PXE Guide

Primary Care

PXE Guide for Clinicians: Primary Care

Pseudoxanthoma elasticum (PXE) is an autosomal recessive systemic disorder characterized by ectopic mineralization of elastic tissue, most prominently affecting the skin, retina, and arteries. PXE is caused by pathogenic variants in ABCC6. Loss of ABCC6 function is associated with reduced circulating inorganic pyrophosphate (PPi), an endogenous inhibitor of ectopic mineralization.

The primary care clinician may be the first to suspect PXE because of skin findings, ocular findings reported by an ophthalmologist, vascular symptoms, family history, or genetic testing performed for another reason. Primary care also plays an important role in coordinating specialty care, monitoring general vascular risk, reviewing medications, and helping the patient and family interpret the condition realistically.

PXE is highly variable. Experience with one individual affected by PXE does not predict the course in another person, even within the same family.

Incidence

PXE is rare. Published estimates generally range from approximately 1 in 25,000 to 1 in 100,000 individuals. The true incidence is uncertain because mildly affected individuals and those with atypical presentations may escape diagnosis. PXE has been reported in all races and ethnicities and is reported more often in women than in men; the reason for this difference is unclear.

Skin manifestations

The characteristic cutaneous lesion is a small, yellowish or flesh-colored papule, often 2–5 mm in diameter, typically irregular or rhomboid in shape. Papules may occur in groups or coalesce into larger plaques. Lesions are usually asymptomatic and tend to be distributed symmetrically in flexural areas.

Common sites include:

- Lateral and posterior neck
- Axillae
- Antecubital fossae
- Groin
- Popliteal fossae

Less common sites include the periumbilical area and oral or anogenital mucosa. Oral lesions on the inner lower lip may resemble Fordyce spots.

Skin findings often begin in childhood or adolescence and progress slowly and unpredictably. In later-stage PXE, redundant or lax folds may occur, particularly on the neck, axillae, groin, or face. Skin involvement varies widely; some individuals have minimal visible lesions.

The differential diagnosis includes solar elastosis and fibroelastolytic papulosis, including PXE-like papillary dermal elastolysis, which can resemble PXE clinically.

Skin biopsy can support or confirm the diagnosis when it demonstrates fragmented, clumped, mineralized elastic fibers in the mid and lower dermis. Special stains for elastic tissue and mineralization, including von Kossa staining, may be useful. The highest diagnostic yield is usually from a primary papule. If no obvious papule is present, biopsy of commonly involved sites such as the neck, axilla, or antecubital fossa may be considered.

Although skin findings are often the most recognizable manifestation of PXE, ocular and vascular manifestations are the main causes of morbidity.

Retinal disease

The earliest ocular manifestation of PXE is often peau d'orange, a subtle mottled appearance of the fundus that may be seen in childhood or adolescence. The characteristic retinal finding is angioid streaks, which are irregular gray, brown, or reddish lines that radiate from or encircle the optic disc. Angioid streaks correspond to breaks in Bruch's membrane, an elastin-rich layer beneath the retinal pigment epithelium.

Peau d'orange and angioid streaks do not usually affect visual acuity by themselves. Visual morbidity occurs primarily when choroidal neovascularization develops through breaks in Bruch's membrane, leading to leakage, hemorrhage, scarring, and central visual loss when the macula or fovea is involved. Peripheral vision is usually preserved.

Anti-VEGF therapy is widely used for PXE-associated choroidal neovascularization and has substantially improved visual prognosis compared with older treatment approaches. Agents used by retina specialists may include aflibercept, ranibizumab, bevacizumab,

faricimab, brolucizumab, and related biosimilars. Choice of agent and treatment interval should be determined by the treating retina specialist. Since no treatments are officially approved for PXE, the ophthalmologist must classify it (ICD-10) as macular degeneration.

Laser photocoagulation and photodynamic therapy were previously used to treat leaking or bleeding vessels in PXE but are no longer typical first-line approaches.

Geographic atrophy or atrophic macular changes may occur in PXE. Treatments approved for geographic atrophy in age-related macular degeneration should not be assumed to have the same role in PXE unless the treating retina specialist believes there is an appropriate indication. PXE is not AMD, although some retinal treatments developed for AMD may be clinically relevant when similar complications occur.

