Review

DOI: 10.5582/irdr.2015.01014

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

Barbara Marconi[1,*], Ivan Bobyr[1,*], Anna Campanati [1,], Elisa Molinelli[1], Veronica Consales[1], Valerio Brisigotti[1], Marina Scarpelli[2], Stefano Racchini[2], Annamaria Offidani[1]**

[1] *Dermatological Unit, Department of Clinical and Molecular Sciences, Polytehnic Marche University, Ancona, Italty;*
[2] *Institute of Pathological Anatomy and Histopathology, Polytechnic University Marche, Ancona, Italty.*

Summary **Pseudoxantoma 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 multi-system 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.

Released online in J-STAGE as advance publication July 6, 2015.

*These authors contributed equally to this works.
***Address correspondence to:*
Dr. Anna Campanati, Dermatological Unit, Department of Clinical and Molecular Sciences, Polytechnic Marche University, Via Conca 71, Ancona 60020, Italty.
E-mail: anna.campanati@gmail.com

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 xanthomas (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 Gla-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

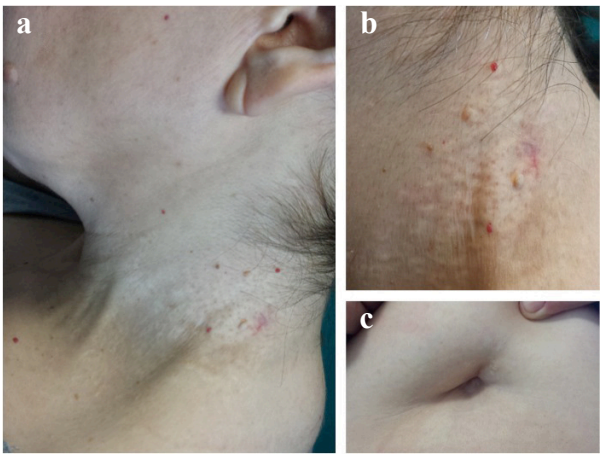

Figure 1. Cutaneous manifestations of PXE. Small yellowish papules coalescing into larger plaques in the neck (a,b), and periumbilical region (c).

alleles of *GGCX* gene generally result in cutaneous lesions consistent with PXE and bleeding disorders (*34*). Recently, it has been demonstrated that MGP in its uncarboxylated form has high expression in calcified tissues of PXE patients as well as in the ABCC6$^{-/-}$ mouse model (*35,36*).

Based on these observations, it has been proposed that ectopic mineralization in PXE could partially reflect deficiency of vitamin K, leading to reduced levels of fully carboxylated active MGP (*37*). The hypothesis has been tested in the animal model, indicating that vitamin K supplementation does not prevent the deposition of minerals in the ABCC6$^{-/-}$ mouse model (*38,39*).

Generalized arterial calcification of infancy (GACI) is a life-threatening, autosomal recessive disease, characterized by extensive arterial calcification, manifesting within the first months of life. It is associated with inactivating mutations in the *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1) gene, which leads to decreased levels of inorganic pyrophosphate, a potent physiological inhibitor of hydroxyapatite-crystal deposition and extracellular matrix calcification (*40*). Interestingly, cutaneous manifestations consistent with PXE have been described in patients with GACI (*32,41*).

Lastly, a lower expression of fetuin-A, an important negative regulator of mineralization, has been demonstrated in serum of patients with PXE, suggesting fetuin-A as a contributing factor of PXE pathogenesis (*42*).

