Intraoperative Diagnosis of a Rare Case of Arthropathy – A Case Report and Review of Literature

Ashraf Shaikh¹, Mohan Desai¹, Radhakrishna Kantanavar¹, Swapneel Shah¹

Learning Point of the Article:
It is important for an orthopaedic surgeon to have a high index of suspicion for other etiologies such as metabolic bone diseases in patients who do not fit into the characteristic clinical and radiological picture of common conditions causing hip arthritis.

Abstract

**Introduction:** Alkaptonuria is a rare metabolic disorder of autosomal recessive pattern of inheritance caused due to homogentisic acid oxidase enzyme deficiency. As a result, polymers of homogentisic acid get deposited in excessive amounts in the connective tissues, leading to brownish-black pigmentation termed as ochronosis. As the disease progresses, chronic inflammation results in arthritis of large weight-bearing joints.

**Case Report:** A 70-year-old female patient presented with complaints of being non-ambulatory since the past 10 days. She gave a history of difficulty in walking for the past 10–15 years associated with pain in the right hip which did not respond to analgesics and physiotherapy. The radiological assessment revealed severe joint destruction of the right hip. The patient underwent a total hip arthroplasty. A provisional diagnosis of ochronosis was made intraoperatively which was later confirmed on histopathological examination of the tissue.

**Conclusion:** At present, there is still no known effective medical treatment to halt alkaptonuria entirely. Ochronotic arthropathy is usually managed conservatively. However, for severely involved hip joints, arthroplasty can provide extremely good results.

**Keywords:** Ochronosis, alkaptonuria, ochronotic arthropathy, arthroplasty.

**Introduction**

Alkaptonuria is a metabolic disorder of autosomal recessive pattern of inheritance. The pathogenesis of the disease revolves around the deficiency of homogentisic acid oxidase enzyme which is involved in the metabolism of tyrosine and phenylalanine. Due to this defect, homogentisic acid accumulates in enormous amounts in the connective tissue (especially cartilage) which leads to brownish-black pigmentation. These changes are called ochronosis. With the progression of the disease, the tissues get damaged due to chronic inflammation which further leads to degeneration and arthritis [1].

At present, there is no specific treatment for alkaptonuria and the accompanying ochronotic arthropathy due to the absence of large studies in the literature [2]. However, there are reports which suggest that the outcome of arthroplasty in ochronotic arthropathy is as satisfactory as in degenerative arthritis [3].

In this case report, we present a 70-year-old female patient with alkaptonuria, who underwent arthroplasty of the right hip due to ochronotic arthritis. The difficulties in clinching the diagnosis and during surgery are reported and discussed. The patient’s informed written consent was taken for print and electronic publication of this case report.

**Case Report**

A 70-year-old female patient presented to us with complaints of being non-ambulatory since the past 10 days. She gave a history of difficulty in walking for the past 10–15 years associated with pain in the right hip which did not respond to analgesics and physiotherapy. She also complained of mild pain in the left hip and both the knees. She did not have any history of trauma or fall. There was no other medical or surgical illness. Family history was insignificant. On examination, the right hip had a 2...
The radiological assessment revealed severe joint destruction of the right hip with a fracture at the neck of femur. Femur head demonstrated irregularity and significantly narrowed hip joint space (Fig. 1).

In addition, the right hip had a restricted abduction and adduction compared to the left hip. There was also a bilateral knee flexion and varus deformity of 10 degrees each. Clinically, we provisionally diagnosed the case as arthritis of the hip joint under evaluation.

The radiological assessment revealed severe joint destruction of the right hip with a fracture at the neck of femur. Femur head demonstrated irregularity and significantly narrowed hip joint space (Fig. 1).

The left hip joint also showed narrowing of joint space. Both the knees revealed severe tricompartmental osteoarthritis (OA) (Fig. 2). The X-ray of the spine demonstrated fusion of vertebral bodies resembling a bamboo spine appearance (Fig. 3).

