Judi Clinical Journal | 2025;1(2):118-121
Journal home page: https://judijournal.com

Case Report

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Late-Onset Alkaptonuria in an Elderly Male: A Case Report and Literature Review

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Received: *Aug 21, 2025* ***Revised:*** *Oct 07, 2025* ***Accepted:*** *Nov 10, 2025* ***First Published:*** *Nov 24, 2025*

Introduction: Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder caused by homogentisate 1,2-dioxygenase deficiency, leading to homogentisic acid accumulation. While AKU typically presents in children and young adults, this report aims to present an unusual late-onset presentation of AKU in an elderly male.

Case Presentation: A 65-year-old male presented with 20 years of black skin discoloration and chronic knee and pelvic pain. Despite early signs, including dark-colored urine, the condition was repeatedly misdiagnosed as melasma and primary osteoarthritis. Computed tomography scan revealed vertebral ankylosis and sacroiliac arthritis, and histopathological examination confirmed ochronotic pigment deposition. Due to financial constraints, the patient declined joint replacement surgery and was managed with diclofenac 100 mg twice daily and dietary restrictions.

Literature Review: Among six case reports of AKU reviewed in the literature, selected with a focus on misdiagnosis or delayed diagnosis, the majority of cases (3/6, 50%) occurred in the 8th–9th decades of life. Although AKU affects both sexes equally, five of the six reviewed cases (83.3%) were male.

Conclusion: This case highlights the unusual late-onset AKU and the risk of prolonged misdiagnosis, emphasizing the importance of early recognition and multidisciplinary management.

Keywords: Alkaptonuria, Ochronosis, Homogentisic acid, Metabolic disorder, Osteoarthritis

How to cite this article: Ahmed RS, Siddiq SO, Mustafa LJ, Ali RM, Jalal RB, Hussein OM et al. Late-Onset Alkaptonuria in an Elderly Male: A Case Report and Literature Review. Judi Clin. J. 2025;1(2):118-121. https://doi.org/10.70955/JCJ.2025.14

1. Introduction

Alkaptonuria (AKU) is a rare, autosomal recessive metabolic disorder, with an estimated prevalence ranging from 1 in 200,000-1,000,000 live births worldwide [1,2].

The primary risk factor for AKU is having two copies of the affected homogentisate 1,2-dioxygenase (HGD) gene, which requires both parents to be carriers of mutations in the HGD gene. Consanguineous marriages significantly increase the risk of AKU due to the higher probability of both parents carrying the same recessive gene inherited from a common ancestor. This is particularly evident in certain populations where consanguinity is more common, such as in Slovakia and the Dominican Republic, which have higher prevalences of AKU (1 in 19,000) compared to the global average [3].

It is caused by a deficiency of the enzyme HGD, primarily produced by liver and kidney parenchymal cells. HGD is responsible for converting homogentisic acid (HGA) into maleylacetoacetic acid as part of the tyrosine degradation pathway [1]. As a result, HGA accumulates in the body and is excreted in urine, which causes the urine to turn dark brown or black upon exposure to oxygen and alkalinization. This characteristic change in urine color can occur early in the disease, but it may not be immediately noticeable. Fresh urine often appears normal, and it may take several hours after voiding for the color change to develop [2,4].

There are three main manifestations of this condition: the presence of HGA in the urine, ochronosis (the deposition of HGA in connective tissue and cartilage), and spondyloarthropathy affecting both the axial and appendicular skeleton, particularly arthritis of the spine and large joints [2].

Although AKU is typically diagnosed in children and young adults, this report describes a rare case identified in a 65-year-old male. The case is structured according to the CaReL guidelines [5]. All references used in the report have been evaluated for eligibility [6].

2. Case Presentation

2.1. Patient Information

A 65-year-old male presented with black discoloration on his face and body, which had been present for 20 years, along with bilateral knee pain and pelvic pain. Medical attention was sought primarily for persistent knee pain. The patient lived in a remote district with limited access to specialized medical services. Although he had sought consultations previously for his lifelong history of dark urine, no definitive diagnosis had been made. His condition was repeatedly misdiagnosed, with the skin pigmentation attributed to melasma and post-inflammatory hyperpigmentation, while the bilateral knee and pelvic pain was considered primary osteoarthritis. He was not born to a consanguineous marriage. His past medical history was notable only for the presence of dark urine since birth. He had previously undergone a total right knee replacement. A positive family history was reported, with his brother and cousin affected by the same condition.

