

xanthomatosis, hyperlipidaemia and a reduced level of high-density lipoprotein cholesterol, the patient displayed no clinical evidence of accelerated atherogenesis.

It was not possible to do any studies on the patient's family because he was referred to our hospital from a distant centre in Natal. Inasmuch as the disorder is believed to be inherited as an autosomal dominant characteristic,<sup>7</sup> our findings imply that the gene occurs among the local Black population.

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# Pseudoxanthoma elasticum with cardiac involvement

## A case report and review of the literature

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### Summary

A young Black man with many features of pseudoxanthoma elasticum (PXE), confirmed by skin biopsy, complained of classic angina pectoris, decreasing effort tolerance, and palpitations. Clinically he was in severe congestive cardiac failure which was confirmed by echocardiography and cardiac catheterization, investigations which indicated the presence of a 'congestive' cardiomyopathy. Selective coronary arteriography showed normal epicardial vessels. Antemortem endomyocardial biopsy in this condition is described for the first time in the literature. This showed abnormal light microscopic and electron microscopic features. It is postulated that the predominant cause of congestive cardiac failure and angina pectoris in this disease is a diffuse

arteriopathy secondary to elastic fibre dysgenesis, involving the small intramural coronary vessels ('small-vessel disease'). Hitherto it has been accepted that the endocardial changes have been most important in the pathophysiology. A review of the literature as it applies to cardiac involvement in PXE is undertaken.

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### Clinical presentation

A 36-year-old Black man was initially admitted to a hospital in SWA. He had a 5-month history of increasing shortness of breath and orthopnoea. In addition, he had noticed the onset of palpitations (unrelated to effort) and typical angina pectoris, as well as intermittent swelling of the lower legs for some 3 months previously. He was otherwise asymptomatic and had never been on any previous medication. When his skin changes were brought to his attention he claimed that these had been present since his childhood. He also thought that his father had similar skin changes.

On examination in SWA he was noted to be in predominant right heart failure, with a blood pressure of 100/80 mmHg and an irregular pulse of 90/min. He had an enlarged left ventricle but no cardiac murmurs. His skin features were accepted as typical of pseudoxanthoma elasticum (PXE). An ECG displayed

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intermittent atrioventricular block, left anterior hemiblock and incomplete right bundle-branch block ('trifascicular block'). Haematological and renal function tests were negative. A chest radiograph showed marked cardiomegaly, and radiography of the forearms and screening of the coronary arteries failed to show any evidence of possible abnormal calcification. The patient was therefore diagnosed as suffering from PXE and a cardiomyopathy and given digitalis and diuretic therapy. Two weeks later he was transferred to Tygerberg Hospital for further investigation and therapy.

On admission the most striking feature was the appearance of the skin. The neck, axillae, inguinal folds and abdominal wall displayed a 'plucked chicken' appearance (Fig. 1a - d), in that there were yellowish papules bounded by skin lines, sometimes partially obscured by redundant folds of lax skin. These skin areas also displayed marked laxity and some sagging of the nasolabial folds was also evident. Soft yellowish papules were noted on the inner aspect of the lips and hard palate, as well as the buccal mucosa. There were fairly firm, non-tender lymph nodes palpable in the submandibular and inguinal regions. The rest of the general examination was negative.

The patient was in moderate right heart failure with a jugular venous pressure elevated to 10 cm above the angle of Louis, a 6 cm, tender, fairly firm hepatomegaly and moderate ankle oedema. The blood pressure was 100/70 mmHg. A prominent finding was the very poorly palpable radial pulse, but the remaining peripheral pulses felt normal and there were no thrills or bruits. The heart was moderately enlarged. The apex beat was not forceful but there was a prominent left parasternal heave and

epigastric pulsation due to right ventricular hypertrophy; a loud pulmonary component of the second heart sound at the base indicated pulmonary hypertension. The first heart sound at the apex was softer than normal but there was a prominent right ventricular third heart sound. At the lower left sternal border there was a grade 2/6, blowing pansystolic murmur which increased on inspiration. This was interpreted as being due to functional tricuspid insufficiency. Mitral insufficiency was not detected and there were no diastolic murmurs. The fundi were thought to be normal, as was the respiratory system. The remainder of the clinical examination was negative.

A chest radiograph (Fig. 2) showed left ventricular cardiomegaly with a fairly prominent main pulmonary artery segment and possible left atrial enlargement. The lung fields were clear.

A resting ECG (Fig. 3a - d) revealed sinus rhythm at 84/min, a mean QRS axis of  $+10^\circ$ , and a PR interval of 0,20 s. There was evidence of bi-atrial hypertrophy, as well as left ventricular hypertrophy and digitalis effect.

