CLINICAL REVIEW

Pseudoxanthoma elasticum

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Summary

Eight cases of pseudoxanthoma elasticum seen in a Medical Unit in Singapore are described. Of these six belonged to one family.

The clinical presentations of these cases, especially the first case who was a diagnostic problem for 5 years, are described. Transmission in this family is autosomal-recessive.

Eye changes were absent. Skin lesions were minimal and the axillary folds were more involved than the skin of the neck.

Of the eight cases, three were asymptomatic except for cutaneous lesions, three had suffered a haemetemesis and four a haemoptysis, while three had mental changes, and two had cerebrovascular involvement. Case 1 had in addition, bleeding from the nose, urinary tract and uterus. She also had a fatty liver, peripheral neuropathy and hysterical fits.

Only one case presented as a cosmetic problem.

The pathogenesis of PXE is discussed; the primary defect is believed to be in the elastic and not the collagenous tissue.

Introduction

Pseudoxanthoma elasticum (PXE) is a rare inherited generalized disorder of the elastic tissue, involving mainly the skin, the eyes, and the vascular system. The etiology of this disease is still unknown, but transmission is believed to be of the autosomal-recessive type.

The cutaneous lesions are characterized by asymptomatic small yellowish papules, 1-3 mm in diameter, arranged in a linear or reticular pattern or in confluent plaques. The common sites affected include both sides of the neck and the axillary and inguinal folds, and occasionally the peri-umbilical, antecubital and popliteal areas. The mucous membrane of the lips, buccal cavity, rectum and vagina may also be involved. In the early cases, skin lesions may be seen only after the skin is stretched. The skin in advanced cases is thickened, soft and lax,

and hangs in loose inelastic folds. Seen predominantly in females, PXE may cause cosmetic defects in the younger age-group, and this is often the presenting symptom in a dermatological practice.

Another important presenting feature is angioid streaks in the retinae. Visual disturbance proceeding to blindness is due to retinal vessel degeneration. The combined skin and eye changes are known as 'Grönblad-Strandberg syndrome'.

A common but particularly troublesome feature of PXE is internal haemorrhage, especially of the gastro-intestinal tract, but other organs are not spared.

In older patients advanced and premature vascular degeneration is often present, and may manifest in various ways such as intermittent claudication, cerebral and coronary occlusions and hypertension. The condition has been reviewed by Eddy & Farber (1962) and by Goodman *et al.* (1963).

Historical background

Blazer (1884) was the first to describe a patient who died of pulmonary tuberculosis and who had xanthomatous lesions in the skin and heart. Five years later Chauffard (1889) reported a case with massive gastro-intestinal bleeding and with the characteristic cutaneous lesions. Skin biopsy of this patient was studied by Darier (1896) who introduced the term 'Pseudoxanthoma Elasticum' to describe the histological changes. Angioid streaks in the retinae had been described by Doyne (1889) and Knapp (1892) but the association of this lesion and PXE was not appreciated until much later, although Hallopeau & Laffitte (1903) noted 'chorioretinitis of central region, involving the macula' in Chauffard's patients. In 1929, Grönblad, an ophthalmologist, and Strandberg (1929), a dermatologist, independently described cases with combined skin and eye lesions. Franceschetti & Roulet (1963) then proposed the name 'Grönblad-Strandberg' syndrome to such cases (of PXE with angioid streaks). Many cases

TABLE 1

Date	Admission No.	Symptoms					Surgery	Radiological investigations	Endoscopies	Clinical findings	Others
		Ciddiness	Abdominal pain	Bleeding PR and PV	Haematuria	Haemoptysis	Epistaxis	Haematemesis			
1962	1										
	2		+				+		Nasal electric cautery		Bleeding Little's area (nose)
	3					+	+		Nasal electric cautery	Bronchograms	Haemorrhagic left bronchus
	4							+		Barium meal	
1963	5							+			
	6	+	+					+			
	7	+					+		First laparotomy, nasal cautery		
	8		+							Sigmoidoscopy	Tender abdomen, hyperventilation, renal colic
	9		+		+				IVP	Cystoscopy	'Fit'
	10		+		+				Barium enema, retrograde pyelogram		
	11		+		+			+	Rectal biopsy	Retrograde pyelogram	
	12					+	+	+	Oesophageal biopsy	Portovenograms (twice)	Liver palms, rectal polypi Depression
	13							+	Second laparotomy	Oesophagoscopy (three times)	
	14	+							Third laparotomy	Oesophagoscopy	
1964	15		+	PR	+			+		Barium swallow + meal	
	16	+				+	+	+	Neck gland biopsy	Barium swallow	Spider naevi, enlarged neck gland
									Oesophagoscopy		Faints

have since then been reported from all over the world.

