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Cervical Myelopathy Due to Ochronosis: An Intraoperative Suspicion

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Statistical Analysis C
Data Interpretation D
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Patient: Female, 55-year-old
Final Diagnosis: Alkaptonuria
Symptoms: Neck pain
Medication: —
Clinical Procedure: —
Specialty: Neurosurgery • Orthopedics and Traumatology

Objective: Rare disease

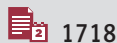
Background: Alkaptonuria (AKU) is a rare metabolic disease caused by a deficiency in homogentisic acid oxidase, which leads to the accumulation of homogentisic acid dark pigments in tissues such as bones, ligaments, and tendons. Long-term duration of this condition, termed ochronosis, can result in degenerative arthropathy involving the spine and large joints.

Case Report: This report describes a 55-year-old Jordanian woman presenting with chronic neck and lower back pain. History, physical examination, and radiological imaging indicated cervical myelopathy and lumbar spine degeneration. Two-level anterior cervical discectomy and fusion was performed successfully. Intra-operatively, the cervical discs were observed to be black, suggesting a diagnosis of alkaptonuria, which was later confirmed by genetic testing. A detailed history and physical examination revealed the absence of classical features of AKU.

Conclusions: Intraoperative detection of black disc material suggests the need for further tests to diagnose AKU, especially in indolent patients who did not have classical clinical features. Surgical management may improve outcomes in patients with cervical myelopathy due to ochronosis.

MeSH Keywords: Alkaptonuria • Neck Pain • Ochronosis

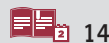
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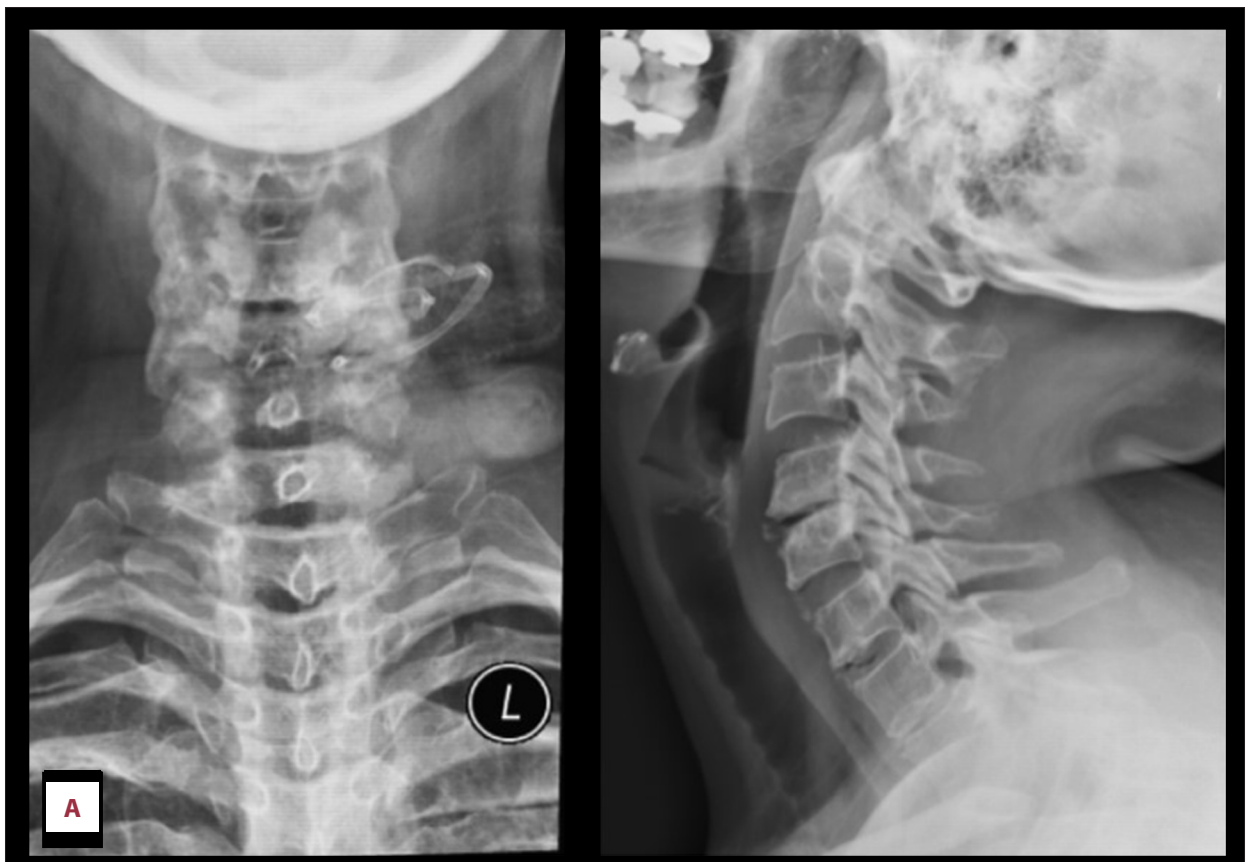
Background

