Joint and tendineous involvement in ochronosis: clinical history and imaging of a case

Sirs,

Ochronosis is a rare metabolic disease first described and so named by Virchow in 1866 as a post-mortem finding (1). The disease is the connective tissue manifestation of alkaptonuria which is an extremely rare hereditary error of metabolism with an estimated incidence of 1 per 250,000–1,000,000 persons (2). This disorder is transmitted as an autosomal recessive trait and it is characterized by the absence of homogentisic acid oxidase, an enzyme that plays a role in the metabolism of aromatic amino acids converting homogentisic acid (HGA) into its end product maleyl acetoacetic acid (3). As a result, homogentisic acid is excreted in the urine that in turn changes color to dark when exposed to the air because of the oxidation of the increased metabolic products (4). Oxidation and polymerization of the elevated levels of HGA give rise to a reactive end product that can bind irreversibly to collagen and accumulate within the connective tissue, causing pathologic blue-black pigmentation (5-7). Moreover, ochronotic pigment can deposit into the cells and matrix causing cartilage changes (8-10). Less common manifestations include cardiovascular abnormalities, renal, urethral and prostate calculi, dyspnoea.

A 56-year-old man, out-patient, was referred to the Rheumatology Unit of "Sapienza", University of Rome, at the beginning of 2004 for the assessment of pain and swelling of the left knee. In his personal history he referred arterial hypertension and pulmonary emphysema. There were no genetic or hereditary diseases in his family history. He reported a 3-year history of polyarthralgia and arthritis of both knees that appeared during the last year. Moreover, he described low back pain and widespread myalgias. The patient was 168 cm tall and weighed 65 kg (BMI of 23 kg/m^2). The physical examination showed a swelling of both knees and tenderness in the lumbar spine with moderate limitation in the flexo-extension movements. Sclera and ear cartilages exhibited a black-grey pigmentation. Laboratory investigations, such as a full blood count, serum biochemistry and ESR were within the ranges. Rheumatoid factor and HLA B 27 typing resulted negative. In order to confirm the diagnosis of alkaptonuria, his urine was left exposed to the air and assessed for the changes of colour that demonstrated a brown-black colour after 24h. Homogentisic acid was detected in the urine by gas chromatography at a concentration of 1720 μmol/mmol creatine (range 1000–5000 μmol/mmol). Moreover, the molecular analysis of 1,2-dioxygenase (HGO) was performed and it showed the IVS7 + 5 G>A mutation.

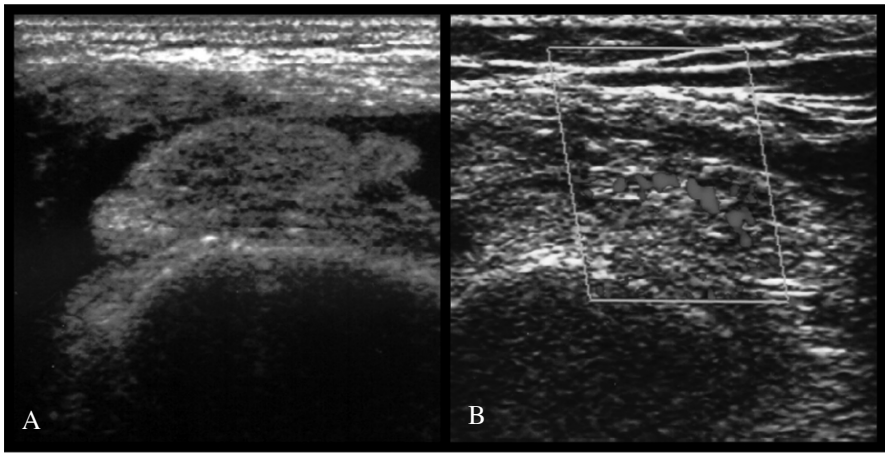

Fig. 1A-B. Ultrasound examination of the knee: severe joint effusion, marked synovial proliferation and increased vascularization.

