International Journal of Research in Orthopaedics
Chaudhari K et al. Int J Res Orthop. 2025 Jan;11(1):239-241
http://www.ijoro.org

DOI: https://dx.doi.org/10.18203/issn.2455-4510.IntJResOrthop20243915

Case Report

The dark side of cartilage: ochronosis unmasked during femoral neck fracture surgery

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Received: 08 October 2024
Revised: 19 November 2024
Accepted: 25 November 2024

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ABSTRACT

Alkaptonuria is a rare autosomal recessive disorder caused by a deficiency in homogentisic acid oxidase, leading to the accumulation of homogentisic acid in connective tissues. It is characterized by bluish-black pigmentation of cartilage and other connective tissues, with progressive joint degeneration and early-onset osteoarthritis. Ochronosis typically becomes symptomatic after the age of 30, affecting larger joints and the spine. A 75-year-old female presented with a transcervical femoral neck fracture and a right distal end radius fracture following a fall. During hip surgery, intraoperative findings included blackish discoloration of the femoral head and acetabulum. The patient had a history of stooped posture and calcified intervertebral discs. Further examination revealed ochronotic pigmentation of the sclera and ear cartilage, and a urine test confirmed the diagnosis of ochronosis. Postoperative recovery was uneventful. Ochronosis should be considered in the differential diagnosis of patients with calcified intervertebral discs and early-onset joint degeneration. The condition is typically asymptomatic until joint involvement occurs. Current treatment options are limited, though nitisinone and dietary modifications show some promise. This case highlights the importance of recognizing ochronosis in patients with joint degeneration, particularly when intraoperative findings reveal characteristic pigmentation.

Keywords: Ochronosis, Alkaptonuria, Homogentisic acid, Pigmentation

INTRODUCTION

Alkaptonuria is a rare autosomal recessive disorder of metabolism. It is characterized by homogentisic acid deposition in connective tissue as a result of a deficiency in homogentisic acid oxidase, an enzyme involved in the catabolism of tyrosine and phenylalanine.[1] In alkaptonuria, ochronotic pigment is deposited in all connective tissues, especially cartilage. An acidic environment produces an inflammatory response in joints and disturbs articular cartilage metabolism, which promotes cartilage degeneration. The three major features of alkaptonuria are dark urine or urine that turns dark on standing, ochronosis (bluish-black pigmentation in connective tissue), and arthritis of the spine and larger joints.[2] Ochronosis can occur in tendons, ligaments, sclera, heart valves, the intima of blood vessels, and the skin. The irreversible binding of the homopolymeric oxidation products of homogentisic acid to collagen causes degenerative changes in the morphologic structure of connective tissue. Ochronosis usually appears after age 30 and, over time, leads to black and brittle bones and cartilage, and early onset osteoarthritis.[3] Ochronotic patients usually present in their 5th decade of life with back pain and arthritic changes in hips and knees. The biochemical diagnosis of alkaptonuria in a proband is based on the detection of a significant amount of homogentisic acid in the urine. The molecular diagnosis is based on identification of biallelic pathogenic variants in homogentisic oxidase gene.

CASE REPORT

A 75 years old female presented to emergency with alleged history of slip and fall sustaining injury to right hip and right wrist. Radiographic evaluation of the right hip showed transcervical femur fracture and extraarticular fracture of right distal end radius. She reported walking with a stooping posture since the last 15 years. She had a family history of her parents walking with a stooping posture. Radiographic evaluation of the spine showed calcification of intervertebral discs and degenerative changes. Intervertebral disc calcification and degenerative changes led to severe angular kyphotic deformity of the spine.

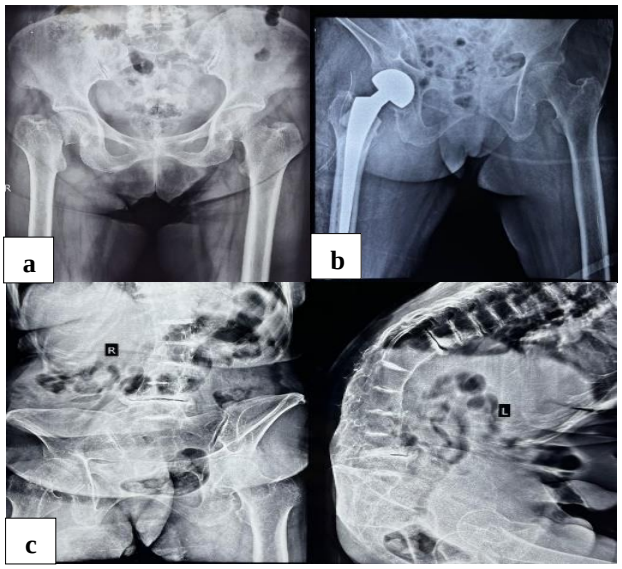

Figure 1: (a) Preoperative radiograph showing right transcervical neck of femur fracture; (b) postoperative radiograph showing right cemented bipolar hemiarthroplasty; and (c) radiograph of spine suggestive of intervertebral disc calcification and degenerative changes.

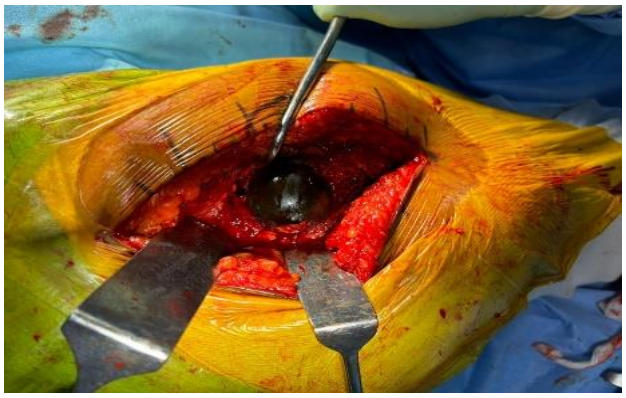

Figure 2: Ochronotic deposits of joint cartilage found intraoperatively.

