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Aesthetic complaints as clue to *Pseudoxanthoma elasticum*

Atzori Laura[1]*, Zucca Myriam[2], Vivanet Caterina[3], Sanna Silvia[1], Pilloni Luca[4] and Ferreli Caterina[1]

[1]Dermatology Clinic, Department of Medical Science "M.Aresu", University of Cagliari, Cagliari, Italy

[2]SC Dermatology, AOU Cagliari, Cagliari, Italy

[3]SC Medical Genetics, Asl8 Cagliari, Cagliari, Italy

[4]Pathology Division, Department of Surgical Science, University of Cagliari, Italy

Abstract

Background: Aesthetic issues might be the clue to systemic disease diagnosis, and undervaluation might postpone appropriate assessment.Pseudoxanthoma elasticum is a heritable metabolic disorder of the connective tissues, clinically affecting the skin, the eyes and the cardiovascular system, with consistent morbidity and eventual severe complications, such as blindness or unexpected gastro-intestinal bleeding.

Case report: A 23-year-old woman presented with multiple smooth yellowish papules and cobblestone plaque on the lateral and posterior side of the neck. The patient was otherwise healthy, but histological examination of a skin biopsy and ophthalmology confirmed the clinical suspect of pseudoxanthoma elasticum. Genetic testing revealed a peculiarcompound heterozygosity, with the typical pathogenic nonsense mutation on exon 9 (c.1132 C>T p.Q378X), and a novel missense mutation on exon 26 (c.3700 G>A p.E1234K), which should be thus added to the list of the disease-causing mutations.

Conclusions: Skilled expertise and careful patient's examination are the clue to recognise minimal signs of systemic disease, such as pseudoxanthoma elasticum. Phenotypical variation and differential diagnosis requires multispecialty cooperation, involving the dermatologist, ophthalmologist, pathologist, geneticist and an internist evaluation, including cardiovascular and gastro-enteric screening. As there is no specific treatment, management focuses on prevention and monitoring of complications.

Introduction

Pseudoxanthoma elasticum (PXE; OMIM 264800) is a heritable metabolic disorder of the connective tissues, clinically affecting the skin, the eyes and the cardiovascular system, whose subtle asymptomatic manifestations might be undervalued until complications develop, especially the progressive central vision loss or the unexpected gastro-intestinal bleeding [1-3]. First described by Balzer in 1884, as a special type of xanthoma, own its name to Darier [4], who described in 1896 the histopathological accumulation of fragmented and calcified elastic fibres in the mid and deep reticular dermis (elastorrhexia). Later, Gronblad and Strandberg described the ocular involvement (in 1929), while Carlborg reported the cardiovascular elastic fibres calcification in 1944 [5-7]. The various spectrum of clinical manifestations is due to an ectopic mineralization of the connective extracellular matrix, especially altering the elastic fibres assemblage [1-3]. The classic form has a Mendelian autosomal recessive transmission, but it is also reported a compound heterozygosity caused by several types of mutations in the ABCC6 gene, which resides on the short arm of chromosome 16, and encodes for the sixth member of the ATP-binding cassette transporter, a transmembrane protein involved in the extracellular matrix turnover [9-14].

We report a young Caucasian woman showing skin lesions since childhood, with an apparent negative familial history, whose histopathology assessment and genetic testing confirmed the diagnosis of PXE, but also revealed a peculiar compound heterozygosity. Beside the typical pathogenic nonsense mutation on exon 9 (c.1132 C>T p.Q378X), it was in fact documented a novel missense mutation on exon 26 (c.3700 G>A p.E1234K), which should be thus added to the list of the disease-causing mutations.

