

Case and Review

# Pseudoxanthoma Elasticum: Report of Two Cases

Israel Antonio Esquivel-Pinto<sup>a</sup> Maria Elisa Vega-Memije<sup>b</sup>  
Araceli Alvarado-Delgadillo<sup>c</sup> Andres Eduardo Campuzano-Garcia<sup>d</sup>  
Amairani Manríquez-Robles<sup>b</sup>

<sup>a</sup>Department of Dermatopathology, Dermatos Clinic, Mexico City, Mexico;

<sup>b</sup>Dermatopathology Service, General Hospital “Dr. Manuel Gea González”, Mexico City, Mexico; <sup>c</sup>Specialized Center for Skin Illnesses, Tula, Mexico;

<sup>d</sup>Department of Dermatology, Dermatos Clinic, Mexico City, Mexico

## Keywords

Pseudoxanthoma elasticum · Elastorrhaxis · Grönblad-Strandberg syndrome · Dermatopathology

## Abstract

Elastic pseudoxanthoma is a rare disease with autosomal recessive inheritance, also known as Grönblad-Strandberg syndrome, characterized by pathological mineralization of the elastic fibers in the connective tissue, affecting principally the dermis of skin, media, and intima of blood vessels and Bruch’s membrane of the eye. The genetic defect of the disorder is located on chromosome 16p13.1 and disease is caused by the lack of functional ABCC6 protein, which in turn causes extracellular accumulation and deposition of calcium and other minerals in the elastic tissue. In this article we present two cases of this rare disease. We emphasize, in the diagnostic criteria, the importance of its early diagnosis and the current therapeutic approaches.

© 2021 The Author(s)  
Published by S. Karger AG, Basel

## Introduction

Elastic pseudoxanthoma (PXE) was initially described by Balzer in 1884 in a paper that reported the association between elastic degeneration of the skin and cardiac alterations. In 1896, Darier coined the term “pseudo-xanthome élastique” [1]. Other contributions made by Grönblad and Strandberg added ocular alterations and Carlborg associated this disease with the calcification of the blood vessels’ wall [2].

## Case Report/Case Presentation

### *Case Number One*

A female patient of 36 years, resident and original of the city of Tula, Hidalgo, Mexico, without pathological antecedents of importance, attended a medical appointment due to presenting dermatosis in the neck with a 3-month evolution. During physical examination, it was described to be characterized by confluent papules, of 2 to 3 mm approximately, discretely hyperpigmented and asymptomatic (Fig. 1a). An incisional biopsy was taken by punching, with diagnosis of PXE versus mucinous papulosis. The biopsy showed anfractuans epidermis, with stratum corneum in basket weave, the stratum spinosum thinned with flattening of the interpapillary projections and hyperpigmentation of the cells of the lower third. A perivascular inflammatory infiltrate formed by lymphocytes was observed in the papillary dermis and the superficial reticular dermis. In the middle reticular dermis, short, basophilic, granular, and irregularly shaped fibers were observed (Fig. 1b). With staining for elastic fibers, they were shown to be fragmented, and Von Kossa staining evidenced their calcification (Fig. 1c). These clinical and histopathological findings confirmed the diagnosis of pseudoxanthoma.

### *Case Number Two*

A female patient of 59 years, resident and originally from the city of Zacatecas, Zacatecas, Mexico, was referred by the ophthalmological service due to severe visual acuity diminution and angioid striae of the retina, with no other important data. During physical examination, bilateral symmetrical dermatosis was observed, predominantly in folds, characterized by loose skin, soft texture, and plaques consisting of skin-colored papules 3–4 mm in diameter (Fig. 2a). An incisional biopsy was taken by punching, with a clinical diagnosis of PXE. In the sections, thin and anfractuans epidermis was observed, with the stratum corneum in basket weave and the stratum spinosum with flattening of the interpapillary projections. In the middle reticular dermis, irregularly arranged short basophilic fibers were observed (Fig. 2b). The staining of elastic fibers (Fig. 2c) showed that the fragmented debris corresponded to these fibers and Von Kosa staining showed the presence of calcium inside. Fundus examination in both eyes revealed classic-appearing angioid streaks with crystalline spots, retinal pigment with epithelial atrophy (peripapillary), and choroidal neovascularization (Fig. 3a, b). With the histopathological study and fundus examination findings, the diagnosis of PXE was confirmed this case.

