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PSEUDOXANTHOMA ELASTICUM WITH ABNORMAL NAILFOLD MICROCIRCULATORY FINDINGS

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Pseudoxanthoma elasticum (PXE) is an inherited disorder of elastic tissue. Here we report a 34-year-old male patient who developed multiple symptomless yellowish papules over his neck for several months. He visited our dermatologic out-patient-clinic because his sister had similar skin lesions and mild visual impairment. The pathologic features of the skin biopsy showed fragmented calcified elastic fibers in the mid-to-lower dermis under the H&E, Verhoeff-van Gieson and Von Kossa stains. Under electron microscopy, calcified degenerated elastic fibers were noted. No other internal organ involvement was found except angioid streaks on the fundus. In addition, morphological changes of the nailfold capillaries, including increased tortuosity, dilated venous limbs of capillary loops, and decreased red-blood-cell velocity, were observed under the capillaroscopy. Though former reports have indicated that cardiovascular manifestations are caused by degeneration of elastic fibers of blood vessels, this study is the first to emphasize the microcirculatory disturbance of nailfold capillary, including morphology and blood-cell velocity, in PXE.

Key words: pseudoxanthoma elasticum, elastic fiber, microcirculation

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Pseudoxanthoma elasticum (PXE) is a systemic heritable connective tissue disorder that is characterized by mid-to-lower dermal elastic degeneration and calcification [1]. PXE manifests itself predominantly in the elastic tissues of skin, retina, and arterial walls. It is transmitted as an autosomal recessive or autosomal dominant gene defect [2-4]. Here, we report a PXE patient with typical skin lesions, eye involvement and family history and review the literature concerning the clinical manifestation, genetic survey and differential diagnoses of PXE.

CASE PRESENTATION

A 34-year-old male patient developed multiple symptomless, small, yellowish, cobblestone-like papules in a reticular pattern over his neck for several months (Fig. 1). No other similar skin lesion was found over other flexural area. He did not pay much attention to the skin lesion because no other systemic symptom was noted. However, his sister told him that she has similar skin manifestations and mild visual impairment. She visited the Taichung Veterans General Hospital, and PXE was diagnosed. Therefore, he was admitted to our ward for a complete study.

After admission, the results of physical examination, routine blood examination, chest X-ray and ECG were all normal. A skin biopsy of the yellowish papules was performed. The pathologic features of the skin biopsy showed basophilic fragmented, clumped elastic fibers in the mid-to-lower dermis under the H&E stain (Fig. 2). These fibers were stained deeply black with the Verhoeff-van Gieson stain (Fig. 3A). They were also stained well with Von Kossa stain for calcium (Fig. 3B). Under the electron microscopy, heavy, irregular, and clumped electron-dense calcified depositions in the elastic fibers were the main feature.

Angioid streaks were observed on ophthalmoscopic examination, but no neovasculization of the retina was seen (Fig. 4). Cardiac echography and

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gastroenteroscopy revealed no abnormal finding. Morphological changes of nailfold capillaries, including increased tortuosity and dilated venous limbs of capillary loops, were observed under the capillaroscopy (Fig.5). Decreased red-blood-cell velocity (0.19mm/s) was also noticed (Table 1). According to the clinical, histopathologic and ophthalmoscopic features, PXE was diagnosed.

DISCUSSION

PXE is a systemic heritable connective tissue disorder first described in 1896 by Jean Darier. This particular disorder primarily affects the elastic tissue network in the body. The prevalence of PXE is approximately 1 in 100,000 [1]. The hypothesis about how the disorder is inherited is controversial [2-4]. The clinical manifestations of PXE typically involve

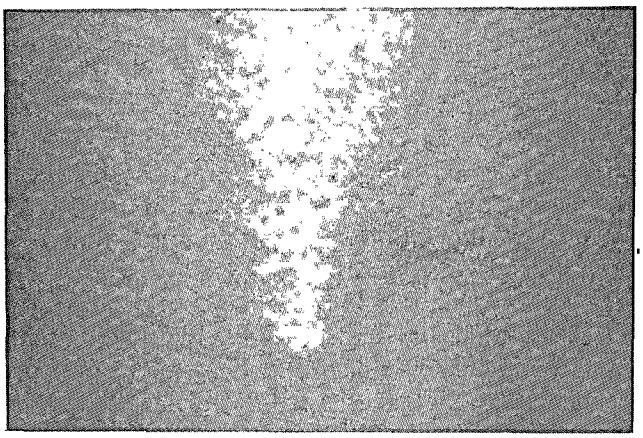

Fig. 1. Numerous yellowish papules were noticed on the neck.

