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Pseudoxanthoma elasticum (PXE): 15 casi clinici e follow up cardiologico

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SUMMARY: **Pseudoxanthoma elasticum (PXE): 15 clinical cases and cadiologic follow-up.**

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Pseudoxanthoma elasticum (PXE; synonym: Gronblad-Strandberg syndrome) is a rare, inherited, multisystem disorder primarily affecting the skin, eyes, and cardiovascular system. It is characterised by progressive calcification and degeneration of elastic fibres. The prevalence is estimated at 1 in 25.000-100.000 with an almost 2:1 female preponderance (3). The genetic defect has been mapped to the ABCC6 gene on chromosome 16p13.1.2. ABCC6 encodes multidrug resistance associated protein 6 (MRP6), which belongs to the ABC (ATP Binding Cassette) transmembrane transporter family of proteins. Its exact biological function is not clear yet but it may play a role in cellular detoxification. The population in the present study consisted of 15 patients (11 female; 4 male; age range 25-70 years) that had been referred to the Department of Dermatology, Multidisciplinary Centre of Rare Diseases at the Umberto I Policlinic in Rome, Italy, between 2000 and 2009. All patients in this study were diagnosed according to the criteria for the definitive diagnosis of PXE (described above). All patients presented skin and ocular lesions typical of PXE.

RIASSUNTO: **Pseudoxanthoma elasticum (PXE): 15 casi clinici e follow up cardiologico.**

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Lo pseudoxantoma elastico (PXE; sinonimo: sindrome di Gronblad-Strandberg) è una malattia rara, ereditaria , multisistemica che interessa principalmente cute, occhi e sistema cardiovascolare. Tale patologia è caratterizzata da progressive calcificazioni e degenerazione delle fibre elastiche. La prevalenza è di 1 su 25.000-100.000 con un rapporto di quasi 2:1 tra femmine e maschi (3). La mutazione genetica è stata mappata sul gene ABCC6 del cromosoma 16p13.1.2. ABCC6 codifica per la proteina 6 associata alla resistenza multidrug *(MRP6), che appartiene alla ABC (ATP Binding Cassette) della famiglia delle proteine di trasporto trans-membrana. L'esatta funzione biologica non è chiara ma sembra svolgere un ruolo nella disintossicazione cellulare. Il campione preso in esame è composto da 15 pazienti (11 femmine; 4 maschi; con un età compresa tra i 25 e i 75 anni) che sono stati trattati presso il Dipartimento di Dermatologia, Centro Multidisciplinare delle Malattie Rare del Policlinico Umberto I di Roma, Italia, tra il 2000 e il 2009. La diagnosi di tutti i pazienti che hanno preso parte a questo studio è stata fatta in accordo ai criteri per la diagnosi definitiva dello PXE. Tutti i pazienti presentavano lesioni oculari e cutanee tipiche dello PXE.*

KEY WORDS: Pseudoxanthoma elasticum - Elastic fibres - ABCC6 gene.
Pseudoxanthoma elasticum - Fibre elastiche - Gene ABCC6.

Introduction

Pseudoxanthoma elasticum (PXE; synonym: Gronblad Strandberg syndrome) is a rare, inherited, multisystem disorder primarily affecting the skin, eyes, and cardiovascular system. It is characterised by progressive calcification and degeneration of elastic fibres (1). There is considerable spectrum of genetic mutations and wide inter- and intra-familial phenotypic variation (2). Mild forms of the disorder can easily be overlooked, and a negative family history does not exclude the diagnosis. It is important to recognise the disease early, in order to minimise the risk of systemic complications.

The prevalence is estimated at 1 in 25.000-100.000 with an almost 2:1 female preponderance (3). The genetic defect has been mapped to the ABCC6 gene on chromosome 16p13.1.2. ABCC6 encodes multidrug resistance associated protein 6 (MRP6), which belongs to the ABC (ATP binding cassette) transmembrane transporter family of proteins. Its exact biological function is not clear yet but it may play a role in cellular detoxification. Interestingly, MRP6 is highly expressed in the liv-

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er and kidneys but only low levels are found in tissues affected in PXE (4).

The usual mode of inheritance is autosomal recessive, but some families with two generation involvement have been observed in keeping with a pseudodominant pattern. Autosomal dominant PXE has been reported in a few families with two-generation PXE but no molecular evidence has been shown so far. Considerable clinical intra- and inter-familial variability, in particular with regard to age of onset, complicate the assessment of inheritance patterns (2).

The histology (Fig. 1) 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 (5).

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 (6,7).

Skin lesions consist of yellowish papules or plaques with loss of dermal elasticity (Fig. 2) . Commonly affected sites are the flexures and periumbilical skin. Mucous membrane involvement is not rare. Skin lesions are usually noted in the second or third decade.

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 (8). Cardiovascular manifestations usually develop last, and result from slowly progressive calcification of elastic arterial walls.

Reduction of vessel lumen causes ischaemia, and excessive fragility of the vessel wall is responsible for haemorrhage (9).

To facilitate and unify the clinical diagnosis for PXE, three major diagnostic criteria (characteristic skin involvement, characteristic histopathological features of lesional skin, characteristic ocular disease) and two minor criteria (characteristic dermatopathological features in non lesional skin, family history of PXE in first-degree relatives) were defined and divided into five categories (I, IIa–d) at the consensus conference in 1992.

