

Pseudoxanthoma Elasticum: Report of Six Cases and Literature Review

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Summary

Pseudoxanthoma elasticum (PXE) is a rare inherited disorder characterized by fragmentation and calcification of elastic fibers with many systemic manifestations. The inheritance patterns can be either autosomal dominant or autosomal recessive. Typical skin lesions include yellowish papules preferentially on flexural sites, such as antecubital, popliteal, cervical, axillary, and periumbilical areas. Cardiovascular system is also involved leading to intermittent claudication, hypertension and diminished peripheral pulses. Ocular manifestations include the so-called angioid streaks. The purpose of this article was to report the clinical cases of PXE presented in the Hospital de Clínicas, Universidade Federal de Uberlândia, MG, Brazil, from January

Key words: elastic fibers, calcification, pseudoxanthoma elasticum, genodermatoses.

Resumen

El seudoxantoma elástico (SXE) es un trastorno heredado poco común caracterizado por la fragmentación y calcificación de fibras elásticas con muchas manifestaciones sistémicas. Los patrones hereditarios pueden ser dominantes autosómicos o autosómicos recesivos. Las lesiones típicas de piel incluyen pápulas amarillentas normalmente en lugares de flexuras, como antecubitales, popliteas, cervicales, axilares y áreas periumbilicales. El sistema cardiovascular también se ve afectado, dando lugar a claudicaciones intermitentes, hipertensión y pulsos periféricos disminuidos. Las manifestaciones oculares incluyen las llamadas estrias angioides. El objetivo de este artículo es el de informar sobre los casos clínicos de SXE que se presentaron en el Hospital de Clínicas, Universidade Federal de Uberlândia, MG, Brazil, desde enero de 1990 hasta abril del 2001 así como también proporcionar una revisión de la literatura en los temas importantes en SXE.

Palabras clave: fibras elásticas, calcificación, seudoxantoma elástico, genodermatosis

Pseudoxanthoma elasticum (PXE) was first reported in 1881 by Rigal as an atypical xanthoma and later named PXE by Darier (1896), who demonstrated a histologic abnormality in elastin [1]. The disease is also known as Grönblad-Strandberg syndrome and systemic elastorrhexis [3]. The denomination Grönblad-Strandberg syndrome was used after these authors have described the association between skin and ocular lesions [1].

Elastic fibers are abundant in the skin, the arteries and the lung from normal individuals, conferring elasticity to these organs. They are capable of distending when tensioned, backing soon after to their normal length. Proportionally, the elasticity of these fibers is at least five-fold higher than that of a rubber filament in same diameter. Elastic fibers are essentially constituted of a highly hydrophobic glycoprotein (elastin), whose partially coiled molecules attach one in each other by covalent bonds between their ends. The elastin aggregates forming fibers, which anastomose to constitute a network, as seen in the

skin and the lung [3]. PXE is a inherited disorder characterized by progressive accumulation of mineral precipitates within the elastic fibers [4].

Skin lesions appear in the first or second decade of life and are characterized by thickening and diminishing of the skin (consistency) with the presence of yellowish papules resembling "plucked-chicken skin" on flexural sites, such as antecubital, popliteal, inguinal, cervical, axillary folds, and periumbilical areas. Oral, vaginal and rectal mucosas are also involved, and the hard palate, the face and the thigh can be affected [5,6,7]. The nasolabial folds and chin creases may be strikingly accentuated [2]. Changes in PXE appear particularly on flexural areas because the elastic tissue production rate in these areas is high due to stretching stresses [8]. The primary cutaneous lesions are relatively small (1 to 3 mm) yellowish papules, which tend to coalesce into larger plaques [2].

The involvement can be progressive and reach the entire skin [6]. The affected skin gradually becomes redundant, lax,

inelastic, and later wrinkled, particularly in the neck, the axillary folds, and thighs [2]. Serpiginous perforating elastosis can coexist in patients with PXE [6]

The pathologic process involves fragmentation and calcification of elastic fibers, resulting in clinical manifestations particularly in the skin, ocular, gastrointestinal and cardiovascular systems [1]

Calcinosis cutis is an unusual finding in PXE and reports of calcinosis cutis associated with angioid streaks, in the absence of PXE, are extremely rare [9].

