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PAPER

PATHOLOGY/BIOLOGY

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Pseudoxanthoma Elasticum and Sudden Death

ABSTRACT: Pseudoxanthoma elasticum (PXE) is a generalized connective tissue disorder in which there is calcification of elastic fibers within arteries, eyes, and skin. Characteristic features include yellow-orange papular skin lesions, angioid streaks radiating out from the optic discs, and arterial calcification. The prevalence in the general population varies widely from 1/70,000 to 1/160,000. PXE has an autosomal recessive inheritance pattern and results from mutations in the ATP-binding cassette transporter C6 (*ABCC6*) that has been mapped to 16p13.1. Over 300 loss-of-function mutations have been identified. Individuals with PXE may come to forensic attention because of sudden death involving accelerated coronary atherosclerosis with acute myocardial ischemia, systemic hypertension, mitral valve prolapse, restrictive cardiomyopathy, gastrointestinal hemorrhage, and cerebral ischemia or hemorrhage. Because of the heritable nature of the disease, family counseling and screening are in order when previously unsuspected cases are encountered at autopsy.

KEYWORDS: forensic science, pseudoxanthoma elasticum, connective tissue disorder, sudden death, calcification, atherosclerosis, hemorrhage

Pseudoxanthoma elasticum (PXE) is a rare, inherited disorder with progressive degeneration and calcification of elastic fibers within the skin, cardiovascular system, and retinas (1,2). While the diagnosis is usually established during life, cases may present to medicolegal autopsy because of sudden death associated with premature coronary artery atherosclerosis or intracranial hemorrhage. It is important for forensic pathologists to be aware of the manifestations of this disorder so that appropriate tissue sampling can be performed and genetic counseling of family members initiated if indicated.

Incidence

The prevalence of PXE in the general population ranges between 1/70,000 and 1/160,000 (3), with a more recent estimate of one case in 25,000–100,000 in the United States (4). PXE has been reported in all races and shows a female predominance, with a male to female ratio of 1:2. The average age of onset is around 13 years, but it may manifest anywhere from infancy to old age (3,4).

Etiology

PXE is usually inherited in an autosomal recessive manner; however, examples of autosomal dominant and sporadic forms have been previously reported (5). Historically, it was suggested that there were two autosomal recessive and two autosomal dominant variants. Autosomal recessive type 1 features vascular and retinal complications, as well as flexural skin involvement, while type 2 has generalized skin involvement, but no systemic involvement. Autosomal dominant type 1 has severe vascular and retinal complications with early blindness and coronary artery disease, while type 2 has marfanoid features with only mild coronary and retinal artery disease. Marfanoid features include hyperextensible joints, blue sclera, and high arched palate (6–8).

Despite this characterization, there has been no molecular confirmation of autosomal dominant inheritance with an exclusively autosomal recessive inheritance pattern now appearing most likely (4,9–11). The clinical heterogeneity noted earlier is thought to result from the influence of epigenetic or environmental factors on the progression and penetrance of the disease (12).

PXE results from mutations in the ATP-binding cassette transporter C6 (*ABCC6*), which is also known as multi-drug resistance–associated protein 6 (*MRP6*) gene, mapped to chromosome 16p13.1 (13–17). The *ABC* (ATP-binding cassette) gene subfamily C also includes *ABCC1-5*, *CFTR*, *ABCC8,* and *ABCC9* (18). Over 300 loss-of-function mutations have been identified that include missense and nonsense mutations (1,9,19–22).

The precise function of *ABCC6* is currently unknown. *ABCC6* expression occurs in several types of affected tissues, including the skin, eyes, and arterial walls. However, it is most abundant in kidney and liver cells (which were not initially thought to be involved in PXE), suggesting that PXE might be a more generalized metabolic disorder of cellular transport that results in an accumulation of metabolites, leading to pathologic changes that manifest in elastic fibers over time (23,24). For example, knockout studies of the *ABCC6* genes in mice have been shown to cause calcification of elastic fibers in blood vessels and in Bruch's membrane in the eye (25).

It appears that a deficiency in *MRP6/ABCC6* leads to an alteration in inhibitors of calcification such as fetuin-A, resulting in

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progressive mineralization of elastic fibers (26). Mouse studies have also shown that the Sp1 transcription factor and the methylation of proximal *ABCC6* promoter synergistically regulate the basal transcriptional activity of the *ABCC6* gene (27). One hypothesis is that mutations in the *ABCC6* gene may reduce vitamin K-dependent gamma-glutamyl carboxylation of matrix gla protein resulting in mineralization of connective tissue (1). The resultant deposits contain calcium carbonate, calcium phosphate, and iron.

