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Pseudoxanthoma Elasticum: A Case Report

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Abstract

BACKGROUND: Pseudoxanthoma elasticum (PXE) is a rare, genetic, metabolic disease with autosomal recessive inheritance caused by mutations in the ABCC6 gene. The lack of functional ABCC6 protein leads to ectopic mineralization that is most apparent in the elastic tissues of the skin, eyes, and blood vessels. Dermatologic manifestations consist of small yellow papules on the nape and sides of the neck and in flexural areas that coalesce into reticulated plaques resembling the cobblestone aspect, and then the skin becomes loose and wrinkled. Histopathologic findings provide characteristic clues such as short, fragmented, clumped, and calcified mid-dermal elastic fibers.

CASE PRESENTATION: A 27-year-old Albanian female was referred to the dermatology clinic with skin complaints for approximately 17 years. On physical examination, we observed "cobblestone pattern" lesion located in the anterior, lateral, and posterior aspects of the neck, bilateral axillary, inguinal, antecubital, and popliteal regions, and periumbilical area. A biopsy was performed and the histopathology confirmed the typical changes in the dermis because of ectopic mineralization. The funduscopy revealed the "peau d'orange" aspect, bilateral angioid streaks but no neovascularization. Carotid echography showed minimal intimate thickening with flow acceleration but without significant stenosis of the right common carotid artery (ACC). Different laboratory exams were conducted that resulted within the normal range.

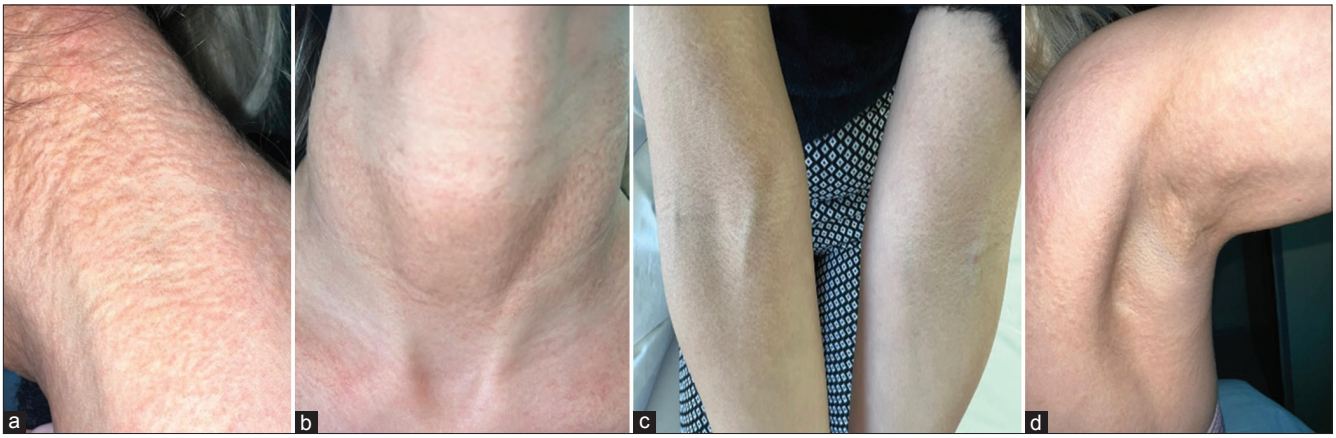
CONCLUSION: There is no specific treatment, and therapeutical management is based on prevention, tracking, and follow-ups to increase surveillance of clinical complications through a multidisciplinary team. The dermatologist is usually the first who faces Pseudoxanthoma elasticum manifestations. Therefore, the dermatologist should provide the patient with the best therapeutical and preventive approaches.

Introduction

Pseudoxanthoma elasticum (OMIM: 177850 264800, ORPHA 758) is a rare, genetic, metabolic disease with connective tissue and eye involvement, characterized by progressive ectopic mineralization and fragmented elastic fibers in the skin, retina, and vascular walls. The prevalence is estimated at between 1/40,000 and 1/100,000 in the general population, with, for an unknown reason, female predominance (female to male ratio 4:1) [1]. From the historical perspective, the first clinical description of the disease was done in 1881 by Rigal, and in 1896 Darier adopted the term pseudoxanthoma elasticum after observing typical dermal histopathological alterations of the process. Ocular involvement was observed for the first time in 1929 by Grönblad and Strandberg, while the vascular component was described in 1944, by Carlbord [2]. More recently, the identification of the gene defects underlying PXE has helped to clarify the clinical constellations and molecular genetics of this disorder [3]. Here, we present a clinical case with cutaneous and ocular involvement.