PXE can have either autosomal dominant or autosomal recessive inheritance, and presents an estimated prevalence ranging from 1/70,000 to 1/1,000,000 [1]. Most of the cases occur in female, with a male:female ratio of 1:2.3 [10].

According to the clinical and histopathologic characteristics, principal and secondary criteria were established for the diagnosis of PXE (Table 1). Thus, PXE could be diagnosed and classified in one out of five categories, based on the concomitant presence of some of these criteria, as demonstrated in Table 2 [11]

The diagnostic method more used is the histopathologic assay of skin lesion biopsy, showing calcification and fragmentation of elastic fibers as demonstrated by von Kossa stain[1].

On funduscopy examination of the eye, the so-called angioid streaks can be seen occurring in 85% of patients with PXE and can also be present in other diseases, such as Paget's disease of the bone, tumoral calcinosis, lead poisoning, idiopathic thrombocytopenia, Ehlers-Danlos syndrome and hemoglobinopathies [2,5,6,12] . Ophthalmoscopy shows that angioid streaks are red dark or gray lesions with irregular ridge-shaped borders and located adjacent to the normal retinal vessels; angiofluorescein assay shows hyperfluorescence caused by a gap-shaped defect of the retinal pigment epithelium above the streaks. The angioid streaks connect one with each other in a ring-like pattern around the optical disk and then irradiate outside in a strip shape starting from the pupillary area. They run a sinuous course and tend to end suddenly. Sometimes, it can be difficult to identify the angioid streaks unless that the posterior pole is carefully examined [12]. Although irregular and

commonly large, they are often confused with blood vessels [6]. The angioid streaks are resultant of gaps in the collagen tissue and the elastic portions of Bruch's membrane (structure rich in elastin situated between the retina and the choroid), with secondary changes in the retinal pigment and choriocapillary epithelium [2,12]. Ocular changes are commonly bilateral and still include hemorrhages and exudates on Bruch's membrane [2]. Another findings associated with angioid streaks in eyes include peau d'orange or leopardic blots, consisting of a yellowish printed spattering in the posterior pole, being more apparent temporal to macula; peripapilar chorioretinal atrophy, focal peripheral chorioretinal scars (salmon points) and reticulated pigment accumulations; optic nerve drusen that occasionally can predict the appearance of angioid streaks; macular degeneration due to leakage of the subretinal neovascularization [12,13].

Regarding the cardiovascular system, structural genetic abnormalities in the glycoproteins can result in vascular fragility. Bleeding can be restricted to the appearance of ecchymoses or hemorrhages in internal organs [14].

The calcification of the media elastic tunica of blood vessels with subsequent proliferation of the intima lead to serious complications as cardiovascular manifestations affecting more commonly the arteries of the extremities with media caliber, but any artery can be involved [6,7].

The early manifestations of arterial involvement include intermittent claudication, hypertension and weak peripheral pulses [2]. Hypertension predominates in adults and seems to be associated with renal artery involvement, and can occur in the onset of disease. The involvement of the peripheral arteries can lead to the disappearance of pulses, although the ischemic phenomena are rare due to good development of collateral circulation in the limbs; there can be angina pectoris or abdominal angina [6].

Table 1. Criteria for the diagnosis of pseudoxanthoma elasticum.