Urine, haemoglobin, white blood cell count, erythrocyte sedimentation rate and serum electrolytes were normal, while fasting glucose, liver function and haematological tests were negative. Blood urea was elevated at 8,2 mmol/l (normal 3,3 - 6,5 mmol/l), as was the serum creatinine at 125  $\mu\text{mol/l}$  (normal 60 - 120  $\mu\text{mol/l}$ ). A serum digoxin estimation was 0,85 ng/dl (therapeutic range up to 2 ng/dl).

An echocardiogram (Fig. 4 a - b) showed a markedly dilated, very poorly contracting left ventricle. The left atrium was slightly enlarged as was the right ventricle and its outflow tract (Table I). Left-sided systolic time intervals confirmed the poor

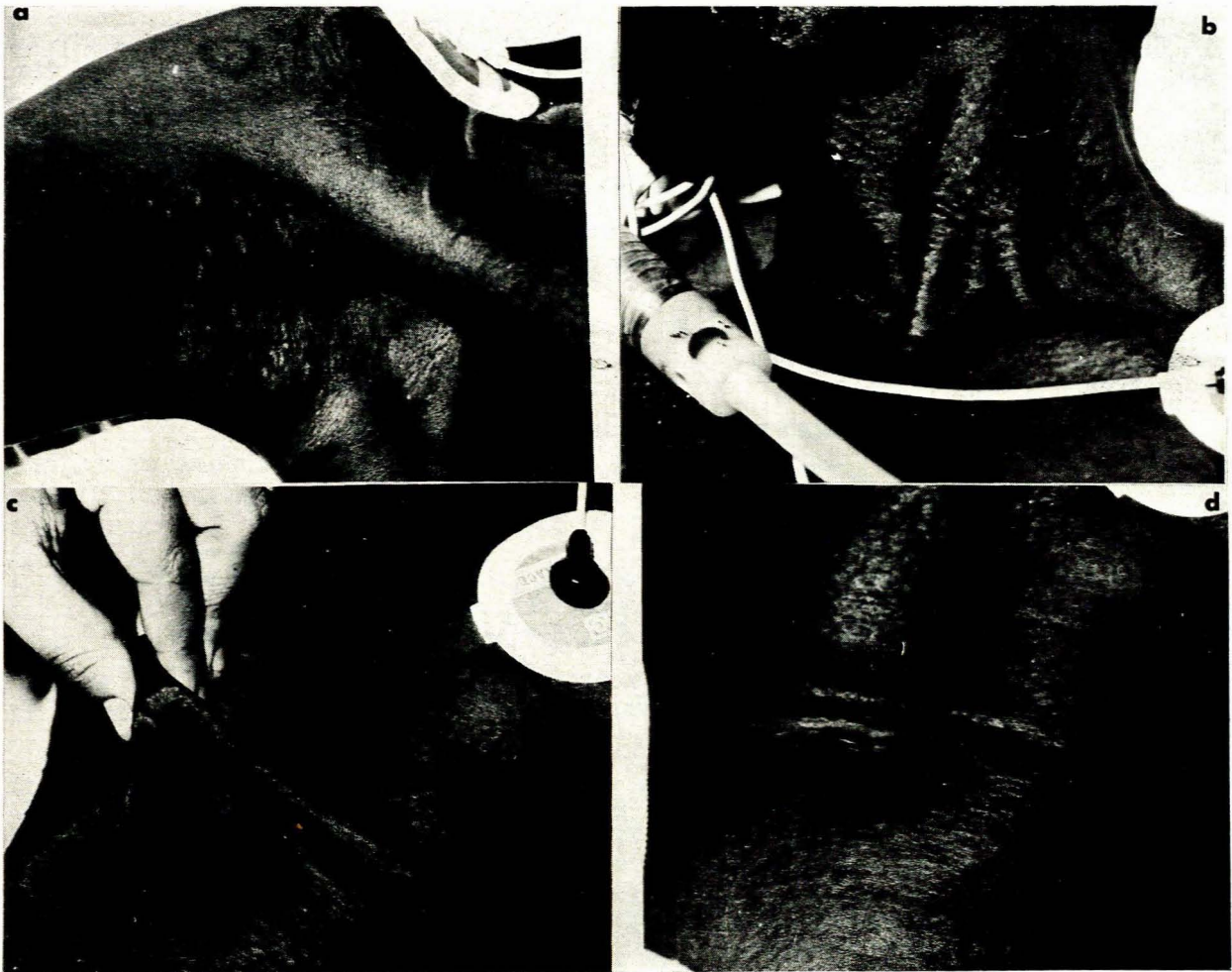


Fig. 1. Typical PXE skin lesions in the axilla, neck and abdomen. Note the marked laxity of the lower abdominal wall skin.