Alkaptonuria (AKU) is a rare hereditary metabolic disorder and the first human disorder to adhere to the Mendelian principles of autosomal recessive inheritance [1]. Current estimates suggest that the incidence of AKU ranges from 1: 250 000 to 1: 1 000 000 live births [2]. AKU is caused by mutations in the homogentisate 1,2-dioxygenase (*HGD*) gene, with 1031 different *HGD* variants currently identified [3]. These mutations lead to a metabolic block, with consequent accumulation of homogentisic acid (HGA). The typical initial presenting sign of AKU during childhood is the presence of black urine due to renal excretion in urine of large amounts of HGA, which turns black upon exposure to free air. HGA that is not eliminated through the kidneys is deposited in various connective tissues as a dark ochronotic pigment. As patients with AKU approach the third decade of life, they usually start to experience severe arthropathy. Nonetheless, clinical manifestations and disease severity vary considerably among affected individuals. The classical presentation of patients with AKU includes black urine and dark pigmentation of the skin, sclerae, and ear pinnae. Many patients, however, do not have all of these features. In addition to the involvement of large joints, such as the knees and hips, the spine is one of the most common areas of the musculoskeletal system in which ochronotic pigment is deposited,

leading to a condition called ochronotic spondyloarthropathy. Myelopathy is a very rare presentation, with a recent literature review finding that only 11 patients with AKU presented with myelopathy and only 5 with cervical myelopathy [4]. Few reports have described patients with lumbar disc herniation but no signs of AKU preoperatively who were diagnosed with AKU post-operatively after intraoperative findings of disc material with black discoloration [5–8]. To our knowledge, the patient described in this report is the first lacking classical clinical features of AKU who presented initially with cervical myelopathy and was later diagnosed with AKU after intraoperative finding of black disc material.

Case Report

A 55-year-old Jordanian housewife of Arab descent presented with a 6-year history of chronic low back pain. During the previous 2 years, she started experiencing neck pain that radiated to the radial aspect of both upper limbs, forearm and hand paresthesia of non-specific dermatomal distribution, and difficulty in fine-object handling. She had no symptoms of bowel or bladder dysfunction. Previous surgical history included uterine fibroid excision and incisional hernia mesh repair.