The diagnosis criteria used were in the first case skin findings like characteristic pseudoxanthomatous papules and plaques on the neck or flexural creases, and histopathological changes in lesional skin: calcified elastic fibers in the mid and lower dermis, confirmed by positive calcium stain. For the second case, the diagnosis criteria included ocular findings.

The difficulty in diagnosing PXE often relates to the observation of PXE-like cutaneous lesions. In both cases, we performed differential diagnosis with Marfan syndrome, papillary dermal elastolysis, papular elastorrhexis body skin hyperlaxity due to vitamin K dependent coagulation factor deficiency, severe actinic damage to the lateral part of the neck, and cutis laxa. However, histopathology of these lesions did not reveal tissue mineralization PXE-like cutaneous changes.

## Discussion

PXE has an autosomal dominant or recessive pattern of inheritance [3] and is characterized by calcification of the elastic fibers of the connective tissue, with special effects on the skin, eyes, and the cardiovascular system. The prevalence is estimated at 1 per 25,000–100,000 inhabitants, with a predominance in women (2:1 in relation to men) [1]. In general, the diagnosis is made during the third or fourth decades of life.

In most cases, it is expressed by mutations of the *ABCC6* gene located in chromosome 16p13.1 that encodes a transmembrane protein of the ATP-binding cassette transporter superfamily. This mutation affects the transport of anionic peptides, which allows some minerals to accumulate and cause the calcification of the elastic fibers [3]. In these cases, none of the patients had a family history of the disease.

Cutaneous manifestations are the first sign of PXE and consist of small papules of 1–5 mm, asymptomatic, yellowish or skin-colored, in a reticular pattern that coalesce progressively in large plaques that affect mainly the areas of the folds (neck, armpits, and groin). Finally, the skin becomes loose, wrinkled, and redundant. The changes are usually observed in childhood and adolescence, and progress slowly and unpredictably until adulthood. The firstly affected part is the back of the neck, then the flexor areas including the armpits, the groin, and the antecubital, popliteal, and periumbilical area. Alterations have also been reported in the inner face of the lower lip and the genital region [2].

The ocular manifestations that have been described are: orange skin, angioid striae, choroidal neovascularization, hemorrhages, and scar formation. The “orange peel” 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. Its pathogenesis is not well established, and it is believed that it is the result of the calcification of Bruch’s membrane transitional area [4, 5]. Comet lesions are chorioretinal atrophic spots in the periphery of the retina, which usually have a tail that points to the optic nerve head (to which they owe their descriptive name) and are the pathognomonic feature of the eye in PXE [2].

Angioid striae appear as irregular brown and gray lines that radiate from the peripapillary ring to the periphery. They are located more commonly in the posterior pole of the eye. In histopathology, they represent the calcification and ruptures of Bruch’s membrane. The neovascularization leads to subretinal hemorrhages, exudation, and formation of fibrovascular scars that result in the loss of visual acuity [5].

Cardiovascular manifestations are very varied and include decreased pulse, hypertension, angina pectoris, and intermittent claudication. Gastrointestinal hemorrhages, melena, and hematemesis can also be observed. Patients also develop atherosclerosis, cardiac arrest, and strokes at younger ages. All these alterations are secondary to the mineralization and fragmentation of the elastic fibers in the internal, medial, and adventitia elastic lamina of the medium-sized arteries and the aorta, as well as the arterioles and coronary vessels of the endocardium, pericardium, and connective tissue of the myocardium [6].

In histopathology, the initial characteristic is the mineralization and fragmentation of the elastic fibers in the middle dermis, which result in a pattern called elastorrhexis. The stain for elastic fibers (Verhoeff-Van Gieson) and Von Kossa show, respectively, the fragmentation and calcification of the fibers [7].

Mineral deposits are made up of hydroxyapatite and calcium biphosphate, but iron, phosphate, and carbonate can also be observed. Abnormal collagen fibers and proteoglycans are also observed. The fibroblasts are numerous and show hypertrophy of endoplasmic reticu-

lum. Macrophages are abundant, with intracytoplasmic calcifications. These changes can be observed in clinically healthy skin [8].

Although clinical suspicion and histopathology are defined by specific characteristics, many pathologies may have clinical manifestations or histological findings similar to PXE. The term “PXE-like” is used to describe the skin, eye, and cardiovascular alterations of PXE, in association with other cutaneous or systemic diseases with genetic mutations different from ABCC6. For example, PXE phenotypes associated with the deficiency of coagulation factors dependent on vitamin K (Factors II, VII, IX, and X) have been described [8].

