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Alkaptonuria Mimicking Axial Spondyloarthritis: A Case Report of a 42-Year-Old Man

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Abstract

Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder caused by deficiency of homogentisate 1,2-dioxygenase, resulting in the accumulation of homogentisic acid (HGA) and deposition of ochronotic pigment in connective tissues. Ochronotic spondyloarthropathy may mimic axial spondyloarthritis (axSpA), creating a diagnostic challenge.

We report the case of a 42-year-old man who presented with a 2.5-month history of progressive low back pain, morning stiffness, marked spinal restriction, and severe functional impairment, initially raising suspicion of axSpA. Physical examination revealed severe restriction of cervical and lumbar spine movements, reduced chest expansion, positive sacroiliac joint provocation tests, and subtle bluish pigmentation of the auricular cartilage.

Laboratory investigations showed normal inflammatory markers and negative HLA-B27. Lumbosacral radiographs demonstrated extensive intervertebral disc calcification, disc-space narrowing, endplate sclerosis, and osteophyte formation, without radiographic evidence of sacroiliitis. Urinary HGA was markedly elevated (833.40%; laboratory reference: <0.99%), supporting the diagnosis of AKU with ochronotic spondyloarthropathy. Molecular genetic confirmation was not available.

AKU should be considered in the differential diagnosis of patients presenting with severe axial pain, spinal restriction, and extensive intervertebral disc calcification without typical radiographic sacroiliitis. Recognising characteristic clinical, radiological, and biochemical features can facilitate timely diagnosis and appropriate multidisciplinary management, even without molecular genetic confirmation.

Categories: Rheumatology, Orthopedics, Internal Medicine
Keywords: alkaptonuria, axial spondyloarthritis, homogentisic acid, ochronosis, ochronotic arthropathy, spondyloarthropathy

Introduction

Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder caused by biallelic pathogenic variants in the HGD gene, resulting in deficiency of homogentisate 1,2-dioxygenase and subsequent accumulation of homogentisic acid (HGA) [1,2]. Oxidation and deposition of HGA-derived ochronotic pigment in connective tissues lead to progressive musculoskeletal and systemic manifestations, which often become clinically apparent in adulthood [3].

Darkening of urine on prolonged standing is a characteristic manifestation of AKU [4]. Ochronotic arthropathy predominantly affects the spine and large joints, causing pain, stiffness, restricted spinal mobility, and functional impairment [5]. Ochronotic spondyloarthropathy may mimic axial spondyloarthritis (axSpA), particularly in patients presenting with inflammatory-pattern back pain, creating a diagnostic challenge and potentially leading to misclassification and delayed diagnosis [6]. Characteristic spinal radiographic findings include extensive intervertebral disc calcification, disc-space narrowing, endplate sclerosis, and osteophyte formation, often without typical radiographic sacroiliitis [7]. However, intervertebral disc calcification is not specific to AKU and may also occur in other conditions, particularly calcium pyrophosphate deposition disease (CPPD), which represents an important differential diagnosis [8]. Auricular or scleral pigmentation and elevated urinary HGA provide additional diagnostic clues supporting AKU [9,10].

We report the case of a 42-year-old man presenting with severe axial pain and marked spinal restriction, initially raising suspicion of axSpA. Characteristic spinal radiographic abnormalities, absence of radiographic sacroiliitis, subtle auricular pigmentation, and markedly elevated urinary HGA supported the diagnosis of AKU with ochronotic spondyloarthropathy. This case highlights the diagnostic challenges of distinguishing ochronotic spondyloarthropathy from axSpA and emphasises the importance of integrating clinical, radiological, and biochemical findings to facilitate timely diagnosis and appropriate management.

This case report was prepared in accordance with the CAse REport (CARE) guidelines [11].

Case Presentation

Patient information

A 42-year-old man, formerly employed as a construction worker in Oman for 12 years, presented with a 2.5-month history of progressively worsening low back pain, accompanied by marked difficulty walking during the five days preceding presentation. He had been well until approximately 2.5 months earlier, when he developed insidious-onset low back pain that gradually increased in severity.