Clinical Manifestations

Cutaneous manifestations are very characteristic of the condition with lesions forming a spectrum from grouped small yellow papules (1–5 mm in diameter) to larger plaques. The lesions usually first appear in early childhood and are characteristically found on the lateral part of the neck, cubital and popliteal fossae, axilla, inguinal and periumbilical areas, and have been described as causing ''plucked chicken'' or ''cobblestone'' skin (3). The oral, vaginal, and rectal mucosa may also be involved. The lesions have a symmetrical distribution and more generalized cutaneous involvement has also been reported. Over time, the skin lesions become soft and lax, with sagging and hanging skin folds (28).

Ocular manifestations present as angioid streaks of the retina, appearing as irregular gray to reddish brown lines that extend outward from the optic disk (3). These result from calcification of elastic fibers in Bruch's membrane of the retina, with cracking and fissuring (4,23,28). The ocular lesions again show symmetrical involvement and usually present several years after the skin lesions. Angioid streaks are not pathognomonic of PXE and may be seen in several other conditions including Paget's disease (osteitis deformans), Marfan syndrome, Ehlers-Danlos syndrome, thalassemia, sickle cell hemoglobinopathies, and familial polyposis (4,8). Fibrovascular proliferation of the retina is a feature of PXE that may lead to hemorrhage with progressive loss of central vision (3,23). In addition, ''leopard spotting'' may be seen at the back of the retina with the onset of the skin lesions, prior to the development of angioid streaks (29).

Cardiovascular manifestations usually present last and are because of calcification of the elastica media and intima of blood vessels with subsequent narrowing and increasing fragility of the vasculature. This can cause diminished peripheral pulses (3), renal artery stenosis with subsequent hypertension, and coronary artery disease with angina pectoris and myocardial infarction. There is also a high prevalence of mitral valve prolapse in PXE (3,27,30). Two cases of mitral stenosis have been reported in association with PXE (31,32) and there have been cases of restrictive cardiomyopathy because of calcified endocardial bands (33).

Involvement of gastrointestinal vessels, particularly of the stomach, may lead to significant hemorrhage requiring treatment (3). Hemorrhage may also occur within the brain and urinary bladder, but this occurs less often (4). Skeletal muscle pain because of ischemia is a common symptom.

Diagnosis

The postmortem diagnosis of PXE can be made on biopsies from involved skin (34) (Fig. 1) showing basophilic elastic fibers with calcium deposition. These calcified and fragmented fibers may also split and unwind and are present in the middle and lower third of the dermis (3,29). The same calcific changes may also occur within the tunica media and tunica intima of blood vessels. Similar vascular findings may, however, be found in other entities such as idiopathic arterial calcification of infancy (35), and certain other inherited diseases will also cause accelerated atherogenesis (36). Von Kossa staining can be used to identify calcium deposits (Fig. 2), and Verhoef van Gieson or Orcein stains can be used to highlight elastic fibers. Electron microscopy may be possible depending on the state of preservation of the skin. Mineralization appears as a central core of electron dense material that may develop defects just before the fibers begin to fragment (3).

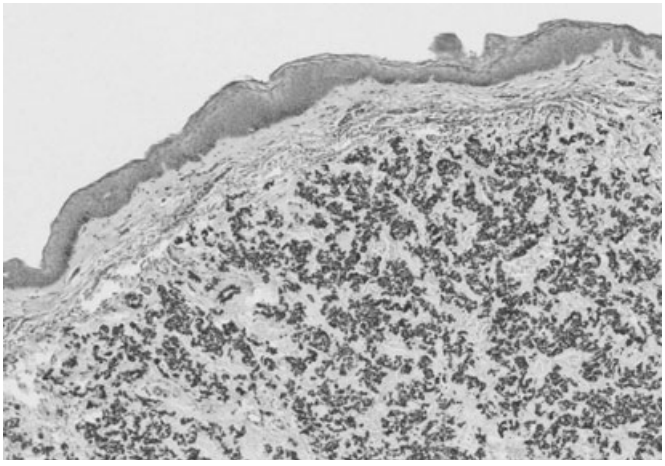

FIG. 1—*A section of a typical skin lesion in a case of PXE showing fragmented and calcified elastic fibers in the mid and deep reticular dermis (Von Kossa ×60).*

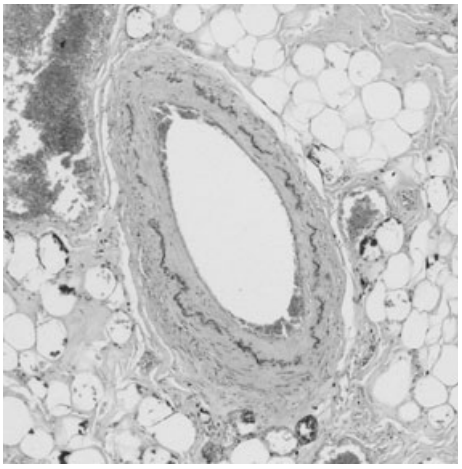

FIG. 2—*Concentric medial calcification of a small arteriole in PXE (Von Kossa ×60).*

Although ophthalmological examination during life may demonstrate angioid streaking within the retina, these can be very difficult to see after death. Radiographs may reveal arterial calcification, and computerized tomographic studies of the head may show aneurysms or intracerebral hemorrhage. At a consensus conference held at Jefferson Medical College in Philadelphia in June 1992, a list of major and minor criteria for the diagnosis of PXE was compiled (37) (Table 1).

