CASE REPORT

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Alkaptonuric patient presenting with "black" disc: a case report

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Although intervertebral disc degeneration usually occurs in the natural course of alkaptonuria, detection of the disease by black disc material in a patient without any other sign of alkaptonuria is an extremely rare condition. The authors report a 45-year-old previously healthy female patient who was operated on for prolapsed lumbar disc herniation, and in whom the nucleus pulposus was discovered to be black intraoperatively. The alkaptonuria was diagnosed after histopathological examination of the black disc material. Elevated urinary concentration of homogentisic acid confirmed the diagnosis.

Key words: Alkaptonuria; black disc material; lumbar disc herniation; ochronosis.

Alkaptonuria is a hereditary inborn error of metabolism due to mutations of the homogentisate 1.2-dioxygenase (HGD) gene causing a deficiency of the HGD enzymatic activity in the tyrosine and phenylalanine degradation pathways. It is inherited as a Mendelian recessive characteristic.[1] The alkaptonuria gene, encoding HGD, has been mapped to human chromosome 3q 21-q23.[2] To date, more than 90 different mutations in the HGD gene have been described worldwide.[3-7] Recently, the molecular analyses in alkaptonuric patients reveal a striking spectrum of HGD mutations, reflecting the disorder's clinical variability.[8]

In the natural course of alkaptonuria, the inherited absence of HGD causes the increased blood levels of homogentisic acid (HGA) leading to excretion of large quantities of HGA daily in the urine and deposition of pigmented benzoquinone polymeric oxidation products of HGA in many tissues of the body, which is called "ochronosis".[9] Although, the disease usually progresses from simple alkaptonuria to alkaptonuric ochronosis and finally to alkaptonuric arthropathy, HGA excretion and disease severity can vary significantly within the same family.

The first sign of the disease in childhood is the typical black colour of the urine. Individuals with alkaptonuria usually have dark urine or urine that turns dark on standing or exposure to an alkaline agent. However, darkening may not occur for several hours after voiding and many individuals never observe any abnormal colour of their urine. Thus, fresh urine may look normal in alkaptonuric patients.[10]

The irreversible binding of homopolymeric oxidation products of HGA to collagen causes degenerative changes on the morphologic structure of connective tis-

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sue, forming fragile complexes. Although degenerative changes of the spinal column most prominently involves the lumbar region, lumbar disc herniation as the presenting feature of alkaptonuria is not common.[11-15] We report an alkaptonuric patient diagnosed by the observation of "black" disc material intraoperatively.

Case report

A 45-year-old female patient presented to our outpatient clinic with low back and left leg pain that aggravated gradually in the last six months. She also suffered from progressive muscle weakness in the left lower extremity. Her lower back pain has been disturbing her for five years and relieved by nonsteroid anti-inflammatory drugs until the last six months. There was no other significant feature in her past medical history.

Neurological examination revealed a positive Laseque sign and a diminished patellar reflex on the left. Motor strength of the dorsiflexor muscles was moderately weak and there was a hypoaesthesia in between the L3 and L4 dermatomes on the left side.

Routine laboratory examinations of the patient were normal. Anteroposterior and lateral roentgenograms of the spine revealed moderate osteophyte formation on the upper and lower corners of the second and third lumbar vertebrae and narrowing of disc space in the L2-3 and L3-4 lumbar levels (Fig. 1). Axial and sagittal sections of lumbar magnetic resonance imaging revealed prominent degenerative changes and a left-sided prolapsed disc herniation at the L3-L4 level (Fig. 2).

The patient was operated on for prolapsed disc herniation. Macroscopically, no abnormality of the skin, muscles or ligaments was observed during surgery. After the annulus was incised, surprisingly it was seen that the nuclues pulposus removed from the L3-L4 disc space was black in colour. The microscopic examination revealed that there were melanin-like pigmentations in the cytoplasms of chondrocytes of the degenerated disc material (Fig. 3).

Afterwards, the patient was re-examined for a possible diagnosis of alkaptonuria, but there was no discoloration of the sclera, cornea or skin of the patient. Furthermore, the patient had not noticed any discoloration of urine or any stain on her underwear and there was no family history. Additionally, there was no calcification of the intervertebral discs on roentgenograms. Interestingly, a fresh urine sample was normal in colour and did not become dark after it was stored for two days. However, the patient's urine gradually became dark in colour after alkalinisation, and the presence of homogentisic acid in the urine was suspected and confirmed by thin-layer chromatography.