In this review, eight cases of PXE seen in the last 3 years in Medical Unit II of the General Hospital, Singapore, are reported, five of whom belong to one family. It is stressed that PXE can present as a great diagnostic problem because of the protean clinical manifestations, the possible absence of eye lesions, minimum cutaneous changes, and a general unawareness of this condition.

Case reports

Case 1

Propositus: T.G.C. (Table 1). This 43-year-old Chinese female was admitted for the first time on 8 May 1962 to a medical ward in Outram Road General Hospital, Singapore, because of haematemesis, associated with mild epigastric pain for 2 days. There was no history of peptic ulcer, alcohol or drug ingestion, bleeding tendency or weight loss. Her general condition was good. There was no clinical evidence of anaemia and no stigmata of liver cirrhosis. Blood pressure was 130/80 mmHg and pulse rate was 90/min. No masses were felt in the abdomen, and there was no tenderness. Clinical lymphadenopathy was not present.

Investigations: Hb 98% with normal red and white cell series. Routine urine analysis was normal, and stool showed presence of occult blood.

While in hospital, she had recurrent small bouts of haematemesis, averaging two to five times a day. She was diagnosed as bleeding from a peptic ulcer and was treated conservatively with antacids, and diet, and discharged 2 weeks later when the bleeding had stopped.

Since then, she has been readmitted thirty-five times over a 5-year period before a diagnosis of PXE was made and confirmed by skin biopsy.

During these 5 years, the commonest presenting complaint for her admission was haematemesis. The blood vomited was fresh and in small mouthfuls, several times a day, but she was never anaemic or in peripheral circulatory failure. Haematemesis was also present between admissions. In addition, she had recurrent episodes of epistaxis, haemoptysis, haematuria, rectal bleeding and menorrhagia. Extensive investigations regarding the basic cause of bleeding from these organs, had been essentially negative. Other symptoms were abdominal colic from post-operative adhesions, giddiness, fainting attacks, hyperventilation and 'fits'. For 4 years, recurrent pedal oedema, puffiness of the face and abdominal swelling were present. Physical signs were always minimal. Anaemia was never detected and her haemoglobin had always been above 75%. She was normotensive with no obliterative vascular lesions. Both lungs were clinically and radiologically normal.

Abdominal signs were equally scanty. Occasional epigastric and left abdominal tenderness were elicited in the earlier admissions. The liver, not palpable in the early stage, later became enlarged three finger-breadths associated with the appearance of palmar erythema and spider naevi. Neurological examination was normal until January 1965 when peripheral neuropathy with glove-and-stocking anaesthesia, foot-drop and muscular weakness was found.

During her thirty-five admissions, innumerable investigations were done. Haematological studies did not reveal any evidence of blood dyscrasia or haemorrhagic diathesis. Liver function tests were normal but later serum albumin was found to be low. She had twelve plain X-rays (of various parts of the body), ten barium studies, four pyelograms, two portovenograms and one bronchogram (and on the thirty-seventh admission, she also had an arch aortogram) making a total of thirty-three radiological studies. She was also subjected to numerous endoscopic examinations, seven oesophagoscopies, three cystoscopies, one gastroscopy, one bronchoscopy, one laryngoscopy and one sigmoidoscopy. A small yellowish nodule on the oesophageal wall was observed on the third oesophagoscopy examination but the histology was reported as normal. Bronchoscopic examination revealed a haemorrhagic mucosal wall of the right bronchus and nothing else. All the other endoscopic examinations were normal.

