Case report

Engelmann's disease of bone—a systemic disorder?

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SUMMARY A patient with Engelmann's disease of bone (progressive diaphyseal dysplasia) also suffered from Raynaud's phenomenon, multiple nail fold infarcts, anaemia, leucopenia, hepatosplenomegaly, and a raised erythrocyte sedimentation rate. Her mother, who also had this inherited bone disease, was known to have Raynaud's phenomenon, necrotising vasculitis, and digital gangrene. Review of other published cases of Engelmann's disease indicates that some of these features are not uncommon. It is argued that Engelmann's disease is not primarily a metabolic bone disease but may be a systemic disorder which might be included within the spectrum of the inflammatory connective tissue diseases. The beneficial effects of steroid treatment on both skeletal and systemic features are compatible with this view.

Engelmann's disease (progressive diaphyseal dysplasia) is commonly regarded as a metabolic disease of bone and has been described in over 100 patients.¹ The features of painful cortical thickening and sclerosis of diaphyses with muscular wasting and weakness are characteristic. Its autosomal dominant inheritance has been emphasised, though sporadic cases are recorded. Smith *et al.*² highlighted the inconstant biochemical changes of raised serum alkaline phosphatase and urinary total hydroxyproline and, occasionally, hypocalcaemia, hyperphosphataemia, and positive calcium balance. Much less attention has been paid to other associated systemic features including anaemia, leucopenia, hepatosplenomegaly, raised erythrocyte sedimentation rate (ESR), and the striking improvement obtained with corticosteroid therapy.³ This paper describes a patient with Engelmann's disease who displayed all these systemic features but who also developed Raynaud's phenomenon and multiple nail fold infarcts. Corticosteroids caused simultaneous resolution of the haematological and biochemical abnormalities as well as an abrupt lessening of bone pain.

Case report

A married woman born 29 January 1947 first

developed pains in her lower legs at the age of 8 years, and the characteristic widened diaphyses were surgically treated on 2 occasions without relief of symptoms.

The diagnosis of Engelmann's disease had previously been made in her mother, who had developed pains in wrists and ankles after a pregnancy at the age of 24 years. Several of her mother's relatives may possibly have been affected but have not been examined. Her mother was never as severely incapacitated by bone pain as herself, but at the age of 51 years the mother developed Raynaud's phenomenon, a necrotising vasculitis leading to digital gangrene and abdominal pain and bloody diarrhoea, which was considered likely to have a vasculitic aetiology. Investigations in her mother included: haemoglobin (Hb) 9.2–11.8 g/dl, ESR 62, a positive antinuclear factor (ANF) on 2 occasions without LE cells, negative Coombs and rheumatoid factors, but raised IgM and IgA levels. Muscle biopsy failed to show evidence of polyarteritis nodosa, but it has not been possible to trace the necropsy record when she died at the age of 53. However, there seems little doubt that a widespread vasculitic process was responsible.

The patient first came under the care of the late Professor Charles Dent in 1973 at the age of 26 (Fig. 1). Her main symptoms were of continuous disabling pain in her tibiae and distal forearms, of tender bones, thigh muscle weakness, and deafness. Examination confirmed the gross bony widening in the

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Fig. 1 The patient in 1976. Note the wide bones in the legs with poor musculature and prominent clavicles.

diaphyses and metaphyses of lower legs and distal forearms with overlying warmth, suggesting increased bone blood flow (Figs. 2, 3, and 4). Proximal myopathy of pelvic girdle muscles, a liver palpable 2 cm below costal margin, and slight frontal

bossing were also noted. Audiometry revealed bilateral sensorineural deafness suggestive of cochlear involvement and presumably secondary to skull hyperostosis.

Initial investigations included: Hb 8.9 g/dl, white cell count $3.1 \times 10^9/l$, ESR 60, serum B_{12} 150 $\mu g/ml$, serum folate 3.6 ng/ml, serum iron 17 $\mu mol/l$, total iron binding capacity 67 $\mu mol/l$, serum calcium (Ca) 2.03 mmol/l, phosphate 1.09 mmol/l, alkaline phosphatase 16 King-Armstrong units/100 ml (3–14), 80% bone isoenzyme, plasma specific gravity 1.023; normal urea and electrolytes, proteins, and protein electrophoresis. Twenty-four hour urine Ca 0.4–0.8 mmol (3.2–8.3), creatinine 7.2 mmol (9–18), phosphate 13–18 mmol (15–50), total hydroxyproline 0.31–0.41 mmol (up to 0.35).