There is no specific or effective treatment for cutaneous or systemic manifestations. It is multidisciplinary and consists of ophthalmological, cardiovascular monitoring and genetic counseling. The abandonment of smoking habits, moderate physical exercise, 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 the loss of vision [9].

For cosmetic alterations in the skin, surgery has been described to eliminate redundant, lax, or indurated skin. Injections of collagen and lipograftings may be other treatment options [10].

## Conclusion

PXE is the prototype of heritable multisystem diseases displaying ectopic mineralization of connective tissues, with clinical manifestations that affect the dermis of skin, media, and intima of blood vessels and Bruch’s membrane of the eye. The penetrance of the disease in individuals with mutations in both ABCC6 alleles appears to be complete, but the severity of the phenotype and the age of onset of the disease are likely modulated by the genetic background, epigenetic factors, diet, and lifestyle variables. The clinical manifestations are late-onset, and the early cutaneous findings, frequently the first diagnostic sign of PXE, are subtle and usually not recognized until the second or third decade of life. This is why the diagnosis depends on clinical and histopathological features. An early diagnosis helps to prevent further complications these patients could develop. There is no cure for PXE. The management is mostly preventive and the patients should be monitored on a regular basis. However, a combination of empiric therapies might improve the quality of life for patients with PXE.

## Statement of Ethics

Both subjects are capable of giving their consent as subjects in medical research. Their participations are voluntary, and they have given their written informed consent to publish their cases (including publication of images). Every precaution has been taken to protect the privacy of research subjects and confidentiality of their personal information. The publication of both cases complies with the guidelines for human studies. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

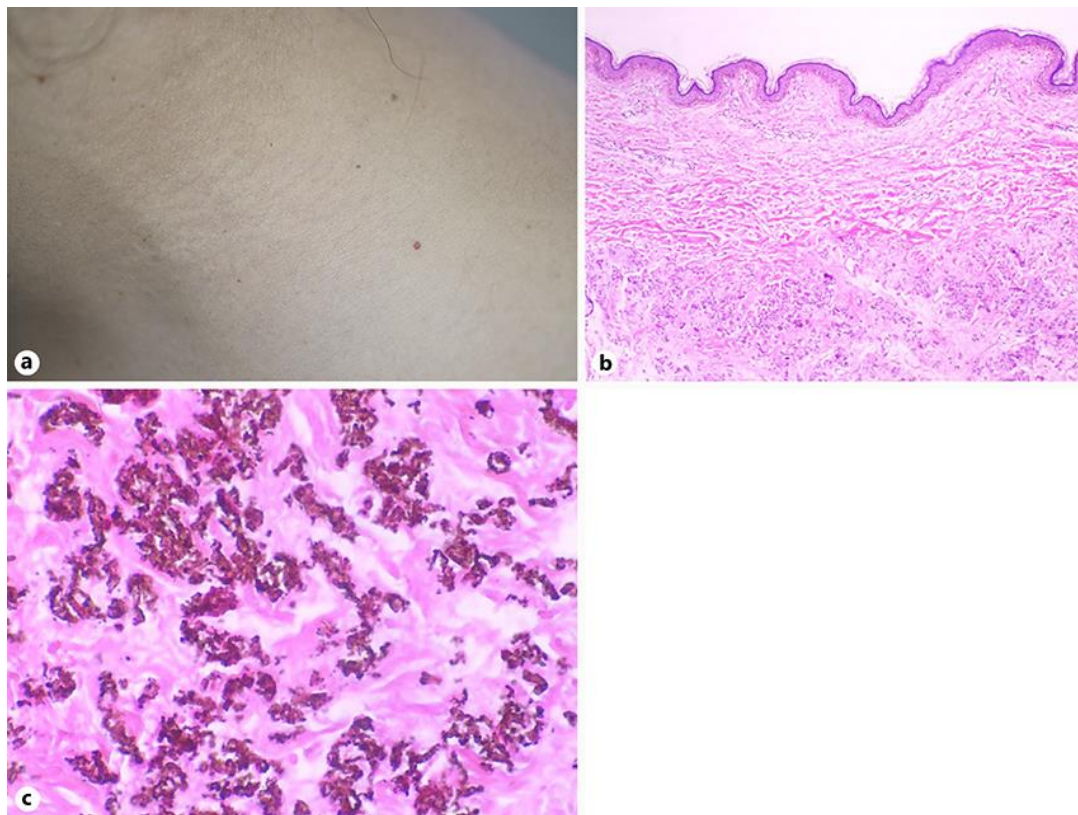
No funding sources.