Main Criteria	Secondary Criteria
- Skin involvement: yellowish papules on flexural areas	- Histopathologic findings of non-affected skin: fragmentation and calcification of elastic fibers
- Histopathologic findings of affected skin: fragmentation and calcification of elastic fibers	- Familiar background of pseudoxanthoma elasticum in first-degree relatives
- Ocular findings in adults over 20 years of age: angioid streaks, peau d'orange, maculopathy	

Lebwohl et al., 1994

Table 2. Classification of pseudoxanthoma elasticum (PXE) in five types.*

I	II a	II b	II c	II d
-Yellowish skin lesions on flexural areas	-Angioid streaks	-Angioid streaks	-Angioid streaks	-Familiar background of PXE in first-degree relatives
-Calcification of elastic fibers on affected skin	-Calcification of elastic fibers on normal skin	-Calcification of elastic fibers on normal skin	-Family history of PXE in first-degree relatives	-Calcification of elastic fibers on normal skin
-Ocular findings in adults	-Familiar background of PXE in first-degree relatives			

* PXE, pseudoxanthoma elasticum

Lebwohl et al., 1994



Figure 1. Yellowish wrinkled papules or plaques with appearance of "plucked chicken skin" on cervical area.

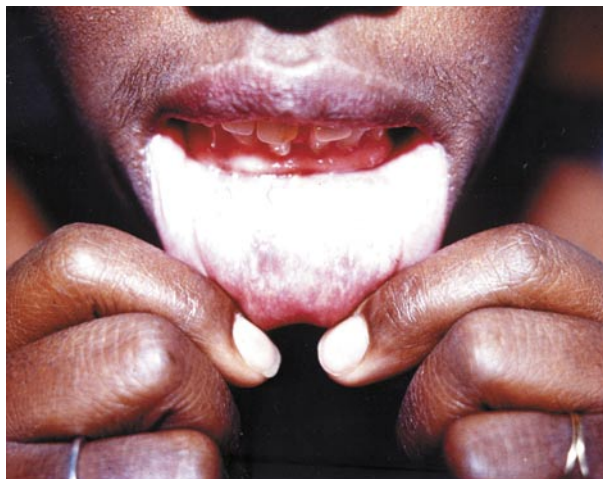


Figure 2. Yellowish diffuse papules in the lower lip mucosa.

Frequently, recurrent bleedings in the gastrointestinal tract are observed, commonly in the gastric mucosa, where the elastic fibers of the arteries are particularly affected, becoming fragile the submucosa vessels; it can also occur bleeding of the urinary tract [2,6].

The most devastating complications develop as a result of coronary occlusion or cerebral hemorrhage [2]. Cerebrovascular disease appears to be less common than it would be expected due to unknown reasons and the myocardial infarction is rare [6,7]. Arteriosclerosis and occlusive vascular changes can still occur [13].

Material and Method

Objective

To evaluate the frequency of PXE cases presented in the Dermatology Ambulatory of the Clinic Hospital de Clínicas, Universidade Federal de Uberlândia (HC-UFU), MG, Brazil.

This was a retrospective study, in which files of all cases of PXE presented in the HC-UFU from January 1990 to April 2001 were examined with respect to sex, age, consanguinity and, particularly, ocular and cutaneous lesions.

Case Reports

Patient 1 – A 28-year old black woman (V.L.S.) living in Uberlândia, MG, presented to the Dermatology Ambulatory with complaint of wrinkled lesions on the neck that started at 10 years old. She had difficult peripheral pulses on palpation and arterial hypertension.

On dermatological assay, yellowish papules or plaques on

cervical (Figures 1), periumbilical and inguinal areas, and lower lip mucosa (Figure 2) were detected.

The patient had family history of PXE, with two brothers presenting similar symptoms and one sister with generalized lesions.

Biopsies were carried out including the affected skin (Figures 3 and 4), the apparently healthy skin, and the oral mucosa, confirming the diagnosis of PXE.

Ophthalmologic evaluations included retinography, angiofluoresceinography, and funduscopic examination of the eye (Figure 5), and demonstrated the presence of red-grayish radial lesions compatible with angiod streaks bilaterally.

System review examinations, such as echodopplercardiogram, electrocardiogram, X-ray thorax and excretory urography, did not show any changes.

Patient 2 – A 40-year old white woman (M.P.S.) living in Uberlândia, MG, presented to the Dermatology Service with a major complaint of wrinkled skin on the neck. On dermatological examination, yellowish and flattened papules on cervical areas and yellowish plaques on the lower lip mucosa were found.

