Cardiac Calcifications and Yellow Papules in a Young Man

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REPORT OF A CASE

A 29-year-old man was admitted to the hospital, complaining of progressive weakness, chills, headache, nausea, and vomiting. On admission, he was cyanotic and in moderate distress. Cardiac examination disclosed a laterally displaced apex beat, a powerful right ventricular parasternal lift, and a loud pulmonary component of the second heart sound. All peripheral arterial pulses were decreased. Other significant findings included asymptomatic yellow papules on the neck and lower abdomen (Fig 1) and abnormal findings on fundus examination (Fig 2). He had been well until three years previously, when he developed progressive dyspnea on exertion and paroxysmal nocturnal dyspnea.

Chest roentgenogram showed an enlarged cardiac silhouette with prominent central and pulmonary arteries, consistent with pulmonary arterial hypertension. Echocardiography showed enlargement of all chambers and extensive calcification of the left ventricular and left atrial endocardium. Computed tomographic scans confirmed the presence of calcifications in the endocardium (Fig 3, arrow). Cardiac catheterization showed severe pulmonary hypertension, depressed left ventricular function, low cardiac output, severe mitral and tricuspid regurgitation, and normal coronary arteries. The pulmonary arterial tree was free of occlusive lesions.

The patient was treated with nasal oxygen, intravenous fluids, digoxin, nitroglycerin, warfarin sodium, and antibiotics. Culture of a sputum sample yielded *Coccidiomycosis immitis*, for which treatment with intravenous amphotericin B was begun. A skin biopsy specimen was obtained (Figs 4 and 5).

What is your diagnosis?

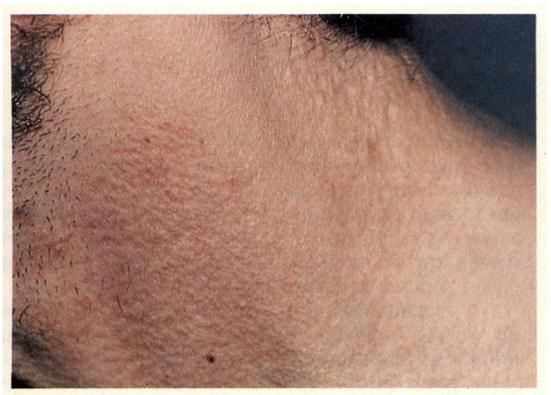

Figure 1.

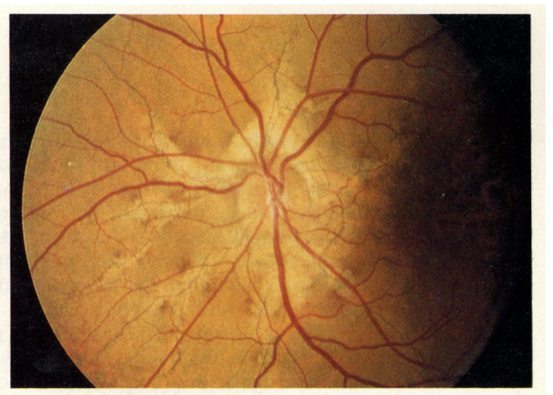

Figure 2.

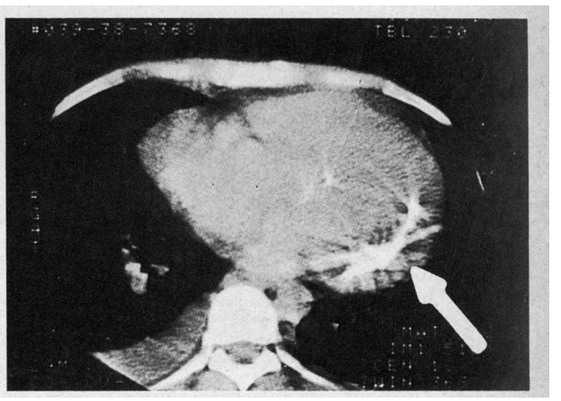

Figure 3.

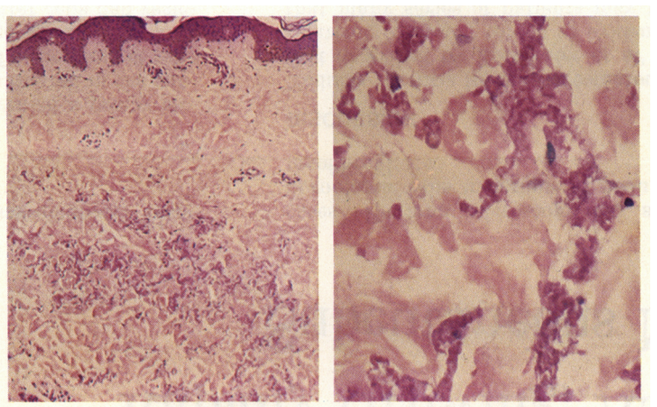

Figure 4.

Figure 5.

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DIAGNOSIS: Pseudoxanthoma elasticum (PXE).