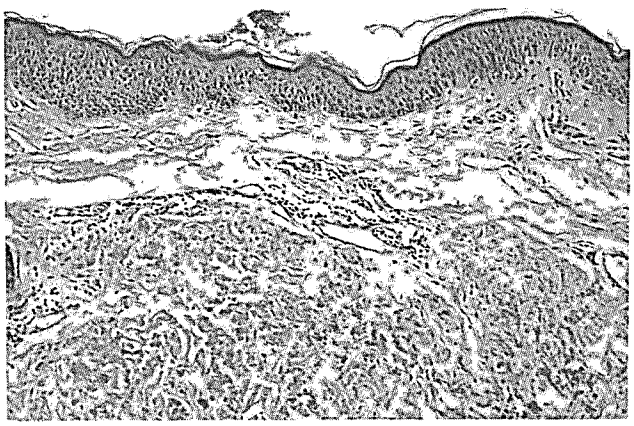

Fig. 2. The histopathology of the skin biopsy showed basophilic fragmented, clumped elastic fibers in the mid-to-lower dermis (H&E, 100X).

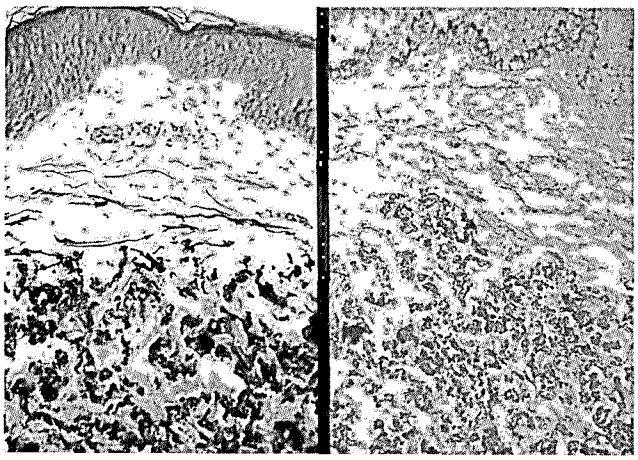

Fig. 3. A. The degenerated, fragmented elastic fibers were stained deeply black with the Verhoeff-van Gieson stain (200X). B. They were also stained well with Von Kossa stain for the deposition by calcium (200X).

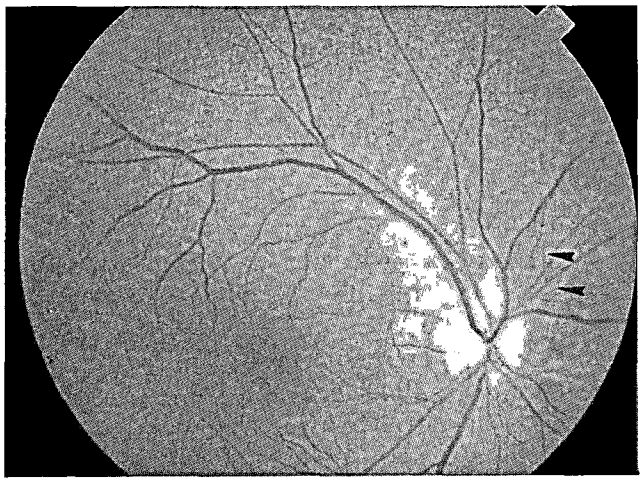

Fig. 4. Angioid streaks (arrow heads) were visible on ophthalmoscopic examination.

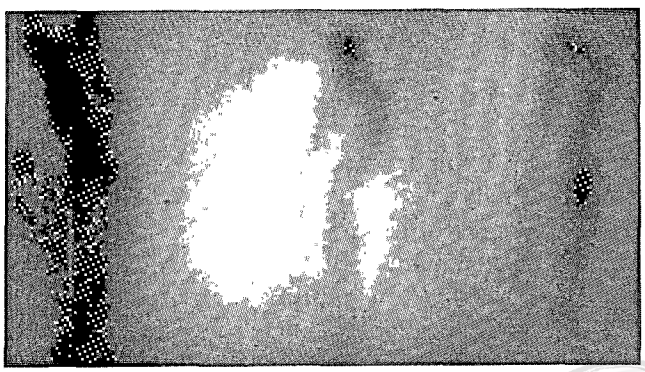

Fig. 5. Increased tortuosity and dilated venous limbs of nailfold capillaries were observed under the capillary microscopy.

Table 1. Results of morphologic and capillary blood flow velocity analysis under the capillary microscopy

	No. of Capillaries in 1mm	Tortuosity (%)	Diameter (μm) Arterial limb	Diameter (μm) Venous limb	Velocity (mm/s)
Patient	10	40	13	20	0.19
Control [9]	10 ± 3	20 ± 12	13 ± 1	15 ± 3	0.36 ± 0.10

the skin, the eye and the cardiovascular system [1].

