux O, Beck K, Sachsinger C, Le Saux O, Beck K, Sachsinger C, Silvestri C, Treiber C, Goring HH, Johnson EW, De Paepe A, Pope FM, Pasquali-Ronchetti I, Bercovitch L, Marais AS, Viljoen DL, Terry SF, Boyd CD. A Spectrum of ABCC6 mutations is responsible for pseudoxanthoma elasticum. Am J Hum Genet. 2001 Oct; 69(4):749-64. [PMID: 11536079]

8. Ringpfeil F, McGuigan K, Fuchsel L, Kozic H, Larralde M, Lebwohl M, Uitto J. Pseudoxanthoma elasticum is a recessive disease characterized by compound heterozygosity. J Invest Dermatol. 2006 Apr; 126(4): 782-6. [PMID: 16410789]
9. Chassaing N, Martin L, Calvas P, Le Bert M, Hovnanian A. Pseudoxanthoma elasticum: a clinical, pathophysiological and genetic update including 11 novel ABCC6 mutations. J Med Genet. 2005 Dec; 42(12): 881-92. [PMID: 15894595]
10. Carlborg U. Study of circulatory disturbances, pulse wave velocity, and pressure pulses in larger arteries in cases of pseudoxanthoma elasticum and angioid streaks: a contribution to the knowledge of the function of the elastic tissue and the smooth muscles in larger arteries. Acta Med Scand. 1944; 151: 209.
11. Le Saux O, Martin L, Aherrahrou Z, Leftheriotis G, Varadi A, Brampton CN. The molecular and physiological roles of ABCC6: more than meets the eye. Front Genet. 2012 Dec; 3:289. [PMID: 23248644]
12. Pfendner EG, Uitto J, Gerard GF, Terry SF. Pseudoxanthoma elasticum: genetic diagnostic markers. Expert Opin Med Diagn. 2008 Jan; 2(1): 63-79. [PMID: 23485117]
13. Panettiere P, Marchetti L, Accorsi D. Arms lift in a case of pseudoxanthoma elasticum. Case Rep Dermatol Med. 2013; 2013. [PMID: 23365766]
14. Uenishi T, Uchiyama M, Sugiura H, Danro K. Pseudoxanthoma elasticum with generalized cutaneous laxity. Arch Dermatol. 1997 May; 133(5): 664-6. [PMID: 9158429]
15. Bahadir S, Cobanoglu U, Siviloglu C, Kapicioglu Z, Baykan M. Cutis laxa-like pseudoxanthoma elasticum with ossification. Int J Dermatol. 2004 may; 43(5): 375-8. [PMID: 15117373]
16. Vanakker OM, MartinL, Gheduzzi D, Leroy BP, Loeys BL, Guerci VI, Matthys D, Terry SF, Coucke PJ, Pasquali-Ronchetti I, De Paepe A. Psuedoxanthoma elasticum-like phenotype with cutis-laxa and multiple coagulation factor deficiency represents a separate genetic entity. J Invest Dermatol. 2007 Mar; 127(3): 581-7. [PMID: 17110937]
17. Lebwohl M, Lebwohl E, Bercovitch L. Prominent mental (chin) crease: a new sign of pseudoxanthoma elasticum. J Am Acad Dermatol. 2003 Apr; 48(4): 620-22. [PMID: 12664032]
18. Viljoen DL, Bloch C, Beighton P. Plastic surgery in pseudoxanthoma elasticum: experience in nine patients. Plast Reconstr Surg. 1990 Feb; 85(2): 233-8. [PMID: 2300628]
19. Salles AG, Remigio AF, Moraes LB, Varoni AC, Gemperli R, Ferreira MC. Pseudoxanathoma Elasticum Treatment with Fractional CO2 Laser. Plast Reconstr Surg Glob Open. 2014 Oct; 2(9):e219. [PMID: 25426402]

FIGURE Legends

Figure 3. Large, clumped, basophilic elastic fibers in the mid dermis.