Skeletal Radiology (2019) 48:819–822
https://doi.org/10.1007/s00256-018-3104-4

CASE REPORT

Alkaptonuria—an atypical case: multi-modality imaging review

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Received: 23 August 2018 / Revised: 16 October 2018 / Accepted: 17 October 2018 / Published online: 8 November 2018

Abstract
Alkaptonuria is a rare inborn metabolic disorder due to a mutation in the homogentisic acid oxidase enzyme (HGO) gene on chromosome 3q. As HGO is deficient in alkaptonuria patients, there is an accumulation of homogentisic acid in the blood and urine. Homogentisic acid gets deposited in the soft tissues, tendons, cartilages, large joints and intervertebral discs. Ochronosis usually affects the dorsolumbar spine and typically spares the cervical spine and sacroiliac joints. However, in this case of isolated ochronosis, we report co-existent extensive cervical spine degenerative changes and cervical vertebral fusion, which has not been described in the literature so far.

Keywords Alkaptonuria · Ochronosis · Spondyloarthropathy · Black urine disease

Introduction

Alkaptonuria (AKU), also known as black bone or black urine disease, is a rare inborn metabolic disorder first described by Sir Archibald Garrod in 1901 [1]. It is the first disease in humans to confirm the principles of Mendelian autosomal recessive inheritance. The worldwide prevalence of AKU is 1 among 250,000 to 1 million births [2]. It is due to a mutation in the HGO gene on chromosome 3q, which leads to defective metabolism of homogentisic acid (HGA). As homogentisic acid oxidase enzyme is deficient in alkaptonuria patients, there is an accumulation of homogentisic acid in the blood and an excessive accumulation of homogentisic acid in urine that turns dark on standing. An oxidized polymer of homogentisic acid gets deposited in the soft tissues, tendons, cartilages, large joints, and intervertebral discs space, which in turn leads to severe spondyloarthropathy and osteoarthritis [2].

Case report

A 49-year-old Indian female presented with bilateral knee pain for the last 2 years, which was insidious in onset, progressive in nature, non-radiating, and associated with difficulty in walking. She also complained of backache and forward bending of posture over the same period. There was no history of trauma or relevant family history. She also reported occasional occurrence of urine turning brownish to black in color. Physical examination showed significant kyphoscoliosis with restriction of movement in the spine, restricted movements of left hip joint and knee joint. Brownish to black discoloration of both the ears was also seen. Total and differential leukocyte count were normal rheumatoid factor was negative. Erythrocyte sedimentation rate was normal. The urine specimen had a dark iron oxide–like discoloration when the urine specimen was kept in the sunlight for 3 h (Fig. 1).

Radiological findings

Radiographs of the cervical spine showed extensive degenerative changes from C2 to C6 levels with loss of intervertebral disc

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Fig. 1 **a** Bilateral pinna discoloration. **b** Urine specimen before and after sunlight exposure for 3 h

spaces. Atlantodental interval was increased with mild kyphotic deformity at C2 and C3 levels. Radiographs of the dorsolumbar spine showed extensive degenerative changes throughout the spine with disc calcification and loss of intervertebral disc space. Significant vacuum phenomenon was seen in lumbar and lower dorsal intervertebral disc spaces. There was a reduction in L4 and L5 vertebral height also (Fig. 2).

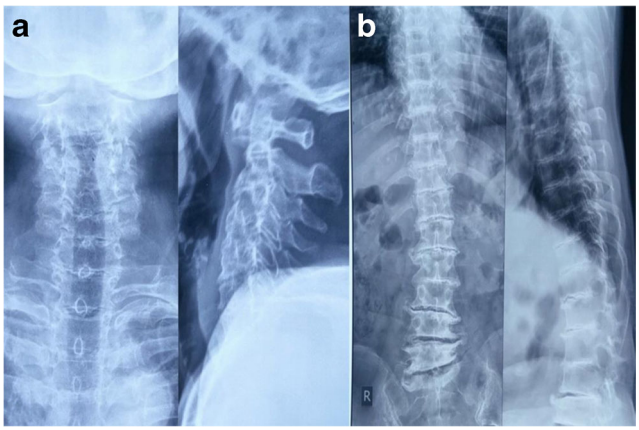

Fig. 2 Cervical spine radiograph of a 49-year-old female (**a**) shows extensive degenerative changes from C2 to C6 levels and loss of intervertebral disc spaces. Atlantodental interval is increased with mild kyphotic deformity at C2 and C3 levels. **b** Radiograph of dorsolumbar spine shows extensive degenerative changes throughout the spine, disc calcification, and loss of intervertebral disc space. Significant vacuum phenomenon was observed in lumbar and lower dorsal intervertebral disc spaces with reduction in L4 and L5 vertebral height

