

Case Report

A case of Alkaptonuria

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A 63 year old man presented with sudden onset of severe hip pain for the past one month. Physical examination revealed black pigmentation of sclera and blackening of ear lobes. The urine darkened on standing. X- Ray showed degenerative changes in the right hip joint. Biochemical investigations which included urine Benedict's test and ammoniacal silver nitrate test were positive, suggestive of alkaptonuria. Intra- operative findings also revealed black pigment depositions on the head of the femur. No other complications or systemic abnormalities were detected.

Key words: Alkaptonuria, ochronosis, homogentisic acid, arthritis.

INTRODUCTION

Alkaptonuria is a rare metabolic disorder first described by Sir Archibald Edward Garrod (Verma, 2005). The disorder results from an autosomal recessive mutation of homogentisate oxidase gene, located on chromosome 3q21-q23. This defect leads to accumulation of homogentisate in fibrous (eumelanin like pigmentation) and cartilaginous tissues leading to degenerative musculo-skeletal deformities (ochronotic arthropathy) in the third or fourth decade of life and excretion of it in the urine (homogentisic aciduria) (Tharini et al., 2011). Here we discuss a case of this rare, benign metabolic disorder.

CASE REPORT

A 63-year-old male patient, known to have diabetes mellitus, hypertension and dyslipidemia for the past five years under regular treatment, presented to the orthopedic department with complaints of severe pain in the right hip for the past one month. The pain was insidious in onset and associated with restriction of movements. He was able to walk only with support for the past one month. He gave a history of his urine turning dark on long standing since childhood.

General physical examination revealed blackening of both ear lobes and black pigmentation of the sclera. Ear cartilage was stiff with absence of elastic recoil (Figure 1). Local examination of the spine revealed a diminished lumbar lordosis. His right lower limb appeared to be flexed and slightly internally rotated. There was restriction of movement of the right lower limb with shortening and wasting of muscles of thigh and leg.

X- Ray of the pelvis with both hips showed degenerative changes of the right hip joint with interspersed irregularity throughout the pelvis. X- Ray of the LS spine showed the evidence of fused vertebral segments with inter -vertebral disc calcification. Results of laboratory investigations were as follows:

Random plasma glucose: 192 mg/dL, serum urea: 22 mg/dL, and creatinine: 0.88 mg/dL.

Together with history, clinical examination and X-Ray findings, a diagnosis of alkaptonuria was suspected and the following qualitative tests were done to assess the presence of homogentisic acid in urine.

- Urine turned dark on standing in atmospheric air for a few hours (Figure 2).
- Urine Benedict's test: Urine turned black on adding Benedict's reagent. Then on heating, slowly, a greenish yellow precipitate was formed. The precipitate also turned black after few hours of standing (Figure 3). Urine glucostix test was negative, that ruled out glucosuria.
- Ammoniacal silver nitrate test: Appearance of black colour was observed (Figure 4).

Based on the aforementioned biochemical investigations, a diagnosis of Alkaptonuria was made.

Treatment

A total hip replacement of the right hip joint was planned



Figure 1. Black discolouration of pinna.



Figure 3. Urine turning dark on exposure to air.



Figure 2. Benedicts test – black precipitate obtained.

