PSEUDOXANTHOMA ELASTICUM (PXE): 25 CASE REPORT AND FOLLOW UP

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Abstract
Pseudoxanthoma elasticum is a rare genetic disorder characterized by progressive calcification and fragmentation of the elastic fibers in the skin, in the retina, and in the cardiovascular system. The aim of our study was to underline the complications of this disease. Twenty-five patients (eighteen women and seven men) were investigated during a period of 11 years. Typical skin lesions and the histological features were present in all patients. Funduscopy revealed retinal changes in all cases, but all were asymptomatic. Seventeen patients had cardiovascular or haemorrhagic events. Eighteen patients showed clinical signs about other organs (kidney, liver, bladder, thyroid and stomach). The early diagnosis of PXE may be important. Indeed, it allows accurate provision of information and lifestyle adjustments that might help to avoid disabling complications and long-term impact on quality of life and planning of follow-up and early detection of complications, even if optimal frequency of follow-up is actually unknown.
Abstract

Lo pseudoxanthoma elastico è un raro disordine genetico caratterizzato dalla progressiva calcificazione e frammentazione delle fibre elastiche a livello della cute, della retina e del sistema cardiovascolare. L’obiettivo del nostro studio è stato di sottolineare le complicazioni di questa patologia. Venticinque pazienti (18 femmine e 7 maschi) sono stati seguiti per un periodo di 11 anni. Tipiche lesioni cutanee e alterazioni istologiche caratteristiche sono state riscontrate in tutti i pazienti. Lo studio del fondo oculare ha rivelato cambiamenti retinici in tutti i casi, ma tutti risultavano essere asintomatici. Diciassette pazienti hanno mostrato eventi cardiovascolari ed emorragici. Diciotto pazienti hanno presentato segni clinici relativi ad altri organi (rene, fegato, vescica, tiroide e stomaco). La diagnosi precoce di PXE dovrebbe essere importante. Infatti, pianificando un follow-up ed effettuando una diagnosi precoce si ottengono informazioni accurate e modifiche dello stile di vita che potrebbero essere utili per evitare complicazioni invalidanti di impatto a lungo termine sulla qualità della vita anche se la frequenza ottimale di follow-up è in realtà sconosciuta.

Case Report

Introduction

Pseudoxanthoma elasticum (PXE; synonym: Gronblad Strandberg syndrome; MIM 264800), described for the first time in 1881 (1), is a rare genetic disorder characterized by progressive calcification and fragmentation of elastic fibers in the skin, the retina, and the cardiovascular system.

The prevalence is estimated at 1 in 25 000–100 000 with an almost 2:1 female preponderance (2). This disease is known as an autosomal-recessive disorder, but autosomal-dominant inheritance has been proposed in rare PXE cases (3). The gene is localized on chromosome 16p13.1.2 and encodes a putative efflux transporter, ABCC6, which is expressed primarily in the liver, the kidneys, the intestine and at very low level, if at all, in tissues directly affected in PXE (4).

Although fully penetrant, clinical findings of PXE are rarely present at birth, and the skin findings usually do not become recognizable until the second or third decade of life. There is a considerable both intra- and inter-familial heterogeneity, so that in some families the skin manifestations may be predominant with relatively little eye or cardiovascular involvement, while in other families the involvement of the latter organ systems may have severe clinical consequences with limited skin findings (5).

Reasons for this phenotypic heterogeneity are currently not clear (6). Though there are recent suggestions, however, linking certain types of mutations with pathognomonic alterations of some organs. Alteration p.R1268Q is associated with early onset of angioid streaks (7, 8), while the stop codon mutation p.R1141X is correlated with to cardiovascular involvement independent of hyperlipidemia (9).

Mild forms of the disorder can easily be overlooked and a negative family history does not exclude the diagnosis. It is important to recognize the disease early, in order to minimize the risk of systemic severe complications. The most apparent clinical feature of this pathology is the skin manifestations, which consist of yellow-orange papules or plaques with loss of dermal elasticity. Skin lesions are usually noted in the second or third decade and commonly affected sites are the flexures and periumbilical region. Mucous involvement is not rare. Ocular involvement is characterized by angioid streaks, breaks in the Bruch’s membrane, with secondary changes of the retinal pigmented epithelium (peau d’orange) and choriocapillaris. While the angioid streaks are asymptomatic at first, they become the sites of choroidal neovascularization and subretinal haemorrhages later in life and central loss of vision may occurs in the case of macular involvement (10). Cardiovascular manifestations usually develop last and result from slowly progressive calcification of elastic arterial walls.
Additionally, PXE can manifest with gastrointestinal haemorrhage and involvement of various organs such as liver, kidneys, spleen, breast, and testes.