Illustrative Case

A 59-year-old man with known PXE experienced central chest pain while lifting and moving heavy boxes. He had been experiencing similar chest pain for the preceding week, but it had been

TABLE 1—*Diagnostic criteria for pseudoxanthoma elasticum (37).*

Major criteria
Typical skin lesions (yellow ''cobblestone'' plaques in skin flexures)
Typical microscopic features in skin lesions
Typical ocular changes (angioid streaks, peau d'orange, or maculopathy) in adults >20 years
Minor criteria
Typical microscopic features in nonlesional skin
A family history of PXE in first-degree relatives

progressively worsening. On arrival to hospital, he suffered a cardiac arrest and was not able to be resuscitated. He had also a history of hypertension and noninsulin-dependent diabetes mellitus.

External examination revealed bilateral symmetrical coalescent yellow plaques forming large tan yellow areas with irregular surfaces on the skin of the abdominal wall, popliteal fossae, cubital fossae, and neck (Fig. 3). Because of postmortem clouding of the vitreous, angioid streaks could not be identified. The major findings on internal examination were of marked stenosis and calcification of all three of the major epicardial coronary arteries (the latter shown clearly on postmortem X-ray—Fig. 4) with no histologic evidence of acute or chronic ischemia. There was also marked atherosclerosis of the aorta and a 4 mm saccular aneurysm of the left middle cerebral artery. There was no evidence of intracerebral or gastrointestinal hemorrhage.

Histologic sections taken from the flexural skin lesions showed abnormal basophilic elastic fibers with a granular appearance filling the middle and deep reticular dermis (Fig. 5*A*). Calcium salts in the elastic fibers were confirmed by Von Kossa staining. Sections from small- to medium-sized arteries, as well as vasculature within representative organ sections from the gastrointestinal tract, showed fragmentation and calcification within the tunica media (Fig. 5*B*). Sections from coronary arteries and larger vessels confirmed the presence of marked atherosclerosis. Death was because of marked coronary artery atherosclerosis against a background of PXE.

PXE in Pregnancy

Pregnancy can accelerate the natural course of PXE and this is associated with an increased incidence of gastric hemorrhage.

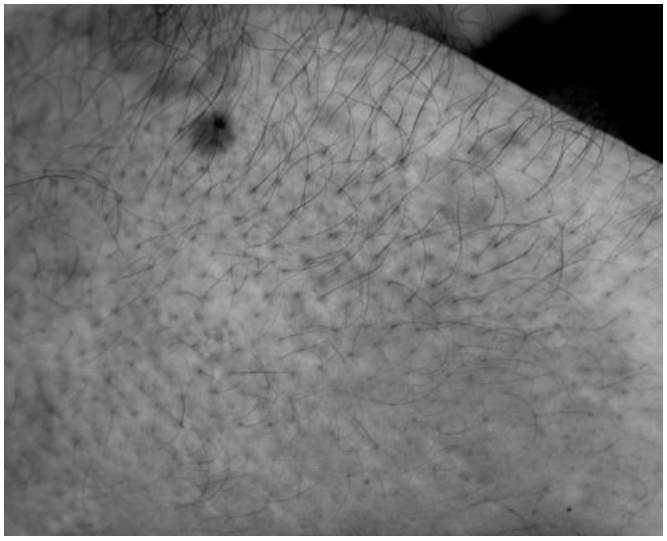

FIG. 3—*Typical ''cobblestone'' appearance of a skin plaque in PXE.*

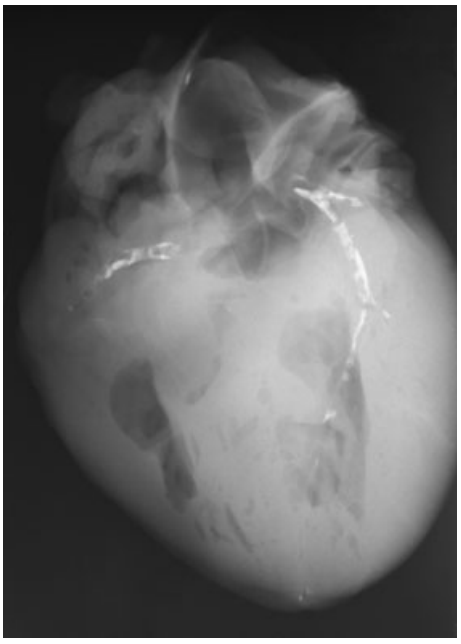

FIG. 4—*Calcification of all three major epicardial arteries in a postmortem radiograph of the heart.*