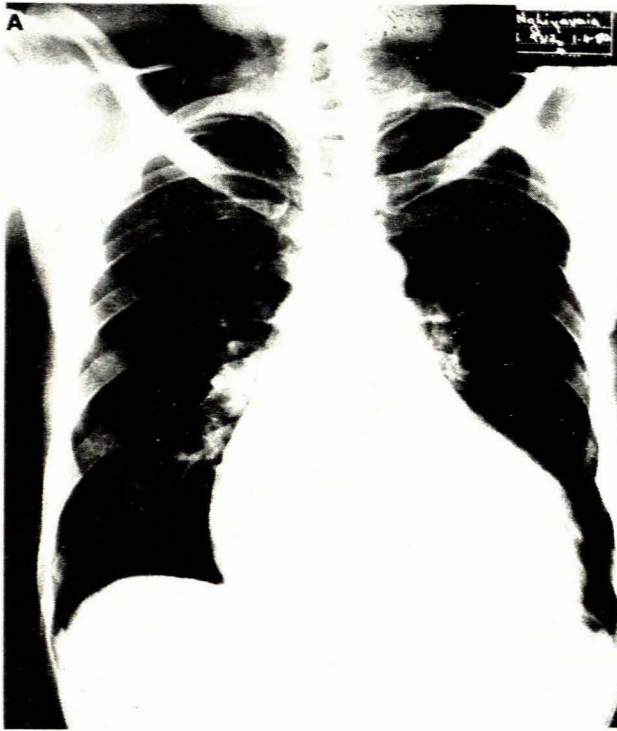


Fig. 2. Postero-anterior chest radiograph showing left ventricular cardiomegaly.

left ventricular function, and the right-sided systolic time intervals demonstrated the presence of pulmonary hypertension. There was no evidence of a pericardial effusion.

The patient was treated intensively for his cardiac failure which improved significantly. His blood urea level returned to normal, indicating that the initial values were due to prerenal failure.

The ophthalmologist demonstrated the presence of 'angioid streaks' bilaterally (Fig. 5), but no impairment of visual function could be found. A radiograph showed calcification of the falx cerebri (Fig. 6).

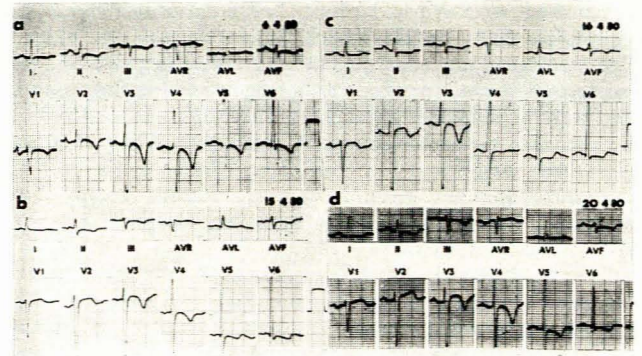


Fig. 3. Serial ECGs demonstrating bi-atrial hypertrophy followed by left atrial hypertrophy after treatment. Left ventricular hypertrophy and digitalis effect seen.

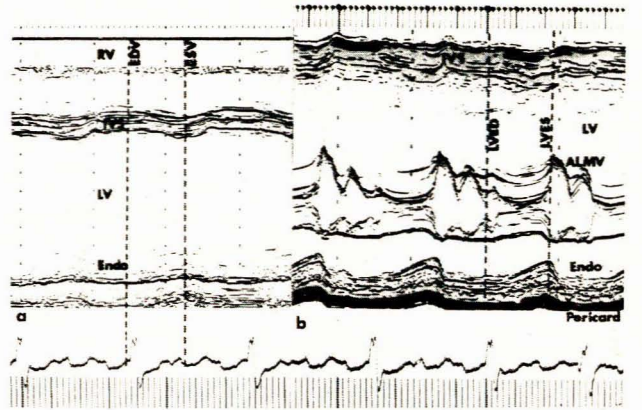


Fig. 4. Echocardiogram showing left ventricular and left atrial dilatation (RV = right ventricle; LV = left ventricle; IVS = interventricular septum; Endo = endocardium; EDV = end-diastolic dimension; ESV = end-systolic dimension; LVED = left ventricular end-diastole; LVES = left ventricular end-systole; ALMV = anterior leaflet mitral valve; pericard. = pericardium).

