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Case Report

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Secondary osteoarthritis due to alkaptonuria: a case report

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Abstract

***Background & Aims*:** Alkaptonuria is a rare autosomal recessive genetic disorder caused by a deficiency of homogentisate 1,2-dioxygenase, leading to the accumulation of homogentisic acid. It presents with a characteristic triad of homogentisic aciduria, ochronosis, and progressive arthritis, often resulting in secondary osteoarthritis, particularly affecting the hip and knee joints.

***Case Description*:** A 58-year-old male presented with severe pain in the right hip and left shoulder. Since childhood, his urine had turned black upon exposure to sunlight. His medical history included multiple fractures and orthopedic interventions. On clinical examination, bluish-black discoloration of the ear lobes and sclera was noted. Biochemical testing, including Benedict's test, ammoniacal silver nitrate test, and a filter paper spot test using 10% sodium hydroxide, confirmed the diagnosis of alkaptonuria. The patient was diagnosed with osteoarthritis secondary to alkaptonuria and underwent a successful total hip replacement.

***Conclusion*:** Early diagnosis and intervention in alkaptonuria are crucial to preventing the debilitating effects of secondary osteoarthritis. A multidisciplinary approach in the management of patients with alkaptonuria can help reduce morbidity and improve quality of life by addressing both symptoms and the underlying disease.

***Keywords*:** Alkaptonuria, Ammoniacal silver nitrate test, Homogentisic acid, Ochronotic arthropathy

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Introduction

Alkaptonuria (AKU) is a rare inherited metabolic disorder that has intrigued scientists for centuries. The condition was first evidenced in ancient Egypt, with a reference to an Egyptian mummy, Harwa, dating back to 1500 B.C. (1). In 1890, Dr. Archibald Garrod famously diagnosed AKU in a 3-month-old child, marking the first recognition of a genetic disorder following Mendelian inheritance patterns (2). Garrod's observations led him to coin the term "Inborn Error of Metabolism" and propose the idea that a defective gene caused a deficiency in the enzyme responsible for the degradation of homogentisic acid (HGA) (3). In 1993, Pollak et al. successfully localized the AKU gene to chromosome 3 (4), cementing the genetic understanding of the disorder. AKU has had a significant impact on the history of medicine, influencing the development of key genetic concepts such as 'allele,' 'heterozygote,' and 'homozygote'—terms introduced by William Bateson (5). Currently, the global prevalence of AKU is approximately 1 per 100,000 to 250,000 people, making it a rare but important condition in medical practice.

Patient Information

The patient was a 58-year-old male with a history of smoking, alcohol use, and hypertension. He presented to the orthopedic outpatient clinic with complaints of severe pain in the right hip and left shoulder. His medical history included multiple orthopedic interventions, including a total knee replacement in 2016, conservative management for a right tibial fracture in 2018, and dynamic hip screw surgery in 2020 for a left femoral fracture. General examination showed bluish-black nodules in the sclera of both eyes (Figure 1) and bluish -black discolouration of the pinna of both ears (Figure 1).