Vascular disease

PXE vascular involvement primarily affects peripheral, medium-sized arteries. Peripheral arteries are arteries outside the heart and brain, especially those supplying the arms and legs.

The vascular pathology in PXE involves mineralization of abnormal elastic fibers in the internal elastic lamina and media of medium-sized arteries. This can contribute to arterial stiffening, stenosis, diminished peripheral pulses, and intermittent claudication. The process may resemble atherosclerotic disease clinically but is not identical to ordinary cholesterol-driven atherosclerosis.

Common vascular manifestations include:

- Diminished peripheral pulses, including in the upper extremities
- Intermittent claudication
- Reduced exercise tolerance due to limb symptoms

Less commonly, individuals may have angina or symptoms suggestive of intestinal ischemia. Severe peripheral vascular disease may occur but is not universal.

Hypertension, dyslipidemia, diabetes, smoking, and other standard cardiovascular risk factors should be managed carefully, because they may add risk in a patient whose arteries may already be affected by PXE.

Gastrointestinal bleeding

Upper gastrointestinal bleeding is an uncommon but important PXE complication. It may be dramatic and can occasionally be an early or presenting manifestation. Bleeding is usually gastric but may occur elsewhere in the gastrointestinal tract. The mechanism is incompletely understood. Endoscopy may show mucosal findings resembling PXE

elsewhere, and histology of involved vessels may resemble that of other PXE-affected arteries.

Patients with PXE should be instructed to seek urgent care for hematemesis, melena, unexplained anemia, syncope, severe weakness, or sudden dizziness. Clinicians should consider PXE as a possible contributor, while still performing a standard evaluation for common causes of gastrointestinal bleeding, including ulcer disease, gastritis, medication-related bleeding, malignancy, and other usual etiologies.

Aspirin and non-steroidal anti-inflammatory drugs, including ibuprofen and naproxen, may increase gastrointestinal bleeding risk. They should be avoided for routine or chronic use when safer alternatives are available. However, antiplatelet or anticoagulant therapy may be clinically necessary for stroke prevention, coronary artery disease, venous thromboembolism, atrial fibrillation, or other indications. In those cases, risks and benefits should be individualized. Patients should not be instructed to stop prescribed antiplatelet or anticoagulant therapy without medical supervision.

Genetics

PXE is autosomal recessive. Most affected individuals have pathogenic or likely pathogenic variants in both copies of *ABCC6*. There are no confirmed autosomal dominant cases of PXE.

Carrier frequency may be higher than historically assumed, and some heterozygous carriers may have mild or subclinical findings. However, carriers do not have PXE.

Genotype does not predict clinical severity. PXE shows variable expressivity, and clinical findings may differ substantially among individuals with the same variants, including siblings.

ABCC6 is located on chromosome 16p13.1 and encodes the *ABCC6* membrane transporter. Loss of *ABCC6* function is associated with reduced circulating inorganic pyrophosphate (PPi), which contributes to abnormal mineralization. The complete biology of *ABCC6* and its downstream effects continues to be studied.

Genetic testing is widely available and may be useful for:

- Confirming an uncertain clinical diagnosis
- Evaluating siblings or other at-risk relatives
- Reproductive counseling
- Interpreting genetic findings discovered incidentally
- Distinguishing PXE from phenocopies or related ectopic mineralization disorders

A variant of unknown significance should not be treated as diagnostic without supporting clinical findings.

Genetic findings in infants and young children

Variants in *ABCC6* are sometimes found when newborns and children undergo whole-genome or exome sequencing for a life-threatening illness. Typical PXE does not explain severe newborn illness, developmental delay, or debilitating early-childhood symptoms. If an infant or young child is found to have biallelic pathogenic *ABCC6* variants in the setting of arterial calcification, cardiac compromise, hypertension, or serious systemic symptoms, generalized arterial calcification of infancy (GACI) should be considered. GACI can be caused by pathogenic variants in *ABCC6* or *ENPP1* and requires urgent specialist evaluation. Even if the newborn or child has PXE, which can be difficult to diagnose definitively because the key signs in the skin and eyes often appear later, a child undergoing cWGS or cWES for symptoms likely has a more serious illness to consider.

