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CASE REPORT

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# A case of ochronotic arthropathy treated with total hip arthroplasty

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**Abstract** We report a case of ochronotic arthropathy treated with total hip arthroplasty. The articular cartilage of the patient's femoral head and synovium displayed black pigmentation. Microscopically, the articular cartilage revealed reddish-brown pigmentation (particularly in deep cartilage), necrotic chondrocytes, and slight black pigmentation in the cytoplasm of chondrocytes. Electron microscopy revealed electron-dense material deposited predominantly along and between collagen fibers.

**Key words** Alcaptonuria · Ochronotic arthropathy · Total hip arthroplasty

## Introduction

Alcaptonuria is a rare, autosomal-recessive, inborn, metabolic disease that causes ochronotic arthropathy leading to disabling arthrosis. Smith and Smith[1] reported that the sole primary abnormality characteristic of this disease is the absence of homogentisic acid oxidase, which is normally present in the liver and kidneys. The absence of this enzyme produces an abnormality in the tyrosine metabolism, resulting in excess amounts of homogentisic acid (HGA) deposited in various tissues and excreted in the urine. This process, in turn, leads to ochronotic arthropathy, in which first the disks, and then the shoulder, knee, and hip joints undergo accelerated degeneration. This case report describes the clinical and histological findings in a 68-year-old woman with ochronotic arthropathy who underwent total hip arthroplasty, leading to a significant improvement in pain.

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## Case report

A 68-year-old woman first complained of lower back, groin, and knee pain during walking when she was 56 years old. As roentgenograms of her lower back demonstrated calcification in all intervertebral discs, she was referred to a physician, and diagnosed with alkaputonuria owing to positive findings in her urine.

At the age of 67, she noted pain in her left groin and both knee joints, which became progressively worse with conservative treatment, and was referred to our clinic. Hip-joint pain led to an admission for surgery. She had noted dark urine during childhood. Her medical history included cholecystectomy for cholecystolithiasis at the age of 56, and a partial hepatectomy for hepatolithiasis at the age of 63. Operative findings with the hepatolithiasis revealed a black stone in the intrahepatic bile duct, which seemed to be related to ochronosis.

Her father had died of a cerebral hemorrhage, her mother had died of a subarachnoid hemorrhage, and her elder brother had died of hepatoma. Her family history was negative for alcaptonuria and ochronosis. She did not have a consanguineous marriage, and urine samples from her four children were negative for homogentisic acid.

A physical examination revealed ochronotic pigmentation of the ears. She limped because of left-hip pain, and the left hip joint was tender on palpation. An examination of the range of motion in the left hip joint showed severe limitations and a positive Patrick sign. Flexion was limited to 80°, extension to −5°, abduction to 10°, internal rotation to 20°, and external rotation to 0°. Her Japan Orthopedic Association (JOA) scores for hip osteoarthrosis were 39 points in the left hip joint and 71 points in the right. Laboratory tests revealed no inflammatory findings except for positive rheumatoid factor (28.7 IU/ml) and slight anemia. Her urine was examined for homogentisic acid, and darkened upon the addition of sodium hydroxide (Fig. 1). An X-ray examination of the left hip joint in September 2000 revealed closing of the joint space in the weight-bearing area, radiolucency in the femoral head, and bone atrophy

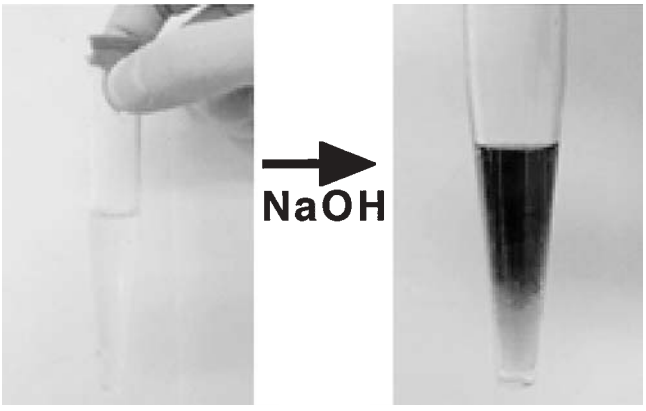


**Fig. 1.** Appearance of the patient's urine before the addition of sodium hydroxide (*left*) and after alkalinization (*right*)

