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Degenerative Arthritis of the Knee Secondary to Ochronosis - A Case Report

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Abstract : This case report describes a 42 years old man with alkaptonuric ochronosis who sustained bilateral quadriceps tendon rupture after trivial fall, necessitating surgical repair, which was done without complications. Subsequently he developed bilateral degenerative arthritis of knee joint. We offered total knee replacement to both the knee joint. Though we were expected complications related to degenerative extensor apparatus of knee, the complications were avoided by careful handling of soft tissues. At short term follow up, the clinical outcome of the patient was satisfactory. Alkaptonuric ochronosis is a rare autosomal recessive metabolic disorder resulting in a deficiency of homogentisic acid oxidase. As the disease progresses, tissue deposition of polymerized homogentisic acid eventually will lead to the progressive degeneration of all affected body systems. In the skeletal system, cervical, thoracic and lumbosacral degenerative disk disease develops, as do widespread arthritic changes in peripheral and weight-bearing joints. There is no definitive cure for alkaptonuric ochronosis, and treatment is aimed at controlling and ameliorating symptoms.

Keyword : Alkaptonuria, ochronosis, Ochronotic arthritis, total knee replacement

INTRODUCTION:

Alkaptonuria (AKU) arises from the Arabic word alkapton for “alkali” and Greek word “to suck up oxygen greedily in alkali” based on the observation that the urine becomes black on standing when it becomes alkaline. This disorder is of considerable historical interest in that it was one of the original “inborn errors of metabolism” described. At the turn of the 20th century, Archibald Garod, a pediatrician, recognized that the syndrome, which has been called AKU, showed a pattern of familial inheritance. It was proposed that AKU and certain other disorders were due to genetic defects, each of which resulted in the lack of activity of a particular metabolic enzyme. Forty five years later, it was confirmed that the biochemical defect in AKU is a lack of homogentisate oxidase in the tyrosine catabolic pathway **(fig.1)**. Ochronosis is characterized by a brownish-black pigmentation of connective tissues. A common symptom of alkaptonuria, ochronosis is the result of excess homogentisic acid (HGA) due to the autosomal recessive mutation of the homogentisate 1, 2- dioxygenase (HGO) gene on chromosome 3.(1) The condition is rare, affecting only one in 100,000 to 250,000 individuals, but there is evidence that certain populations may have a much higher incidence. (2) The pathogenesis of the disease is 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, degeneration, and eventually osteoarthritis.(3) There are a myriad of presentations of the disease, including darkening of the urine when exposed to air; bluish pigmentation of the skin of the face, hands, ear cartilage, sclera, and fingernails; aortic and cardiac valve calcification; lumbar intervertebral disc calcification and disc space narrowing; and osteoarthritis of the hip and knee.(4-6) Currently, there is no specific treatment for ochronosis, and management of symptoms as they manifest or worsen is the general, accepted approach. However, in cases of significant degenerative arthritis, joint replacement can be performed with anticipation of outcomes comparable to osteoarthritic patients without ochronosis.(7) Due to its rarity in the prevalence rate, We report the case of a 42-year-old male with a family history of ochronosis, who developed degenerative arthritis of the knee.

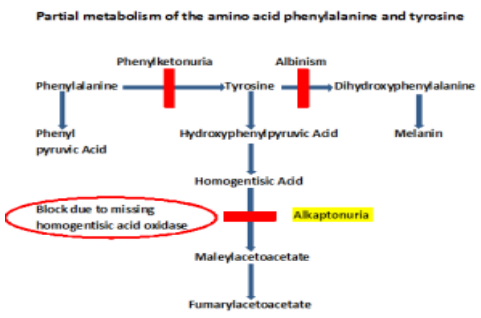

fig.1

CASE REPORT:

A 42 years old male, who is a supervisor in a company, was apparently normal 1 year back. Since birth he had blackish discoloration of urine upon exposed to air. He had a trivial fall at home one year back followed which he couldn't walk immediately and taken to a private hospital. He was diagnosed as bilateral quadriceps tendon rupture **(fig.2)** for which he underwent bilateral quadriceps tendon repair with suture anchors **(fig.3)**. Then he was on physiotherapy. After 3 months he started walking. 6 months after he started feeling pain in both knees, the pain was insidious in onset, more on left side, progressive in intensity, burning in nature, aggravated by movements and walking, relieved by rest. He was unable to walk for the past one month. He had difficulty in squatting, sitting crossed legs and climbing stairs.