2.2. Clinical Findings

The patient's vital signs were normal. The examination revealed blue-black pigmentation on the face, the dorsum of the hands, and the feet (sun-exposed areas). The lesions also involved the sclera (Osler's sign) and the ear cartilage (Figure 1). On musculoskeletal examination, the patient had a fixed flexion deformity of both knees and reduced range of motion in both hips. Further examination could not be performed due to severe pain.

Figure 1. A) Extensive blue-black pigmentation of the face, especially in the nose and periorbital region, with visible scleral involvement (Osler's sign) (white arrow) and pigmentation of the external ear (blue arrow). **B)** Diffuse hyperpigmentation and bluish discoloration of the dorsal aspects of both hands

2.3. Diagnostic Assessment

Rheumatoid factors (IgM, IgG), anti-cyclic citrullinated peptide, and uric acid were normal. Computed Tomography (CT) scan revealed vertebral ankylosis, sacroiliac joint arthritis, and diffuse osteopenia, which were consistent with AKU-related ochronotic osteoarthritis (Figure 2). The patient underwent a facial skin punch biopsy. The histopathologic examination revealed deposition of round and elongated yellow-brown material in the dermis, accompanied by surrounding fibrosis and basophilic degeneration of collagen. Based on these findings, the diagnosis of ochronosis was confirmed (Figure 3). The delayed diagnosis was due to the lack of correlation between the skin pigmentation and musculoskeletal symptoms.

2.4. Therapeutic Intervention

Total knee and bilateral hip replacement was planned, but the patient refused the procedure due to financial constraints. Instead, he was prescribed diclofenac 100 mg twice daily to manage his severe pain. He was recommended to avoid sun exposure to prevent further skin pigmentation. A dietary restriction of foods rich in phenylalanine, tyrosine, and protein was also advised.

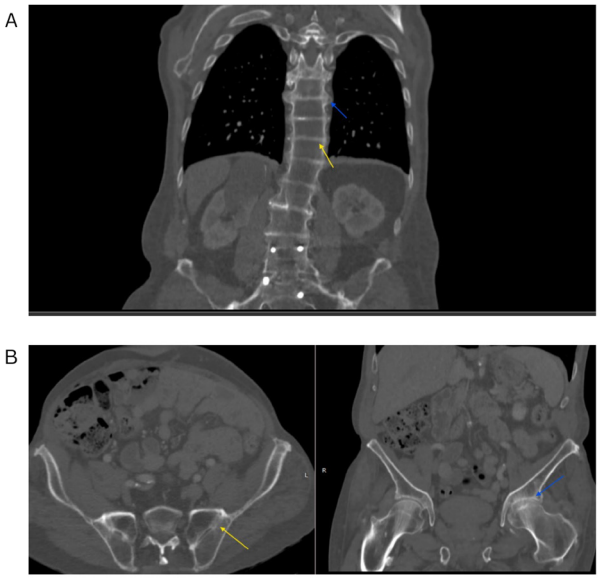

Figure 2. A) Coronal CT image of the abdomen with IV contrast showing diffuse osteoporosis, multilevel disc calcification and disc space narrowing (yellow arrows), syndesmophyte formation at multiple levels (blue arrows), and scoliosis. **B)** Axial and coronal CT images of the abdomen with IV contrast demonstrating bilateral sacroiliac joint space narrowing and ankylosis (yellow arrows), along with features of hip osteoarthritis (blue arrows).