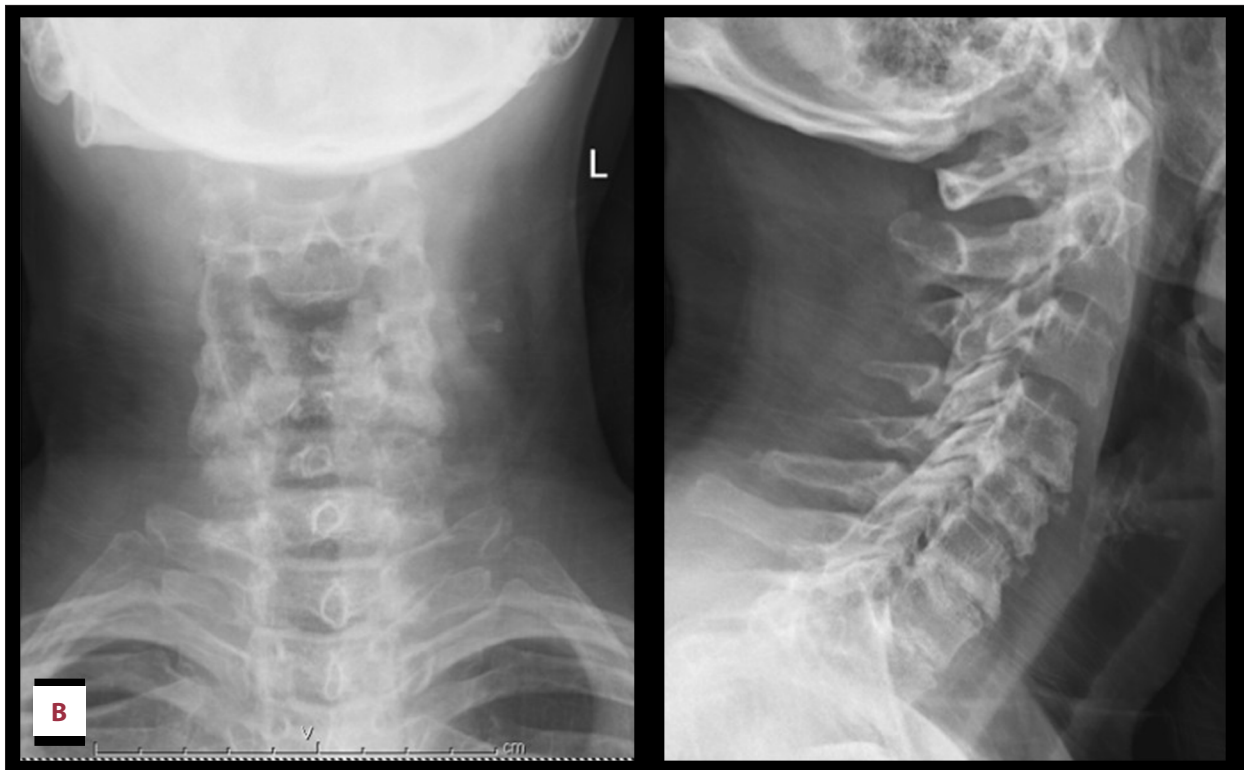


Figure 1. AP and lateral radiographic views of the cervical spine of our patient at her initial visit (A) and 2 years later (B).

Physical examination showed that her neck muscles were tender and stiff. Her cranial nerve was fully intact. Bilateral hypoesthesia with C5/C6 distribution was observed. Motor power examination using the Medical Research Council (MRC) Muscle Grading System showed 3/5 strength on the right side and 4/5 strength on the left side for hand grip, wrist flexion/extension, and elbow flexion/extension, and 5/5 strength for bilateral lower limb power.

The tone was spastic on both upper and lower limbs, with intact deep tendon reflexes. Hoffmann's sign and Babinski reflex were positive on both sides. The patient had a spastic gait and was negative for Romberg sign. Her preoperative Japanese Orthopaedic Association (JOA) score was 12.

Radiographs of the cervical spine showed calcifications and degenerative changes involving more than 1 level, evident loss of lordosis, and significant intervertebral joint space narrowing when compared with radiographs taken 2 years earlier (Figure 1A, 1B). Lumbar spine radiographs also showed reduced disc spaces with notable calcifications and loss of lordosis (Figure 2). Mid-sagittal T2 magnetic resonance imaging (MRI) of the cervical spine showed multiple level spinal cord compression with significant degenerative changes (Figure 3A), mainly at the C3/4 and C4/5 levels (Figure 3B, 3C).

Because conservative measures were unable to relieve this patient's symptoms, surgical treatment being the only remaining option. Anterior cervical microdiscectomy and fusion were performed using a standard approach. The sole unusual intraoperative finding was the black colored, stiff tissue material of the disc (Figure 4). The operation was completed routinely, with proper decompression and fusion at 2 levels (C3/4 and C4/5) using size 7 and size 4 cages (Cornerstone® PSR (Verte-Stack® PEEK Vertebral Body Spacers; Medtronic Sofamor Danek USA, Inc.), respectively (Figure 5). The patient's postoperative course was uneventful and she was discharged home 2 days later.

Because of a high clinical suspicion of AKU, samples of disc tissue were sent for histopathologic examination and a blood sample was taken for genetic testing. Genetic testing showed a homozygous variant (c.673C>T; p.Arg225Cys) of the *HGD* gene that was likely pathogenic, indicating that AKU in this patient was of genetic origin.

A detailed history and physical examination revealed absence of the classical findings of AKU, such as black colored urine (Figure 6A, 6B), black pigmentation of the underwear, and dark pigmentation of the sclerae, ear pinnae, and/or oral cavity (Figures 7–9). Her family history was unremarkable.

