CASE REPORT

Case Report: Pseudoxanthoma elasticum [version 1; peer review: 1 approved, 3 approved with reservations]

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Abstract

Pseudoxanthoma elasticum (PXE) is a rare inherited disorder, characterised by a progressive mineralization and fragmentation of elastic fibres of the skin, retina and cardiovascular system. At an initial stage, the skin usually exhibits distinctive lesions and subsequently extra-dermal manifestations. The diagnosis is based on clinical manifestations, histological analysis of the lesions and genetic analysis.
This is a case report of a 12-year-old child complaining of painless, mildly itchy yellow papules in the cervical region with 1 year of evolution.
PXE is currently an incurable disease and has a favourable prognosis when cardiovascular and retinal complications are prevented and monitored.

Keywords

Pseudoxanthoma elasticum, ABCC6 gene, retina angioid streaks, hypertension

Open Peer Review

Reviewer Status ? ? ✓ ?

	Invited Reviewers			
	1	**2**	**3**	**4**
version 1 09 Jan 2020	? report	? report	✓ report	? report

1 **Olivier M. Vanakker**, Ghent University Hospital, Ghent, Belgium

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Lucas C: Investigation; **Aranha J**: Investigation, Writing – Review & Editing; **da Rocha I**: Investigation; **Sousa D**: Investigation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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Introduction

Pseudoxanthoma elasticum (PXE), also known as Grönblad-Strandberg syndrome, is a rare inherited disorder presenting an autosomal recessive inheritance with a mutation in the *ABCC6* gene (ATP-binding cassette transporter C6), mapped in the chromosome 16. It has an estimated prevalence of 1/25.000 to 1/100.000 inhabitants and is 10 times more prevalent in women[1,2].

The disease is characterised by a progressive mineralization and fragmentation of elastic fibres of the skin, retina, gastrointestinal and cardiovascular systems.

PXE results in a variety of signs and symptoms that vary in their number, type, and severity from person to person. Certain effects of PXE can cause serious medical problems, while others have less impact. Effects may include: skin changes, changes in the retina of the eye that may result in significant loss of central vision, changes in the cardiovascular system that may involve calcification of arteries and decreased blood flow in the arms and legs, and/or changes in the gastrointestinal system that may lead to bleeding in the stomach or intestines. At present, there is no way to predict the exact progression of the disorder for an individual[2]. Some people have no skin lesions; others have no vision loss. Many people do not experience gastrointestinal complications or cardiovascular difficulties. A few have no manifestations of PXE except for a positive skin biopsy or irregular streaks resembling a blood vessel (angioid) in the retina of the eye[1,2].

The diagnosis is based on major and minor criteria defined in 1994 taking into account the clinical manifestations described above (Table 1), positive histological on Von Kossa stain for reticular dermis, family history and genetic analysis of the *ABCC6* gene[1–3].

PXE is currently an incurable disease but has a favourable prognosis with appropriate follow-up by multidisciplinary teams.

Case description

A 12-year-old Caucasian girl presented for a dermatology appointment in November 2016 due to sporadically painless, slightly itchy yellow papules in the cervical region with 1 year of evolution. These lesions remained stable throughout this period with no medication or treatment. The child had no pain complaints, or inflammatory signs on the lesions or around them, and did not have any associated symptoms. Previously she was a healthy child, was not taking any daily medication and had no relevant personal or family medical history of dermatosis.

On examination, painless, uneven, rough and yellow plaques without inflammatory signs in the posterior cervical region that merged bilaterally and symmetrically into the right and left side cervical region was found (Figure 1). It was similar to a goose bump pattern, giving it a parchment-like skin appearance. The remaining integument had no changes.

No other abnormalities were found on the rest of physical examination.

In this appointment, the following exams were conducted: hemogram, general biochemistry with lipid profile and phosphorus-calcium balance and urinary sediment that were unremarkable. Moreover, a skin biopsy was promptly performed.

In the next appointment, still in November, the skin biopsy results revealed limited changes to the superficial/medium reticular dermis with a long strip of elastic fibre fragmentation. They were thick, granular, basophilic, with bizarre shapes between the collagen fibres with a normal appearance. There was no evidence of mineralization or deposits of mucin.