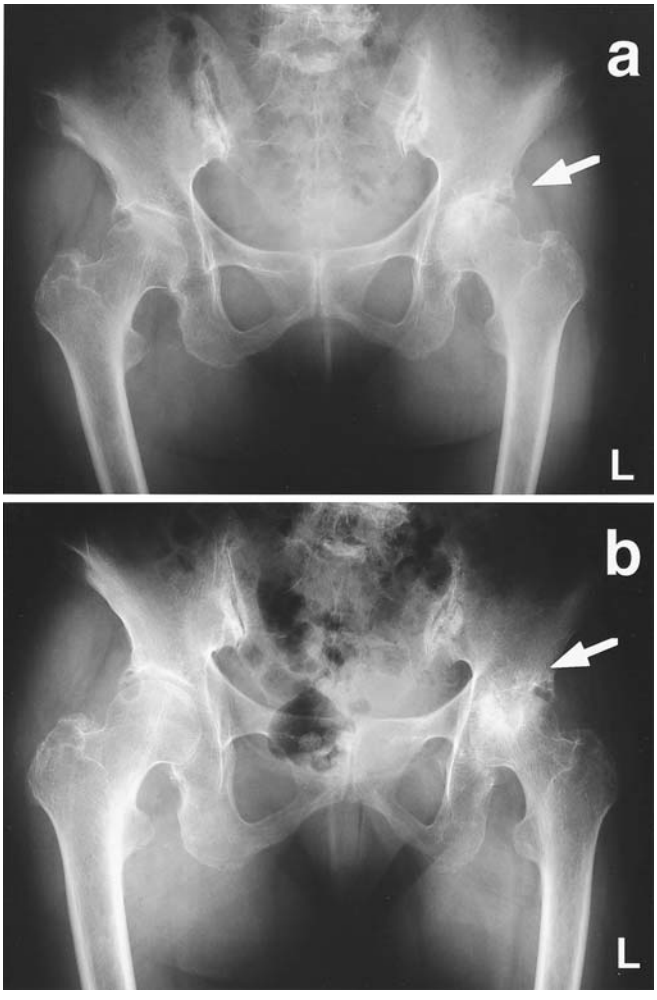


**Fig. 2.** Radiographs of both hips. **a** X-ray examination of the left hip joint in September 2000, showing closing of the joint space in the weight-bearing area, a radiolucent area in the femoral head, and bone atrophy. **b** Preoperative radiograph 4 months later, showing medial deviation of the left femoral head and extension of the radiolucent area, resulting in progressive joint destruction

(Fig. 2a). Dysplasia of the acetabulum was not evident. Osteoarthritic changes such as osteophyte formation, subchondral sclerosis, and subchondral cysts were minimal. The right hip joint showed a radiolucent area in the femoral head and osteophyte formation on the margin of the acetabulum. The left knee joint showed slight narrowing of the medial joint space, but no osteophyte formation.

Preoperative radiography 4 months later revealed medial deviation of the left femoral head and extension of the radiolucent area, resulting in progressive joint destruction (Fig. 2b). Preoperative computed tomograms revealed radiolucent areas in the femoral head and the acetabulum, and marked destructive change (Fig. 3). T1-weighted magnetic resonance imaging showed low signal intensity in the femoral head and acetabulum (Fig. 4a), while T2-weighted imaging showed high signal intensity in the femoral head (Fig. 4b). Radiography of the lumbar spine revealed narrowing of the intervertebral disk space, calcification of disks, and the fusion of vertebral bodies to produce a bamboo-like spine (Fig. 5). Delayed static anterior and posterior bone scanning demonstrated focal increases in the uptake of radionuclide in the left hip, both shoulders, the right knee, both sacroiliac joints, and the spine (Fig. 6). Mean bone mineral densities in the second to fourth lumbar vertebrae were within normal limits at 0.7299 by DXA. A diagnosis of osteoarthritis secondary to alcaptonuria was made.