Biopsies of skin lesions on the cervical area were carried out, whose histological sections showed fragmentation of elastic fibers in dermis and calcium deposition as identified by von Kossa stain.

The retinal mapping showed bilateral changes in the retinal pigment epithelium. An endoscopic examination was also performed, showing gastritis in both body and antral mucosa in addition to small hiatus hernia by gliding.

Patient 3 – A 12-year old white boy (W.M.Q.) living in Uberlândia, MG, presented to the dermatological clinic with a six-year

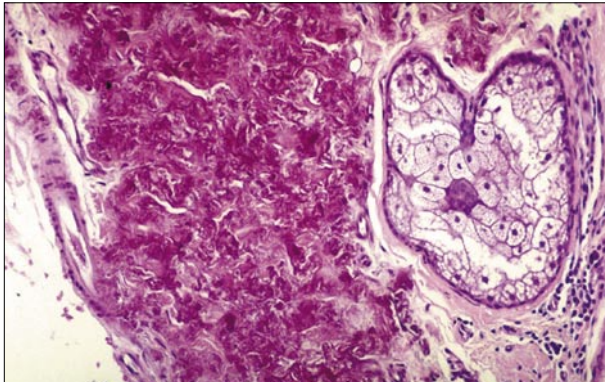


Figure 3. Presence of amorphous basophilic material in the superficial and deep dermis.

history of skin lesions, which were diagnosed by other services as PXE, as informed by the child's mother. In the last three years, there was a increasing in the number of lesions.

On dermatological examination, yellowish papules on the neck, the abdomen and the inguinal area were detected as characteristic lesions of PXE.

The patient was guided for ophthalmologic and cardiovascular examinations, but they were not performed because the mother did not take the child by unknown reasons.

Patient 4 – A 22-year old white woman (F.A.A.) living in Uberlândia, MG, presented to the clinic with a more ten-year history of yellowish lesions on the neck and the mammary glands, with gradual growing.

On dermatological examination, yellowish confluent plaques in the lower lip mucosa, the mammary glands, the cervical, the periumbilical, and the superior limb flexural areas were found. Biopsy of the cervical skin lesion was performed confirming the diagnosis of PXE.

The patient was guided to the Ophthalmology Service, where funduscopy examination of the eye detected retina pigmentation changes.

Patient 5 – A 34-year old brown woman (O.R.R.X.) living in Uberlândia, MG, presented to the Dermatology Ambulatory with complaint of wrinkled skin and yellowish blots on the neck.

On dermatological examination, yellowish papules on cervical and periumbilical areas were detected. Ophthalmologic examination showed normal eye fundus.

Anatomopathologic assay revealed bundles of basophilic swollen elastic fibers, irregularly aggregated, particularly in the inferior portion of the dermis. On the superficial and intermediate dermis irregular basophilic and heterogeneous masses of various sizes were observed. In addition, a discrete perivascular mononuclear infiltrate was also found.

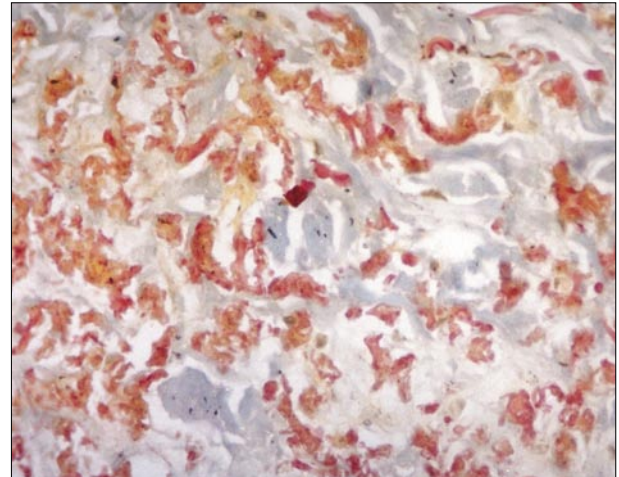


Figure 4. Elastic fibers with calcification as shown by amorphous black material (von Kossa).