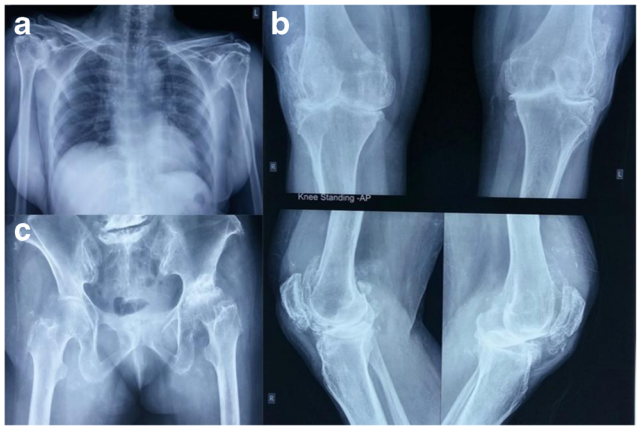

Fig. 3 **a** Radiographs of the shoulder of a 49-year-old female shows dysmorphic humeral heads, subchondral cystic changes, and joint space narrowing. **b** Imaging of the knee shows extensive degenerative changes involving both tibiofemoral and patellofemoral joints, global reduction of tibiofemoral joint spaces, and bilateral loose bodies. **c** Hips show dysmorphic left femoral head, extensive marginal sclerosis, subtle juxta-articular cystic changes, and loss of hip joint space (ankylosis)

Radiographs of the hip joint showed dysmorphic left femoral head with extensive marginal sclerosis, subtle juxta-articular cystic changes, and loss of hip joint space (ankylosis). Radiographs of the knee joint showed extensive degenerative changes involving both tibiofemoral and patellofemoral joints with global reduction of tibiofemoral- joint spaces and bilateral loose bodies. Radiographs of the shoulder joint showed dysmorphic humeral heads with subchondral cystic changes and joint space narrowing (Fig. 3). Plain radiographs of the hand and feet were unremarkable.

Ultrasound study of the ankle and knee joints shows tendon thickening, specks of calcifications in the Achilles,

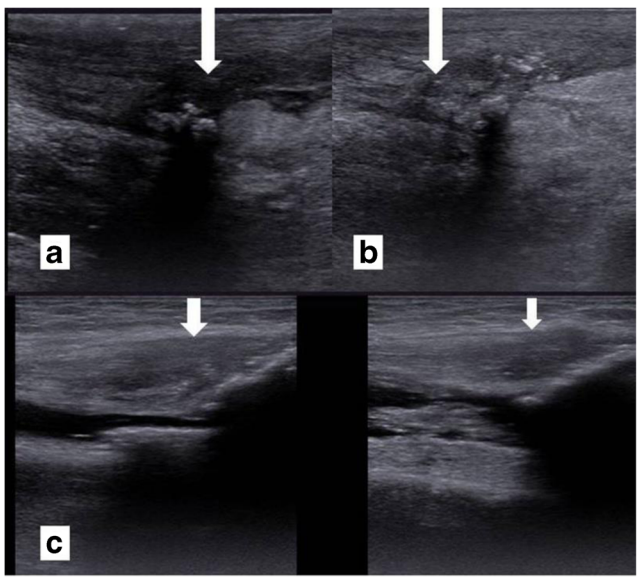

Fig. 4 Ultrasound of ankle (**a**, **b**) and knee (**c**) shows tendon thickening, specks of calcifications in the Achilles, and quadriceps

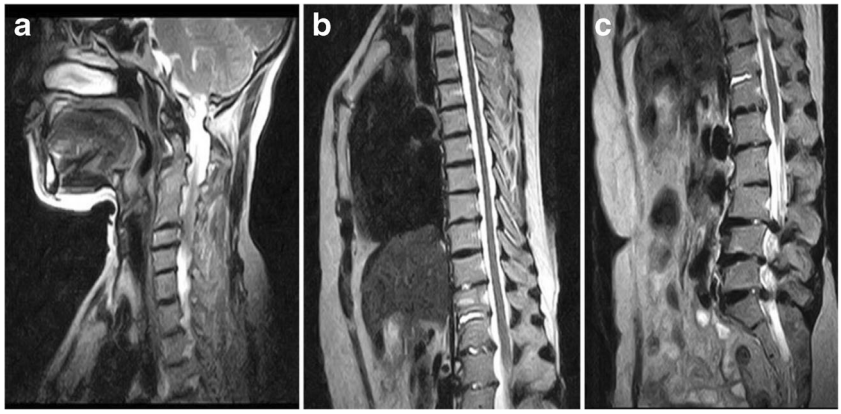

Fig. 5 MRI of the spine shows extensive multilevel degenerative spondylo disc disease involving the entire spine (**a**). Vertebral body fusion was seen at C2 to C5 levels. **b** Disc calcification in lower dorsal vertebral levels. **c** Disc calcification in all lumbar levels except at L2-L3 level. Large posterior disc extrusions are shown at L3-L4 to L5-S1 levels causing significant canal stenosis and cauda equina compression

quadriceps, and patellar tendons. Minimal effusion was seen in both knee joints (Fig. 4).