Reduction of vessel lumen causes ischaemia and excessive fragility of the vessel wall is responsible for haemorrhage (10).

The histology (fig.2) of PXE is characteristic: in skin lesions swollen, clumped, and fragmented elastic fibres and calcium deposits are found in the mid and deep reticular dermis. Similar changes occur in elastic fibres of the blood vessels, Bruch’s membrane of the eye, endocardium and other organs. Transepidermal elimination of altered calcified elastic fibres may occasionally be seen in PXE (11). The use of elastic stains (for example, Verhoeffvan Gieson or Orcein) and stains for calcium deposits (for example, von Kossa) are recommended. Electron microscopy may be used to show the characteristic abnormalities. Initially the mineralisation of elastic fibre occurs in the core. As the disease progresses the outer rim becomes increasingly dense and eventually when maximum calcification is reached fragmentation occurs. Ultrastructurally, extracellular matrix components such as fibronectin, vitronectin, and proteoglycans associated with altered elastic fibres in PXE accumulate in lesional skin. It has been suggested that these matrix proteins which are not present in normal fibres have a high affinity to calcium ions or induce mineral precipitation. Raised levels of glycosaminoglycans have been found in affected skin and urine of some patients with PXE (12).

To facilitate and unify the clinical diagnosis for PXE, were defined three major diagnostic criteria and two minor criteria at the consensus conference in 1992 (Table 1) (13).

**Tab. I - Diagnostic criteria defined at the consensus conference in 1992.**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>• Characteristic skin signs (yellow cobblestone lesions in flexural areas)</td>
<td>• Characteristic histological features of non-lesional skin (elastic tissue and calcium or von Kossa stains)</td>
</tr>
<tr>
<td>• Characteristic ophthalmologic features (angioid streaks, peau d’orange, maculopathy)</td>
<td>• Family history of PXE in first-degree relatives</td>
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<tr>
<td>• Characteristic histological features of lesional skin (elastic tissue and calcium or von Kossa stains)</td>
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**Materials and Methods**
The population in the present study consisted of twenty-five patients (eighteen female; seven male; age range 25-70 years) that have been followed at the Department of Dermatology, Multidisciplinary Centre of Rare Diseases at the Umberto I Policlinic in Rome, Italy, between 2000 and 2011. All patients in this study were diagnosed according to the criteria for the definitive diagnosis of PXE (13).

The diagnosis of PXE was made by dermatologists, histopathologists and ophthalmologists.

In the skin, white–yellow papules were present, more or less coalescent, with a rough and redundant appearance to the skin. Also, typical streaks angiodi have detected with funduscopic examination.
Then the diagnosis was confirmed by a skin biopsy, which revealed the presence of Von Kossa-positive precipitates within elastic fibers and electron microscopy, such as fragmentation and calcification of elastic fibres, collagen flowers, and aggregates of microfilaments in the reticular dermis.

The patients were referred by cardiologists and guests were also subjected to blood pressure measurement, an electrocardiogram (ECG) and also an examination of arterial stiffness. Patients who had a history of cardiovascular disease or who showed abnormal results interests were further subjected to a Holter ECG and computed tomography (CT) angiography.

Furthermore, the patients have been subjected to an abdominal echography.

ABCC6 gene mutation analysis was not performed in all cases as no clear cut genotype/phenotype correlation has yet been demonstrated in PXE.

**Results**

The age at which symptoms appeared was between 10 and 15 years. PXE was diagnosed at a mean age of 15 years. The age range on first referral to our centre was 20 years. Severe complications of PXE were uncommon before the age of 15 years.

Typical skin lesions were present in all patients.

The first skin lesions were yellowish laterocervical and inguinal papules (Fig. I) or plaques with loss of dermal elasticity (Fig. II), strikingly sparing the nape and the anterior aspect of the neck.

