

Pseudoxanthoma elasticum – rare hereditary disease with coronary and organ calcifications (RCD code:I-2.A.O)

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Abstract

Background: Pseudoxanthoma elasticum is a rare hereditary disease with estimated prevalence of 1 in 25,000 to 1 in 100,000 with cutaneous lesions and organ calcifications.

Methods and results: We report a case of a young female with a cutaneous manifestation of pseudoxanthoma elasticum. Calcium deposits were found in coronary arteries and major vessels as well as in the lung and liver by means of computer tomography (CT) assessment. No members of the family were found to have the disease, so it was considered a sporadic case.

Conclusion: Exceeding rare this cutaneous disease is associated with organ and vessels calcifications and is worth knowing as a rare cause for calcium depositions in the coronary arteries and potential myocardial ischemia or myocardial infarction in the very young. JRC D 2013; 1 (2): 78–81

Key words: pseudoxanthoma elasticum, coronary artery calcifications, cutaneous lesions, organ calcifications

Background

Pseudoxanthoma elasticum (PXE) – (OMIM [Online Mendelian Inheritance in Man]# 264800) is a rare progressive autosomal recessive connective tissue disorder of elastic fibers in the skin, eyes and arterial walls caused by mutations in the ABCC6 gene. The phenotypic presentation comprises specific skin lesions and increased skin laxity in flexural body areas, eventual retinal haemorrhages and streaks in the ocular fundus with central vision loss, and multiple organ vessel involvement with accelerated atherosclerosis leading to cardiovascular complications [1,2]. Although this may be an underestimation due to the high variability of the phenotype, the incidence of this rare disease has recently been estimated to be 1:75 000–from 1:25 000 to 1:100 000 [3]. Morphologic substrate of vessel involvement however is different from that of atherosclerosis. Clinical manifestations of the disease are attributed to alterations of elastic fibres within the extra cellular matrix undergoing progressive mineralization and fragmentation „elastorrhexia” with collagen, fibrillins and proteoglycans having either an abnormal morphology or abnormal distribution [2,4,5].

The gene responsible for PXE – ABCC6 is located on chromosome 16p13.1 and encodes the protein ABCC6 (also known as MRP6) – an ATP-dependent transporter of yet unknown substrate. Multiple mutations are identifiable in most of the 31 ABCC6 exons and consist of missense, nonsense, frameshift mutations, or large deletions. Some current hypotheses state that PXE should be considered a metabolic disorder with yet undetermined circulating molecules interacting with the synthesis, turnover, or maintenance of elastic fibres [1]. The relationship between this protein and the phenotype of patients is also a matter of debate, since PXE presents clinically by high heterogeneity in age of onset and extent and severity of organ system involvement. No correlation between the nature or location of the mutations and phenotype severity has yet been established [6-8]. It has been shown that healthy carriers of PXE have similar cutaneous abnormalities but only at ultra structural level, suggesting that a mild phenotype may be seen in these individuals with some calcification in various organs, but no retinal involvement [9]. One ABCC6 mutation – that of the R1141X locus – is found much more frequently in about 80% of PXE patients. Strikingly higher incidence of cardiovascu-

Conflict of interest: none declared.

