

# Pseudoxanthoma Elasticum-like Syndrome: Report of a Case and Discussion of Pathogenesis

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## Abstract

Pseudoxanthoma elasticum is a disorder of degenerating elastic fibers that may develop in either a hereditary or acquired fashion. The classic histologic finding of pseudoxanthoma elasticum is fragmentation of elastic fibers in the dermis. The acquired variant of this entity, pseudoxanthoma elasticum-like syndrome, has been described in many different clinical settings, with periumbilical lesions in multiparous African-American females being the best recognized. However, pseudoxanthoma elasticum-like syndrome may develop in a number of other situations. We present a case of localized, pseudoxanthoma elasticum-like syndrome in a patient with rheumatoid arthritis, sickle cell trait, and a history of a burn injury, and also discuss the possible mechanisms involved in the pathogenesis of all cases of this dermatologic disorder.

## INTRODUCTION

Hereditary pseudoxanthoma elasticum (PXE) is a disorder that results from degeneration and calcification of elastic fibers in cutaneous, ocular, and cardiovascular systems.<sup>1,2,3,4,5,6,7</sup> PXE is progressive with considerable morbidity and mortality, depending on the extent of extracutaneous involvement.<sup>1,2</sup> Histologically, PXE is characterized by degenerated elastic fibers in the reticular dermis, which become infiltrated with calcium.<sup>2</sup> The hallmark cutaneous lesions usually begin by the second decade of life, and commonly involved areas include regions of repeated stress, particularly the flexural folds.<sup>1,3</sup> These lesions generally appear as yellow macules and papules that coalesce into plaques.<sup>2,3,4</sup> The skin first appears thickened, but with further progression the skin in affected areas become soft, flaccid and redundant.<sup>2,3,5</sup>

An acquired form of PXE has been described with skin lesions having histologic and sometimes clinical features similar to those seen in hereditary PXE, though affected individuals generally lack extracutaneous manifestations.<sup>3,4,5,6,7</sup> This category of disorders has been referred to as pseudoxanthoma elasticum-like syndrome, acquired pseudoxanthoma elasticum, pseudo-pseudoxanthoma elasticum, and other similar names; for the sake of uniformity, we will use the term pseudoxanthoma elasticum-like syndrome to encompass all of these entities.<sup>7,8,9</sup> In some of these cases, cutaneous perforation is

present, for which the term perforating calcific elastosis is applied.<sup>1,3</sup> Herein we report a case of pseudoxanthoma elasticum-like syndrome occurring in a nulliparous, African-American female with rheumatoid arthritis, sickle cell trait, and a history of a burn in the affected area.

## CASE REPORT

A 57-year-old African-American female with a history of rheumatoid arthritis and sickle cell trait, presented with a non-healing lesion of a few month's duration on her left elbow where she had suffered a thermal burn a few decades prior to presentation. The remainder of her cutaneous examination was normal. The patient reported no history of pregnancies. Notably, she also had a personal history of a cerebrovascular accident at age 30, attributed to uncontrolled hypertension.

Cutaneous examination at presentation revealed an 8 by 15 mm ulceration with an indurated rim on her left elbow (Figure 1).

