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A Case of Pseudoxanthoma Elasticum with Microvascular Alterations: Possible Explanations and Causes

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Abstract

Pseudoxanthoma elasticum is a rare autosomal recessive disease, which is well-known for its affection of three major organ systems: skin, eye and cardiovascular systems, in particular large elastic arteries. This case is one of the first demonstrations of microvascular alterations in patients Pseudoxanthoma elasticum and offers hypotheses for their explanation.

Keywords: Pseudoxanthoma elasticum; Nailfold capillaroscopy; Capillaries; Microvascular alterations; Peripheral artery disease

Introduction

Pseudoxanthoma elasticum (PXE) is a rare autosomal recessive disease, which leads to ectopic mineralization of soft connective tissue [1]. Main features are progressive loss of vision, mineralization of arterial vessels and formation of yellowish papules in the skin. Therefore clinical manifestations of PXE are mostly attributed to three major organ systems: skin, eye and cardiovascular system [2], particularly large arteries with high amounts of elastic fibers. Microvascular alterations in PXE have been reported before [3,4], though there no explanations for this phenomenon up to now.

Case Presentation

The patient presented at the age of 69, male, Caucasian without any chronic diseases but PXE. Physical examination was appropriate for the patients age and condition. The only cardiovascular risk factor was a history of smoking (5 packyears). Other risk factors such as diabetes, hypercholesterolemia and hypertension were excluded. He showed the typical pattern of PXE with a strong affection of the eye (retinal bleeding and scarring), cutaneous lesions and arterial alterations (according to Fontaine I/ Rutherford 0 - atherosclerosis without intermittent claudication). Color-coded duplex sonography of common femoral arteries, femoral arteries and popliteal arteries showed various small atherosclerotic lesions with neither limitations of the blood flow nor stenosis. Genotype revealed a compound heterozygous mutation with different PXE-inducing mutations on each complementing allele (p.R1141X/c.3883-6G>A). Mutational analysis was performed by the cooperating Institute of Laboratory and Transfusion Medicine of the Heart and Diabetes Center North Rhine Westphalia of the Ruhr University of Bochum in context of previous research [5,6]. The Patient caught our attention due to a pathological decrease of ankle-brachial-indices (ABI) after 5 minutes of exercise on the treadmill (12° inclination; 3.2 km/h) without a detectable correlate in color-coded duplex sonography. Table 1 shows the systolic blood pressure (RR) and ABI values of posterior tibial artery (pta) and dorsalis pedis artery (dpa) before and after exercise.

Further examination by magnetic resonance angiography with contrast agent (MRA) also showed no proximal (aorta, common and external iliac arteries) or distal (arteries of the lower leg down to dorsalis pedis arteries and posterior tibial ateries) stenosis. We found no evidence for popliteal entrapment syndrome. Acral oscillations of both hands were bilateral equal and decreased after exposure to cold water for 10 minutes consistent with Raynaud's syndrome. Nailfold capillaroscopy demonstrated a reduced dense of capillaries and perivascular edema without real avascular areas. We found several atypical capillaries with torsions, elongations, dilations, ramifications and various isolated hemorrhage but no mega capillaries (Figure 1). A rheumatic disease - which would be the preeminent differential diagnosis of capillary alteration - was excluded by blood testing (Table 2).

Discussion and Conclusion

These findings show no explanation for the decrease of the ABI values following exercise but a microvascular alteration of capillaries. Reports of the influence of microcirculatory alterations on macrocirculation are rare and inconsistent [7-9]. Yet, recent publication of Humeau-Heurtier et al. [10] described alterations in microvascular perfusion in PXE patients. This may connect to the decrease of ABI values after exercise, however, further research is needed on this matter. In this case, peripheral artery occlusive disease (pAOD) with relevant stenosis was excluded by color-coded duplex sonography and MRA. Medical history and blood tests did not reveal signs of a small vessel vasculitis due to a rheumatic disease. Sporadic case reports of PXE associated with systemic lupus erythematodes seem unlikely due to negative titer of antinuclear antibodies (ANA) [11]. Therefore, a microvascular manifestation of PXE may be responsible for the decrease of AB-Indices following exercise.

Both mutational variants occurring in the patients genotype have been described before. The p.R1141X is a nonsense mutation and the most frequent mutational variant in the Caucasian population [5,12]. c.3883-6G>A is a missense mutation generating a new splice site, which results in an abnormal and truncated protein [13]. However, most studies trying to reveal genotype-phenotype patterns in PXE showed were unsuccessful up to now [5,14]. Recently Legrand et al. [15] revealed a predisposition for eye and vascular alterations in patients with partial or total loss-of-function mutations in the ABCC6 gene. Therefore, genotype may influence the capillary pattern in patients with PXE. Also, there are various modifying genes described up to now [16], which influence in this patient remain unclear.

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	Brachial	Right pta	Right dpa	Left pta	Left dpa	Mean
RR before treadmill [mmHg]	131	151	162	200	187	175
ABI		1.15	1.24	1.53	1.43	1.34
RR after treadmill [mmHg]	175	170	150	160	150	160
ABI		0.97	0.85	0.91	0.86	0.9
Difference of RR [%]	25.1	12.6	-7.4	-20	-19.8	-8.7
Difference of ABI [%]		-15.7	-31.5	-40.5	-39.9	-31.9
RR: Systolic blood pressure; ABI: Ankle-brachial-index; pta: posterior tibialis artery; dpa: dorsalis pedis artery						

Table 1: Change of systolic blood pressure ABI after exercise.

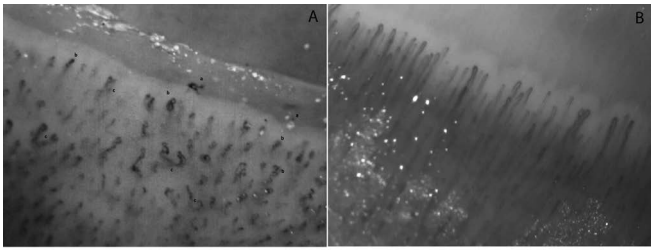

Figure 1: Nailfold capillaroscopy of the presented patient (A) and a healthy adult (B).

	Value	Reference value
C-reactive protein [mg/l]	0.9	≤ 3.00
Rheuma factor [IU/ml]	<10.00	0 - 15
Complement C3 [g/l]	1.03	0.90 - 1.80
Complement C4 [g/l]	0.31	0.10 - 0.40
ANA	negative	
pANCA	negative	
cANCA	negative	

Table 2: Serologic testing for rheumatic diseases.

A possible explanation for altered capillaries in PXE may be a local chronic oxygen mismatch due to a thickening of the capillary basement membrane. Capillary alterations, in particular ramifications and bushy capillaries, are a common sign of (neo-)angiogenesis due to tissue hypoxia [17]. Underlying pathology may be similar to histopathologic processes in diabetics [18,19] or due to a deposition of deformed collagen fibrils and abnormal amounts of proteoglycans around pericytes [20]. This hypothesis is corroborated by Pingel et al. [21] which showed significantly diminished values for carbon monoxide diffusion capacity in PXE patients, most likely caused by a thickening of blood-air barrier. Potentially, this may be due to calcified deposits, fragmented elastic fibers and collagen flowers in alveolar septa [22,23]. A similar process is expectable around periphery capillaries since PXE as a systemic connective tissue disease [24].

Conflict of Interest

The author declares that there is no conflict of interest in matters of this case report.

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