5. Clinical phenotype

5.1. *Cutaneous manifestations*

Cutaneous features 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

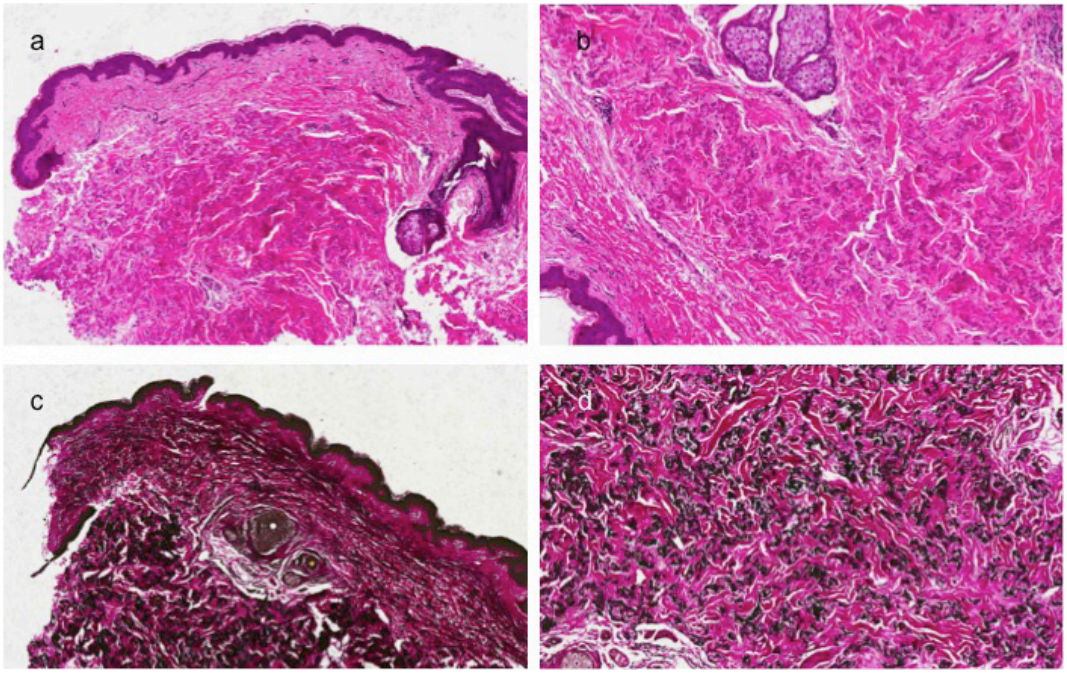

Figure 2. Histological characteristics of PXE skin biopsy of the neck with fragmentation and calcification of middermal elastic fibers on hematoxylin and eosin staining (a,b) and Verhoeff-Van Gieson staining (c,d).

Table 1. Differential diagnosis of PXE

Items	PXE	PXE-like	Cutis laxa	GACI
Generalized skin folds/laxity	Not present	Always present	Often present	Not present
Positive Von Kossa stain of reticular dermis	Present	Present	Not present	Not present
Electron microscopy of elastic fibers	Mineralized in the core of fibers	Mineralized in marginal areas of fibers	Scarce and mottled elastic fibers	Calcification of the arterial internal elastic lamina
Retinopathy	Present and often severe	Present but mild	Not present	Not present
Decreased visual acuity	60%	Not present	Infrequent	Not present
Clotting deficiency	Not described	Always present	Not described	Not described
Atherosclerosis	(Sub)clinical in 55%	Subclinical in 50%	Infrequent	Present and often severe
Hypertension	Present but mild	Infrequent	Not present	Severe
Arterial calcification	Present but mild	Infrequent	Not present	Present and often severe
Cerebral aneurysms	Infrequent	Present	Infrequent	Present
Abnormal bleeding tendency	Infrequent (10%)	Present (50%)	Not described	Not described
Mutations	ABCC6 (96%)	GGCX	ELN,ATP6V0A2, FBLN4-5, PYCR1	ENPP1 (75%)
First manifestations	Childhood or adolescence	Adult	At birth	In utero or the first 6 months of life
Prognosis	Good	Good	Variable	Infaust

yellowish-colored nonfollicular papules arranged in cobbelstone-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 choroidal 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 subcutaneuos 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 hydrocloride (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 ABCC6a 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

