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LETTER TO THE EDITOR

PSEUDOXANTHOMA ELASTICUM AND LIGHT-CHAIN AMYLOIDOSIS

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Pseudoxanthoma elasticum is a heritable disorder of connective tissue characterized by cutaneous, vascular and ocular changes that result from the accumulation of fragmented elastic fibres. Even though the etiopathogenesis is not still completely understood, in recent years in literature some Authors have considered pseudoxanthoma elasticum as a metabolic disorder. We present the case of a 45-year-old man affected by pseudoxanthoma elasticum and light-chain amyloidosis and we discuss the possible reasons that led to this association.

We report the case of a 45-year-old man who presented pseudoxanthoma elasticum, associated with light-chain amyloidosis. This association is quite rare, even though in literature there are a few cases reported. This study would like to stress and underline the importance of considering pseudoxanthoma elasticum as a metabolic disorder and not as a primary elastic disorder. Moreover, we would like to underline the importance of considering that pseudoxanthoma elasticum could favour amyloidogenesis and fibril stabilization.

MATERIALS AND METHODS

A 45-year-old Caucasian Italian man was admitted to our hospital for the onset of progressively less exertion dyspnea and lower limb edema. A complete medical history was taken and general physical examination was performed. A complete familial medical history was performed. Routine laboratory tests included complete blood count, erythrocyte sedimentation rate, routine biochemistry. Echocardiographic and electrocardiographic tests were carried out, in addition to a cardiac MRI. A bone marrow biopsy, an accessory salivary gland biopsy and a skin biopsy of the affected area were taken. The material was fixed in formalin and embedded in paraffin. Routine histologic skin sections were stained with Hematoxylin-eosin, Weigert stain and red Congo stain.

RESULTS

History

In May 2011, a 45-year old man was admitted to our hospital for the onset of progressively less

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exertion dyspnea and lower limb edema.

Laboratory examinations

Hematochemical and instrumental tests showed a red blood cell count at the lower limit of normal range, hypoalbuminemia (2.7 g/dl) and a proteinuria of 2.7 g/24 h. Further investigations revealed monoclonal lambda light-chain component in serum and a Bence-Jones lambda type proteinuria. Echocardiographic and electrocardiographic tests were carried out, in addition to a cardiac MRI, the findings of which suggested a restrictive cardiomiopathy of infiltrative type.

Physical examination

Cutaneous examination revealed small, yellowish, non-pruriginous papules coalescing into plaques, located on the periorbital region, the neck, the trunk and the groin. Oculistic examination excluded the presence of angioid streaks of the retina.

Histological examination and immunohistochemical assay

A bone marrow biopsy showed a plasmacellular infiltrate rate of 20% of the total bone-marrow cell population and focal areas of amyloid deposits. An accessory salivary gland biopsy was made, confirming the presence of amyloid deposits. Skin biopsy of a papule of the trunk highlighted aberrant somewhat calcified, clumped and fragmented elastic fibers in the mid-dermis, compatible with the diagnosis of pseudoxanthoma elasticum. (Figs. 1a and 2b). Numerous, small, distorted elastic fibers were seen and the red Congo stain was negative for the presence of substance amiloidea (Fig. 2 a and b).

Diagnosis, treatment and clinical course

The diagnosis of light-chain amyloidosis with cardiac involvement was finally made, unusually associated with pseudoxanthoma elasticum. The patient was immediately treated with cyclophosphamide 500 mg weekly and bortezomib 1.3 mg/m^2 twice a week (CYBORD). After two chemotherapy cycles no improvement was observed in the patient's conditions and the rapid worsening of cardiac functions led to the patient's death for a cardiac arrest.

DISCUSSION

The association between pseudoxanthoma elasticum (PXE) and light-chain amyloidosis (AL-amyloidosis) is rarely described in literature and only two other cases of PXE, associated with Familiar Mediterranean fever-related amyloidosis (FMF-amyloidosis) are reported (1-2). PXE is a multisystem heritable disorder, characterized by ectopic mineralization of peripheral connective tissue, with particular involvement of elastic fibers, affecting primarily the skin, the eyes and

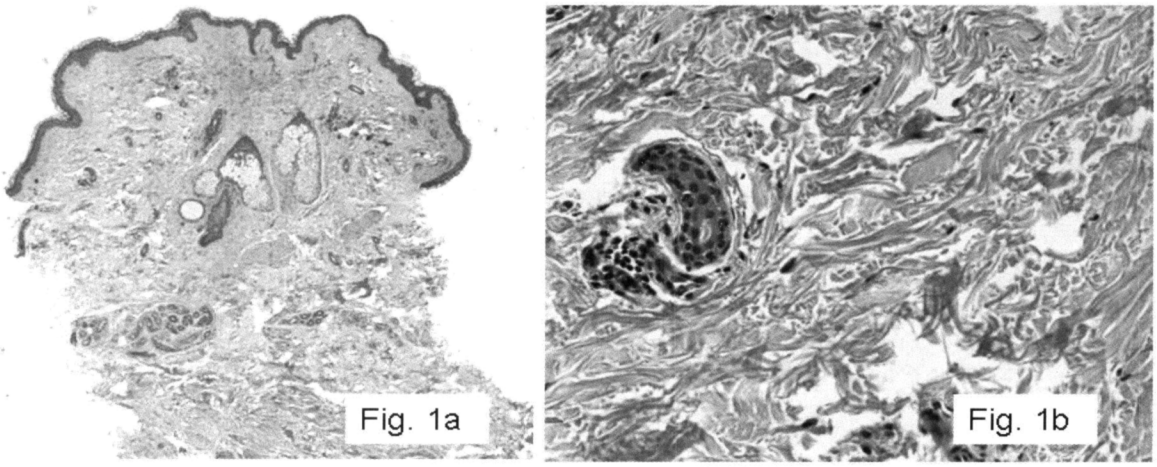

Fig. 1. ***a, b)*** *Pseudoxanthoma elasticum (a: 25X, hematoxylin-eosin; b: 200x hematoxylin-eosin).*