Case Report

A 27-year-old Albanian female was referred to the dermatology clinic with skin complaints present for approximately 17 years. That was the first time she was investigated by a dermatologist because her clinical pathologic appearance was subtle for many years. On physical examination, we observed yellowish papules similar to the "cobblestone pattern" located in the anterior, lateral, and posterior aspects of the neck, bilateral axillary, inguinal, antecubital, and popliteal regions, and periumbilical area (Figure 1a-d). The skin changes first appeared in the neck and then have involved the other parts of the body, with excessive involvement during pregnancy. These lesions were asymptomatic and were only subject to esthetic embarrassment. No other abnormalities were found on the rest of the physical examination. She did not report personal or family dermatological diseases and no medications were taken. Her two pregnancies resulted in normal delivery and both her children do not appear such dermatological signs. Based on the above observation, a clinical diagnosis



Figures 1: (a-d) Dermatological examination. Irregular, small, yellowish papules aggregating in plaques resembling `cobblestone` appearance in anterior-posterior neck area, antecubital and axillary regions

of Pseudoxanthoma elasticum was established and the patient was hospitalized to undertake the proper examinations to confirm the diagnosis.

A biopsy was performed in the lateral posterior aspect of the neck. The histopathology confirmed the typical changes in the dermis because of ectopic mineralization (Figure 2a-c). An ophthalmic consult was made and funduscopy revealed the `peau d`orange` aspect, bilateral angioid streaks but no neovascularization (Figure 3a-c). The patient was referred to the cardiologist to assess her cardiovascular involvement. She had no arterial hypertension, while ECG, echocardiogram, and coronary angioCT did not indicate any pathological changes. Carotid echography showed minimal intimate thickening with flow acceleration but without significant stenosis of the right common carotid artery (ACC) and internal carotid artery (ACI) while the left ACC and ACI had normal flow and walls. Different laboratory exams were conducted. Complete blood count, urine analysis, renal and hepatic tests, stool sample, calcium, phosphorus, magnesium levels, ferritin, and lipidogram were within normal range; no Vitamin K dependent coagulopathy was observed and hemoglobin electrophoresis was compatible with the normal variant. Chest radiography had no changes. A detailed personal and familiar history was obtained by the geneticist to reveal the type of Mendelian inheritance, but the patient denied any similar clinical evidence in any of her familiars or siblings. The Whole Sequencing Exam was recommended to interpret the genetic mutation but it was not performed because the patient did not give her consent.

Regarding the new proposed criteria of Pseudoxanthoma elasticum in 2010, the patient fulfilled two major criteria: clinical and histopathological skin criteria and ocular changes. We also excluded other PXE- like conditions through laboratory examinations. A definitive diagnosis of PXE was made.

Then, the patient was advised for annual ophthalmologic and cardiovascular evaluation to prevent severe scenarios and undertake prompt medical management.

