Pseudoxanthoma elasticum and skin: Clinical manifestations, histopathology, pathomechanism, perspectives of treatment

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Summary

Pseudoxanthoma elasticum (PXE), also known as Groenblad-Strandberg syndrome, is a rare heritable disease with an estimated prevalence of 1:50,000 in the general population. PXE is considered a prototype of multisystem ectopic mineralization disorders and it is characterized by aberrant mineralization of soft connective tissue with degeneration of the elastic fibers, involving primarily the eyes, the cardiovascular system, and the skin. Cutaneous lesions consist of small, asymptomatic, yellowish papules or larger coalescent plaques, typically located on the neck and the flexural areas. PXE is caused by mutations in the ABCC6 (ATP-binding cassette subfamily C member 6) gene that encodes a transmembrane ATP binding efflux transporter, normally expressed in the liver and the kidney; however, the exact mechanism of ectopic mineralization remains largely unknown. The histological examination of cutaneous lesions, revealing accumulation of pleomorphic elastic structures in middermis, is essential for the definitive diagnosis of PXE, excluding PXE-like conditions. PXE is currently an intractable disease; although the cutaneous findings primarily present a cosmetic problem, they signify the risk for development of ocular and cardiovascular complications associated with considerable morbidity and mortality. The purpose of this review is to present a comprehensive overview of this rare form of hereditary connective tissue disorders, focus on the pathogenesis, the clinical manifestation, and the differential diagnosis of PXE. Emphasis is also placed on the management of cutaneous lesions and treatment perspectives of PXE.

Keywords: Pseudoxanthoma elasticum, skin, orphan disease

1. Introduction

Pseudoxanthoma elasticum (PXE), also known as Gröenblad-Strandberg syndrome, is an heritable multisystem disorder, characterized by aberrant mineralization of soft connective tissue resulting in fragmentation of elastic fibers, involving primarily the skin, eyes and cardiovascular system (1). Notably, PXE is caused by mutations in the ABCC6 (ATP-binding cassette subfamily C member 6) gene, located on short-arm of human chromosome 16, encoding a transmembrane ATP binding driven anion transporter, normally expressed in the liver and the kidney. However, the pathophysiology, particularly the mechanism of ectopic mineralization remains largely unknown (2,3). PXE, as other genodermatoses (4), is currently an intractable disease, associated with considerable morbidity and occasional mortality due to cardiovascular complications (5). In this review, we discuss the clinical and histological features of PXE, focusing on cutaneous manifestations of the disease. In addition, we summarize the recent evidence concerning molecular genetics and pathomechanisms underlying PXE, and finally we present a comprehensive overview of treatment perspectives.
2. Epidemiology, historical background and terminology

PXE is a rare disease, with an estimated prevalence of 1:50,000, which affects approximately 150,000 people in the world, assuming the same global prevalence (1). Females are more commonly affected than males (2:1); the clinical manifestations are rarely present at birth and usually become evident during the second or third decade of life (6,7).

The disease was previously described by the French dermatologist Rigal in 1881, whereas Ferdinand-Jean Darier coined the term pseudoxanthoma elasticum in 1896, delineating the connective disorder as a clinical entity, distinct from xanthoma (hence pseudoxanthoma) (8,9). Angioid streaks of the retina were initially described by Robert W. Doyne and by Otto Pflange in 1889 and 1892, respectively (10,11). In 1929 two Swedish physicians, ophthalmologist Ester Gröenblad and dermatologist James Strandberg, first defined the association between angioid streaks and pseudoxanthoma elasticum and coined the term Gröenblad-Strandberg syndrome, currently used synonymously with PXE (12,13).

3. Molecular genetics

PXE is considered as a paradigm of heritable connective tissue disorders, characterized by ectopic mineralization and consequently fragmentation of elastic fibers in the extracellular matrix (14). PXE is a multisystem orphan disease with autosomal recessive patterns of inheritance. Currently, no molecular evidence of autosomal dominant inheritance has been reported; the recurrence of PXE in successive generations could be explained through a pseudo-dominant pedigree pattern, due to familial consanguinity (15). In addition, a relatively small proportion of cases occurs sporadically (16).