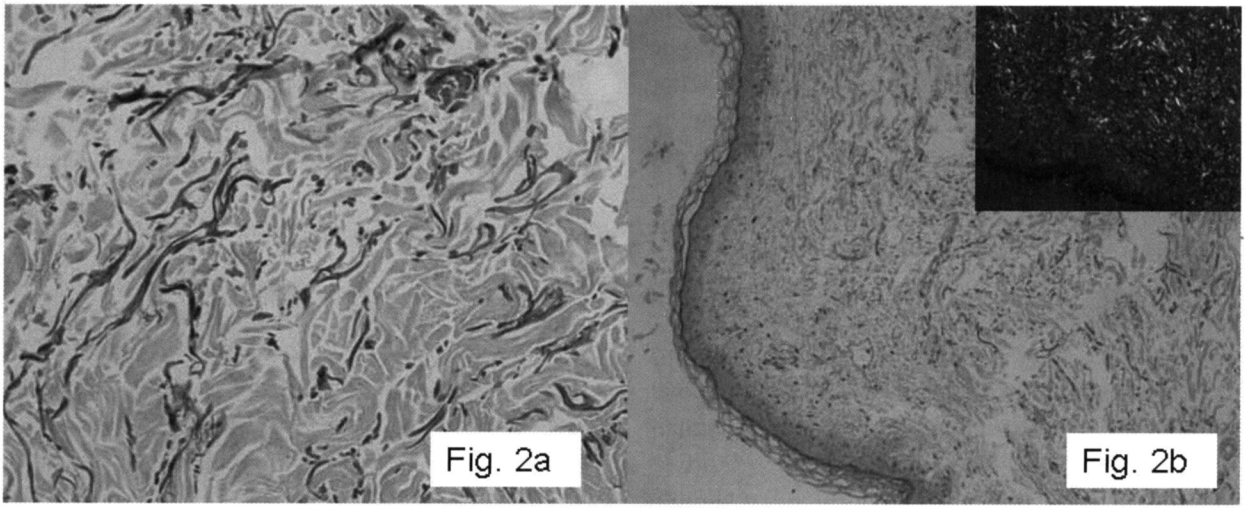

Fig. 2. ***a)*** *Pseudoxanthoma elasticum a.200X, Weigert stain. Numerous, small, distorted elastic fibers are seen.* ***b)*** *The red Congo stain is negative for the presence of substance amiloidea.*

cardiovascular system (3). The precise prevalence of PXE is currently unknown, but is estimated to be around one in 50,000 (3). Some cases have only skin manifestations, other have only eyes or cardiovascular involvement, suggesting that the role of additional variables like epigenetics, dietary factors and life style need to be considered.

Cutaneous lesions are yellowish papules (4), and histological features show fragmented, basophilic and calcified elastic fibers in mid-dermis, known as "elastorrhexia", observed also in apparently normal skin. To date PXE has been considered a primary disorder of elastic fibers.

In some cases, the genetic mutations in PXE involve the ABCC6 gene, which encodes a transmembrane transporter protein, expressed primarily in the liver and the kidneys, organs not known to be affected by the disease (5-6-7). The exact function of the ABCC6 protein is not completely understood. All these observations would suggest that PXE is not a primary disorder of elastic fibers but a metabolic condition (8).

AL-amyloidosis is the most common form of systemic amyloidosis and clinically presents with cardiac involvement in 50% of cases (9), with an incidence of 8 to 10 cases per million person-years, a median age at diagnosis of 63, and a median survival time if left untreated of 12 months. Systemic light-chain amyloidosis (AL) is caused by misfolded immunoglobulin light-chain proteins that aggregate and deposit as unique fibrils, ultimately leading to organ failure and death. Tissue biopsy, either of an involved organ or a surrogate site (e.g., abdominal fat), must demonstrate amyloid deposition by classic Congo red staining or electron microscopy. For typing, immunohistochemical staining is frequently unreliable and inaccurate, and immunogold electron microscopy is reliable but limited by serologic dependence (1-2).

Regarding the unusual association of PXE and AL-amyloidosis, the link, supposed between these two diseases, is not yet completely understood and can not explain the rarity of their concurrent manifestation. Some Authors have reported in literature that PXE could favour amyloidogenesis and amyloid fibril stabilization, in fact in PXE there is an increased production of glycosaminoglycans, especially heparan sulphate, that colocalize with amyloid proteins (10). In accordance with Cattan et al., the changes in glycosaminoglican metabolism present in PXE, could lead to a worsening of AAL-amyloidosis. This fact values Uitto's hypothesis that PXE can be considered a metabolic disorder. Moreover, other genes, still unknown, are probably involved. Therefore we can conclude that PXE is the result of a metabolic disorder induced by genetic alteration and other acquired factors. This framework explains the existence of patients predominantly with skin involvement and patients with organ system

involvement. We describe this case report for its rarity and its particular nosographic interest; further studies, however, are necessary to increase knowledge on diagnosis, pathomechanisms and treatment of PXE and to find new possible correlations between these two pathologic conditions.

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