The pain was dull and aching, moderate to severe in intensity, and predominantly localized to the lumbosacral region, with radiation to both buttocks and thighs. It persisted throughout the day and night and was more pronounced at night and in the early morning. Morning stiffness lasted approximately 15 minutes. Progressive axial pain and stiffness resulted in substantial functional limitation. He had been unemployed for two months because of pain and severe restriction of lumbar movement. During the five days preceding presentation, he required walking aids and physical assistance to ambulate.

There was no history of fever, night sweats, weight loss, ocular inflammation, peripheral joint swelling, dactylitis, or skin lesions. He denied gastrointestinal symptoms, dysentery, urethral discharge, and other genitourinary symptoms. He also denied bowel or bladder dysfunction, chest pain, dyspnea, or subjective neurological symptoms. There was no family history of similar symptoms or parental consanguinity.

Eight years before presentation, while working for a construction company in Oman, he had fallen from a single-storey building and sustained injuries to his back and upper limbs. He was managed conservatively and subsequently returned to Bangladesh. Over the following eight years, he experienced recurrent, self-limiting episodes of low back pain, for which he intermittently used oral and injectable nonsteroidal anti-inflammatory drugs (NSAIDs) without formal medical evaluation or diagnostic investigation.

Clinical findings

On examination, the patient appeared mildly ill and was of average build and nutritional status. His temperature was 99°F (37.2°C), pulse rate was 80 beats/min, respiratory rate was 15 breaths/min, and blood pressure was 95/65 mmHg.

No visible scleral pigmentation was observed; however, subtle bilateral bluish discoloration of the auricular cartilage was noted. Chest expansion was reduced to approximately 1.5 cm. Chest percussion was resonant, and auscultation revealed normal vesicular breath sounds.

Musculoskeletal examination revealed an antalgic gait with a left-sided limp. Upper-limb function was preserved, whereas muscle power in both lower limbs was graded as 4/5. Cervical spinal mobility was markedly restricted, with severe restriction of lumbar mobility in all planes.

Neurological examination revealed normal higher mental functions and speech, intact cranial nerves, preserved muscle bulk and tone, normal deep tendon reflexes, bilateral flexor plantar responses, and intact sensation. No other focal neurological abnormalities were identified.

The patient's urine darkened upon standing and became brown after 72 hours (Figure *1*).



FIGURE 1: Single urine specimen photographed after 72 hours of standing.

Sacroiliac joint examination and imaging findings

Bilateral sacroiliac joint provocation tests, including the flexion, abduction, and external rotation (FABER) test, Gaenslen's test, compression, distraction, and sacral thrust tests, elicited pain. The FABER test produced posterior pain. Schober's test was not performed because of the severe restriction of lumbar spinal mobility.

Anteroposterior and lateral lumbosacral spine radiographs demonstrated extensive intervertebral disc calcification, disc-space narrowing, endplate sclerosis, and osteophyte formation, suggestive of ochronotic spondyloarthropathy (Figures *2*, *3*).