An iliac crest bone biopsy was described as follows: "Normal bone architecture and structure although amount of bone decreased to osteoporotic levels. More than half of the bone surface is covered by thin osteoid seams but osteoblasts are not prominent. There is an active but not excessive resorption. Mineral deposition and marrow are normal" (P. Byers, Institute of Orthopaedics). This was radiologically noninvolved bone, and so little conclusion can be drawn from it.

Treatment with cellulose phosphate to deplete her of calcium had already been started, and these histological changes may have been secondary. Some lessening of bone pain was obtained, but both her hypocalcaemia and proximal myopathy worsened and cellulose phosphate was abandoned.

Repeated ESR values were 65, 75, and 27/h, for which no cause was found. Rheumatoid factor and ANF remained persistently negative. Percutaneous needle muscle biopsy⁴ in 1977 revealed an increased prominence of some nuclei and occasional fibres with internal nuclei but was otherwise normal.

Between 1975 and 1978 her bone pains persisted, but transient and partial relief was obtained with intravenous infusions of glucagon⁵ with no biochemical improvement. Calcitonin produced improvement in neither pain nor alkaline phosphatase. Bone blood flow estimations were performed (Dr J. Reeve, Northwick Park Hospital) and showed that whereas before glucagon infusion bone was receiving 31% of total blood flow, after treatment bone blood flow was reduced to 14%.

In December 1977 the patient first described typical Raynaud's phenomenon. Splenomegaly was first noted, but investigations remained essentially unchanged: Hb 8.5–9.9 g/dl, white cell count $2.6\text{--}3.3 \times 10^9/l$ with a normal differential count, a hypochromic but normocytic blood film; a low serum iron and iron binding capacity; reticulocytes 0.2–0.8%; platelets $261\text{--}326 \times 10^9/l$; ESR 44–75/h. Coombs,

Fig 2 X-rays of patient. (Left) Left forearm. Age 17 years. Diaphyseal sclerosis only. Normal metaphyses. (Right) Right forearm. Age 30 years. Abnormal trabecular patterning through diaphysis and metaphyses. Abnormal modelling with new subperiosteal bone. Note the deterioration over the years.

Fig. 3 Patient aged 28–34 years. (Left) Right hand and wrist. (Right) Humerus. Note the abnormal widening, modelling, and trabeculation of bone, and new subperiosteal bone.

Fig. 4 Patient aged 28–34 years. Pelvis and hips. Note the abnormal widening, modelling, and trabeculation of bone, and new subperiosteal bone.

rheumatoid and antinuclear factor tests were negative. An ^{52}Fe scan showed a normal distribution of iron with no evidence of extramedullary haemopoiesis, thus excluding significant bony encroachment on marrow cavities typical of osteopetrosis (Fig. 5). The half life of red cells was 21 days (control 28 days), perhaps indicating increased splenic consumption. Bone marrow examination was normal. Isotope bone scanning (technetium polyphosphonate) showed increased uptake in femora, tibiae, and forearm bones with a lesser increase in ribs, pelvis, hands, and skull.

In October 1978 a trial of oral prednisolone, initially 60 mg daily, was started, and the clinical

Fig. 5 CT scan across mid femur. Note the wide mid femur with large medullary cavity.

improvement was no less than dramatic. One month later it was recorded: "Her pains have been virtually absent apart from slight aching in the ankles rather worse in the evenings." Both liver and spleen were no longer palpable. Hb rose to 14.7 g/dl; white cell count $6.3 \times 10^9/\text{l}$, and ESR values fell to 3/h (Fig. 6). Both serum calcium and alkaline phosphatase returned to normal. This remarkable clinical, haematological, and biochemical improvement has been maintained by prednisolone 7 mg daily, although she has developed cushingoid features, hypertension, and obesity. An attempt to withdraw steroids in March 1979 precipitated a prompt return of her bone pain and hepatosplenomegaly, and this was reflected by both haematological and biochemical relapse: Hb 10.2 g/dl, white cell count $3.0 \times 10^9/\text{l}$, reticulocytes 4.6% ESR 30/h; Ca 2.12 mmol/l, phosphate 1.15 mmol/l, alkaline phosphatase 14 King-Armstrong units, plasma specific gravity 1.0232. Adequate prednisolone again abolished her symptoms and relieved her anaemia and leucopenia.