**Skin biopsy**

Biopsy specimens of skin from the lower abdominal wall revealed the classic histological features of PXE. Light

**TABLE I. ECHOCARDIOGRAPHIC MEASUREMENTS**

Parameter	Result	Normal (mean)
Left ventricle end-diastole (LVED)	74 mm	35 - 56 (46 mm)
Left ventricle end-systole (LVES)	62 mm	
Interventricular septum thickness (IVS)	8 mm	7 - 11 (9 mm)
Left ventricular posterior wall (LVPW)	10 mm	7 - 11 (9 mm)
IVS/LVPW ratio	0,8	<1,3
Left atrium dimension (LAD)	48 mm	19 - 40 (29 mm)
Right ventricular end-diastole (RVED)	25 mm	10 - 26 (17 mm)
Left ventricular end-diastolic volume (LVEDV)	289 cc	130 cc/m <sup>2</sup>
Left ventricular end-systolic volume (LVESV)	193 cc	25 cc/m <sup>2</sup>
Ejection fraction (EF)	33%	>60%
Shortening fraction (SF)	16%	28 - 38%
Systemic isovolumic contraction time (ICT)	81 ms	28 - 38 ms
Pulmonary isovolumic contraction time (ICT)	31 ms	0 - 20 ms
Systemic pre-ejection period (PEP)	185 ms	
Left ventricular ejection time (LVET)	195 ms	
PEP/LVET ratio	0,94	<0,28 - 0,38
Pulmonary pre-ejection period (PEP)	145 ms	
Right ventricular ejection time (RVET)	250 ms	
PEP/RVET ratio	0,58	>0,25 - <0,30

elastic fibre had the same irregular, fragmented and electron-dense appearance as that observed in the skin, although as could be expected the elastic fibres were much more abundant in the skin. In the endocardium, only occasional elastic fibres appeared relatively normal. Collagen fibres were within normal limits. A diligent search was made for possible small-vessel involvement but we could only demonstrate normal-looking capillaries in our material. Apart from minor nonspecific changes such as mitochondriosis the myocardium itself was unremarkable.



Fig. 9. PXE endocardium; note fragmented and calcified elastic fibres (arrows) (uranium and lead stain x 8300).

Some days later angiography of both upper limbs demonstrated abnormalities in keeping with a severe obliterative arterial process. The right brachial artery had a normal appearance but the muscular branches were thin and atretic. The right radial artery was extremely thin, atretic and terminated above the midshaft of the radius. The anterior interosseous and right ulnar arteries were also very reduced in size and tapered rapidly. No distal forearm arteries or palmar arches could be seen. On the left side, only a thin atretic ulnar and an interosseous artery were present, and there was no sign of the left radial artery. No calcification of these vessels was noted.

## Discussion

PXE is a rare multisystem disease, usually inherited as an autosomal recessive. It was first described by Rigal<sup>1</sup> in 1881 and in 1884 Balzer<sup>2</sup> first described postmortem endocardial thickening in the right atrium and ventricle. The basic defect is accepted as a derangement of elastic fibre metabolism and synthesis, which leads to an increase of abnormal elastic tissue undergoing premature calcification and degeneration.<sup>3,4</sup> The disease can affect the skin (usually only cosmetic), eyes ('angioid streaks', haemorrhage, decreased visual acuity, blindness), gastro-intestinal tract (haemorrhage), blood vessels (hypertension, premature atherosclerosis, intermittent claudication, angina pectoris) and the heart (acute myocardial infarction, congestive cardiac failure, sudden death). The association of angioid streaks (in some 85% of cases) and skin involvement has been known as the Grönblad-Strandberg syndrome.<sup>5,6</sup>

Why these patients commonly present with congestive cardiac failure is poorly understood, but this may well be due to the fact that the great majority of patients with cardiac involvement were only diagnosed at autopsy, and thus antemortem haemodynamic and echocardiographic assessment is virtually absent.

The present publication describes extensive cardiac evaluation of a classic case of PXE. In addition, right ventricular endomyocardial biopsy was undertaken during cardiac catheterization. This seems to be the first time endomyocardial biopsy has been recorded in PXE.

## Aetiology and pathogenesis

This connective tissue disease is inherited as an autosomal recessive trait and appears to be more prevalent among females. Much controversy surrounds the exact pathogenesis of PXE. Balzer<sup>2</sup> initially accepted that it was due to an abnormality of elastic tissue. However, later on, many workers challenged this concept and favoured the theory of abiotrophy of collagen fibres. McKusick<sup>4</sup> indicated that the classic lesions were also seen in tissues in which elastic fibres are usually sparse, while tissues with a rich supply of elastic fibres are seldom involved by the disease process. He therefore suggested that the fibres originated from abnormally altered collagen fibres. The concept of 'elastotic degeneration' of collagen into pseudo-elastic fibres, proposed by Gillman *et al.*,<sup>7</sup> was further supported by electron microscopy and biochemical and histochemical studies.<sup>8-14</sup>

Huang *et al.*<sup>8</sup> demonstrated masses of 'granulofilamentous material' either related to abnormal elastic precursors or degenerated and disorganized elastic units. This material transformed to calcified masses among which were seen normal collagen fibres which did not transform to abnormal elastica. These workers strongly favoured abnormal elastogenesis and recommended the pathogenetic term, 'elastodysplasia calcificans', for this disease. There is still some disagreement concerning the exact time of calcification, but most workers accept that it is a primary manifestation.