At a 3-month follow up visit, the patient reported significant improvements in neck pain, paresthesia, and functioning of

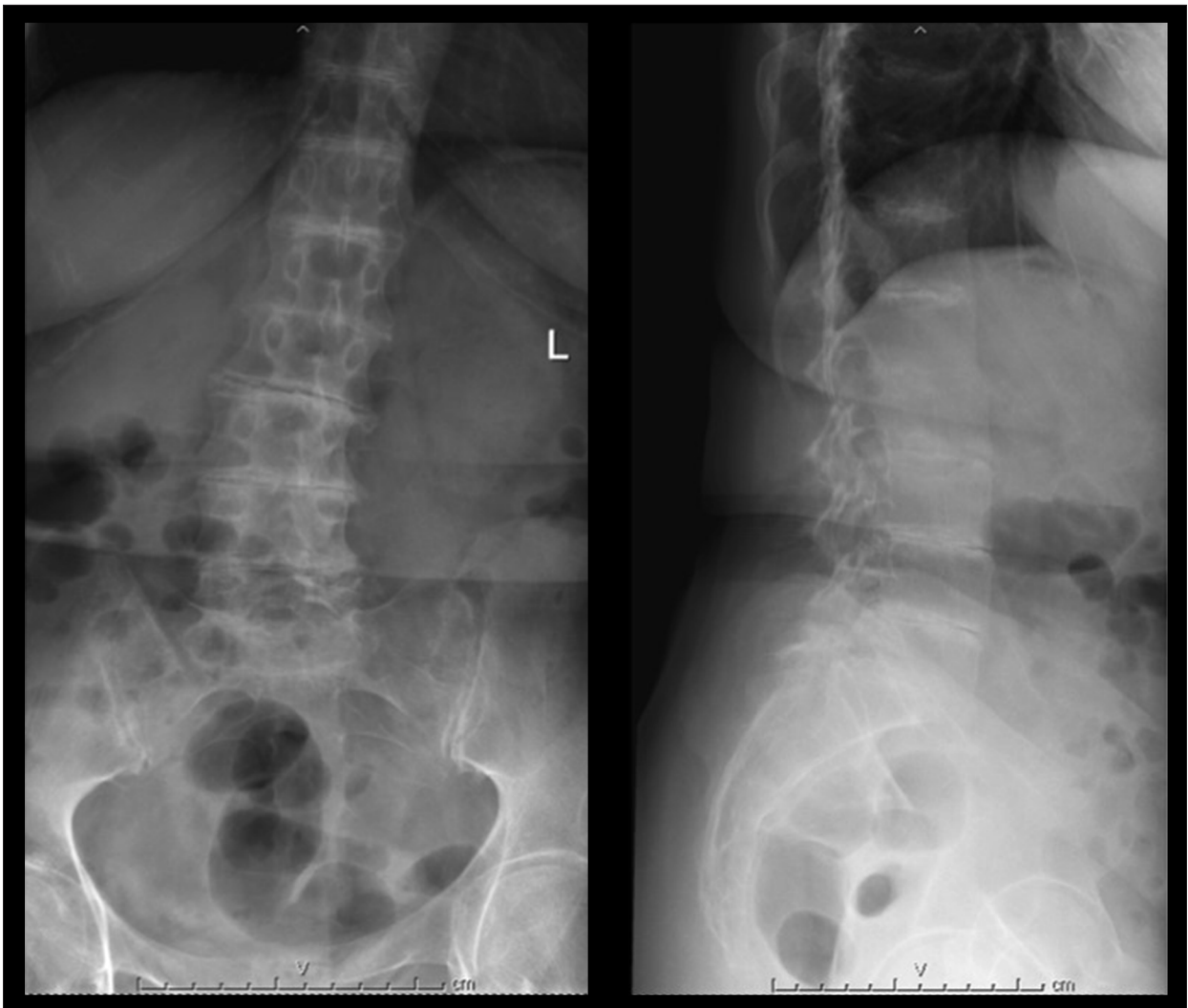


Figure 2. AP and lateral views of lumbar spine radiographs.

both hands, including fine-object maneuvering. Her JOA score was 16. The MRC muscle grading system showed 5/5 strength on both sides for hand grip, wrist flexion/extension, and elbow flexion/extension bilaterally, as well as 5/5 strength for bilateral lower limb muscle power. Hoffmann's sign and the Babinski reflex were resolved on both sides.

The patient provided written informed consent for publication of this study, thereby allowing the sharing of information and images.

Discussion

The incidence of AKU ranges from 1: 250 000 to 1: 1 000 000 live births. However, the prevalence of AKU in Jordan is likely underestimated, primarily because of the high rates of consanguineous marriage throughout the country [9]. North West

Slovakia is believed to have the highest global incidence of AKU, at 1: 19 000 live births [10].