On magnetic resonance imaging, significant bony destruction of the right femoral head-and-neck regions with superior subluxation of the right greater trochanter and femur was seen (Fig. 4). Inflammatory marrow changes in the residual upper femur raised the possibility of an associated osteomyelitis. Inflammatory or hemorrhagic fluid collections were seen in the acetabular fossa. The sacroiliac joint appeared normal.

The erythrocyte sedimentation rate (ESR) and C-reactive protein were within normal limits. Rheumatoid factor and HLA-B27 were negative as well.

Under local anesthesia and aseptic precautions, aspiration of the involved hip was done in the operating room and joint fluid sent for culture sensitivity and GeneXpert. The aspirate did not show any growth on culture. The results of the GeneXpert turned out to be negative as well.

A total hip arthroplasty was planned. Intraoperatively, on lifting the short external rotators, we found the joint capsule to be black. The capsule had lost its natural consistency and had turned hard and contracted. Moreover, the joint surfaces, ligaments, and tendons were blackish too with pieces of black cartilage. The capsule was excised posteriorly and the femur head was removed. Reaming of the acetabulum revealed poor bone quality. An uncemented acetabular cup was used (44 mm) with a ceramic liner (Fig. 5, 6).

After the reaming and broaching of the femoral canal, an uncemented femur stem (Smith and Nephew, cone 12/14, size 1) was inserted and the hip joint was reduced. There were no intraoperative or post-operative complications. The bone and soft-tissue specimens were sent for histopathological evaluation. The patient was mobilized full weight-bearing on the 1st post-operative day and was discharged on the 3rd day.

Postoperatively, reexamination of the patient revealed brownish-black pigmentation of the ear pinna as well as the sclera (Fig. 7). The urine of the patient was also tested and it turned dark on standing for 24 h (Fig. 8).

On histopathological examination, the articular cartilage showed brownish-black pigmentation throughout, sparing only the part adjacent to the underlying bone. Soft-tissue demonstrated brownish-black fragments of pigmentation which were sharply defined and irregularly shaped. The surrounding tissue revealed fragments of non-viable bone, inflamed synovial tissue, foreign body type giant cells, and fibroblastic proliferation with few hyalinized areas. The synovial lining was denuded. All of the features mentioned above are consistent with the diagnostic findings of ochronosis (Fig. 9).

The follow-up of the patient at 1 year revealed that her right hip pain had completely subsided along with a full range of motion. The Harris Hip Score of the patient had shown significant improvement.
from 32 preoperatively to 81 at 1 year follow-up. The patient was also counseled for a bilateral total knee replacement.

Discussion

Alkaptonuria is a rare disease which affects approximately 1 in 1 million people according to the statistics in the European countries [4]. However, there is no published literature on the incidence of the disease in India as very few of them have been reported. It is the first genetic disease described with autosomal recessive trait caused due to a mutation in the HGD gene on chromosome 3q which is responsible for the functioning of the enzyme homogentisate 1, 2-dioxygenase [1]. This enzyme breaks down homogentisic acid (HGA). The non-functioning defective enzyme causes accumulation of HGA in soft tissues over a period of time. The excess HGA is converted to benzoquinone acetic acid which, in turn, undergoes polymerization to form compounds which are similar to the pigment melanin. This leads to the dark pigmentation in these patients [5, 6, 7]. Ochronosis, being a musculoskeletal manifestation of alkaptonuria, affects the entire body causing brownish-black pigmentation of connective tissue, articular cartilage pathology, internal organ dysfunction, osteoporosis, and advanced arthropathy of the weight-bearing joints [6, 7].

The disorder is generally asymptomatic until the fourth decade when the joints start getting involved. The most common joint involved in ochronotic arthropathy is the knee. It is followed by hip, shoulder, lumbar intervertebral discs, and sacroiliac joints.

It is important to distinguish between ochronotic arthropathy, OA, and ankylosing spondylitis (AS) as they may resemble each other [8].

Table 1 differentiates between the characteristics of these disorders [11].

Another condition to be considered in the differential diagnosis is pigmented villous nodular synovitis of the hip. However, it most commonly occurs between the age of 20 and 40 years and is almost always monoarticular. Cystic bony erosions, hyperplastic synovium, and low signal intensity on both T1- and T2-weighted images are seen on magnetic resonance imaging. The tissues are pigmented brownish orange due to the deposition of hemosiderin. On histopathology, it shows fibrous stroma, hemosiderin deposition, giant cells, and histiocytic infiltration [12].