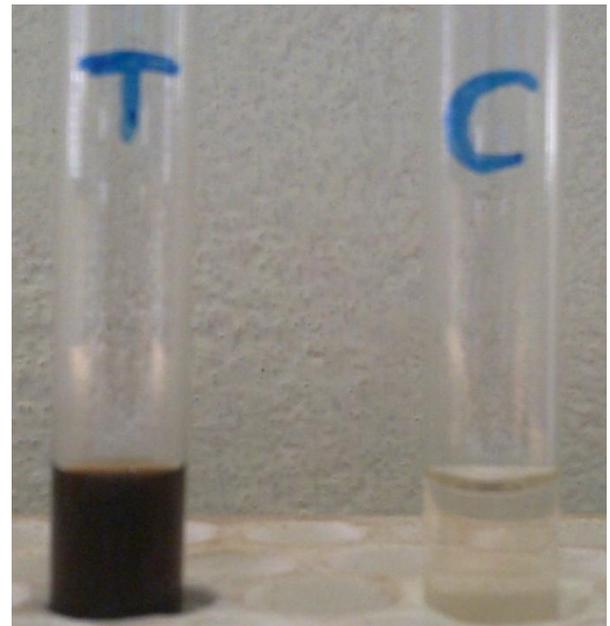


Figure 4. Ammoniacal silver nitrate test.

intra- operatively and there was extensive black pigment deposition from the soft tissues to the head of femur. Post- operative images of the head of femur revealed black pigment deposition (Figure 5). On cut section of the head of femur there was extensive pigment deposition. He was treated with antibiotics, analgesics and his regular medications. Patient was mobilized in a week with adequate physiotherapy. He was also advised for regular follow up.

DISCUSSION

Alkaptonuria is a benign, rare, inherited condition affecting 1 in 250,000 to 1 million people world-wide. This

disorder usually appears early in life and the skeletal deformities can occur after third decade of life (Verma, 2005).

The homogentisic acid oxidase (HGD) gene provides instructions for making an enzyme called homogentisate oxidase. This enzyme helps break down homogentisate into maleyl acetoacetate. This results in a derangement of metabolism of phenylalanine and tyrosine, which are building blocks of proteins. Mutations in the HGD gene impair the enzyme's role in this process. As a result, homogentisate accumulates in the body (Tharini et al., 2011).

Upon contact with air, homogentisate is oxidized to



Figure 5. Intraoperative image of head of femur showing black deposits.

form a pigment- like polymeric material responsible for the black color of urine. Although blood homogentisate levels are kept very low through rapid kidney clearance, over a period of time, homogentisate is deposited in cartilage throughout the body and is converted to the pigment- like polymer through an enzyme-mediated reaction that occurs chiefly in collagenous tissues. As the polymer accumulates within cartilage, a process that takes many years, the normally transparent tissues become slate blue, an effect ordinarily not seen until adulthood (Biju et al., 2009).

The earliest sign of the disorder is the tendency for diapers to stain black. Throughout childhood and most of early adulthood, an asymptomatic, slowly progressive deposition of pigment- like polymer material into collagenous tissues occurs. In the fourth decade of life, external signs of pigment deposition, called ochronosis, begin to appear. The condition gets its name from alkapton, which means a class of substances with an affinity for alkali (Sridhar et al., 2012).

The slate blue, gray, or black discoloration of the sclerae and ear cartilage is indicative of widespread staining of the body tissues, particularly cartilage. The hips, knees, and inter-vertebral joints are affected most commonly and show clinical symptoms resembling rheumatoid arthritis. Because of calcifications that occur in these sites, however, the radiologic picture is more consistent with osteoarthritis (John et al., 2009).

Despite many speculations that this polymer deposition is associated with cardiac pathology, no reports of mortality directly related to the homozygous state for alkaptonuria exist. Reports exist of calcification and stenosis of the aortic annulus leading to coronary artery disease, and the risk of myocardial infarction is higher than normal in older patients with ochronosis.

Therapeutic approach include mega dose of vitamin C for the degradation of homogentisic acid. Diet restricted in phenyl alanine, tyrosine have not yielded any significant positive results. However, reversing the primary defect is not possible by the available treatment options. Nitisinone, a triketone herbicide has shown to reduce the excretion of homogentisic acid by inhibiting the enzyme 4-hydroxy phenyl pyruvate dioxygenase that is responsible for the synthesis of homogentisic acid. But long term trials are needed to prove the safety profile and efficacy of this compound in the treatment of Alkaptonuria (John et al., 2009; Ashok et al., 2008).

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