## Clinical features

The most important cardiovascular clinical presentation in PXE is related to symptoms and signs of premature peripheral vascular disease, hypertension, angina pectoris, congestive cardiac failure and sudden death (probably related to a ventricular arrhythmia).

**Intermittent claudication** of the lower limbs is a prominent symptom of premature atherosclerosis and has been described in patients ranging from 9 years<sup>15</sup> to 36 years, as well as in older patients. In the series reported by Carlborg,<sup>16</sup> 14 of 15 patients had decreased pulsation and a reduced pulse wave velocity in the peripheral arteries. Furthermore, many patients had decreased or absent pulses in the upper limbs without symptoms of ischaemia or any obvious atrophic features. Carlborg *et al.*<sup>17</sup> showed arteriographic evidence of arterial occlusive disease in the lower limbs in 7 of 11 patients, and narrowing of forearm vessels in 1 of 4. In the Goodman *et al.*<sup>3</sup> series of 12 patients, all 6 who were investigated showed occlusion or narrowing of the radial or ulnar artery, as in our patient but only 1 of the 6 also had occlusion of a lower limb artery. The remaining literature shows a far greater incidence of arteriographic abnormality in the upper limbs.

**Hypertension** has been reported in some 25% of cases,<sup>18</sup> especially in patients over the age of 40 years. The probability of a renovascular aetiology has been considered strongly by some workers but complications of this, especially cerebrovascular disease, appear to be most rare. A possibility of predisposition to acute myocardial infarction in the presence of coronary artery disease is very real.

**Angina pectoris** has been reported in 15 of 29 patients by Carlborg *et al.*<sup>17</sup> One of the patients was only 7 years of age and the mean age of the symptomatic patients was 38 years (others have indicated an incidence up to 50%). Subsequent acute myocardial infarction is rather rare,<sup>19,20</sup> although a 6-week-old infant of a mother with PXE suffered an infarction and may well have had the same disease.<sup>21</sup> Our patient had a classic history of angina pectoris, a symptom rare in the Black population, and yet had angiographically normal coronary arteries.

**Congestive cardiac failure** has been reported in some 70% of patients. This symptom was often associated with underlying hypertension, which was most probably an important

precipitating factor. Some of the patients had additional mitral valve disease, especially mitral stenosis, which almost certainly aggravated the cardiac failure. The endocardial lesion has been reported infrequently in PXE and its relationship to congestive cardiac failure is unclear. It would appear that 'global' myocardial dysfunction, secondary to ischaemia caused by 'small-vessel disease' of the coronary arteries, may well be more important pathophysiologically.

**Sudden death** during strenuous exercise has been documented in 3 teenagers.<sup>19</sup> Autopsy demonstrated an acute myocardial infarction probably due to coronary artery involvement by PXE, but this is unusual.

### Electrocardiographic characteristics

There is no pathognomonic ECG of PXE, but most cases have shown varying degrees of left ventricular hypertrophy, especially asymmetrical T-wave inversion ('strain pattern'). The concomitant presence of systemic hypertension in approximately 25% of the patients would increase the incidence of left ventricular hypertrophy on ECG. Also, the majority were over the age of 50 years, making the likelihood of hypertension unrelated to PXE much greater. Associated, nonspecific, ST-T segment changes were common and probably secondary to hypertensive and ischaemic heart disease.

Left atrial hypertrophy was quite striking in patients with valvular heart disease (probably non-rheumatic), especially if the predominant lesion was mitral stenosis. Our patient's ECG (Fig. 3a) demonstrated left and right atrial hypertrophy, explicable on the grounds of biventricular failure. However, once his right-sided heart failure responded to therapy his ECG no longer showed right atrial enlargement (Fig. 3b). The depth of T-wave inversion decreased following treatment, but never returned to normal (Fig. 3c-d). Cases of atrioventricular block and bundle-branch block have been reported,<sup>17</sup> but these changes have not been thought to be secondary to PXE. Paroxysmal atrial tachycardia, particularly resistant to therapy, has rarely been described.<sup>22</sup> Atrial fibrillation, especially in older hypertensive patients, was sometimes a feature.