Discussion

Pseudoxanthoma elasticum (OMIM: 177850 264800, ORPHA 758) is a rare, genetic,

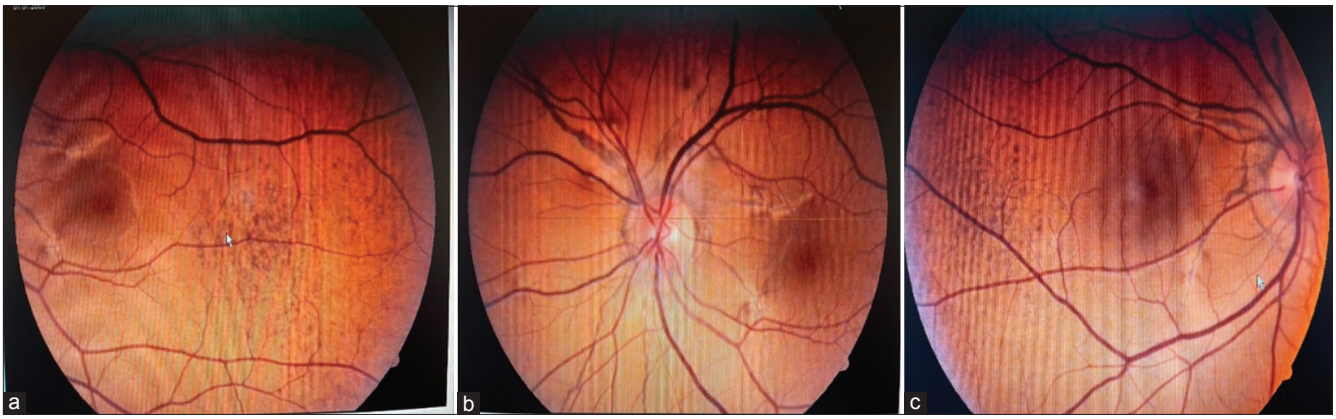


Figure 2: (a-c) Funduscopy. Peau d`orange aspect and angioid streaks

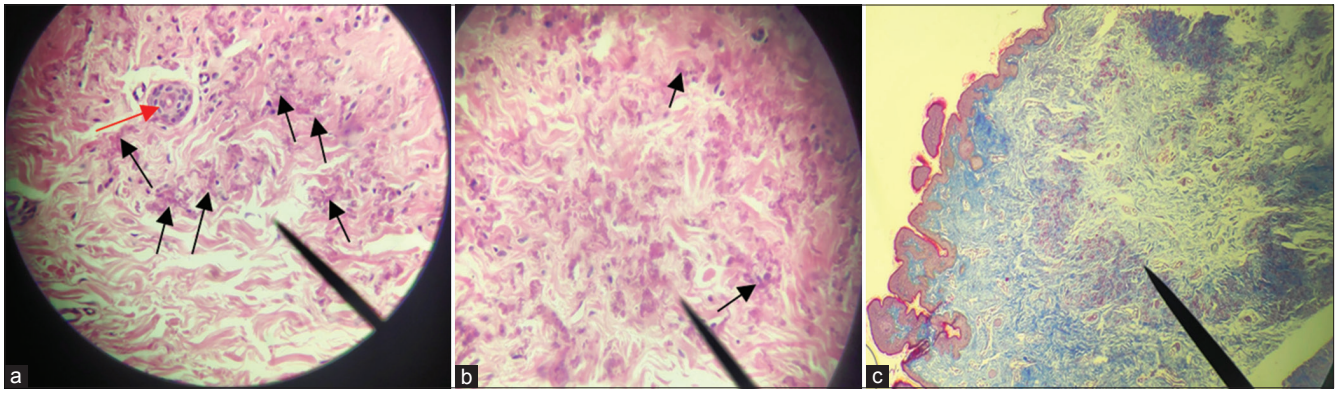


Figure 3: Anatomopathological examination. (a) HE staining: In the middle dermis, between the normal collagen fibers, fragmented, tortuous, fibrous elastic fibers with pronounced eosinophilia (black arrows) are observed. The blood vessels appear thicker intima with eosinophilic imbibition (red arrow). (b) HE staining: at large magnification, some of the elastic fibers begin to show basophilia, because of deposits and precipitations of Calcium (with arrows). (c) Trichrome staining: normal connective tissue fibers in the upper and lower dermis, and the presence of abnormal red fibers in the middle dermis are observed

metabolic disease with connective tissue and eye involvement, characterized by progressive ectopic mineralization and fragmented elastic fibers in the skin, retina, and vascular walls. Prevalence is estimated at between 1/40,000 and 1/100,000 in the general population, with female predominance for an unknown reason (female to male ratio 4:1) [1]. From the historical perspective, the first clinical description of the disease was done in 1881 by Rigal, and in 1896 Darier adopted the term pseudoxanthoma elasticum after observing typical dermal histopathological alterations of the process. Ocular involvement was observed for the first time in 1929 by Grönblad and Strandberg, while the vascular component was described in 1944 by Carlbord [2]. More recently, identifying the gene defects underlying PXE has helped clarify the clinical constellations and molecular genetics of this disorder [3]. Here, we present a clinical case with cutaneous and ocular involvement.