**Figure 1**

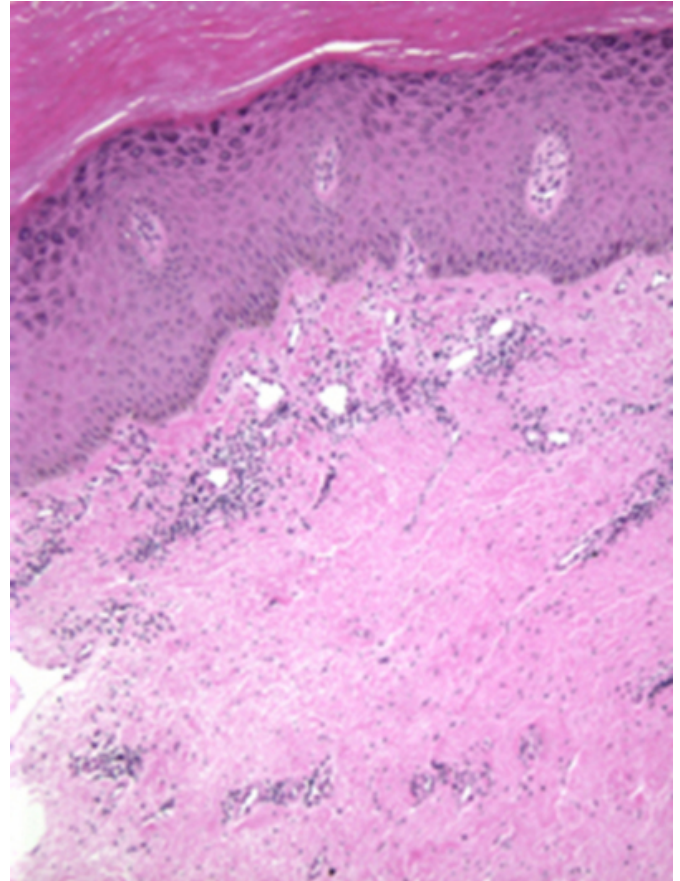
Figure 1: Sclerotic yellow plaques on the elbow with superimposed ulceration.



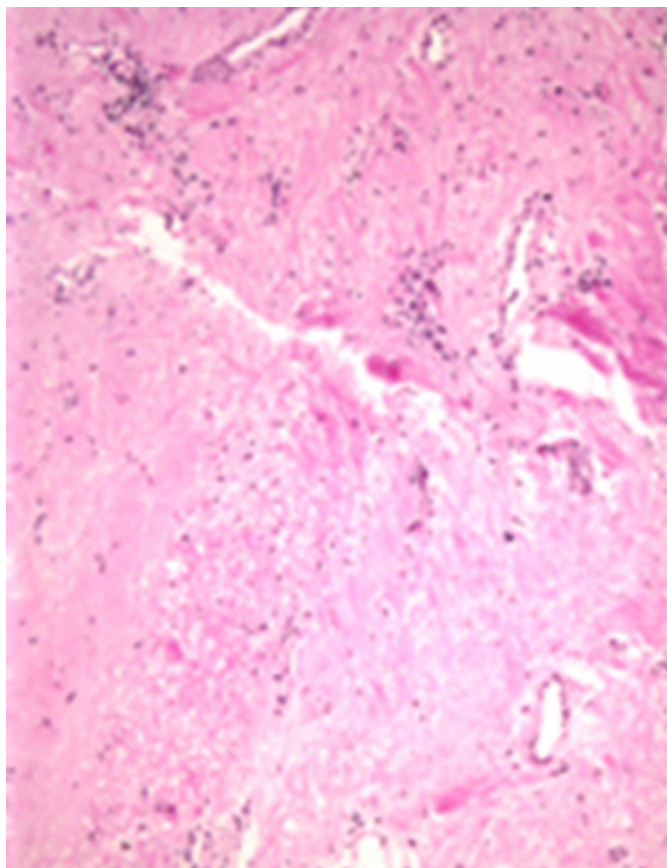
Sclerotic yellow to flesh-colored plaques consistent with her burn history were present around this area. Initially this lesion was thought to be an ulcerated rheumatoid nodule, however a punch biopsy was obtained from its rim for further investigation. Pathologic evaluation of the biopsy demonstrated clumps of degenerated connective tissue fibers in the dermis—these fibers were identified as elastic fibers on Verhoeff-Van Gieson stain, suggestive of pseudoxanthoma elasticum (Figures 2-3). In addition, ophthalmologic evaluation revealed no abnormalities. All of these findings support a diagnosis of pseudoxanthoma elasticum-like syndrome.

**Figure 2**

Figure 2: Histologic findings including clumps of degenerated connective tissue fibers (Hematoxylin-eosin stain, A original magnification X10, B original magnification X20).

