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Case Report

An unusual case in total knee replacement surgery: alkaptonuric ochronosis

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Abstract

Alkaptonuria is a rare autosomal recessive metabolic disorder caused by homogentisic acid oxidase deficiency, leading to the accumulation of homogentisic acid and ochronotic pigmentation in connective tissues. Although it typically presents with dark urine and arthropathy in later life, it often remains undiagnosed until advanced degenerative changes occur. We report a 54-year-old male patient who underwent total knee arthroplasty due to advanced degenerative arthritis. Intraoperatively, unexpected black pigmentation of the articular cartilage and surrounding connective tissues was observed. The patient had no previous diagnosis of alkaptonuria and was managed with postoperative metabolic evaluation, dietary advice, and follow-up. Ochronosis may remain undetected until late adulthood and can be encountered incidentally during orthopedic procedures. Awareness of this rare entity is crucial for orthopedic surgeons to ensure accurate intraoperative assessment and appropriate postoperative management.

Keywords: Alkaptonuria, ochronosis, total knee arthroplasty, degenerative joint disease, surgery

Introduction

Ochronosis was first described by Virchow in 1866 as a post-mortem finding and was named based on his observation of pigment accumulation in certain body tissues as black (or dark yellow) granules under the microscope [1-3]. Alkaptonuria develops due to abnormal metabolism of phenylalanine and tyrosine as a result of homogentisic acid (HGA) oxidase deficiency [1]. This enzyme normally oxidizes HGA into maleylacetoacetic acid, and its deficiency leads to gradual accumulation of the substrate (Figure 1) [1-5].

There is no associated protein deficiency or other evident biochemical or hormonal abnormality. The incidence is approximately 1 in 250,000 to 1,000,000 live births [1]. Pigment deposition occurs in the articular cartilage of the affected joints, as well as in periarticular collagen-rich ligaments and menisci [1-5]. The tissues darken, lose their elasticity, and develop poor resistance to mechanical stress [1-5]. Small, darkened cartilage fragments may become dislodged into joints and embed within the synovial membranes [1-5]. The spine and major peripheral joints, especially the knees, are primarily affected, leading to progressive disability, pain and stiffness in affected individuals [2].

Although ochronosis is typically seen in adults, the disorder may also be detected during childhood [1-3]. Males tend to experience more complications than females, likely due to higher physical activity levels [3]. A pathognomonic feature of ochronosis is the darkening of urine upon exposure to air [1-3]. A diagnostic test involves adding reducing agents such as glucose to the urine, which darkens immediately [4].

Ochronotic arthropathy (OCA) can mimic the symptoms of rheumatoid arthritis, especially with chronic painful swelling and restricted joint function [1-6]. Radiological findings include joint space narrowing, subchondral bone sclerosis, and degenerative changes [1-6]. Spinal involvement often presents with chronic lower back pain and stiffness [1,5,6]. Radiographs reveal widespread disc degeneration, compression, and narrowing accompanied by dense calcification [5-7]. The pattern of involvement differs from degenerative joint disease (DJD), where lumbosacral changes are more common, whereas dorsolumbar involvement predominates in ochronosis [5-7]. Extra-articular manifestations include pigmentation of the auricle, sclera, and nasal cartilage [1-6]. Less frequently observed findings include aortic valve calcification and stenosis, as well as renal and prostatic calculi [5,6].

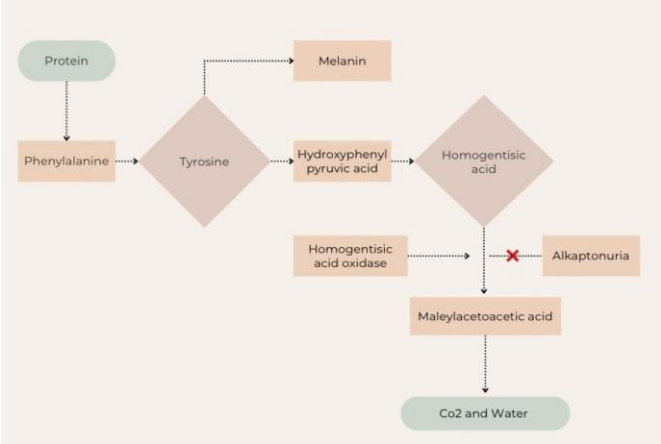

Figure 1. Pathophysiology of alkaptonuria. Disruption of the homogentisic acid oxidase enzyme in the phenylalanine and tyrosine catabolic pathway results in the accumulation of homogentisic acid, leading to alkaptonuria.

In this study, we present a patient with ochronosis that was noticed incidentally in a patient who underwent total knee arthroplasty surgery due to degenerative arthritis.

