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CASE REPORT

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Ochronotic spondylarthropathy: two case reports of progressive destructive changes in the hip

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Abstract We report two cases of ochronotic spondylarthropathy who presented with spinal involvement followed by progressive destructive changes in the hip joint, which led to total hip replacement with a satisfactory outcome. Pathological examination revealed severe deterioration of the affected hip with unique cartilage degeneration associated with active inflammation in the synovium and bone marrow. These features were also evaluated by magnetic resonance imaging in one case which presented with rapidly destructive changes in the hip. Spinal involvement may contribute to progressive destructive hip arthropathy in ochronosis.

Key words Alkaptonuria (AKU) · Ochronosis · Rapidly destructive hip joint · Spondylarthropathy

Introduction

Alkaptonuria (AKU; MIM 203500), the first disorder to be interpreted as an in-born error of metabolism,[1,2] is a rare disorder caused by a deficiency of homogentisate-1,2-dioxygenase (HGO, EC 1.13.11.5), and characterized by homogentisic aciduria, ochronosis, and spondylarthropathy.[3,4] It is an autosomal recessive disease, affecting males and females at equal rates, with an incidence of one per million births, although a few cases have been suspected to represent dominant hereditary transmission.[4,5] The gene is carried in an asymptomatic heterozygous state in 1:500. Consanguineous marriages have been suggested to contribute to a high prevalence in certain areas.[6] The gene coding for HGO, an enzyme found solely in kidney and liver tissues, is absent and/or has lost its function in alkaptonuria. The enzyme catalyzes the conversion of homogentisic acid to maleylacetoacetic acid. A deficit or dysfunction of the enzyme causes an accumulation of homogentisic acid in connective tissues, where polymerization with collagen fibers occurs. This leads to the formation of bluish-black pigment, especially in the intervertebral discs and cartilage of the joints. The pigment and/or degenerate stains ochre under a microscope, and its deposition produces a multisystemic disorder with characteristic discoloration of the skin and cartilage, termed ochronosis by Virchow.[7] Accumulation of homogentisic acid modifies the biochemical quality of the intervertebral disc. This induces spondylopathy, which is observed in middle-aged ochronosis patients. Accumulation of homogentisic acid also means that the joint cartilage becomes fragile and degenerates. Peripheral arthropathy in ochronosis usually occurs about 10 years after spinal changes have developed, and involves large joints, namely, knee, hip, and shoulder.[8,9]

In spite of the rarity of the disease, numerous studies have been published on its inheritance, clinical manifestations, histopathology, molecular aspects, and pathogenesis. However, the method of development of the destructive hip arthropathy is not yet understood. We report two cases of ochronotic spondylopathy with progressive destructive changes in the hip. In one of these patients, rapidly destructive hip changes were evaluated by magnetic resonance (MR) imaging. Total hip arthroplasty was performed in both cases and resulted in a satisfactory outcome so that the patients regained their walking ability.

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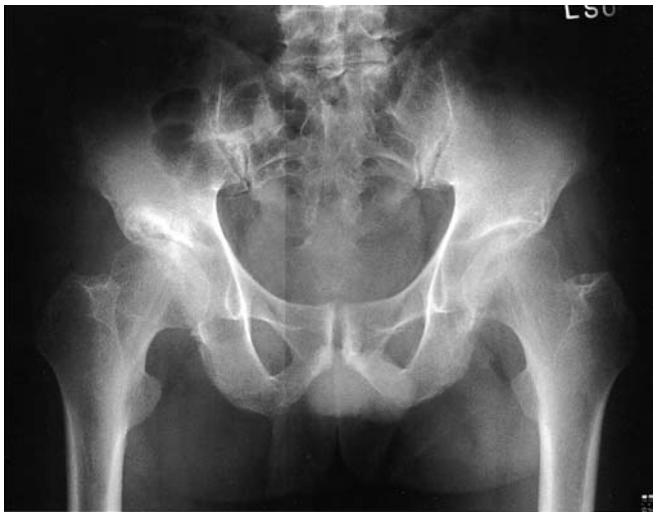