The postoperative course was uneventful and the patient was free from low back and leg pain after sur-

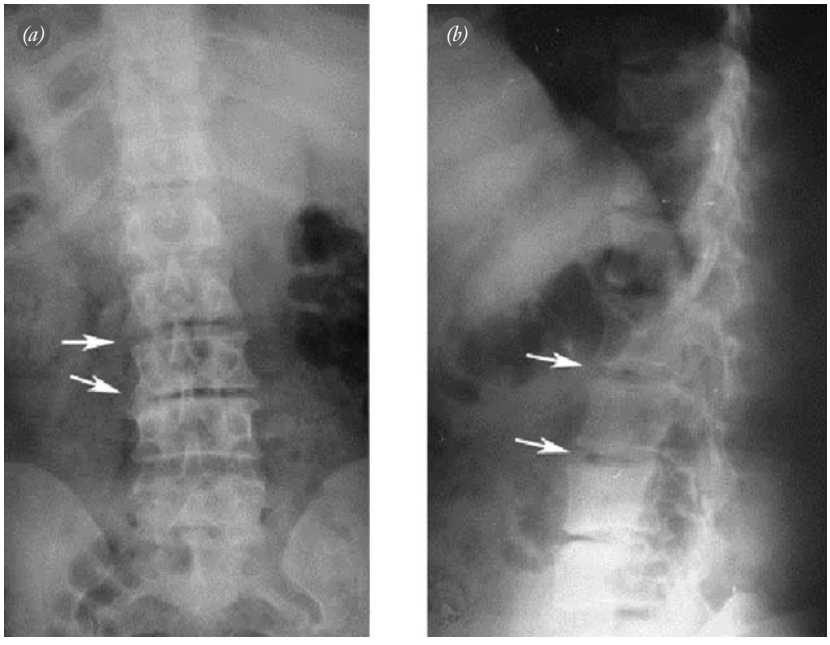

Fig. 1. **(a)** Spine radiographs showing moderate osteophyte formation and narrowing of disc space in the L2-3 and L3-4 lumbar levels (white arrows), **(b)** but there is no calcification of the intervertebral discs (white arrows).

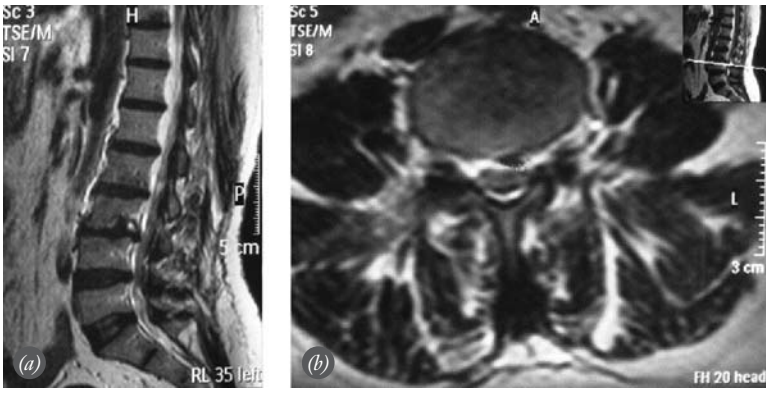

Fig. 2. Sagittal **(a)** and axial **(b)** lumbar MRI showing left-sided L3-L4 intervertebral disc prolapse.

gery. She was discharged with oral ascorbic acid (1000 mg per day) treatment and dietary restrictions. Six months after surgery the patient had recovered full motor and sensory functions, and only complained of mild back pain.

Discussion

Alkaptonuric ochronosis is a bluish-black pigmentation of connective tissue due to a slow accumulation of HGA and its oxidation products (e.g., benzoquinone acetic acid). The earliest physical sign of ochronosis is a slight pigmentation of sclera or ears, manifestating in individuals at age 20 to 30 years, but only a small proportion of patients with alkaptonuria develop ochronosis or ochronotic arthropathy.[16] It is known that the human liver produces enough HGD to convert over 1.5 kg of HGA per day.[9] Therefore, a patient to display alkaptonuria symptoms, a loss of more than 99% of the enzyme activity is required. Variability in residual HGD enzymatic activity may explain the absence of a clear correlation between genotype and phenotype.[7] Furthermore, in patients with alkaptonuria, a second enzyme, homogentisic acid polyphenoloxidase is present in the skin and cartilage catalyzing the overall oxidation and polymerization of HGA to a "ochronotic-like" pigment that damages and blackens connective tissues. Some authors stated that in alkaptonuric patients without ochronotic signs and symptoms, homogentisic acid polyphenol oxidase might be absent or diminished in addition to HGD.[17]

Ochronotic arthritis is a regular manifestation of longstanding alkaptonuria. The musculoskeletal manifestations of alkaptonuria are likely to be noted first in the spine. The most characteristic abnormality of the spine in this disease is widespread calcification of the intervertebral discs. Degenerative changes may be seen along the whole spine; however, the most prominent involvement is in the lumbar region.