The clinical presentation of AKU varies due to differences in the residual activity of the HGD enzyme. However, minor pigmentation of the sclerae is widely regarded as the earliest physical manifestation of ochronosis. With longstanding disease, ochronotic arthritis commonly develops. The spine is usually the first musculoskeletal site to be affected by ochronosis, with degenerative changes in the spine being more notable in the lumbar region. Pathologically, however, this disease is characterized by diffuse calcification of the intervertebral discs [5]. In contrast, cervical spine involvement is quite rare in AKU.

Cervical myelopathy due to ochronosis is very rare in patients with AKU and usually presents later in the course of disease. As in our patient, the absence of the classic clinical features of AKU may delay the diagnosis of the primary disease that caused the



Figure 3. T2 MRI results in our patient. (A) Mid-sagittal T2 MRI of the cervical spine. (B) Sagittal and axial T2 MRI of the C3/4 level, showing large central disc protrusion compressing the thecal sac and spinal cord. (C) Sagittal and axial T2 MRI of the C4/5 level showing a large broad-based disc osteophyte complex compressing the thecal sac and narrowing both nerve root exit foramina.

myelopathy. In most patients, this myelopathy is falsely attributed to age-related degeneration. Some radiological features might aid in diagnosis, especially in the absence of typical findings, including involvement of multiple intervertebral levels, progressive calcification of the discs within a relatively short period of time, and the presence of large numbers of osteophytes [4].

Black discoloration of disc material that is first discovered intra-operatively can be considered a pathognomonic sign for AKU. This discoloration has been reported to be the leading sign for the diagnosis of AKU in several patients lacking the typical features of ochronosis [5–8]. To our knowledge, this patient is the first to present with signs of cervical myelopathy without evidence of the classical findings of ochronosis, with the black disc discoloration being the telltale sign. Ochronosis