PXE is characterized by considerable intra- and inter-familial heterogeneity, with respect to the age of onset, the entity of tissue mineralization, and the severity of clinical manifestations, suggesting a putative role of genetic and environmental modifying factors in PXE phenotypic expression (17). Specifically, genetic polymorphisms in the promoter of the SPP1 gene (also known as osteopontin) may represent a genetic risk factor contributing to PXE susceptibility (18). Moreover, dietary factors, a high intake of dairy products rich in calcium and phosphate during childhood and adolescence or intake of aluminium hydroxide, a phosphate binder, may play a role in the pathologic mineralization process in PXE (19,20).

Notably, PXE is caused by mutations of the ABCC6 gene transporter protein, also known as multidrug resistance-associated protein 6 (MRP6), a member of adenosine triphosphate-binding cassette proteins, predominantly expressed in the liver and in minor amounts in the proximal tubules of kidneys and intestine (12). To date, over 300 mutations in the ABCC6 gene, including missense and nonsense mutations, intronic mutations, small deletions and insertions, have been described in PXE patients (12,13-21). The most recurrent loss-of-function mutations are p.R1141X and g.del23-29, which account for up to approximately 45% of all pathogenic PXE mutations (21).

Although the substrate specificity of ABCC6 is currently unknown; recent evidence suggests that it functions as a transmembrane transporter of polyanionic glutathione-conjugated molecules (22).

4. Pathomechanism

The pathophysiology of elastic fiber mineralization, including the exact correlation with the defective ABCC6 transporter, is still unclear (23). A systematic experimental study confirmed that targeted ablation of the mouse ABCC6 gene results in progressive mineralization of connective tissue, representing a cardinal feature of PXE phenotype. In addition, it has been demonstrated that mineral deposits in mice models consist of calcium and phosphate forming hydroxyapatite crystals, as in the human affected tissue (24).

To explain the potential relationship between defective ABCC6 transporter and pathological mineralization, two theories have been proposed. The first hypothesis (metabolic hypothesis) postulates that the absence of ABCC6 activity in the liver results in deficiency of circulating anti-mineralization factors which are necessary to prevent precipitation of calcium/phosphate complexes and aberrant mineralization in homeostatic conditions (25). The second hypothesis (cellular hypothesis) states that the accumulation of minerals in soft connective tissues may be associated with the absence of ABCC6 expression in resident cells of the affected organs, primarily fibroblasts, resulting in cell perturbation (changes of biosynthetic expression profile, proliferative capacity, and cell-cell and cell-matrix interactions) and consequent local mineralization and elastic fiber alterations (26,27).

Moreover, growing evidence appears to indicate that the ABCC6 mutations may contribute to alter redox potential restoration following oxidative stress, leading to soft tissue calcification in PXE patients (28,29). Defects in additional genes, including the GGCX and the ENPP1 genes, have recently been implicated in the development of PXE-like cutaneous findings, associated with unusual phenotypes (30-32). The GGCX gene encodes a vitamin K-dependent enzyme responsible for γ-glutamyl carboxylation of Glα-proteins, including several vitamin K-dependent coagulation factors and matrix-Gla proteins (MGP) (33).

MGP in fully carboxylated form is a potent anti-mineralization factor expressed in peripheral connective tissues. The inactivating missense mutations in both
Cutaneous manifestations are usually the first sign of pseudoxanthoma elasticum and consist of small (1 to 5 millimetres), asymptomatic, yellowish or skin-colored papules, presenting in a reticular pattern, that progressively coalesce into larger plaques (Figure 1).

The affected skin typically becomes lax, wrinkled, and redundant (23).

Skin alterations commonly appear during childhood or adolescence and progress slowly and unpredictably during adulthood. They are initially located on the lateral and posterior regions of the neck. Flexural areas, including axillae, inguinal region, antecubital and popliteal fossae, and periumbilical area, are frequently involved during the progression of the disease (43). Mucosal lesions of the oral cavity, especially the inner lower lip, and genital area, can also be detected and resemble cutaneous changes (44). Although the cutaneous lesions principally represent a cosmetic problem, they predict the risk for development of ocular and cardiovascular manifestations, with a considerable morbidity and occasional mortality (41).

5.2. Ocular manifestations

Ophthalmological features of PXE include primarily peau d’orange, comet lesions, angioid streaks, choroidal neovascularization (CNV), hemorrhages, and scar formation (41).