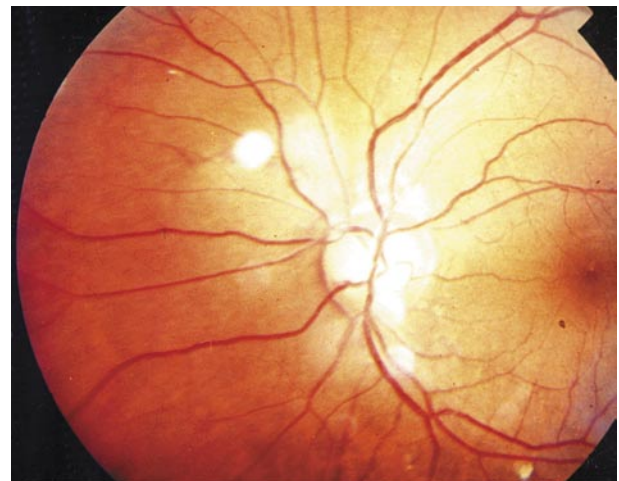


Figure 5. Funduscopy examination of the eyes showing red-dark angioid streaks with ridge-shaped borders adjacent to the retinal vessels.

Patient 6 – A 29-year old white woman (V.C.S.O.) living in Uberlândia, MG, presented to the Dermatology Service with yellowish linear papules and plaques on the cervical, sternal, axillary and antecubital areas, in addition to whitish papules in the oral mucosa. The patient had a history of hypothyroidism, fatigue, palpitation, limb and chest pains.

The patient's parents were consanguineous. She had one sister with similar lesions, three brothers with diabetes mellitus and the mother with systemic arterial hypertension.

Biopsies of skin lesions as well as ophthalmologic, angiologic and cardiologic examinations were performed. Results of biopsy of the lower lip mucosa, the cervical and axillary areas were compatible with PXE.

On ophthalmologic examination, low visual acuity was found and the fundusoscopic examination of the eye revealed angioid streaks bilaterally, which were confirmed by retinal mapping, evidencing also the presence of chorioretinitis scar.

Cardiovascular examination revealed that the patient had non-irradiated, sharp-like pain on the area precordial with spontaneous regression. She had non-visible and non-palpable ictus cordis, rhythmic and jugular engorgement in the dorsal decubitus position.

Comment

The present study demonstrated that PXE was extremely rare (six cases presented in the HC-UFU in 136 months) and the importance of skin lesions for the diagnosis of PXE.

All of the six patients of this study had skin lesions on the cervical area, as already reported by other authors [10,15]. The second predominant site was the lower lip mucosa, which was affected in four patients (66.7%), although no report of oral mucosa involvement was found in the literature. Another involved sites were the mammary glands, the sternal, antecubital, abdominal, periumbilical and inguinal areas. No case corresponded to the perforating periumbilical pseudoxanthoma elasticum or it was associated with calciphylaxis, as reported by other authors [16,17].

It must be emphasized that four patients (66.7%) had systemic involvement, except for the patient that did not present to the ophthalmologic and cardiovascular examinations. Des-

pite the angioid streaks occur in 85% of patients with PXE [6], in the present study only two patients (33.3%) showed such streaks. However, out of six patients studied, one did not perform the ophthalmologic examination. On the other hand, Neves et al., (1997) observed angioid streaks in two cases of PXE studied. Mansur et al. (1988) stated that hiatus hernia and peptic ulcer lesions can be found and aggravated in the presence of PXE. In one of six patients of the present study, hiatus hernia and gastritis were detected, confirming the findings of these authors.

From the reported cases, one had family history of PXE and other had sister with suggestive lesions, thus demonstrating the predominantly recessive genetic inheritance of the disease. In one of the patients, the consanguinity of her parents possibly has contributed for the involvement of PXE. The present study showed a higher frequency of PXE in female with a female:male ratio of 5:1.

