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Ochronosis: A report of three cases and review of the literature

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Ochronosis is the deposition of polymerized products of homogentisic acid in the connective tissues resulting in bluish black discoloration. It is one of the major manifestations of alkaptonuria, which is a rare autosomal recessive metabolic disorder characterized by deficiency of homogentisate 1,2-dioxygenase enzyme.[1] The major manifestations include the following: Urinary elimination of homogentisic acid, arthritis of large joints, deposition of pigment in soft tissues, and rarely cardiac, renal (nephrolithiasis), and ocular affliction. The joint involvement is generally clinically manifested in the third decade.[2] We encountered 3 cases of ochronosis with hip joint involvement and pigmented macules at multiple sites. The rare and interesting cases with varied manifestations have prompted us to report these cases.

Three cases of ochronosis were encountered by us over a period of 3 years at our general hospital. The details of the cases are as follows:

A 40-year-old woman presented with chronic pain in the left hip joint and history of passing dark colored urine since childhood. She also had a history of progressive bluish black pigmentation of the skin and nails [Figures 1 and 2]. Similar history was also present in 3 of her siblings. Skin involvement was noted over both hands and pinna. Roentgenogram of the spine showed extensive calcification of the intervertebral discs. Urine alkalinization showed development of black color. Diagnosis of severe ochronotic arthritis was made on the basis of the clinical and laboratory findings and the patient underwent total hip replacement surgery of both hip joints. Intraoperatively, dislocation of the left hip joint with erosion of the overlying cartilage was noted. Gross examination showed blackish discoloration of the femur head. Histopathological examination revealed a brittle fragmented cartilage with granular greyish brown pigment extracellularly as well as extracellularly within chondrocytes and synovial cells. Postoperative period followed 6 months was uneventful.

A 55-year-old man presented with chronic pain in the right hip joint, difficulty in walking and sitting cross-legged. There was no other significant medical or family history. The physical examination did not reveal pigmentation of the skin or sclera.

A diagnosis of right hip osteoarthritis

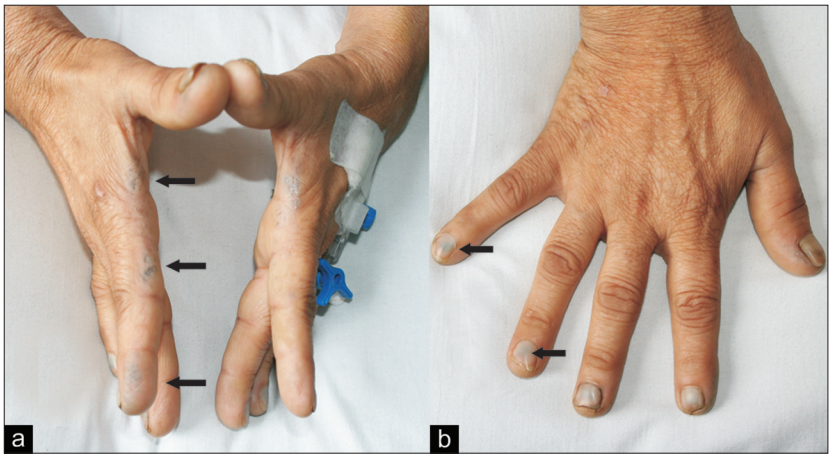

Figure 1: (a) Bluish black discoloration on skin and soft tissue of index fingers of both hands. (b) Similar bluish black discoloration of nail beds

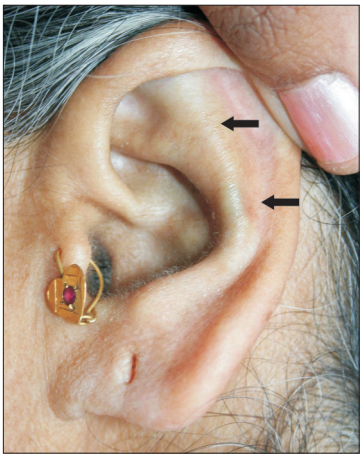

Figure 2: Bluish black discoloration over the skin and cartilage of ear

was made and total hip replacement surgery was performed. The excised femur head was subjected to histopathological examination, which revealed a blackish-brown pigment intracellularly as well as extracellularly [Figure 3]. In the light of the histopathological findings, a diagnosis of ochronosis was suspected. Urine alkalinization resulted in development of black color [Figure 4], and the diagnosis was confirmed by Benedict's test. Postoperative recovery of the patient was good. This case did not reveal involvement of any other organ.

A 50-year-old lady was admitted with symptoms of acute gastroenteritis since 5 days. History of gradual onset skin discoloration, severe backache, and pain in both the hip joints was elicited. Physical examination revealed bluish black macules and papules over the face, forearms, hands, palms and feet, nails, and sclerae.

The results of the routine laboratory investigations were within normal limits; however, urine alkalinization and Benedict's test were positive for alkaptonuria. Magnetic resonance imaging of the lumbosacral spine showed multilevel disc calcification [Figure 5]. The histopathological findings were similar to those described in the previous cases.