Pseudoxanthoma elasticum (PXE) is a genetic metabolic disease with autosomal recessive inheritance caused by mutations in the ABCC6 gene. The lack of functional ABCC6 protein leads to ectopic mineralization that is most apparent in the elastic tissues of the skin, eyes, and blood vessels [4], [5], [6].

While the genetic nature of the disease is well recognized, the pathophysiological mechanism of PXE has yet to be fully understood. Two main hypotheses can be considered. First, the cell-based hypothesis holds that a lack of functional ABCC6 protein at peripheral sites leads to ectopic mineralization. The second predominant paradigm for PXE is systemic, metabolic disease. The liver's lack of production or release of one or more circulating factors (where ABCC6 is usually most strongly expressed) leads to ectopic mineralization. One variant of this metabolic hypothesis holds that the circulating factor usually suppresses or controls mineralization. There is good evidence to suggest that the factor is inorganic pyrophosphate (PPi). The low circulating levels of PPi and decreased PPi/Pi ratio result from the lack of ATP release by hepatocytes harboring the mutant ABCC6 protein. However, the substrate(s) bound, transported, or modulated by the ABCC6 protein remain unknown [6]. Identification of mutations in the ABCC6 gene can be used for confirmation of the clinical diagnosis, carrier detection, and presymptomatic identification of affected individuals [3]. It has also been suggested that oxidative stress is a pathophysiologic factor in PXE because some PXE patients display biochemical signs of oxidative stress. Some patients with ß-thalassemia or sickle cell anemia (both conditions in which systemic free radical levels are elevated) can display PXE-like manifestations. Oxidative stress inhibits expression of ABCC6 gene in human cell lines [6].

Clinical manifestation occurs in the skin, eyes, oral mucosa, gastrointestinal tract, and arteries [2]. The first clinical sign of PXE, with onset typically in childhood or adolescence, from 10 to 15 years, tends to be the characteristic skin changes (small yellow papules with a diameter of up to 10 mm) on the nape and sides of the neck and in flexural areas (e.g., the axillae, the antecubital fossae, and periumbilical, inguinal and popliteal areas) [6], [7]. Because of their subtle and asymptomatic nature, an average diagnostic delay is 9 years [7]. The oral, vaginal, and rectal mucosae may also be affected. The papules are initially isolated or found in patches but coalesce into reticulated plaques as the disease progresses, giving a cobblestone aspect to the skin. The skin subsequently becomes loose and wrinkled, albeit not to the extent seen in cutis laxa [6]. Although few patients are reported, they can suffer PXE without typical skin manifestations [8]. The cutaneous findings present a cosmetic problem primarily and do not interfere with normal life activities. However, the presence of characteristic skin lesions signifies the risk of developing ocular and vascular complications that can be quite debilitating with considerable morbidity and even mortality [3].

The ophthalmological manifestations of PXE are the most serious since they can lead to blindness

in late-stage disease [6]. The ocular manifestations that have been described are orange skin, angioid striae, choroidal neovascularization, hemorrhages, and scar formation. The “peau d’orange” is the first ocular alteration and consists of small dark spots that give a mottled appearance to the periphery of the temporal zone of the retina [9]. The peau d’orange sign was observed in 96% of patients with skin signs of PXE [6]. Angioid streaks are not pathognomonic for PXE because they may be present in sickle cell disease, thalassemia, and, more rarely, Ehlers-Danlos syndrome. The neovascularization leads to subretinal hemorrhages, exudation, and the formation of fibrovascular scars that result in the loss of visual acuity. Comet lesions are chorioretinal atrophic spots in the retina’s periphery, which usually have a tail that points to the optic nerve head and is the pathognomonic feature of the eye in PXE [9]. The cases of ocular involvement must be monitored by periodical fluorescein angiography and ophthalmoscopy [2].