Following the investigation, further exams were conducted: electrocardiogram and echocardiogram, carotid and aortoiliac venous and arterial ultrasonography, retinogram with full ophthalmological examination (angioid streaks). The results were normal. There was the possibility of a genetic disorder, but the pathology specialist decided there was no need to perform a study of the *ABCC6* genes based on the clinical aspect of the lesions, which were highly characteristic of PXE.

The child has been having annual follow-up with ophthalmologic, paediatric cardiology and dermatology appointments. Until February 2019 no systemic manifestations were reported.

Table 1. Diagnostic criteria for Pseudoxanthoma elasticum (PXE) defined at the consensus conference in 1994[3].

Major criteria
• Characteristic skin signs – Yellow cobblestone lesions in flexural areas • Characteristic histological features of lesional skin – Elastic tissue and calcium or von Kossa stains • Characteristic ophthalmologic features – Angioid streaks, peau d'orange maculopathy – In adults > 20 years old
Minor criteria
• Characteristic histological features of non-lesional skin – Elastic tissue and calcium or von Kossa stains • Family history of PXE in first-degree relatives

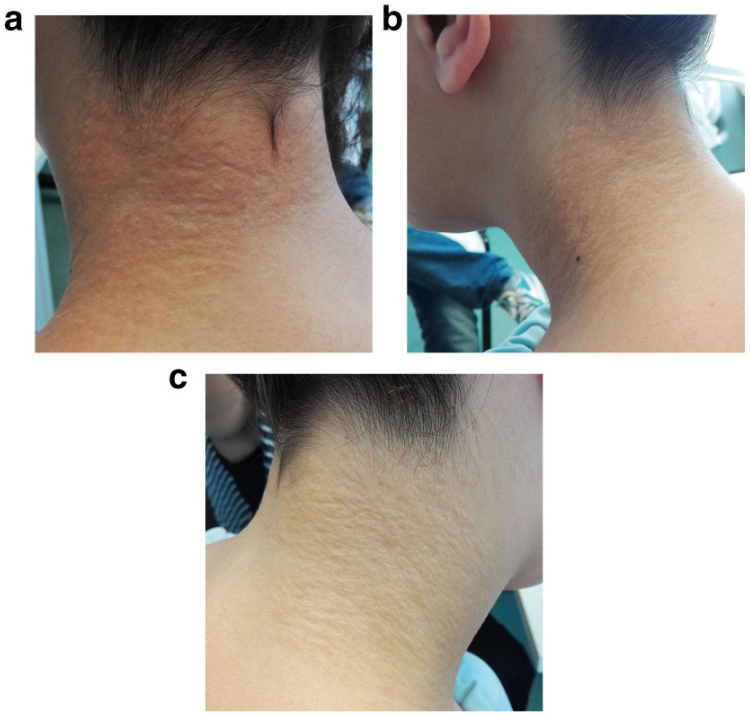

Figure 1. Photographs of the skin lesion taken from (**a**) behind, (**b**) the left and (**c**) right side of the patient's neck. Uneven, rough and yellow plaques can be seen in the cervical region.

Discussion

PXE is a rare inherited disorder, characterised by mineralization disturbances of the connective tissue with elastic fibre degeneration, mainly involving skin, eyeballs and cardiovascular system[1–4].

At the consensus conference, in 1994, the PXE diagnosis criteria were defined (Table 1)[3]. The patient presented two of these major criteria: characteristic yellow cobblestone lesion in the skin and positive von Kossa stain.

Although the cutaneous manifestation is frequently flesh-colored to yellow macules or papules which progressively agglutinate into bigger plaques, and the affected skin that becomes lax and wrinkled, the clinical manifestation is variable and can occur at any age. At an early stage, the skin lesions are found on the right, left and rear sides of the neck and flexion creases, including armpits, inguinal region, popliteus region, and periumbilical area, as seen in this patient. The lesions may also affect the genital area and oral mucosa[2,4,5].

