Case Report

A rare case of avascular necrosis of the hip joint secondary to ochronosis

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ABSTRACT

This is a case report of a 53-year-old female patient who presented with long-standing hip pain secondary to avascular necrosis of the hip joint. She underwent total hip replacement and her intraoperative findings raised suspicion of ochronosis and was retrospectively evaluated for alkaptonuria both clinically and through biochemical investigations to confirm the diagnosis.

Key words: Alkaptonuria, Avascular necrosis, Ochronosis, Total hip replacement

Alkaptonuria is a rare (1: 200, 000) disorder of amino acid metabolism which affects tyrosine catabolism [1]. Deficiency of the enzyme homogentisate 1, 2–dioxygenase [1] (also called homogentisic acid oxidase) leads to the excretion of large amounts of homogentisic acid in urine and also the accumulation of oxidized homogentisic acid pigment in connective tissue. This is known as ochronosis [1-8]. Many patients may not be diagnosed with alkaptonuria until middle age as they do not have significant symptoms before this time [2,8]. Some patients may notice the presence of dark urine on exposure to air at an early age. Foci of grey-brown scleral pigmentation and darkening of the concha, anthelix, and lastly, the helix of the ear usually develop after the age of 30 [1,8]. The degenerative joint disease usually develops around midlife [1,6,7] which may prompt the patient to seek medical attention. The cardiovascular system may also be involved as age progresses, especially above 60 years as there is pigment deposition in the heart valves leading to aortic stenosis [1,5,6] and also in the blood vessels. The diagnosis is through urine analysis for homogentisic acid. The arthritis is treated symptomatically with medications for pain relief and arthroplasty when indicated [1-8].

CASE REPORT

A 53-year-old female presented to our hospital complaining of chronic, aching pain in her right hip and knee. The pain in the hip was more bothersome to the patient. The pain had started around 4 years ago and was being managed with analgesics off and on. Initially, the patient would experience the pain episodically 3–4 times/month. However, she had experienced an increase in the severity and frequency of the pain over 2 months such that pain was continuous and had minimal or temporary relief with analgesics. This resulted in difficulty in walking, climbing stairs, and carrying out her regular activities. She had no other comorbid illnesses and no history of alcohol or substance abuse.

The patient was admitted for further evaluation. Her vital parameters were stable at admission. Systemic examination was unremarkable. There was tenderness over the right hip joint with a flexion-abduction attitude and a grating sound on movement of the hip joint. The movements of the right hip were grossly restricted and painful. There was no abnormality at the knee joint. Examination of the contralateral hip joint was normal.

Complete hemogram, renal and liver function tests, and blood sugar profile were normal. An electrocardiogram was done which was also normal. A radiograph of the pelvis with both hips showed a decrease in the joint space of the right hip with flattening and sclerosis of the right femoral head suggestive of avascular necrosis (Fig. 1). A radiograph of the knee was normal while that of the calcaneum demonstrated plantar and dorsal spurs. Furthermore, magnetic resonance imaging of both hips was done which confirmed our suspicion of avascular necrosis of the right hip joint (Fig. 2).

The patient was initiated on analgesics (intravenous Tramadol and oral NSAIDs as required), low molecular weight heparin (Enoxaparin), and other supportive measures. Based on her clinical presentation and imaging studies, she was then advised to undergo a right total hip replacement. Broad-spectrum antibiotics were started preoperatively.

Written informed consent of the patient was taken before surgery. The surgery was scheduled under spinal and epidural

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anesthesia. She was shifted to the operation theater where she was positioned in the left lateral position. A posterolateral approach was taken. The fascia and external rotators were cut and retracted. The joint capsule was cut and there was blackening of the femoral head and acetabulum with erosions inside the joint (Fig. 3a). Synovial tissue was also blackish in color and a specimen was collected for histopathology (Fig. 3b). A thorough pulse lavage wash was given. Reaming of the acetabulum was done and an uncemented pinnacle cup was fitted with two cancellous screws. A polyethylene liner was fitted. A ceramic head was fixed and the hip was reduced. The external rotators were sutured to the bone. A drain was inserted. The fascia and subcutaneous tissue were sutured and skin stapled. There were no intraoperative complications.

The patient had an uneventful recovery postoperatively. Immediate pain relief postoperatively was through an epidural infusion of 0.1% bupivacaine which was continued for 24 h and tapered and stopped. The radiographs of the right hip done on the day after surgery revealed a good placement of the prosthesis components. Due to the intraoperative findings of pigmentation of the femoral head and synovium, the possibility of ochronosis was considered. The patient was retrospectively examined for other features of alkaptonuria. She had not observed any discoloration of her urine on standing. She had no other symptoms besides hip and knee pain. There was no significant family history. She was noted to have grey to black pigmented areas in both sclerae, more prominent in the left eye (Fig. 4). However, there was no obvious pigmentation of the ear cartilage, skin, or web spaces of the hands.

