PXE and Dermatology

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Pseudoxanthoma elasticum (PXE) is a heterogeneous inherited disorder of connective tissue. Its hallmark is dystrophic mineralization of elastic tissue of the skin, retina, and arteries. Because the cutaneous findings are often prominent and visible, the dermatologist is frequently the specialist who makes the initial diagnosis and coordinates the care of the individual affected by PXE.

Skin manifestations

The *primary lesion* of PXE is a small 2-5 mm yellowish or yellow-orange papule, irregular or rhomboid in shape (hence the term *pseudoxanthoma*), which may form groups or coalesce into larger plaques. The lesions are *asymptomatic* and tend to be distributed symmetrically on flexural areas progressing downward from the neck to the axillae and antecubital fossae, and later to the groin and popliteal fossa. Less common areas of involvement include the periumbilical area, oral and anogenital mucosa. Oral lesions, seen on the inner aspect of the lower lip, resemble Fordyce spots.

The lesions may give the affected skin a "plucked chicken" or "cobblestone" appearance. The lesions may cause the skin of the neck to appear unwashed. Solar elastosis must be considered in the differential diagnosis. Acneiform, scarring, and perforating lesions have been observed within plaques of PXE. The perforating lesions resemble elastosis perforans serpiginosa (EPS), but the eliminated material in PXE is calcified, unlike EPS.

The skin lesions develop during childhood or adolescence, and progress slowly and unpredictably with age, spreading from the neck downward. The neck, axillae, groin, or face may sometimes manifest lax, redundant folds of skin in late stage PXE.

Skin biopsy of lesional (and sometimes non-lesional) skin confirms the diagnosis if it shows calcification of fragmented, clumped elastic fibers in the mid- and lower dermis.. The highest yield is from biopsy of a primary lesion (papule). In the absence of primary lesions, punch biopsy of neck, axillary and/or antecubital fossa is recommended.

The skin lesions are asymptomatic. Affected individuals with unsightly redundant folds can undergo cosmetic surgical correction, usually with uncomplicated wound healing, although healing may sometimes be poor or accompanied by calcium extrusion through the wound.

Although skin manifestations are most characteristic of PXE, the ocular and cardiovascular manifestations are responsible for the morbidity of the disease. Indeed, in some cases the skin lesions are not visible.

Retinal Disease

The earliest, and often subtle, manifestation of PXE in the retina is peau d'orange, a diffuse yellowish mottling of the fundus usually seen in the first two decades of life. The characteristic retinal lesion is the angioid streak, seen in most adult affected individuals, and seen sometimes in children. Angioid streaks are gray to brown or dark red, spoke-like bands radiating out from the optic disc or encircling the disc with peripapillary streaks. Angioid streaks correspond to breaks in Bruch's membrane, an elastin rich layer of the choroid. Neovascular capillary nets can grow through these breaks, leading to hemorrhage. These can lead to central visual loss (not true blindness), if they occur in the macula or fovea. Laser photocoagulation may be effective in obliterating neovascularization, but it often recurs, and disciform scarring can further compromise central vision.

Vascular Disease

The basic vascular pathology in PXE is dystrophic calcification of the elastic tissue of the media. Subsequent intimal elastic calcification and atherosclerosis and intimal fibrous proliferation leading to vascular occlusion or fragility may occur. The most common manifestations of arterial disease in PXE are diminished peripheral pulses and intermittent claudication. Angina and symptoms of intestinal ischemia may occur relatively early in life. Hypertension may be more common among affected individuals with PXE. If present, this increases the risk of vascular complication in the individuals affected by PXE, and needs to be well controlled. GI bleeding, usually gastric, may be an early manifestation and even the presenting sign of PXE. The mechanism is unknown, but gastroscopy shows gastric mucosal changes resembling mucosal PXE elsewhere (yellowish papules), and the histology of the gastric vessels resembles that of other arteries affected by PXE.

Genetics of PXE

While current research has suggested that PXE is inherited as an autosomal recessive disorder, the carrier frequency may be higher than previously thought and some recessive carriers may have mild subclinical manifestations on biopsy. Clinical expression is not helpful in predicting the severity for other family members. PXE has variable expressivity and environmental influences may modify the clinical expression. The gene is on the short arm of chromosome 16 (16p13.1) and codes for the membrane transport protein, ABCC6/MRP6. Mutational analysis is in progress, as are functional studies of the gene.

Workup of the Affected Individual

General workup of the individual affected by PXE should include:

- A history detailing onset, symptoms of vascular and ocular disease, and family history.
- Examination of the skin and cardiovascular system, including peripheral pulses.
- Confirmation of diagnosis by skin biopsy with appropriate calcium stains.
- Laboratory evaluation of lipids.
- Examination of first-degree relatives.

Ophthalmologic consultation should include:

- Recording visual acuity.

- Dilated indirect ophthalmoscopic exam.
- Amsler grid monitoring of central visual fields and fluorescein angiogram if signs or symptoms warrant.

Cardiovascular consultation should include:

- Non-invasive studies of the peripheral vasculature (Doppler ankle-brachial ratios).
- Baseline stress test and sonogram of heart valves.
- EKG's (if symptoms or clinical findings warrant).

Management of Individuals Affected by PXE

As are most inherited diseases, PXE is incurable. Management should focus on education of the affected individual, genetic counseling, monitoring and treatment of complications, and dietary and lifestyle modifications to delay or possibly prevent complications. This may involve a team approach including dermatologist, primary care physician, ophthalmologist, cardiologist, vascular surgeon, plastic surgeon, genetic counselor, nutritionist and support groups. Support groups are of tremendous benefit in helping affected individuals cope with the disorder.

The affected individual (or parent) needs to be educated in understandable terms regarding the various manifestations of the disease and the prognosis (which is not as dire as some affected individuals are led to believe). Genetic counseling is limited to risk assessment until genetic testing is available. Regular ophthalmologic examination by a physician with expertise in retinal disease is essential, and affected individuals should learn to use the Amsler grid to monitor for central visual disturbances. Regular physical examinations with specific attention to the gastrointestinal and cardiovascular systems are essential. Lipid levels should be monitored periodically.

Surgical intervention may be indicated for gastrointestinal bleeding, severe peripheral vascular disease (if correctable), and the improvement of cosmetic deformities of the face, neck, axilla, and groin. Wound healing seems to be uncomplicated in PXE, although cosmetic acceptability is less predictable.

Weight control, avoidance of smoking, and aggressive management of hypertension and lipid disorders are all essential in delaying or reducing the severity of vascular complications. Pentoxifylline may be of value in managing claudication. Aspirin and other non-steroidal anti-inflammatory medications should be avoided due to the risk of gastrointestinal hemorrhage.

Most women with PXE have normal pregnancies, however gastric or uterine bleeding may rarely complicate them. Fetal complications due to impaired uteroplacental blood flow do not appear to be a problem. There is no basis for women affected by PXE to avoid becoming pregnant. There are at present no tests for prenatal diagnosis of this disease. With characterization of the defective gene and gene products, such tests may eventually become available.

It is recommended that one follow the Recommended Daily Allowance for intake of calcium and all vitamins and minerals.

PXE International, Inc. maintains a Blood and Tissue Bank and an international registry. Please encourage affected individuals to register with us.

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