Degenerative Arthritis of the Knee Secondary to Ochronosis

A Case Report

Obafunto Abimbola, B.S., Greg Hall, B.S., and Joseph D. Zuckerman, M.D.

Abstract

Alkaptonuria is a rare disease in which a deficiency in the homogentisate 1, 2-dioxygenase enzyme results in a buildup of homogentisic acid. Ochronosis, the deposition of excess homogentisic acid in connective tissue, causes brownish-black pigmentation and weakening of the tissue ultimately resulting in chronic inflammation, degeneration, and osteoarthritis. There is currently no definitive cure for alkaptonuric ochronosis, and management is usually symptomatic. However, total joint replacements in severe cases of ochronotic osteoarthritis have comparable outcomes to osteoarthritic patients without ochronosis. We report a case of a patient with ochronotic arthritis of the knee treated with total knee arthroplasty.

Ochronosis is a rare metabolic disorder that is characterized by a brownish-black pigmentation of connective tissues. A common symptom of alkaptonuria, ochronosis is the result of excess homogentisic acid (HGA) due to the autosomal recessive mutation of the homogentisate 1, 2-dioxygenase (HGO) gene on chromosome 3.[1] The condition is rare, affecting only one in 100,000 to 250,000 individuals, but there is evidence that certain populations may have a much higher incidence.[2]

The pathogenesis of the disease is the polymerization of deposited HGA that discolors and weakens the connective tissue, ultimately resulting in brittle tissue that is easily disrupted and leads to chronic inflammation, degeneration, and eventually osteoarthritis.[3] There are a myriad of presentations of the disease, including darkening of the urine when exposed to air; bluish pigmentation of the skin of the face, hands, ear cartilage, sclera, and fingernails; aortic and cardiac valve calcification; lumbar intervertebral disc calcification and disc space narrowing; and osteoarthritis of the hip and knee.[4-6]

Currently, there is no specific treatment for ochronosis, and management of symptoms as they manifest or worsen is the general, accepted approach. However, in cases of significant degenerative arthritis, joint replacement can be performed with anticipation of outcomes comparable to osteoarthritic patients without ochronosis.[7] We report the case of a 48-year-old male with a family history of ochronosis, who developed degenerative arthritis of the knee.

Review

Ochronosis is a musculoskeletal manifestation of alkaptonuria, a rare disease caused by a loss-of-function mutation on chromosome 3q, which leads to a defect in the HGO, or homogentisate 1, 2-dioxygenase enzyme.[1] This enzyme is responsible for the breakdown of HGA, an intermediate product of the metabolism of the amino acids tyrosine and phenylalaine. The defective enzyme leads to a build-up of HGA in tissues and blood. Over the years, polymers of HGA are deposited in the tissues, causing the dark pigmentation encountered in these patients. Ochronosis, or the deposition of this pigment, affects the entire body and can cause cardiovascular, genitorurinary, ocular, cutaneous, and musculoskeletal complications.[8,9] HGA is also excreted in the urine in large quantities and oxidized to a dark colored urine that manifests in early childhood. Apart from the dark urine, most of the symptoms of alkaptonuria are not observed until the fourth to fifth decade.[9]

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Alkaptonuria causes progressive ochronotic arthropathy of the large weightbearing joints (knees, hips, shoulders, vertebrae).[8-10] However, there have been case reports of ribs also being affected. Although the smaller joints do not appear to develop arthritis, the cartilage within these joints also demonstrates pigmentation. The build-up of deposited HGA that leads to brittle articular cartilage eventually becomes fragmented, creating loose shards and leading to joint deterioration and degenerative arthritis.[9] The arthropathy is similar to an osteoarthritic pattern with a small inflammatory component; the shards cause synovial irritation, with an associated inflammatory response. In their review of the world literature, O'Brien and colleagues identify the knee as the most frequently affected joint, followed by the hip.[11] The intervetebral discs are also affected, with pigmentation and ossification of the nucleus pulposus, leading to degenerative changes.[8] Tendons and ligaments also are heavily pigmented due to their collagen content. As a result, tendon inflammation, calcification, and rupture can develop.[12]