1. Uitto J. Rare heritable skin diseases: Targets for regenerative medicine. J Invest Dermatol. 2012; 132:2485-2488.
2. Le Saux O, Urban Z, Tschuch C, Csiszar K, Bacchelli B, Quaglino D, Pasquali-Ronchetti I, Pope FM, Richards A, Terry S, Bercovitch L, de Paepe A, Boyd CD. Mutations in a gene encoding an ABC transporter cause pseudoxanthoma elasticum. Nat Genet. 2000; 25:223-227.
3. Matsuzaki Y, Nakano A, Jiang QJ, Pulkkinen L, Uitto J. Tissue-specific expression of the *ABCC6* gene. J Invest Dermatol. 2005; 125:900-905.
4. Campanati A, Marconi B, Penna L, Paolinelli M, Offidani A. Pronounced and early acne in Apert's syndrome: A case successfully treated with oral isotretinoin. Eur J Dermatol. 2002; 12:496-498.
5. Trip MD, Smulders YM, Wegman JJ, Hu X, Boer JM, ten Brink JB, Zwinderman AH, Kastelein JJ, Feskens EJ, Bergen AA. Frequent mutation in the *ABCC6* gene (R1141X) is associated with a strong increase in the prevalence of coronary artery disease. Circulation. 2002; 106:773-775.
6. Li Q, Jiang Q, Pfendner E, Váradi A, Uitto J. Pseudoxanthoma elasticum: Clinical phenotypes, molecular genetics and putative pathomechanisms. Exp Dermatol. 2009; 18:1-11.
7. Chassaing N, Martin L, Calvas P, Le Bert M, Hovnanian A. Pseudoxanthoma elasticum: A clinical, pathophysiological and genetic update including 11 novel *ABCC6* mutations. J Med Genet. 2005; 42:881-892.
8. Rigal D. Observation pour servir a l'histoire de la chéloïde diffuse xantelasmique. Annal Dermatol Syphiligraphie. 1881: 2:491-501.
9. Darier J. Pseudoxanthoma elasticum. Monatshefte Praktische Dermatologie. 1896:609-617.
10. Doyne R. Choroidal and retinal changes the result of blows on the eyes. Trans Ophthalmol Soc UK. 1889; 9:128.
11. Pflange O. Pigmentary striae with secondary changes in the retina after haemorrhage. Arch Ophthalmol. 1892; 21:282.
12. Strandberg J. Pseudoxanthoma elasticum. Zeitschrift fur Haut- und Geschlechtskrankheiten. 1929; 31:689.
13. Groenblad E. Angioid streaks-pseudoxanthoma elasticum. Acta Ophtal. 1929; 7:329.
14. Neldner KH. Pseudoxanthoma elasticum. Clin Dermatol. 1988; 6:1-159.
15. Ringpfeil F, McGuigan K, Fuchsel L, Kozic H, Larralde M, Lebwohl M, Uitto J. Pseudoxanthoma elasticum is a recessive disease characterized by compound heterozygosity. J Invest Dermatol. 2006; 126: 782-786.
16. Georgalas I, Papaconstantinou D, Koutsandrea C, Kalantzis G, Karagiannis D, Georgopoulos G, Ladas I. Angioid streaks, clinical course, complications, and current therapeutic management. Ther Clin Risk Manag. 2009; 5:81-89.
17. Uitto J, Varadi A, Bercovitch L, Terry PF, Terry SF. Pseudoxanthoma elasticum: Progress in research toward treatment: Summary of the 2012 PXE international research meeting. J Invest Dermatol. 2013; 133:1444-1449.
18. Hendig D, Arndt M, Szliska C, Kleesiek K, Götting C. SPP1 promoter polymorphisms: Identification of the first modifier gene for pseudoxanthoma elasticum. Clin Chem. 2007; 53:829-836.
