

Ochronotic Arthropathy: Two Case Reports from a Developing Country

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ABSTRACT: Alkaptonuria is a rare inborn error of metabolism, which is classified as an orphan disease. It is due to the lack of an enzyme homogentisate 1,2-dioxygenase, which results in an accumulation of homogentisic acid in different areas of the body, including sclera, skin, cardiac valves, articular cartilage of the large joints and intervertebral disks. We present two cases of alkaptonuria resulting in ochronotic arthropathy with advanced secondary generalized osteoarthritis, intervertebral disk calcifications, skin and scleral pigmentation. In these case reports, both patients had symptoms for >10 years before being diagnosed. Conservative management in the form of high-dose ascorbic acid, exercises, and gait aids was offered to both of them, which resulted in some symptomatic improvement in the first case, while the second case was lost to follow-up. Alkaptonuria is a rare disease, and although it does not clearly impact mortality, early diagnosis may improve the quality of life.

KEYWORDS: alkaptonuria, homogentisic acid, ochronosis, orphan disease, osteoarthritis, Pakistan

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Introduction

Ochronosis (alkaptonuria) is a rare inborn error of metabolism with an incidence of <1 per 250,000 live births.¹ The cause of alkaptonuria is the lack of an enzyme homogentisate 1,2-dioxygenase, which results in an accumulation of homogentisic acid. Some of the homogentisic acid is secreted in urine, while the rest is accumulated in skin and connective tissue leading to hyperpigmentation of skin and sclera, and the degeneration of cartilage inducing premature arthritis. The color of the pigment is brownish-yellowish (ochre) under a microscope; hence the term ochronosis was coined by Virchow in 1866 for this disease.¹ It forms stiff complexes with the cartilage making it more susceptible to mechanical damage during normal loading, leading to its speedy breakdown and early development of osteoarthritis.² Homogentisate 1,2-dioxygenase levels are elevated from birth, but pigmentation takes many years to become noticeable. Recently, interleukin-6 has been implicated to be involved in increasing ochronotic pigmentation in alkaptonuria.³

The typical presentation of ochronosis includes darkening of urine due to oxidation and discoloration of diapers in children. In addition, there may be grayish discoloration of skin, sclera, eyelids, ear cartilage, forehead, cheeks, nail beds, buccal mucosa, tympanic membrane, and palmar aspects along with early degenerative arthritis involving the axial skeleton and large joints. Sacroiliac joints (SIs) are usually spared in

ochronosis. The pigment may also be deposited in outer eye structures, cardiovascular system, and in urinary calculi.⁴ In early cases, obvious scleral discoloration or degenerative arthritis may not be observed, but the discoloration of urine is a universal symptom. Alkaptonuria can lead to early extensive degenerative arthritis that might require seeking medical attention. Other systems affected by the disorder include cardiovascular and genitourinary systems.

We present two cases of alkaptonuria from Pakistan who had ochronotic arthropathy with ossifications of the intervertebral disks, skin changes, and scleral pigmentation. The patients have given their consent for publication of this report.

Case Descriptions

Case 1. A 48-year-old male presented to the outpatient department with a 15-year history of chronic pain in lower back and both knees. Pain was nontraumatic, progressive, dull-aching in nature, and aggravated on exertion. He denied rash, fever, morning stiffness, sciatica, night pains, and other associated symptoms. He had been taking nonsteroidal anti-inflammatory drugs (including ibuprofen, naproxen, diclofenac, and piroxicam) and muscle relaxants for the last 10 years with temporary pain relief. He did not smoke tobacco or consume alcohol. His father had a similar problem with joint pains at a young age and died when he was 59 years old. The patient was

a retired navy sailor and recalled that his knee and back pain made his job very difficult for him. He took losartan potassium, and simvastatin for hypertension and hyperlipidemia respectively. He lived in a hilly area with his wife and four children.