In February 2001, the patient underwent left total hip arthroplasty, which revealed significant findings. A distinct black region marked the femoral head in the area corresponding with the lip of the acetabulum. The femoral head also showed the complete disappearance of the cartilage in the weight-bearing zone (Fig. 7a). The cut surface revealed that black pigmentation was selectively localized at the cartilage layer, but not in the bone (Fig. 7b). The synovium showed black thickening (Fig. 7c). A radiograph 8 months after surgery showed the bi-fix, cementless hip prosthesis, which was manufactured by Kyocera (Kyoto, Japan; Fig. 8). The patient's left hip joint now gave no pain, she had a better walking function, and 98 points better JOA score. Microscopically, the articular cartilage revealed reddish brown pigmentation, especially in the deeper area of cartilage, as shown by the arrow in Fig. 9a. In other cartilage regions, fragments of cartilage were dissociating (Fig. 9b). Chondroclasts had infiltrated under the cartilage layer and showed cartilage erosion (Fig. 9c). At high magnification, some chondrocytes had disappeared and others appeared necrotic (Fig. 9d). Slight black pigmentation had appeared in chondrocytes (Fig. 9e, arrow). The synovial membrane was thickened owing to the proliferation of synovial lining cells and the infiltration of round cells, including lymphocytes, plasma cells, and macrophages, in addition to large foreign body-type giant cells. Numerous pigmented cartilaginous bodies (shards) were present in the synovial tissue (Fig. 10a). At high magnification, large foreign body-type giant cells appeared to have phagocytosed fragments of cartilage (Fig. 10b). The subchondral region displayed extensive erosion of bone and inflammatory cell infiltration (Fig. 11a), and high magnification revealed that a group of osteoclasts had extensively absorbed bone tissue, leading to bone destruction (Fig. 11b). Electron microscopy revealed

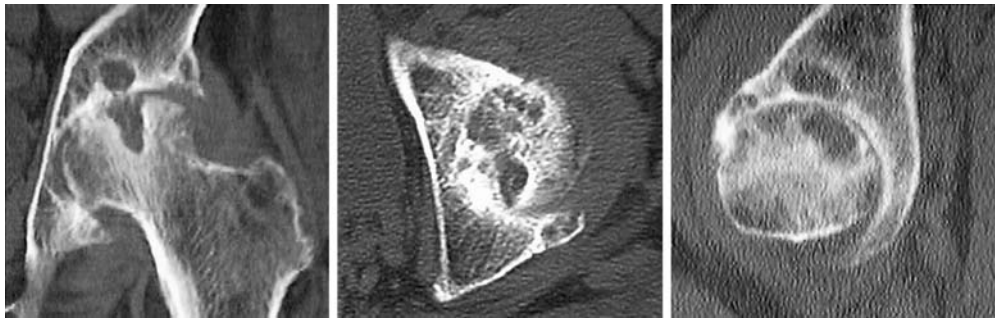

**Fig. 3.** Preoperative computed tomograms (coronal, axial, and sagittal views from left to right) showing radiolucent areas in the femoral head and acetabulum, and marked destructive change

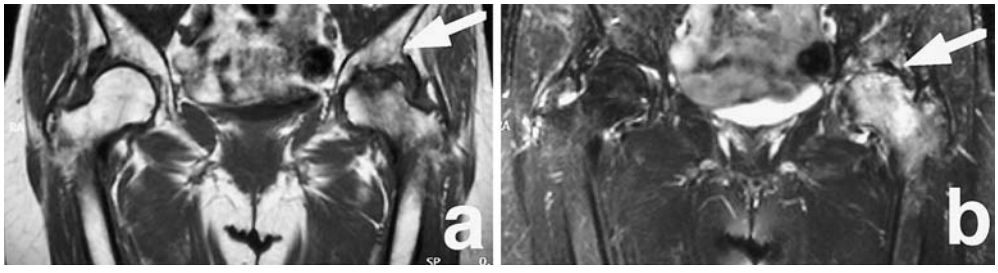


**Fig. 4.** **a** T1-weighted magnetic resonance imaging showing low signal intensity in the femoral head and acetabulum. **b** T2-weighted imaging showing high signal intensity in the femoral head