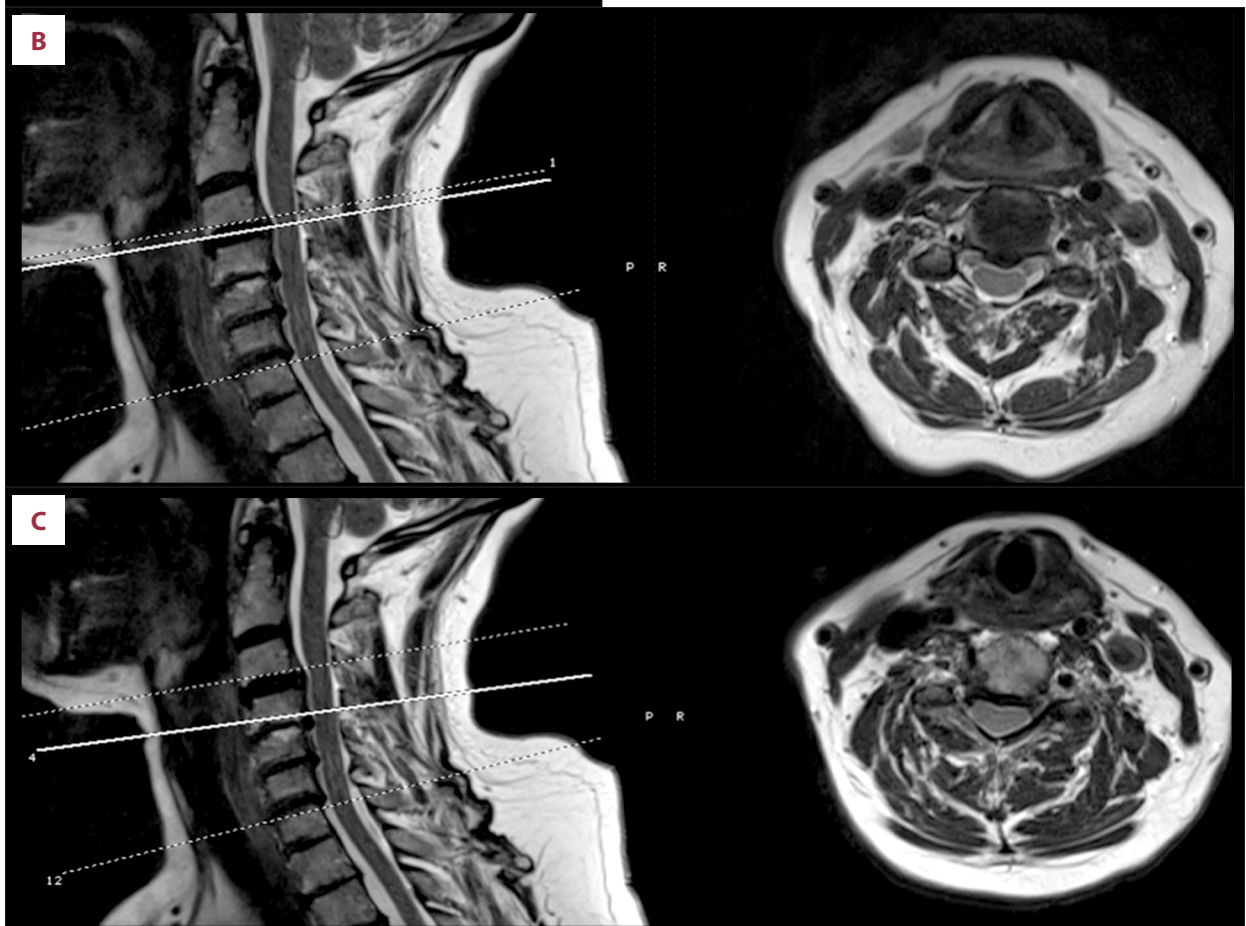




Figure 4. Intraoperative photograph showing the black colored disc.

should be suspected in patients with advanced degenerative changes in the spine at a relatively early age, the involvement of multiple intervertebral levels, progressive disease within a short period of time, and black disc discoloration.

Symptomatic treatment is the mainstay for patients with AKU due to the lack of curative measures. Nitisinone is becoming essential in AKU management, especially in patients with musculoskeletal disease. Nitisinone has been shown to reduce HGA concentrations in serum and urine. Although it may not be curative, it can decrease the rate of disease progression and arrest the ochronotic process [11,12]. Further studies are needed to explore the effect of combination therapy (surgery and nitisinone) on outcomes in patients with AKU. Surgery may include joint replacement in patients with large joint involvement or spinal decompression in patients with spine involvement.

Intraoperative findings of black disc material should suggest the need for further tests to diagnose AKU, especially in indolent patients. Proper diagnosis can lead to proper treatment (surgical/medical), reducing the rate of disease progression and preventing the involvement of other systems, including cardiovascular and renal systems.

Spine surgery to provide symptomatic relief is indicated in patients with spinal cord compression or degenerative disc disease. Different pathologies can lead to cervical myelopathy due to ochronosis, with these pathologies determining the surgical approach. Few articles to date have described the surgical management of patients with ochronotic cervical myelopathy. One case report described a patient with ochronotic cervical myelopathy caused by pannus formation at the atlantoaxial joint, which was treated surgically with decompression and posterior