On physical examination, he was a middle-aged male, looking older than his chronological age. Vital signs were normal. His height was 150 cm. He disclosed that his height had been 165 cm at enrollment in navy 25 years back. The minimum standard for induction into Pakistan Navy is 162 cm, which confirmed that he actually lost his height in the last 15 years. Examination also revealed gray pigmentation in both sclera (Figs. 1A and B) and grayish blue papules on the bilateral extensor surface of the second finger (Fig. 1C). The cardiopulmonary and neurologic examinations were unremarkable; abdomen was soft and without organomegaly. He had a forward stooping posture with loss of curvature of the lumbar spine. Musculoskeletal examination revealed no active inflammation. His straight leg raise was 80° on both sides (normal, 90°) with mildly reduced spinal flexion. There was palpable crepitus in both knee joints with flexion reduced to 100° (normal, 130°) because of pain.

The laboratory analysis, including a complete blood count, liver, and renal function tests were normal. X-rays of the cervical and lumbosacral spine showed advanced degenerative changes with intervertebral disk space narrowing and osteophyte formation (Figs. 2A–D). There were disk calcifications visible in the lumbosacral spine. X-rays of the knee joints

showed reduced joint space and osteophyte formation with loose bodies, suggestive of osteoarthritis knees (Figs. 2E and F).

Based on history, physical examination, and investigations, a provisional diagnosis of ochronotic arthropathy was made. When the patient's urine sample was allowed to stand, it changed color to brownish black (Fig. 3). To further confirm the disease, a silver nitrate test was performed. An ophthalmologist consultation for his scleral discoloration ruled out other associated eye diseases. Two-dimensional echocardiogram analysis revealed calcification of aorta and tricuspid valves. He was advised to take antiplatelet drugs by the cardiologist along with losartan potassium. His family screening was initiated and two of his children were found to be positive.

The patient was educated about the nature of the disease. Counseling was provided regarding disease prognosis. Physiotherapy and hydrotherapy sessions were advised for his back and associated large joints pain. Home-based stretching and strengthening exercises were taught, and he was provided with a walking stick to aid in his gait and offload the arthritic joint. He was prescribed acetaminophen for his pain along with 1 g of ascorbic acid (vitamin C) daily and advised to continue medication for hypertension and hyperlipidemia. He is doing well with the treatment and is living with his disease with regular follow-up at the outpatient rehabilitation and cardiac departments. He has been briefed about the option of joint replacements of the large weight-bearing joints, if the condition becomes worse or unbearable.



Figure 1. (A) and (B) Scleral pigmentation is visible in both eyes. (C) Greyish blue discoloration on the bilateral extensor surface of second finger.