Nearly all patients noticed the onset of skin lesions over the lateral neck in the second or third decade of life. Number and severity of lesions were progressive. The skin rash ranging from ivory yellow papules to confluent "peau d'orange" changes is commonly distributed over the flexural area. The reversibility of skin lesions of PXE observed by Martinex-Hermamdex, Eng and Bryant is an intriguing but unresolved question [5-7]. Also, mucosal lesions are quite common, particularly those of the oral cavity, where they are usually confined to the inner aspect of the lower lip [1]. In our patient, typical yellowish papules were noticed over the lateral neck but not over other flexural areas or oral mucosa.

The arteries throughout the body could be affected, and death may result from cerebral hemorrhage, coronary occlusion or massive gastrointestinal tract hemorrhage [8]. No abnormal finding was noticed by the cardiac echography and gastroenteroscopy in this patient. Under the capillaroscopy, morphological and hemodynamic changes of the nailfold capillaries, such as increased tortuosity, dilated venous limbs, and decreased velocity were observed [9]. Corresponding change, such as dilated capillaries, was not seen under the histopathologic examination. This is not a unique feature since nailfold microcirculatory disturbance could also be observed in other systemic diseases, such as diabetes mellitus and connective tissue diseases. The red-blood-cell velocity was reduced in all diabetic patients. Moreover, in diabetics with retinopathy, the capillary density was not changed, but the percentage of tortuosity and the diameter of capillaries were increased [9]. Similar morphological changes include normal density and increases in degree of dilatation and percentage of tortuous and crossed capillaries could be seen in patients with systemic lupus erythematosus [10,11]. Low capillary density, avascular zone and dilated capillaries were the characteristic features of systemic sclerosis described by Maricq [12]. We proposed that the abnormal capillaroscopic findings in PXE might be caused by either the occult changes of cardiovascular system or the minimal changes of peri-capillary matrix. It may suggest that these microvascular manifestations could serve as an early indicator for cardiovascular disease. Further work-up such as capillary permeability could be done in the future.

Attempts to establish the precise mode of inheritance within a given family are of critical importance for genetic counseling. Recently, a major PXE locus, MRP6, has been mapped on chromosome 16p13.1 [13-16], an area without any apparent candidate gene such as Elastin, Fibrillin-1, Fibrillin-2, Fibrillin-3, Lysyl oxidase, and human matrix Gla protein [17-20]. It has been suggested that the function of MRP6 protein relates to cellular detoxification, and may lead to calcification of elastic fibers. The other possibility of pathogenesis of PXE is that the perturbed metabolism of cells lacking functional MRP6 may cause alternations in the cellular microenvironment, resulting in the synthesis of aberrant elastic fibers that become calcified [14].

The differential diagnoses of PXE include pseudopseudoxanthoma elasticum (PPXE), pseudoxanthoma elasticum-like papillary dermal elastolysis (PXEPDE) and cutis laxa. The skin lesions of these diseases may appear similar, but etiology, histopathologic features and systemic manifestations could differentiate PXE from the others. In PPXE, prolonged penicillamine administration that inhibited collagen and elastin cross-linking results in production of increased amounts of abnormal non-calcified elastin in the dermis [21,22]. PXEPDE is an idiopathic elastolytic disorder with family history and cutaneous lesions clinically resembling PXE [23]; however, no systemic complications have been described. Partial or total band-like loss of elastic fibers in the papillary dermis is the characteristic histopathologic feature. Cutis laxa can be a feature of an autosomal recessive form of PXE [3]. It may be inherited or acquired following inflammatory skin diseases [24,25]. The elastic fibers are sparse, short, fragmented, clumped but not calcified, particularly in the upper dermis [26]. The internal elastic tissue may also be affected, as in PXE,

and cardiovascular abnormalities occur in some cases.

Herein, we report a case of PXE with typical cutaneous lesions, pathologic features, and angioid streaks. The obvious abnormal microcirculatory findings may serve as an early indicator of cardiovascular disturbance though more data are needed before a definite correlation between capillaroscopic finding and clinical manifestation can be made.

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彈性纖維假黃瘤合併異常指甲皺襞微小循環之表現

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彈性纖維假黃瘤是一彈性組織之遺傳疾病。在此，我們報告一34歲男性病患自數月前發現其頸部有許多無自覺症狀黃色小丘疹，當其妹妹告知她也有類似之皮膚症狀與視力受損，即前來本院就診。在皮膚病理切片下經由H & E，Verhoeff-van Gieson以及Von Kossa染色可見在眞皮層之中下段有斷裂且鈣化之彈性纖維，在電子顯微鏡下亦可見彈性纖維有鈣化性退化的現象。除了皮膚的病灶與眼底的血管狀條紋外，並無其他器官受影響。此外，經由微血管顯微鏡觀察可見手指甲皺襞處微血管有彎曲程度增加，靜脈端之管徑擴張等變化，同時其血球流速亦有減緩。因此除以往報告中指出因血管壁之彈性纖維退化所引起之心血管疾病表外，本文首度提出彈性纖維假黃瘤患者手指甲皺襞處之微小循環其型態學與血球流速之障礙。

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