Fig. 1. Roentgenographic examination showing osteoarthritic change of the right hip joint in case 1. Moderate joint space narrowing, subchondral bone sclerosis, and cyst formation in the acetabulum were observed. The shape of the femoral head was preserved, and no evidence of osteonecrosis or cyst formation was present

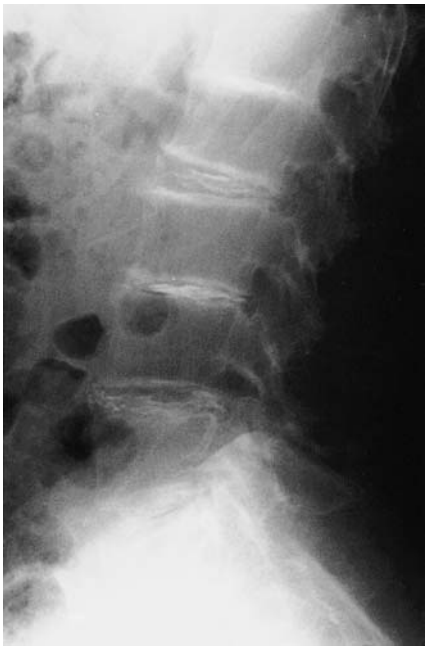

Fig. 2. Spondylotic change included widespread wafer-like discal calcification in the lumbar spine. Narrowing of intervertebral disc spaces and bony fusion were also observed (case 1)

Case reports

Case 1

A 59-year-old man complained of acute-onset pain on walking in April 1999, without any clear reason. A general orthopedic surgeon found mild osteoarthritic changes in his right hip, and gave him conservative treatment of medication with a nonsteroidal anti-inflammatory drug, and two crutches to take the weight off his hip for 3 weeks. However, this failed to relieve the symptoms. He was referred to Yamagata University Hospital in May 1999. In addition to a markedly restricted movement of his right hip joint and severe pain, moderate and mild restrictions of the range of motion were observed in his left shoulder and thoracolumbar spine, respectively. He had a previous history of low back pain with moderate stiffness of the spine, and adhesive capsulitis of his left shoulder. Roentgenographic examination revealed osteoarthritic changes with mild acetabular dysplasia in the right hip. Moderate joint-space narrowing with subchondral bone sclerosis and cyst formation were observed in the acetabulum. The shape of the femoral head was preserved, and no evidence of osteonecrosis or cyst formation was present (Fig. 1). Osteoarthritic changes were also observed in his left glenohumeral and patellofemoral joints. Spondylotic changes included widespread wafer-like discal calcifications in the whole spinal column. Narrowing of the intervertebral disc spaces and osteophyte formation in the thoracolumbar spine with bony fusion from Th11 to L2 were evident (Fig. 2).

Slight bluish-black pigmentation was observed in both groins. A genitourinary tract obstruction by calculus had been treated, but discoloration of the urine had not previously been noticed. In laboratory investigations, a yellow urine sample changed color to brown–black after 24 h exposure to air. The presence of homogentisic acid in the urine was proven by high-performance liquid chromatography. Rheumatoid factor was negative. HLA B locus contained B51 and B61 alleles. C-reactive protein concentration in the serum was 0.1 mg/dl.