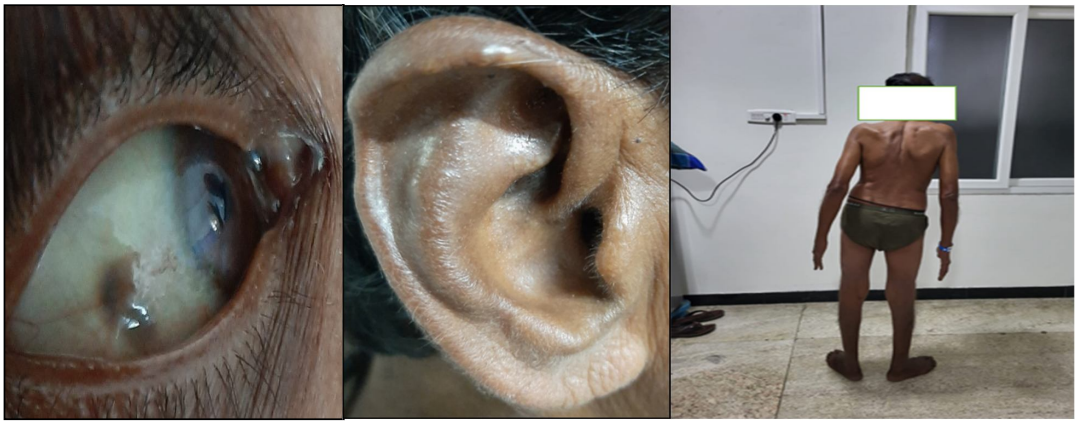

Fig. 1. (From left to right) Right eye showing blackish pigmentation of sclera; Right ear showing mild blackish discolouration of pinna; Patient with arthritis of right hip and left shoulder

Salient Findings on Local Examination

On physical examination, the patient presented with a left shoulder that appeared elevated and a stiff hip gait on the right side, indicating possible joint involvement. There was also a limb length discrepancy with shortening of the right lower limb (Figure 1). In the supine position, the right lower limb demonstrated shortening, abduction, and external rotation, consistent with hip joint involvement. Notably, there was a fixed flexion deformity of the right knee, with flexion restricted to 90 degrees.

Lab Investigations

Lab investigations revealed a normal hemogram and other tests were as follows:

Random plasma glucose - 86 mg/dL [Normal reference range: < 200 mg/dL]

Serum urea - 28 mg/dL [Normal reference range: 15-40 mg/dL]

Serum creatinine - 0.66 mg/dL [Normal reference range for males: 0.7-1.4 mg/dL]

Serum uric acid - 4.58 mg/dL [Normal reference range: 2-6 mg/dL]

Metabolic Screening of Urine

a) The urine turned black on exposure to atmospheric air for a few minutes **(**Figure 2**)**.

b) Urine Benedict's Test: The sample was added to Benedict's reagent and heated. Upon observation, the sample turned greenish, confirming the presence of a reducing substance. However, the Glucostix test was negative for the sample (Figure 2).

c) Ammoniacal silver nitrate test: The appearance of a black colour was observed after adding the sample to the chromatography paper sprayed with ammoniacal silver nitrate which indicated the presence of HGA in the urine sample (Figure 2).

d) Filter paper spot test: Two circles were marked on Whatman filter paper impregnated with alkali (10% sodium hydroxide solution) and labeled as "patient urine" and "normal control urine." Upon

adding a few drops of the respective samples into the marked circles, the spot where the AKU patient's sample was added turned brown, whereas the normal urine sample failed to show any colour change (Figure 2).

e) Test with sodium hydroxide solution: Upon adding 5mL of the patient's urine sample to 1-2mL of 1M/L NaOH, the urine turned black within a few seconds, confirming the presence of HGA. When the same procedure was performed on normal urine as a control, no color change was observed.