MRI showed extensive multilevel degenerative spondylo disc disease involving the entire spine with disc calcification in lower dorsal and all lumbar levels except at L2-L3 level. Cervical vertebral body fusion was seen at C2 to C5 levels. Large posterior disc extrusions were seen at L3-L4 to L5-S1 levels causing significant canal stenosis and cauda equina compression, which again is unusual in ochronosis [3] (Fig. 5).

Gas chromatography/mass spectrometry (GC/MS) of urine, the diagnostic test for alkaptonuria, confirmed this case as alkaptonuria (observed value of homogentisate was 0.8; control value 0.001) (Fig. 6).

Discussion

Ochronosis is a multisystem disorder mainly affecting connective tissues like auricular cartilage, sclera, heart valves, articular cartilage, ligaments, and tendons. In developing countries, there are no neonatal screening programs for alkaptonuria, so very few patients are diagnosed in early childhood because of discoloration of the diaper. However, the diagnosis could be delayed until the patient presents with knee pain or a low backache. Ochronotic pigment accumulation in the tendons and ligaments begins in the second decade of life [4]. Symptoms usually begin from the third or fourth decades of life. Hardening of ligaments, muscles, and tendons predispose them to rupture after minimal injury. Renal stones that occur may be due to high HGA levels in the urinary tract. Renal failure, respiratory failure, and hearing loss have also been reported [5, 6]. Ochronotic arthropathy occurs in joints of axial and peripheral skeleton except in cervical spine and sacroiliac joint [7]. However, in our case, we observed extensive degenerative changes in the cervical spine. One should always suspect alkaptonuria in the presence of the following clinical triad: degenerative arthritis in young adults, brownish to black pigmentation of connective tissues, and urine turning brownish to black color on standing [8]. Characteristic radiological findings are vertebral disc calcification, vacuum phenomenon, chondrocalcinosis, subchondral cysts, and osteoarthritis of multiple joints in young adults [8]. Plain radiographs have a limited role in diagnosing early

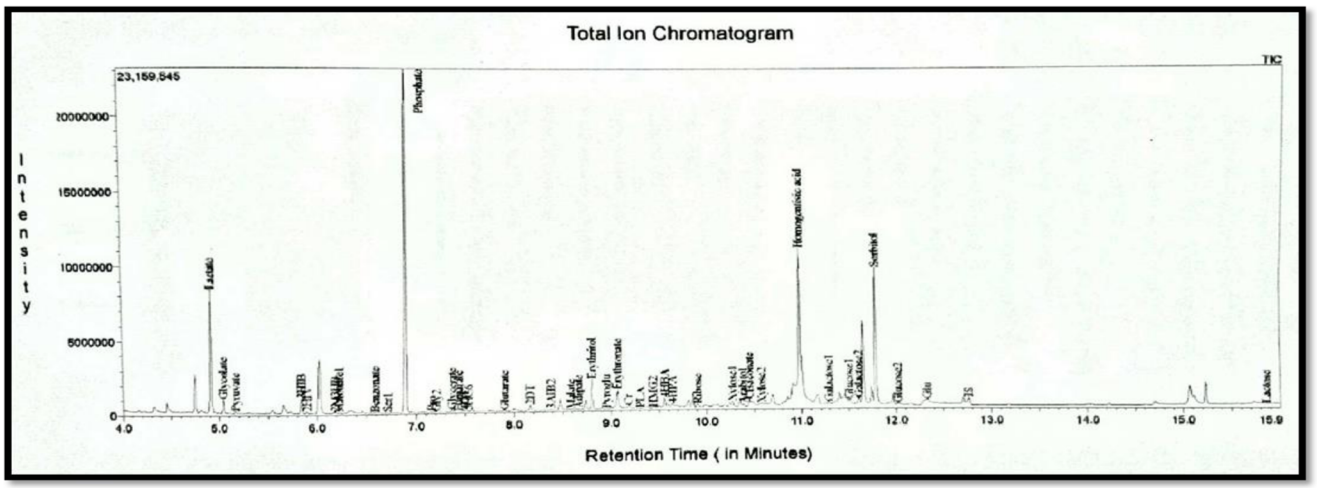

Fig. 6 Gas chromatography/mass spectrometry of urine showing elevated homogentisic acid

tendonitis, but ultrasound examination can detect early tendonitis features like calcification and tendon thickening [9]. Though bony ankylosis of the vertebral bodies and cervical spondylosis has been described in ochronosis in separate instances, they have not been described in coexistence in ochronosis so far [10–12].