### Echocardiographic features

Detailed echocardiographic assessment of cardiac involvement in cases of PXE is lacking in the reviewed literature. The only reference is in the report of Bete *et al.*<sup>20</sup> who noted 'normal mitral valve excursions'. Referring to Fig. 4a-b and Table I it can be seen that our patient displayed features of a severely, diffusely hypokinetic left ventricle which was significantly dilated in the presence of slight left atrial enlargement, probably secondary to mitral insufficiency. This was further verified by the very low ejection and shortening fractions, in keeping with 'congestive cardiomyopathy'. The added feature of pulmonary hypertension, as demonstrated by the right-sided systolic time intervals,<sup>23,24</sup> indicated a degree of cardiac failure substantiated by increased left ventricular end-diastolic and end-systolic volumes. Mitral stenosis was confidently excluded as was the 'restrictive cardiomyopathy'<sup>25</sup> seen in diffuse endomyocardial fibrosis, 'restrictive endocarditis' and certain infiltrative diseases, such as amyloidosis.<sup>26,27</sup> Echocardiographic findings and the results of cardiac catheterization were closely correlated.

### Pathology of cardiac PXE

Premature atherosclerosis in these patients is not particularly unique or distinguishable from the well-known form, although the upper extremities are often more affected and there is usually little involvement of the aorta. The first detectable histological

change in the peripheral muscular arteries is fragmentation of the internal elastic lamina, and sometimes the external elastic lamina. This stage is followed by calcification along the length of the elastic lamina and finally by extensive medial and intimal calcification. These changes are morphologically identical to those seen in Mönckeberg's arteriosclerosis. It has been suggested<sup>28</sup> that these features may indicate that Mönckeberg's sclerosis is the end-result of ageing and degeneration of the elastic laminae of muscular arteries, and that the changes seen in PXE are a transient stage in the development of Mönckeberg's sclerosis. Nevertheless, calcification appears at an earlier stage in PXE and is more extensively distributed than in Mönckeberg's sclerosis.

### Endocardial involvement

The present case is the first in which endomyocardial biopsy was successfully carried out. Only some 12 cases<sup>2,3,17,20,29,30</sup> with endocardial lesions have been described despite the fact that some 200 cases with skin involvement have been documented. Some authors<sup>28</sup> claim that the endocardial lesion is the only pathognomonic manifestation of cardiac involvement by PXE.

The normal endocardium consists of some five to eight layers (endothelium, subendothelium, connective tissue, elastic tissue, smooth muscle and deep connective tissue containing conduction fibres).<sup>31</sup> Normally it is thicker in the atria than in the ventricles, and it also becomes thinner with progression from the atrioventricular valves towards the apex. The endocardium of the inflow tracts is thinner, with fewer collagen and elastic fibres than the ventricular outflow tracts.

The endocardial lesion consists of intimal fibro-elastotic thickening, disorganization, calcification and fragmentation of the elastic fibres in the deep endocardial layers. Involvement of the atria is much more extensive and uniform than in the ventricles.

In analysing the possible extent of endocardial involvement in PXE it is important to appreciate that cardiac dilatation *per se* causes hyperplasia of the collagen and elastic fibres, especially in the left atrium,<sup>32,33</sup> which would be of significance in those patients who had valvular involvement, especially mitral stenosis. Our patient had significant cardiac chamber dilatation and hypertrophy which makes interpretation of the endomyocardial biopsy findings so much more difficult. Also, the specimens were obtained from the right ventricular apex, which is known to contain small amounts of elastic tissue.

### Valvular involvement

PXE has rarely been associated with valvular heart disease and this relationship is still controversial. McKusick<sup>34</sup> initially described abnormal mitral, aortic and tricuspid valves at autopsy, with histological findings similar to the mural endocardial changes described by Balzer.<sup>2</sup> Coffman *et al.*<sup>30</sup> had a patient who died of congestive cardiac failure due to clinical mitral stenosis and tricuspid insufficiency. Autopsy revealed elastic tissue degeneration in the left atrial endocardium, as well as the mitral valve, but the remaining valves were normal; there was no evidence of rheumatic heart disease. Five of the patient's sibs had skin changes due to PXE, and 3 had clinical mixed mitral valve disease without a past history of acute rheumatic fever.

Wilkins and Sommers<sup>35</sup> described a patient with clinical mixed mitral valve disease and histological changes of the mitral valve in keeping with PXE. Yoffee and Derbes<sup>22</sup> reported on a 19-year-old woman with repeated episodes of acute pulmonary oedema and paroxysmal atrial tachycardia, and with clinical mitral stenosis and insufficiency but no calcification of the valve. Mendelsohn *et al.*<sup>28</sup> had a patient who had no clinical valvular disease, but in whom the tricuspid valve showed striking

disorganization and calcification of elastic fibres in the deeper endocardial layers.

Our patient had clinical tricuspid insufficiency, but significant mitral insufficiency on angiography. It may therefore be argued that he had clinical mitral insufficiency which was not obvious because of the concomitant tricuspid insufficiency. Biopsy material of the mitral valve is not available, and therefore one cannot be absolutely certain that PXE is the cause.