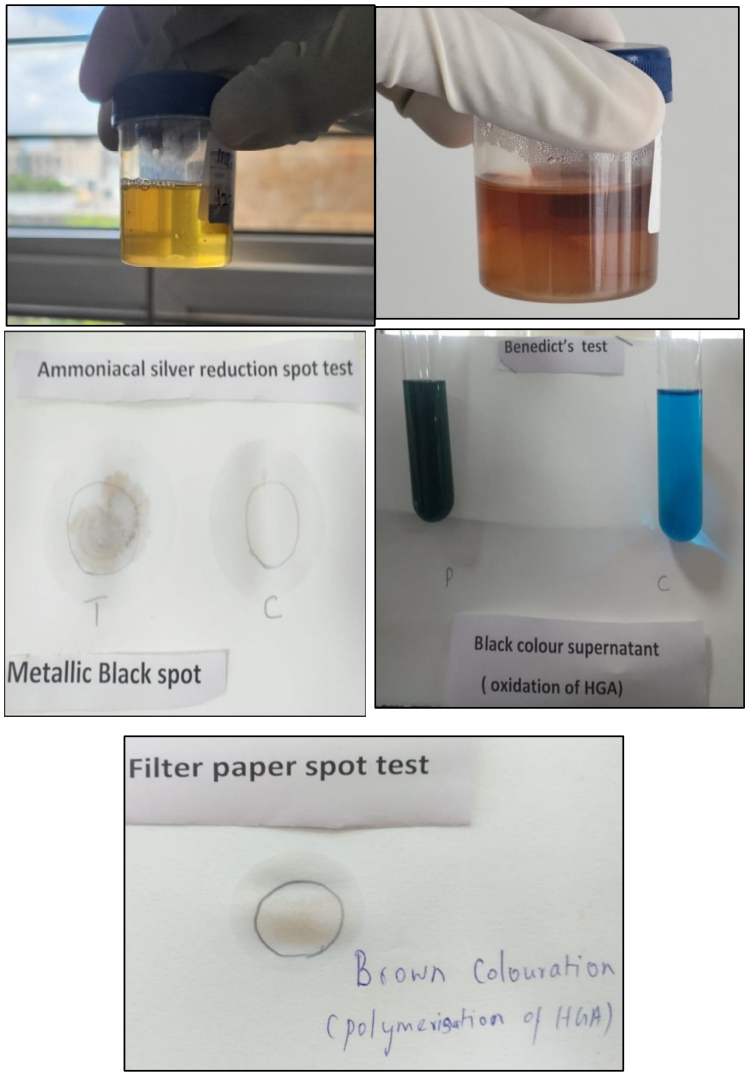

Fig. 2. (Clockwise from above) Shows the patient's urine before and after exposure to sunlight. The urine turned black upon exposure due to the oxidation of homogentisic acid forming benzoquinone acetate, a key indicator of alkaptonuria; A positive ammoniacal silver nitrate test showed brownish-grey discolouration in the spot marked for the test [T], where the AKU patient's urine was added, whereas there was no colour change in the control spot [C], where the control's urine was added; Filter paper spot test showing brown colouration of the spot upon adding the AKU sample; Positive Bendict's test (Left, AKU sample (P); Right, Control's urine (C))

The final diagnosis was "osteoarthritis of the right hip secondary to alkaptonuria". The patient underwent a right total hip replacement under spinal and epidural anaesthesia and an uncemented acetabular cup was fixed during the surgery (Figure 3). Intraoperatively, black deposits on the head of the right femur were evident due to AKU (Figure 3 (middle) & Figure 4). Post-operative X-ray after total hip replacement of right hip is shown in the Figure 5. The intraoperative and postoperative periods were uneventful. He was treated with antibiotics, analgesics, low-dose aspirin, and antihypertensives. The patient was advised to undergo physiotherapy, including non-weight-bearing mobilization, starting on the second post-operative day. He showed symptomatic improvement and was discharged with advice for follow-up. The anteroposterior view of the pelvic X-ray showed osteoarthritis of the right hip. (Figure 3)

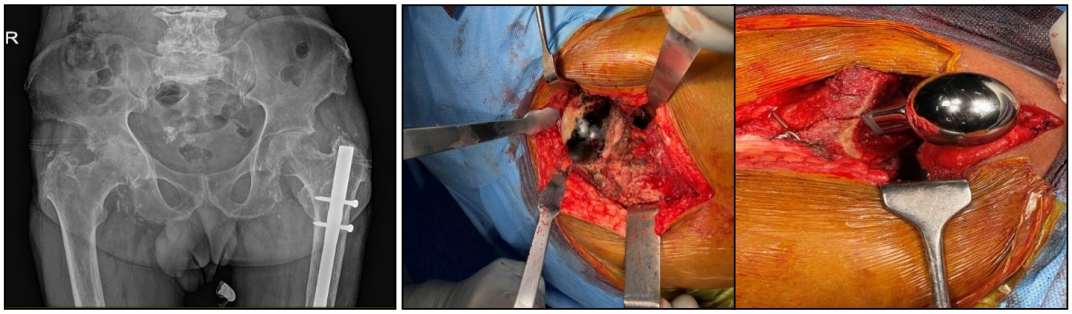

Fig. 3. (From left to right) Preoperative X-ray showing osteoarthritis of the right hip and dynamic hip screw with intramedullary nailing of the left femur performed 3 years ago; Intraoperative image of black pigmentation of the head of the femur (middle,); Uncemented acetabular cup fixed for the patient during surgery (right)