19. Sherer DW, Singer G, Uribarri J, Phelps RG, Sapadin AN, Freund KB, Yanuzzi L, Fuchs W, Lebwohl M. Oral phosphate binders in the treatment of pseudoxanthoma elasticum. J Am Acad Dermatol. 2005; 53:610-615.
20. LaRusso J, Jiang Q, Li Q, Uitto J. Ectopic mineralization of connective tissue in Abcc6$^{-/-}$ mice: Effects of dietary modifications and a phosphate binder--a preliminary study. Exp Dermatol. 2008; 17:203-207.
21. Pfendner EG, Vanakker OM, Terry SF, *et al*. Mutation detection in the *ABCC6* gene and genotype-phenotype analysis in a large international case series affected by pseudoxanthoma elasticum. J Med Genet. 2007; 44:621-628.
22. Hosen MJ, Coucke PJ, Le Saux O, De Paepe A, Vanakker OM. Perturbation of specific pro-mineralizing signalling pathways in human and murine pseudoxanthoma elasticum. Orphanet J Rare Dis. 2014; 9:66.
23. Uitto J, Li Q, Jiang Q. Pseudoxanthoma elasticum: Molecular genetics and putative pathomechanisms. J Invest Dermatol. 2010; 130:661-670.
24. Kavukcuoglu NB, Li Q, Pleshko N, Uitto J. Connective tissue mineralization in Abcc6$^{-/-}$ mice, a model for pseudoxanthoma elasticum. Matrix Biol. 2012; 31:246-252.
25. Jiang Q, Li Q, Uitto J. Aberrant mineralization of connective tissues in a mouse model of pseudoxanthoma elasticum: Systemic and local regulatory factors. J Invest Dermatol. 2007; 127:1392-1402.
26. Passi A, Albertini R, Baccarani M, de Luca G, de Paepe A, Pallavicini G, Pasquali Ronchetti I, Tiozzo R. Proteoglycan alterations in skin fibroblast cultures from patients affected with pseudoxanthoma elasticum. Cell Biochem Funct. 1996; 14:111-120.
27. Quaglino D, Boraldi F, Barbieri D, Croce A, Tiozzo R, Pasquali Ronchetti I. Abnormal phenotype of *in vitro* dermal fibroblasts from patients with Pseudoxanthoma elasticum (PXE). Biochim Biophys Acta. 2000; 1501:51-62.
28. Mueller CF, Widder JD, McNally JS, McCann L, Jones DP, Harrison DG. The role of the multidrug resistance protein-1 in modulation of endothelial cell oxidative stress. Circ Res. 2005; 97:637-644.
29. Cole SP, Deeley RG. Transport of glutathione and glutathione conjugates by MRP1. Trends Pharmacol Sci. 2006; 27:438-446.
30. Vanakker OM, Martin L, Gheduzzi D, Leroy BP, Loeys BL, Guerci VI, Matthys D, Terry SF, Coucke PJ, Pasquali-Ronchetti I, De Paepe A. Pseudoxanthoma elasticum-like phenotype with cutis laxa and multiple coagulation factor deficiency represents a separate genetic entity. J Invest Dermatol. 2007; 127:581-587.
31. Li Q, Larusso J, Grand-Pierre AE, Uitto J. Magnesium carbonate-containing phosphate binder prevents connective tissue mineralization in Abcc6$^{(-/-)}$ mice-potential for treatment of pseudoxanthoma elasticum. Clin Transl Sci. 2009; 2:398-404.
32. Nitschke Y, Baujat G, Botschen U, *et al*. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either *ENPP1* or *ABCC6*. Am J Hum Genet. 2012; 90:25-39.
33. Stafford DW. The vitamin K cycle. J Thromb Haemost.