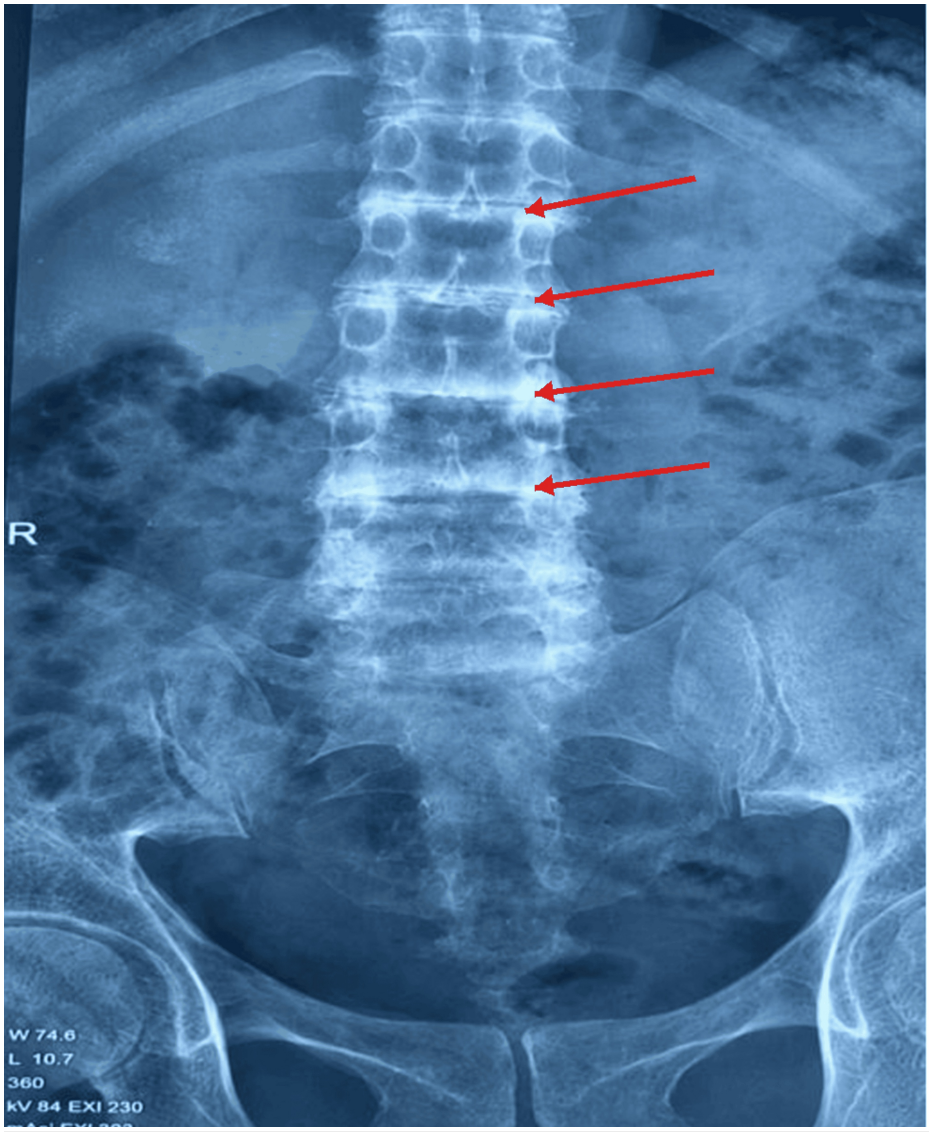


FIGURE 2: Anteroposterior lumbosacral spine radiograph

Anteroposterior radiograph of the lumbar spine showing characteristic wafer-like intervertebral disc calcifications, predominantly involving L1–L2 through L4–L5 (arrows), consistent with ochronotic spondyloarthropathy.