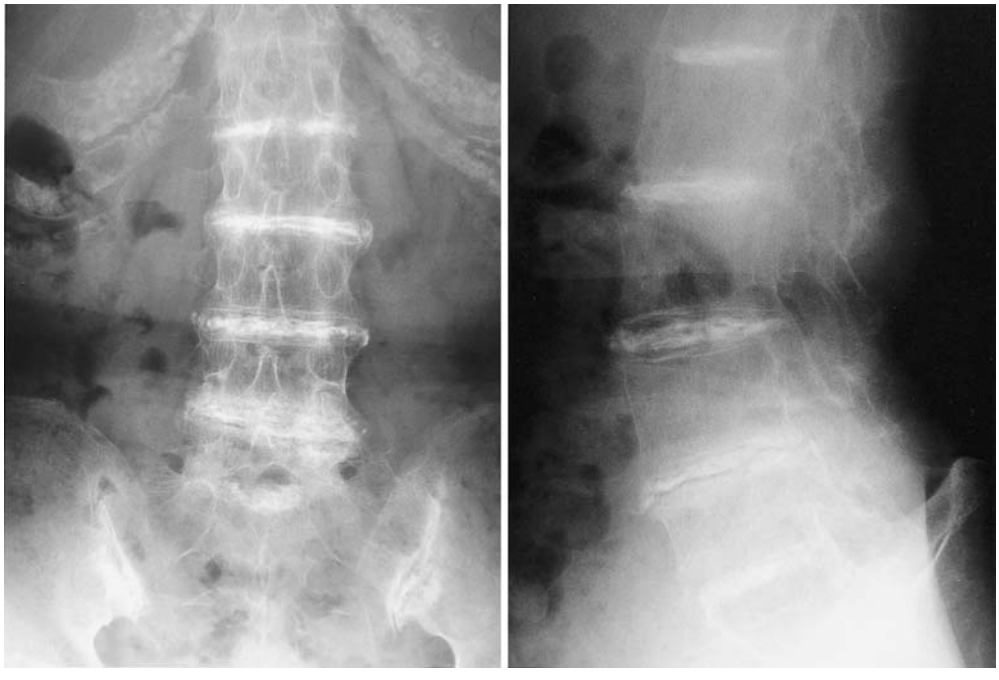

**Fig. 5.** Radiographs of the lumbar spine showing narrowing of the intervertebral disk space, calcification of disks, and fusion of vertebral bodies to produce a bamboo-like spine

several severely degenerated chondrocytes, characterized by no nuclear structure and the presence of dilated vacuoles containing ochronotic pigments (Fig. 12a, arrow). Electron-dense material (Fig. 12b, stars) was deposited primarily along and between collagen fibers, and occasionally in chondrocytes and chondrocyte lacunae. Collagen fibers had lost their periodicity (Fig. 12b, arrow).

## Discussion

Alcaptonuria is an inborn, metabolic disease transmitted by an autosomal recessive gene, with an incidence varying from 1 in 1 000 000 to 1 in 10 000 000, and with an approximately equal sex distribution. O'Brien et al.[2] reported the geographic and racial distribution, especially in areas with a high incidence of consanguinity. In Japan, more than 90 cases have been reported, with a higher incidence in the northern part of Kyushu.

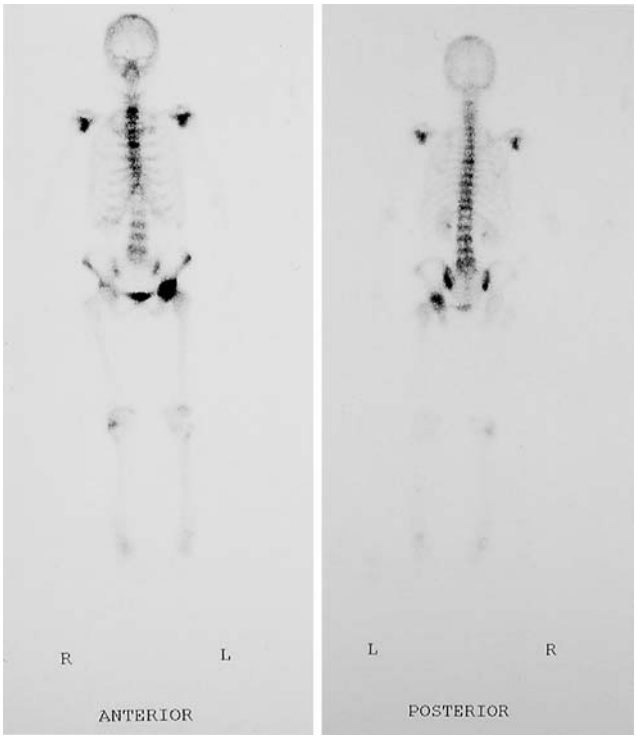


**Fig. 6.** Delayed static anterior and posterior bone scans showing focal increases in the uptake of radionuclide in the left hip, both shoulders, the right knee, both sacroiliac joints, and the spine