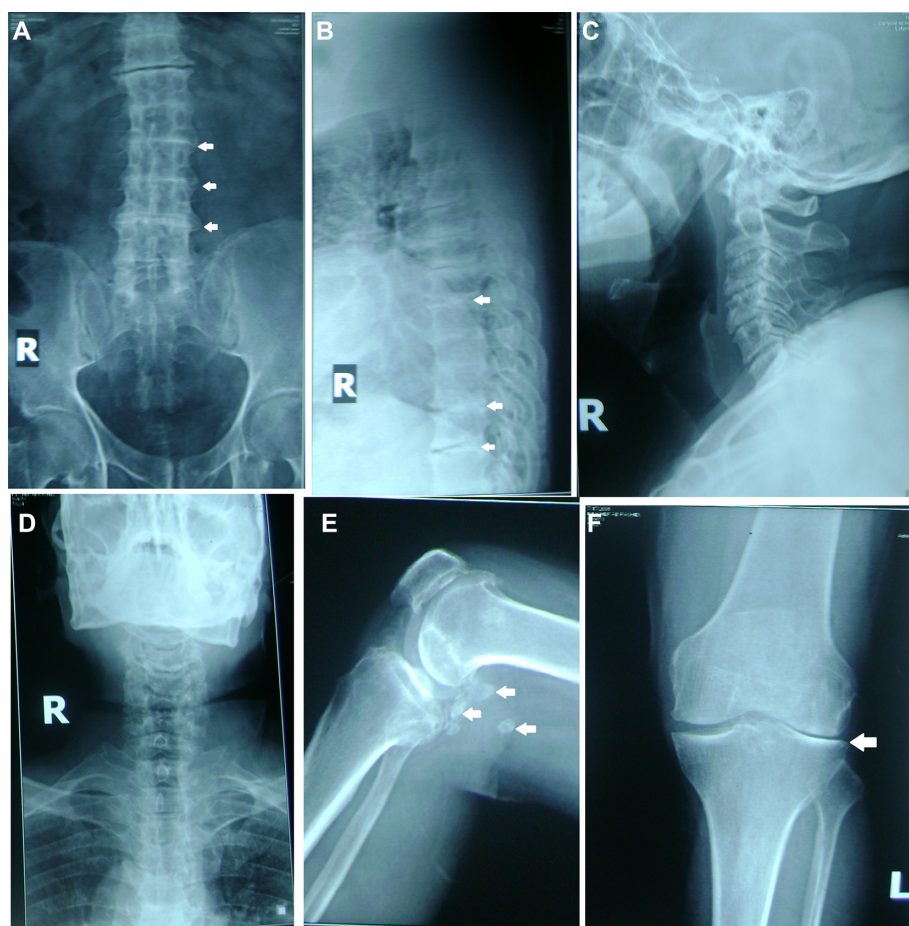


Figure 2. (A–D) X-rays of the cervical and lumbosacral spine showing advanced degenerative changes with intervertebral disc space narrowing and osteophyte formation. Disk calcifications are visible in the lumbosacral spine. (E and F) X-rays of the knee joints showing reduced joint space and osteophytes formation with loose bodies, suggestive of knee osteoarthritis.

Case 2. A 60-year-old female presented with insidious onset of a chronic, dull, aching pain in both knees and dorsal spine for the past 15 years. She had a fall one year before, which resulted in spinal cord compression and incomplete thoracic paraparesis. She had a gradual, but partial recovery in legs, following open discectomy and laminectomy. She regained bladder continence and an acceptable bowel program. She had diabetes and hypertension for the past two years but was not taking regular medications. Twenty years ago, she had noticed gradual grayish-blue discoloration of her nose, index fingers, palms, and thumbs. She was unable to get an explanation for her problem, because there was no physician in her remote rural area. She denied any family history of such complaints.

On examination, she was an old woman, lying in bed with flexion contractures at both knees. She had a normal pulse with a blood pressure of 160/90 mmHg. She had grayish-blue patches over her nose, proximal palms, index fingers, thumbs, dorsal foot, and macules in sclera and over face, ears, and knees (Figs. 4A and B). Knee crepitus bilateral was observed. She had a normal tone and power in upper limbs with grade 1+ spasticity (modified Ashworth scale) in both legs. Muscle power was reduced in L1–S2 myotomes. Muscle

stretch reflexes were grade 3+ in legs, while the plantar reflex was down going. Her urine turned dark, when kept in the open for 24 hours (Fig. 4D). The knee X-rays showed degenerative changes (Fig. 4C). The X-rays of her dorso-lumbosacral



Figure 3. Urine sample changed color to brownish-black when allowed to stand in light for 24 hours.