She had had a total of fifteen major and minor surgical operations during the 5 years: four laparotomies, three electric cauteries to nasal septum, three liver biopsies and one biopsy each of oesophagus, rectum, lymph node, skin and muscle. The first laparotomy revealed a 1 cm mucosal tear on the posterior wall of the stomach. No other lesions were detected. During the third laparotomy, an area of fibrosis and fatty necrosis with calcification was found at the right gastro-epiploic artery of the stomach, and on the last laparotomy, the liver was noted to be enlarged; a gastro-jejunostomy was performed on this occasion. Liver histology revealed fatty changes.

In 1967, when she was admitted for the thirty-sixth time, a small number of pinpoint yellowish papules were observed over the skin of both sides of the neck (Fig. 1). Slight thickening was found on stretching the skin. The axillary skin was lax, inelastic and hung in folds (Fig. 2). No skin changes were demonstrated at other sites. Retinal examination showed no angioid streaks. All peripheral vessels were normal. The heart, blood pressure and lungs were normal. Hepatomegaly, spider naevi, palmar erythema and peripheral neuropathy found in previous admissions, were present.

Biopsies of the papules of the neck and the leg were done and both showed fragmentation and

FIG. 1. Case 1. Pinpoint papules at the side of the neck.

degeneration of elastic fibres with clumping and swelling of these fibres in the dermis, both with haematoxylin and eosin and silver nitrate staining (Fig. 3). Later, an arch aortogram revealed arterial narrowing of the major vessels.

Family studies were then conducted (Fig. 4). Only the patient's mother, two of her sisters, one of her brothers and one paternal cousin were available for study. All proved to have PXE (see Cases 2–6).

Her grandparents, who had three sons and a daughter, died in China many years ago. There was no history suggestive of PXE in these two generations. All of them, including the father of the *propositus*, died in China over 20 years ago from unknown causes, although she was told that her father developed retention of urine some time before he died. The parents of the *propositus* were not related to each other, and they came from different parts of the province in China. They had nine offspring, four sons and five daughters.

Of the four brothers of the *propositus*, only the youngest brother was available for studies. He had haemoptysis and haematemesis (Case 3).

FIG. 2. Case 1. Lax, inelastic axillary skin hanging in folds.

Of the five girls, the eldest sister of the patient was asymptomatic; the second sister, who was not examined by us, had a severe psychiatric disorder and was warded in a mental hospital. Our patient was the third. The two younger sisters (Cases 4 and 2) had haemoptysis.

The patient's 75-year-old mother (Case 5) had marked skin changes of PXE. She had no symptoms all these years but she perished suddenly from one single bout of haematemesis. One of her paternal cousins (Case 6) too had also marked skin changes with no systemic involvement.

The patient's husband died of carcinoma of the stomach and pulmonary tuberculosis 7 years ago. She had two sons and four daughters, ages ranging from 13 to 21 years. None of them exhibited any cutaneous, eye or vascular lesions. However, her two older girls had recurrent attacks of giddiness but no organic cause was found.

Comment. This interesting case presented as a

most challenging problem for the physicians and surgeons who looked after her for 5 years. She was one of the most investigated and operated patients of this hospital (General Hospital, Singapore) having a record number of over thirty radiological studies, fourteen endoscopies and over a dozen major and minor operations. All these failed to contribute much information to the diagnosis which was made later by mere inspection of the skin and confirmed by a skin biopsy.

Haematemesis was the main problem. This was recurrent but never massive and did not give rise to significant anaemia. Investigations had ruled out the common causes of haematemesis, such as peptic ulcer, oesophageal varices, hiatus hernia, polyps or carcinoma. However, in retrospect, some of the operative findings were suggestive of the diagnosis of PXE; the spontaneous tear in the gastric mucosa, the fatty necrosis and calcification of the gastric vessels and the yellowish nodule, most likely a xanthomatous lesion, in the oesophageal wall. Although the nodule was biopsied, special stains were not requested as the diagnosis was not thought of. Besides suffering from gastro-intestinal bleeding, this patient also bled from the nose, the bronchus, the bladder and the uterus. Cardiovascular changes were minimal and the only arterial changes were narrowing of the major vessels from the arch of the aorta. Recurrent attacks of giddiness in the patient and in some members of her family could be attributed to cerebral insufficiency, but neurological signs were lacking. Mental changes in her second sister and the patient herself could be due to PXE, though the chronic ill-health of our patient might be the cause of her depressive illness.