Case report

A 54-year-old male patient with a known history of hypertension and coronary artery disease also had a history of frequent urinary tract infections and previous hospitalization in the urology department due to renal calculi. The patient was a long-distance truck driver. Past urine cultures showed bacterial growth. Imaging revealed macroscopic prostatic calcifications, and the patient had a history of nephrectomy. The patient presented to our clinic with complaints of knee pain. Physical examination revealed restricted flexion and hip joint range of motion upon musculoskeletal assessment. Radiographs showed Kellgren-Lawrence grade 3 osteoarthritis of the knee and the patient reported persistent symptoms despite conservative treatment (Figure 2). Laboratory tests revealed no abnormalities. Surgical treatment was recommended. A total knee arthroplasty was performed via medial parapatellar incision, during which black pigmentation of the bone was observed intraoperatively. The procedure was completed as a routine total knee replacement without complications (Figure 3).

Postoperative radiographs showed no complications (Figure 4). The patient regained full range of motion in the knee and resumed daily activities. Additionally, laboratory investigations to support the diagnosis, such as urine darkening test or homogentisic acid measurement, were not available.

Discussion

Individuals with ochronosis (alkaptonuria) are typically asymptomatic for 4–10 years [5-7]. Thereafter, the condition progresses into symptomatic arthropathy [5-7]. The first clinical sign of alkaptonuria is often a change in urine color; however, diagnosis is frequently delayed until joint symptoms develop [2-7]. Our patient presented with progressive knee pain in early middle age

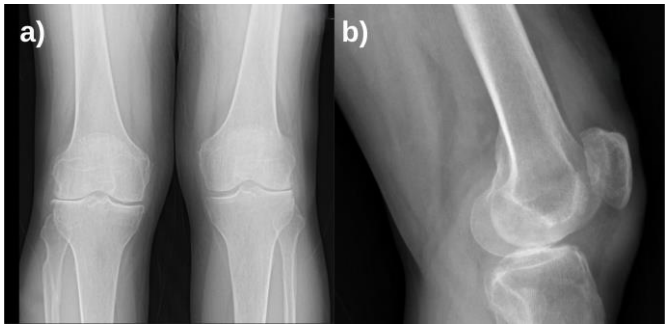

Figure 2. a) Preoperative antero-posterior radiograph showing grade III osteoarthritis in the knee. **b)** Preoperative lateral radiograph of the left knee demonstrating joint space narrowing and osteophyte formation.

[3-7]. Although alkaptonuria is present from birth, a possible explanation for the delayed onset of ochronotic arthropathy is the presence of an effective secondary clearance mechanism for homogentisic acid [5-7]. This involves renal tubular excretion systems capable of effectively eliminating HGA, similar to other organic acids [4-7]. Therefore, an adult with alkaptonuria who adheres to a regular diet can excrete several grams of HGA per day [1-3]. Renal clearance of HGA is highly effective in youth [3,5]. Over time, this efficiency declines, leading to a gradual rise in plasma HGA levels, which accelerates tissue deposition [5,6]. Radiologic findings include joint space narrowing, marked sclerosis, small cysts, periarticular calcification, and mild osteophyte formation. The severity of radiographic changes is often disproportionate to the patient's age [7].

Benzoquinone acetic acid, a derivative of oxidized HGA, may inhibit lysyl hydroxylase and reduce collagen cross-linking [3-7]. This increases susceptibility of connective tissues to stress and shear damage, leading to cartilage erosion and progressive degenerative changes [3-7]. There is currently no curative treatment for alkaptonuria. However, nitisinone, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase – the enzyme that produces HGA – is considered a promising therapeutic agent for reducing symptoms associated with HGA accumulation [5,6].

Patients over the age of 40 with alkaptonuria may develop cardiovascular complications such as aortic dilation and valvular insufficiencies, as well as urinary complications such as prostatic and renal calculi [4-7]. In our patient, macroscopic prostatic calcifications and a history of nephrectomy were consistent with this pattern. Despite these complications, the overall prognosis for survival in alkaptonuria is generally favorable. Thus, symptomatic treatment is important [4-6]. Physical therapy is often provided to maintain muscle strength and flexibility, pain is managed with analgesics and joint replacement surgery is considered in patients with advanced joint destruction [6,7].

Joint destruction in alkaptonuria results from organic changes due to HGA accumulation on cartilage surfaces, leading to the loss of elasticity [5-7]. Subsequent mechanical stress causes damage to cartilage and subchondral bone [5-7]. Gil et al. reported a case of joint space narrowing in the early stages of the disease, resembling coxarthrosis [5]. In addition, numerous cases have described knee joint involvement with arthropathic features secondary to cartilage degeneration [7].

