CASE REPORT

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Alkaptonuric Ochronosis: A case-based review

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Alkaptonuria (AKU) is an extremely rare autosomal recessive metabolic disorder caused by deficiency of homogentisic acid oxidase and resulting in accumulation of homogentisic acid in collagenous structures. It is characterized by a triad of homogentisic aciduria, bluish-black discoloration of connective tissues (ochronosis) and arthropathy of large weight bearing joints. We report on a middle-aged female patient with bilateral severe ochronotic arthritis of both hips and shoulder joints requiring total joint replacements as staged procedures which were done without complications offering a complete pain relief and a satisfactory clinical and functional outcome. Ochronosis can cause severe arthropathy of peripheral joints. Multiple joint affection is common. Total joint replacement can yield persistent pain relief with complete functional recovery in patients with severe ochronotic arthropathy.

Keywords: Alkaptonuria, black joints, Ochronosis, ochronotic arthropathy, Arthroplasty.

INTRODUCTION

Alkaptonuria (AKU) is an extremely rare enzymatic disorder of amino acid metabolism affecting 1-4 in a million people[1-4]. It is caused by deficiency of homogentisic acid oxidase (HGO) that normally oxidises homogentisic acid (HGA) to malylacetoacetic acid (MAA), through an autosomal recessive gene mutation on chromosome 3q21-q23[4]. This results in systemic accumulation of homogentisic acid and its oxidized product benzoquinone acetic acid (BQA) as polymerized deposits in collagenous tissues and its excessive renal excretion causing urinary discoloration on standing or on alkalinisation (alkaptonuria)[1,3,5-6]. The disease is characterized by a triad of homogentisic aciduria, bluish-black discoloration of the connective tissues in the skin, finger nails, sclera, nose, ear pinna and hyaline cartilage (ochronosis) and progressive degeneration of all affected body systems with widespread arthritic changes (ochronotic arthritis) causing persistent pain, disability and impaired quality of life[2,5,7].

A wide spectrum of manifestations in alkaptonuria is described. In the cardiovascular system, coronary and valvular calcifications frequently occur, sometimes with aortic stenosis[2,8-10]. In the genitourinary system, renal, urethral, and prostate calculi are common[1,2]. In the respiratory system, limited chest expansion with dyspnea can develop because of stiffness of the costal cartilage[11]. Skeletal affection usually presents as cervical, thoracic and lumbosacral disk degeneration and spondylotic changes[6,11]. The knee is the most common peripheral joint affected[12]. Upper limb affection is extremely rare[13]. Ochronotic tendinopathy mostly affects the Achilles or patellar tendon causing enthesopathy and sometimes spontaneous tendon ruptures[6]. Systemic metabolic disease causes diminution in bone density with osteopenia and osteoporosis[6].

Owing to the rarity of this disorder, only few case reports are available. This work describes a 57-year-old woman with bilateral severe ochronotic arthritis of both hips and shoulder joints requiring total joint replacements as staged procedures which were done without complications. Furthermore, an overview of the etiology, pathogenesis, clinical presentations and management of alkaptonuric ochronosis is presented and its skeletal manifestations are discussed.

MATERIALS AND METHODS

We report on a middle-aged female patient suffering from diffuse ocronotic arthropathy of the large joints. At the age of 53 years, she developed painful bilateral advanced shoulder joint arthritis with severe limitation of movement necessitating the implantation of anatomic shaftless Eclipse™ total shoulder arthroplasty system (Arthrex, Naples, FL) in June and December 2016 respectively (Figure 1). In September 2020 she presented with severe hip pain and inability to bear weight on the right side. The x-ray pictures showed advanced narrowing of the joint space (Figure 2). The pelvic MRI examination revealed bone marrow changes involving the whole right head of femur with osteonecrosis as well as advanced osteoarthritic changes of the right hip joint (Figure 3). Due to refractory pain not responding to conservative treatment and nonsteroidal anti-inflammatory drugs she was admitted to the hospital and treated using a cementles short-stem total hip replacement (ArtiQo GmbH, Lüdinghausen) in October 2020 (Figure 4). The operation was done using a minimally invasive posterior approach under general anaesthesia in a standard operation room in the lateral decubitus position. Intraoperative pictures have shown the deep black discoloration of the joint and synovium with complete articular cartilage separation of the right femoral head (Figure 5). The histopathologic examination confirmed the ocronotic arthropathy with subchondral bone necrosis (Figure 5). Six weeks later, she presented with severe left-sided hip pain with radiologically evident chondrolysis of the left hip joint. She couldn't walk on the left side any more and was again treated using minimally invasive cementles short-stem total hip replacement. The