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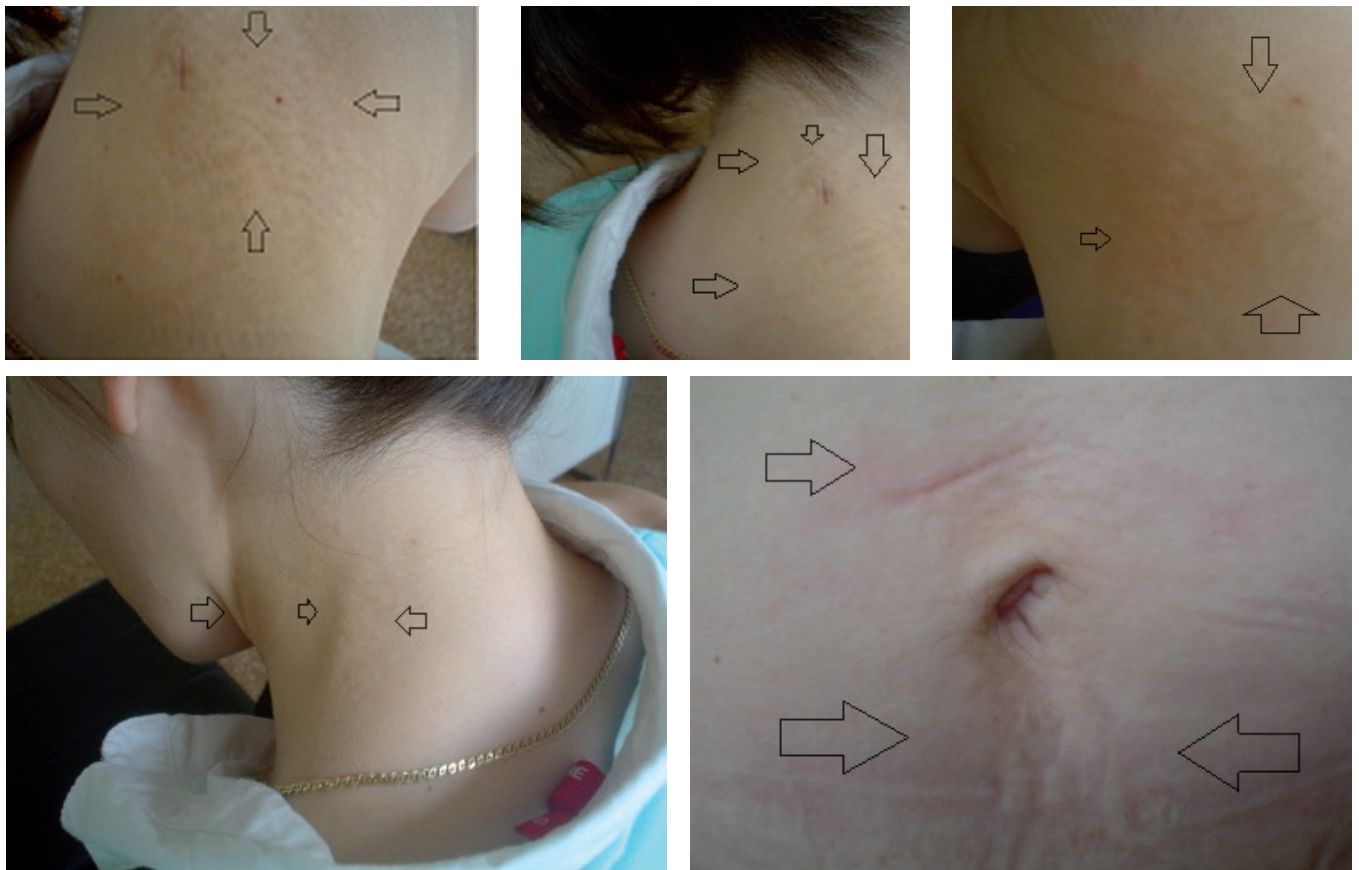


Figure 1. Cutaneous changes consisting of linear and reticular pattern of yellow plaques forming papules with cobblestone appearance of both lateral aspects of the neck and peri-umbilical areas with some skin laxity at these sites

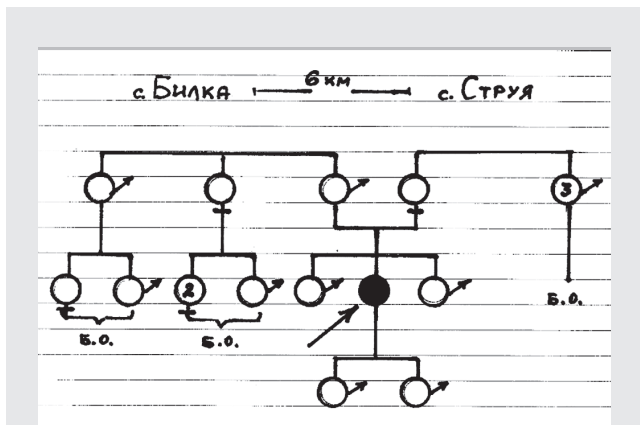


Figure 2. Proband pedigree- an uncle, a first cousin and the two children had no cutaneous manifestation of PXE

lar disease has been reported in carriers of R1141X mutation in the Netherlands, but later no other manifestations of PXE such as cutaneous and/or retinal disease have being found in this cohort. And it was concluded “that patients with premature coronary artery disease who carry the *ABCC6* – R1141X mutation have no Pseudoxanthoma Elasticum phenotype” [10-11].

