Cardile et al., J Clin Trials 2019, 9:6
DOI: 10.4172/2167-0870.1000385

Journal of Clinical Trials
ISSN: 2167-0870

Case Report Open Access

The Black Knee: A Rare Case of Knee Ochronotic Arthopathy in an Elderly Patient with Unknown Alkaptonuria

Carlo Cardile[1], Paolo Ragni[1], Carlo Cazzaniga[1], Roberto Marasco[2], Angela Brivio[3*], Monica Onorati[4] and Franca Di Nuovo[4]

[1]Department of UOC Orthopedics and Traumatology, Garbagnate Milanese Hospital, Milan, Italy
[2]Department of Orthopedics and Traumatology, University of Milano, Bicocca, Milan, Italy
[3]Department of Orthopedics and Traumatology, Cernusco S/N Hospital, Milan, Italy
[4]Department of Pathology, University of Milano, Bicocca, Milan, Italy

Abstract

Alkaptonuria and consequent ochronotic arthropathy are often a challenging diagnosis to carry out. Most of times patients are not aware of their illness and the surgeon discovers the diagnosis intraoperatively thanks to typical synovium and cartilage blackish color.

We report the case of a 79 years old patient who found his alkaptonuria out after knee arthroplasty initially performed for degenerative knee joint. Diagnosis was supposed to be alkaptonuria intraoperatively by the signs and confirmed after surgery with histological examination and laboratory tests.

Keywords: Alkaptonuria; Ochronosis; Ochronotic arthropathy; Total knee arthroplasty; Black knee

Introduction

Ochronotic arthropathy is a peculiar expression of alkaptonuria, a rare Mendelian autosomal recessive disorder of tyrosine metabolism caused by deficiency of homogentisate 1,2 dioxygenase (HGD) activity with deposition of ochronotic pigment (homogentisic acid, HGA) in all connective tissues and in cartilage [1].

The alkaptonuria gene, encoding HGD, has been mapped in human chromosome 3q 21-q23 showing several mutations. The prevalence of the disease is estimated between 1 out of 250000 to 1 out of 1000000 [2]. This disorder has been the first inborn metabolic error to be described: in the Egyptian age people suffered by alkaptonuria. Scibonius was the first to describe the urinary manifestations of the disease in 1584. So far the term alkaptonuria was introduced for the first time by Virchow in 1866 to describe the urine's affinity for the alkaline solution. A congenital error of metabolism causing Alkaptonuria was suggested first by Garrod in 1908 whereas Neubauer mapped the complete tyrosine-catabolic pathway confirming that the biochemical defect was a lack of homogentisate oxidase in 1909. Usually alkaptonuria, with the inherited absence of HGD, causes HGA increased blood levels, leading to excretion of a large amount of HGA in urine as well as deposition of pigmented benzoquinone polymeric oxidation products of HGA in many tissues (Ochronosis). The disease usually progresses from simple alkaptonuria to alkaptonuric ochronosis till alkaptonuric arthropathy. HGA excretion and disease severity can vary significantly within the same family. The first sign in childhood is typical blackish urines. Alkaptonuria patients have usually black urine or urine becoming dark with alkaline agent exposure. Anyway, darkening may not occur for hours and fresh urine may appear normal in alkaptonuric patients.

The diagnosis is usually made by three features: degenerative arthritis of large joints and vertebral discs, ochronotic tissue pigmentation (skin, sclera and ear cartilage) and urine turning dark brown or black on alkalizing. Less common manifestations include renal, urethral and prostate calculi as well as cardiovascular abnormalities, especially severe damages of heart valves. The knee is the most commonly affected joint (64% of cases) [3]. In ochronotic arthropathy, HGA metabolites polymerize causing irreversible bindings with collagen-rich surfaces, leading to excessive deposition and soft-tissue surfaces becoming brittle and more vulnerable to mechanical stress, resulting in articular cartilage degeneration.

Here in we report the case of a patient who came to our attention for an arthropathy of the knee and in whom an ochronosis was suspected intraoperatively and confirmed later by histological examination. We focus the attention on the clinical aspect, laboratory investigation and management of the ochronotic arthropathy according to the recent literature.

Case Report

A 79 years old man was admitted to our hospital with chronic weakness and progressive chronic knee, hip and lumbar pain, affecting daily activities. No former traumatic events were reported. Walking distance was limited because of bilateral hip and knee pain, getting worse at the end of the day and by mobilization.

The patient was submitted to a prostatectomy, a bilateral hip arthroplasty and an aortic valve replacement. No sign of metabolic disorder were noted. A monoclonal gammopathy has recently been highlighted during a routine blood.