Case report

A 23-year-old woman presented to the outpatients ambulatory of our Dermatology Clinic asking for any kind of treatment to remove several asymptomatic papules of the neck, present since the age of 13, slowly increased in number and size, asymptomatic, but causing embarrassment and aesthetic complaints. The patient was otherwise healthy, except for a severe myopia, diagnosed at primary school admittance, and never re-evaluated. Dermatological examination revealed multiple yellowish ovalshaped papules, with a diameter of 2-5 mm, smooth, soft, tending to coalesce into larger cobblestone-like plaque, over the lateral and posterior side of the neck (Figure 1); similar lesions mixed with atrophic *striae distensae* were also present on the groin, while there was no mucosal involvement. A complete blood test including calcium level results. One of the lesions of the neck was biopsied and histopathological examination showed an increased amount of fragmented, clumped elastic fibres in the mid dermis, with calcium deposition confirmed by the specific Weigert-van Gieson and von Kossa stains (Figure 2). Stating the first 2 major criteria for PXE diagnosis following Lebwohl [15], an ophthalmic examination was performed, complete of fundoscopy and fluorescein angiography. The presence of a pale optic disc, with angioid streaks and a "salt and pepper-

Correspondence to: Dr. Atzori Laura, Clinica Dermatologica, Via ospedale 54 – 09126, Cagliari, Italy, Tel: 00390706092324; Fax: 00390706092580; **E-mail:** atzoril@unica.it

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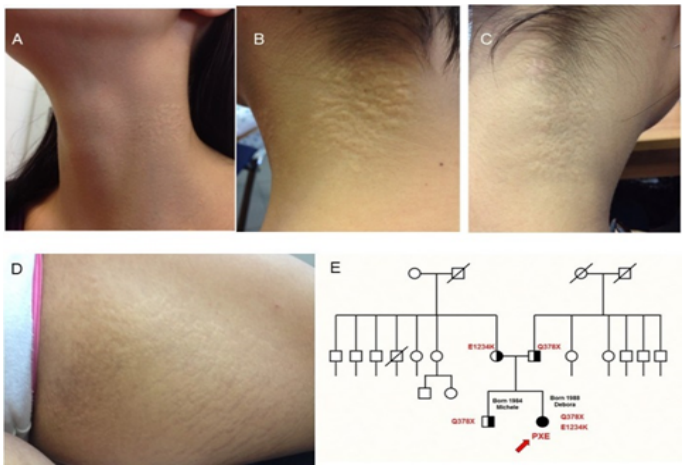

Figure 1. Skin manifestations were characterized by multiple yellowish oval shaped papules, with a diameter of 2-5 mm, tending to coalesce into larger cobblestone-like plaque, over the lateral and posterior side of the neck (Figure 1, inset A,B,C); similar lesions mixed with atrophic *striae distensae* were also present on the groin (Figure 1, inset D). Inset E illustrates the genetic consultation results with molecular testing by sequence analysis of the coding and flanking intronic regions of ABCC6 of the patients and her first degree relatives.

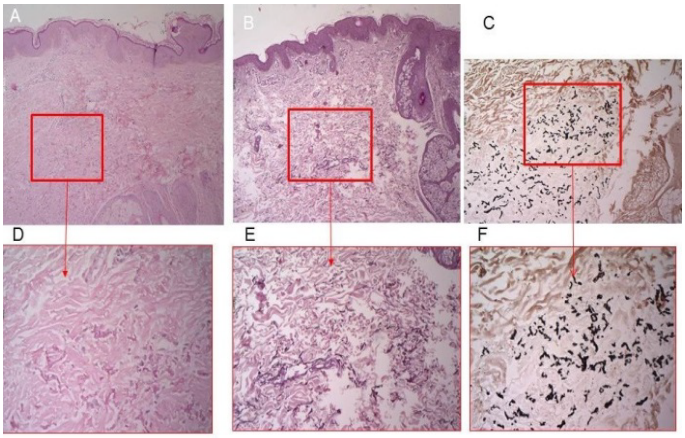

Figure 2. The skin biopsy histology showed a normal epidermis with lamellar orthokeratosis, and in the mid-dermis an increased amount of short, fragmented, granular and curled basophil fibers, morphologically attributable to elastic fibers (Haematoxylin-eosin staining;4x inset A; 20x inset D). The aberrant clumped and fragmented elastic fibers are more evident with specific stains (Weigert-van Giesonstain, 4x inset B and 20x inset E), as well as calcium deposition (von Kossa stain; 10x inset C; 40x inset F).