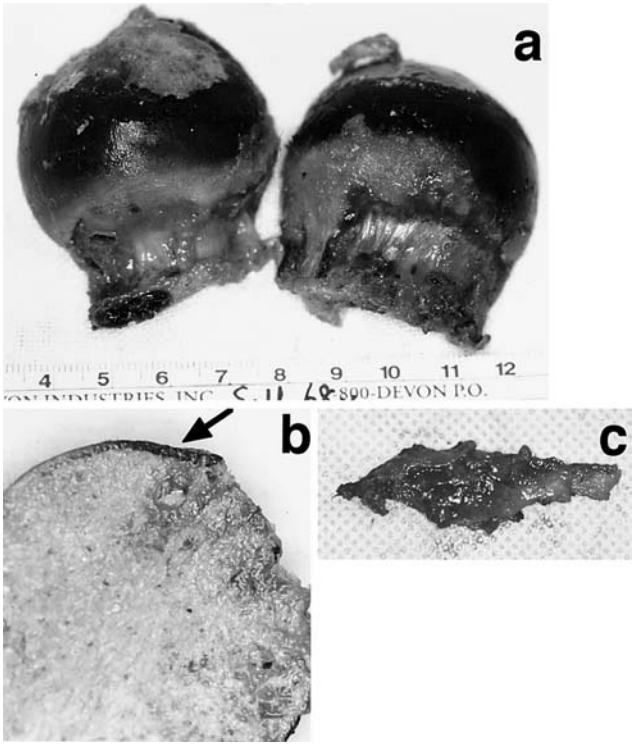


**Fig. 7.** Macroscopic aspects of the left femoral head. **a** No pigmentation is evident in the eburnated area. A distinct black region marked the femoral head in the area corresponding with the lip of the acetabulum. **b** Black pigmentation corresponding with the cartilage layer. **c** The synovium revealed black thickening

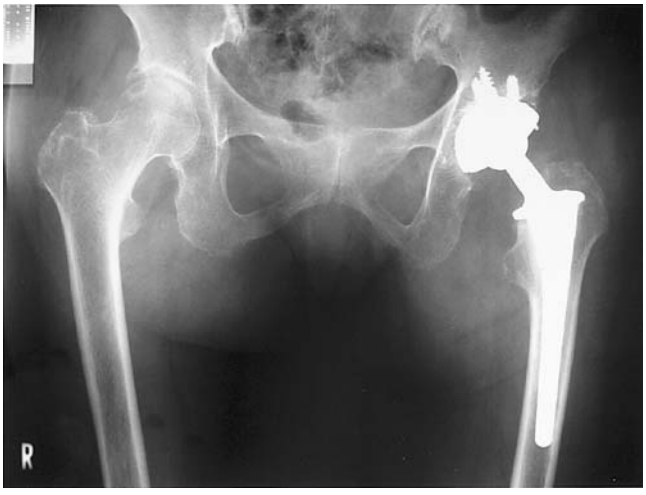


**Fig. 8.** Radiography 8 months after surgery showing a bi-fix, cementless hip prosthesis, manufactured by Kyocera

The metabolic defect is a deficiency of the enzyme homogentisic acid oxidase,[1,3] which metabolizes homogentisic acid (HGA). Nonmetabolized HGA and an undetermined pigmented polymer accumulate in the absence of the oxidase. HGA is partially excreted in the urine, which then turns black when oxidized or alkalized. Another portion of the HGA is deposited in various connective tissues such as cartilage, sclera, and skin, and is converted to a melanin-like HGA polymer. The resulting gray to bluish-black pigmentation of connective tissue is called ochronosis.[4]

Ochronotic arthropathy results from ochronotic deposits in the joints of the appendicular and axial skeleton. As ochronotic pigment is preferentially deposited in cartilage, chronic degenerative arthropathy is an almost inevitable complication of alcaptonuria. In most sufferers ochronotic arthropathy develops in the 30s or 40s, and leads to spinal ankylosis and peripheral progressive joint destruction. The present patient first complained of lower back pain at age 56.