## Author Contributions

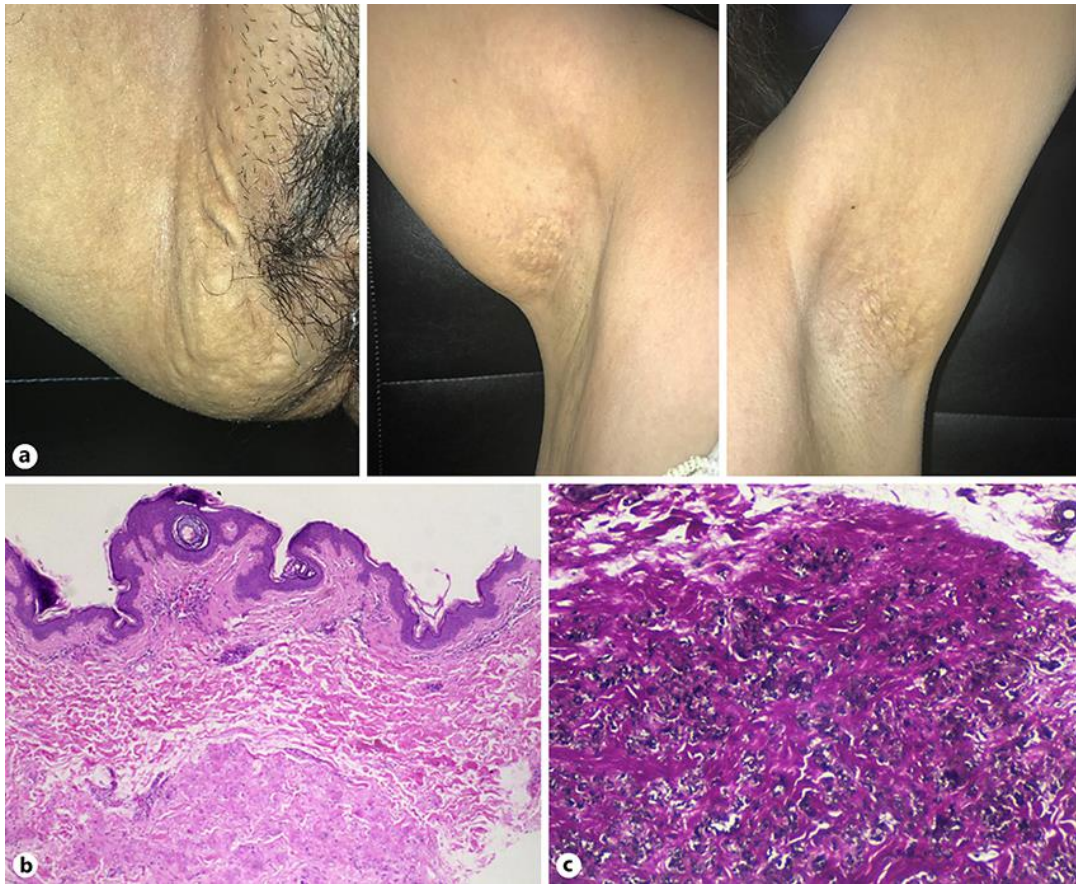
Maria Elisa Vega-Memije: reviewed the histopathological study of patient 1 and 2, confirmed the diagnosis, performed analysis of the information, and made the final revision of the manuscript. Israel Antonio Esquivel-Pinto: reviewed the histopathological study of patient 1 and 2, search and analysis of information. Araceli Alvarado-Delgadillo: medical history and clinical examination of patient 1, biopsy, and information search. Andres Eduardo Campuzano-Garcia: medical history, clinical examination of patient 2, biopsy, and information search. Amairani Manríquez-Robles: reviewed medical history of patient 1 and 2, looking for information, writing the case, and uploading the manuscript to the journal.