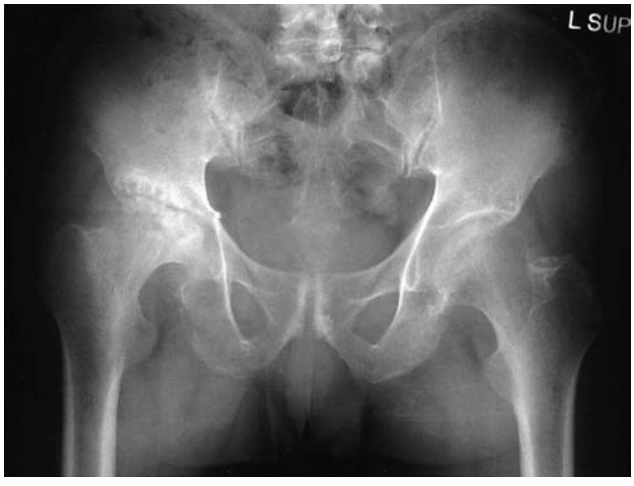

Fig. 3. During the following 3 months, rapidly destructive changes to the femoral head were observed in case 1. The shape of the femoral head became flattened, and subchondral bone sclerosis developed

These clinical data confirmed alkaptonuria and ochronotic spondylarthropathy. During the following 3 months, rapidly destructive changes of the femoral head developed. It became flattened, with subchondral bone sclerosis (Fig. 3). This hip was also examined with MR imaging 2 weeks before surgical treatment. T1-weighted images revealed focal, oval, low-intensity changes associated with an iso-

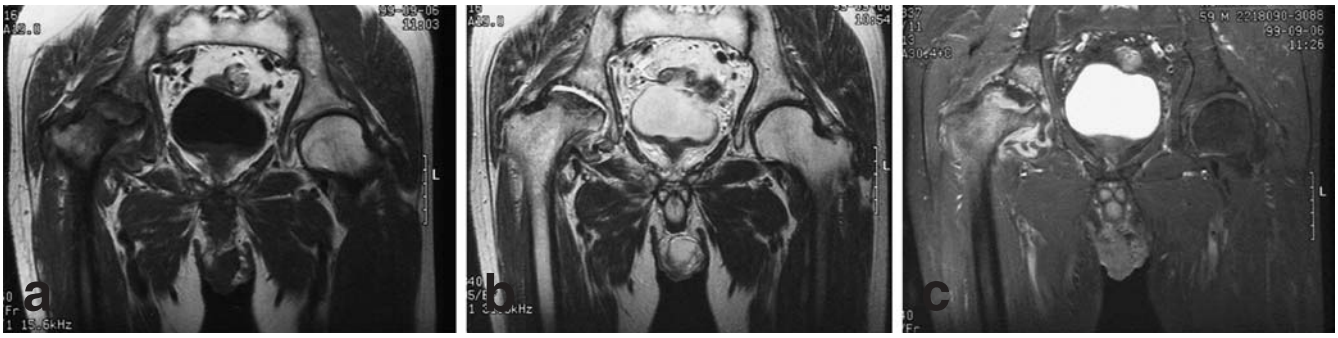

Fig. 4. **a** T1-weighted magnetic resonance images revealed focal, oval, low-intensity changes associated with the isointensity of a marginal band in the destroyed femoral head when compared with normal bone marrow. **b** T2-weighted magnetic resonance images. The area detected by T1-weighted imaging showed low intensity. **c** Magnetic resonance imaging with gadopentetate dimeglumine enhancement and fat suppression. The marginal area, which revealed the isointensity of the bone marrow in T1-weighted imaging, was strongly enhanced. Marked synovial proliferation was also much enhanced

