Werner’s syndrome is a rare condition usually presenting as premature ageing in adults. Over a period of 30 years we have followed two siblings with extensive musculoskeletal manifestations including a soft-tissue tumour, insufficiency fractures, nonunion and tendonitis, with associated problems of management. The literature is reviewed.

Received 10 August 1999; Accepted after revision 11 October 1999

Werner’s syndrome is extremely rare and is attributed to an autosomal recessive mutation on chromosome 8\(^1,2\) leading to disorders of ectodermally-derived cells, and manifesting as premature ageing.\(^3\) We describe a middle-aged brother and sister with the syndrome who have many musculoskeletal manifestations of the disease which demonstrate the main features of the orthopaedic management of the syndrome.

Case reports

A 58-year-old man presented with a two-year history of a mass in the right forearm, the origin of which he related to overuse when tearing raffle tickets. It had gradually increased in size and become painful. His past medical history included surgery for a cataract in the right eye, replacement of a heart valve for calcific aortic stenosis, chronic ulceration of the lower limbs and an increasingly hoarse, squeaky voice.

On examination, he was a small, balding man with a fusiform swelling, 4 × 6 cm in size, in the flexor compartment of the right forearm. The ‘tumour’ was clinically separate from the skin and mobile over the radius, with no evidence of attachment to neurovascular structures or to tendon. Ultrasonography revealed an echogenic mass originating from the muscles of the forearm but separate from the radius. MRI (Fig. 1) showed a large elliptical mass in the flexor compartment of the forearm (3 × 3 × 6.5 cm) confined to the flexor carpi radialis and flexor digitorum superficialis extending distally to the flexor tendons. The probability of malignancy led to radical excision. Histological examination confirmed the diagnosis of malignant fibrous histiocytoma with clear margins of excision.

His sister had been seen initially at the age of 23 years with stunted stature and failure to thrive. A diagnosis of anorexia nervosa had been suggested. She was also noticed to have a spondylolisthesis at L5-S1. A few years later she presented with bilateral hallux valgus. Keller’s operation was performed bilaterally but was complicated by poor wound healing and chronic ulceration; amputation through the mid-foot was eventually required. The skin had repeatedly ulcerated thereafter.

Several years later, she sustained a fracture of the right fibula which failed to unite and induced a stress fracture of
the tibia and a valgus deformity of the ankle (Fig. 2). A corrective osteotomy above the ankle was attempted but this failed to unite. Further stabilisation was required and the ankle was transfixed with a Steinmann pin in a functional position. This remains but there is no sign of bony union at the osteotomy (Fig. 3).

She also sustained fractures of the olecranon of both elbows at different times. Both went on to nonunion. One was treated conservatively and resulted in a dislocation of the elbow (Fig. 4).

She developed generalised osteopenia at an early age, with an anterior wedge fracture of T10. There was also severe Achillis tendonitis with calcification, clawing of the hand, notably at the metacarpophalangeal joints, marked distal wasting of muscles of the lower limbs, and ulceration of the elbows requiring skin grafts.

Over a 40-year period, she also developed bilateral cataracts, alopecia, scleroderma-like skin lesions with hyperkeratosis, temporal lobe epilepsy, and duodenal ulceration.

In both cases, the clinical diagnosis of Werner’s syndrome was made late. All blood biochemistry and haematology investigations were normal except for a mildly raised glucose level in the sister.

Discussion

Werner’s syndrome was first described in 1904 and later elaborated upon by Epstein et al in 1966. Originally, it was reported as a combination of scleroderma-like skin lesions on the face, hands and feet, resulting in furrowing of the mouth, pseudo-exophthalmos due to loss of periorbital subcutaneous fat pads, increased skin pigmentation and hyperkeratosis with thin dry skin, and small stature (mean...
height, 157 cm male; 146 cm female). Premature greying, early balding and non-senile cataracts were present in 80% of patients. A hoarse, weak and high-pitched voice, calcific deposits in the heart valves, premature atherosclerosis and diabetes were all commonly associated. Almost all patients also had chronic skin ulceration, particularly on the legs. Both of the cases which we present have the defining features of the syndrome, but because of its rarity, the diagnosis was reached many years after the initial presentation, as also happened with most of the reported cases. The syndrome is most common in patients of Japanese origin, possibly associated with consanguineous marriage, but it has been described throughout the world. Differential diagnoses include Rothmund’s disease and progeria.