Workup of an individual with suspected or confirmed PXE

Initial evaluation should include:

- Detailed personal history, including age of onset and progression of skin, ocular, vascular, gastrointestinal, renal, and reproductive history
- Family history, including consanguinity if relevant, siblings with suggestive findings, unexplained vascular disease, and known abcc6 variants
- Skin examination with attention to the neck and flexural creases
- Review of prior dermatopathology, ophthalmology reports, genetic testing, and vascular studies when available
- Confirmation by skin biopsy when diagnosis is uncertain and clinically appropriate
- Genetic counseling and abcc6 testing when useful for diagnosis or family planning
- Evaluation of siblings when feasible and clinically appropriate

Ophthalmologic evaluation should include:

- Dilated examination by an ophthalmologist, preferably with retina expertise
- Assessment for peau d'orange, angioid streaks, choroidal neovascularization, and macular changes
- OCT and retinal imaging as clinically indicated
- Fluorescein angiography or other angiographic imaging when cnv, leakage, or bleeding is suspected
- Patient instruction in Amsler grid use or equivalent home monitoring when appropriate

Vascular evaluation is unnecessary unless the patient is presenting with symptoms. If so, it should be guided by symptoms and examination findings. It may include:

- Pulse examination in upper and lower extremities
- Blood pressure monitoring
- Lipid and diabetes screening according to standard guidelines
- Ankle-brachial index or Doppler studies if claudication, diminished pulses, non-healing wounds, or other signs of peripheral arterial disease are present
- Referral to vascular medicine, cardiology, or vascular surgery when clinically indicated

Routine invasive or extensive vascular testing is not necessary for every asymptomatic patient.

Management

There is no approved disease-modifying therapy for PXE. Management should focus on education, genetic counseling, monitoring for complications, treating complications when they arise, and reducing modifiable vascular risk factors.

Care may involve dermatology, ophthalmology or retina specialists, primary care, cardiology, vascular medicine, vascular surgery, gastroenterology, plastic surgery, genetics, nutrition, and low vision services. Not every patient needs every specialist. Referrals should be guided by symptoms.

For all individuals, regular retinal care is the most important specialty follow-up.

Ophthalmology follow-up

Regular follow-up with an ophthalmologist or retina specialist is recommended. Patients should be instructed to report new central visual distortion, blurred central vision, missing areas, or sudden visual changes promptly. Early treatment of choroidal neovascularization offers the best chance of preserving central vision.

Protective eyewear is reasonable for sports or activities that carry a risk of direct eye trauma. However, patients should not be told to avoid these sports, precautions can protect them and they can continue to be active.

Exercise and activity

Patients with PXE should be advised to engage in exercise. Regular physical activity supports vascular health, mobility, strength, and general health.

Weight lifting and resistance training are not automatically contraindicated. The main caution is to avoid unnecessary extremes of straining and breath-holding, especially during

heavy lifting. Breath-holding with straining is the Valsalva maneuver and may be relevant to ocular risk in some patients. Patients should be counseled to breathe steadily, use appropriate loads, progress gradually, and seek individualized advice if they have active eye disease, recent retinal bleeding, significant vascular symptoms, or other medical concerns.

Kidney stones

The prevalence of kidney stones in PXE remains uncertain. One survey-based study of 563 participants aged 20 years and older reported a history of kidney stones in 23.4% of individuals with PXE, compared with 9.2% in the general population. However, a CT-based study did not identify a difference in kidney stone prevalence between individuals with PXE and controls.

Clinicians should ask about a history of nephrolithiasis and evaluate or refer according to standard clinical indications.

Vascular risk reduction

General vascular risk reduction is appropriate. This includes:

- Smoking avoidance and cessation support
- Management of hypertension
- Management of dyslipidemia
- Diabetes prevention and treatment when relevant
- Regular physical activity
- Nutrition that supports cardiovascular health
- Maintaining a weight that supports mobility, blood pressure, and overall health

Avoid language that implies a specific appearance or relies only on BMI. Vascular risk should be assessed using the full clinical picture.