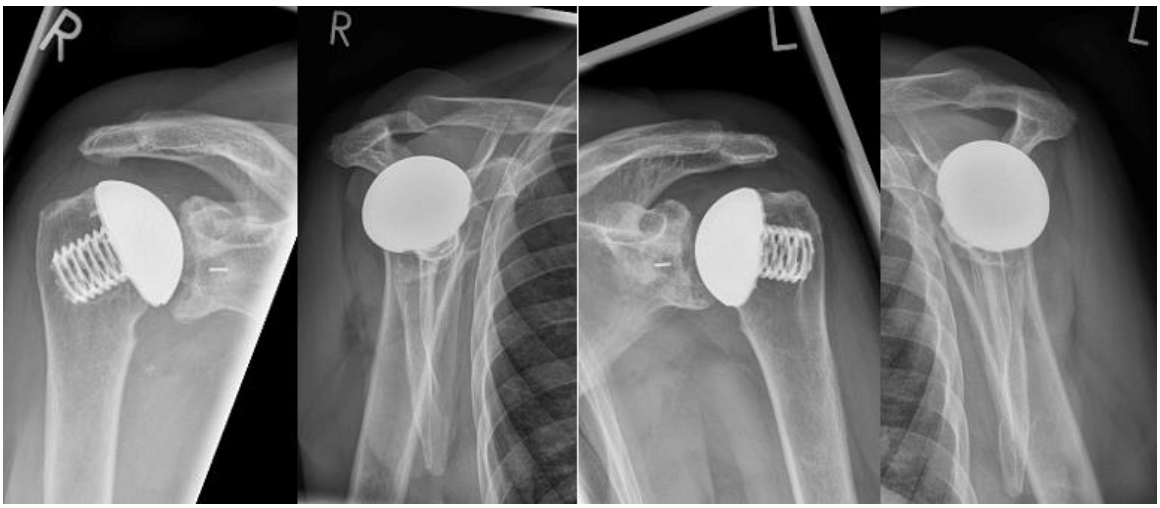

Fig. 1 — Postoperative x-rays showing bilateral total shoulder replacement.

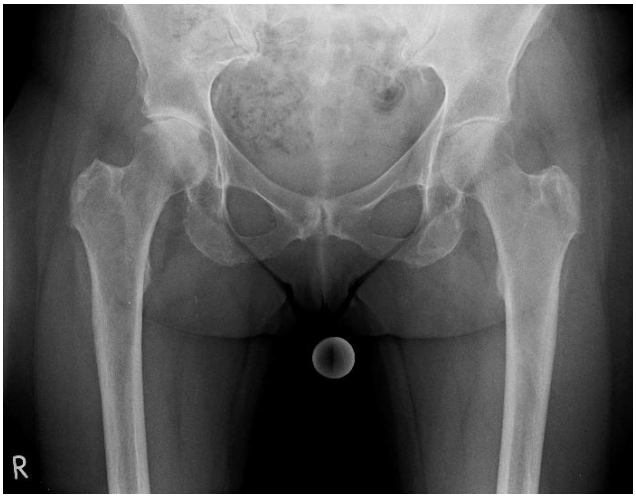

Fig. 2 — Preoperative pelvic view showing advanced right-sided hip arthritis.