Routine laboratory examination of the patient was normal. A cemented bipolar hemiarthroplasty of right hip was performed. Intraoperatively upon opening the hip joint capsule there was blackish discoloration of the femoral head and the acetabular cavity. While performing volar plating for distal end radius fracture, flexor carpi radialis tendon was found to be black. The patient was re-examined and found to have blackish pigmentation of the sclera and bluish black pigmentation of the ear cartilage. Urine homogentisic acid test was done which was suggestive of ochronosis. HLA B27 was done which ruled out seronegative arthropathies. Radiographs of bilateral knees suggested osteoarthritic changes. The patient progressed well postoperatively.

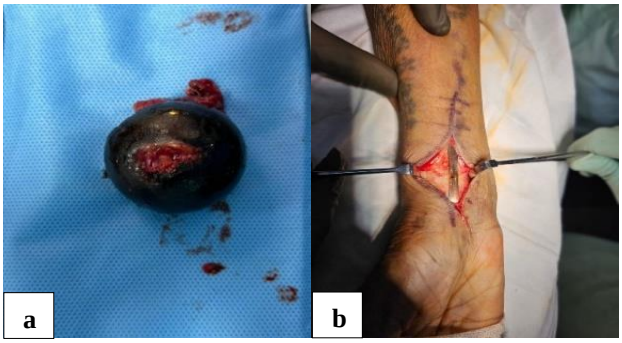

Figure 3: (a) Intraoperatively resected portion of femoral head, and (b) intraoperative finding showing black flexor carpi radialis tendon.

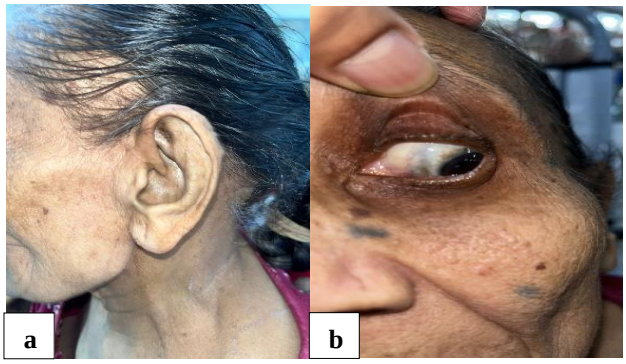

Figure 4: (a) Bluish black pigmentation of ear cartilage, and (b) blackish pigmentation of sclera of the eyes.

DISCUSSION

This case emphasizes the importance of considering ochronosis in patients presenting with early-onset joint degeneration and intervertebral disc calcification, particularly when intraoperative findings reveal characteristic pigmentation. Although typically asymptomatic until joint involvement, ochronosis can mimic other degenerative conditions such as ankylosing spondylitis. Its hallmark findings, such as pigmentation in connective tissues, aids in diagnosis. Current treatments, including nitisinone and dietary modifications, may reduce homogentisic acid levels but have limited efficacy in reversing degenerative changes. This highlights the need for heightened clinical awareness, detailed patient history,

and appropriate biochemical testing to confirm diagnosis and guide management.

This is a rare case report where the findings suggestive of ochronosis were incidentally found intraoperatively. Ochronosis usually presents after age 30 and is predominantly asymptomatic until the involvement of the spine and large joints. Ochronosis must be considered in the differential diagnosis in patients with Intervertebral disk calcification.[4,5] Ochronosis involving the spine can be distinguished from ankylosing spondylitis based on sacroiliac joint evaluation and HLA B 27. The diagnosis of this disease can be confirmed based on quantitative measurement of HGA in the urine and mutation analysis of the HGD gene. Whether it is essential to do this mutation analysis remains controversial because it is not economic while hardly yields any change for the treatment. The mechanisms underlying cartilage destruction remains largely unknown in this condition. Oxidation of HGA results in formation of benzoquinone acetic acid, which inhibits lysine hydroxylase, thereby reducing the cross-linkage between collagen fibers.[6] Ligament destruction reduces joint stability, which further aggravates cartilage abrasion. Currently, drugs for management of progressive ochronosis remains unavailable. Nitisinone, which inhibits the 4-hydroxyphenylpyruvic acid dioxygenase enzyme (an important component of the tyrosine catabolic pathway) is a promising drug for treatment of ochronosis and was approved for the treatment of hereditary tyrosinemia.[7] However, whether nitisinone therapy may reverse ochronotic arthritic changes remains unclear. Vitamin C intake can suppress urinary excretion of benzoquinone acetic acid however, long-term efficacy of this approach remains unproven.[8] Restriction of tyrosine and phenylalanine intake can reduce HGA excretion but increases the risk of nutritional deficiencies. Our case report emphasizes that clinicians should be familiar with the pathological mechanism underlying ochronotic arthritic changes, the possible outcomes, and importance of accurate detailed history taking with regard to the patient's personal and family histories.

CONCLUSION

This case report on an incidental finding of ochronosis highlights the importance of recognizing ochronosis in patients with joint degeneration, intervertebral disc calcification particularly when intraoperative findings reveal characteristic pigmentation of cartilage and tendons.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Chaudhari K, Parth K, Kothari M, Bava SS, Phunde R, Somani R. The dark side of cartilage: ochronosis unmasked during femoral neck fracture surgery. Int J Res Orthop 2025;11:239-41.