2005; 3:1873-1878.
34. Li Q, Grange DK, Armstrong NL, Whelan AJ, Hurley MY, Rishavy MA, Hallgren KW, Berkner KL, Schurgers LJ, Jiang Q, Uitto J. Mutations in the *GGCX* and *ABCC6* genes in a family with pseudoxanthoma elasticum-like phenotypes. J Invest Dermatol. 2009; 129:553-563.
35. Li Q, Jiang Q, Schurgers LJ, Uitto J. Pseudoxanthoma elasticum: Reduced gamma-glutamyl carboxylation of matrix gla protein in a mouse model (Abcc6$^{-/-}$). Biochem Biophys Res Commun. 2007; 364:208-213.
36. Gheduzzi D, Boraldi F, Annovi G, DeVincenzi CP, Schurgers LJ, Vermeer C, Quaglino D, Ronchetti IP. Matrix Gla protein is involved in elastic fiber calcification in the dermis of pseudoxanthoma elasticum patients. Lab Invest. 2007; 87:998-1008.
37. Vanakker OM, Martin L, Schurgers LJ, Quaglino D, Costrop L, Vermeer C, Pasquali-Ronchetti I, Coucke PJ, De Paepe A. Low serum vitamin K in PXE results in defective carboxylation of mineralization inhibitors similar to the GGCX mutations in the PXE-like syndrome. Lab Invest. 2010; 90:895-905.
38. Jiang Q, Li Q, Grand-Pierre AE, Schurgers LJ, Uitto J. Administration of vitamin K does not counteract the ectopic mineralization of connective tissues in Abcc6 $^{(-/-)}$ mice, a model for pseudoxanthoma elasticum. Cell Cycle. 2011; 10:701-707.
39. Gorgels TG, Waarsing JH, Herfs M, Versteeg D, Schoensiegel F, Sato T, Schlingemann RO, Ivandic B, Vermeer C, Schurgers LJ, Bergen AA. Vitamin K supplementation increases vitamin K tissue levels but fails to counteract ectopic calcification in a mouse model for pseudoxanthoma elasticum. J Mol Med. 2011; 89:1125-1135.
40. Rutsch F, Ruf N, Vaingankar S, *et al*. Mutations in *ENPP1* are associated with 'idiopathic' infantile arterial calcification. Nat Genet. 2003; 34:379-381.
41. Li Q, Schumacher W, Jablonski D, Siegel D, Uitto J. Cutaneous features of pseudoxanthoma elasticum in a patient with generalized arterial calcification of infancy due to a homozygous missense mutation in the *ENPP1* gene. Br J Dermatol. 2012; 166:1107-1111.
42. Hendig D, Schulz V, Arndt M, Szliska C, Kleesiek K, Götting C. Role of serum fetuin-A, a major inhibitor of systemic calcification, in pseudoxanthoma elasticum. Clin Chem. 2006; 52:227-234.
43. Varadi A, Szabo Z, Pomozi V, de Boussac H, Fülöp K, Arányi T. *ABCC6* as a target in pseudoxanthoma elasticum. Curr Drug Targets. 2011; 12:671-682.
44. Hu X, Plomp AS, van Soest S, Wijnholds J, de Jong PT, Bergen AA. Pseudoxanthoma elasticum: A clinical, histopathological, and molecular update. Surv Ophthalmol. 2003; 48:424-438.
45. Naouri M, Boisseau C, Bonicel P, Daudon P, Bonneau D, Chassaing N, Martin L. Manifestations of pseudoxanthoma elasticum in childhood. Br J Dermatol. 2009; 161:635-639.
46. Charbel Issa P, Finger RP, Gotting C, Hendig D, Holz FG, Scholl HP. Centrifugal fundus abnormalities in pseudoxanthoma elasticum. Ophthalmology. 2010; 117:1406-1414.
47. Gass JD. "Comet" lesion: An ocular sign of pseudoxanthoma elasticum. Retina. 2003; 23:729-730.
48. De Zaeytijd J, Vanakker OM, Coucke PJ, De Paepe A, De Laey JJ, Leroy BP. Added value of infrared, red-free and autofluorescence fundus imaging in pseudoxanthoma elasticum. Br J Ophthalmol. 2010; 94:479-486.