The patient used to work in a black carbon factory fulltime and was therefore probably exposed to carbon nanoparticles and aromatic hydrocarbons for about 50 years before retiring. Due to his chronic pain he underwent plain X-Ray of the knee that revealed a severe osteoarthritis. According to this diagnosis a cemented total knee arthroplasty was performed. (Figure 1).

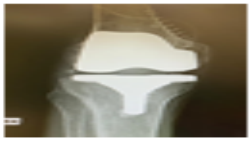

Figure 1: According to this diagnosis a cemented total knee arthroplasty was performed. During surgery, black/gray discoloration was observed in all cartilaginous surfaces with subchondral bone sclerosis/hardening.

***Corresponding author:** Angela Brivio, Department of Orthopedics and Traumatology, University of Milan Bicocca, Milan, Italy, Tel: +393333999902; E-mail: angelina1978@me.com

Received: October 27, 2019; **Accepted:** November 12, 2019; **Published:** November 19, 2019

Citation: Cardile C, Ragni P, Cazzaniga C, Marasco R, Brivio R et al. (2019) The Black Knee: A Rare Case of Knee Ochronotic Arthropaty in an Elderly Patient with Unknown Alkaptonuria. J Clin Trials 9: 385.

The synovial tissue was hypertrophic looking black/brown (Figure 2).

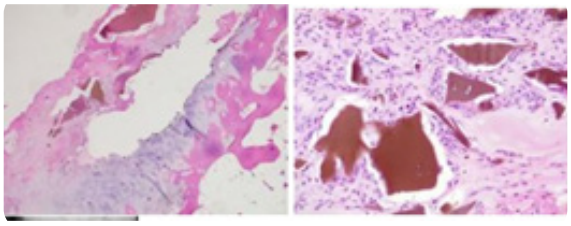

Figure 2: Histological evaluation showed a widespread degeneration of the collagen fibers of the synovial tissues and accumulation of an amorphous, acellular, golden-brown material in both bony and synovial tissue.

No carbon nano-particles were found at microscopically examination–Therefore these histological features suggested the diagnosis of ochronotic arthropathy and consequently the patient was re-examined for a possible diagnosis of alkaptonuria. He reported to have noticed dark discoloration of his urine since early childhood. A general body examination showed a bilateral black pigmentation of sclera and ear cartilage (Figures 3 and 4).

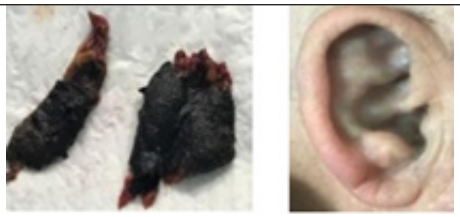

Figure 3: Bilateral black pigmentation of sclera and ear cartilage.

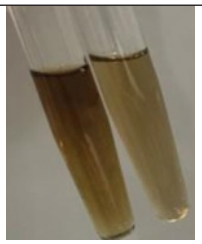

Figure 4: Preliminary biochemical tests (alkalizing with NaOH) were performed and showed gradual urine darkening.

Radiographs of the spine showed calcification and severe degeneration of multiple vertebral dis ks with reduction of inter-vertebral spaces, showing typical "wafer like" disk aspect.

A new urine sample was then tested for HGA and showed high level of this component. Results confirmed alkaptonuria diagnosis. Physiotherapy was carried out after surgery and till now the patient is asymptomatic. A genetic screening of the relatives was performed without positive signs or blood tests.

Discussion

Alkaptonuria is a rare, hereditary autosomal-recessive metabolic disorder that affects males and females equally, even if symptoms tend to be more severe in males. The disease has an incidence of 1:125.000 up to 1:1 million worldwide and more than 1,000 cases have been reported in the medical literature [4]. The disease is caused by a partial or total deficiency of the enzyme "Homogentisate 1,2 dioxygenasi" (HGD), responsible for the turnover of Homogentisic Acid (HGA) in phenylalanyne and tyrosine catabolism.

HGD deficiency results partly in HGA excretion in urine and partly in an excessive deposition of HGA and its derivative Benzoquinone in connective tissue, including hyaline cartilage, tendons, intervertebral disks, skin, ears, sclera and other organs. The progression of the disease range from simple alkaptonuria to alkaptonuric ochronosis and finally to ochronotic arthropathy, that leads to chronic joint pain and inflammation, especially in the spine and large joints. Arthritis can be severe and disabling. Low back pain and stiffness are common symptoms sometimes observed before the age of 30. Intervertebral disks become flattened and calcified, showing the typical radiological "wafer like" aspect [5]. Vertebrae or other bones may fuse causing ankylosis. Spinal involvement may lead to abnormal curvature of the spine causing kyphosis and loss of height. Hips, knees and shoulders are commonly affected as well. Joint abnormalities are progressive and might need joint replacement. Joint disease related to alkaptonuria tends to begin earlier and worsen more rapidly in males than females.