According to the modified staging system for ochronosis of the spine proposed by Jerbaraj et al., our patient falls under stage 3 and 4 of ochronosis (fibrous ankylosis with sandwich-spine appearance in thoracolumbar vertebrae and bony ankylosis in the cervical spine) [4]. The close differentials for ochronosis include ankylosing spondylitis (AS) rheumatoid arthritis (RA), calcium pyrophosphate deposition disease (CPPD), and osteoarthritis (OA). Disc calcification in ochronosis may mimic diffuse idiopathic skeletal hyperostosis, amyloidosis, hyperparathyroidism, and hemochromatosis. Osteophytes seen in ochronosis are horizontally oriented and are different from vertically oriented syndesmophytes of AS and no intervertebral discs calcification is seen in AS [4]. Though peripheral joint involvement of CPPD can mimic ochronosis, the spinal involvement is unusual in CPPD. RA typically shows the involvement of small joints with painful movements and involvement of the cervical spine, specific agglutination test may positive in RA. OA mostly affects the lumbar and cervical spine, disc calcification is uncommon, peripheral joint involvement is difficult to differentiate with ochronosis unless menisci calcification, and periarticular calcification is absent in OA [13].

There is no effective treatment currently for this disorder. Nitisinone helps in reducing the level of HGA in the urine by inhibiting its production, but is not yet fully licensed. A high dose of vitamin C is also used but is not very effective. Symptoms are usually managed with analgesics, wax therapy, and dietary restriction of tyrosine and phenylalanine [2, 7]. Joint replacements are offered for those with end-stage joint disease with ankylosis. This patient was also advised to undergo knee replacement but the patient refused to undergo the procedure.

Conclusions

Ochronosis usually affects the dorsolumbar spine and usually spares the cervical spine, unlike in this patient. Large posterior disc extrusions causing significant canal stenosis and cauda equina compression are also unusual in ochronosis. Coexistent extensive cervical spine degenerative changes and cervical vertebral fusion in ochronosis has not been described in the literature so far. It is important to be aware of these atypical presentations of ochronosis.

Compliance with ethical standards

Financial support and sponsorship Nothing to disclose.

Conflict of interest There are no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Research involving animals Not applicable.

References

1. Garrod AE, Oxon MD. The incidence of alkaptonuria: a study in chemical individuality. 1902. Mol Med. 1996;2:274–82.
2. Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, et al. Natural history of alkaptonuria. N Engl J Med. 2002;347:2111–21. https://doi.org/10.1056/NEJMoa021736.
3. Kalevski SK, Haritonov DG, Peev NA, et al. Spine J. 2007;7:495–8.
4. Jebaraj I, Chacko BR, Chiramel GK, Matthai T, Parameswaran A. A simplified staging system based on the radiological findings in different stages of ochronotic spondyloarthropathy. Indian J Radiol Imaging. 2013;23:101–5.
5. Calero Paniagua I, Montilla Morales CA, Carranco Medina TE, Sánchez González MD. Ocronosis y osteoporosis: a propósito de un caso. Reumatol Clin. 2015;11:330–1.
6. Phatak SV, Kolwadkar PK, Hemnani TJ, Phatak MS, Hemnani JT. Pictorial essay: Alkaptonuria. Indian J Radiol Imaging. 2006; cited 2017 Dec18;16:573–6.
7. Baeva M, Bueno A, Dhimes P. AIRP best cases in radiologic pathologic correlation: ochronosis. Radiographics. 2011;31:1163–7.
8. Haridas VM. Alkaptonuria, a rare cause for low back pain. IJRCI. 2013;1(1):CS5.
9. Jebaraj I, Rao A. Achilles tendon enthesopathy in ochronosis. J Postgrad Med. 2006; cited 2018 Jan 17;52:47–8.
10. Karadag A, Sandal E, Middlebrooks EH, Senoglu M. Surgical management in cervical spondylotic myelopathy due to alkaptonuria. World Neurosurg. 2018;113:308–11. https://doi.org/10.1016/j.wneu.2018.02.148.
11. Kusakabe N, Tsuzuki N, Sonada M. Compression of the cervical cord due to alcaptonuric arthropathy of the atlanto-axial joint. A case report. J Bone Joint Surg Am. 1995;77(2):274–7.
12. Spota BB, Bardeci CA, Vazquez E, Parvis D. Radiculo-medullo-cervical compression due to ochronosic spondyloarthropathy. Rev Medica Hosp Esp. 1952;22(10-12):135–42.
13. Gandhi R, et al. Literature and MR findings in ochronosis. Gujarat Medical Journal. 2010;65(1):39–46.