PXE ophthalmological manifestations include mainly angioid streaks due to Bruch membrane lesions (characteristic but not pathognomonic), deformed macular degeneration, retina pigmentation, choroidal neovascularization, haemorrhage and scar formation on the retina. For the ocular complications, vascular endothelial growth factor antagonists have been used to prevent neovascularization, thus reducing the occurrence of the most severe complication: loss of vision[4,6].

Cardiovascular manifestations are a major cause of morbidity in these patients: hypertension, angina pectoris and intermittent claudication are some of the examples. Patients with PXE may also develop early atherosclerosis due to the mineralization of the internal elastic lamina of the blood vessels and lipid alteration with high density lipoprotein (HDL) cholesterol levels reduction in blood plasma and hypertriglyceridemia. This contributes to a higher incidence of acute myocardial infarction and cerebrovascular accident[6].

Histopathology exams in PXE patients reveal agglutination and mineralization of elastic fibres and fragmentation of the elastic fibres in the medium/deep dermis[2,7].

PXE and papillary dermal elastosis share similar lesions. Therefore, a differential diagnosis shall be performed. At a histopathology level, papillary dermal elastosis with the Von Kossa stain is negative to calcium in elastic fibres. Moreover, there is no systemic involvement in papillary dermal elastosis[7].

The patient's general practitioner shall be responsible for early detection of the ocular and cardiovascular complications of the PXE because the mineralization in the centre of the fibres predisposes the development of secondary hypertension. Therefore, the morbidity and mortality caused by the disease can be monitored and reduced.

To conclude, PXE is a rare disease, the recognition of which is important since it can cause systemic severe cardiovascular and retinal manifestations. The diagnosis is based on histology result. Patients can be further tested for a mutation in the *ABCC6* gene. The earlier the diagnosis, the sooner preventive measures and close observation can be adopted to prevent and control the possible adverse events caused by this disease.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the parent of the patient.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

References

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Reference Source

Open Peer Review

Current Peer Review Status: ? ? ✔ ?

Version 1

Reviewer Report 31 July 2020

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?

Wilko Spiering
Department of Vascular Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

This case report reports on a 12 year old child with PXE.

I have the following comments:

- Some references used are outdated and even contains a non-English paper. Please update and replace.
- The male-female ratio is not correct. PXE is 2-3 times more prevalent in women.
- The diagnostic criteria used are from 1994. I would recommend using the updated criteria from Plomp *et al.* (http://www.ncbi.nlm.nih.gov/pubmed/20358627), published in 2010.[1]
- The authors state that PXE 'has a favourable prognosis with appropriate follow-up by multidisciplinary teams'. What is meant by favourable? Although recommended, it is not proven that multidisciplinary teams improve any outcome in PXE.
- I disagree with the decision of the pathology specialist that there was no need to perform a genetic analysis for mutations in ABCC6, or other genes like ENPP1 and GCCX. A genetic analysis always should be done. This obviously cannot be changed in the manuscript, but maybe the authors can make a statement on this.
- Eyeballs are not affected in PXE. Please change into Bruch's membrane of the eye or retina.
- I would prefer to use vascular manifestations instead of cardiovascular as the heart is usually not more affected compared with healthy controls. Also, hypertension is probably not more prevalent in PXE.
- It is stated that there is a 'higher incidence of acute myocardial infarction and cerebrovascular accident in PXE'. The reference (Hosen *et al.*) used for this statement is a histopathology paper

and does not even discuss this. Cerebrovascular accidents, but not myocardial infarctions, are indeed increased in PXE. Please use an appropriate reference.

- It is stated that 'Patients with PXE may also develop early atherosclerosis due to the mineralization of the internal elastic lamina of the blood vessels and lipid alteration with high density lipoprotein (HDL) cholesterol levels reduction in blood plasma and hypertriglyceridemia.' Atherosclerosis is not more common in PXE, as this is an intimal disease with accumulation of cholesterol in the intima. The appropriate vascular manifestation in PXE is arteriosclerosis, with calcification of the internal elastic layer and media of the vessel wall. The lipid alterations described are pathophysiological not correct and should be deleted.