### Myocardial involvement

Virtually nothing has been written with regard to the involvement of the myocardium in PXE. Some authors<sup>29</sup> have commented on autopsy evidence of 'localized endomyocardial fibrosis' which usually resembles a healed myocardial infarction. These cases usually showed no involvement of the large coronary arteries, except for the 3 patients of Wilhelm and Paver,<sup>19</sup> who died suddenly and at autopsy had severe premature coronary atherosclerosis and massive myocardial infarctions.

Concentric left ventricular hypertrophy is often seen, especially if hypertension is present and this contributes to the cardiac decompensation.

Previous authors have emphasized the endocardial lesion as the main cause of congestive cardiac failure but no explanation for this has been volunteered. It is also unlikely that primary myocardial disease is responsible for the clinical presentation in PXE, especially as the disease primarily affects the elastic tissue. The present authors suggest that the global myocardial dysfunction in this patient is due to a diffuse arteriopathy involving the small coronary vessels ('intramyocardial'; 'intramural') which are not visible angiographically ('small-vessel disease'). Otherwise, one would have to postulate that this patient has a coincidental congestive cardiomyopathy of unknown aetiology, which would be most surprising.

### Coronary artery involvement

Reviewing the English language literature indicates that the changes of elastic tissue fragmentation and calcification in the coronary arteries were initially demonstrated at autopsy.<sup>3,4,36</sup> Nellen and Jacobson<sup>37</sup> were the first to identify coronary artery calcification radiologically, as well as calcification of the falx cerebri in PXE. Huang *et al.*<sup>29</sup> reported a case with fragmentation of the coronary elastica interna and calcification. Wilhelm and Paver<sup>19</sup> described sudden death during strenuous exercise in 3 teenage boys in whom autopsy verified myocardial infarction and coronary atheroma.

Selective coronary arteriography was first carried out by Bete

*et al.*<sup>20</sup> in an 18-year-old girl who was shown to have significant triple vessel coronary artery disease as well as a previous transmural anteroseptal myocardial infarction. She then underwent successful triple coronary artery-saphenous vein bypass grafting; coronary artery biopsy proved involvement by PXE. Mendelsohn *et al.*<sup>28</sup> found severe coronary atherosclerosis in 3 older patients aged 47, 63 and 79 years. Our patient is the second on whom coronary arteriography was performed because of angina pectoris, but these vessels were not calcified and appeared angiographically free of any obstructive atheromatous disease.

The endocardial biopsy in our case failed to show the presence of any coronary arterioles; the latter may be involved with early atherosclerosis. Many normal capillaries were visualized.

This feature and atherosclerosis have never been demonstrated in previous publications relating to PXE in which the only postmortem abnormalities were premature atherosclerosis of the large epicardial coronary arteries. 'Small-vessel disease' has been documented at autopsy in a patient with severe atherosclerosis following cardiac transplantation, in whom the large epicardial coronary arteries were patent and free of any significant atherosclerosis.<sup>38</sup> Crall and Roberts<sup>39</sup> demonstrated 'intimal fibrous proliferation' in the intramural coronary arteries of juvenile diabetics at autopsy. An excellent review of the pathology of small coronary arteries has been published by James,<sup>40</sup> who claims that diffuse small-vessel disease can affect many foci in the ventricular myocardium and cause mechanical and electrophysiological disturbances in cardiac function. Apart from patients with diffuse atherosclerosis, polyarteritis nodosa,<sup>41</sup> systemic lupus erythematosus,<sup>42</sup> rheumatoid arthritis,<sup>43-44</sup> rheumatic fever<sup>45-47</sup> and scleroderma, PXE must now also be considered as a cause of 'small coronary arteriopathy'. This is probably of more significance than the patchy endocardial involvement which previous authors<sup>28</sup> have emphasized as the predominant cardiac lesion in PXE.

### Haemodynamic features

The literature contains virtually no data relating to cardiac catheterization in PXE, apart from the report of Bete *et al.*<sup>20</sup> Their patient had documented triple vessel disease and was successfully operated on for severe angina. The intracardiac pressures were completely within normal limits, apart from an abnormally elevated left ventricular end-diastolic pressure (LVEDP) of 16 mmHg following right atrial pacing at 144 beats per minute. However, left ventricular (LV) cine angiography in their patient showed infero-apical hypokinesia and a systolic ejection fraction of 50%.