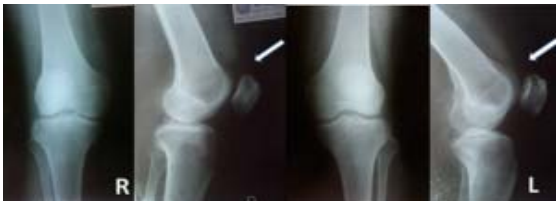

fig.2

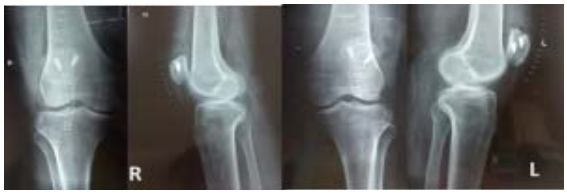

fig.3

Patient described family history of two more affected persons in his previous generations, but his parents were not affected and they had third degree consanguineous marriage. The constructed family tree has shown below **(fig.4).**

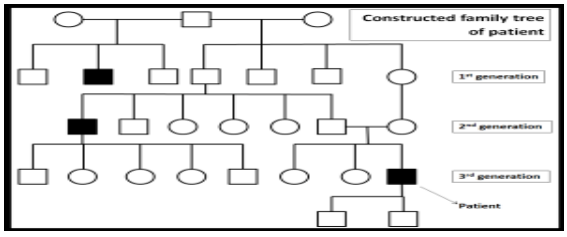

fig.4

On General examination, there was blackish discoloration of skin over the anterior aspect of both the ankle and distal part of leg **(fig.5).** There was also blackish discoloration gums **(fig.6).** The urine of the patient collected in a bottle turned into black on exposed to air for more than 8 hours.

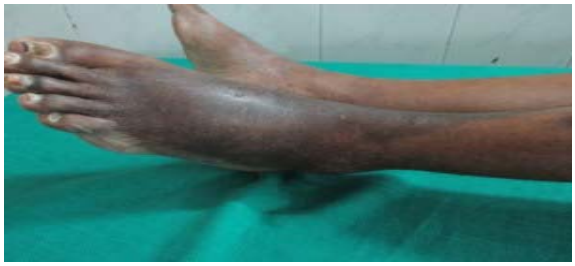

fig.5

fig.6

On Local examination**,** there was a healthy midline scar over anterior aspect of the both knee joints **(fig.7).** Both the knee joints were swollen. There was neutral alignment of the knee. The skin over the knee joints was stretched and shiny. On palpation, both knee joints were warm and there was tibiofemoral and patellofemoral joint line tenderness. Quadriceps tendon and extensor apparatus were normal. There was no laxity of the collateral or cruciate ligaments. There was fixed flexion deformity of 30 on left side and 20 on right side **(fig.8)**, further movement to 45 was available on right side and only a jog of movement was available on left side. Distal neurovascular examinations of the lower extremities were intact and symmetric. Preoperative knee society score on right side was 38 and left side was 10. Spine and hips were clinically normal.

fig.7

fig.8

Roentgenographic findings: X-rays of spine and hips were normal. X-ray of both knees shows severe osteoarthritis **(fig.9&10)**. There was severe reduction of joint space with scalloped articular margins. Mild lateral subluxation of joints was noted. Suture anchors were seen in the patella.

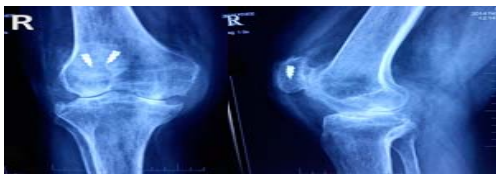

fig.9

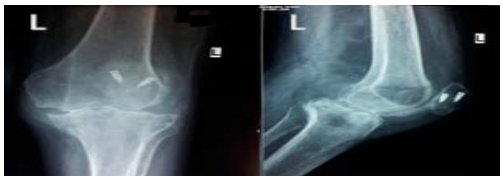

fig.10

Other routine laboratory investigations were normal, taking into consideration general examination, local examination and radiological findings AKU was suspected and to confirm the diagnosis, following biochemical tests were performed. Benedicts and Fehlings test reported that urine contains strong reducing agent. Based on clinical and radiological evaluation and biochemical investigations AKU was diagnosed.

Treatment: Patient was treated symptomatically with analgesics and physiotherapy and was given Vitamin C 500mg daily. Patient was advised to take Vitamin C rich diets. As the patient had more symptomatic arthritis on left side, a cemented left total knee replacement (Smith & Nephew) was performed **(Fig.11&12).**

