Ochronosis, the musculoskeletal manifestation of alkaptonuria, is known to lead to degenerative changes of the spine and weight-bearing joints. Symptoms related to degeneration of tendons or ligaments with spontaneous ruptures have not previously been reported. Three patients are described with four spontaneous ruptures of either the patellar tendon or tendo Achillis as the first symptom of ochronosis.

**Case reports**

**Case 1.** A 40-year-old carpenter had a sudden pain in his ankle which gave way while attempting to stand from a crouching position at work. He continued to work and reported to the hospital three days later with a persistent dull aching pain and an alteration in his gait. He was healthy, with no previous symptoms related to the musculoskeletal system. There was a palpable defect of tendo Achillis close to its insertion. He had weakness of plantar flexion and was unable to stand on his toes on the affected side. At operation it was found that the entire tendon was stained dull yellow and the ruptured surface deep black giving rise to the suspicion of ochronosis. The stump of the tendon appeared to be degenerate with multiple pigmented black nodules (Fig. 1a). The pigmentation was restricted to a few millimetres from the ruptured surface and the fibres of the tendon were fibrillated and degenerated in the area close to the rupture. There was also some deposition of pigment at the site of the insertion of the tendon to the calcaneum. The restriction of the pigment to a few millimetres on either side of the ruptured surface indicated that the tendon had been weakened in this region. Resection of the pigmented margins gave two healthy ends and the tendon was repaired using prolene. The ankle was immobilised in 20° equinus for three weeks and later the patient was mobilised partially weight-bearing in a neutral position for three further weeks. There was good healing of the repair and the patient remains asymptomatic four years later.
able to distinguish homogentisate-derived pigment from melanin.

Case 2. A 53-year-old bank employee tripped while walking and felt a snap in the right knee. He developed a swelling and had difficulty in extending the joint and walking. He presented to hospital immediately. He had no history of previous musculoskeletal symptoms. He had normal sclera and skin colour. There was swelling of the anterior aspect of the knee with a palpable depression at the lower end of the patella. Clinically, a rupture of the patellar tendon was suspected. The radiographs of the knee were normal. At operation, exposure of the knee by a midline incision revealed avulsion of the tendon from the inferior pole of the patella (Fig. 2a). The margins of the tendon were frayed and black. A few fibres, still attached to the patella, were also stained black, but the bone was normal. Examination of the joint revealed meniscal pigmentation and brownish discolouration of the articular cartilage of both the femur and the tibia. The degenerative changes of the patella were more extensive with large craters in the articular cartilage exposing subchondral bone. The areas of intact cartilage were stained brown and there was black pigmentation in the margins of the crater (Fig. 2b). There was a tear of the retinaculum which looked macroscopically normal. This was repaired using polydioxanone sutures and the patellar tendon was anchored by stainless-steel wires. The joint was immobilised for three weeks before gentle movements were started. Examination of the spine revealed reduced disc spaces with calcification and osteophytes (Fig. 2c). Radiographs of the major joints were normal. The patient confirmed that his urine turned dark when left to stand for a few hours.

Case 3. A 55-year-old man had a spontaneous rupture of his left tendo Achillis while running to catch a bus. Six months earlier he had had a spontaneous rupture of the right tendo Achillis while running downstairs. Radiographs of the ankle were normal. Ochronosis had been diagnosed because of the dark pigmentation at the ruptured ends of the tendons. Subsequently, he had noticed that his urine turned dark on standing. At operation, the tendon was found to be ruptured 1.5 cm from its insertion. There was dark pigmentation of the frayed ends. The pigmented margins were debrided to healthy tendon and the tendon was repaired. Postoperatively, he was immobilised in equinus for three weeks and with a splint for a further three weeks. He regained normal function.

Discussion

Alkaptonuria (urine which darkens on exposure to air) is a rare hereditary metabolic disorder with an incidence of 1 : 1 000 000 individuals. It is transmitted as an autosomal recessive disorder as a result of dysfunction of homogentisic acid oxidase, which is an important enzyme involved in the metabolism of the aromatic amino acids phenylalanine and tyrosine. The urine usually appears normal, but starts to darken upon standing because of oxidation and polymerisation of the homogentisic acid. The patients are usually asymptomatic until early adulthood. Pigmentation of the sclera or cartilage of the ear may appear by the second decade and this may also be seen in the teeth, buccal mucosa and in the nails or the skin, giving these areas a dusty colour. The clinical manifestations are caused by the accumulation of homogentisic acid in the fibrillar collagens of connective tissues to which it binds irreversibly by
polymerisation and oxidation. Alkaptonuric arthropathy, the only disabling effect of the disease, is due to brittleness and fragmentation of the articular cartilage, which also causes a non-specific synovitis. The spine and major weight-bearing joints are most commonly affected and symptoms usually start by the fourth decade. In ochronotic spondylosis, although the entire spine is affected, symptoms are mainly related to the lumbar region. There is flattening of the lumbar lordosis, decreased movements, narrowing of the disc spaces with calcification of the cartilage and prominent osteophytes. The features which differentiate this condition from ankylosing spondylitis are the absence of syndesmophytes, annular ossification and the bamboo sign. Extensive calcification of the intervertebral discs which appear elliptical and opaque is very characteristic. The hip, knees and other weight-bearing joints are also often involved and the changes may be severe enough to require total joint arthroplasty.
The numerous reports on alkaptonuria are limited to degenerative manifestations in joints, but there are no reports of the effects of the deposition of homogentisic acid in tendons leading to spontaneous rupture. Homogentisic acid is widely deposited in connective tissue and such pigmentation must include tendons, which contain mainly type-I collagen. The accumulation of homogentisic acid inhibits collagen cross-linking leading to reduction of the structural integrity of collagen, thus increasing the likelihood of spontaneous rupture.

All of our patients had characteristic radiological changes, particularly of the spine, but were asymptomatic. The diagnosis of alkaptonuria was retrospective in all patients. The patient with rupture of the patellar tendon had extensive degenerative changes in the articular cartilage of the femur, tibia and patella, but without previous symptoms. The trivial nature of the injury leading to the ruptures and the incidence of bilateral rupture of tendo Achillis in one patient indicates that spontaneous rupture of tendons is an important clinical feature of ochronosis. This has not been previously reported. In our patients the tendons healed well after debridement and primary repairs.

There is no specific treatment for alkaptonuric arthropathy; it includes physiotherapy, analgesia, and rest. Reduction of tyrosine and phenylalanine in the diet has been reported to reduce the excretion of homogentisate. It is not known whether dietary restriction from early life would avoid or minimise later complications, but such an approach is reasonable. Vitamin C, up to 1 g/day, is recommended for older children and adults. The mild antioxidant nature of ascorbic acid helps to retard the conversion of homogentisate to the polymeric material which is deposited in the cartilaginous tissues. Genetic advances offer hope that corrective measures are forthcoming. Of note, in a murine model of alkaptonuria, 2 (2 nitro-4-trifluoromethylbenzoyl)1,3-cyclohexanedione (NTBC) was a potent inhibitor of p-hydroxy phenyl pyruvate dioxygenase, which catalyses the formation of homogentisic acid. Development of the active compound may result in the first pharmacotherapeutic agent for this metabolic disease.

No benefits have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References