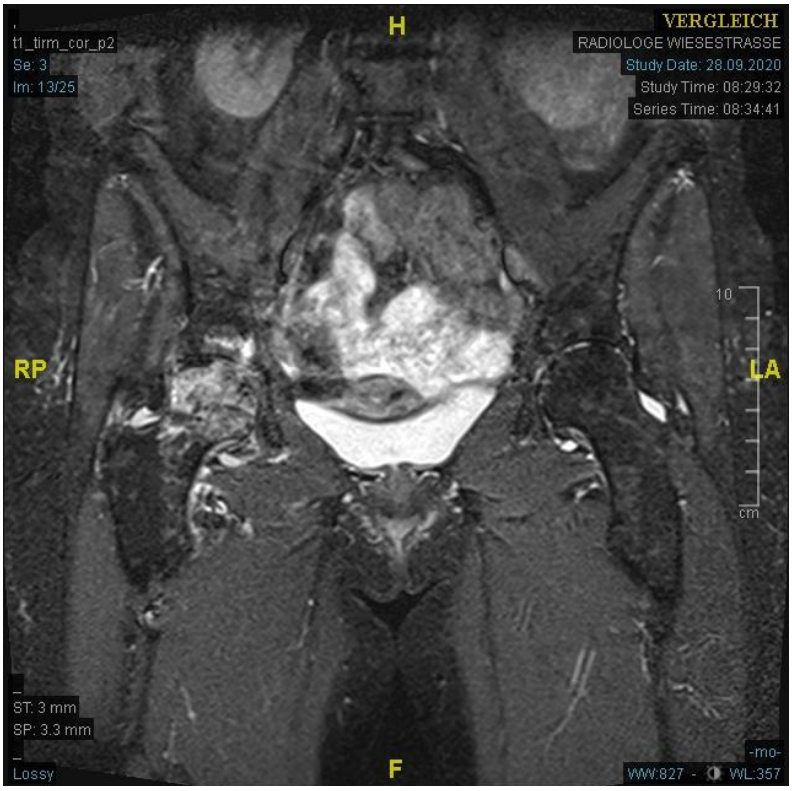

Fig. 3 — MRI-examination showing destruction of the right hip joint.

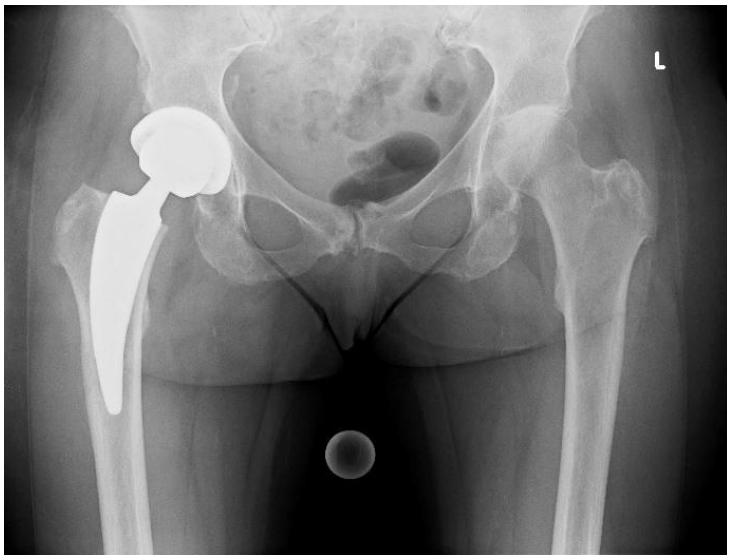

Fig. 4 — Postoperative x-ray showing short-stem total hip replacement on the right side.

intraoperative findings resembled those of the right side. The postoperative period of all surgeries went uneventful. No complications occurred during any procedure and the patient was able to walk with aids with complete pain relief on the first day after surgery. For successful mobilization the patient received daily physiotherapy, gait training with crutches and range of motion exercises (up to 90 degrees of hip flexion). Hip adduction and excessive rotation were avoided to prevent prosthetic dislocation. She was discharged to continue ambulatory rehabilitation that she tolerated quite well. Crutches were needed no longer than 3 weeks postoperatively. At the last follow-up two years postoperatively, the patient was fully satisfied with her functional outcome. She showed an excellent range of motion and was totally independent in activities of daily