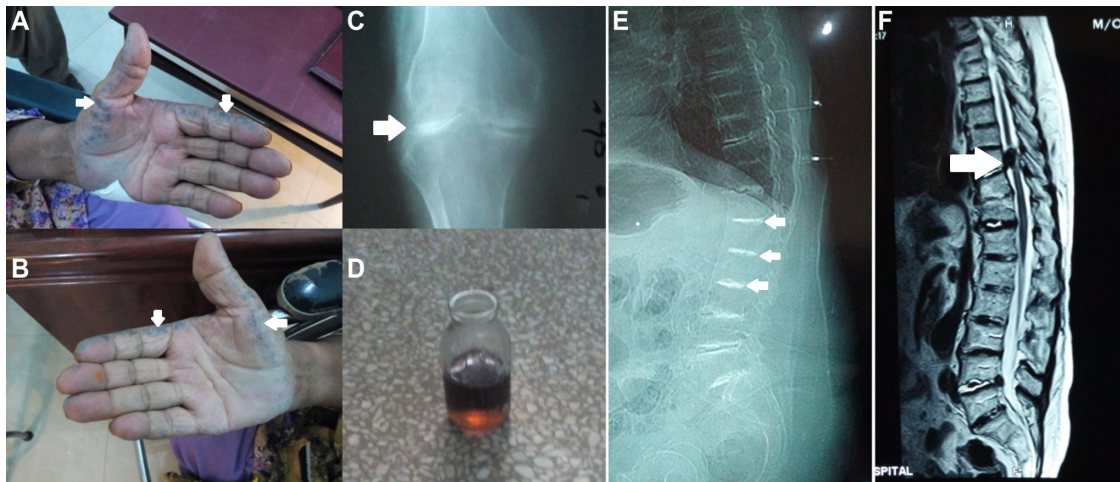


Figure 4. (A) and (B) Grayish-blue patches over proximal palms, index fingers, and thumbs. (C) Advanced degenerative changes in the knee suggesting secondary osteoarthritis. (D) Urine sample changed color to brownish-black when left in light for 24 hours. (E) Intervertebral disk calcifications with reduced bone density and advanced degenerative changes. (F) Magnetic resonance imaging reveals anterior wedging with partial fusion of T₁₀ and T₁₁ vertebrae, postsurgical architectural distortion, and loss of posterior elements.

spine showed reduced intervertebral disk spaces consistent with age and calcification of the intervertebral disks, which were more prominent in the lumbosacral region. (Fig. 4E) The SIs were spared. The postsurgical magnetic resonance imaging revealed anterior wedging with partial fusion of T₁₀ and T₁₁ vertebrae, postsurgical architectural distortion, and loss of posterior elements, seen also at that level. There was spinal canal stenosis at T_{10–11} with myelomalacia at T_{9–10} level. (Fig. 4F). Her hemoglobin value was low (8.7 g/dL, normal >12 g/dL), while total leukocyte count, platelet count, liver and renal function tests, plasma glucose profile, and electrocardiogram results were normal. The two-dimensional echocardiogram revealed grade-I diastolic dysfunction with mild left ventricular hypertrophy.

Because caregivers were not available, she could not be managed thoroughly on inpatient rehabilitation. However, she and her caregivers were educated regarding her disease nature and prognosis. Her caregivers were also trained in applying superficial heat modalities and range of motion, stretching, and strengthening exercises. She was given high-dose ascorbic acid and amlodipine tablets for hypertension. For analgesia, she was prescribed acetaminophen and meloxicam tablets and local application of flurbiprofen gel. She was lost to follow-up.

Discussion

A total of 950 patients of alkaptonuria have been identified worldwide, including four cases from Pakistan.⁵ In a hospital-based study from Pakistan, out of 2000 children under two years screened for inborn errors of metabolism, only one case of alkaptonuria was detected.⁶ Five cases of ochronosis from Pakistan have been documented in the literature. All except one were adults (26–55 years), who presented with joints and back pain.^{7–11} All of these cases, similar to our cases, were prescribed high-dose ascorbic acid (vitamin C), although there

is not much evidence to support its use in ochronosis. These vitamins mostly serve as placebo rather than actually altering the course of the disease.

Musculoskeletal manifestations in ochronosis usually become apparent in the third or fourth decade, starting with the axial spine followed by the involvement of weight-bearing large joints.¹² Small joint involvement of hands and feet is uncommon. Symptoms initially present as low back pain, stiffness, and limitation of range of motion that gradually ascends involving the thoracic spine and chest, occasionally leading to decreased chest expansion.¹³ Osteoarthritis is common among patients with ochronosis, but pathological fractures are rare. Rupture of intervertebral disks may occur. At times, there is an acute onset of sharp pain due to rupture of nucleus pulposus, and this may be the initial presentation of the disease especially in males. The probable cause of the late onset of musculoskeletal complaints is the progressive inability of kidneys to excrete homogentisic acid. With age, the high tissue turnover and a gradual decline in renal functions cause homogentisic acid accumulation in the body and symptoms manifest. Ochronosis usually leads to osteoarthritic-type changes, but in few cases it can manifest as inflammatory changes in the joints as well. Tendons are collagen rich and hence are the sites of pigment deposition. The weakened architectural structure of the soft tissues leads to tendonitis and occasionally causes tendon rupture at these sites.¹