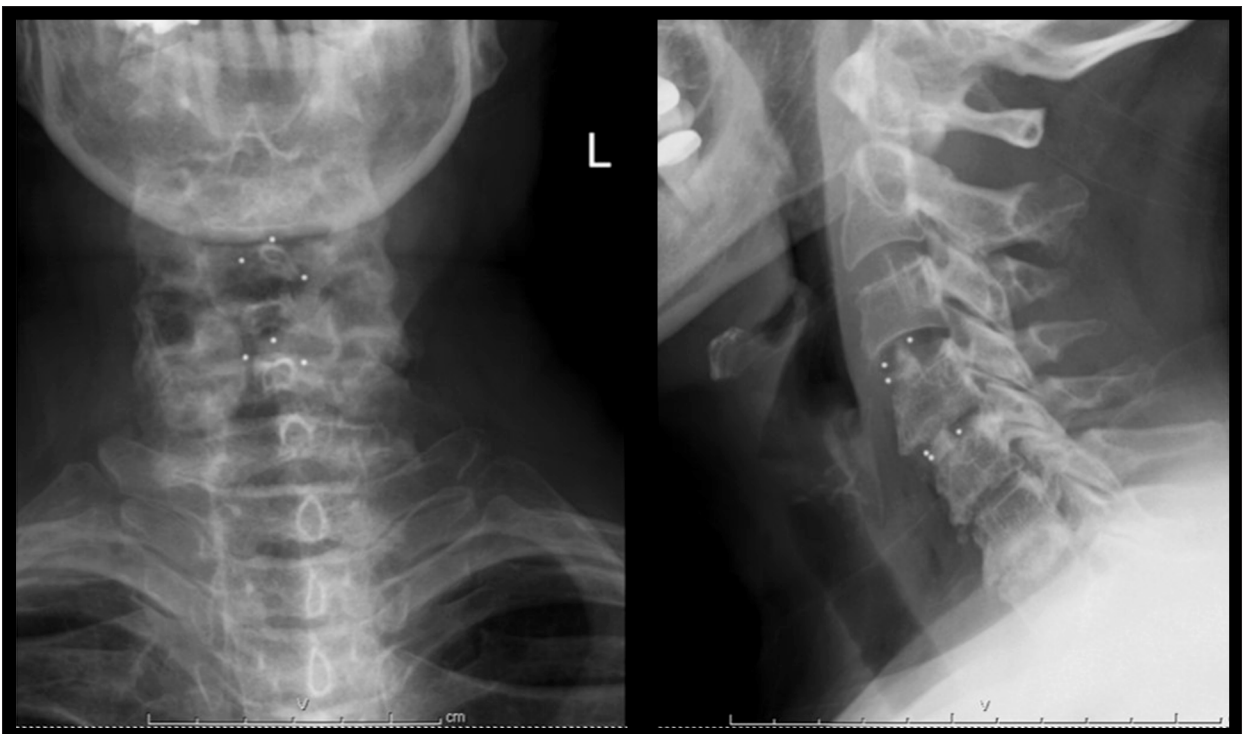


Figure 5. Postoperative AP and lateral radiographic views of the cervical spine.

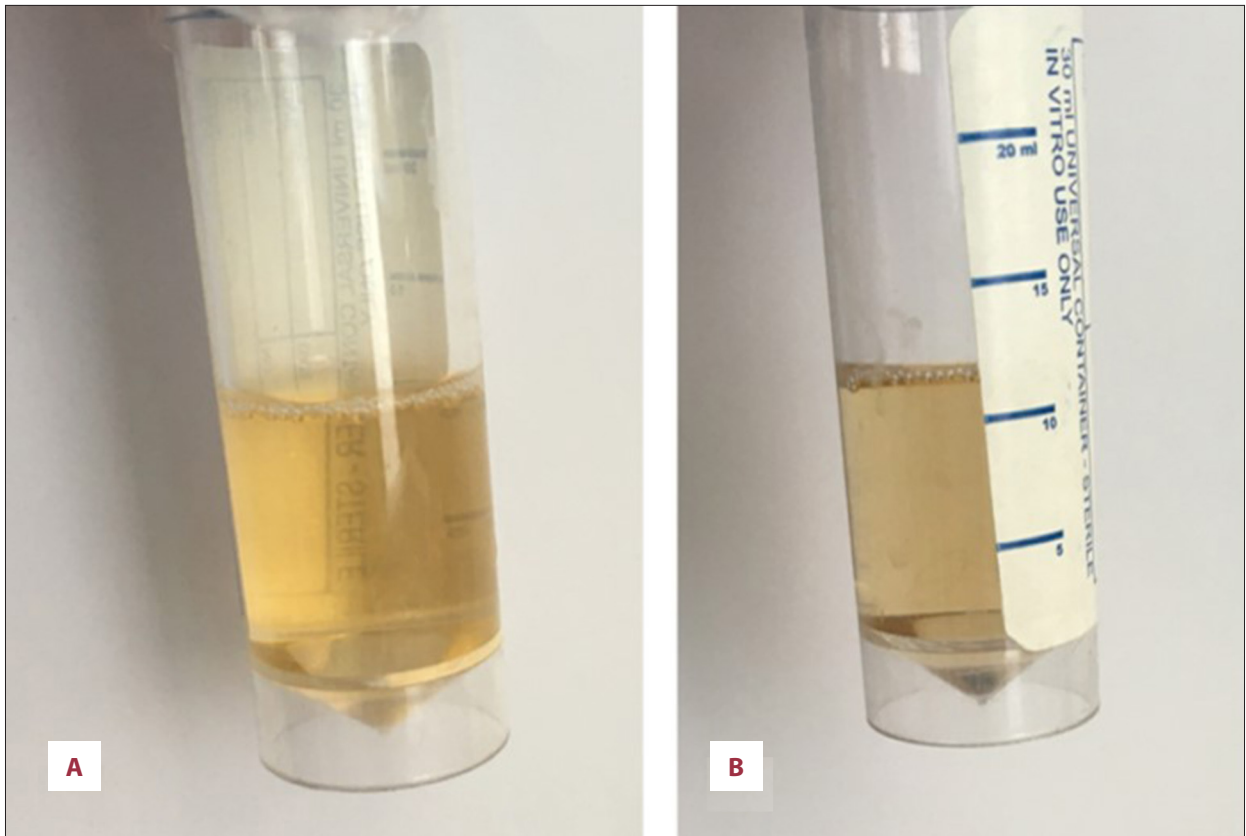


Figure 6. Urine sample showing the same color initially (A) and after 6 hours (B).