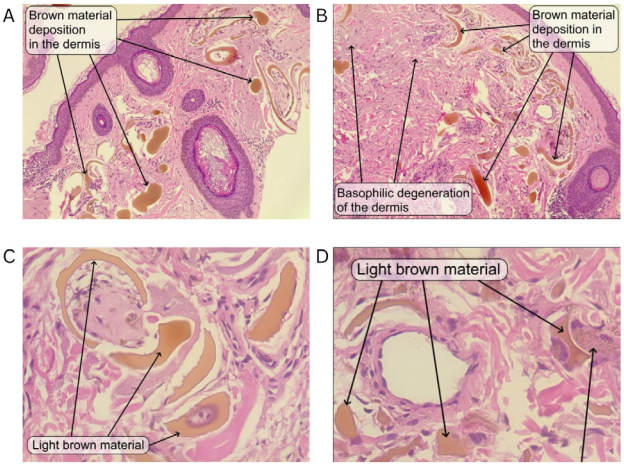

Figure 3. A-D) There is deposition of a light brown material in the dermis of the skin with surrounding basophilic degeneration, fibrosis, and focal reaction by histiocytes and giant cells with cytoplasmic pigment. [Hematoxylin and eosin stain; Original magnification x 100 (**A and B**), x 400 (**C and D**)].

2.5. Follow-up

Regular follow-ups with an orthopedist, cardiologist, and ophthalmologist were recommended for comprehensive monitoring for related complications. The cardiologist performed an echocardio-

gram, which revealed mitral regurgitation, tricuspid regurgitation, a small ventricular septal defect, and mild pulmonary hypertension. Since the condition was stable, follow-up appointments were advised every three months to ensure early detection of any progression or complications.

3. Discussion

In the AKU, patients are frequently misdiagnosed with spondyloarthritis or other degenerative musculoskeletal diseases [7]. This systemic condition can impact connective tissues and joints, potentially leading to complications such as cardiac valvular disease and kidney stones [1].

The literature review of six case reports of AKU presenting with joint pain showed that most cases were either diagnosed late or initially misdiagnosed [1,7-11] (Table 1). In most cases, the condition was identified in the fourth or fifth decade of life [11]. Although AKU is an autosomal recessive disorder that affects both sexes equally [8], some studies suggest that males may develop more severe symptoms [2,9]. In contrast, the current literature review Showed that five of the six reported AKU cases involved male patients, and the majority (3/6, 50%) occurred in the 8th–9th decades of life [1,7-11].

In patients with AKU, the urine appears normal but gradually darkens over time due to the oxidation and polymerization of HGA. However, diagnosis is often delayed until adulthood when symptoms such as arthritis or ochronosis develop, as acidic urine may not darken even after prolonged exposure to air [12]. According to the literature, AKU is frequently misdiagnosed or identified late, with ankylosing spondylitis being a common initial misdiagnosis. Although the patient exhibited early signs, such as darkened urine, a definitive diagnosis was not made until ochronosis became evident [1,9].

Multiple case reports have documented ochronosis in patients with AKU, making it an important diagnostic indicator [1]. However, misdiagnosis of ochronosis-related symptoms as other degenerative conditions remains a common challenge [1]. For instance, and Kumar Upadhyaya reported a case in which a 38-year-old male was initially treated for ankylosing spondylitis before ultimately being diagnosed with ochronosis [7]. In the present case, ochronotic pigmentation persisted for 20 years with bilateral knee and pelvic pain but was repeatedly misdiagnosed despite multiple consultations. While early detection of ochronosis can facilitate the diagnosis of AKU, many cases experience delays due to its rarity and overlapping clinical features with other musculoskeletal disorders such as ankylosing spondylitis [7, 8].

The hereditary nature of AKU has been well-documented through various case reports, highlighting its strong genetic component. Gundersen et al. and Tseliou et al. reported cases highlighting the genetic influence on disease manifestation through siblings with similar symptoms [1,10]. The present case also provides evidence for this hereditary pattern. However, in some cases, no family history of the disease has been reported [7]. This variability complicates early diagnosis, especially when the carrier status is unknown. Despite being a genetically inherited disorder, AKU frequently goes undiagnosed or misdiagnosed due to its rarity and the wide range of clinical manifestations [1,8].