Symptomatic management is the primary treatment for ochronotic arthropathy.[12,13] Exercise and analgesics have proven beneficial but do not slow joint degeneration.[13] In cases of significant ochronotic arthritis, total joint replacement has been an effective approach to alleviate pain and restore function.[14]

Case Report

A 48-year-old male presented for evaluation of left knee pain that started 2 years previously and was associated with "locking." Within 1 year, the knee pain had become constant. At the time of the initial evaluation, the patient described walking that was very painful and limited to one or two blocks. He reported that walking up and down stairs was very difficult as well. He denied pain at rest or pain at night that interfered with sleep. He had been treated with antiinflammatory medications, a series of three injections

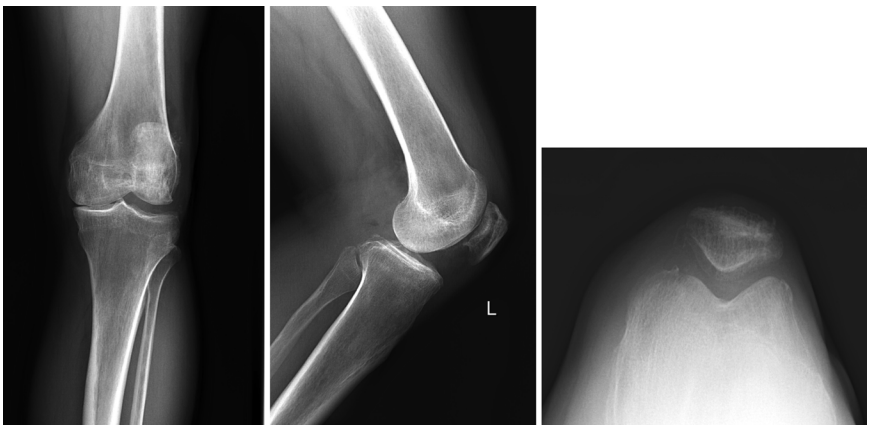

Figure 1 Preoperative radiographs showing extensive degenerative changes.

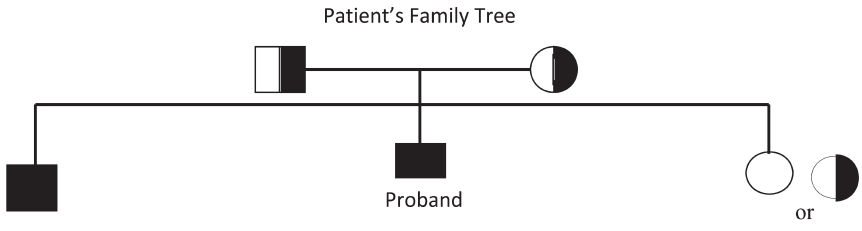

Figure 2 Constructed family tree of patient in which one can observe the autosomal recessive nature of the inheritance of alkaptonuria.

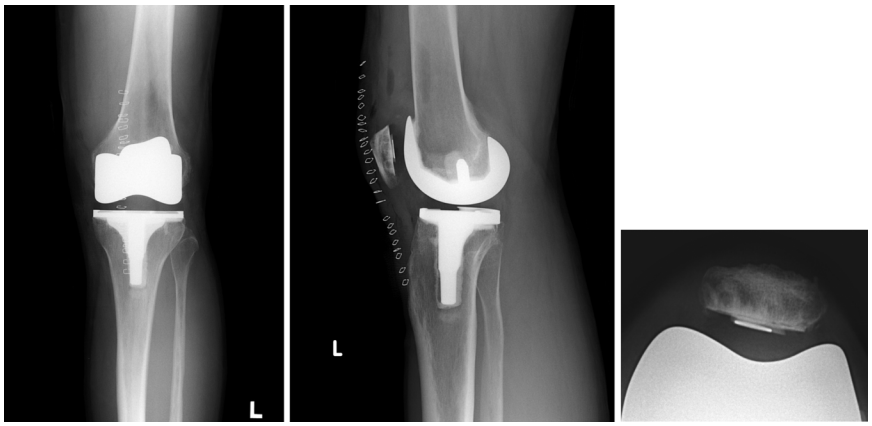

Figure 3 Radiographs following total knee arthroplasty.