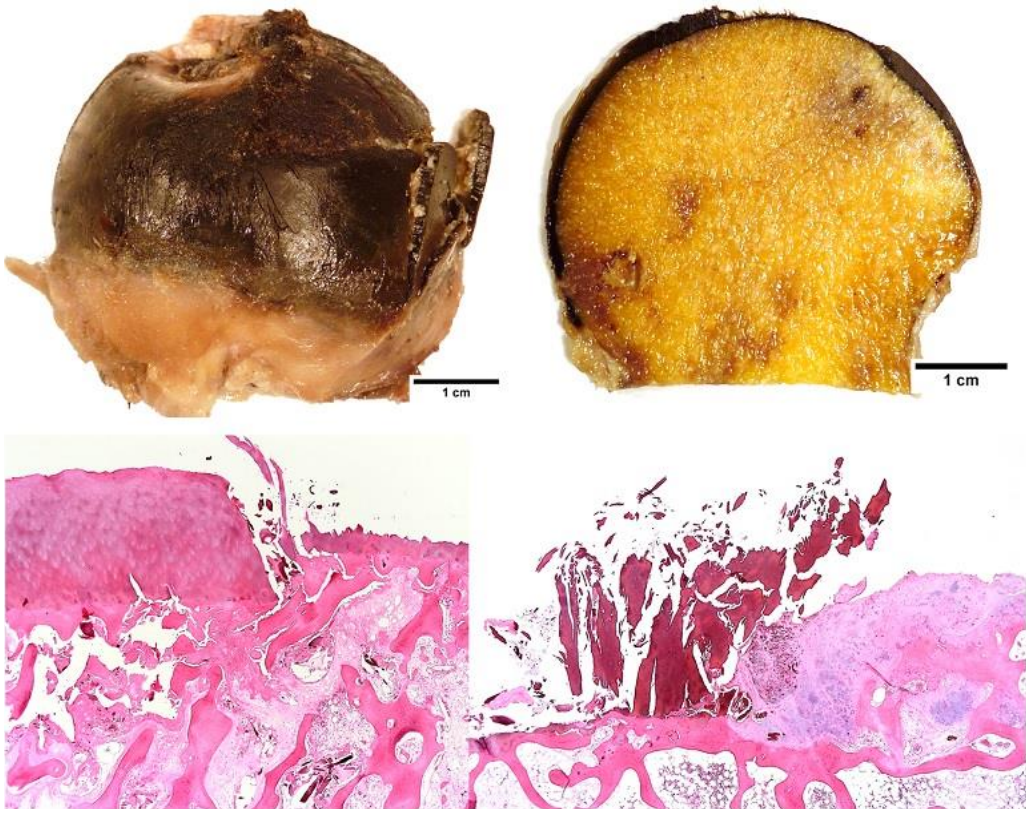

Fig. 5 — Macroscopic and microscopic picture of the resected femoral head showing ochronotic arthropathy.

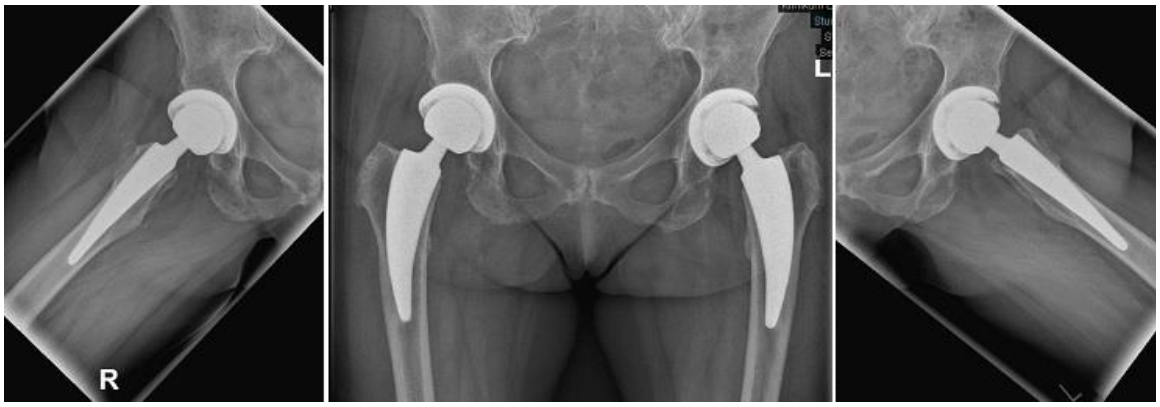

Fig. 6 — Postoperative radiographs showing bilateral short-stem total hip replacement.

living (ADL). There was consistent pain relief with no radiologic signs of prosthetic lossening or subsidence (Figure 6).

DISCUSSION

Ochronosis is the deposition of macroscopically bluish black but microscopically ochre (i.e. yellow in Greek) pigmented metabolic byproducts in the connective tissue, specially in hyaline cartilage[1,13]. The earliest proven case of ochronosis was described in the Egyptian mummy Harwa dating to 1500 B.C.[14] In 1584 the German Scribonius described a boy whose urine was as black as ink[15]. The term "Alcapton" was first used by Boedeker in 1859 to describe a second urinary reducing substance in a patient with glycosuria due to its behavior with alkali[16]. This substance was later identified by Wolkow and Baumann as 2,5-dihydroxyphenylacetic acid, or homogentisic acid in January 1891[17]. In October 1866, Rudolph Virchow in Berlin named this condition ochronosis (yellow disease) as the accumulated pigment appears yellow

microscopically[18]. Albrecht in 1902 was the first to realize that ochronosis and alkaptonuria represented different components of the same disease[19]. In the same year, Sir Archibald Garrod in London identified the hereditary nature of the disease[20]. In June 1908, he described alkaptonuria in his Croonian lectures as the first inborn metabolic error in humans that obeys Mendelian autosomal recessive inheritance[21]. By 1909, Neubauer mapped the complete tyrosine degradation pathway[22]. Half a century later, the hepatic enzyme defect in alkaptonuria was found to be a deficiency of homogentisic acid 1,2-dioxygenase activity, one of six enzymes necessary for aromatic amino acid catabolism[23].