She remained relatively free of pain but in August 1979 admitted to intense digital vasoconstriction, first noted in 1977. Multiple nail fold infarcts were noted in all digits of both hands, but no evidence of arthritis or arthralgia—other than a chronic stiffness

Fig. 6 Haemopoietic response to steroids.

of hips—was found. An immunological profile was sought: Hb 14.6 g/dl; white cell count $5.7 \times 10^9/l$ ESR 5/h; ANF weakly positive 1 in 20, speckled pattern, antibody to IgM; rheumatoid factor negative; anti-DNA antibodies 7 units/ml (normal less than 30); C3 1263 mg/l⁻¹ (860–1652); no immune complexes detected by the C1q binding technique. HLA typing A1, X, B7, B8.

Discussion

Although the name of the syndrome is sometimes lengthened to Camurati-Engelmann disease, it was first described by Cockayne⁶ in 1920 before the Royal Society of Medicine as an obscure case for diagnosis. Its inheritance was suggested by Camurati,⁷ who reported a father and son both with painful lower extremities caused by cortical thickening and sclerosis of diaphyses. Engelmann's single case report⁸ associated the constant finding of muscle weakness and wasting with the marked bone involvement. Sparkes and Graham¹ in their comprehensive review of all cases recorded up to 1972 emphasise the wide range of severity, and it is possible that many cases are diagnosed as Paget's disease to which it has a superficial resemblance in visual appearance, warmth overlying affected bones, and raised alkaline phosphatase. However, the autosomal dominant inheritance, the age of onset in childhood or adolescence, and the proximal myopathy all serve to distinguish it.

The systemic features described in our patient are not a chance finding. Lennon *et al.*⁹ considered splenomegaly as more than an occasional feature of Engelmann's disease, and scant attention given to it in previous reports seems to follow from the conclusion that the hyperostosis encroaches on marrow cavities with secondary extramedullary haemopoiesis in the spleen and liver.² Osteopetrosis (Albers-Schönberg disease) may be considered the bone prototype of this. A leucoerythroblastic peripheral blood would seem more likely, but, where hepatosplenomegaly has been recorded in Engelmann's disease, a normocytic (or microcytic) and normochromic (or hypochromic) picture is present. The ⁵²Fe scans in this patient revealed haemopoiesis at normal sites rather than in liver or spleen. CT scans of the femur revealed a wide medullary cavity and not a marrow space reduced by hyperostosis. The reduced red cell life could be explained by destruction in the enlarged spleen. Steroids may have cured the anaemia and leucopenia either by reducing this destruction or by stimulating the marrow.

Raised ESR values in Engelmann's disease have been widely recorded previously. Smith *et al.*² described 4 patients, and 3 had values of 27, 40, and

40/h for which no explanation is offered. Their fourth case shows more than a superficial resemblance to our own. Progressive bilateral conductive and nerve deafness occurred, and involvement of middle ear bones and overgrowth of bony canals would seem a likely explanation. More striking were the features of splenomegaly, Hb 8.9 g/dl with normochromic, normocytic indices, and an ESR of 110/h. Although the ANF was positive in only a titre of 1 in 20, both slide latex and LE cell preparations were positive on 3 occasions. This patient succumbed after a hysterectomy operation, and, although cerebral infarction was clinically suspected, no evidence of such was found at necropsy. No comment is made on the presence of histological vasculitis, but the possibility of cerebral vasculitis is an intriguing one. Moreover, one of the cases of Allen *et al.*³ had splenomegaly and lymphadenopathy with an Hb of 7.4 g/dl and thrombocytopenia, and 2 of their cases had raised gamma globulin levels.

The abrupt response to corticosteroid therapy is perhaps the primary feature that removes Engelmann's disease from the spectrum of purely 'metabolic bone diseases.' Allen *et al.*³ described the clinical improvement with steroids in 3 patients and histologically confirmed increased bone resorption and secondary remodelling, with increased osteoclastic activity and decreased lamellar bone deposition. The mode of action of corticosteroids on the bone pathophysiology is obscure. They may suppress periosteal overactivity, which presumably leads to the excessive bone deposition. What vascular, immunological, or other fundamental defects trigger this overactivity is unknown.

It is acknowledged that the autosomal dominant inheritance of Engelmann's disease may just include an increased predisposition to a connective tissue disease. At least there is much evidence to conclude that it is more than a rare locomotor syndrome confined to bone and muscle. No previous record of HLA typing in Engelmann's disease is available, and further reports are awaited. Although the ANF was weakly positive, no evidence of complement consumption or of immune complexes was found. However, these tests were performed during clinical and haematological remission on steroid therapy and should be performed in other untreated cases.

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