DISCUSSION

The characteristic skin lesions of PXE were first described by Rigal in 1881 as atypical xanthomas.[1] Systemic manifestations were recognized by Balzer in 1984.[2] The disease was named *pseudoxanthoma elasticum* by Darier in 1896 because of the atypical elastic fibers.

Pseudoxanthoma elasticum is a rare, genetically inherited disorder with a reported prevalence of one in 160 000 to one in 1 000 000. In this disorder, abnormal elastic fibers that tend toward calcification and eventual degeneration occur in the skin, retina, and walls of arteries. Consequently, clinical lesions occur primarily in the skin, eyes, and cardiovascular system. There are four clinical variants, two exhibiting autosomal dominant (AD) and two exhibiting autosomal recessive (AR) modes of inheritance.[3] Type 1 (AD) manifests flexural skin lesions, severe cardiovascular disease, choroiditis, and myopia. Type 2 (AD) exhibits macular or focal skin lesions, hyperextensible skin, high arched palate, angioid streaks, blue sclerae, loose-jointedness, and mild or absent cardiovascular manifestations. Type 3 (AR), intermediate in severity between types 1 and 2, shows flexural skin lesions, mild cardiovascular disease, and mild localized retinopathy. Type 4 (AR), the rarest variant, exhibits generalized cutaneous laxity without cardiovascular, ocular, or joint manifestations.

Cutaneous lesions usually appear in the second decade of life and consist of 1- to 3-mm yellow papules that eventually coalesce to form plaques distributed in the flexural areas. These plaques may have a cobblestone or "chicken skin" appearance. The mucosa of the palate, lips, vagina, and rectum may be similarly affected. Golden yellow macules and patches also occur. With time, the skin becomes lax with poor elastic recoil. Histologic examination of skin biopsy specimens shows swollen, clumped elastic fibers, most prominent in the middle and lower dermis. The fibers stain well with the Verhoeff elastic stain (Fig 4, right) and the von Kossa stain for calcium. There is a striking contrast between the relatively normal elastic fibers in the superficial dermis and the fragmented, degenerated fibers in the deep dermis. The abnormal elastic fibers appear faintly basophilic in routine hematoxylin-eosin-stained sections owing to calcium imbibition.

The most characteristic and common ocular finding is angioid streaks, occurring in up to 85% of patients.[4] These are breaks in Bruch's membrane, an elastic layer between the retinal pigment epithelium and the choroid.[5] Angioid streaks appear as grayish red linear lesions both circumferential to and radiating from the optic disc. Hemorrhage is the primary life-threatening complication, affecting up to 15% of cases[4] and usually occurring before ocular and cutaneous changes. Gastrointestinal hemorrhage, particularly gastric, is the most common site. Other cardiovascular lesions can also occur at a relatively early age. Presentations include intermittent claudication, decreased pulsation in the peripheral arteries, hypertension, angina pectoris, heart failure, heart murmurs, and cerebral vascular abnormalities.

As our patient demonstrates, cardiac manifestations can be the presenting aspect of PXE. Our patient's cardiac lesions include endocardial calcification, four-chamber enlargement with reductions in global systolic function, severe diastolic dysfunction, and pulmonary hypertension. Biopsy specimens of endocardial lesions have shown striking elastotic thickening of the endocardium, accompanied by fragmentation, clumping, disorganization, and calcification of elastic fibers in the deeper endocardial layers.[2,6,7] Global myocardial dysfunction accompanied by a normal coronary angiogram has also been described in another case of PXE.[2] Severe pulmonary hypertension has not been a reported manifestation of PXE; its severity in our patient would be expected, however, in view of the endocardial calcification. Other reported cardiovascular changes include restrictive cardiomyopathy,[7] mitral valve prolapse,[8] and vascular changes indistinguishable from Mönckeberg's arteriosclerosis.[9]

Results of recent ultrastructural and histochemical studies confirm initial observations that the primary location of calcification in PXE is within elastic fibers. Electron microscopic scans[10] demonstrate that the altered elastic fibers can be divided into three parts: a normal-appearing slender part; a thickened, tortuous part covered with an amorphous substance; and a markedly damaged part where calcium is exposed to the surface of the fibers. Electron x-ray microanalysis confirmed the presence of calcium and phosphorus on the fibers. Surrounding the calcified elastic fibers is a granulofilamentous or thready material that consists in part of fibrinogen, collagenous protein, and glycoprotein.[11] The biochemical alterations in the disease may be associated with the abnormal presence of a zinc-dependent cysteine protease in PXE fibroblasts.[12]

At this time, there is no specific treatment for PXE.

References

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Clinicians, local and regional societies, and residents and fellows in dermatology are invited to submit quiz cases to this section. Cases should follow the established pattern and be submitted double-spaced and in triplicate. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35 mm). Do not submit color prints unless accompanied by original transparencies. If photomicrographs are not available, the actual slide from the specimen will be acceptable. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to Antoinette F. Hood, MD, Department of Dermatology, The Johns Hopkins Medical Institutions, 600 N Wolfe St, Baltimore, MD 21205. Reprints are not available.

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