The gold-standard test for confirmation is detecting HGA in a 24-hour urine sample using gas chromatography-mass spectrometry [7]. Genetic analysis of mutations in the HGD gene also aids in diagnosis and family counseling. In low-income countries, simpler biochemical tests may be used when GC-MS or genetic testing is unavailable [8]. In this case, most laboratory tests, including rheumatoid factors (IgM, IgG) and uric acid, were within normal ranges, indicating that inflammatory and metabolic markers may remain unchanged in AKU. Radiographic imaging helps confirm the diagnosis by revealing characteristic skeletal changes, such as joint space narrowing, osteoporosis, osteophytosis, and vertebral calcifications [9]. The CT scan in this case identified vertebral ankylosis, sacroiliac joint arthritis, and diffuse osteopenia, consistent with ochronotic osteoarthritis. These findings underscore the crucial role of imaging in diagnosing AKU and differentiating it from other forms of arthritis [4]. A skin biopsy can serve as a diagnostic tool for AKU by detecting ochronotic pigment deposition in collagen-containing tissues. This method can confirm diagnosis even in cases with limited clinical history [13]. In this case, ochronosis was confirmed through histopathological examination.

Although AKU does not reduce life expectancy, it significantly impacts quality of life. Currently, no curative treatment exists, and management focuses on alleviating symptoms. Nonsteroidal anti-inflammatory drugs and physiotherapy help relieve arthropathies, while surgery may be necessary in severe cases. Dietary restrictions on tyrosine- and phenylalanine-rich foods, such as dairy products, eggs, soy, nuts, and meat, offer limited benefits [8]. High-dose vitamin C (1 g/day) has mild antioxidant properties that may slow HGA deposition in cartilage, but its effectiveness remains minimal. In this case, the patient required total knee and bilateral hip replacements but declined the procedure due to its high cost. Instead, a restricted diet low in phenylalanine, tyrosine, and protein was recommended. Despite these strategies, no definitive treatment is available, highlighting the need for further research [9].

This case report is limited by two limitations:: the lack of availability of nitisinone, which precluded its therapeutic application, and the inability to quantify HGA levels due to the unavailability of the requisite diagnostic infrastructure.

Table 1. Summary of Six Reported Cases of Alkaptonuria

Author (Year)	Gender	Age (Y)	Misdiagnosis or Delay	Hereditary/ Family History	Ochronosis	Treatment
Tseliou et al. (2018) [1]	Male	81	Misdiagnosed as Ankylosing Spondylitis	Yes	Yes	Analgesics, Vitamin C, Diet
Shah and Kumar (2024) [7]	Male	38	Misdiagnosed as ankylosing spondylitis	N/A	Yes	Physiotherapy, Palliative
Singh et al. (2023) [8]	Female	80	Late Diagnosis	N/A	Yes	Vitamin C
Gupta et al. (2021) [9]	Male	58	Misdiagnosis	N/A	Yes	Vitamin C, Diet
Gundersen et al. (2024) [10]	Male	70s	Delayed Diagnosis	Yes	Yes	Nitisinone, Diet
Sharma et al. (2015) [11]	Male	6	None (early detection)	No	No	Vitamin C

***Y:** Years, **N/A:** Not available*

4. Conclusion

This case highlights the unusual late-onset presentation of alkaptonuria and underscores the potential for prolonged misdiagnosis. Although no curative treatment is available, early recognition and multidisciplinary management are essential for improving patient outcomes and preventing complications.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethical approval: Not applicable.

Consent for participation: Not applicable.

Consent for publication: Written informed consent for publication was obtained from the patient.

Funding: The present study received no financial support.

Acknowledgments: None to be declared.

Authors' contributions: RSA, SOS, SFA, LJM, SMM and RMA: Major contributors to the conception of the study, as well as the literature search for related studies, and manuscript writing.RBJ, OMH, SKA, AKG and LAS: Literature review, critical revision of the manuscript, and processing of the figures. All authors have read and approved the final version of the manuscript.

Use of AI: ChatGPT-4.5 was used to assist with language refinement and improve the overall clarity of the manuscript. All content was thoroughly reviewed and approved by the authors, who bear full responsibility for the final version.

Data availability statement: Not applicable.

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