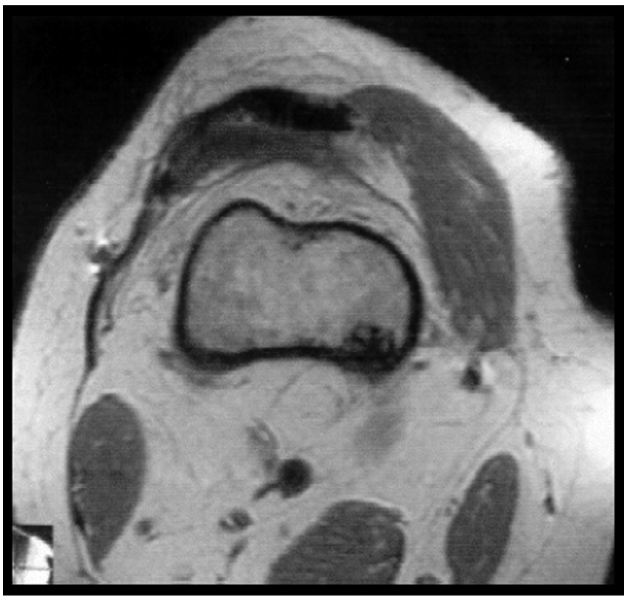

Fig. 2. MRI of the left knee: diffuse perimeniscal flogistic and degenerative changes in the medial and ventral compartment of the posterior ligament; diffused synovial involvement partially organized with a moderate effusion in the upper recess.

Radiography of the knees showed degenerative changes with a slight joint space narrowing, initial osteophytes and partial meniscal calcification compatible with a degenerative disorder. The spine x-ray exhibited a wafer-like image.

The ultrasound examination of both knees demonstrated a severe joint effusion, marked synovial proliferation with a villous aspect in the joint cavity and an increased vascularization Femoral condylar cartilage surface was irregular with a conserved thickness (Fig. 1A-B)

Synovial fluid analysis of the left knee showed a pH 7, 200 cells/mmc (PMN 5%, monocytes 95%), absence of crystal bodies and a 2nd type Ropes test. Therefore, a concomitant chondrocalcinosis was excluded.

A diagnosis of ochronotic arthropathy was done and non-steroidal anti-inflammatory drugs (NSAIDs) commenced.

However, one month later, the patient presented a persistent synovitis in both knees together with pain and swelling in both ankles. MRI scans of the knees revealed diffuse perimeniscal flogistic and degenerative changes in the medial and ventral compartments of the posterior ligament. A diffused synovial involvement, partially organized with a moderate effusion in the upper recess, was also detected (Fig. 2). Initial osteoarthritic changes were evident in the femoro-patellar joint. MRI scan of the ankles showed a pre-Achilles bursitis and high signal intensity in the insertional and pre-insertional portion of the Achilles tendon, due to degenerative changes. Erosive changes and osteophytes were also demonstrated in the great calcanear tuberosity of the postero-superior calcanear region.

The patient was treated with cycles of NSAIDs with partial and transient improvement. Thus, two intra-articular injections of steroid (metilprednisolone depot 40 mg) and three of hyaluronic acid (>1500 kDa) were performed in both knees with clinical

improvement. Ultrasound examination of the knees showed a marked reduction of the effusion and synovial proliferation with negative power Doppler technique.

In June 2007 the patient experienced an atraumatic total rupture of the right Achilles tendon, although he did not refer any articular swelling, pain or clinical symptoms of disease in the last year.

Surgical repair was performed confiding in the structural integrity of the tissue surrounding the site of rupture. Of particular interest, the macroscopic examination of the tendon showed hyperpigmentation of the fibres suggesting a tendineous involvement of ochronosis in course.

Deposition of ochronotic pigment in the connective tissue can be completely symptomless until the fourth or fifth decade; clinical signs appear only when articular cartilage is brittle, fissured and fragmented with the establishment of a severe ochronotic arthropathy (11).

Usually ochronotic spondyloarthropathy is the most common complication and the large peripheral joint involvement occurs several years later (12). On the contrary, in our patient a synovitis localised in the knees was the initial and most severe clinical sign of disease, followed by non-traumatic tendon rupture that should be considered as a manifestation of ochronotic artropathy (13, 14). It is possible to hypothesize that the synovitis is due to the joint involvement because of the presence of ochronotic pigment with a subsequent inflammatory reaction. However, it is not possible to exclude a concomitant chondrocalcinosis promoted by joint damage, although the synovial fluid analysis was negative for crystal deposition.

This case suggests that:

1) The onset of ochronotic arthritis can involve large joints before the spine and requires differential diagnosis with inflammatory arthritis

2) Both ultrasound examination and MRI techniques can demonstrate joint synovitis and tendons involvement in ochronosis and they appear useful tools in monitoring the disease. Moreover, MRI was more sensitive than ultrasounds to detect initial erosive changes.

3) Intra-articular combined therapy with steroids and hyaluronic acid could be a pharmaceutical choice in ochronotic peripheral arthritis not responding to NSAID treatment

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