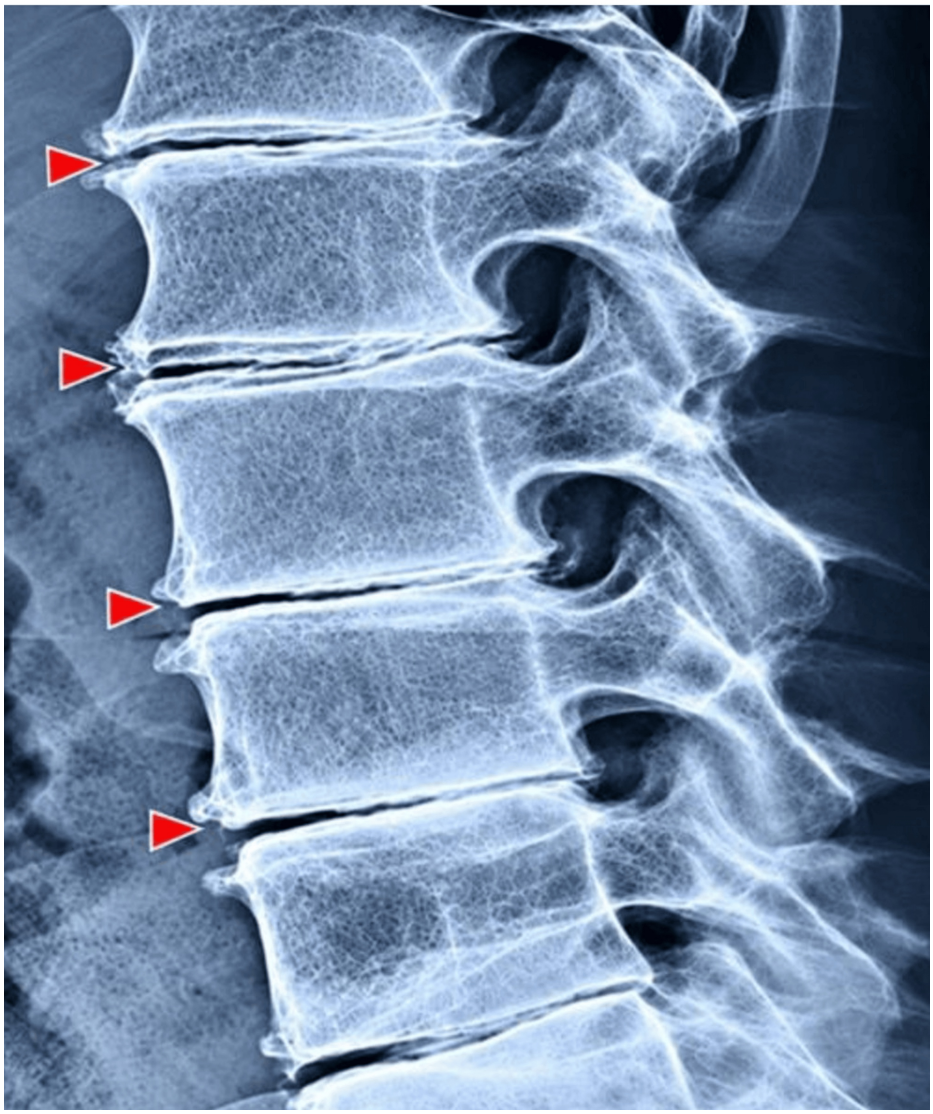


FIGURE 3: Lateral lumbosacral spine radiograph

The radiograph shows dense intervertebral disc calcification with associated disc-space narrowing and degenerative endplate changes, consistent with ochronotic spondyloarthropathy. Red arrowheads indicate disc calcification.

No radiographic evidence of sacroiliitis was identified. Whole-spine MRI screening demonstrated relatively preserved intervertebral disc signal and height in the T11-L3 region, with marked disc desiccation and loss of disc height at L4-L5. Associated vertebral endplate degenerative changes and anterior marginal osteophyte formation were also observed (Figure *4*).