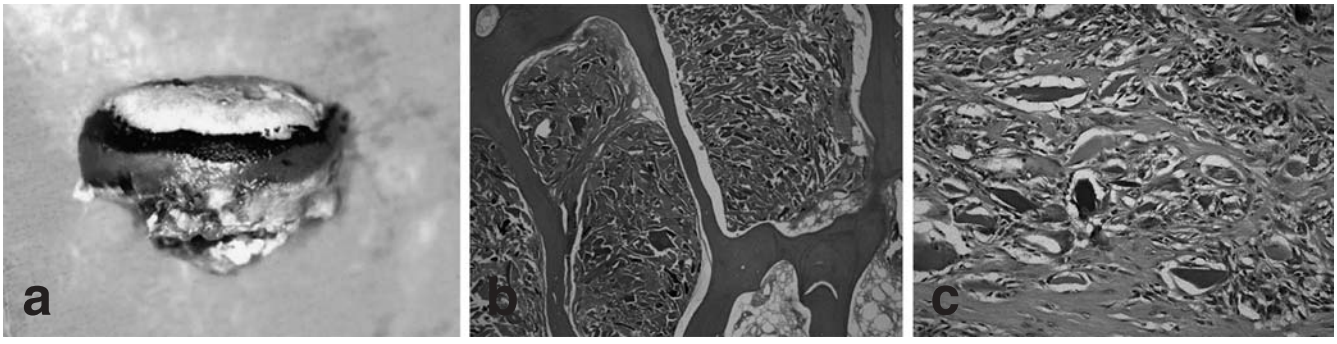

Fig. 5. **a** Macroscopic image of the femoral head. Hyaline articular cartilage was pigmented. **b** The intertrabecular space below the subchondral bone was occupied to a large extent by pigmented fragments of degenerating cartilages. **c** An inflammatory reaction was observed below those areas where fragmented cartilage occupied intermedullary spaces. Macrophages and foreign-body giant cells phagocytozed fragments of cartilage. Numerous mononuclear cell infiltrates and much fibrous granulomatous tissue were also observed

intensity marginal band in the destroyed femoral head when compared with normal bone marrow in the femoral neck (Fig. 4a). In T2-weighted images, the area detected by T1-weighted imaging showed a low intensity (Fig. 4b). The marginal area was strongly enhanced by gadopentetate dimeglumine with fat suppression (Fig. 4c). Marked synovial proliferation was detected as an irregular mosaic of low to high intensity in both T1- and T2-weighted images, and this change was further enhanced by gadopentetate dimeglumine (Fig. 4a–c). Fluid retention was detected as an area of high intensity in the T2-weighted image and after gadopentetate dimeglumine enhancement with fat suppression (Fig. 4b,c). Because of severe hip pain and an inability to walk, total hip joint arthroplasty was performed 4 months after the initial symptoms. This resulted in a satisfactory outcome, so that the patient regained his walking ability without the need to use a cane.

In macroscopic observations, eburnation of the denuded and flattened superior pole of the femoral head was noticed, with a black pigmentation ring in the cartilage surrounding the eburnated area (Fig. 5a). Pigmentation was also observed in the subchondral and intramedullary areas of the femoral head, which corresponded to the low-intensity areas detected in T1- and T2-weighted images. Microscopy showed that the intertrabecular spaces below the subchondral bone were occupied by pigmented fragments of degenerating cartilage replacing the fat and cellular bone marrow components (Fig. 5b). This area was surrounded by an inflammatory rim with macrophages and giant cells, which had phagocytozed the fragments of cartilage. Numerous mononuclear cells and some fibrous granulomatous tissue were also observed (Fig. 5c). This area corresponded to the marginal area, with low intensity in T2-weighted imaging and isointensity in T1-weighted imaging in comparison with the bone marrow of the femoral neck. The area was strongly enhanced by gadopentetate dimeglumine with fat suppression. The fragments of cartilage focally embedded in the synovium appeared black. Active synovitis was apparently elicited by these cartilage fragments, which had frequently been phagocytozed by macrophages and foreign-body giant cells. No crystals of calcium pyrophosphate dihydrate were seen in the cartilage or synovial membrane.

Case 2

A 68-year-old man complained of acute-onset pain on walking in April 1999. A general orthopedic surgeon found mild