49. Georgalas I, Tservakis I, Papaconstaninou D, Kardara M, Koutsandrea C, Ladas I. Pseudoxanthoma elasticum, ocular manifestations, complications and treatment. Clin Exp Optom. 2011; 94:169-180.
50. Gliem M, Finger RP, Fimmers R, Brinkmann CK, Holz FG, Charbel Issa P. Treatment of choroidal neovascularization due to angioid streaks: A comprehensive review. Retina. 2013; 33:1300-1314.
51. Finger RP, Charbel Issa P, Ladewig M, Götting C, Holz FG, Scholl HP. Fundus autofluorescence in Pseudoxanthoma elasticum. Retina. 2009; 29:1496-1505.
52. Campanati A, Giuliodori K, Ganzetti G, Liberati G, Offidani AM. A patient with psoriasis and vitiligo treated with etanercept. Am J Clin Dermatol. 2010; 11(Suppl 1):46-48.
53. Ganzetti G, Campanati A, Offidani A. Alopecia Areata: A possible extraintestinal manifestation of Crohn's disease. J Crohns Colitis. 2012; 6:962-963.
54. Jiang Q, Endo M, Dibra F, Wang K, Uitto J. Pseudoxanthoma elasticum is a metabolic disease. J Invest Dermatol. 2009; 129:348-354.
55. Braun SA, Finis D, Helbig D. Pseudoxanthoma elasticum. More than a skin problem. Hautarzt. 2013; 64:222, 224-225. (in German)
56. Campens L, Vanakker OM, Trachet B, Segers P, Leroy BP, De Zaeytijd J, Voet D, De Paepe A, De Backer T, De Backer J. Characterization of cardiovascular involvement in pseudoxanthoma elasticum families. Arterioscler Thromb Vasc Biol. 2013; 33:2646-2652.
57. Kuzaj P, Kuhn J, Michalek RD, Karoly ED, Faust I, Dabisch-Ruthe M, Knabbe C, Hendig D. *et al*. Large-scaled metabolic profiling of human dermal fibroblasts derived from pseudoxanthoma elasticum patients and healthy controls. PLoS One. 2014; 9:e108336.
58. Gheduzzi D, Sammarco R, Quaglino D, Bercovitch L, Terry S, Taylor W, Ronchetti IP. Extracutaneous ultrastructural alterations in pseudoxanthoma elasticum. Ultrastruct Pathol. 2003; 27:375-384.
59. Hosen MJ, Lamoen A, De Paepe A, Vanakker OM. Histopathology of pseudoxanthoma elasticum and related disorders: Histological hallmarks and diagnostic clues. Scientifica (Cairo). 2012; 2012:598262.
60. Maccari F, Gheduzzi D, Volpi N. Anomalous structure of urinary glycosaminoglycans in patients with pseudoxanthoma elasticum. Clin Chem. 2003; 49:380-388.
61. Walker ER, Frederickson RG, Mayes MD. The mineralization of elastic fibers and alterations of extracellular matrix in pseudoxanthoma elasticum. Ultrastructure, immunocytochemistry, and X-ray analysis. Arch Dermatol. 1989; 125:70-76.
62. Baccarani-Contri M, Vincenzi D, Cicchetti F, Mori G, Pasquali-Ronchetti I. Immunochemical identification of abnormal constituents in the dermis of pseudoxanthoma elasticum patients. Eur J Histochem. 1994; 38:111-123.
63. Passi A, Albertini R, Baccarani Contri M, de Luca G, de Paepe A, Pallavicini G, Pasquali Ronchetti I, Tiozzo R. Proteoglycan alterations in skin fibroblast cultures from patients affected with pseudoxanthoma elasticum. Cell Biochem Funct. 1996; 14:111-120.
64. Limas C. Late onset focal dermal elastosis: A distinct clinicopathologic entity? Am J Dermatopathol. 1999; 21:381-383.
65. Le Corvaisier-Pieto C, Joly P, Thomine E, Lair G, Lauret