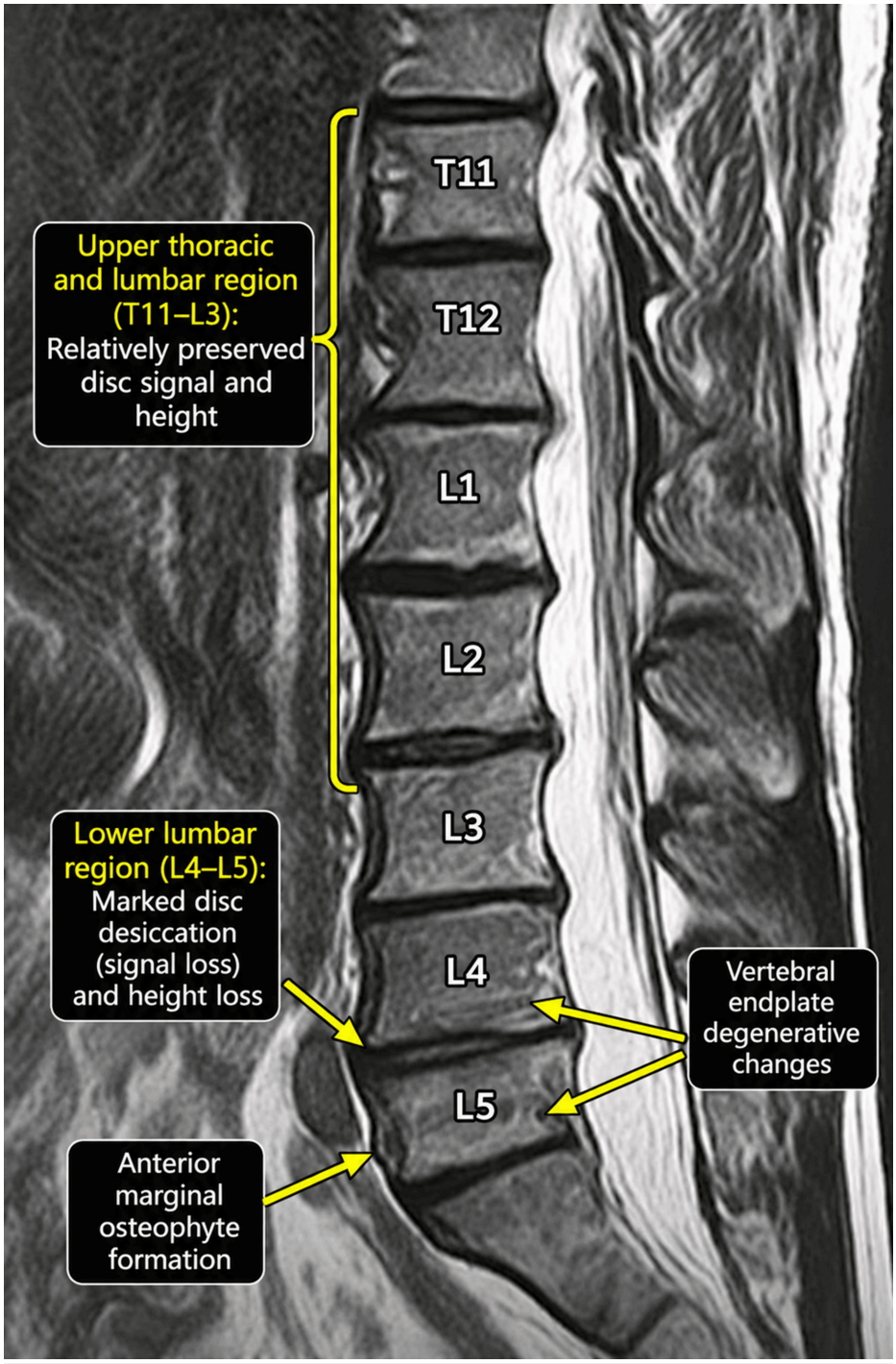


FIGURE 4: Sagittal MRI of the thoraco-lumbar spine T2 image sagittal view

Sagittal MRI of the thoracolumbar and lumbar spine demonstrates relatively preserved intervertebral disc signal and height in the upper thoracic and lumbar regions (T11–L3), with marked disc desiccation and loss of disc height at L4–L5. Associated vertebral endplate degenerative changes and anterior marginal osteophyte formation are also evident (yellow arrows).

No radiographic evidence of sacroiliitis was identified. Whole-spine MRI screening demonstrated relatively preserved intervertebral disc signal and height in the T11-L3 region, with marked disc desiccation and loss of disc height at L4-L5. Associated vertebral endplate degenerative changes and anterior marginal osteophyte formation were also observed (Figure *4*).

Table *1* summarises vital signs, clinical measurements, laboratory investigations, and imaging findings. Table *2* presents the clinical course chronologically.