During the later stage of her illness, oedema, hypoalbuminaemia, enlarged fatty liver and peripheral neuropathy developed as a result of gastric bypass, malnutrition from excessive vomiting and lack of intake from mental depression.

In this patient, the hallmark of this disease, the small yellowish papules and the lax, thickened skin over the neck, was early and atypical. The axillary lesions, however, were more advanced, but were often concealed by clothing with long sleeves, and unless these were specially looked for, they would have been easily missed.

The family study revealed four more cases of PXE including the mother of the propositus. It is believed that her father was either a case of PXE or a heterozygous carrier as the usual transmission of this disease is autosomal recessive. Furthermore, one of her paternal cousins (Case 6) was also involved. None of the children of the propositus had skin, eye or other vascular changes. Skin biopsies were found to be normal. However, it is generally known that cutaneous lesions appear at a later

stage, between the ages of 30 and 50 years. It is therefore difficult to predict at this stage whether some or all of them will develop PXE eventually.

Case 2

T.C.G., sister of Case 1. This 42-year-old Chinese female had attacks of giddiness for many years. Five years ago, she had a haemoptysis, and was found to have tuberculous involvement of the apex of the left lung. Following chemotherapy and a left upper lobectomy, she was well until 12 months ago when she started to have repeated haemoptyses again. Chest X-rays, laryngeal and sputum cultures and ESR did not reveal active tuberculosis. She had no symptoms referable to the eyes, cardiovascular or cutaneous systems. The skin of the neck, axillae, groins, and the other areas appeared normal but on stretching the skin over the neck, the creases were found to be exaggerated and thickened. Papules were not seen. Fundi and cardiovascular systems were normal. A 'blind' skin biopsy of the neck revealed changes of PXE.

Case 3

T.O.L., brother of Case 1. This 40-year-old man had a haemoptysis 4½ years ago and was found to have pulmonary tuberculosis. After 1½ years of chemotherapy the haemoptyses stopped. For 2½ years, he began to have recurrent attacks of haematemesis and melaena. There was no history of ulcer pain and repeated barium meal examinations were negative. He had no visual or cardiovascular symptoms. The only positive finding on examination was slightly thickened skin over the neck. Papules were absent and other areas were normal. Angioid streaks were not found. Skin biopsy over the neck was positive for PXE.

Case 4

T.C.B., sister of Case 1. This 33-year-old woman had had recurrent haemoptyses for 2 years, and was thoroughly investigated in a chest hospital but no obvious cause was found. There was no history of haematemesis, bleeding from other organs, visual or vascular disturbances. A few small yellowish papules along the thickened skin creases over the neck were present and skin biopsy over it confirmed the presence of PXE. No cutaneous changes were seen in other sites and angioid streaks were absent.

Case 5

Y.Y.J., mother of Case 1. This 75-year-old woman had no symptoms except for occasional attacks of mild giddiness. Examination of the skin over the neck revealed five to six small papules of a yellowish colour. Advanced skin changes were present on both axillae which showed redundant, inelastic, hanging

FIG. 5. Case 6. Loose, lax, inelastic axillary skin hanging in folds on both sides.

skin folds. The skin of other areas was normal. Angioid streaks were not seen and she had no cardiovascular lesions. Skin biopsy from the neck was consistent with PXE. While this paper was being prepared she had a sudden bout of severe haematemesis and died at home. No necropsy could be performed. There was no history of PXE in her parents or her brothers and sisters.

Case 6

T.A.B., first (paternal) cousin of Case 1. This 60-year-old woman had no history of bleeding, visual or cardiovascular disturbance. Since childhood, she had noted increasing skin folds in both axillae, but this did not cause her any undue concern. On examination, she had no retinal or cardiovascular lesions. There were no papules on the skin over the neck, but the creases were slightly thickened. The axillary skin on both sides was loose, lax and inelastic and hung in folds (Fig. 5). Skin biopsy of her neck showed PXE.