Peau d’orange is the earliest funduscopically visible alteration in patients with PXE, preceding the development of angioid streaks. It consists of pigment small dark spots resulting in a mottled aspect prominently of the temporal retinal midperiphery (45). The pathogenesis of peau d’orange remains unclear. Notably, the ocular phenotype is the consequence of the progressive calcification of Bruch’s membrane (BM) which is composed primarily of elastic fibers. It has been hypothesized that peau d’orange represents a visible transition zone of BM calcification (46).

Comet lesions are characterized by chorioretinal atrophic spots, preferably with peripheral localization; occasionally they present a tail pointing toward the optic nerve head, leading to the descriptive term comet tail lesions (47). It has been suggested that comet and comet tail lesions are the only ocular pathognomonic features of PXE (47).

Angioid streaks are the most obvious and consistent features of PXE fundus abnormalities. They present as irregular and jagged brownish-grey lines that radiate from a concentric peripapillary ring into the periphery. The streaks are most pronounced at the posterior pole of the eye and typically taper and fade toward the equator of the eye, usually dividing into smaller branches (48). Histopathologically angioid streaks represent breaks of the calcified and thickened Bruch’s membrane. It has been postulated that calcification of BM increases the vulnerability of the membrane, inducing ruptures in calcifying BM and resulting in angioid streak formation (16,49).

CNV of the macular region is a frequent complication in patients with PXE; it usually occurs in association with angioid streaks leading to subretinal hemorrhages,
exudation and fibrovascular scar formation, with consequent visual acuity loss (50). Pattern dystrophy-like changes and chorioretinal atrophy, originating secondary to CNV or developing in the context of areas of pattern dystrophy, are recognized features in PXE patients (51).

Additionally, PXE patients have an increased risk of developing optic nerve head (ONH) drusen. The exact mechanism is incompletely understood but it is probably related to abnormal mineralization of the lamina cribrosa (48,51).

5.3. Cardiovascular manifestations

As in many other cutaneous diseases (52,53), the cardiovascular manifestations in PXE patients are numerous and include reduced peripheral pulse, hypertension, angina pectoris, and intermittent claudication. Gastrointestinal hemorrhages, manifesting as hematemesis and melena, are frequently observed. PXE patients can also develop premature atherosclerosis with early acute myocardial infarcts and cerebrovascular accidents (54,55).

Specifically, cardiovascular changes in PXE patients are mainly caused by mineralization and fragmentation of elastic fibers of the internal elastic lamina, medial and adventitial layers of medium-sized arteries and aorta, as well as of the endocardium, pericardium, connective tissue in the myocardium and intramyocardial arterioles and epicardial coronary arteries (56).

In addition, alterations in lipoprotein composition with lowered plasma HDL cholesterol levels and hypertriglyceridemia were found in plasma samples of PXE patients (57).

6. Histopathology

The histological examination of cutaneous lesions is essential for the definitive diagnosis of PXE. The primary histological feature of PXE is progressive mineralization and fragmentation of mid-dermal elastic fibers, resulting in a histological image pattern known as elastorrhexis (Figure 1) (58).

In particular, light microscopy (LM) using Verhoeff-Van Gieson (VVG) stain, specific for the elastic fibers, or von Kossa or Alizarin Red calcium stains, showing respectively fragmented elastic fibers and mid-dermal calcified, is crucial for the diagnosis of PXE (59) (Figure 2). Calcification mostly affects the elastic fibers core; electron microscopy (EM) observation can reveal two types of mineralization: fine deposits in the center of the fibers and bulky precipitates deforming the fibers (60).

Mineral precipitates are usually composed of hydroxyapatite and calcium biphosphate. Other mineral precipitates, as iron, phosphate and carbonate, have also been detected in altered connective tissue. Rarely, dermal mineralized areas evolve to ossification (27,61).