like" distrophy of the retinal pigment epitheliumfurther confirmed the PXE diagnosis. Cardiovascular examination, echocardiography and echo Doppler evaluation of peripheral vasculature were within normal standard.

A genetic consultation was performed at the local reference University Department, and molecular-genetic testingby sequence analysis of the coding and flanking intronic regions of ABCC6 gene, responsible of PXE, detected a typical nonsense mutation on exon 9 (c.1132 C>T p.Q378X), but alsoa novel missense mutation on exon 26 (c.3700 G>A p.E1234K). Thus, molecular diagnosis was consistent witha compound heterozygosity for PXE [13], as the association of one allele exon 9 nonsense mutation with the exon 26 missense mutation on the other alleleshould be considered disease causing in this patient. Molecular-genetic screening of the first-degreerelatives detected the nonsense mutation on exon 9 in the father and the brother andthe missense mutation on exon 26 in the mother (Figure 1, inset E), who might be considered "healthy carriers" because heterozygotes for a singular mutation, without any sign and symptom of the disease at complete clinical assessment.

The patient, still coming to our department for periodical screening, has been using topical devices to improve the skin texture with inconsistent results. General measures were suggested to control calcium intake, avoid traumatic sports, and reduce risk factors for atheromatosis, intake of drugs potentially causing mucosal bleeding. Beside, visual acuity continued to worsen dramatically, in spite of several laser-coagulation treatments, and intraocular injection of VEGF antagonist. No gastro-intestinal bleeding or signs of cardiovascular complications has occurred in 2-year follow-up.

Discussion

Pseudoxantoma elasticum shows a considerable phenotypic variability with respect to age of onset, the degree of tissue mineralization and clinical severity [1-3,15]. The prevalence is estimated between 1:25,000 and 1:100,000, without racial or geographic predilection, and a minimal female prevalence (2:1 ratio) [11]. The specific role of genotype-phenotype correlations, epigenetic factors, dietary factors and life-style are still not clear. About 300 mutations in the 31 exons of the ABCC6 gene have been associated with PXE, but the physiological function of the gene is still unknown [18]. The transmembrane protein is highly expressed in the liver and kidneys [19], while low level are detectable in the skin, retina and vessel walls, primarily affected by PXE [1,12]. In homozygous or compound heterozygous carriers, the metabolic disorder is both from liver deficient release of circulating factors and/or local defect of factors interacting with the synthesis and turnover of elastic fibers, which causes fragmentation, accumulation and mineralization, despite normal serum level of calcium and phosphate [2,18-21].

Diagnostic criteria of PXE include 3 major (skin, ocular, histopathology) and 2 minor (histopathology of non-lesional skin, family history of PXE) criteria [15], but an update of the classification have been suggested to include molecular testing results [22]. Heterozygous carriers are defined "healthy carriers" and may develop limited manifestations of the disease [23].

Cutaneous abnormalities often rise between the age of 8 and 12 years: small yellowish papules with symmetrical distribution appear on the lateral sides of the neck, antecubital and popliteal fossae, axillae and groins, and confluence into larger plaque rendering skin redundant and inelastic [1-3]. Similar lesions can also be present at the oral mucosa, especially in the lower lip, and anogenital mucosa [1,15,22].