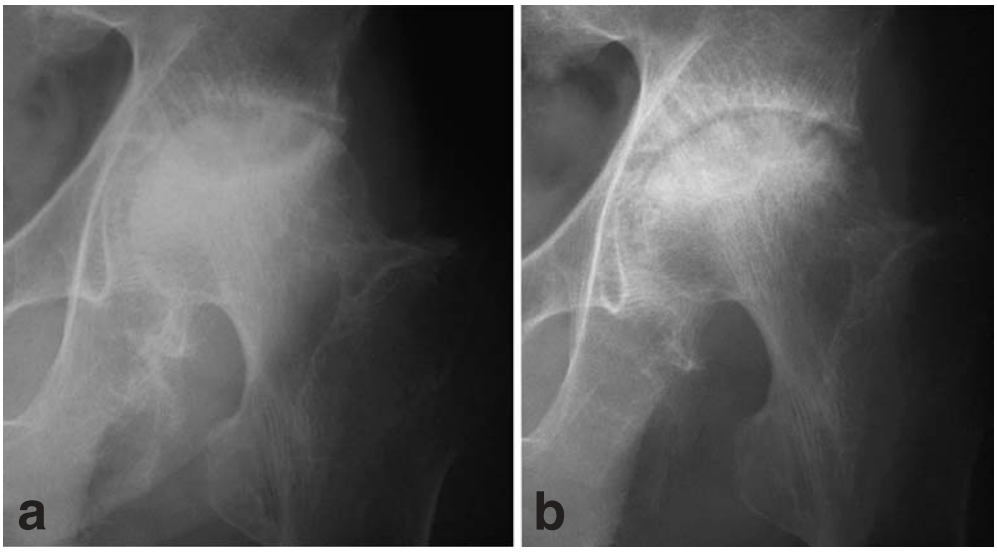

Fig. 6. a Roentgenographic examination revealed osteoarthritic change in the left hip joint. Narrowing of the hip joint space was accompanied by an osteonecrosis-like radiolucent area on the left femoral head. **b** During the following 3 months, the destructive changes to the hip were accelerated. The osteonecrosis-like radiolucent lesion of the femoral head was progressively enlarged, and this was accompanied by sclerotic change below that and an irregular shape on the lateral side of the femoral head. Osteoathritic changes of the acetabulum were also advanced

osteoarthritic changes in his left hip, and gave him conservative treatment of medication with a nonsteroidal anti-inflammatory drug for 4 weeks. However, this failed to relieve the symptoms. The patient first attended Saiseikai Yamagata Hospital in June 1999. In addition to markedly restricted movement of his left hip joint with pain on walking, a moderate restriction of movement was observed in both knees, with pain and severe stiffness of the thoracolumbar spine. He had a previous history of low back pain, which had been diagnosed as senile spondylarthropathy, and bilateral gonalgia, which was diagnosed as osteoarthritis. Roentgenographic examination revealed osteoarthritic changes in the left hip joint and both knees. Narrowing of the hip joint space was accompanied by an osteonecrosis-like radiolucent area in the left femoral head (Fig. 6a). Spondylotic changes included narrowing of the intervertebral disc spaces with partial ankylosis of the lumbar spine with loss of lordosis.

Bluish-black pigmentation was observed in both groins and ear lobes, while brown–black pigmentation was obvious in sclerae. Although discoloration of the urine had not been noticed before, a yellow urine sample changed color to brown–black after 24 h exposure to air. A homogentisic acid test was positive, and rheumatoid factor was negative. HLA B halotype was B35 and B55. C-reactive protein concentration was 0.2 mg/dl.

The clinical data led to a diagnosis of alkaptonuria and ochronotic spondylarthropathy with progressive destructive changes in the left hip joint. During the following 3 months, the destructive change in the hip accelerated. An osteonecrosis-like radiolucent lesion of the femoral head progressively enlarged, and was accompanied by sclerotic change below it. The round femoral head became oval, with an irregular shape on the lateral side. Osteoarthritic change was also advanced in acetabulum (Fig. 6b). Because of severe hip pain and an inability to walk, total hip arthroplasty was performed 4 months after the initial hip symptoms to restore gait function. The histopathology showed the same pattern as was seen in case 1.