Figure 7. Absence of dark pigmentation of the sclerae of both eyes.

occipitocervical fixation with lateral mass screws [13]. Another case report described a patient with compression caused by thickened ligamentum flavum; this patient was treated surgically by modified cervical laminoplasty to relieve the compression [14]. In our patient, the cord was compressed anteriorly by a centrally protruding ochronotic disc at 2 levels, with the patient undergoing anterior cervical microdiscectomy and fusion using 2 cages.

The patient reported substantial improvement after surgical treatment. Her JOA score increased from 12 to 16, suggesting that surgical management of ochronotic cervical myelopathy may improve patient outcomes. Nevertheless, the relationship between myelopathy and AKU cannot be determined



Figure 8. Absence of clear dark pigmentation of the pinnae of both ears.

based on findings in 1 patient. Further studies, involving larger numbers of patients, are required to assess this relationship.

Due to the rarity of the disease and the limited number of reports describing patients treated surgically for cervical spine involvement in AKU, the long-term results remain unclear.



Figure 9. Absence of dark pigmentation of the oral cavity.

Disease in adjacent levels and recurrence of symptoms are possible complications. Long-term monitoring is required to document the occurrence of these complications.

References:

1. Garrod AE: The incidence of alkaptonuria: A study in chemical individuality. 1902 [classical article]. *Yale J Biol Med*, 2002; 75(4): 221–31
2. Phornphutkul C, Introne WJ, Perry MB et al: Natural history of alkaptonuria. *N Engl J Med*, 2002; 347(26): 2111–21
3. Zatkova A: HGD mutation database. October 24, 2010, http://hgddatabase.cvtisr.sk/home.php?select_db=HGD
4. Donaldson CJ, Mitchell SL, Riley LH 3rd, Kebaish KM: “As black as ink”: A case of alkaptonuria-associated myelopathy and a review of the literature. *Spine (Phila Pa 1976)*, 2019; 44(1): E53–59
5. Kahveci R, Ergünger MF, Günaydin A, Temiz A: Alkaptonuric patient presenting with “black” disc: A case report. *Acta Orthop Traumatol Turc*, 2013; 47(2): 134–38
6. Emel E, Karagöz F, Aydın IH et al: Alkaptonuria with lumbar disc herniation: A report of two cases. *Spine (Phila Pa 1976)*, 2000; 25(16): 2141–44
7. Mirzashahi B, Tafakhori A, Najafi A, Farzan M: Neglected alkaptonuric patient presenting with steppage gait. *Arch Bone Jt Surg*, 2016; 4(2): 188–91
8. Farzannia A, Shokouhi G, Hadidchi S: Alkaptonuria and lumbar disc herniation. Report of three cases. *J Neurosurg*, 2003; 98(1 Suppl.): 87–89
9. Al-Sbou M, Mwafi N, Lubad MA: Identification of forty cases with alkaptonuria in one village in Jordan. *Rheumatol Int*, 2012; 32(12): 3737–40
10. Zatková A, de Bernabé DB, Poláková H et al: High frequency of alkaptonuria in Slovakia: Evidence for the appearance of multiple mutations in HGO involving different mutational hot spots [published erratum appears in *Am J Hum Genet*, 2001; 68(5): 1313]. *Am J Hum Genet*, 2000; 67(5): 1333–39
11. Ranganath LR, Khedr M, Milan AM et al: Nitisinone arrests ochronosis and decreases rate of progression of alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. *Mol Genet Metab*, 2018; 125(1–2): 127–34
12. Zatkova A, Ranganath L, Kadasi L: Alkaptonuria: current perspectives. *Appl Clin Genet*, 2020; 13: 37–47
13. Karadag A, Sandal E, Middlebrooks EH, Senoglu M: Surgical management in cervical spondylotic myelopathy due to alkaptonuria. *World Neurosurg*, 2018; 113: 308–11
14. Li N, Tian W, Yuan Q, He D: Cervical spondylotic myelopathy due to the ochronotic arthropathy of the cervical spine. *J Korean Neurosurg Soc*, 2016; 59(1): 65–68

Conclusions

Intraoperative findings of black disc material in patients undergoing surgery for cervical myelopathy should suggest the need for further tests to diagnose AKU, especially in indolent patients who do not have classical clinical features. An accurate diagnosis may lead to proper treatment, which may arrest the ochronotic process and prevent the involvement of other systems. Surgical treatment of ochronotic cervical myelopathy can improve patient outcomes. Further studies are needed to evaluate the effects of combined surgical and medical therapies.

Conflicts of interest

None.