- Recent developments on potential treatments in PXE are lacking, e.g. etidronate (Kranenburg *et al.* 2018) and oral pyrophosphate (Väärämäki *et al.* 2019).[1,2] I would recommend adding this to the discussion.

References

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Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vascular medicine, pseudoxanthoma elasticum, hypertension.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 July 2020

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Annamaria Offidani
Dermatological Clinic, Department of Clinical and Molecular Sciences, Polytechnic University of the Marche Region, Ancona, Italy

- The title is written in SEO terms.
- The text is clear and well written, the case is described in detail. Our response is to approve the manuscript as it doesn't present flaws or incomplete descriptions of the steps from diagnosis to management.
- It would be nice if the authors could add some details of dermoscopic characteristic features they saw as dermoscopy could substitute histopathology for early and confirmed diagnosis.[1]

References

1. Singh A, Bhari N, Bhari A: Dermoscopy of pseudoxanthoma elasticum. *BMJ Case Reports*. 2017. bcr-221365 Publisher Full Text

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunological skin diseases, psoriasis, atopic dermatitis, genetic and rare disease of the skin

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 July 2020

https://doi.org/10.5256/f1000research.23605.r66211

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Márta Medvecz
Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary

This manuscript for a case report presents the well-documented case of a 12-year-old girl with PXE. In addition, the discussion section of the paper also includes a short review on PXE, highlighting systemic manifestations, histopathologic alterations, and management. However, there are some minor issues to be clarified by the authors:

1. A more informative title could be useful, e.g. one that implies that an interesting aspect of this case is that early skin lesions in a young patient are documented.

2. It would raise the quality of the manuscript if, in addition to the description of the skin biopsy findings, histopathologic images could also be included. Also, for the histology, it should be mentioned, which stainings were performed.

3. The necessity of genetic testing should be decided by a clinical geneticist and not a pathologist, as implied in the Case description of the manuscript.

4. In the Discussion section, it can be debated if the patients' general practitioner should be responsible for the early detection of systemic manifestation. PXE should be managed by a multidisciplinary team at specialized rare disease centers with sufficient expertise and experience.

5. Certain papers cited by the manuscript are outdated or are not available in English. These should be replaced by citing more recent, high-quality publications.

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genodermatoses

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 17 February 2020

https://doi.org/10.5256/f1000research.23605.r58434

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Olivier M. Vanakker
Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium

This case report describes a classic presentation of PXE in a young girl.
I have a few comments on the current manuscript:

1. The manuscript refers in the introduction and discussion to the detection of a mutation in ABCC6, but PXE is an autosomal recessive disease, so this should be mutations in ABCC6.

2. PXE can also be caused by mutations in the ENPP1 gene. This should be added.

3. The difference between women and man is approximately 3:1, not 10:1

4. In the description of the ocular lesions, there should be a distinction between the angioid streaks due to Bruch's membrane abnormalities - which are almost always present - and retinal changes, i.e. a retinal dystrophy which can occur but is much more rare.

5. The idea of not analyzing ABCC6 when the histology is typical is not correct for two reasons:
   a. in its initial presentation - both clinical and histological - PXE can high resemble the PXE-like syndrome with coagulation factor deficiency due to GGCX mutations. The natural history and follow-up of these patients is however completely different.
   b. identification of the causal mutations - either in ABCC6 or ENPP1 - will allow to detect subclinical patients in the family (as said, some have no skin lesions and angioid streaks do not have to become symptomatic immediately) as well as heterozygous carriers. The latter also have a higher cardiovascular risk and a higher risk for stroke and are candidates for primary prevention.
   So every patient should have molecular analysis performed!

6. In the first paragraph of the discussion, the authors mention the eyeballs. But there is nothing wrong with the eyeballs themselves.

7. PXE patients have media calcification in their arteries, which leads to arteriosclerosis, not atherosclerosis (which reflects intima calcification).

8. The differential diagnosis is absolutely not complete: one should exclude the hemoglobinopathy-associated phenocopy, the PXE-like syndrome with coagulation factor deficiency, the PXE-like phenotype with pigmented retinopathy, ...

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ectopic mineralization diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.