Parameter/investigation	Patient result	Reference range/expected result	Interpretation
Vital signs and clinical measurements	-	-	-
Body temperature	37.2 °C (99 °F)	36.1-37.2 °C	Within the usual range
Pulse rate	80 beats/min	60-100 beats/min	Within the usual range
Respiratory rate	15 breaths/min	12-20 breaths/min	Within the usual range
Blood pressure	95/65 mmHg	120/80 mm Hg	-
Chest expansion	1.5 cm	2.5-5 cm	Reduced
Modified Schober test	Not performed because of severe lumbar movement restriction and pain	5 cm or more	Not assessed
Cervical flexion	45°	40°-80°	Within the normal range
Cervical extension	40°	50°-85°	Restricted
Cervical lateral flexion	45°	Approximately 45°	Within the normal range
Cervical rotation	70° bilaterally	80°-90°	Restricted
Lower-limb muscle power	4/5 bilaterally	5/5	Reduced
Laboratory investigations	-	-	-
Hemoglobin	16.0 g/dL	13.0-17.0 g/dL	Within the normal range
Total leukocyte count	10,000 cells/mm³	4,000-11,000 cells/mm³	Within the normal range
Erythrocyte sedimentation rate (ESR)	3 mm/hour	0-15 mm/hour	Not elevated
C-reactive protein (CRP)	5.23 mg/L	Less than 5 mg/L	Slightly elevated
Serum creatinine	1.08 mg/dL	0.7-1.3 mg/dL	Within the normal range
Alanine aminotransferase (ALT)	13 U/L	7-40 U/L	Within the normal range
Hepatitis B surface antigen (HBsAg)	Negative	Negative	Negative
Anti-hepatitis C virus antibody (anti-HCV)	Negative	Negative	Negative
Interferon-gamma release assay (IGRA)	Negative	Negative	Negative
Human leukocyte antigen-B27 (HLA-B27)	Negative	Negative	Negative
Serum calcium	2.52 mmol/L	2.15-2.55 mmol/L	Within the stated range
Serum phosphate	0.90 mmol/L	0.81-1.45 mmol/L	Within the stated range
Alkaline phosphatase (ALP)	78 U/L	40-129 U/L	Within the stated range
Parathyroid hormone (PTH)	17.70 pg/mL	15-65 pg/mL	Within the stated range
Urine dipstick	No protein detected	Negative for protein	No protein detected
Routine urine microscopy	Normal	No significant abnormality	No abnormality reported
Urinary homogentisic acid (HGA), assessed by gas chromatography with total ion chromatogram analysis of urinary metabolites	833.40%	Less than 0.99%	Markedly elevated according to the laboratory-reported

			measurement
Imaging investigations	-	-	-
Sacroiliac joint radiography	No radiographic sacroiliitis	Not applicable	No radiographic evidence of sacroiliitis
Lumbosacral spine radiography	Extensive intervertebral disc calcification, disc-space narrowing, sclerosis, and osteophyte formation	Not applicable	Findings compatible with ochronotic spondyloarthropathy
Whole-spine MRI screening	Disc-space narrowing, degenerative changes, and osteophyte formation	As described in the formal radiology report	Nonspecific findings

TABLE 1: Vital signs, clinical measurements, laboratory investigations, and imaging findings at presentation

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCS, Glasgow Coma Scale; HBsAg, hepatitis B surface antigen; HGA, homogentisic acid; HLA-B27, human leukocyte antigen-B27; IGRA, interferon-gamma release assay; MRI, magnetic resonance imaging; PTH, parathyroid hormone.

Time	Clinical event	Key findings
Eight years before presentation	Occupational trauma	Fall from a one-story building while working in construction in Oman, resulting in back and upper-limb injuries treated conservatively.
Eight years to 2.5 months before presentation	Recurrent low back pain	Intermittent, self-limiting episodes treated with oral and injectable nonsteroidal anti-inflammatory drugs (NSAIDs) without formal diagnostic evaluation.
2.5 months before presentation	Onset of current illness	Insidious-onset, progressively worsening low back pain radiating to both buttocks and thighs, accompanied by approximately 15 minutes of morning stiffness.
Five days before presentation	Acute functional deterioration	Worsening pain and stiffness with difficulty walking, requiring walking aids and physical assistance.
At presentation	Clinical examination	Marked cervical and lumbar spinal restriction, reduced chest expansion, antalgic gait with a left-sided limp, bilateral lower-limb muscle power graded as 4/5, positive bilateral sacroiliac joint provocation tests, and subtle bilateral auricular cartilage pigmentation.

TABLE 2: Clinical timeline of the patient's presentation

Clinical interpretation

The combination of extensive intervertebral disc calcification, disc-space narrowing, endplate sclerosis, osteophyte formation, subtle auricular pigmentation, and darkening of urine upon standing raised strong suspicion of AKU with ochronotic spondyloarthropathy. The reported urinary HGA result provided additional biochemical support, although the analytical meaning of its percentage-based unit requires laboratory verification.

