a gradual decrease in the number of proliferated bile ductules and serum CA19-9 is normalised.

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A case of systemic pseudo-pseudoxanthoma elasticum with diverse symptomatology caused by long term penicillamine use

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Accepted for publication
9 December 1997

Abstract

A 47 year old man presented with a two year history of increasing cervical dysphagia, dyspnoea, and cutaneous signs. He had been diagnosed 27 years previously with Wilson's disease and was treated with penicillamine (1.5 g daily). Systemic abnormality of elastic fibres was confirmed by light and electron microscopy following biopsy of skin, lung, oesophageal muscle, gum, pharyngeal tissue, and cervical connective tissue. Dysphagia was relieved by cricopharyngeal myotomy. Substitution of trientene dihydrochloride for penicillamine relieved cutaneous and systemic manifestations. This is possibly the first case demonstrating an association between prolonged penicillamine use and biopsy proved systemic pseudo-pseudoxanthoma elasticum. The presenting symptoms may have resulted from the abnormal numbers and properties of elastic fibres, and the changes were caused by penicillamine use, rather than by idiopathic, inherited pseudoxanthoma elasticum.

(*J Clin Pathol* 1998;**51**:169–171)

Keywords: penicillamine; pseudoxanthoma elasticum; trientene dihydrochloride; Wilson's disease

Penicillamine (D-B-B-dimethylcysteine) is a heavy metal chelator used to treat Wilson's disease (an autosomal recessive abnormality of hepatic copper excretion). Prolonged use at high doses (1–2 g daily) may cause elastic fibre disorders in skin, lung, viscera, blood vessels, and connective tissues.[1–6] The term pseudo-pseudoxanthoma elasticum (PPXE)[3] distinguishes the acquired condition from idiopathic, genetically controlled pseudoxanthoma elasticum (PXE). We report the manifestations and management of a patient with histologically proved, systemic, penicillamine induced PPXE.

Case report

A 47 year old white man (a non-smoker with no previous lung disease) presented with a two year history of increasing cervical dysphagia necessitating a liquid diet, dysphonia, and progressive effort dyspnoea. He had been diagnosed with Wilson's disease 27 years previously, following an acute psychotic illness, and was treated with penicillamine (1.5 g daily). The Wilson's disease, inherited with an autosomal recessive pattern, affected three of his siblings. There was no history of idiopathic PXE in the family. None of the three affected siblings had PXE-like symptoms (although one has coarse skin), despite treatment with long term penicillamine.

Ten years earlier a benign vocal cord nodule of our patient was excised to relieve dysphonia. Over three years, excision biopsies of skin, a gum dermatofibroma, and thickened pharyngeal tissue indicated changes of PPXE.[7] Clinical examination consistently revealed a yellow "plucked chicken" appearance of the folded skin of the neck and axillae but no angioid streaks in the retina. Barium studies showed hold-up to flow through the oesophagus at the cricopharyngeus. Manometric investigation demonstrated an abnormal, incomplete or non-relaxing upper sphincter zone with premature closure following deglutition with a pressure of > 40 mm Hg (normal, 53 (23) mm Hg). Oesophagoscopy revealed normal squamous mucosa. Dilatation of the narrowed zone by a 60 F gauge Maloney

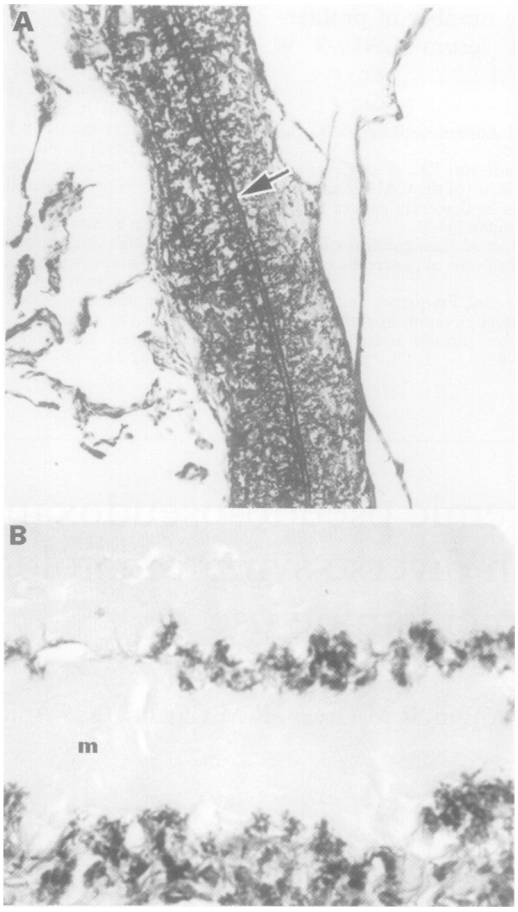

Figure 1 (A) Section of lung stained with elastic Van Gieson. The abnormal elastic fibres are seen as a double contour in the pleura (arrow). (B) Section of upper oesophagus showing the lateral budding of dense groups of elastic fibres running between bundles of striated muscle (m).