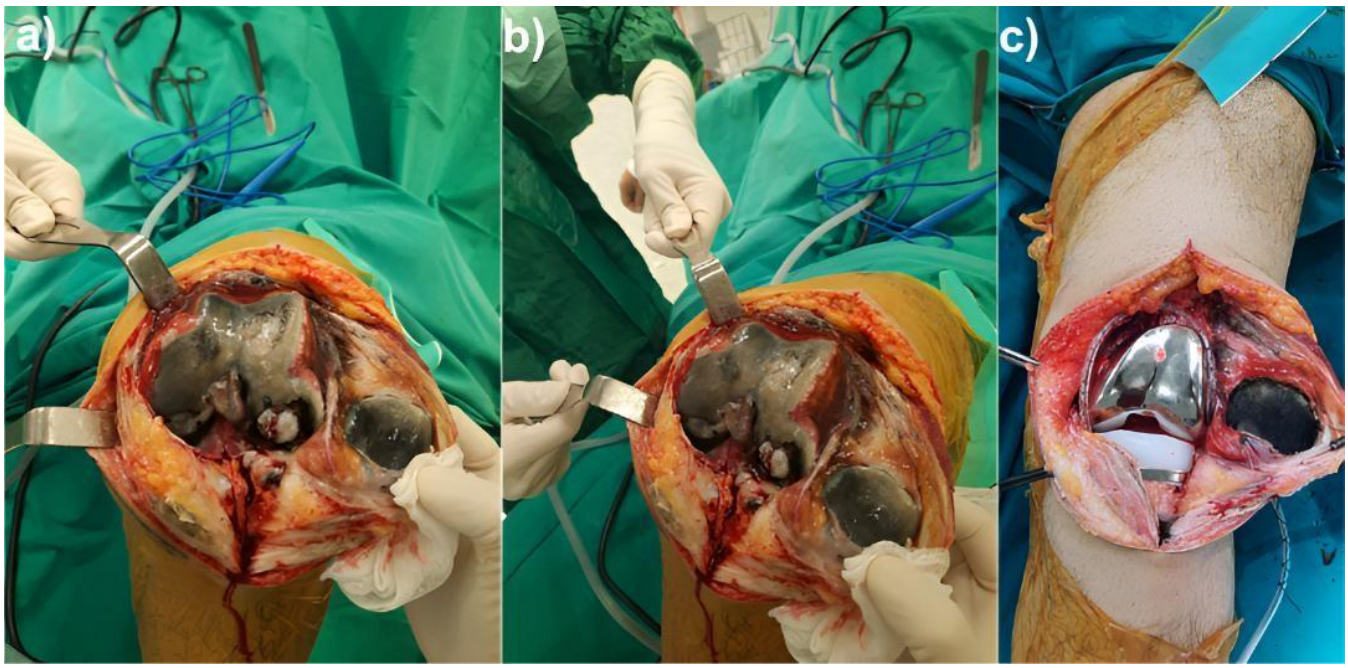

Figure 3. a, b, c) Diffuse dark pigmentation in the joint chondral structures, noted during surgery and consistent with ochronosis. c) Appearance of the joint after placement of total knee arthroplasty components.

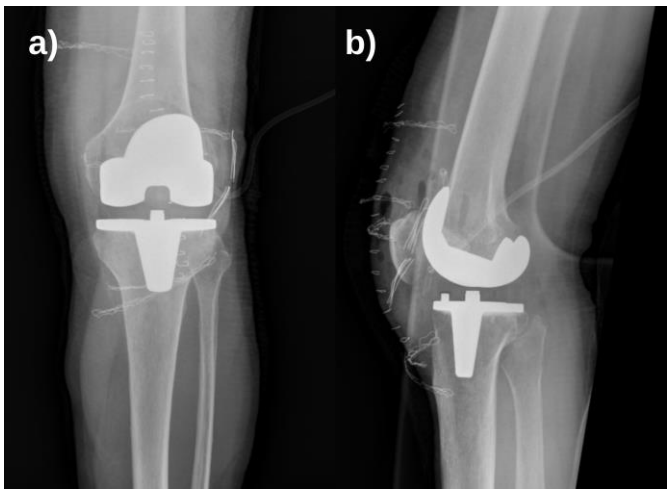

Figure 4. a, b) Radiographic images of the patient after total knee arthroplasty surgery.

In this study, we presented a patient with early-onset knee osteoarthritis due to alkaptonuria, which was detected incidentally intraoperatively. Early therapeutic interventions, similar to those for osteoarthritis, are recommended to prevent rapid joint destruction in major joints such as hips and knees.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AYS, MAD and OT. The first draft of the manuscript was written by AYS, MAD and OT and all authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

Statements and declarations

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical statement

The authors confirm that this retrospective study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and its later amendments.

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