The absence of radiographic sacroiliitis makes radiographic axSpA less likely but does not, in itself, exclude non-radiographic axSpA. Although the patient had advanced spinal changes, the sacroiliac joints appeared normal on plain radiographs. MRI of the sacroiliac joints was not performed, which limits the ability to definitively exclude non-radiographic axSpA. Nevertheless, the characteristic spinal radiographic abnormalities, together with the clinical findings, favoured ochronotic spondyloarthropathy as the more likely explanation for the patient's presentation.

Molecular genetic confirmation was not available. Therefore, the diagnosis was based on the overall clinical, radiological, and reported biochemical findings.

Discussion

AKU is a rare autosomal recessive metabolic disorder caused by deficiency of homogentisate 1,2-dioxygenase, resulting in the accumulation of HGA and its oxidation products. Progressive deposition of ochronotic pigment in connective tissues causes characteristic pigmentation and degenerative changes in the spine and large joints [1-4]. Ochronotic spondyloarthropathy may remain unrecognised for years and can closely mimic axSpA, particularly in patients presenting with chronic back pain, morning stiffness, restricted spinal mobility, and functional impairment [6,10,12,13]. This case illustrates the diagnostic challenge of distinguishing these conditions in a patient presenting with severe axial pain and substantial functional limitation.

The spinal radiographic findings were particularly important in directing the diagnostic assessment. Extensive intervertebral disc calcification, often accompanied by disc-space narrowing, endplate sclerosis, and osteophyte formation, may be observed in ochronotic spondyloarthropathy [4,7,10,14]. In contrast, axSpA is primarily characterised by inflammatory changes involving the sacroiliac joints and spine, including sacroiliitis, vertebral corner inflammatory lesions, and, in advanced disease, syndesmophyte formation [6,15]. Although the absence of radiographic sacroiliitis does not exclude early or non-radiographic axSpA, the combination of extensive disc calcification and degenerative changes strongly favoured ochronotic spondyloarthropathy in this patient. Nevertheless, intervertebral disc calcification is not pathognomonic for AKU and may also occur in other conditions, including degenerative disc disease, diffuse idiopathic skeletal hyperostosis (DISH), and CPPD, all of which should be considered in the differential diagnosis [8]. Therefore, imaging findings should be interpreted alongside clinical and biochemical features.

The clinical presentation initially raised suspicion of axSpA. Inflammatory-pattern back pain, morning stiffness, nocturnal symptoms, and restricted spinal mobility are common features of axSpA but are not specific to this condition. Furthermore, positive sacroiliac joint (SIJ) provocation tests indicated reproduction of pain in the SIJ region but did not establish inflammatory sacroiliitis. Such tests have limited ability to confirm SIJ-mediated pain and should not be interpreted as evidence of inflammatory sacroiliitis in isolation [16]. Similarly, negative HLA-B27 testing and inflammatory marker results cannot independently exclude axSpA [15]. In this patient, the erythrocyte sedimentation rate was 3 mm/hour, while the C-reactive protein (CRP) level was slightly elevated at 5.23 mg/L relative to the laboratory reference limit of less than 5 mg/L. Therefore, the diagnostic conclusion was based on the overall clinical and radiological pattern rather than any single clinical, laboratory, or imaging finding.

A particularly valuable diagnostic clue was the subtle bluish discoloration of the auricular cartilage. Ochronotic pigmentation commonly affects connective tissues, including the ear cartilage and sclera, although its clinical recognition may be difficult in the early stages [1,3,4]. In this patient, the absence of obvious scleral pigmentation did not exclude AKU, as the auricular findings provided an additional clinical clue. The history of urine darkening on standing, with brown discoloration after 72 hours, further supported the clinical suspicion. Urinary HGA measurement is an important biochemical investigation for AKU, and liquid chromatography-tandem mass spectrometry provides a reliable analytical method for its quantification [17]. In the present case, gas chromatography-mass spectrometry (GC-MS) analysis of a spot urine sample yielded a laboratory-reported HGA value of 833.40% (reference value: less than 0.99%). However, because this percentage-based reporting format is non-standard, the result requires clarification regarding its analytical meaning and the assay-specific reference interval. Accordingly, the reported value should be interpreted cautiously until the original laboratory report and reporting methodology have been verified.