Discussion

The involvement of the large peripheral joints usually occurs about 10 years after the spinal changes in ochronosis.[8,9] Joint symptoms are the presenting complaint in the majority of patients. In a series of peripheral joints affected in ochronotic arthropathy, the frequency was 64% in knees, 43% in shoulders, and 35% in hips.[10] Degenerative hip arthropathy in ochronosis has been biomechanically related to idiopathic atrophic osteoarthritis.[11] The rapid disappearance of the femoral head was initially reported in two cases of ochronosis.[12] This report was followed by several reports on rapidly progressive changes in the hip joint.[11,13–16] However, the number of destructive ochronotic hip arthropathies reported in the literature is limited, and its pathogenesis is still unclear. Several disorders can lead to rapid and/or severe destruction of the large joints. Crystal-induced arthropathy,[17] ischemic necrosis,[18] iatrogenic drug-induced arthropathy,[18] septic arthritis,[19] and neuroarthropathy[20] have been reported as its etiological factors. In addition, an idiopathic form of rapidly destructive head disease has been reported.[21–24] In ochronotic hip arthropathy, the presence of denatured cartilage caused by an underlying metabolic disorder has been related to the onset and progressive change of hip arthropathy. In this theory, rapid destructive changes of the ochronotic hip differ from idiopathic rapidly destructive head disease/rapidly destructive coxoarthropathy. Cartilage debris embedded in the bone marrow space[13,14] and reduced microhardness of the subchondral plate[11] have been reported as potential pathogenetic factors in destructive ochronotic hips. In addition, active synovitis with a macrophage reaction to denatured

cartilage fragments may enhance and/or accelerate arthropathy, thus occasionally leading to rapid destructive change. Acute mechanical overload has also been suggested to play a role in its onset.[25] It is interesting that the hip changes usually follow spinal changes.[8,9] Spinal involvement may accelerate progressive hip destruction. Spinal involvement, such as stiff back, loss of lordosis, or kyphosis, has been suggested as a mechanical etiological factor contributing to the progression of hip arthropathy.[26] An inappropriate mechanical transfer to the hip joint may accelerate cartilage degeneration, followed by fragmentation of the cartilage and active synovitis, thus leading to hip arthropathy with progressive destructive changes. In particular, in cases presenting with rapidly progressive destructive changes in the femoral head, spinal involvement combined with acetabular dysplasia may accelerate hip arthropathy in a short period of time.

In a previous report, findings in MR imaging were considered as non-specific in cases with destructive hip joint disease in ochronosis.[25] However, that study only documented findings observed before destructive changes developed in the femoral head and acetabulum. In the present study, MR imaging was performed in one case during the rapidly destructive phase of hip arthropathy, and was compared with a pathological examination. The MR imaging clearly showed the severe destructive changes of ochronotic hip arthropathy.

The low-intensity areas in both T1- and T2-weighted images were comparable to subchondral and intramedullary areas occupied by pigmented fragments of degenerating cartilage observed between the bony trabeculae, where fat and cellular marrow components were absent. The MR imaging findings resembled those seen in ischemic necrosis of the femoral head with rapidly destructive hip disease, as reported by Ryu.[27] In spite of some similarities in the MR imaging findings, the deposition of denatured cartilage in the suchondral and intramedullary spaces was different from that seen in ischemic necrosis, in which necrotic femoral bone and fibrous scar tissues predominate. In addition, the oval area observed in ochronosis was accompanied by a marginal area. This showed isointensity with the bone marrow of the femoral neck at the side in T1-weighted imaging, and low intensity in T2-weighted imaging. These change were also enhanced by gadopentetate dimeglumine with fat suppression. This area corresponded to inflammation characterized by the macrophages and giant cells which had phagocytozed cartilage fragments. Numerous mononuclear cell infiltrates and considerable fibrous granulomatous tissue were also observed. These findings were similar to those seen in the inflammed synovium, indicating a cellular host reaction to degenerated cartilage debris in both bone marrow and synovium. This differs from the changes seen in ischemic necrosis of the femoral head with rapidly destructive hip disease,[27,28] and also rapidly destructive hip coxoarthropathy.[29] Thus, MR findings revealed some unique pathological features of ochronotic destructive hip arthropathy.

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