Additionally, deposits of abnormal collagen fibrils, as collagen flowers, and abnormal amounts of proteoglycans in the context of mineralized elastic fibers can be observed (61,62). Fibroblasts are usually numerous and characterized by hypertrophy of endoplasmic reticulum. Macrophages are also abundant within the calcified deposits (58). LM alterations in non-lesional skin are generally absent. Conversely, ultrastructural elastic tissue degeneration can be observed in both lesional and clinically non-involved skin (63). Dermoscopy examination may reveal multiple

![Figure 2. Histological characteristics of PXE skin biopsy of the neck with fragmentation and calcification of middermal elastic fibers on hematoxylin and eosin staining (a,b) and Verhoeff-Van Gieson staining (c,d).](image-url)
yellowish-colored nonfollicular papules arranged in cobblestone-pattern. No specific dermoscopic features of PXE have been described in literature.

7. Differential diagnosis

Numerous systemic and dermatologic disorders could manifest clinical and histological features resembling classic PXE (43, 59) (Table 1). Moreover, the absence of skin alterations does not exclude a diagnosis of PXE (64).

The term PXE-like syndrome has been used to describe cutaneous, ocular, and cardiovascular alterations characteristic of PXE that occur in association with other systemic or dermatologic diseases or secondary to genetic mutations different from ABCC6 (56). Cutaneous lesions of PXE-like phenotype have been described in association with vitamin-K dependent coagulation factor deficiency (factor II, VII, IX, and X) (65).

Cutaneous peau d’orange lesions distributed symmetrically on the neck and flexural regions may be the first sign of PXE-like; skin alterations tend to progress towards thick and leathery redundant folds, especially in the flexural areas. The ocular and cardiovascular manifestations are usually mild or absent (30, 59).

As mentioned above, the PXE-like is caused by loss-of-function mutations in the GGCX gene, encoding a gamma-carboxylase that mediates the activation of vitamin K-dependent coagulation factors and several inhibitors of mineralization (as MGP) in the liver and peripheral tissue, respectively (66).

The histological finding is indistinguishable from classic PXE on light microscopy. Conversely, electron microscopy reveals mineralized aggregates confined to the periphery of the elastic fibers, while PXE usually shows deposits in the core of the fibers (59).

Clinical features closely resembling PXE are also reported in association with inherited hemoglobinopathies, such as thalassemia and sickle cell disease. Specifically, yellowish papular eruption and ocular changes are comparable to PXE manifestations, except for the elderly onset of the symptoms. In this circumstance, hemoglobin electrophoresis should be performed in patients exhibiting clinical and/or histological findings mimicking PXE (67).

Other dermatologic disorders resembling PXE are cutis laxa, fibroelastolytic papulosis, PXE-like papillary dermal elastolysis, late-onset focal dermal elastosis, and perforating calcific elastosis (68-73). Lastly, several dermatologic diseases, including elastosis perforans serpiginosa, upper and middermal elastolysis, papular elastorrhexis and linear focal elastosis, can manifest similar histological phenotypes as observed in PXE (70, 74-77).

8. Treatment of cutaneous manifestations

No specific or effective treatment is currently available for the systemic mineralization and fragmentation of elastic fibres in the skin, eyes and arterial blood vessels caused by PXE. Based on literature reports, we propose a review of therapeutic options for this intractable disease. However, significant progress has been made in the
therapy of ocular complications. Treatment options for chorioidal neovascularisation (CNV) of Retinal Pigment Epithelium (RPE) secondary to pseudoxanthoma elasticum include laser photocoagulation, transpupillary thermotherapy and photodynamic therapy, macular translocation surgery and anti-vascular endothelial growth factor (anti-VEGF) treatments (51). It is beyond the scope of this paper to examine the myriad of therapeutic possibilities for ocular complications.

8.1. Surgical treatment

Rare reports of the surgical management of PXE for cosmetic improvement of skin manifestations have been described in the literature as one of the therapeutic options available (78). Few cases with surgical implication (presence of redundant, lax and indurated skin of the neck, axillae and groin region with a typical "hound dog" appearance) have been treated by cutaneous rhytidectomy with SMAS (superficial musculoaponeurotic system) (79).

Cosmetic surgery usually consists of lower subcutaneous rhytidectomy and neck skin lift performed through a standard preauricular facelift incision with postauricular extension and transverse extension into the hairline with excellent results and minimal complications. Furthermore, revision surgery using a vertical elliptical skin excision, incorporating a Z-plasty after a standard rhytidectomy, which produced minimal improvement, resulted in a satisfactory outcome (80). A characteristic horizontal "mental" crease connecting deep rhytides of the lower jaw was successfully treated with injectable collagen, providing a temporary but immediately visible improvement (81).