Degeneration of the elastic laminae of medium-sized arteries and calcium deposition is the cause of vascular manifestations of PXE [7]. Clinically, intermittent claudication is often the first sign of accelerated atherosclerosis and the most common cardiovascular symptom, occurring in 30% of patients. Coronary artery disease and renovascular hypertension may occur at a much younger age in PXE patients and can result in angina pectoris, myocardial infarction, congestive cardiac failure, renal failure, or stroke. Although cardiovascular disease rarely presents before the third or fourth decade, it has been reported in children as nine years of age. Echocardiography may show marked calcification and calcified thrombi, and a characteristic hyperechogenicity with a dotted pattern is observed in renal ultrasonography. Similar sonographic findings were seen in the spleen and pancreas [7]. Carotid rete mirabile has been reported in association with PXE [6]. PXE has been described as a unique monogenic model of peripheral artery disease, in which arterial wall remodeling is associated with an abnormally low ankle-brachial index, independently of cardiovascular risk factors [6]. The risk for cardiovascular complications is somewhat increased during pregnancy and labor. Despite extensive mineralization of the placenta, PXE is not associated with markedly increased fetal loss or adverse obstetrical outcomes. Thus, with appropriate counseling, there is no basis for advising women with PXE to avoid becoming pregnant [3], [4], [5].

About 10% of PXE patients experience bleeding complications, especially gastrointestinal hemorrhage, due to the fragility of calcified submucosal vessels. Bleeding may also affect other organs such as the cerebrovascular system, uterus, urinary tract, or joints [7]. Calcification of the kidneys, breasts, pancreas, testicles, liver, and spleen has variously been observed in patients with PXE. With the possible exception of the kidneys, this calcification is not thought to have a major clinical impact. PXE may have an impact on some aspects of lung function [6].

Diagnosis of PXE is based on Prompt *et al*. classification in 2010 that is divided into major and minor criteria that combined conclude on a definitive diagnosis, probable diagnosis, and possible diagnosis [10]. Differential diagnosis includes dermatological and connective tissue diseases (Intense solar elastosis of the nape of the neck, perforating calcific elastosis, dermal elastosis, and Ehlers-Danlos syndrome), β-thalassemia, sickle cell anemia, and body skin hyperlaxity due to Vitamin K dependent coagulation factor deficiency. All these differential diagnoses can be ruled out by genetic testing for ABCC6 mutations. Hemoglobin profiling and Vitamin-K-dependent coagulation factor assays may be used to rule out sickle cell disease, beta-thalassemia, and multiple coagulation factor deficiency [6].

Histochemical assessment of skin lesions is better characterized with Verhoeff–van Gieson reagent, which stains elastin, and Von Kossa staining, which reveals calcium deposits [6], [7], [11]. The mid-dermal elastic fibers are short, fragmented, clumped, and calcified. Electron microscopy may be used to show the characteristic abnormalities. Similar changes occur in elastic fibers of the blood vessels, Bruch’s membrane of the eye, endocardium, and other organs. Due to the impossibility of performing genetic analysis, our case’s logical algorithm consists of performing additional laboratory examinations and histopathology to exclude PXE-like disorders.

There is no specific treatment, and the therapeutical management is based on the prevention, tracking, and monitoring of complications associated with the disease through a multidisciplinary team. Ophthalmological, cardiovascular monitoring and genetic counseling are essential. Complementary exams such as blood count, lipid profile, echocardiogram, and ophthalmologic monitoring should be made. The abandonment of smoking habits, moderate physical exercise, avoidance of some medical drugs, and a proper diet with supplements intake of magnesium, phosphate, and pyrophosphate analogs can reduce the progression of the disease. Laser photocoagulation, transpupillary thermotherapy, photodynamic therapy, macular translocation surgery, and anti-endothelial growth factor improve and delay vision loss. For cosmetic alterations in the skin, surgery has been described to eliminate redundant, lax, or indurated skin and injections of collagen and lipografting [2], [7], [9]. Pseudoxanthoma elasticum is a candidate for gene therapy [12].

Conclusion

Pseudoxanthoma elasticum is a rare genetic metabolic disease with cutaneous, ophthalmological,

and vascular involvement. Cutaneous manifestations are the first to appear, marking the dermatologist's role in early diagnosis and the proper management according to a specific algorithm to prevent and minimize associated complications. Regarding pseudoxanthoma elasticum, there are still many uncertainties mainly related to genetic data and limited human capabilities to fully understand them. The few cases reported, as it is a rare disease, and difficulties in predicting the progression over the years are special features of this disease. This case report aims to raise awareness of the dermatologist and general physician's role in how not to miss pseudoxanthoma elasticum diagnosis. It is important to diagnose in time such peculiar cases with a substantial impact on morbidity and mortality and to refer for future contributions to clinical research.

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