Ochronotic arthropathy (OcA) is the most frequent complication of alkaptonuria[2]. It usually remains asymptomatic till the 4th decade due to age-related reduction of renal clearance of HGA[1,6,24]. Thereafter the condition progresses rapidly with joint pain, swelling and stiffness causing disability and reduced quality of life[2,5-7,24]. Several aetiopathologic mechanisms have been described behind the development of OcA. Taylor et al. attributed OcA to the altered mechanical properties of the pigmented hyaline cartilage that becomes weak and brittle, lose elasticity and show poor resistance to mechanical strain[13]. Hamdi et al. suggested that BQA may inhibit lysine hydroxylase and subsequently decrease cross-linkage of collagen fibers[24]. This enhances their vulnerability to stress and shearing injury causing connective tissue failure, cartilage erosion and fragmentation[24]. Cartilage fragments may adhere to the synovial membranes causing inflammation, fibrosis, loose bodies or chondromatosis[25,26]. It is also suggested that HGA oxidation produces free radicals that may induce inflammatory and degenerative reactions[6]. Furthermore, pigment deposits may initiate aggressive osteoclastic resorption underneath hyaline cartilage causing complete loss of the subchondral plate[13] and impair mineralization of the newly formed osteoid matrix with decreased bone mineral density and increased risk for fragility fractures[6]. Synovial fluid aspiration often reveals black floating particles (ground pepper sign)[27]. Coexistence of ochronosis and rheumatoid arthritis, ankylosing spondylitis or chondrocalcinosis has been reported as well[2].

Currently, there is no definite cure for alkaptonuric ochronosis[1]. A low protein diet (with less phenylalanine and tyrosine) would theoretically decrease HGA production and consequently reduce clinical symptoms and radiographic changes[28]. Vitamin C and antioxidants could decrease urinary BQA but has no effect on HGA excretion[28]. Nitisinone (NTBC), a triketone herbicide and a potent competitive inhibitor of 4-hydroxyphenylpyruvate dioxygenase can decrease production and excretion of HGA up to 70%; however, its long-term results and side effects are yet unknown[2]. In alkaptonuric mice, nitisinone treatment from birth can prevent ochronosis in adult mice, whereas treatment from mid-life stops disease progression[29]. An international multicenter trial showed that nitisinone reduces HGA excretion in a dose-dependent manner and increases tyrosine levels[30]. In ochronotic arthritis, non-steroidal anti-inflammatory drugs and physical therapy can ameliorate symptoms without affecting disease progression[31]. In end stage ochronotic arthritis, total joint replacement remains the best treatment option[5,26].

Our study confirms the promising outcome of joint replacement in ochronotic arthritis. The female patient in our report had bilateral total shoulder and hip replacements with an excellent outcome and no complications after two years of follow-up. Her condition and mobility improved significantly and she got back to daily activities without pain. This compares favorably to other reports that demonstrated that joint arthroplasty can yield excellent short-term outcomes in OcA[1,2,5,26,32-34]. Despite reduced quality of the adjacent bone, we didn't face intraoperative problems in achieving primary stability of the prosthetic components with cementless implantation and no subsidence of the bone-preserving short stem was seen until the last follow-up. This compares favourably to the long term results reported by Ilyas et al. and Pachore et al with cementless total hip replacement[2,5]. Pachore et al. recommended en-block resection of the affected synovium wich we largely followed in our hip replacements[5]. Complete removal of the joint capsule as recommended by Cebesoy et al. was however avoided because of stability concerns in association with the surgical posterior approach used[35].

CONCLUSION

Ochronosis is an extremely rare but disabling metabolic disorder causing severe arthropathy with cartilage and bone destruction. Multiple joint affection is common. Joint replacement can yield persistent pain relief with satisfactory functional recovery in patients with severe ochronotic arthropathy. Bone sparing short stems and cementless implantation techniques can be successfully used in these relatively young patients.

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