Methods and results

We report a case of a 29-year old female with a clinical manifestation of PXE and no previous clinical complaints. She was referred to a specialist because of her cutaneous lesions at the abdominal area which she found disturbing. Dermatologist judgement was that these changes were compatible with pseudoxanthoma elasticum- a rare cutaneous condition consisting of linear and reticular pattern of yellow plaques forming papules with cobblestone appearance on the lateral aspects of the neck and peri-umbilical areas of the patient with skin laxity at these sites (Fig. 1).

Genetic counselling was performed and a pedigree of the proband was constructed This young woman was the only affected pedigree member in a large family of Turkish origin and her parents came from small villages 6 km apart in an isolated population group (Fig. 2). No proband relatives were found to have the disease, so it was determined to be a sporadic form of the disease.

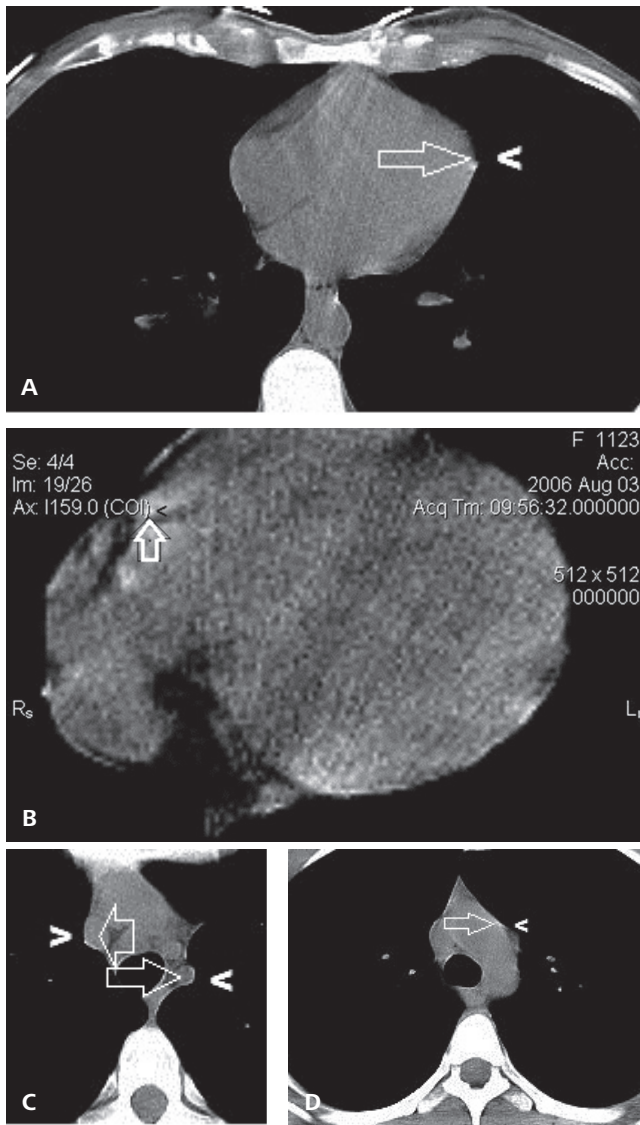
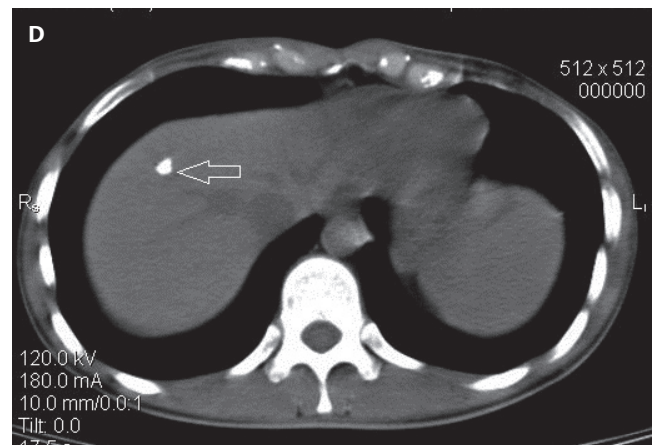
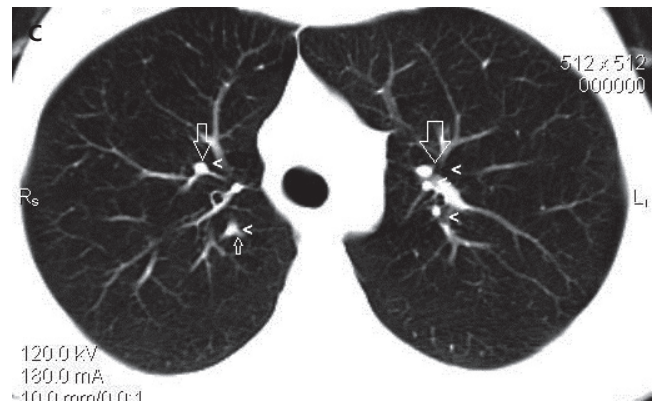
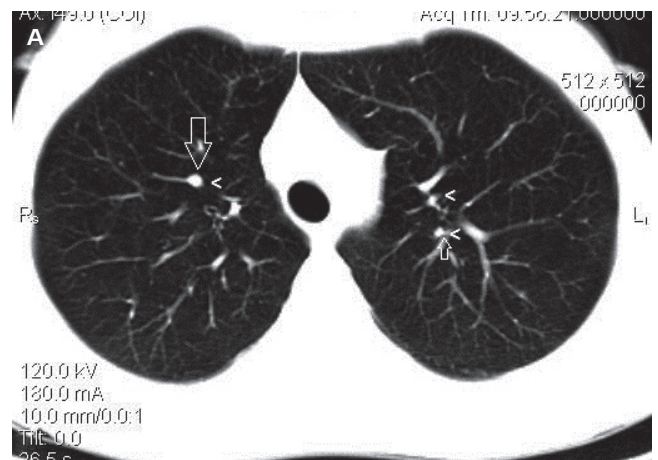