The distinction between ochronotic spondyloarthropathy and axSpA is particularly important in patients with a history of trauma. This patient reported a significant fall approximately eight years before presentation, followed by recurrent episodes of back pain. Although previous trauma may have contributed to musculoskeletal symptoms, it does not adequately explain the characteristic pattern of extensive intervertebral disc calcification and the associated clinical features of ochronosis. The combination of spinal imaging abnormalities, auricular pigmentation, and urine darkening therefore provided a more coherent explanation than trauma alone and made AKU an important alternative diagnosis to axSpA [6,7,10,12-15]. Nevertheless, HGD genetic testing was not performed; therefore, molecular confirmation was unavailable in this case [18].

Management of AKU is challenging because treatment aims to reduce HGA production, manage musculoskeletal complications, and preserve functional ability. Nitisinone inhibits 4-hydroxyphenylpyruvate dioxygenase, an upstream enzyme in the tyrosine degradation pathway, thereby reducing HGA production [1,9]. The SONIA 2 trial demonstrated substantial biochemical reduction in HGA with nitisinone treatment, although the relationship between biochemical improvement and clinical outcomes requires careful interpretation [19]. A separate three-year randomised trial evaluated longer-term nitisinone treatment, while observational data from the UK National Alkaptonuria Centre provided additional information on disease progression [20,21]. A recent systematic review further assessed the efficacy and safety of nitisinone in patients with AKU [22]. Despite these findings, treatment-related considerations, including dietary management, monitoring of tyrosine concentrations, potential adverse

effects, treatment accessibility, and long-term follow-up, remain important [1,8,9]. In the present case, nitisinone was recommended but could not be initiated because of limited access to treatment in Bangladesh. Consequently, no treatment response or therapeutic outcome could be assessed.

Management should also include appropriate symptomatic treatment, physiotherapy, maintenance of mobility, and monitoring for progressive spinal and large-joint complications. A multidisciplinary approach involving rheumatology, metabolic medicine, orthopaedics, physiotherapy, and other relevant specialties may help address the diverse manifestations of AKU [1,8,9]. Early recognition is important to facilitate appropriate metabolic assessment, counselling, and long-term management.

This report has several limitations. First, HGD sequencing was not performed; therefore, molecular confirmation of AKU was unavailable. Second, the urinary HGA result requires verification against the original laboratory report, including clarification of its percentage-based reporting format and assay-specific reference interval. Third, nitisinone treatment could not be initiated because of limited accessibility, preventing assessment of therapeutic response. Finally, the absence of longitudinal follow-up prevented evaluation of subsequent disease progression and functional outcomes.

This case highlights the importance of considering AKU in patients presenting with severe axial pain and restricted spinal mobility, particularly when extensive intervertebral disc calcification occurs without definite radiographic sacroiliitis. Recognition of subtle ochronotic pigmentation and urine darkening on standing, together with appropriate biochemical investigations, may facilitate timely diagnosis. Early recognition and multidisciplinary management are essential to address the musculoskeletal complications and long-term consequences of this rare metabolic disorder.

Conclusions

AKU should be considered in patients presenting with severe axial pain and restricted spinal mobility when radiographs demonstrate extensive intervertebral disc calcification, particularly in the absence of typical radiographic sacroiliitis. Subtle ochronotic pigmentation and urine darkening on standing are important diagnostic clues, while urinary HGA measurement can provide important biochemical evidence supporting the diagnosis. Although molecular genetic testing of the HGD gene is valuable for confirming the diagnosis, AKU can be diagnosed based on characteristic clinical and biochemical findings, even without genetic confirmation. Recognising this clinicoradiological pattern may help prevent misdiagnosis of ochronotic spondyloarthropathy as axSpA and support timely diagnosis and appropriate long-term multidisciplinary management.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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