In O'Brien's study of 604 patients with alcaptonuria, 163 (26.9%) patients showed the involvement of ochronotic spondylosis and arthropathy.[5]

Our case presented with typical involvement of both shoulders, left hip joint, right knee joint, both sacroiliac joints, and the spine, as shown by bone scintigraphy. The electron microscopic study revealed large amounts of deposit concentrated in the cartilage matrix, whereas only small amounts were detected in the cytoplasm of the chondrocytes compared with amounts in matrix, as presented in the reports of Mohr et al.[6] and Ishikawa and Hirohata.[7]

Interfibrillar localization, in addition to preferential deposition in deep cartilage, may indicate the binding of ochronotic pigment to proteoglycans in cartilage. Altered proteoglycans are thought to be responsible for the increased fragility of articular cartilage, leading to cartilage fragmentation. On the other hand, Kutty et al.[8,9] and Fukumoto et al.[10] reported that electron microscopy revealed granules of pigment only in chondrocytes at the early

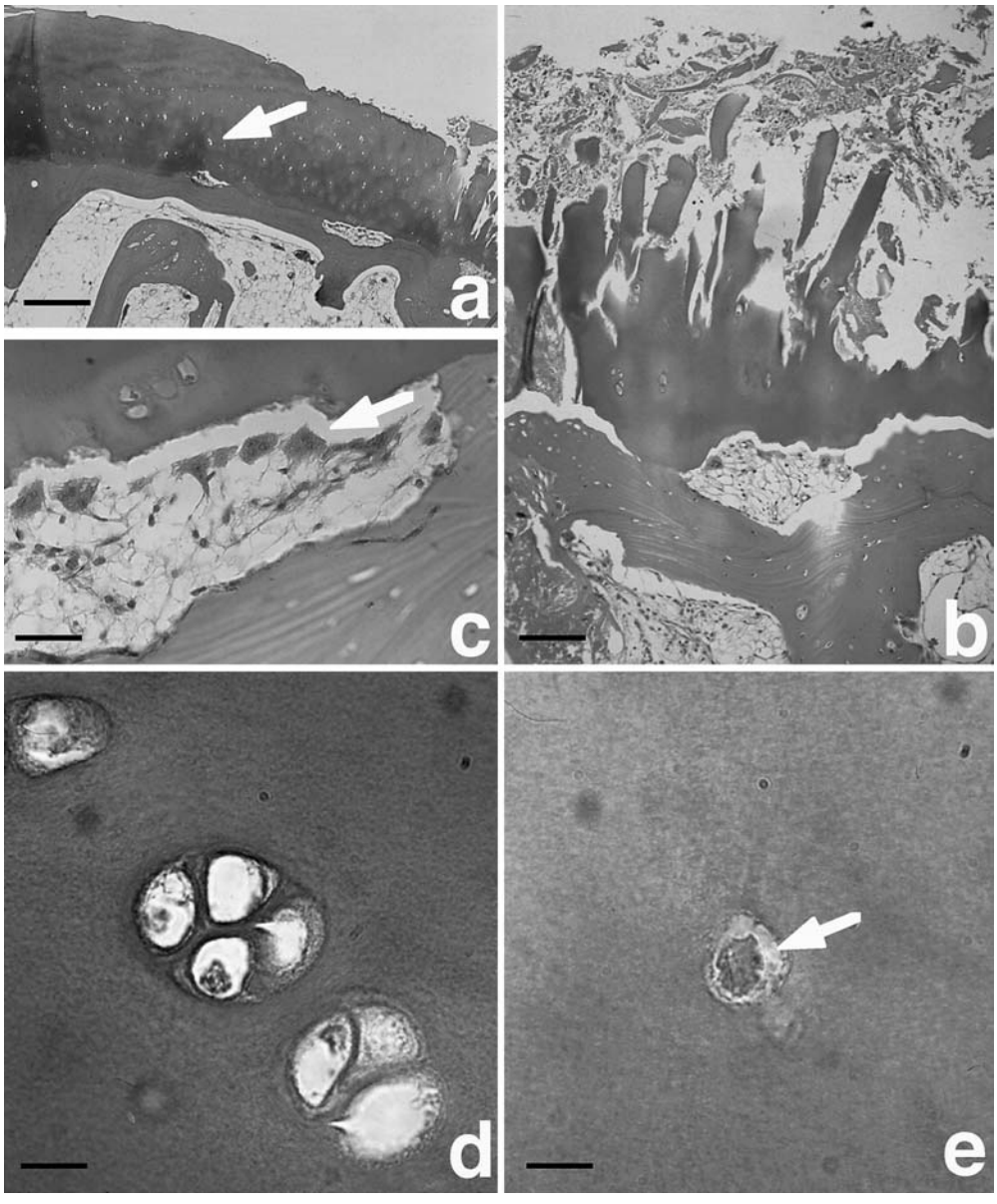