Comment. Cases 1–6 came from the same family. Cases 2, 3 and 4 were brother and sister of the propositus, and Cases 5 and 6 were her mother and paternal first cousin, respectively. Apart from the propositus, two had recurrent haemoptyses and active tuberculosis was ruled out; two had gastrointestinal bleeding of unknown aetiology; and two had attacks of giddiness of mild degree. Cutaneous changes on the whole were unimpressive in all cases and were it not for the discovery of PXE in the first

patient, the diagnosis would have been missed. Not only were xanthomatous papules absent, but some cases had hardly any skin changes at all, and a 'blind' skin biopsy was necessary to demonstrate the presence of PXE. Both her mother and her cousin, however, being older than the rest, had more advanced cutaneous changes, especially over both axillae. The former died from a fatal gastro-intestinal bleeding due to the disease.

Case 7

L.C.L., Chinese female age 60. This patient was first admitted to the ward for congestive cardiac failure due to mitral stenosis. Ten years before she had been admitted to a mental hospital for severe depression and frank psychosis. There was no history of bleeding, visual disturbance or ischemic pains. She came from China and there was no family history suggestive of PXE.

On examination she had cardiac failure, rheumatic mitral stenosis and atrial fibrillation. Blood pressure was 110/60 mm Hg. Vessel walls were slightly thickened. Neurological examination including fundoscopy was normal. The skin on both sides of the neck had a number of tiny yellowish papules and the creases were thickened. Axillary folds were prominent and redundant. Skin biopsy of the neck papules revealed PXE.

She was readmitted 1 month later for the sudden onset of giddiness, vertigo, tetraplegia and deepening coma. No carotid bruit was heard and the

cerebrospinal fluid was clear. She succumbed to terminal bronchopneumonia 3 weeks later without regaining consciousness.

Necropsy. The aorta and the cerebral, renal and coronary vessels were atheromatous. An area of softening 1 cm in size was found in the centre and to the left of the pons. The left common carotid artery which showed gross atheromatous changes, had organized thrombus at the bifurcation. The mitral valves were thickened, fibrotic and fused at their edges with the orifice barely admitting the tip of index finger. Bronchopneumonia was present.

Comment. The presence of PXE in this elderly woman with rheumatic valvular disease and widespread vascular degeneration could be a mere coincidental finding without any significance. On the other hand, PXE might well be responsible for the generalized atheromatous changes with a vascular occlusion; and possibly, for the mental illness she had 10 years ago. Unfortunately, we were unable to study her family as they were all in China.

Case 8

T.S.G., Chinese female age 25. This girl presented at the skin clinic as a cosmetic problem. She had no bleeding, no visual trouble and no cardiovascular disturbance. She complained of having had multiple small discrete yellowish papules over both sides of the neck, shoulders, upper arms, forearms and thighs for 2½ years. Minimal skin thickening was present. Angioid streaks were absent. All the other systems were normal. Family history was negative. Skin biopsy of the papule was consistent with PXE.

Comment. As a young fashion-conscious girl, she presented purely as a dermatological disorder because of the cosmetic defect due to skin changes of PXE. Systemic lesions were not present.

Discussion

PXE is a rare systemic disease with mucocutaneous manifestations. Eddy & Farber (1962) in a statistical review found about 200 cases from the literature. In this study at Singapore, eight cases have been collected over the last 3 years of whom six belonged to one family (Table 2). It is possible that more members of this family would be affected if they were available for examination and skin biopsy.

All these patients were Chinese. As in other series, females predominated in this group (87.5%). All except one was over 30 years old, and the oldest was 75. Eddy & Faber (1962) found 48% of the cases between ages 30–50. Most authors including Van Embden (1952) and his colleagues believed that the majority of PXE cases probably had minimal asymptomatic skin changes from an early age. Time and the ageing process or other factors could cause the disease to manifest itself at a later stage. This

observation might be applied to the offspring of Case 1, all of whom were young and had no demonstrable evidence of PXE. With increasing age, as seen in those cases over 50, the cutaneous lesions were more prominent.