8.2. Systemic treatment

Some investigators have noted an association of idiopathic hyperphosphatemia and PXE (82). Moreover, it was found that the imposition of low-calcium diet could produce clinical, histopathologic, and electron-microscopic improvement in the number of abnormal calcified elastic fibers in the dermis (83). These observations suggest a possibility of clinical use of oral phosphate binders in the treatment of PXE. Administration of aluminium hydroxide in 6 patients has produced marked improvement of skin lesions in 3 of those patients (19). Moreover, all 3 patients had reduced von Kossa’s staining of histopathological changes in their target lesions. In a 1-year follow-up, there was no clinically significant deterioration of eye damage.

Subsequent studies examined the efficacy of sevelamer hydrochloride (aluminium-free phosphate binder) in the normalization of the serum calcium-phosphate products and clinical outcome in patients with PXE (84). In the randomized, double blind, placebo-controlled study, sevelamer hydrochloride produced an improvement in clinical scores and in calcification during the first year of treatment. However, the difference was not statistically significant compared with placebo, because of the addition of magnesium stearate (an agent that has been implicated in reducing calcium levels) in the composition of each of the pills used in control and study groups. The authors discovered that sevelamer hydrochloride's phosphate-binding capacity is not as strong as aluminium hydroxide, and did not prove to be as efficacious. Furthermore, a diet addition of sevelamer hydrochloride did not improve mineralization as compared with Abcc6−/− mice fed a normal diet (20). The drug caused a compensatory increase in serum phosphorous concentration produced by impaired intestinal absorption of phosphate. Within these results, has been an option to use lanthanum carbonate, an alternate phosphate binder, which has a similar phosphate-binding capacity as aluminium hydroxide. Experiments with diet supplementation using lanthanum carbonate did not interfere with the mineralization process in Abcc6−/− mice (20).

A potential way of preventing ectopic mineralization revolves around supplementation with fetuin-A, a major systemic inhibitor of calcification. A set of experiments has suggested that concentration of fetuin-A in PXE patients, as well as Abcc6−/− mice, were lower than in unaffected first-degree relatives and controls (42). Overexpression of fetuin-A in Abcc6−/− mice due to construct containing full-length mouse fetuin-A complementary DNA (cDNA), linked to a His-tag, resulted in elevated serum levels of this protein. These results suggest that normalization of serum fetuin-A can reduce soft tissue mineralization by approximately 70% at 12 weeks, but its effect is transient (85). Studies of mouse Abcc6−/− models suggest that increasing magnesium content of the diet (fivefold) may be useful to prevent the ectopic mineralization in these animals (86).

Furthermore, treatment of mice with a magnesium carbonate-enriched diet (magnesium concentration being 5-fold higher than in the control diet) completely prevents mineralization of the vibrissae up to 6 months of age. The magnesium carbonate-enriched diet also prevents the progression of mineralization when mice were placed on that experimental diet at 3 months of age and followed up to 6 months of age. These results suggest that magnesium carbonate may offer a potential treatment modality for PXE (31).

As confirmation of the above conclusions, recent studies have demonstrated that the magnesium poor diet accelerates the connective tissue mineralization in PXE mice (87). Considering the results of the preclinical studies, the research team of Dr. Mark Lebwohl initiated in 2013 a study to test the efficacy of magnesium-enriched diet (900 mg daily) in a double-blind 2 years long clinical trial to evaluate the progress of the mineralization in a cohort of patients with PXE.

In this context, it should be noted that until now
standardized methodologies are not available to monitor progress of mineralization in PXE except for clinical follow-up and skin biopsy. However, recent studies have demonstrated that measurement of carotid intima-media thickness (CIMT), a risk factor for cardiovascular events and stroke, might provide a predictive biomarker of clinical response in PXE patients in future clinical trials. This type of assessment has been used in Abcc6−/− mice fed standard rodent diet with or without magnesium oxide supplementation. Baseline CIMT was significantly higher in Abcc6−/− that in Abcc6+/− mice and CIMT was significantly lower in the magnesium-treated Abcc6−/− mice group than in untreated Abcc6−/− mice (88).