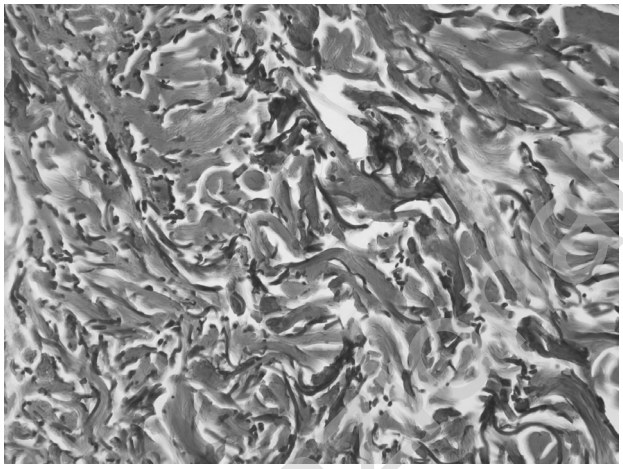

Fig. 1 - Skin biopsy charachterized by the presence of fragmented basophil reticoular fibers of ondulate and spiral-shaped aspect in the intermediate dermis.

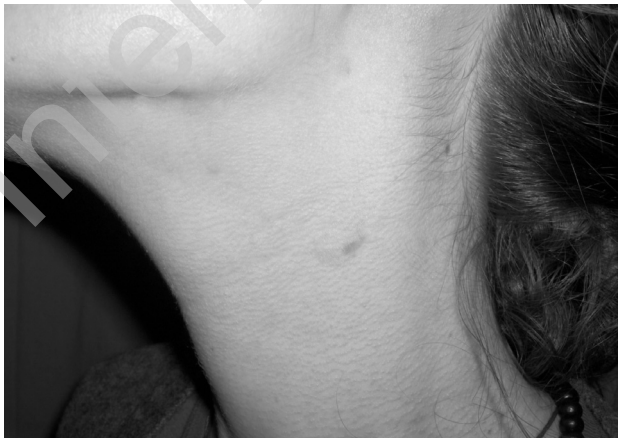

Fig. 2 - Yellowish laterocervical papules on the neck.

Major criteria

- Characteristic skin signs (yellow cobblestone lesions in flexural areas)
- Characteristic ophthalmologic features (angioid streaks, peau d'orange, maculopathy)
- Characteristic histological features of lesional skin (elastic tissue and calcium or von Kossa stains)

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.

Category I patients fulfil all three major criteria and definitely have PXE. However, in children ocular changes are not required to establish the diagnosis as they often do not develop until early adulthood. Category II patients do not have typical skin lesions but have either angioid streaks with at least one minor criterion, or two minor criteria (10).

Methods and materials

The population in the present study consisted of 15 patients (11 females; 4 males; age range 25-70 years) that had been referred to the Department of Dermatology, Multidisciplinary Centre of Rare Diseases at the Umberto I Policlinic in Rome, Italy, between 2000 and 2009. All patients in this study were diagnosed according to the criteria for the definitive diagnosis of PXE (described above). All patients presented skin and ocular lesions typical of PXE.

Skin alterations were in the form of white-yellow papules, more or less coalescent, giving a rough and redundant appearance to the skin.

The diagnosis of PXE, made by dermatologists and ophthalmologists, those revealed the presence of bilateral "angioid streaks" with funduscopic examination, indicating impairment of visual function, was confirmed by structural analysis of a skin biopsy, which revealed the presence of Von Kossa-positive precipitates within elastic fibers, and electron microscopy, which showed alterations typical of PXE, such as fragmentation and calcification of elastic fibres, collagen flowers, and aggregates of microfilaments in the reticular dermis.

The patients were asked by cardiologists and were also subjected to a series of tests, including blood pressure measurement, effect of palpation on the arteries of the extremities, an electrocardiogram (ECG) and furthermore to an arterial stiffness exam. Patients who had a history of cardiovascular disease or who showed abnormal findings in the examinations were further subjected to a Holter ECG and computed tomographic (CT) angiography.

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

Discussion and conclusion

Of the 15 patients evaluated, eleven were females and four were males. 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.

Cutaneous lesions were the presenting symptoms in all cases. The initial manifestation in the remaining patient was microcalcifications in the kidneys, seen fortuitously on ultrasound examination performed for incidental abdominal pain.

The first skin lesions were yellowish laterocervical papules or a yellowish network in eight cases, strikingly sparing the nape and the anterior aspect of the neck.

The typical cutaneous lesions allowed diagnosis of PXE in all cases, including the patient discovered through the presence of ultrasound renal calcifications.

Funduscopy revealed retinal changes in all cases, but all were asymptomatic. Nine had angioid streaks and all had peau d'orange changes.

Eleven patients had experienced cardiovascular or haemorrhagic events. Furthermore these patients had hyperlipidemia (two cases), diabetes (one case), hypertension (four cases), and smoking history (three cases). In all cases, dermal elastorrhexis and angioid streaks were demonstrated between 12 and 20 years of age.

Therefore, 13 patients showed clinical signs about other organs (kidney, liver, ovary).

Severe complications of PXE were uncommon before the age of 15 years.

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 (11).

PXE is a rare and progressive disease, which worse in the lifetime.

Despite the recent identification of the molecular basis of PXE (ie, mutations in the *ABCC6* gene), the pathogenesis of vascular lesions 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 middermis. 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 red-brown macules, even in older age patients. In addition, phenotypic manifestations of PXE within a family appear to vary considerably. These observations together suggest that cardio vascular 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, treated by aortocoronary bypass. In some cases coronary artery disease has led to sudden death (13). Stroke may also occur as the consequence of ischaemic or haemorrhagic cerebrovascular disease. Gastrointestinal haemorrhages are often dramatic and recurrent (14).

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 unknown.

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