Figure 3. Calcium depositions on non-contrast CT of left anterior descending (A) and right coronary arteries (B) and in the wall of the ascending and descending aorta (C, D)

Electrocardiogram was normal, no changes were found in the retina on ocular examination, laboratory investigation of haemoglobin, white blood cell count, blood urea nitrogen, fasting blood glucose were entirely normal as well.

Apart from a minor mitral valve prolapse echocardiography was normal, no specific calcium deposits on cardiac and valvular structures were found.

Non-contrast CT investigation of the chest and abdomen were performed. Calcium depositions were found in the coronary arteries, aorta, (Fig. 3) multiple calcifications in the lung vessels and a single calcification (Fig. 4) in the liver. No calcium deposits were found in the kidneys, spleen, pancreas or breasts and no enlarged



→ **Figure 4.** Multiple calcium deposits in the lung (A, B, C) and a single but larger calcium spot in the right lobe of the liver (D)

lymph nodes were detected. No contrast investigation of coronary arteries was undertaken because neither clinical signs, nor ECG evidence of ischemia were present.

Discussion

Pseudoxanthoma elasticum (PXE) is a rare hereditary disease, characterized by progressive calcific degeneration of elastic fibres in the skin, blood vessels and the heart. Calcifications in several organs including lung, kidney, pancreas, spleen, breasts and testicles have been observed suggesting a possible association of organ calcifications and PXE. No end organ damage has been reported however [12-15].

The involvement of the vascular internal elastic membrane is associated with vascular rigidity, fragility and bleeding. Vascular changes can be found in virtually all arteries- coronary, cerebral, gastrointestinal, renal and peripheral. Infrequent but specific are the calcific depositions in the atrio-ventricular valves, mural endocardium of ventricles and atria, resulting in mitral valve prolapse or restrictive cardiomyopathy [16-18].

Data presenting the natural history, follow-up and possible complications are few. Accelerated coronary artery disease in patients with PXE represents the major cause of morbidity and mortality and acute myocardial infarction can affect even young patients without any associated coronary risk factor. Reported cases in the literature comprise mostly young girls from 15 to 28 years of age with no risk factors but significant high grade coronary stenosis. Problems are reported also in CABG operations because of the use of arterial ducts for grafting is controversial in these cases since calcifications are found even in internal thoracic arteries or surgically damaged arteries [19-25]. Up to now, only two reports on the use of intracoronary vascular ultrasound and visualization of the calcified arteries in patients with PXE with ensuing percutaneous coronary intervention exist while most patients are treated with aorto-coronary bypass surgery [26,27].

Conclusions

Exceeding rare this cutaneous disease is associated with organ and vessels calcifications and is worth knowing as a rare cause for coronary ischemia and myocardial infarction in the very young especially women and also as a potential cause for mitral valve prolapse or endocardial mural calcifications and restrictive cardiomyopathy.

Appreciations

We highly appreciate the kind agreement and cooperation of the patient and its relatives and family members for elucidation of this rare condition.

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