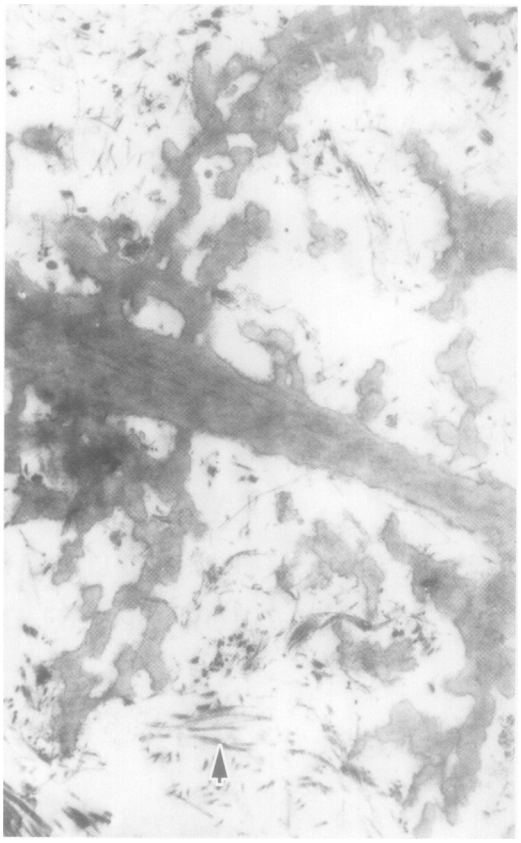

Figure 2 Transmission electron micrograph of an abnormal, arborising, elastic fibre from cervical connective tissue. Normal collagen fibres are arrowed. (Original magnification, ×14 300).

dilator was achieved easily. Open lung biopsy was performed at the time of dilatation. As the dysphagia was unrelieved, a longitudinal cricopharyngeal myotomy through the muscle layers of the oesophagus was performed. The toughness of connective tissues within the neck made dissection difficult. Biopsy specimens were taken of skin at the incision site, of muscle fascia, and of oesophageal muscle; these were fixed freshly in formalin and glutaraldehyde. No impairment of wound healing was seen following the procedure.

Light microscopy of all tissues (skin, lung, oesophageal muscle, and connective tissue) showed excess elastic fibres with thickening and lateral budding and the characteristic "lumpy bumpy" appearance of PPXE.[1 8] In the lung, the pleura (fig 1A) and bronchial walls were involved. Lung parenchyma, otherwise normal, showed some early emphysematous change. Comparison of the oesophageal biopsies with tissue from a normal oesophagus (from an organ donor at transplant harvest) demonstrated the excess and abnormality of elastic fibres within all levels of the wall (fig 1B). Fibres within walls of arteries and veins of all tissues were abnormal. The elastic fibres showed no accumulation of calcium (von Kossa stain was negative).

Transmission electron microscopy confirmed irregularity of the elastic fibres. No normal elastic fibres were seen in any of the biopsies (normal elastic fibres are seen as long wavy strands, forming a delicate anastomosing network between collagen fibres). The abnormal fibres consisted of a central core of uneven thickness with many lateral arborisations. There were branches at right angles to the main fibre with perpendicular lateral arborisations off these producing a "stag-horn" or "fractal" appearance (fig 2). Elastic fibres from skin had shorter and plumper arborisations than those from connective tissue. In the central core, thin microfibrils were embedded in amorphous material. There were no microfibrils in the lateral buds. In oesophageal muscle, some smooth and striated muscle cells were thinned and pulled apart by the abnormal fibres, with fragmented elastic material deposited between them. In contrast to the abnormal elastic fibres, the adjacent collagen fibres were normal in structure (with a normal banding repeat pattern of 64 nm) and arrangement.

Radiographic and symptomatic resolution of cervical dysphagia followed myotomy. Chest radiography and computed tomography showed bilateral pulmonary shadowing with no pleural thickening or lymphadenopathy. Pulmonary function tests[9] showed a restrictive defect with FEV1 of 3.12 litres (81% of predicted normal), forced vital capacity (FVC) 4.00 litres (84% of predicted), a total lung capacity (TLC) 77% of predicted, and gas transfer 64% of predicted. An immunological screen was negative.