Thweatt and Goldstein suggested that the syndrome is attributed to a defect in a counting gene which controls the number of times cells can divide before terminal differentiation. Also, several overexpressed gene sequences have the capacity to inhibit DNA synthesis, disrupting biochemical processes and leading to early cellular senescence. As many as nine mutations of the gene have been described in Japanese and Caucasian populations. Oshima et al observed that all these mutations create a stop codon, or cause frameshifts which lead to premature termination of cell differentiation. Yu et al confirmed that defective metabolism of DNA is involved in the complex process of ageing in Werner’s syndrome, the features of which are probably the result of complete loss of function of the normal gene product. These genetic defects manifest on a cellular level in a number of ways. Abnormalities of insulin-like growth factor binding protein 3 and reduced mRNA for insulin-like growth factor 1 and epidermal-growth factor have been noted, leading to altered bioavailability of growth factors.

The musculoskeletal manifestation first noted by Werner was muscle wasting. Epstein et al also described muscle wasting, most notably in the lower limbs with normal muscle biochemistry. This has been shown to be a consistent finding in almost all reported cases. He also noted asymptomatic calcific deposits in ligaments and tendons, especially in the knees, ankles and hands, and further reports have confirmed this. Our second case, that of the sister, was unusual in that her calcific deposits in tendo Achillis were painful and her muscle weakness generalised.

Werner’s syndrome has been linked with malignancy with 10% of all patients developing tumours, 50% of which are sarcomata. Both soft-tissue and bony sarcomata have been reported and attention should be paid to the chance of concurrent, multiple, primary neoplasms. It is therefore important to diagnose Werner’s syndrome early and to investigate any uncomfortable swelling.

Osteoporosis has been reported in a number of patients with the syndrome and is thought to be the commonest radiological manifestation, occurring in 40% to 100% of cases. Rubin et al reported a nearly normal bone mineral density with a marked decrease in osteoid volume. This was also observed by Laroche et al who described histomorphometric findings revealing virtually no osteoid with normal osteoclastic resorption. The osteoporosis usually presents as vertebral deformity, with 17% of male and 4.9% of female patients in one study showing such a deformity. This took the form of vertebral wedging, spondylolistheses, pathological fractures and lumbar lordosis. More rarely, insufficiency fractures of the radius, ulna and metatarsus have also been reported. All failed to unite with conservative management.

We have found no other record of surgical treatment. Internal fixation failed in the sister despite repeated surgery. Nonunion occurs almost without exception irrespective of the mode of management of the fracture. Treatment of
osteoporosis in such cases has been attempted with recombinant, human insulin-like growth factor, but with equivocal results. 18

Minimal to moderate osteoarthritic changes have been noted in peripheral joints by Epstein, 3 and by Jacobson et al. 14 An erosive arthritis mutilans has also been observed in the digital interphalangeal joints of the hands and feet, 19 and osteomyelitis and septic arthritis are not uncommon. 14 Such infections may be a complication of the chronic skin ulceration which is a constant feature of the syndrome. Many patients with Werner’s syndrome have deformities of the feet with pes planus, hallux valgus and flexion contractures of the ankle most commonly mentioned. 14 As our attempts at surgical correction illustrate, these deformities are probably best managed by orthotics.

Further radiological abnormalities include reduced metacarpal cortical thickness scores, 17 and it has been proposed that the radiological combination of osteosclerosis of the distal phalanges of the hand or foot, osteoporosis and periarticular calcification, suggests the diagnosis of Werner’s syndrome. 20 Bones can also develop a moth-eaten appearance on radiographs, which is said to mimic myeloma 21 but it should be noted that myeloma has not been reported in Werner’s syndrome. 22

The most notable musculoskeletal features in our cases were malignant fibrous histiocytoma, osteoporosis and insufficiency fractures. A lack of bone healing led to non-union of all fractures despite appropriate conservative and surgical methods of treatment. In addition, very poor soft-tissue repair gave slow, ineffective wound healing and chronic ulceration which required amputation at a young age.

Serious complications must be expected by surgeons undertaking simple surgical procedures in patients with Werner’s syndrome. Salvage is difficult and problems have even been described with skin flaps. 23 A high index of suspicion for malignancy in the case of the brother was justified, and early radical surgery seems to have been successful. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References