A characteristic ocular finding is the presence of retinal angioid streaks, caused by breaks in Bruch's membrane, best observed on examination of the retina with an ophthalmoscope through a dilated pupilla and visualised using fluorescin or indocyanine green angiography [24-26]. Angioid streaks result in progressive neovascularization with subsequent subretinal haemorrhages and scarring, leading to progressive loss of visual acuity and eventual blindness.Although typical, they are not by themselves diagnostic for PXE because they can be encountered in other metabolic and heritable disorders [1,22]. Other ocular signs of PXE include "*peaud'orange*" of the retina (mottling of retinal pigment epithelium), drusen and comet-like streaks [24,25].

The diagnosis of PXE is established by histologic findings: increase of fragmented, clumped elastic fibres in the mid-dermis of clinically

affected skin, with calcium deposition detected with the specific von Kossa staining [1-3,15,22,27]. Elastic fibres calcification of non-lesional, usually flexural skin is an additional feature, included among minor diagnostic criteria [22,28].

The cardiovascular involvement, due to calcification of the internal elastic laminae of small and middle-sized arteries [1,29-31], is characterized by intermittent claudication in the lower limbs and tiredness in the upper limbs, ischaemic brain infarction, angina pectoris, myocardial infarction, digestive angina, mitral prolapse, reno-vascular hypertension, gastrointestinal bleeding because of vasal fragility [1,22,28-32]. Multiple asymptomatic calcifications on ultrasound examination in liver, spleen, breast, kidneys, testicles and pancreashave been reported in PXE [33,34]. Most women with PXE have normal pregnancies, except for a possible augmented gastro-intestinal bleeding, and the disease has no significant effect on the fetus [35-37].

Several other dermatological disease such as fibroelastolytic papulosis (papillary dermal elastolysis and white fibrous papulosis of the neck), focal dermal elastosis, papular mucinosis, Buschke-Ollendorff syndrome, solar elastosis, cutis laxa can resemble PXE clinically but not histologically [26,38-40]. Genetic testing is mandatory to further exclude other diseases, called "PXE-like", clinically and histologically indistinguishable from PXE but not associated with ABCC6 gene-mutation. They can occur in combination with vitamin-K-dependent coagulation deficiency (due to mutations in GGCX gene), haemoglobinopathies, and elastosis perforans serpiginosa, associated with D-penicillamine treatment [22,41-44].

In order to establish the extent and the severity of the disease after diagnosis, people affected by PXE should have complete skin and ophthalmic examinations, cardiovascular examination with echocardiography, cardiac stress testing and doppler evaluation of peripheral vasculature [1,15,22]. The same examinations should be repeated periodically, but no guidelines have yet established timing of long-term follow-up.

At present there is no specific therapy for PXE. General measure are suggested to people affected by PXE to reduce the risk of vascular complications, such as controlling diabetes, lipid disorder, hypertension, body weight and avoiding smoking [1,15,22]. Sports or activity at risk for facial trauma are contraindicated and aspirin, FANS or other hypo coagulant drugs should be avoided if not strictly necessary. Diet is another controversial issue with limitation of calcium intake and supplementation with high level dietary magnesium to prevent connective tissue mineralization [45-50]. Skin lesions are usually treated with cosmetic devices to improve skin texture and local destruction of single more anaesthetic lesions by using cryotherapy, diatermocoagulation and CO_2 laser-coagulation [1-3,15]. Intraocular injection of VEGF antagonist, laser-coagulation and photodynamic therapy can be used to counteract sub-retinal neovascularization and subsequent progressive blindness in patients suffering from PXE [25].

Conclusions

This case-report highlight the importance of small skin abnormality, that can appear like a simple aesthetic imperfection, but hide a systemic disease with considerable morbidity, severe quality of life compromising when the loss of visual acuity occurs and occasional mortality. Since the identification of ABCC6 gene as responsible of PXE, over 300 mutations have been detected. In our case-report, a novel mutation (c.3700 G>A p.E1234K), has been identified. Guidelines on follow-up timing and treatment protocols are necessary to improve patient's quality of life, at present limited to general measures to prevent complications.

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