Figure 4 **A**, Resected portion of the tibial plateau shows heavy pigmentation of the articular cartilage, with sparing of the bone. Note extensive loss of cartilage of the medial compartment. **B**, Heavy pigmentation of the articular surfaces of the patient's femoral condyles and meniscus.

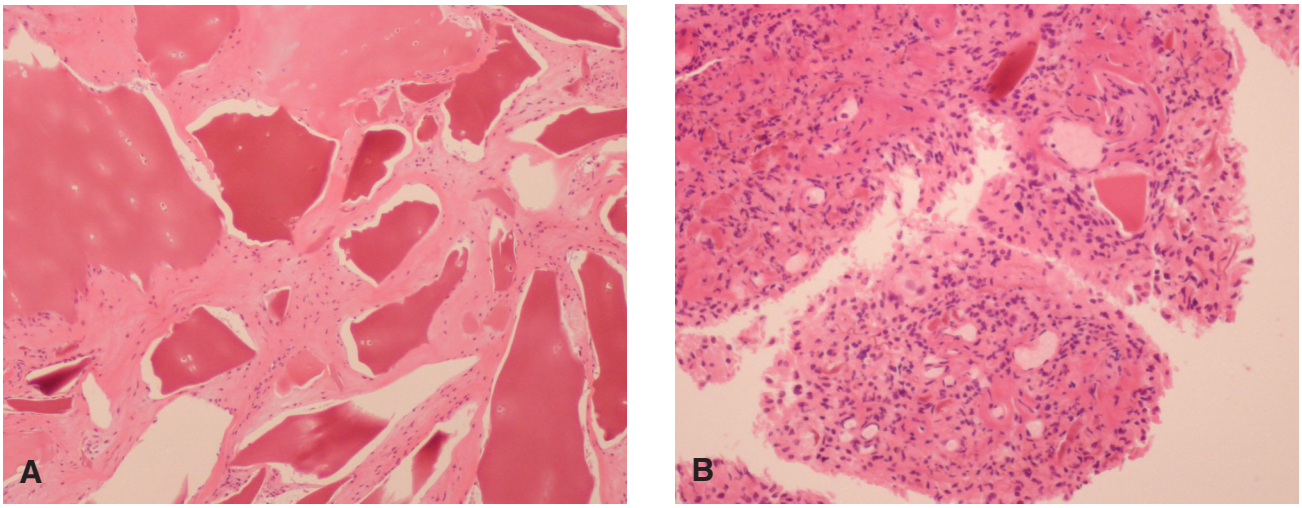

Figure 5 **A**, Numerous fragments of brittle cartilage have broken off and are now embedded in synovium (**B**) multiple pigmented areas, reactive giant cells, and inflammatory cells within the thickened synovium.

with viscosupplementation, and a single intra-articular steroid injection without sustained improvement.

On physical examination, he walked with a secure, stable gait, without antalgic component. There was neutral alignment of the left knee. Further examination showed a moderate effusion, with tenderness over the medial and lateral joint line. Mild tenderness occurred on compression of the patella. Range of motion was 0° to 130° of flexion, accompanied by discomfort in extreme flexion. There was no laxity of the collateral or cruciate ligaments. Distal neurovascular examinations of the lower extremities were intact and symmetric.

Radiographic evaluation of the left knee showed moderately advanced degenerative arthritis, with significant loss of medial joint space (Fig. 1). There was more significant involvement of the medial compartment, with less significant lateral and patellofemoral degenerative changes.

The patient described a family history of ochronosis (Fig. 2). A brother had been treated with bilateral total knee replacement and unilateral shoulder arthroplasty. A younger sister had not shown any signs or symptoms of the disease. The patient denied knowing about any other family members who may have noticed dark urine or experienced painful joints or signs of arthritis. Therefore, although neither parent had the disease, because it is an autosomal recessive disorder, both parents would have to have been carriers.