The high family incidence, six in our series, had been shown before by Touraine (1940) and others. An incidence of 15.5% in families, 24.5% in siblings and 2.5% in consanguinity has been reported (Eddy & Farber, 1962). Consanguinity in parentage strengthened the hypothesis that most cases are inherited as an autosomal-recessive trait (Berlyne, Bulmer & Platt, 1961). In the present family, the fact that both the mother and the first cousin from the paternal side of the propositus (Case 1) were affected, strongly suggests that the father was either affected or a heterozygous carrier. It was unfortunate that the families of the last two cases were not available for examination.

The cutaneous lesion, which is one of the hallmarks of PXE was nevertheless mild to minimum in all our cases. In three instances where the skin of the neck showed no changes, blind biopsy confirmed the presence of the disease. This procedure was suggested by Rook, Wilkinson & Ebling (1967) for asymptomatic and suspected cases. Without a high index of suspicion of PXE and close inspection of the skin over the neck and axillae, the small number of papules and the thickened skin folds would have certainly been missed. Skin changes alone were reported in 8% of cases collected by Eddy & Farber (1962). Three of our patients had cutaneous manifestations only, and only one presented with a cosmetic problem.

Another important feature associated with PXE is angioid streaks in the retinae. It was absent in all these eight cases. Angioid streaks appear as broad, irregular brownish-red streaks radiating like spokes of a wheel from the peripapillary ring and are due to rupture of the elastica of Bruch's membrane. About 50–85% of PXE have eye changes (Goedbloed, 1938; Hannay, 1951). Only 5% have retinal lesions alone, but angioid streaks may occur in Paget's disease of the bone and sickle-cell disease (Cawley & Waery, 1962). Visual disturbances may occur from degeneration of the retinal vessels.

Since Chauffard's report in 1889, gastro-intestinal bleeding from PXE has been widely reported (Reinertson & Farbere, 1955; McCaughey, Alexander & Morrish, 1956; Whitcomb & Brown, 1962). In a minority of cases, haemorrhage is due to concomitant lesions such as peptic ulcer, hiatus hernia, or neoplasm, but the usual cause of bleeding is due to disease of gastric vessels. Microscopic studies reveal elastic degeneration in the media of small and medium-sized arteries with microaneurysmal capillaries and veins. Gastric mucosa is

TABLE 2

Case No.	Relationship to Case No. 1	Sex	Age	Haemorrhagic episodes	Other symptoms	Retinal changes	Skin lesions		Other findings	PXE skin biopsy
							Neck	Axillae		
1	—	F	43	Haematemesis, epistaxis, haematuria, haemoptysis, bleeding per rectum, menorrhagia	Giddiness, faintings, 'fit', depression, oedema of face, legs, abdomen, numbness	—	+	+	Gastric mucosal tear, fatty necrosis and calcification of gastric vessel, hepatosplenomegaly, ascites, neuropathy, generalized narrowing of major vessels	+
2	Sister	F	42	Haemoptysis	Giddiness	—	—	—	—	+
3	Brother	M	40	Haematemesis, haemoptysis	—	—	—	—	—	+
4	Sister	F	33	Haemoptysis	—	—	+	—	—	+
5	Mother	F	75	Haematemesis	Giddiness	—	—	+	—	+
6	Cousin	F	61	—	—	—	—	+	—	+
7	Not related	F	60	—	Psychosis, cerebral thrombosis, cardiac failure	—	+	+	Generalized atheroma of vessels. Pontine softening, carotid artery thrombosis, mitral stenosis	+
8	Not related	F	25	—	Cutaneous papules	—	+	—	—	+

found to be oedematous, friable, ulcerative and even necrotic (Kaplan & Hartman, 1954; Woo & Chandler, 1958; Carlborg *et al.*, 1959).

Three of our cases presented with gastro-intestinal bleedings of unknown origin and one (Case 5) died from severe bleeding. Case 1 bled for 5 years and presented as a great diagnostic problem before the disease was recognized. The discovery saved her from further surgical intervention. Features of PXE lesions were observed but were not appreciated until later. These were the spontaneous gastric 'tear' of the mucosal wall, fatty necrosis and calcification of the gastric vessels, and the yellowish nodule on the oesophageal wall. In Eddy's review, 13% of PXE had gastro-intestinal tract bleeding and the majority of the cases occurred between 20 and 30 years of age. Typically, the unexplained bleeding in young patients is recurrent, never massive, and seldom causes severe bleeding.