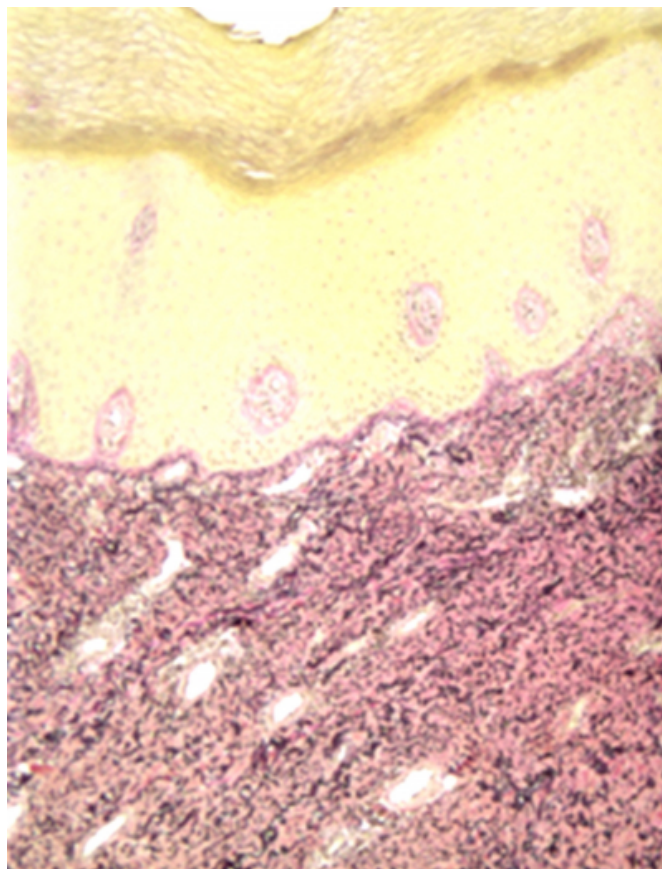


**Figure 3**



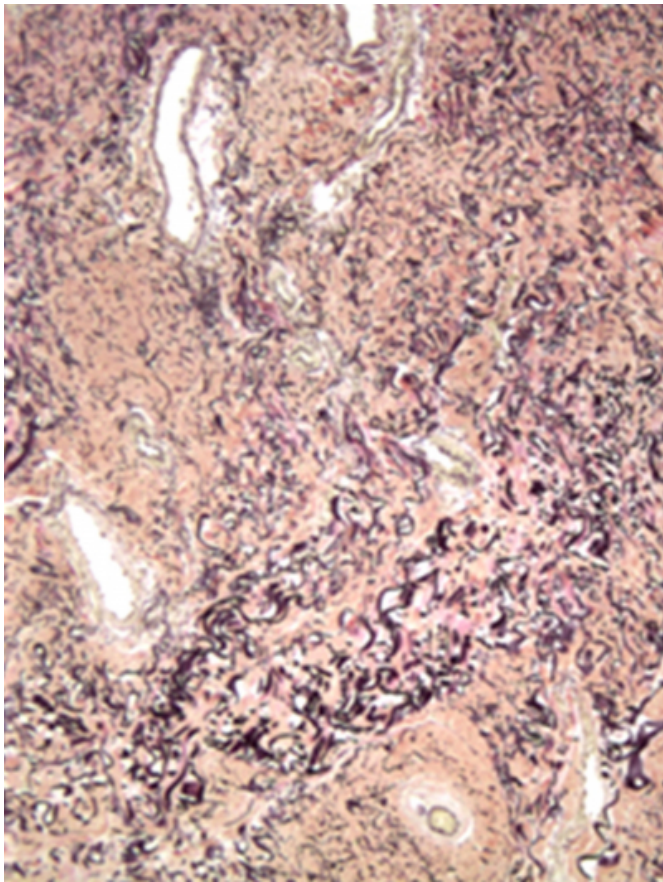
**Figure 4**

Figure 3: Elastic tissue stain (Verhoeff-Van Gieson stain, A original magnification X10, B original magnification X20).





**Figure 5**



Per our recommendation, the patient applied white petrolatum twice daily to the ulceration, and it was completely healed within 2 months. Since that time, the ulceration has recurred, but again responded well to similar conservative measures.