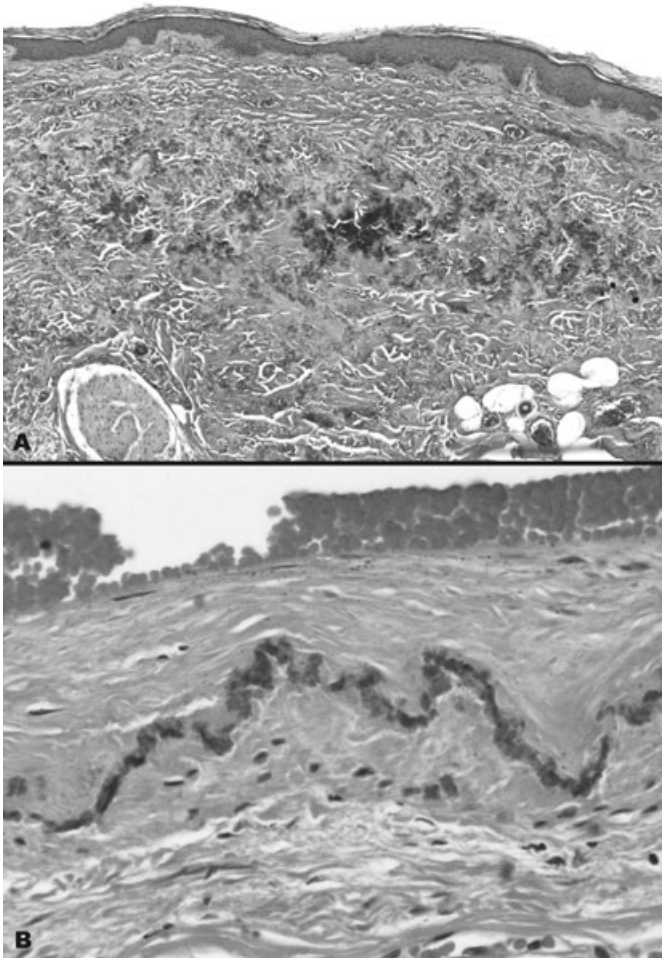

FIG. 5—*Calcification of the deep reticular dermis (Hematoxylin and eosin × 45) (A). Linear medial calcification of a small arteriole in PXE (Hematoxylin and eosin ×200) (B).*

Placental insufficiency because of an excessive degree of calcification may also lead to intrauterine growth retardation and increased risk of spontaneous abortion (38–40).

Mechanisms of Death

Sudden death may occur at all ages in adults with PXE often because of severe coronary artery atherosclerosis with acute myocardial ischemia. Affected individuals may also have systemic hypertension, gastrointestinal bleeding, and mitral valve prolapse, all of which may lead to sudden death. Cerebral ischemia or hemorrhage from vessel rupture may occur, and restrictive cardiomyopathy may lead to rapid clinical decline.

Management and Treatment

Recognition of this disease at autopsy may be essential for family follow-up for *ABCC6* mutations (3,30,41), and rapid polymerase chain reaction (PCR)–based diagnostic detection systems are currently under development that may assist with diagnosis (42). There is no definitive treatment for PXE at present.

Clinical management, therefore, involves the minimization of cardiac risk factors such as smoking and hyperlipidemia, avoiding drugs that can potentiate gastric hemorrhage or inhibit platelets, avoiding estrogens such as oral contraceptives or hormone replacement therapy, avoiding heavy lifting and straining that can potentiate retinal hemorrhages, and restricting dietary calcium (3,4,43).

Laser eye therapy can be sight sparing, and eye care and awareness of early signs of retinopathy are important (3). Coronary artery bypass grafting can be performed for patients with marked coronary artery disease (44,45). Pentoxifylline has been reported to successfully relieve ischemia-associated skeletal muscle pains (46).

Conclusion

PXE is a complex multisytem disorder with variable manifestations. Although often associated with a normal life span, extracutaneous involvement may result in an early death. The diagnosis can be made at autopsy if there has been histologic sampling of skin lesions and small- to medium-sized blood vessels. Given the autosomal recessive inheritance of cases, identification of previously undiagnosed cases at autopsy should initiate genetic counseling and screening of family members.

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