Pharmacologic treatment for claudication or peripheral artery disease may be appropriate in selected individuals and should follow usual clinical practice, with attention to PXE-specific bleeding considerations.

Pregnancy

Pregnancy is not contraindicated in women with PXE. In a questionnaire-based study of 407 women with PXE, 306 respondents reported 795 pregnancies; 83% resulted in live births and 1% in stillbirth. Hypertension occurred in 10% of pregnancies, which is broadly comparable to rates reported in the general obstetric population. Gastric bleeding and retinal complications each occurred in fewer than 1% of pregnancies, substantially lower

than suggested by earlier case-based literature. Worsening of skin manifestations was reported in 12% of pregnancies.

Because the PXE data were questionnaire-based and collected over many years, direct comparison with contemporary population-based obstetric statistics should be made with caution. Overall, however, these data do not support advising women with PXE to avoid pregnancy or to have cesarian sections. Obstetric care should follow standard indications, with attention to blood pressure control and prompt evaluation of gastrointestinal bleeding symptoms or new visual changes.

Breast calcifications

Women with PXE may have mammographic findings related to mineralization of skin, vascular, and soft-tissue elastic fibers. In a systematic study comparing mammograms from 51 women with confirmed PXE with those from 109 women without PXE, women with PXE had significantly higher rates of skin thickening, vascular calcification, and breast microcalcifications. Breast density, masses, macrocalcifications, and skin calcification did not differ significantly between the PXE and control groups.

Breast microcalcifications and vascular calcifications can occur in the general population and are not, by themselves, diagnostic of PXE. However, the combination of breast microcalcifications and vascular calcifications, particularly when accompanied by skin thickening or axillary skin calcification, should raise consideration of PXE in the appropriate clinical context.

Available pathology from women with PXE showed calcification involving dermal elastic fibers, subcutaneous arteries, and elastic fibers in the deep fascia and interlobular septae of fat adjacent to breast parenchyma. The majority of breast calcifications observed in PXE appear to be benign.

Radiologists should be informed when a patient has PXE so that mammographic calcifications can be interpreted in context. PXE does not eliminate the need for standard breast cancer screening or usual diagnostic evaluation of suspicious findings. Breast findings should be managed according to standard radiologic and clinical criteria, with awareness that benign PXE-related calcifications may be present.

Testicular Microlithiasis

Testicular microlithiasis has been reported in males with PXE. In a small study of 12 males with confirmed PXE who underwent testicular ultrasonography, 11 had classic testicular microlithiasis, and one had limited microlithiasis. No participant had evidence of testicular malignancy on ultrasound or physical examination. Histopathologic examination in one autopsy case showed intratubular microlithiasis, without the arterial elastic fiber calcification typical of cutaneous PXE.

These findings suggest an association between PXE and testicular microlithiasis, although the study size was small and the clinical significance remains uncertain. Available data do not establish that PXE-associated testicular microlithiasis increases testicular cancer risk.

Clinicians should interpret testicular ultrasound findings in the context of the PXE diagnosis and manage patients according to standard urologic guidance. PXE should not be assumed to explain a testicular mass, pain, asymmetry, or other concerning finding; these should receive usual clinical evaluation.

Calcium intake

Restricting calcium intake is not recommended as a treatment for PXE. Although early observations raised questions about the relationship between calcium intake and disease severity, this has not been debunked. Published papers recommended reduced calcium. Calcium restriction can be harmful and may increase risk of osteopenia or osteoporosis.

Patients should generally meet age-appropriate recommended dietary calcium intake. Supplements should be considered only when dietary intake is inadequate or when clinically indicated, such as for osteopenia, osteoporosis, or other relevant conditions.

Role of PXE International

PXE International conducts research, maintains educational resources, registry infrastructure, and research programs for individuals and families affected by PXE. Patients are encouraged to register with PXE International to receive updated information and learn about research opportunities.

PXE International's medical advisors may serve as a resource for clinicians treating individuals with PXE.

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