Thus, the diagnosis of ochronotic arthropathy is complex and may be made intraoperatively during the joint replacement surgery, as in our case.
Ochronotic arthropathy is usually managed conservatively. However, for severely involved hip and knee joints, arthroplasty can provide extremely good results. There are no large published series regarding the results of arthroplasty in alkaptonuria, the reason for this being the very rare occurrence of this disease. However, the limited number of case reports in literature demonstrates promising results with respect to pain management and preservation of joint mobility (Fig. 10).

**Conclusion**

With the lack of medical management preventing the progression of joint destruction, arthroplasty proves to be a highly effective management surgery for ochronotic arthropathy in alkaptonuria patients.

**Clinical Message**

Ochronotic arthropathy is a manifestation of a rare disease and therefore likely to be missed in an orthopedic clinic during the initial diagnosis. High index of suspicion is required for clinching the diagnosis and thus initiating early medical and necessary surgical management.

### References

1. Selvi E, Manganelli S, Mannoni A, Benucci M, Minacci C, Marcolongo R. Chronic ochronotic arthritis: Clinical, arthroscopic, and pathologic findings. J Rheumatol 2000;27:2272-4.
2. Keller JM, Macaulay W, Nercessian OA, Jaffe IA. New developments in ochronosis: Review of the literature. Rheumatol Int 2005;25:81-5.
3. Zatková A, de Bernabé DB, Poláková H, Zvarík M, Feráková E, Bosák V, et al. High frequency of alkaptonuria in Slovakia: Evidence for the appearance of multiple mutations in HGO involving different mutational hot spots. Am J Hum Genet 2000;67:1333-9.
4. Spencer JM, Gibbons CL, Sharp RJ, Carr AJ, Athanasou NA. Arthroplasty for ochronotic arthritis: No failure of 11 replacements in 3 patients followed 6-12 years. Acta Orthop Scand 2004;75:355-8.
5. Fernández-Cañón JM, Granadino B, de Bernabé DB, Renedo M, Fernández-Ruiz E, Peñalva MA, et al. The molecular basis of alkaptonuria. Nat Genet 1996;14:19-24.
6. Gaines JJ Jr. The pathology of alkaptonuric ochronosis. Hum Pathol 1989;20:40-6.
7. O’Brien W, Bert ND, Bunim JJ. Biochemical, pathologic and clinical aspects of alkaptonuria, ochronosis, and ochronotic arthropathy. Am J Med 1963;34:813-38.
8. Laskar TH, Sarginson KD. Ochronotic arthropathy-review of four cases. J Bone Joint Surg Br 1970;52:653-66.
9. Gemignani G, Olvieri I, Semeria R, Giustarini S, Pasero G. Coexistence of ochronosis and ankylosing spondylitis. J Rheumatol 1990;17:1707-9.
10. Yagan R, Khan MA. The coexistence of ochronosis and ankylosing spondylitis. J Rheumatol 1991;18:1639-40.
11. Konttinen YT, Hoikka V, Landtman M, Saari H, Santavirta S, Metsärinne K, et al. Ochronosis: A report of a case and a review of literature. Clin Exp Rheumatol 1989;7:435-44.
12. Frassica FJ, Bhimani MA, McCarthy EF, Wenz J. Pigmented villonodular synovitis of the hip and knee. Am Fam Physician 1999;60:1404-10.
13. Ranganath LR, Khedr M, Milan AM, Davison AS, Hughes AT, Usher JL, et al. Nitisinone arrests ochronosis and decreases rate of progression of alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. Mol Genet Metab 2018;125:127-34.
14. Mannoni A, Selvi E, Lorenzini S, Giorgi M, Airò P, Cammelli D, et al. Alkaptonuria, ochronosis, and ochronotic arthropathy. In: Seminars in Arthritis and Rheumatism. Vol. 33. Philadelphia, PA: WB Saunders; 2004. p. 239-48.