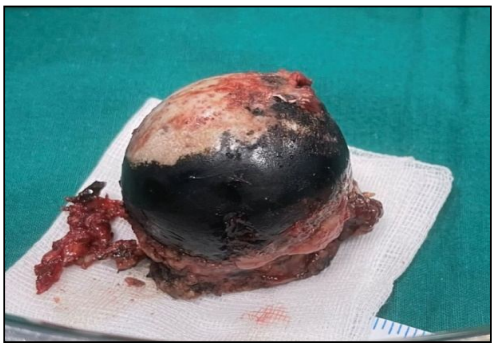

Fig. 4. Blackish pigmentation of the patient's femur head due to AKU, shown after surgical removal

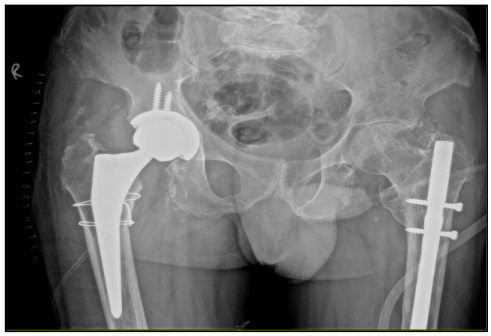

Fig. 5. Post-operative X-ray after total hip replacement of right hip

Discussion

Pathophysiology

Alkaptonuria (AKU) is caused by a deficiency of homogentisate 1, 2-dioxygenase (HGD), an enzyme responsible for converting HGA to maleylacetoacetic acid in the tyrosine degradation pathway. This deficiency leads to the accumulation of HGA in connective tissues, resulting in ochronosis (pigment deposition) and its excretion in urine. The oxidation of HGA produces benzoquinone acetate, which polymerizes and binds to connective tissues, causing the characteristic pigmentation observed in AKU.

AKU is an autosomal recessive disorder resulting from mutations in the HGD gene located on chromosome 3q13.33, which comprises 14 exons. Most affected individuals exhibit homozygous or compound heterozygous mutations in this gene. The HGD mutation database (http://hgddatabase.cvtisr.sk/) offers a comprehensive resource for identifying and studying global variants of the HGD gene.

Clinical Manifestations

The hallmark triad of AKU includes urine that darkens upon exposure to air, ochronosis, and arthropathy. The darkening of urine is due to the oxidation of HGA into benzoquinone acetate. External pigmentation typically becomes noticeable in patients during their 20s or 30s and includes slate-blue or grey discoloration in the sclera and ear cartilage (6. In the sclera, pigmentation often appears near the insertion of the rectus muscles and can be misdiagnosed as melanosarcoma (6). Ear pigmentation begins in the concha and antihelix, later involving the tragus. Sweat-stained clothing, particularly in the axillae, may also indicate ochronosis.

Internally, pigmentation affects various tissues, including costal, laryngeal, and tracheal cartilage, often described as coal black (6). Fibrous tissues, fibrocartilage, tendons, and ligaments also exhibit pigmentation, particularly during perioperative or postmortem examination in elderly AKU patients (6).

Systemic Complications

Systemic complications arise from widespread ochronotic pigment deposition. Cardiovascular manifestations include calcification of the aortic and mitral valves, which can lead to aortic stenosis or regurgitation, necessitating valve replacement (6). Coronary artery calcification has also been reported. Renal involvement is significant due to the kidneys' role in excreting large amounts of HGA. Prostatic calculi are common and may lead to complications like obstructive uropathy requiring prostatectomy (6). Bone and joint involvement begins in the spine, resembling ankylosing spondylitis. Symptoms initially involve the lumbar and thoracic spine, sparing the sacroiliac joints, and progress to calcification and fusion of intervertebral discs and osteophyte formation (7). Radiographs often reveal joint space narrowing, subchondral cysts, and osteophyte formation (7). In some cases, the diagnosis of AKU is only established perioperatively when blackened articular cartilage is observed (7). Enthesopathy, characterized by calcification at muscle insertions, is another notable feature (8).