## **DISCUSSION**

Both acquired and hereditary forms of PXE have been described. Hereditary PXE is a rare disorder which is autosomal recessive in nature.<sup>2</sup> The ATP-binding cassette, subfamily C, member 6, transporter gene (ABCC6), located on chromosome 16, has been identified as the defective gene in PXE.<sup>1,2,9,10</sup> This gene encodes multidrug resistance associated protein 6 (MRP6), a transporter of glutathione conjugates.<sup>1,2,9,10</sup> Although the exact influence of the MRP6 protein on connective tissue is unknown, it has been suggested that this protein may be responsible for altering the initial assembly of elastic fibers, thereby compromising their durability and function.<sup>2</sup> This may result in the accumulation of fragmented, calcified elastic fibers and altered collagen fibrils in the skin, retina, and arterial walls.<sup>1,2</sup> Similarly, pseudoxanthoma elasticum-like syndrome involves abnormal elastic fibers, but occurs for

different reasons.

Pseudoxanthoma elasticum-like syndrome has developed in a number of clinical settings. Multiparous African-American females are one of the most commonly affected populations, developing lesions in a periumbilical distribution.<sup>1,3,4</sup> Pseudoxanthoma elasticum-like syndrome has also been reported in association with the following disorders and circumstances: hypothyroidism, uremia, hyperphosphatemia, L-tryptophan-induced eosinophilia myalgia syndrome, and dermal contact with dry saltpeter fertilizer (calcium-ammonium-nitrate salts).<sup>2,4</sup> In addition, pseudoxanthoma elasticum-like syndrome has been reported in a number of patients with autoimmune diseases such as rheumatoid arthritis and autoimmune thyroiditis.<sup>5,6,9</sup> Rarely patients taking D-penicillamine for the treatment of Wilson's disease, cystinuria, rheumatoid arthritis, and scleroderma have also developed PXE skin lesions.<sup>7</sup> Finally, PXE cutaneous manifestations have been identified in some patients with congenital anemias, such as beta-thalassemia, sickle cell disease, and spherocytosis.<sup>5,9</sup> All of these situations associated with pseudoxanthoma elasticum-like syndrome have in common a disruption in elastic fibers, creating the histologic and clinical changes that are observed.<sup>1,3,9,10</sup>

Mechanical stress and trauma may be important in the pathogenesis of PXE.<sup>1,3,8,9</sup> This theory is supported by reports of pseudoxanthoma elasticum-like syndrome lesions developing in patients with severe ascites, recent abdominal surgery, and in areas of traumatic injury such as elbow flexures.<sup>1,4,8</sup> It has been proposed that focal irritation, either mechanical or biochemical, to connective tissue can induce a foreign body reaction, leading to degeneration and fragmentation of the elastic fibers.<sup>1</sup> Pseudoxanthoma elasticum-like syndrome in areas previously exposed to dry saltpeter fertilizer has been reported in Scandinavian farmers.<sup>4</sup> Furthermore, a number of case reports have described pseudoxanthoma elasticum-like syndrome localized to the periumbilical region in obese, multiparous females.<sup>1,3,10</sup> The traumatic effect of repeated pregnancies on elastic tissue explains the localization of the skin lesions in these cases.<sup>1,3</sup>

Injury to elastic fibers via other mechanisms may also lead to pseudoxanthoma elasticum-like syndrome. In terms of the congenital anemias, the proposed mechanism of elastic tissue injury involves oxidative damage.<sup>2,9</sup> Patients with congenital anemias accumulate an excess of free hemoglobin as well as microparticles derived from damage to erythrocyte

membranes, both which have oxidative properties.<sup>5</sup> Furthermore, prolonged tissue injury in these patients leads to activation of neutrophils and monocytes which further enhances elastase activity.<sup>5</sup> Penicillamine induced elastic fiber changes occur because this medication impairs the formation of stable cross-links in both collagen and elastin.<sup>7</sup> Penicillamine depletes copper which is a co-factor for lysyl oxidase, an enzyme essential for elastin cross-linking.<sup>7</sup> The association between PXE and autoimmune diseases, such as rheumatoid arthritis, has been rarely reported and may be the result of local immunologic tissue destruction causing secondary damage to elastic fibers, resulting in pseudoxanthoma elasticum-like syndrome.<sup>6</sup> In our patient, rheumatoid arthritis, sickle cell trait, and the previous tissue injury related to a burn may have all contributed to the development of pseudoxanthoma elasticum-like syndrome.

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