**Fig. I - Yellowish papules of the inguinal region**
**Fig. II** - Plaques with loss of dermal elasticity of the axillary region

![Plaques with loss of dermal elasticity of the axillary region](image)

**Fig. III** - Skin biopsy characterized by the presence of basophilic fragmented reticular fibers of wavy appearance and sometimes spiral in the medium and superficial dermis

![Skin biopsy](image)
Funduscopy revealed retinal changes in all cases, but all were asymptomatic. Nine had angioid streaks and all had peau d’orange changes. Seventeen patients had experienced cardiovascular or haemorrhagic events. Six patients had mitral insufficiency, five had tricuspid insufficiency and six premature atrial complexes. Furthermore these patients had smoking history (nine cases), hypertension (seven cases), hyperlipidemia (four cases) and diabetes (two case). In all cases, dermal elastorrhexis and angioid streaks were demonstrated between 12 and 20 years of age.

Therefore, eighteen patients showed clinical signs about other organs: chronic renal failure (five cases), renal cysts (five cases), chronic gastritis (four cases), hepatic cysts (three cases), prolapse of the urinary bladder (three cases) and thyroid nodules (three cases).

The usual presentation of the disease in children is similar to that in young adults and is often limited to typical cutaneous changes. Other skin lesions of PXE such as perforating elastosis serpiginosa, reticulated pigmentation and inflammatory acneiform papules have only very rarely been described in childhood. All our patients with PXE starting in childhood had asymptomatic retinal changes, representing the primary involvement of Bruch’s membrane and preceding angioid streaks by several years. Only a few patients with unquestionable angioid streaks have been described before 15 years of age. As ophthalmological lesions are asymptomatic and because reasons for fundus examination are few in children, ophthalmologists rarely make the initial diagnosis of PXE in this age (14).

Discussion and Conclusions

PXE is a rare and progressive disease. Despite the recent identification of the molecular basis of PXE (i.e., mutations in the ABCC6 gene), the pathogenesis is still unknown. One hallmark of PXE is the coexistence in the affected and nonaffected skin of huge amounts of microfibrillar matter, corresponding to the accumulation of fragmented, swollen, and incomplete elastin fibers, together with various types of proteoglycans. Cardiovascular involvement is common, and patients with PXE sometimes present at young age calcifications at the site of large arteries and occlusive vascular changes indiscernible from atherosclerosis. The fortuitous observation of asymptomatic visceral calcifications is suggestive of the diagnosis of PXE in childhood and should lead to skin and ophthalmological evaluations.

Pseudoxanthoma elasticum causes narrowing of the vessel lumina and results in symptoms similar to those of arteriosclerosis. The PXE-associated calcification of the internal elastic lamina of arteries resembles the degeneration and calcification of elastic fibers in the mid-dermis. This suggests that the severity of skin and mucous membrane lesions could correlate with the degree of cardiovascular involvement.

Contradicting this view is that the skin lesions associated with PXE vary considerably in both distribution (usually flexural areas) and clinical manifestations, which range from typical yellow-white papules to redbrown macules, even in older age patients. In addition, phenotypic manifestations of PXE within a family appear to vary considerably. These observations together suggest that cardiovascular diseases may not correlate well with the severity of the skin manifestations.

Cases of renovascular hypertension have also been reported. Valvular changes, mainly mitral valve prolapse, may be present. Early PXE-related coronary artery disease is often severe, most cases presenting as early angina pectoris or myocardial infarction. In some cases coronary artery disease has led to sudden death (15). Stroke may also occur as the consequence of ischaemic or haemorrhagic cerebrovascular disease. Gastrointestinal haemorrhages are often dramatic and recurrent (16). Despite significant advances in molecular genetics of PXE in the last decade, there is currently no effective or specific treatment for PXE. Recently, however, new innovative approaches have been developed, some of which can potentially lead to a treatment of PXE at the molecular level.

PXE is associated with considerable morbidity and mortality. Patients are advised to abstain from high-risk sports that may cause ocular trauma and encouraged to modify their diet and lifestyle to delay cardiovascular complications. However, currently there are no established treatment regimens for PXE. Therapeutic approaches to treat subfoveal choroidal neovascularization (CNV) have included surgery, photocoagulation, and photodynamic therapy with varying success. More recently, vascular endothelial growth factor inhibitors such as bevacizumab have led to the slowing of CNV growth and the concomitant deterioration of visual function (17). The early diagnosis of PXE may be important. Indeed, it allows accurate provision of information and lifestyle adjustments that might help to avoid disabling complications and long-term impact on quality of life, and planning of follow-up and early detection of complications, even if optimal frequency of follow-up is actually unknown.
Reference


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