The patient was mobilized on the day after surgery. Physiotherapy was started. Intravenous antibiotics were continued for 3 days after the surgery. The patient was discharged 4 days after the surgery as her vital parameters were stable and she was walking with support. She returned for a follow-up after 3 weeks. Her progress was satisfactory. She had a significant reduction in pain in her right hip and could walk without any support at this time. Her knee pain which was most likely referred pain from the hip had also resolved. The histopathology report was obtained at this time. The tissue specimen was reported to consist of inflammatory cells composed of lymphocytes, polymorphs, plasma cells, and acellular eosinophilic to brownish depositions surrounded by multinucleated giant cells and was opined to be suggestive of ochronosis. A urine sample was then tested for the presence of homogentisic acid by the alkali, ferric chloride, silver nitrate, and Benedict tests all of which were positive. The urine also turned dark on standing for a few hours.

The diagnosis of alkaptonuria was made taking into consideration clinical findings, and biochemical and histopathological analysis. The patient was advised dietary

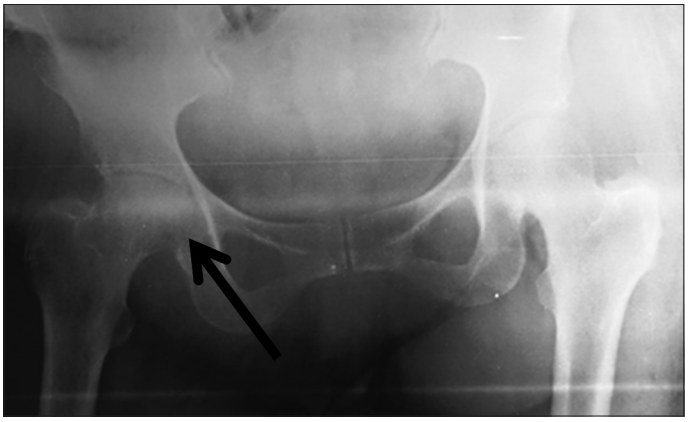

Figure 1: Radiograph of pelvis with both hips showing flattening of the right femoral head

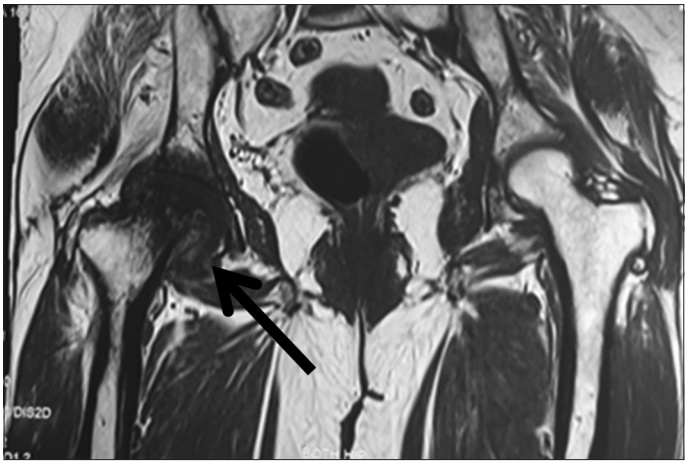

Figure 2: Magnetic resonance imaging showing avascular necrosis of the right hip

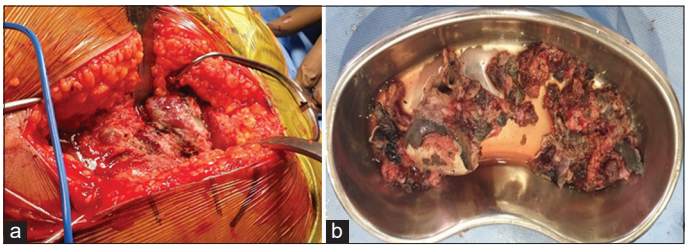

Figure 3: (a) Intaroperative findings of blackening of the femoral head and acetabulum and (b) blackish pigmentation of the synovial tissue; specimen was sent for histopathology

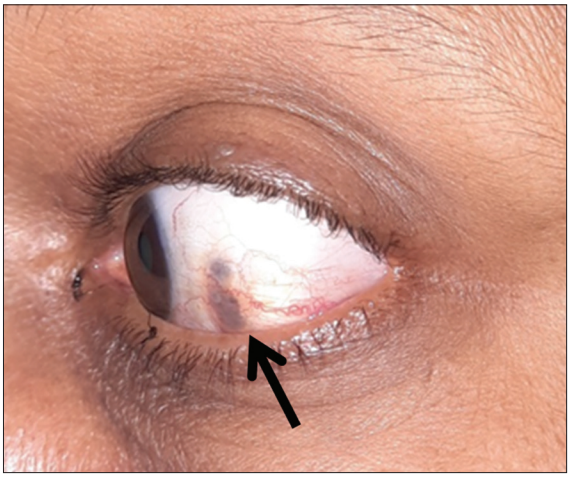

Figure 4: An area of grey-black pigmentation in the sclera of the left eye

modifications in terms of protein restriction and regular medical follow-up visits. This is a rare case of alkaptonuria with its first presentation as ochronosis leading to avascular necrosis of the hip joint.

