Degenerative Osteoarthritis with Multiple Joint Arthroplasties Due to Alkaptonuria: A Rare Inborn Error of Tyrosine Metabolism

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A lkaptonuria is a rare autosomal recessive inborn error of tyrosine degradation caused by mutations in the HGD gene, encoding the homogentisate 1,2-dioxygenase enzyme. This enzyme, located in the tyrosine degradation pathway, converts homogentisic acid (HGA) to maleylacetoacetic acid. Deficient activity of this enzyme leads to an accumulation of HGA in connective tissues, mainly in cartilage, resulting in dark-bluish discoloration known as ochronosis [1].

The typical clinical features of alkaptonuria are distinguished by a classic triad including dark discoloration of urine on alkalization or when exposed to air. These effects may have been evident since infancy. Ochronosis, which develops slowly and is usually evident during adulthood, is a progressive debilitating osteoarthritis involving weight-bearing joints such as hips, knees, shoulders, sacroiliac joints, and lumbar intervertebral discs. The effects lead to significant orthopedic morbidity. The knee is the most common joint involved in the disease [1].

In this report, we discuss the case of an elderly male patient who presented with progressive degenerative osteoarthritis necessitating total hip and knee replacements caused by alkaptonuria. The diagnosis was made by the typical black bone appearance seen at surgery.

PATIENT DESCRIPTION

The patient was a 65 year old man who was born to first degree cousins of Arab Muslim descent. His history is remarkable for diabetes mellitus, hypertension, and hyperlipidemia. He was initially referred to the orthopedic clinic for evaluation of longstanding bilateral shoulder, hip, and knee pain, as well as lower back pain.

At the time of initial evaluation, the patient’s gait was painful and significantly impaired his quality of life. Conservative treatments with analgesics, as well as non-steroidal anti-inflammatory drugs were ineffective in providing relief of symptoms.

Radiographic evaluation displayed degenerative arthritis in both hips and knees with the left side being more affected than the right.

At the age of 60 years the patient underwent a left, cement-less total hip arthroplasty with installation of a hip prosthesis (Zimmer Biomet, Indiana, USA). Two years later, the patient underwent an uncomplicated cement-less right total hip arthroplasty.

On orthopedic follow-up the patient had satisfactory hip mobility and function but showed a progression of his degenerative disease involving both knees, which required bilateral surgical total knee replacement.

Intra-operatively, an exceptional black pigmentation of the patellar tendon, menisci, and cartilage tissue was observed [Figure 1A, 1B]. Histological examination revealed thickened and fibrotic cartilage with dark pigmentation [Figure 1D, 1E].

A meticulous physical examination of the patient revealed black pigmented spots in both sclerae [Figure 1C], finger nail beds, and ear cartilage.

In accordance with the differential diagnosis of this ochronotic tissue, assessment of urinary organic acids identified massive excretion of homogentisic acid consistent with the diagnosis of alkaptonuria. The diagnosis was confirmed by DNA sequencing in this patient, which identified the previously described homozygous genomic deletion involving exon 2 of the HGD gene (c.16-272_c.87+305del) (HGD gene mutation database AKU_DB_232 a,b) [3,4].

COMMENT

The finding of intra-operative dark discolored cartilage tissue is extremely rare and suggests an underlying cause that could include metabolic bone diseases, metalosis (metal deposits), sequestrum, minocycline use, metastatic diseases, exposure to topical phenols, and ochronosis [2].

Ochronotic osteoarthritis is caused mainly by alkaptonuria, with pathogenesis related to 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, and eventually to the development of osteoarthritis involving mainly the major weight bearing joints.
Our patient presented with adulthood progressive osteoarthritis necessitating total hip and knee arthroplasties. The diagnostic clue was the black discoloration of the cartilage that was seen during surgery, which was later confirmed by analysis of a random sample of urinary organic acids. In the patient, urinary organic acids showed massive excretion of HGA, a compound that in normal individuals is not accumulated and is found in the urine in only trace amounts. Interestingly, the homozygous mutation identified in our patient is an unusual genomic deletion of 649 bp encompassing the 72 bp of exon 2 as well as the surrounding DNA sequences in flanking introns. The mutation was initially reported in a Lebanese child with alkaptonuria [3] and recently in two Israeli patients of Arab Muslim descent [4]. It seems to be common in the Middle Eastern Arab population, probably due to a shared founder. Notably, a first cousin of our patient also had progressive osteoarthritis for which he underwent total hip replacement. This patient did not present with darkly discolored synovial tissue during surgery but analysis of his urinary organic acids, performed because of his family history, revealed massive excretion of HGA, suggesting he also has alkaptonuria, a diagnosis later confirmed by the presence of the same homozygous mutation in the HGD gene as in our patient. This finding illustrates the clinical variability where ochronosis may be absent even in patients with confirmed alkaptonuria and long standing joint disease.

Arthroplasty of multiple affected joints is the current treatment of choice for alkaptonuria patients with ochronotic osteoarthritis when conservative treatment is no longer beneficial. However, in recent years, nitisinone, a potent inhibitor of 4-hydroxypyruvate dioxygenase, the enzyme that produces HGA, was proposed as a potential treatment for alkaptonuria by blocking the accumulation of HGA in multiple tissues and preventing its devastating effects. Initial evidence seems to support this exciting therapy, but long-term future studies are needed to confirm its usefulness [5].

CONCLUSIONS

Our study highlights the role of the orthopedic surgeon in the clinical identification of ochronotic joints and the diagnosis of alkaptonuria. The emergence of novel therapies for this disease further emphasize the importance of early diagnosis.

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