Usually Alkaptonuria is diagnosed in childhood due to blackish urine noted by the parents, which lead the children to the medical attention.

Nevertheless, occasionally dark urine is not observed and the illness not diagnosed during childhood. In this patient case, blackish urine was underestimated in youth so he developed a history of low back pain which became relevant at the age of 35 years, soon followed by involvement of hips and knees. Due to the strong pain, the patient required first a bilateral hip replacement. At the same time he developed a severe aortic valve stenosis due to accumulation of homogentisic acid causing calcification of the valve flaps that required surgical replacement. Unluckily, clinicians did not suspect a metabolic disorder at that time. After a long history of uncontrolled joint pain the patient came to our attention and later on underwent a right knee cemented replacement due to severe osteoarthritis (Figure 5).

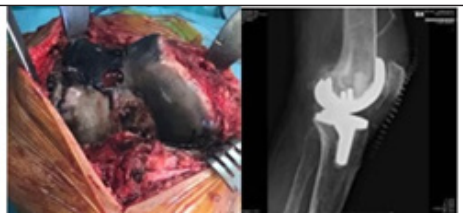

Figure 5: Right knee cemented replacement due to severe osteoarthritis.

Excluding physical/occupational therapy and surgery, the treatment of alkaptonuria is actually not defined. An author reported that a low protein diet , without tyrosine and phenylalanine, can help to delay the onset of symptoms of ochronosis in children under 12. However, recent literature data showed that dietary restrictions have widely proven to be ineffective. In older children and adults, high-doses of vitamin C have also been used to treat alkaptonuria because it hinders the accumulation and deposition of homogentisic acid. Similarly long-term use of C vitamin has generally proven to be ineffective and definite clinical studies on its efficacy are lacking. Activities that place significant physical stress to the spine and joints such as high impact sports or heavy manual labor should be avoided. Nitisone is a drug that reduces blood and urine level of HGA but its safety profile and long-term outcome of clinical progression are not definitively established [6].

Ochronotic arthropaty in alkaptonuria is considered a metabolic degenerative joint disease with very little treatment possibilities, barring surgical treatment of the latest stages of the disease. Actually, joint replacement is the only solution to improve quality of life the patients.

Ideal treatment of this disease should be enzyme replacement but this target, at moment, needs further research [7-10].

Conclusion

Clinicians should keep in mind that alkaptonuria is a rare disorder that have a high probability to be misdiagnosed, especially in regions with low incidence of the disease. For this reason, clinicians should suspect alkaptonuria in middle-age patients with low back pain matched with dark urine. However, since some patients with alkaptonuria may not have dark urine, it could be appropriate to exclude this metabolic disease for all patients with an early history of symptomatic osteoarthritis, confirming it by laboratory and radiological investigations, or in older patients with a delayed clinical history like in our case. A cemented implant should be preferred, according to literature, in order to ensure a safe and long lasting stability of the bone/implant interface. Furthermore the disease does not seem to affect the outcome of the surgical treatment of arthropathy, even in the long-term follow-up, as reported in literature.

References

1. Evangelista P, Parente JS, Brasileiro R Paiva JG, Freitas MV et al. (2018) Secondary osteoarthritis to ochronotic arthropathy: A diagnostic challenge. Rev Assoc Med Bras 64: 583-585.
2. Steger CM (2011) Aortic valve ochronosis: A rare manifestation of alkaptonuria. BMJ Case Rep
3. Gil JA, Wawrzynski J, Waryasz GR (2016) Orthopedic manifestations of ochronosis: Pathophysiology, presentation, diagnosis and management. Am J Med 129:536.
4. Azami A, Maleki N (2015) Alkaptonuric ochronosis. J Res Med Sci 20: 1018-1019.
5. Lal M, Thakur M, Kashyap S (2014) Alkaptonuric Ochronosis. Orthopedics 37:1141-1149.
6. De Haas V, Carbasius Weber EC, de Klerk JB (1998) The success of dietary protein restriction in alkaptonuria patients is age-dependent. J Inherit Metab Dis 21: 791-798.
7. Ozmanevra R, Güran O, Karatosun V, Günal I (2013) Total knee arthroplasty in ochronosis: A case report and critical review of the literature. Eklem Hastalik Cerrahisi 24: 169-172.
8. Mukand L, ManojT, Sandeep K (2014) Alkaptonuric ochronosis. Orthopedics 37: 1141-1149.
9. Kragel AH, Lapa JA, Joyce A Lapa, William C Roberts (1990) Cardiovascular findings in alkaptonuric ochronosis. Am Heart J 3: 130.
10. Morava E, Kostolanyi G (2003) Reversal of clinical symptoms and radiographic abnormalities with protein restrictions and ascorbic acid in alkaptonuria. Ann Clin Biochem 40: 108-111.