The patient was treated for acute gastroenteritis and therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and Vitamin C was started for the ochronotic arthritis. A total hip replacement surgery was advised; however, the patient was not willing for it and therefore was discharged.

DISCUSSION

Ochronosis was first described by Scribonius in 1584 in a boy whose urine was "as black as ink." The term alkaptonuria was first coined by Boedeker in 1891, as quoted by Fischer *et al.*[2] The term ochronosis was first used by Virchow due to the accumulation of the granular yellowish pigment in the connective tissue, which resembled ochre (yellow).[2]

One of the earliest manifestations of alkaptonuria is darkening of urine. The urine is of a normal color on voiding; however, it darkens on standing for several hours. This may not be observed due to the use of modern plumbing; hence many individuals never notice any abnormal color to their urine.[2,3] Only one of our patients gave history of passing dark urine, thus highlighting the utility of the simple urine alkalinization test for diagnosis.

Degenerative joint disease usually develops after the third decade. Low back pain was observed in 94% of patients before the age of 40 years in one large series.[1] The knee, hip, and shoulder joints are also frequently affected. By the age of 55 years, 50% of patients required at least one joint replacement surgery.[1] In all our cases, hip arthropathy was the most troublesome symptom and necessitated total hip replacement surgery.

Discoloration of the skin is usually observed after the third decade.[2] The most commonly involved sites are the ear cartilage, eyelids, sclera, and nails. Tendons may also be involved, frequently observed as discoloration over the knuckles. Two of our patients showed significant skin discoloration. Notably one of our patients did not show any abnormal pigmentation of the skin or the sclera and diagnosis was made on the basis of intraoperative and investigation findings. Discoloration of the cartilages and tendons was noted in all three.

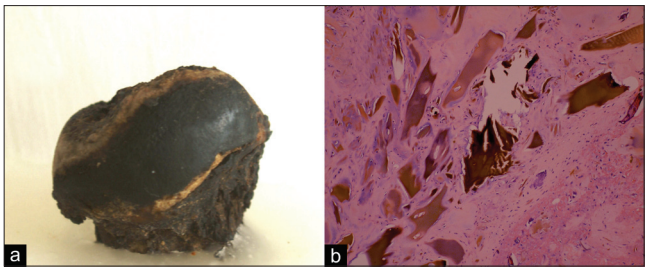

Figure 3: (a) Excised head of femur showing black discoloration of the articular cartilage and surrounding soft tissue. (b) Photomicrograph showing granular yellowish brown pigment intracellularly and extracellularly (H and E, ×100)

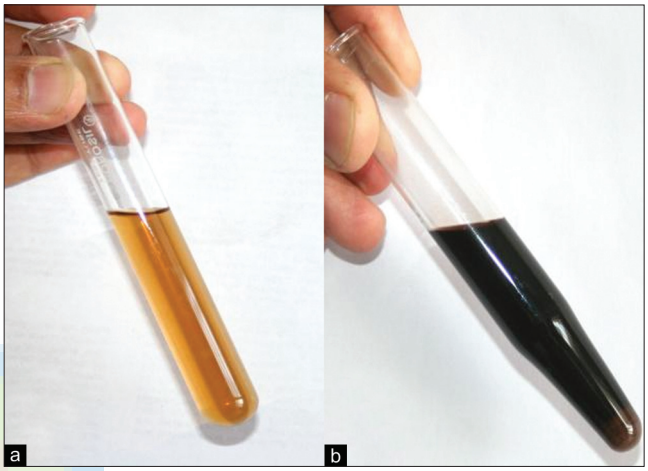

Figure 4: (a) Color of freshly passed urine; and (b) development of dark color after alkalinization

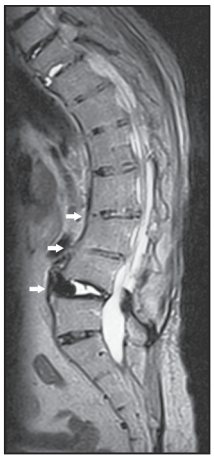

Figure 5: T2-weighted sagittal magnetic resonance images of lower dorsolumbar spine revealing central intervertebral disc calcification

Reviewing the literature, ochronosis has been documented to be associated with affection of the heart in the form of valvular dystrophic calcification, aortic stenosis, and coronary disease. Some workers have reported occurrence of nephrolithiasis. Ocular manifestations in ochronosis have been reported to be mistaken for melanoma.[2] It must be mentioned that in all our cases there was absence of cardiac, renal, or ocular complications and these were ruled out by relevant investigations.

Macroscopically the tissue pigmentation varied from brown to black. Ochronotic pigment is documented to be deposited in the form of ochre colored granules in all layers of the cartilage.[4] In 2 of the 3 present cases, microscopic examination of the synovium and periarticular soft tissue showed shards of yellowish brown pigment deposits as noted by other workers.[5]

Currently there is no effective treatment for alkaptonuria and management is symptomatic. Arthropathy is usually treated with NSAIDs; however, in advanced cases, joint replacement surgery provides significant relief from symptoms.

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