## References

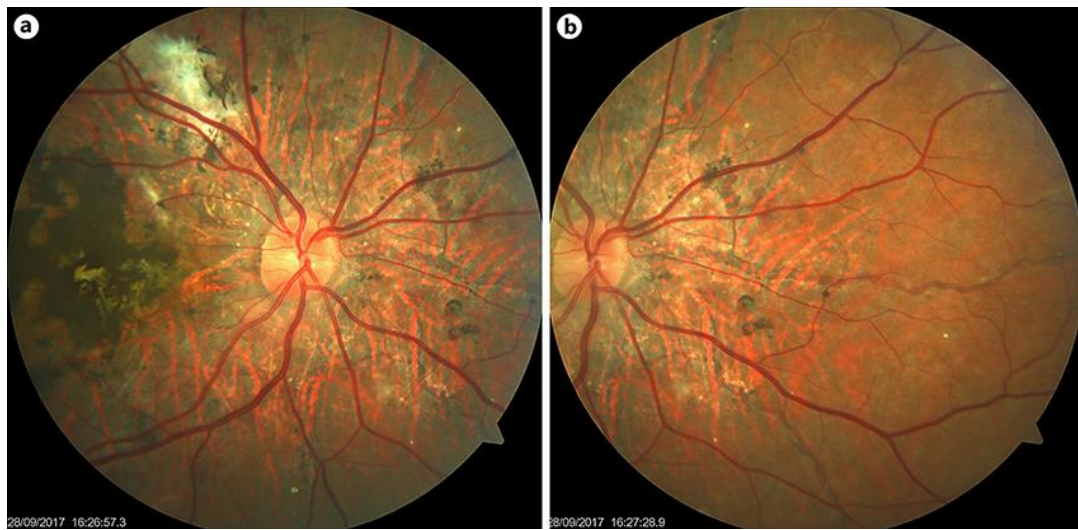
- 1 Marques GF, Nakandakari S, Coelho AP, Nigro MH, Sabage J. Pseudoxanthoma elasticum: report of two cases. *An Bras Dermatol*. 2014 Sep-Oct;89(5):812–5.
- 2 Gass JD. “Comet” lesion: an ocular sign of pseudoxanthoma elasticum. *Retina*. 2003 Oct;23(5):729–30.
- 3 Chassaing N, Martin L, Calvas P, Le 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.
- 4 Hu X, Plomp AS, van Soest S, Wijnholds J, de Jong PT, Bergen AA. Pseudoxanthoma elasticum: a clinical, histopathological, and molecular update. *Surv Ophthalmol*. 2003 Jul-Aug;48(4):424–38.
- 5 Naouri M, Boisseau C, Bonicel P, Daudon P, Bonneau D, Chassaing N, et al. Manifestations of pseudoxanthoma elasticum in childhood. *Br J Dermatol*. 2009 Sep;161(3):635–9.
- 6 Braun SA, Finis D, Helbig D. [Pseudoxanthoma elasticum. More than a skin problem]. *Hautarzt*. 2013 Apr;64(4):222–5.
- 7 Roach ES, Islam MP. Pseudoxanthoma elasticum. In: *Handbook of clinical neurology*. 2015. p. 215–21. <https://doi.org/10.1016/B978-0-444-62702-5.00015-9>.
- 8 Marconi B, Bobyr I, Campanati A, Molinelli E, Consales V, Brisigotti V, et al. Pseudoxanthoma elasticum and skin: clinical manifestations, histopathology, pathomechanism, perspectives of treatment. *Intractable Rare Dis Res*. 2015 Aug;4(3):113–22.
- 9 Shiraki K, Kohno T, Moriwaki M, Yanagihara N. Fundus autofluorescence in patients with pseudoxanthoma elasticum. *Int Ophthalmol*. 2001;24(5):243–8.
- 10 Galadari H, Lebwohl M. Pseudoxanthoma elasticum: temporary treatment of chin folds and lines with injectable collagen. *J Am Acad Dermatol*. 2003 Nov;49(5 Suppl):S265–6.



**Fig. 1.** **a** Clinical photograph: multiple papules on the lateral aspect of the neck. **b** Hematoxylin and eosin staining (40×) in the reticular dermis shows medium and short fibers, basophilic, granular, irregularly arranged. **c** Von Kossa staining: the calcification of the elastic fibers (400×) is evident.



**Fig. 2.** **a** Clinical image of inguinal region and right and left armpits, where loose skin is observed, with yellowish patches, conformed by papules. **b** In histopathological description with hematoxylin and eosin staining, basophilic material is observed in the middle dermis (40×). **c** With the staining of elastic fibers, short and fragmented fibers (400×) are observed.



**Fig. 3.** **a** Fundus photograph of the left eye with mottled hyperpigmentation to the periphery of the temporal zone of the retina and angioid streaks with crystalline spots. **b** Fundus photograph of the left eye with classic-appearing orange peel and choroidal neovascularization.