Far less common presentations were epistaxis, haemoptysis, haematuria, bleeding gums, sub-arachnoid haemorrhage, epicardial haemorrhage, menorrhagia and metrorrhagia. Occurring only in about 3%, bleeding from various organs was attributed to vascular degeneration of the affected viscera.

Four (50%) of our cases had haemoptysis. In addition to haematemesis and haemoptysis, Case 1 also bled from the nose, urinary tract and uterus. Pulmonary tuberculosis was found in two patients with haemoptysis, but after treatment at the Chest hospital with chemotherapy and surgery, symptoms recurred although the pulmonary tuberculosis was considered to be quiescent. Repeated search in all four cases failed to reveal any aetiology, although Case 1, on bronchoscopy, showed a haemorrhagic mucosal wall on the right bronchus.

Symptoms of arterial insufficiency caused by PXE are common and protean. Premature atherosclerosis in this disorder is due to elastic tissue fragmentation and degeneration in the media of the arteries leading to secondary deposition of calcification. Virtually every organ in the body can be affected (Loria *et al.*, 1957; Carlborg *et al.*, 1959; McKusick, 1956-60). Of about 200 cases reviewed by Eddy & Farber (1962), 18% had intermittent claudication, 25% had diminished or absent peripheral pulses (Carlborg, 1944), 19% had angina, and 14% had calcification of peripheral vessels on X-rays. Nearly a quarter of the cases had varying degrees of hypertension but most of these patients were over 50 years of age, and sometimes they were thought to have essential hypertension.

None of our cases had any ischemic pain in the heart or limbs, and arterial calcification was not encountered. Attacks of giddiness, sometimes associated with sudden posture changes in Case 1,

and also in her sister, mother and two of her daughters could have been due to vertebro-basilar insufficiency from the atherosclerosis of PXE, but none of them had any demonstrable neurological signs. These symptoms were most likely psychogenic in origin. However, arch aortography in Case 1 did demonstrate some narrowing of all the major arteries of the aortic arch, including the cerebral arteries. Necropsy study of Case 7 also revealed generalized atheromatous changes of major vessels as well as multiple thromboses involving the basilar and carotid arteries. The pathology was also compatible with degeneration due to aging since she was 60 years old.

Psychiatric illness ranging from 'neurasthenia' to frank psychosis were found in 6.5% of cases (Carlborg *et al.*, 1959; Eddy & Farber, 1962). Two of our patients (Case 1 and Case 7) and the second sister of Case 1 had depression and marked psychosis and all these three cases had admissions to the Psychiatric Hospital for treatment. Neurological manifestations of PXE are rare and only 1.5% of the cases had epilepsy. Case 1 had fits with loss of consciousness, but they were more like hysterical seizures than grand-mal attacks and were associated with hyperventilation, tetany and negative neurological signs. She developed polyneuropathy with marked sensory loss of glove-and-stocking distribution at a later stage. This condition, which has not been reported before, might be attributed to vascular damage of vasa nervosa. Thiamine deficiency, alcoholism and other like causes had been excluded.

The pathogenesis of PXE is entirely unknown. Darier's concept (1896) that the fault lies in the elastic tissue was recently challenged by Hannay (1951), Tunbridge *et al.* (1952) and McKusick (1960) who argued that the basic defect is in the abnormal collagen fibres which take on histochemical features simulating that of elastic tissue. The original 'elastic' theory however had many supporters, and recently with improved techniques and modern equipments such as electronic microscopy, micro-incineration, elastase digestion and purification methods (Loria *et al.*, 1957; Moran & Lansing, 1958; Smith, Sams & Davidson, 1962) it has been established that the primary site of the abnormality in PXE is the elastic tissue.

Acknowledgments

I thank Professor Khoo Oon Teik for permission to publish these cases, Dr Beatrice Chen for reading the script and Mr. Chua for secretarial assistance.

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