All the six patients of this study underwent histopathologic examinations of their cutaneous and/or oral lesions in order to ensure the diagnosis of PXE. These biopsies showed fragmentation and calcification of the elastic fibers. Histopathologic changes of PXE can be seen in patients with calciphylaxis as a concurrent finding. Calciphylaxis is a rare condition of diffuse calcification of tissues and blood vessels resulting in thrombosis and ischemic necrosis. Most cases develop in patients with hyperparathyroidism associated with chronic renal failure [18]. In these patients, high level of parathyroid hormone associated with high levels of calcium can lead to the vascular calcification process. Probable triggering agents of this process include corticosteroids, albumin, tobramycin, dextran, immunosuppressives, calcium heparinate and vitamin D [16].

Table 3. Clinical cases of pseudoxanthoma elasticum (PXE) presented in the Hospital de Clínicas, Universidade Federal de Uberlândia (HC-UFU) from January 1990 to April 2001.*

Case (n°)	Sex/Age (year)	Cutaneomucous lesion sites	Additional manifestations	Familiar background	Diagnostic approach
1	F / 28	Cervical, periumbilical, inguinal, lower lip mucosa	Angioid streaks, arterial hypertension	2 brothers and 1 sister with PXE	Cutaneous lesions
2	F / 40	Cervical, lower lip mucosa	Bilateral RPE changes, gastritis, hiatus hernia	Non	Cutaneous lesions
3	M / 12	Cervical, abdominal, inguinal	No backing	Non	Cutaneous lesions
4	F / 22	Cervical, periumbilical, antecubital fossae, mammary glands, lower lip mucosa	RPE changes	Non	Cutaneous lesions
5	F / 34	Cervical, periumbilical	None	Non	Cutaneous lesions
6	F / 29	Cervical, sternal, axillary, antecubital fossae, lower lip mucosa	Low visual acuity, angioid streaks, chorioretinitis scar	Consanguineous parents and sister with similar lesions	Cutaneous lesions

* F, female; † M, male; ‡ PXE, pseudoxanthoma elasticum; § RPE, retinal pigment epithelium.

There are several conditions in which coincidental histologic findings of PXE have been found in patients without clinical evidence of PXE. Most of these have been associated with abnormal calcium metabolism and include renal failure associated with systemic lupus erythematosus, idiopathic hypercalcemia to secondary calcinosis cutis, osteoectasia (juvenile Paget's disease of the bone), administration of saltpeter, and necrobiosis lipoidica. Although these cases could all represent acquired and localized PXE, it is more probable that the abnormal calcium metabolism leads to microscopic calcification of elastic fibers, appearing in some cases histologically as PXE. In inherited PXE, the calcium binding activity of fibrillin, a major component of elastin, is markedly increased, suggesting that the abnormality of elastin leads to calcification of elastic fibers. In PXE-like changes associated with calcium, perhaps chronically increased levels of calcium saturate fibrillin lead to calcification and fragmentation of elastic fibers. The exact role of calciphylaxis in inducing these changes is unclear, however, ischemia and increased circulating levels of parathyroid hormone may also contribute to this process. Finally, although unlikely, a form of PXE can predispose to the development of calciphylaxis. Additional studies of pa-

tients with both of these rare disorders are required to evaluate ultimately these theories [18].

Importantly, in all cases here reported, the diagnosis of PXE was obtained from cutaneomucous lesions. It should be pointed out that people just seek medical assistance when the lesions are evident and in advanced growing stage. Once the diagnosis was confirmed by anatomopathological assay, the patients must be guided for ophthalmologic and cardiovascular examinations.

PXE is a disorder, although rare, that is often underdiagnosed probably due to lack of familiarity with the disease among physicians. As there is no treatment for the disease, a sensitive conduct would be the genetic counseling.

Conclusion

Since the dermatologist is the responsible for the diagnosis of the majority of cases, we pointed out the importance of a detailed dermatological evaluation and skin biopsy with further guiding of patients to the Cardiovascular and Ophthalmologic Services, in view of the fact that the systemic manifestations are very frequent.

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