DISCUSSION

Alkaptonuria is a rare (1: 200,000) [1] autosomal recessive [3-8] disorder caused by a loss-of-function mutation on chromosome 3q [2,5,6]. It affects tyrosine catabolism [1,8] and occurs due to a deficiency of the enzyme homogentisic acid oxidase [1-6]. This leads to the excretion of homogentisic acid in urine and also the accumulation of oxidized homogentisic acid pigment in connective tissue called ochronosis [1-6] and in the blood [2,6]. There is a slight predominance of males over females [6]. The pathogenesis of the disease includes pigment deposition, an induced inflammatory reaction, and superadded dystrophic calcification [6].

The majority of patients with alkaptonuria are diagnosed in their middle age (4th or 5th decade of life [6,7]) as they are relatively asymptomatic before that [2,7,8]. This is because homogentisic acid has a high renal clearance (400–500 microns/mL) and low plasma levels (50–400 micromol/mL) and hence, it takes nearly 30–40 years for the manifestations to occur [6]. Some patients may notice earlier in life that their urine turns dark after a few hours upon exposure to air. This is because homogentisic acid in the urine turns it black on oxygenation or alkalinization due to the formation of benzoquinone acetic acids[6,8]. Homogentisic acid has a high affinity to proteoglycans of hyaline cartilage [8]. Scleral and skin pigmentation and darkening of the tympanic membrane, concha, anthelix, and helix of the ear are other features seen [1,4-6,8]. The arthritis is progressively degenerative as inflammation increases [1,2] and predominantly affects the large joints [2,8] causing pain, stiffness, and loss of ability to withstand the mechanical strain, and may be associated with restriction of motion of the hips, knees, and shoulders [1,3,8]. The most common joint affected is the knee [2,3]. Clinically, joint involvement may simulate other common arthritic disorders like osteoarthritis [5,7,8].

Arthropathy is the leading cause of morbidity in patients with alkaptonuria [3]. Pigment may also be deposited in the intervertebral discs [3], leading to narrowing of the disc spaces and sclerosis and hence severe degeneration of the spine [5,6] causing low back ache [1]. This may mimic ankylosing spondylitis if the spine is primarily involved [6]. Other features seen in the spine may include thoracolumbar spine disc herniation, porotic vertebral bodies, and osteophyte formation [5]. Rupture of the patellar or Achilles tendons may be seen [5,6,8]. Pigmentation of the heart valves can also occur leading to cardiac valve calcification and stenosis [1,5,6,8]. Coronary artery and aortic calcifications may also be seen [5,8]. Occasional patients develop pigmented renal or prostatic calculi [1,5,6]. A variable combination of features may be seen in different patients. However, the most common clinical triad includes homogentisic aciduria, pigmentation of connective tissue, and ochronotic arthropathy [5,6].

The diagnosis is through urine analysis by chromatographic, enzymatic, or spectrophotometric tests for homogentisic acid [5]. Darkening of urine occurs with exposure to air or to reducing agents [5]. Histopathological analysis of the remains of operative specimens should be done [6]. The classical features seen are multiple pigmented areas [3,8], reactive giant cells, thickened and inflamed synovium [2,8], and areas of necrosis [8]. Similar findings were obtained in our case.

There is no specific treatment for alkaptonuria [2]. The arthritis is treated symptomatically [5,6,8] with analgesics and physiotherapy, and arthroplasty [1-8] when indicated. Alleviation of pain and significant improvement in activity has been noted in patients who have undergone total joint replacement of the hips, knees, or elbows [5]. Arthroplasty performed for ochronotic arthritis is believed to be as effective as when performed for osteoarthritis [2,8]. In case of tendon ruptures, primary repair may be done [5,6]. Protein restriction [1] is advised for patients with alkaptonuria in a bid to reduce homogentisic acid production. Nitisinone [1,5] is a drug being tried as it reduces the production and urinary excretion of homogentisic acid and might prevent the long-term complications of alkaptonuria. It inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase [5] which is involved in the conversion of hydroxyl phenylpyruvate to homogentisic acid. Although high-dose Vitamin C decreases urinary benzoquinone acetic acid, it has no effect on homogentisic acid excretion. It was tried in the past for the treatment of alkaptonuria but its benefit is negligible and it is no longer recommended for such cases [5].

CONCLUSION

Alkaptonuria can present with its first manifestation as ochronosis. In patients with severe ochronotic arthritis of the hip, total hip replacement is a highly successful modality of treatment and its effectiveness is comparable to performing a similar procedure for osteoarthritis of the hip. We found that our patient had significant relief from her pain at her follow-up visit as has been noted in other similar case reports. Hence, we would recommend total hip replacement as the treatment of choice in patients with severe ochronotic arthritis.

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