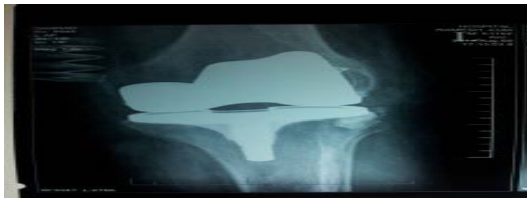

fig.11

fig.12

Procedure: As the patient had bilateral quadriceps tendon repair, we took necessary preparations to overcome the possibility of intra operative quadriceps or patellar tendon rupture. Skin incision made through the previous scar, Medial parapatellar approach was used. Generalized degeneration of articular cartilage throughout the knee joint was observed. A deposition of black pigment was seen throughout the articular cartilage **(Fig.13)**. The degenerative menisci were hard, blackish in color and brittle, and found loose in the joint cavity **(Fig.14&15).** The under surface of patella was found to be devoid of cartilage with large areas of pigmentation **(Fig.16)**. Though we are anticipating friable tendons, intraoperatively found that the quadriceps and patellar tendon were strong enough. We did careful retraction of tendons. We have done an usual TKR. Histological sections of removed bone and soft tissue demonstrated classic findings of ochronosis, including multiple pigmented areas, reactive giant cells, and thickened, inflamed synovium.

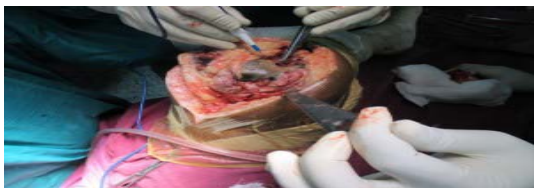

fig.13

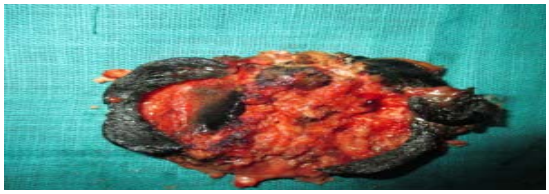

fig.14

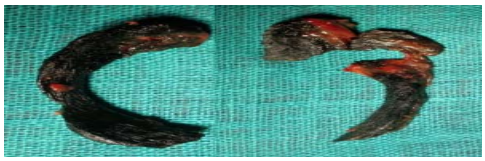

fig.15

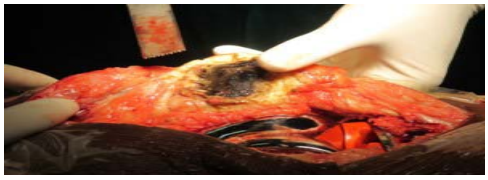

fig.16

Post-operative period: The patient progressed well postoperatively, regaining good range of motion and independent ambulation immediately after surgery. At that time, active range of motion was from full extension to 90° of flexion **(fig.17,18&19)**. Post-operative knee society score was 78 on left side. Postoperative radiographs showed total knee components were in good position and alignment.

fig.17

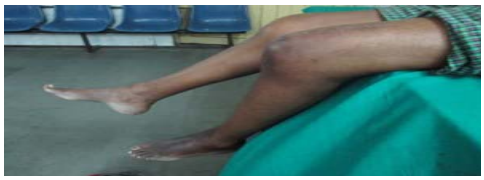

fig.18

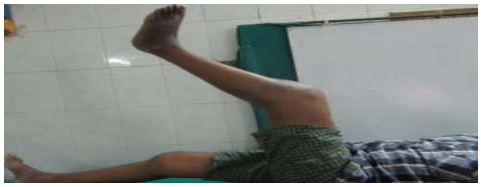

fig.19

After an interval of 4 months, right side total knee replacement was done **(fig.20,21&22)** to alleviate the symptoms of right side knee. At 4 months following surgery, described no knee pain, and was very satisfied with the outcome.

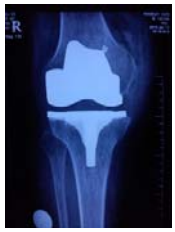

fig.20

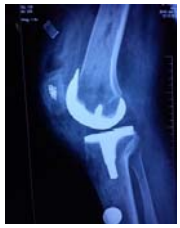

fig.21

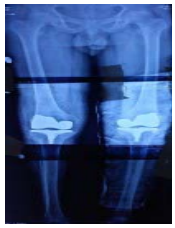

fig.22

DISCUSSION

AKU, a metabolic disorder characterized by a triad of homogentisic aciduria, arthritis and ochronosis enjoys the historic distinction of being one of the first conditions in which Mendelian recessive inheritance was proposed and is also one of the conditions in the charter of group of inborn errors of metabolism.(8) Alkaptonuria, or the excretion of urine which darkens on exposure to air, is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase, an important enzyme in the catabolism of aromatic amino acids. It catalyzes the conversion of homogentisic acid to maleylacetoacetic, which is ultimately converted to fumaric and acetoacetic acid **(fig.1)**.(9) The urine of an alkaptonuric individual usually appears normal when passed. However, it starts to darken upon standing. This is caused by oxidation and polymerization of the homogentisic acid, and it is enhanced with an alkaline pH. Therefore, an acidic urine may not become dark even after many hours of standing. This is one of the reasons why darkening of the urine may perhaps never be noted in an affected person, and the diagnosis may be delayed until adulthood, when arthritis or ochronosis occurs.