P. Generalized pseudoxanthoma elasticum combined with vitamin K dependent clotting factors deficiency. Ann Dermatol Venereol. 1996; 123:555-558. (in French)
66. Berkner KL. The vitamin K-dependent carboxylase. Annu Rev Nutr. 2005; 25:127-149.
67. Aessopos A, Farmakis D, Loukopoulos D. Elastic tissue abnormalities resembling pseudoxanthoma elasticum in beta thalassemia and the sickling syndromes. Blood. 2002; 99:30-35.
68. Song YC, Oh BH, Ko JH, Kim JY, Hwang YJ, Lee YW, Choe YB, Ahn KJ, Song KY. A case of fibroelastolytic papulosis on the neck of a young man. Ann Dermatol. 2011; 23:193-197.
69. Alves R, Ferreira L, Vale E, Bordalo O. Pseudoxanthoma elasticum papillary dermal elastolysis: A case report. Dermatol Res Pract. 2010; 2010.
70. Akagi A, Tajima S, Kawada A, Ishibashi A. Coexistence of pseudoxanthoma elasticum-like papillary dermal elastolysis and linear focal dermal elastosis. J Am Acad Dermatol. 2002; 47:S189-S192.
71. Kossard S. Pseudoxanthoma-like late-onset focal dermal elastosis. Australas J Dermatol. 2005; 46:47-50.
72. Camacho D, Machan S, Pielasinski U, Revelles JM, del Carmen Fariña M, Santonja C, Requena L. Familial acral localized late-onset focal dermal elastosis. Am J Dermatopathol. 2012; 34:310-314.
73. Kocaturk E, Kavala M, Zindanci I, Koç M. Periumbilical perforating pseudoxanthoma elasticum. Indian J Dermatol Venereol Leprol. 2009; 75:329.
74. Mehta RK, Burrows NP, Payne CM, Mendelsohn SS, Pope FM, Rytina E. Elastosis perforans serpiginosa and associated disorders. Clin Exp Dermatol. 2001; 26:521-524.
75. Choi Y, Jin SY, Lee JH, Kwon HB, Lee AY, Lee SH. Papular elastorrhexis: A case and differential diagnosis. Ann Dermatol. 2011; 23(Suppl 1):53-56.
76. Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: Part II. decreased elastic tissue. J Am Acad Dermatol. 2004; 51:165-185.
77. Patroi I, Annessi G, Girolomoni G. Mid-dermal elastolysis: A clinical, histologic, and immunohistochemical study of 11 patients. J Am Acad Dermatol. 2003; 48:846-851.
78. Viljoen DL, Bloch C, Beighton P. Plastic surgery in pseudoxanthoma elasticum: Experience in nine patients. Plast Reconstr Surg. 1990; 85:233-238.
79. Ng AB, O'Sullivan ST, Sharpe DT. Plastic surgery and pseudoxanthoma elasticum. Br J Plast Surg. 1999; 52:594-596.
80. Akali AU, Sharpe DT. Cervical midline Z-plasty revision surgery for pseudoxanthoma elasticum. Br J Plast Surg. 2003; 56:289-291.
81. Galadari H, Lebwohl M. Pseudoxanthoma elasticum: Temporary treatment of chin folds and lines with injectable collagen. J Am Acad Dermatol. 2003; 49:S265-S266.
82. Mallette LE, Mechanick JI. Heritable syndrome of pseudoxanthoma elasticum with abnormal phosphorus and vitamin D metabolism. Am J Med. 1987; 83:1157-1162.
83. Martinez-Hernandez A, Huffer WE, Neldner K, Gordon S, Reeve EB. Resolution and repair of elastic tissue calcification in pseudoxanthoma elasticum. Arch Pathol Lab Med. 1978; 102:303-305.
84. Yoo JY, Blum RR, Singer GK, Stern DK, Emanuel PO, Fuchs W, Phelps RG, Terry SF, Lebwohl MG. A randomized controlled trial of oral phosphate binders in the treatment of pseudoxanthoma elasticum. J Am Acad Dermatol. 2011; 65:341-348.
85. Jiang Q, Dibra F, Lee MD, Oldenburg R, Uitto J. Overexpression of fetuin-a counteracts ectopic mineralization in a mouse model of pseudoxanthoma elasticum (abcc6$^{(-/-)}$). J Invest Dermatol. 2010; 130:1288-1296.
86. LaRusso J, Li Q, Jiang Q, Uitto J. Elevated dietary magnesium prevents connective tissue mineralization in a mouse model of pseudoxanthoma elasticum (Abcc6$^{(-/-)}$). J Invest Dermatol. 2009; 129:1388-1394.
87. Jiang Q, Uitto J. Restricting dietary magnesium accelerates ectopic connective tissue mineralization in a mouse model of pseudoxanthoma elasticum (Abcc6$^{(-/-)}$). Exp Dermatol. 2012; 21:694-699.
88. Kupetsky EA, Rincon F, Uitto J. Rate of change of carotid intima-media thickness with magnesium administration in Abcc6$^{(-)/(-)}$ mice. Clin Transl Sci. 2013; 6:485-486.
89. Bercovitch L, Martin L, Chassaing N, Hefferon TW, Bessis D, Vanakker O, Terry SF. Acquired pseudoxanthoma elasticum presenting after liver transplantation. J Am Acad Dermatol. 2011; 64:873-878.
90. Zhou Y, Jiang Q, Takahagi S, Shao C, Uitto J. Premature termination codon read-through in the *ABCC6* gene: Potential treatment for pseudoxanthoma elasticum. J Invest Dermatol. 2013; 133:2672-2677.
91. Pomozi V, Brampton C, Fulop K, Chen LH, Apana A, Li Q, Uitto J, Le Saux O, Váradi A. Analysis of pseudoxanthoma elasticum-causing missense mutants of **ABCC6** *in vivo*; pharmacological correction of the mislocalized proteins. J Invest Dermatol. 2014; 134:946-953.
92. Jansen RS, Kucukosmanoglu A, de Haas M, Sapthu S, Otero JA, Hegman IE, Bergen AA, Gorgels TG, Borst P, van de Wetering K. *ABCC6* prevents ectopic mineralization seen in pseudoxanthoma elasticum by inducing cellular nucleotide release. Proc Natl Acad Sci U S A. 2013; 110:20206-20211.
93. Uitto J, Jiang Q, Varadi A, Bercovitch LG, Terry SF. Pseudoxanthoma elasticum: Diagnostic features, classification, and treatment options. Expert Opin Orphan Drugs 2014; 2:567-577.
94. Li Q, Uitto J. Heritable ectopic mineralization disorders: The paradigm of pseudoxanthoma elasticum. J Invest Dermatol. 2012; 132:E15-E19.

(Received April 16, 2015; Revised June 9, 2015; Accepted June 10, 2015)