A cemented left total knee replacement (Genesis SPC; Smith & Nephew, Inc., Memphis, Tennessee) was performed (Fig. 3). Generalized degeneration throughout the knee was observed, with extensive loss of articular cartilage involving the medial compartment. A deposition of black pigment was seen throughout the articular cartilage. The menisci were

in a degenerative condition and brittle, with large areas of pigmentation (Fig. 4). Histological sections of removed bone and soft tissue demonstrated classic findings of ochronosis, including multiple pigmented areas, reactive giant cells, and thickened, inflamed synovium (Fig. 5). The patient progressed well postoperatively, regaining good range of motion and independent ambulation 6 weeks after surgery. At that time, active range of motion was from full extension to 110° of flexion. Postoperative radiographs showed total knee components were in good position and alignment. At 2 years following surgery, the patient had returned to full activities, described no knee pain, and was very satisfied with the outcome.

Conclusion

Ochronotic arthritis is a very uncommon disease that can be potentially misdiagnosed with osteoarthritis in patients with knee pain and radiographic evidence of joint space narrowing. Early management of ochronosis can be challenging and is limited to controlling the patient's symptoms. More advanced cases of ochronotic arthritis necessitate surgical intervention. As we have reported, total knee replacement has excellent outcomes in a patient with significant degenerative arthritis secondary to ochronosis.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References

1. Fernández-Cañón JM, Granadino B, Beltrán-Valero de Bernabé D, et al. The molecular basis of alkaptonuria. Nat Genet. 1996 Sep;14(1):19-24.
2. Zatková A, de Bernabé DB, Poláková H, 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 Nov;67(5):1333-9; Epub 2000 Oct 2.
3. Selvi E, Manganelli S, Mannoni A, et al. Chronic ochronotic arthritis: clinical, arthroscopic, and pathologic findings. J Rheumatol. 2000 Sep;27(9):2272-4.
4. Nas K, Gür A, Akdeniz S, et al. Ochronosis: a case of severe ochronotic arthropathy. Clin Rheumatol. 2002 May;21(2):170-2.
5. Wauthy P, Seghers V, Mathonet P, Deuvaert FE. Cardiac ochronosis: not so benign. Eur J Cardiothorac Surg. 2009 Apr;35(4):732-3; Epub 2009 Feb 10.
6. Farzannia A, Shokouhi G, Hadidchi S. Alkaptonuria and lumbar disc herniation. Report of three cases. J Neurosurg. 2003 Jan;98(1 Suppl):87-9.
7. Spencer JM, Gibbons CL, Sharp RJ, et al. Arthroplasty for ochronotic arthritis: no failure of 11 replacements in 3 patients followed 6-12 years. Acta Orthop Scand. 2004 Jun;75(3):355-8.
8. Albers SE, Brozena SJ, Glass LF, Fenske NA. Alkaptonuria and ochronosis: case report and review. J Am Acad Dermatol. 1992 Oct;27(4):609-14.
9. Gaines JJ Jr. The pathology of alkaptonuric ochronosis. Hum Pathol. 1989 Jan;20(1):40-6; Erratum in Hum Pathol. 1989 May;20(5):500.
10. La Du BN Jr. Alcaptonuria and ochronotic arthritis. Mol Biol Med. 1991 Feb;8(1):31-8.
11. O'Brien W, La Du BN, Bunim JJ. Biochemical, pathologic and clinical aspects of alcaptonuria, ochronosis, and ochronotic arthropathy. Am J Med. 1963 June;34:813-38.
12. Mannoni A, Selvi E, Lorenzini S, et al. Alkaptonuria, ochronosis, and ochronotic arthropathy. Semin Arthritis Rheum. 2004 Feb;33(4):239-48.
13. Borman P, Bodur H, Ciliz D. Ciliz. Ochronotic arthropathy. Rheumatol Int. 2002 Mar;21(5):205-9.
14. Kerimoglu S, Onder C, Aynaci O, Malkoc CH. Hip arthroplasty for ochronosis. Saudi Med J. 2005 Nov;26(11):1812-4.