Homogentisic acid is a strong reducing agent that produces a positive reaction with Fehling or Benedict reagent, a feature that was also recognized in 1859.(10) The diagnosis is confirmed by measurement of homogentisic acid by enzymatic spectrophotometry,(11) or by using gas liquid chromatography.(12) The diagnosis could also be confirmed by the high-pressure liquid chromatography method for the quantitation of homogentisic acid and its derivative benzoquinone acetic acid.(13) Measurement of this product by this method is used for therapy monitoring. Excretion of homogentisic acid in the urine is usually massive—as much as 4 to 8 g of this compound is excreted daily in the urine,(14) and very little is found in the plasma. Alkaptonuric patients are usually asymptomatic as children or young adults.(15-17) When they get older, pigmentation of the sclera or the cartilage of the ear start to appear. Pigmentation may be seen in the teeth,(18) buccal mucosa, and in the nails or the skin, giving these areas a dusty coloration.

The widespread deposition of pigment in alkaptonuric patients is called ochronosis,(19,20) a term used to describe the darkening of tissues, which is due to a slow accumulation of the black polymer of homogentisic acid in the cartilage and other mesenchymal tissues. Arthritis is the only disabling effect of this condition, and occurs in almost all patients with advancing age. (21,22) The earliest symptoms are usually in the hips, spine and knees, the large weight-bearing joints. In their review of the world literature, O'Brien and colleagues identify the knee as the most frequently affected joint, followed by the hip.(23) The arthritis has the clinical characteristics of rheumatoid arthritis; however, the radiological picture is of severe osteoarthritis. In contrast to osteoarthritis, the large joints at the hip and shoulder are most commonly involved, whereas the sacroiliac joint may be spared. The degenerative changes in the lumbar spine are quite characteristic, with narrowing of joint spaces and fusion of vertebral bodies, resulting in marked limitations of motion with ultimate ankylosis. The intervetebral discs are also affected, with pigmentation and ossification of the nucleus pulposus, leading to degenerative changes.(24) Ochronotic arthropathy in the hips and the knees may be so severe as to require total joint arthroplasty.(25) Tendons and ligaments also are heavily pigmented due to their collagen content. As a result, tendon inflammation, calcification, and rupture can develop.(26)

The disease is more severe in men, although the incidence in the two sexes is equal.(27) There is a high incidence of heart disease,(28) commonly due to mitral and aortic valvulitis. Secondary calcification of the aortic valve may be so severe as to necessitate urgent aortic valve replacement.(29) Ischemic heart disease with ultimate myocardial infarction is a common cause of death. Genetically, alkaptonuria is inherited as an autosomal recessive trait.(28) Janocha et al.(30) demonstrated linkage to microsatellite markers from proximal 3q. Markers on that chromosome were selected for study because of previously demonstrated homology of synteny with mouse chromosome 16.(31) Independently, Pollak et al.(32) used homozygosity mapping to locate the alkaptonuric gene to 3q 2 in a 16-cM region. Sucrase-isomaltase deficiency(33) and neonatal hyperparathyroidism(34) could be co-inherited with alkaptonuria. In 1996, Fernandez-Canon et al. cloned the gene for homogentisate 1,2 dioxygenase (HGD,EC1.13.11.5), and they demonstrated that HGD harbors the mutation that co-segregates with the disease and provided biochemical evidence that at least one of these missense mutations is a loss of function mutation.(1) Treatment of alkaptonuric patients is a challenge for a physician. No treatment has been completely successful. Dietary restrictions on the intake of tyrosine and phenylalanine substantially reduced the excretion of homogentisic acid; however, the long-term compliance with this diet is the major drawback of this approach.(13) Homogentisic acid inhibits the growth of cultured human articular chondrocyte, and binds to connective tissue in rats.(35) Ascorbic acid prevents these effects. Wolff et al. treated two adults with high doses of ascorbic acid. The level of excretion of homogentisic acid did not change, whereas its derivative, benzoquinone acetic acid, completely disappeared from the urine. (13) Symptomatic management is the primary treatment for ochronotic arthropathy.(36) Exercise and analgesics have proven beneficial but do not slow joint degeneration. In cases of significant ochronotic arthritis, total joint replacement has been an effective approach to alleviate pain and restore function.(37)

CONCLUSION

Ochronotic arthritis is a very uncommon disease that can be potentially misdiagnosed with osteoarthritis in patients with knee pain and radiographic evidence of joint space narrowing. Early management of ochronosis can be challenging and is limited to controlling the patient's symptoms. More advanced cases of ochronotic arthritis necessitate surgical intervention. As we have reported, total knee replacement has excellent outcomes in a patient with significant degenerative arthritis secondary to ochronosis.

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