Aortic valve stenosis and calcifications have been observed in patients with ochronosis,¹⁴ and pericardial calcifications have been reported.¹⁵ Cholelithiasis, renal calculi, and prostatic calculi also occur in the course of disease in some patients. Osteoporosis occurs in patients with ochronosis leading to the loss of bone architecture and increased risk of fractures.¹⁶

The X-ray findings of the axial skeleton are similar to those of degenerative arthritis and ankylosing spondylitis

(AS) and hence must be differentiated from the two. They include diffuse narrowing, osteophyte formation, wafer-like calcification of intervertebral disks, vacuum phenomenon, and osteoporosis.⁵ X-rays of peripheral large joints show changes of osteoarthritis, including decreased joint space, marginal sclerosis, and osteophyte formation.

The differential diagnosis includes AS in those exhibiting axial skeleton involvement. In ochronosis, calcification of intervertebral disks due to calcium hydroxyapatite and marked sclerosis including SIs can also be observed. Apart from history and age of presentation, ochronosis can be differentiated from AS in that it does not have annular sclerosis and SI erosions are usually absent. The SI joints can have narrowing and marked sclerosis in ochronosis.¹⁷ Other differential diagnoses include rheumatoid arthritis, hyperparathyroidism, amyloidosis, and diffuse idiopathic skeletal hyperostosis. The most common ocular findings in ochronosis include symmetric brown sclera pigmentation, oil drops (brown pigment spots in the limbus), conjunctival pigmentation, conjunctival vessels with increased diameter, and chamber angle pigmentation.¹⁸

The simplest diagnostic tests are observation of urine for discoloration, silver nitrate test, and urine test for the presence of homogentisic acid. The silver nitrate test is a simple qualitative assay for the detection of homogentisic acid. A few drops of 10% ammonia are added to a fresh sample of urine followed by the addition of 3% silver nitrate solution. The development of greenish-black color indicates the presence of a substantial amount of homogentisic acid.¹⁹ The management options in ochronosis are many, but they have not proven to be of much benefit. These include high-dose ascorbic acid, low protein diet, and physiotherapy.²⁰ Another possible management option is, nitisinone, a drug that inhibits 4-hydroxyphenylpyruvate, which is an enzyme involved in the conversion of hydroxyphenylpyruvate to homogentisic acid.²¹ Currently, the US Food and Drug Administration has approved it only for the treatment of hereditary tyrosinemia type I, and there are concerns about the side effects. These side effects can be ameliorated by reducing dietary intake of tyrosine

Patients with ochronosis have a normal life expectancy, despite the debilitating arthritis that may lead to a poor quality of life. Ochronosis is rare, but it should be kept in mind as a differential diagnosis to other spondyloarthropathies including AS.

These and similar case reports highlight the aspects of management of rheumatologic disorders in low-resourced countries with inadequate health care systems. Both cases reported here had symptoms for more than a decade but could not get a clear-cut diagnosis. Even when the diagnosis was made, one of them had no resources to continue treatment, left in the middle, and was lost to follow-up. The health care systems in developing countries mostly focus on the prevention and management of communicable diseases. Musculoskeletal disorders, although common, are not a priority, and complaints related to the musculoskeletal system can be

ignored or cannot be investigated. This is further complicated by the strong presence of a parallel traditional health care system and untrained quacks posing as health care professionals who can be readily accessed and start their treatment for pain relief. There is a need for developing better health care systems in the low-resourced countries and improve the management of musculoskeletal disorders.

Conclusion

Ochronosis is a rare metabolic disorder leading to characteristic clinical and radiological findings. It manifests late mainly due to musculoskeletal conditions and skin discoloration. No specific treatment is available, but early diagnosis, regular follow-up, and conservative management can improve the quality of life. Prognosis is usually good in terms of normal life expectancy.

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Author Contributions

FAR conceived the idea, collected data of patient No1, performed the literature review and wrote the initial manuscript. SBA contributed case No 2, performed the literature search and revised the manuscript. SNM collected data of patient No1 and critically revised the manuscript. All the authors reviewed and approved the final manuscript.

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