9. Treatment perspectives

Novel potential treatments of PXE have been explored by a number of molecular and cell-based approaches. For example, transplantation of bone marrow derived mesenchymal stem cells (MSCs) has demonstrated homing of cells to the liver and their ability to contribute to liver regeneration. These data suggest that purified MSCs have the capability of differentiating into hepatic lineages with an aim for partial correction of the PXE phenotype in Abcc6−/− knockout mice (38).

As confirmation of the importance of liver cells in the pathway of PXE, 3 cases of pseudoxanthoma elasticum have been reported that occurred after deceased donor liver (and in one case, subsequent kidney) transplantation from a donor with unrecognized PXE (89).

Furthermore, a possible correction of nonsense ABCC6 mutation by a read-through mechanism through PTC124 (a non-aminoglycoside nonsense mutation suppressor molecule) has been evaluated (90). Considering the redundancy of the genetic code, it was postulated that in the case of the most common recurrent nonsense mutation, p.R1141X, the read-through may result in substitution of arginine 1,141 by glycine, tryptophan, or cysteine. In a recently developed zebrafish messenger RNA (mRNA) rescue assay it was demonstrated that all three mRNA transcripts were able to rescue the ABCC6α morpholino-induced phenotype of zebrafish. Thus, the results suggest that read-through of nonsense mutations in ABCC6 by PTC124 may provide a novel means to treat PXE patients.

A recent study suggests that allele-specific therapy with 4-phenylbutyrate (4-PBA), a drug that has already been approved by FDA for clinical use, can be useful for PXE patients as well as for GACI (generalized arterial calcification of infancy) patients (91). Efficacy of pharmacological correction of the plasma membrane localization of four ABCC6 mutants (R1114P, S1121W, Q1347H, and R1314W) could be studied in upcoming clinical trials.

Other studies suggest that the factor that normally prevents PXE is pyrophosphate, which is provided to the circulation in the form of nucleoside triphosphates via an as-yet unidentified but ABCC6-dependent mechanism (92). This finding provides leads for the treatment of this intractable disease.

10. Conclusions

There is no effective and specific treatment for the systemic manifestations of PXE until now, but effective therapies for the ocular complications are currently available (93). All clinical manifestations in the skin, eyes and arterial blood vessels are consequence of calcium phosphate deposition in elastic fibers. A number of observations have indicated different potential treatment modalities for PXE. Specifically, studies of mouse Abcc6−/− models suggested that the mineral composition of diet, particularly supplementation with magnesium, could prevent deposition of minerals in connective tissue and can influence the severity of the mineralization phenotype (12,86,87).

Another potential way for prevention of mineralization processes is possible through introduction of anti-mineralization factors to the circulation. Several molecules (aluminium hydroxide (19), sevelamer hydrochloride (81), and fetuin-A (82)) have proven to be effective in mouse Abcc6−/− models and in some patients with PXE.

Modern molecular approaches for correction of nonsense ABCC6 mutation read-through of translation by PTC124 (90) and chaperon-assisted corrections of the cellular localization of the mutant protein by allele-specific therapy with 4-PBA (88) would be expected to be useful in the treatment of patients with PXE. A further aim of restoring functional ABCC6 transporter activity by cell-based approaches is possible. For example, transplantation of allogenic mesenchymal stem cells (MSCs) has demonstrated homing of cells to the liver and their ability to contribute to liver regeneration (66). In addition to this strategy, liver transplantation or a partial lobe replacement would be a way to safeguard ABCC6 activity (82,94). Furthermore, correction of the anaesthetic skin manifestations could be performed by plastic cosmetic surgery (78). Early identification of ABCC6 mutation can be used for confirmation of the clinical diagnosis, carrier detection, and presymptomatic recognition of affected individuals. Furthermore, early diagnosis of the disease could be helpful for increased surveillance of the clinical complications, allowing prevention and timely therapy. These observations suggest that appropriate dietary interventions, oral phosphate binders, allele-specific, molecular and cell-based approaches, coupled with lifestyle modifications, including smoking cessation, might alleviate the symptoms and improve the quality of life of affected individuals.

Meanwhile, continued progress in understanding the pathomechanisms, genetic and epigenetic factors of the severity of phenotype is required for development
of effective, pathophysiology-related therapy of this currently intractable clinical syndrome (17).

References


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