**Fig. 9.** Histological appearance of the left femoral head. **a** Articular cartilage showed reddish-brown pigmentation, particularly in deeper areas of the cartilage (*arrow*) (H&E, *bar* 400 μm). **b** Fragments of cartilage dissociating (H&E, *bar* 400 μm). **c** Chondroclasts (*arrow*) had infiltrated under the cartilage layer and displayed cartilage erosion (H&E, *bar* 200 μm). **d** At high magnification, some chondrocytes disappeared in the lacunae and others appeared to be necrotic (H&E, *bar* 40 μm). **e** Slight black pigmentation in chondrocytes (*arrow*) (BH&E, *bar* 40 μm)

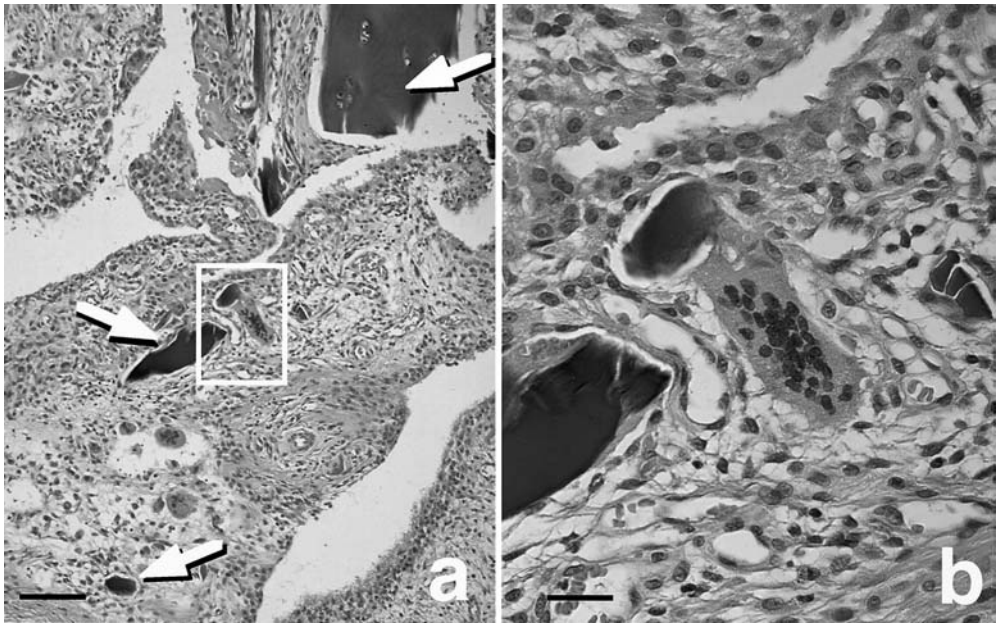


**Fig. 10.** Histological appearance of synovium. **a** Synovial membrane was thickened, with a proliferation of synovial lining cells and infiltration of round cells, including lymphocytes, plasma cells, and macrophages, in addition to large foreign body-type giant cells. Numerous pigmented cartilaginous bodies (*arrows*) were present in synovial tissue (H&E, *bar* 1 μm). **b** At high magnification, large foreign body-type giant cells phagocytosed fragments of cartilage (H&E, *bar* 100 μm)