TABLE II. INTRACARDIAC PRESSURES

Catheter position	Pressure (mmHg)	Comment
Right atrium	'a' wave 22, 'v' wave 27, mean 18	Markedly elevated pressures
Right ventricle	66/4 - 21	Raised systolic and diastolic
Main pulmonary artery	66/31, mean 45	Moderately severe pulmonary hypertension
Ascending aorta	120/100, mean 106	Narrow pulse pressure No aortic stenosis
Left ventricle dp/dt	120/8 - 30 (mm/s), 728	Very raised end-diastolic pressures, markedly reduced
Pulmonary capillary wedge	'a' wave 4, 'v' wave 34, mean 28	Very raised pressures, large 'v' waves, no mitral stenosis

The cardiac catheterization and echocardiographic data on our patient (Tables I - III) demonstrated severely depressed myocardial function as determined by the markedly reduced LV dp/dt, cardiac output and index, ejection fraction and shortening fractions, and the raised LVEDP of 30 mmHg. The LV systolic time intervals were very abnormal and there was evidence of biventricular failure as depicted by moderately severe pulmonary hypertension (elevated pressures as well as abnormal right ventricular systolic time intervals), an elevated right ventricular end-diastolic pressure of 21 mmHg, a low pulse pressure of 120/100 mmHg, and a significantly raised pulmonary capillary wedge pressure (PCWP) of 28 mmHg (mean), with very large 'v' waves of 34 mmHg indicative of the mitral insufficiency confirmed on LV cine angiography. Functional tricuspid insufficiency was illustrated by the large 'V' waves of 27 mmHg recorded in the right atrium. Furthermore, the poor LV function was confirmed by the diffuse hypokinesia of the free wall and interventricular septum which failed to show paradoxical movement.

**TABLE III. HAEMODYNAMIC CALCULATIONS**

Parameter	Result
Oxygen consumption (l/min)	180
Arteriovenous O <sub>2</sub> diff. (vol. %)	8,9
Cardiac output (Fick) (l/min)	2,0
Cardiac index (Fick) (l/min/m <sup>2</sup> )	1,3
Pulmonary vascular resistance (U)	8,5
Index (U/m <sup>2</sup> )	13,0
Systemic vascular resistance (U)	44,0
Index (U/m <sup>2</sup> )	67,7
Resistance ratio (pulmonary/systemic) (%)	19
Stroke volume (cc/beat)	18
Stroke work index (G-M/m <sup>2</sup> )	14,3

The preceding description would fit that of a congestive cardiomyopathy, or the terminal stage of a restrictive cardiomyopathy such as is seen in some infiltrative diseases, for example amyloidosis. Although the endocardial changes seen on endomyocardial biopsy are not those of florid PXE, these changes are known to be very patchy in the right ventricular apex and their exact relationship to the haemodynamic alterations is still far from clear. It has been suggested<sup>31</sup> that the endocardium undergoes continual variation in shape and structure according to the variety of pressures it is subjected to. In all probability the elastic tissue, and possibly the smooth-muscle layer, have a role to play in the recoil mechanism. This variation in response to differing degrees of stretch and recoil differs in the various parts of the endocardium. PXE involvement to the heart can be compared with that of endocardial fibro-elastosis, but the exact mechanism by which it leads to congestive cardiac failure is not understood. We postulate a global hypokinesia on the basis of diffuse involvement by PXE of the intramural coronary arteries, viz. 'small-vessel disease', which could account for our patient's haemodynamic characteristics, as well as possibly those of the other cases in which death was due to congestive cardiac failure and described at autopsy.

## Treatment and prognosis

To date there is no specific effective therapy for cardiac involvement by PXE. Since the most important and common clinical presentation of this disease is congestive cardiac failure, initial medical management consists of standard diuretics with the addition of digitalis preparations, but the cardiac failure is more often than not refractory to this therapeutic approach and death usually results from the cardiac failure *per se*, renal failure,

hypertensive cerebrovascular complications, acute myocardial infarction (sudden death), or sometimes acute pulmonary embolism or coronary embolism.

A possible complication is systemic embolization, originating from atrial or ventricular mural thrombi, and the use of antiplatelet agents and anticoagulants should also be considered in management.

Surgical therapy has very infrequently been undertaken in these patients because the diagnosis was first made at autopsy, but triple bypass grafts were performed in a single patient for severe angina pectoris, with a most rewarding outcome.<sup>20</sup> Valvular involvement might indicate the need for mitral valve replacement. In our patient this would be ill-advised because of the nature of his left ventricle.

The question of cardiac transplantation might be considered but the outcome would be most uncertain. Thus, a heterotopic transplant ('piggy-back') would not ensure return to normality of his diseased heart, while giving him an orthotopic transplant would run the risk of organ rejection.

If endomyocardial biopsy were used more frequently when a diagnosis of myocardial disease of uncertain origin is suspected, the early stages of the disease could be detected without much harm being done to the patient. We hope that the future will produce specific therapeutic regimens to counteract this rare but uniformly fatal disease.

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