With worsening pulmonary function, empirical treatment with 30 mg prednisolone daily was prescribed. After six weeks there was

a symptomatic improvement in his dyspnoea. This was not sustained, TLC falling to 60% of predicted and gas transfer to 53%. Furthermore, the patient developed a steroid psychosis. The deterioration in physical and mental states, together with histological evidence of multisystem PPXE, triggered the decision to initiate treatment with trientene dihydrochloride (Trientene; K & K-Greeff Ltd, Croydon, UK) at a dose of 300 mg four times a day, and to discontinue penicillamine. Twelve months after the change of medication the cutaneous PXE-like changes were very diminished. Systemically the patient was improved, without dysphagia or dyspnoea. Pulmonary function was stable (FEV1 2.84 litres, FVC 3.79 litres, TLC 77%, and gas transfer 58% of predicted). At 36 months (48 months postoperative), he is neurologically controlled, is swallowing easily, and has stable pulmonary function and chest radiology.

Discussion

We believe this is the first case demonstrating an association between prolonged penicillamine administration and biopsy proved systemic PPXE. We postulate that the presenting symptoms resulted from the abnormal numbers and properties of elastic fibres, and that the changes were caused by penicillamine use, rather than by idiopathic, inherited PXE. It is not known why only one of the four siblings should manifest the changes of PPXE. PPXE, although producing similar cutaneous manifestations to those seen in PXE, has different structural abnormalities and a different aetiology. In PPXE, penicillamine impairment of stable fibre cross links is implicated rather than calcification of fibres (as is the case in PXE).[5 8] The lack of family history and ocular signs, together with systemic abnormalities of non-calcified elastic fibres, all serve to define our case as one of PPXE.

In normal extracellular space, elastin polypeptides align into a fibrillar structure that is stabilised by desmosomal interchain cross links, requiring the catalysis of a copper dependent enzyme (mapped to human chromosome 5q23), lysyl oxidase, which is also required for the cross linking of collagen fibres. Penicillamine could possibly chelate extracellular copper, interfering with lysyl oxidase. The correct formation of elastic tissue and collagen needs aldehydes to form stable cross links. Lysyl oxidase mediates the oxidation of lysine residues in collagen and elastin and hydroxylysine residues in collagen. They are oxidised to their respective aldehydes, which react with one another to form stable cross links.[5 10] Penicillamine reacts with aldehydes to form thiozolidine compounds, thus impairing the formation of such stable cross links.[8] Penicillamine does not affect mature collagen but interferes with new production; it may be many years before collagen defects manifest themselves as dermatopathies. PXE-like changes appear particularly in flexural areas, where the elastic tissue production rate may be high because of stretching stresses.

Myotomy relieved the patient's dysphagia, suggesting that this symptom was predominantly caused be local abnormalities of muscle and connective tissue compliance. Similarly, his restricted pulmonary function may have resulted from abnormal fibres reducing lung elasticity. Penicillamine gave long term control of neurological functions but provoked a diverse symptomatology. The systemic nature of the PPXE made treatment difficult, and there was an insidious progression of symptoms. Penicillamine and trientene dihydrochloride both act as chelating agents, which mobilise abnormally deposited copper and result in a cupriuresis. Trientene dihydrochloride is being developed for use in Wilson's disease for patients who are intolerant to penicillamine. Penicillamine has the property of impairing stable cross links of newly formed elastic fibres with collagen. If penicillamine treatment is abandoned (and trientene has no deleterious effect on the availability of copper for the dependent enzyme lysyl oxidase) switching to the new drug may allow formation of normal elastic linkages, permitting relief from systemic symptoms caused by abnormal numbers and structures of elastic fibres, with a rate of improvement depending on the rate of turnover of fibres in different tissues. Thirty six months after substitution with trientene dihydrochloride in our patient, Wilson's disease was controlled, with objective evidence of improvement in the patients' systemic complications.

The patient is also under the care of Professor H R Matthews (Consultant Thoracic Surgeon) and Dr M Anderson (Consultant Neurologist) of Birmingham Heartlands Hospital. Miss K A Noble (Oesophageal Function Laboratory, Birmingham Heartlands Hospital) performed preoperative manometry. Mr G Mannion gave skilled photographic support. SJD is supported by the Oesophageal Cancer Fund (OCF), Birmingham.

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