Renal compromise, such as acute or chronic failure, may lead to acidosis, hemolysis, or methemoglobinemia, likely resulting from oxidative stress caused by HGA and its by-products (9). Hypothyroidism is also more prevalent in AKU patients (16%) compared to the general population (3.7%) (10).

Diagnosis

The diagnosis of AKU is based on clinical symptoms, biochemical tests, and molecular analysis. Biochemical tests include Benedict’s test, ammoniacal silver nitrate test, and sodium hydroxide spot tests, which confirm the presence of HGA in urine. Radiographs typically show joint space narrowing, subchondral cysts, and calcification. Molecular analysis of the HGD gene is a critical diagnostic tool for identifying mutations. Gene sequencing and deletion or duplication analyses can confirm the diagnosis and aid in family screening.

High-resolution accurate mass spectrometry (HRAMS) has proven valuable in monitoring AKU patients undergoing nitisinone treatment, particularly

by assessing the serum metabolome (11). Early molecular diagnosis enables effective genetic counseling for at-risk families.

Management

The cornerstone of AKU management is early intervention with nitisinone, a triketone herbicide that inhibits 4-hydroxyphenyl pyruvate dioxygenase (4-HPPD), reducing HGA production. Nitisinone has been shown to decrease serum and urinary HGA levels, slowing disease progression. However, elevated tyrosine levels associated with nitisinone therapy can cause keratopathy due to tyrosine crystallization in the cornea. Patients undergoing nitisinone therapy are therefore advised to follow a phenylalanine- and tyrosine-restricted diet to minimize adverse effects (12).

Vitamin C has demonstrated limited efficacy in reducing urinary benzoquinone acetate levels but does not significantly affect HGA excretion. Surgical interventions, including joint and valve replacements, are often necessary to address advanced complications of ochronosis (6). A multidisciplinary approach, including orthopedic surgeons, geneticists, nephrologists, and cardiologists, is essential for optimizing long-term outcomes in AKU patients.

Conclusion

Based on this case of alkaptonuria, early preventive measures are recommended for asymptomatic elderly patients and younger siblings of the proband who are HGD gene mutation-positive. Frequent surveillance for cardiac, urological, and orthopedic complications is strongly suggested. Debilitation due to ochronotic arthritis can be prevented or significantly reduced by avoiding physically stressful jobs, maintaining a healthy weight, and engaging in joint-friendly exercises.

Acknowledgments

Nil.

Ethical statement

This case report was approved by the Institutional Human Ethics Committee of PSG Institute of Medical Sciences and Research, Coimbatore, India (Project No – 23/430). The case report was conducted in accordance with ethical standards and guidelines for medical research involving human subjects. The patient provided informed consent for the publication of their medical history, clinical findings, and associated images. All identifying details have been anonymized to protect the patient's privacy. No invasive procedures or experiments were conducted outside the scope of standard clinical care. The study complies with the ethical principles outlined in the Declaration of Helsinki, and the institutional review board (IRB) approval was not required as it is a single case report based on routine clinical practices.

Data availability

Data will be provided by the authors on reasonable request.

Conflict of interest

The authors declare no conflict of interest regarding the publication.

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No funding was received for this case report.

Author contributions

Dr. Sabina Lois Nagarajan was responsible for the concept, design, lab investigations, lab report interpretation, data collection and monitoring, and drafting the final report. Mrs. Aruna Veeruswamy contributed to the concept, design, lab investigations, lab report interpretation, and drafting the final report. Dr. Major K. Kamalanathan Kulandaivelu was involved in the design, selection and recruitment of patients, treatment decisions, patient evaluation, examination of patients during follow-up, interpretation of data, and drafting the final report. Dr. Mohan Prasad Muthusamy contributed to the selection and recruitment of patients, treatment decisions, examination of patients during follow-up, interpretation of data, and drafting the final report. Dr. Yee Tun Oo was responsible for lab investigations,

data collection and monitoring, examination of patients during follow-up, and drafting the final report.

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