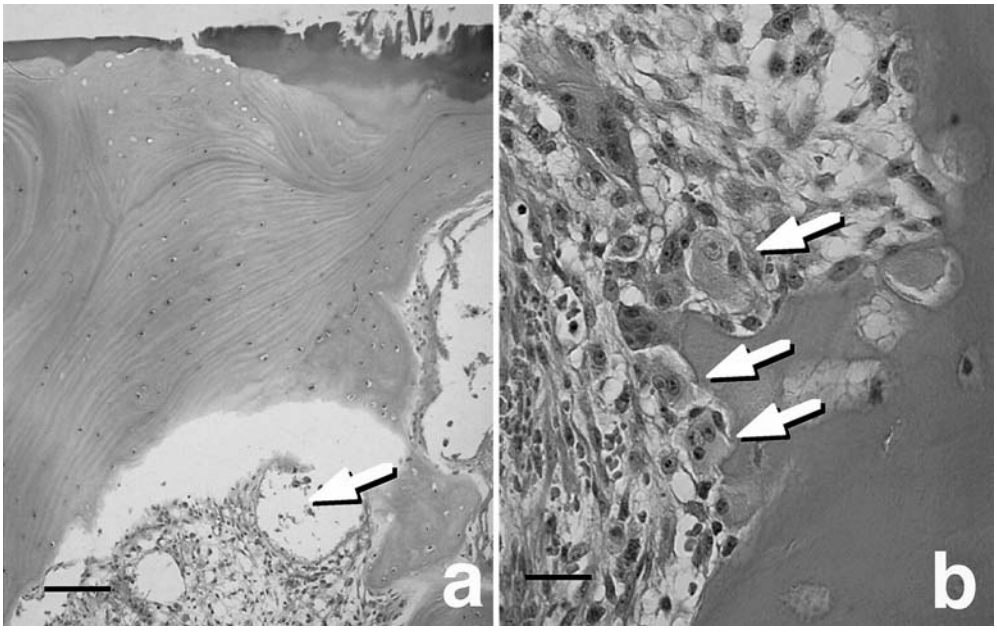


**Fig. 11.** Histological appearance of subchondral bone. **a** The subchondral region displayed extensive erosion of bone and inflammatory cellular infiltration (H&E, *bar* 1 mm). **b** High magnification revealed extensive absorption of bone tissue by a group of osteoclasts, leading to bone destruction (H&E, *bar* 100 μm)

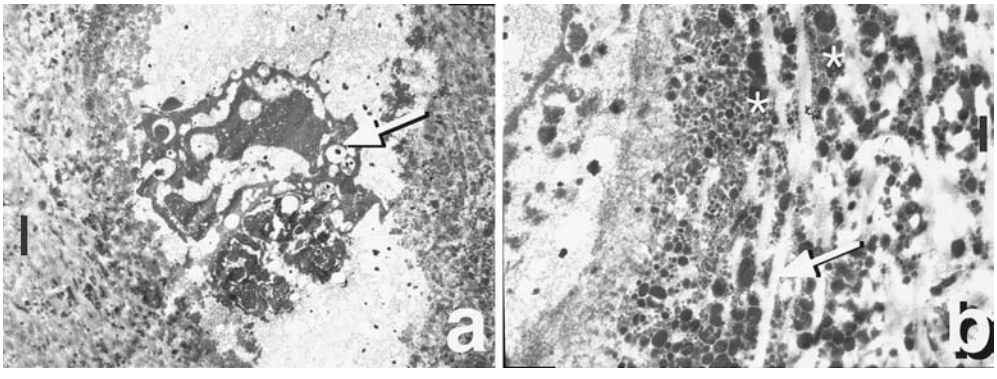


**Fig. 12.** Electron micrographs of articular cartilage. **a** Severely degenerated chondrocytes characterized by no nuclear structure and the presence of dilated vacuoles containing ochronotic pigments (*arrow*), were often observed (*bar* 1 μm). **b** Electron-dense materials (*stars*) were deposited predominantly along and between collagen fibers (*arrow*). Collagen fibers (*arrow*) lost their periodicity (*bar* 500 nm)

phase of degeneration, suggesting that chondrocytes were the primary site affected, leading to pigmentation in the matrix.

Although the mechanism for joint destruction is unknown, fragments of ochronotic cartilage are released from articular cartilage and phagocytosed by macrophages and multinuclear giant cells in synovium. Cytokines released from macrophages may promote the inflammatory reaction, with proteinases released from inflammatory cells destroying cartilage and bone. Cell infiltration into subchondral bone may explain osteolysis of the femoral head due to cytokine and proteinase released from inflammatory cells.

Arthropathy may severely limit activity levels, and such patients may benefit significantly from arthroplasty. The total hip arthroplasty performed on our patient greatly increased her activity level. The total hip arthroplasties reported elsewhere were also successful.[11–23]

For operations such as total hip arthroplasty, two complications of alcaptonuria are important. One is a tendency to form urinary tract stones from HGA product, which predisposes the patient to urinary tract infection. Preoperative, prophylactic antibiotic treatment may be necessary. The other complication is calcification of the aortic and mitral valves and the valvular anuli. This may impede heart function and impair tolerance for surgery.

We have reported the case of an ochronotic patient who underwent total hip arthroplasty. Histological examination demonstrated pigmentation of the deeper zone of articular cartilage, synovitis, and bone destruction. Electron microscopy revealed interfibrillar deposition of pigment, with a few granules present in chondrocytes.

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