

# Multiple Arthroplasty in a Patient with Alkaptonuric Arthritis

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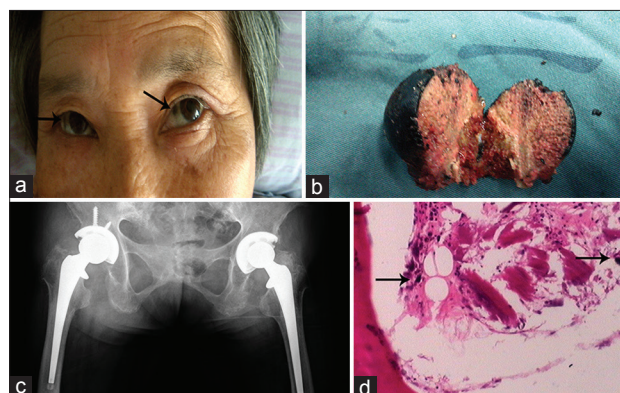
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**Key words:** Alkaptonuria; Ochronosis; Ochronotic Arthritis; Total Hip Replacement

Alkaptonuria (AKU) is an extremely rare autosomal recessive metabolic disorder characterized by a triad of homogentisic aciduria, arthritis, and ochronosis, affecting only 2–5 in a million individuals.<sup>[1]</sup> The management of AKU is usually symptomatic. However, surgical intervention necessitates in cases of significant arthritis. Here, we presented a 64-year-old female who underwent bilateral total hip and right total knee arthroplasties achieving a successful clinical outcome throughout the 3 years of follow-up.

In April 2012, a 64-year-old woman presented for evaluation of arthralgia, lower back pain and difficulty in walking that started 20 years previously. Past medical histories, including a total right knee and left hip arthroplasties, to relieve the intractable pain. For the last 2 years, she had complaints of increasing right hip pain with stiffness in her lower back, causing limited mobility, which could not be relieved by physiotherapy or nonsteroidal anti-inflammatory drugs (NSAIDs). Physical examination revealed a remarkably limited range of motion and a flexion contracture of 30° for the right hip as well as an active hip flexion of 80°. Patrick sign was positive. Brownish pigmentation was noticed on her sclerae and ears [Figure 1a]. When a urine sample was taken, it was initially of normal color but gradually became dark brown after several hours' exposure to the sun. The urine contained no blood or protein. The radiographic evaluation of the skeletal system showed severe arthritis of the right hip joint and the left knee, as well as calcified disc spaces with marginal intervertebral bridges and ankylosis of the dorsolumbar spine. Other laboratory investigations revealed that human leukocyte antigen B 27 and rheumatoid factor were negative. Interestingly, her family history for genetic and heritable diseases was also negative.

The patient subsequently underwent a right total hip arthroplasty [Figure 1c]. Macroscopically, black pigmentation and major arthritis was found in the cartilage



**Figure 1:** (a) Ochronotic pigmentation of the sclera of both eyes; (b) Black-hip found in the ochronotic patient. (c) Postoperative anteroposterior radiograph of the hip; (d) Microscopic examination revealed "synovial tissues with multiple pigmented areas" (H and E, original magnification,  $\times 20$ ). The patient had signed the informed consent.

of the femoral head [Figure 1b], which we also observed on the opposite side in the previous operation performed by the same surgeon (He RX). The histologic features of the surgical specimen were compatible with ochronosis and osteonecrosis [Figure 1d]. The patient's surgery and recovery were uneventful. Three years postoperatively, the patient had adequate range of motion and was pain-free on the right hip.

AKU is caused by the deficiency of the homogentisate 1,2-dioxygenase enzyme which results in excretion of

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large quantities of homogentisic acid (HGA) in the urine and a slowly progressive deposition of HGA and its oxidative product in cartilage, intervertebral disk and other connective tissues, leading to ochronotic arthropathy. The most clinically relevant organ systems involved in AKU are musculoskeletal, cardiovascular, genitourinary, eye, and skin. Clinical manifestations including darkening of the urine when exposed to air; bluish pigmentation of the skin of the face, hands, ear cartilage, sclera, and fingernails; aortic and cardiac valve calcification; lumbar intervertebral disk calcification and disc space narrowing; and osteoarthritis of the hip and knee.

In 50% of cases, concern over dark-colored diapers prompts investigation for AKU in early life. Others are usually asymptomatic and present in the fourth or fifth decade with chronic joint pain. It has been suggested that the delayed appearance of ochronosis is associated with decreased renal clearance of HGA with aging.<sup>[2]</sup>

Clinical symptoms of alkaptonuric arthropathy are similar to rheumatoid arthritis, especially at an advanced stage.<sup>[3]</sup> However, small joints are affected in rheumatoid arthritis, whereas the large joints are affected in alkaptonuric arthritis. It is also reported that AKU resembles ankylosing spondylitis (AS) in its particular damage to the spine and large joints, but differs in sparing the sacroiliac joint in its radiographic appearance. Besides, although advanced ochronotic spinal disease may also resemble abnormalities in AS, the sacroiliac joints in ochronotic spondylosis are not fused, interfacetal articulations retain a normal radiographic appearance, and annular ossification with a “bamboo” pattern does not appear.

No medications have been found to cure the disease, even though various symptomatic therapeutic options like NSAIDs, exercise and physiotherapy have been described for the management of AKU. The commonly recommended treatment is a dietary restriction of phenylalanine and tyrosine intake.<sup>[4]</sup> High-dose Vitamin C is also widely used because it decreases urinary benzoquinone acetic acid. However, few

credible studies have shown that treatment with Vitamin C is clinically effective. Phornphutkul *et al.*<sup>[5]</sup> proposed that nitisinone (NTCB), a triketone herbicide that inhibits 4-hydroxyphenylpyruvate dioxygenase by reversible rapid, avid binding (50% inhibitory concentration, 40 nmol/L), should be a therapeutic step. In both murine models and humans, NTCB has been shown to decrease significantly urinary HGA excretion. However, the safety of its prolonged use is still under question. In end-stage cases of ochronotic arthropathy, total joint replacements should be considered.

In conclusion, alkaptonuric arthritis is a very rare disorder that can be potentially misdiagnosed with osteoarthritis in patients with joint pain and radiographic evidence of joint space narrowing. We report such a rare case and conduct a critical review of the literature, concluding that arthroplasty is a good choice for patients with severe alkaptonuric arthritis. However, more experience and further investigation is needed in the future.

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### Conflicts of interest

There are no conflicts of interest.

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