Alkaptonuria, a Rare Cause of Osteoarthritis – Case Report

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Abstract

Alkaptonuria is a rare metabolic disease, caused by the lack of the homogentisic acid (HGA) oxidase, resulting in the accumulation of HGA in connective tissues, conferring them a dark-bluish discoloration known as ochronosis. It is a progressive condition, causing degenerative alterations of weight-bearing joints.

We report the case of a 67 year old woman, with pain in the left knee and clinical and radiological evidence of knee osteoarthritis, who underwent cemented total knee arthroplasty. During surgery, black discoloration of cartilage was observed. Histologic evaluation suggested alkaptonuria, confirmed upon detection of high levels of HGA in urine.

Alkaptonuria is usually asymptomatic until the development of ochronotic arthropathy and its discovery is often a finding during a joint replacement. There is no specific therapy for alkaptonuria and its treatment is symptomatic and based on osteoarthritis management. When conservative treatment can no longer mitigate symptomatology and joint replacement should be done.

ABBREVIATIONS

HGA: Homogentisic Acid; NSAID: Non-Steroidal Anti-inflammatory Drugs

INTRODUCTION

Bone and joint surfaces hyper pigmentation is rare and can occur due to several causes: metabolic bone diseases, metal deposits, sequestrum, metastatic disease, minocycline use and ochronotic arthropathy [1].

Alkaptonuria is a rare metabolic disease, with a prevalence of 1 case per 250,000 to 1 million live births, in the United States [2]. This was the first human disorder found to conform to the principles of mendelian autosomal recessive inheritance [3]. The disease is caused by an in born error of tyrosine metabolism – the lack of the homogentisic acid (HGA) oxidase enzyme, which is normally highly expressed in hepatocytes [4] - resulting in the accumulation of HGA in connective tissues, mainly in cartilage but also in tendons, ligaments, sclera, heart valves, the intima of blood vessels and skin [5]. The accumulation of HGA confers a dark-bluish discoloration to tissues and is known as ochronosis.

Alkaptonuria is a progressive condition and the patients are distinguished by a classic triad: dark urine since birth, ochronosis becoming evident around the fourth decade of life and osteoarthritis secondary to ochronotic arthropathy around the sixth. Most of the patients are only diagnosed when they develop arthropathy, i.e., late on the natural history of the disease.

Ochronotic arthropathy usually affects weight-bearing joints, like hips, knees and lumbar spine. The spine involvement resembles ankylosing spondylitis but differs in sparing the sacroiliac joints [3] and the most characteristic findings are narrowing and calcification of the intervertebral disks. The peripheral arthritis closely resembles that of primary osteoarthritis, however, hands and feet are usually spared [6]. Another characteristic of ochronotic arthropathy is the sparse osteophytic reaction seen, when compared with primary osteoarthritis.

Other disease manifestations include renal and prostate stones, aortic valve calcification and stenosis, and coronary artery calcification [7].

CASE PRESENTATION

We report the case of a 67 year old woman who was referred to orthopedic consultation for evaluation of a longstanding left knee pain. The pain was characterized as mechanical, which increased with motion and was more intense at the end of the day. Other complaints involved knee edema after moderate distance walks. Pain during bedtime impairing ability to sleep was denied. Withal, the patient reported pain on the contra lateral knee, both hips and lower back. Non-steroidal anti-inflammatory drugs were prescribed by her primary care physician, which no longer provided relief of symptomatology.

On physical examination, the patient walked with stable gait, felt tenderness on palpation over the joint line of the left knee and had a diminished range of motion associated with crepitation.
Instability of the knee was not detected. The contra lateral knee and both hips also showed signs of osteoarthritis, although to a lesser degree.

The patient was submitted to bilateral knee and hip and lumbar spine radiographies. Both knees showed characteristic findings of osteoarthritis, more evident on the left side, such as narrowing joint space and subchondral sclerosis (Figure 1). Surprisingly, no osteophytosis was seen in either side. Same changes were found in hip radiographies, although not so evident (Figure 2). Lumbar spine radiographies showed narrowing of intervertebral spaces with severe calcification of intervertebral discs (Figure 3).

The patient underwent cemented total left knee arthroplasty and, during surgery, black discoloration of cartilage and of surrounding ligamentous and tendinous structures was observed (Figures 4,5). No other intra- or post-surgery complications were reported.

Histologic evaluation of bone and soft tissues showed thickened and fibrotic areas of cartilage with dark pigmentation.

After these findings, the patient was re-examined and we found black spots on both sclerae, ear cartilage and nail beds of both thumbs (Figures 6,7). Alkaptonuria was diagnosed upon detection of high levels of HGA in urine. We referred the patient to Genetic consultation.

At 15 month follow-up, the patient is fully independent, ambulates without support, has an adequate range of motion and is pain-free. Plain radiographies of the knee do not show any abnormality on the components of the prosthesis (Figure 8).
DISCUSSION

In most of the case reports found in literature, alkaptonuria is asymptomatic until the development of ochronotic arthropathy [8]. Usually, patients only seek for medical evaluation when the effects of the disease on weight-bearing joints is noticed, namely pain. This was true for our patient as well. The diagnosis was considered upon intra operative findings, when the patient was submitted to an arthroplasty.

Alterations on bone and cartilage characteristics found intraoperatively are worrisome and raises doubts about the potential integration of prosthetic components. For this, it is essential that the Orthopedist is able to recognize the typical clinical signs of alkaptonuria when he first evaluates a patient with presumed osteoarthritis of the knee.

Alkaptonuria may be confused with exogenous ochronosis, the ochre like pigment deposition in the skin and sometimes in the cartilage or other organs as a result of exposure to a variety of exogenous compounds [9]. These compounds include topical phenol, topical hydroquinone bleaching creams, quinine injections, oral antimalarial drugs, amiodarone, cytotoxic drugs, minocycline and levodopa and methyl dopa [9]. They are distinguished from alkaptonuria by the absent HGA excretion in urine. The distinction is necessary because the prognosis of the two conditions is quite different and so the management.

Treatment is symptomatic and is based on osteoarthritis management. It can decrease symptoms in early stages of the disease but it cannot decrease the rate of joint degeneration. One prospective study showed that regular swimming, spine mobilization and development of good truncal strength likely provide benefit to these patients, when initiated early in the disease [10]. The same study demonstrated that the average age of arthroplasty in alkaptonuric patients is lower than the national mean (53 vs. 67) [10].

Here upon, when conservative treatment (NSAID’s, physical therapy) no longer can mitigate symptomatology, joint replacement should be done.

There is no specific pharmacologic therapy for alkaptonuria treatment. Ascorbic acid, once considered a potential therapy for alkaptonuria, showed inconsistent results and overall it has not been dramatically effective [10]. Nitisone, approved by de FDA for hereditary tyrosinemia treatment, has been investigated for use in alkaptonuria [3]. Although a randomized study involving 40 patients treated for 3 years with nitisone showed a great reduction in plasma and urine HGA levels, hip motion range and musculoskeletal functions were not different when compared with no-treated patients [11].

Since alkaptonuria can cause cardiovascular alterations, these patients should be monitored for aortic dilatation and valvular calcification. They should also be treated for prostate and renal stones as needed [12].

Joint replacement is the treatment of choice for primary or secondary knee osteoarthritis, when conservative treatment is no longer effective. So far, the information available indicates that total knee arthroplasty has similar results in alkaptonuric patients, when compared with general population. Nevertheless, there are few case reports of this pathology and the time of follow-up of the patients is not long yet. More investigation in this condition is needed so we can conclude if the durability of prosthetic components is compromised.

REFERENCES