In the some aspects of clinical and radiological features, ochronosis may resemble with ankylosing spondilitis (AS), hemachromatosis and idipathic chondrocalcinosis. The first disesase to be considered in dif-

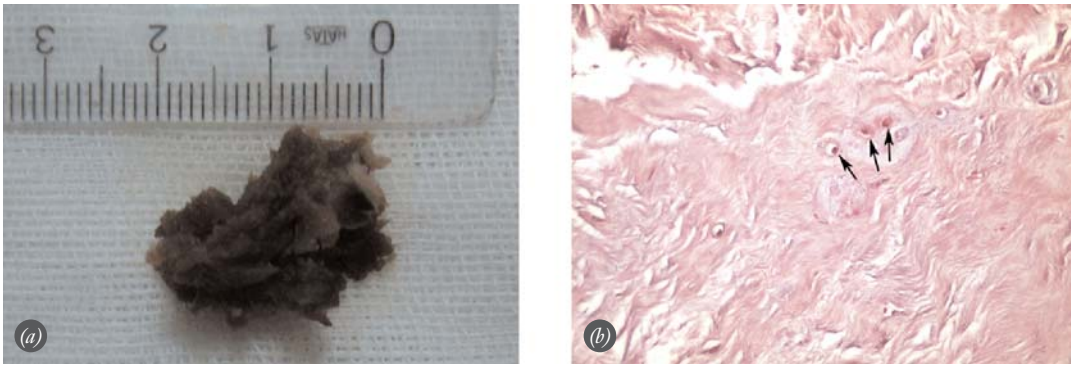

Fig. 3. **(a)** Macroscopically, the nuclues pulposus removed from the L3-L4 disc was black in colour. **(b)** Microscopic examination revealed melanin-like pigmentation in the cytoplasm of chondrocytes (black arrows) (H&E x400). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

ferential diagnosis is AS, which has similar complaints and clinical characteristics. Ankylosing spondilitis exhibits sacroiliac and facet joint involvement in radiographs, and no calcification in intervertebral discs. No localized pigment changes in the skin, sclera and cartilage tissues are seen. In addition, the HLA B27 antigen is highly positive. Intervertebral disc calcifications, which is the typical radiological sign of ochronosis, may albeit rarely be seen in hemochromatosis and idiopathic chondrocalcinosis. Differential diagnosis of these diseases is based on clinical examination and laboratory findings.[18]

The retrospective diagnosis of alkaptonuria by a "black" disc material removed during disc surgery is an extremely rare condition. Eight cases have been reported until now, and age, gender, clinical presentation, physical and radiological examination signs, and clinical progress of all these reported cases (including the present case report) are summarized in Table 1.[13-16] All of them were diagnosed retrospectively by the observation of "black" disc material intraoperatively. Male to female ratio is 3:1. Low back pain with leg pain is the most common complaint of the patients. Discoloration of the skin, sclera and cartilages has been reported in the physical re-examination of five cases. Homogentisic acid levels increased in urine samples of all cases, but urine samples turned into dark after standing for several hours in only four of them. Disc calcifications, vacuum

Table 1. Demographic features of previously reported cases and the present case.

	Age /sex	Complaints	Physical signs	Laboratory examination	Radiologic examination			Follow-up
					X-ray	CT	MRI	
Emel et al.,[12] 2000	34/M	Low back pain, left leg pain, urinary incontinans	No pigmentation	Increased HGA excretion in the urine, urine turns dark after waiting	Narrowing of disc spaces, osteophytes	Vacuum phenomenon osteophytes, protrusions, schmorl nodules	Degenerative changes, narrowing of disc spaces, schmorl nodules, calcified disc protrusions	No back or leg pain
	43/F	Lumbago, bilateral sciatica	Scleral and corneal discoloration	Increased HGA excretion in the urine, urine turns dark after waiting	Spondylotic changes, vacuum phenomenon	Schmorl nodules, L4-5 extrusion	Schmorl nodules, L4-5 extrusion	Some back pain, no leg pain
Choudhury et al.,[13] 2000	35/M	Low back pain, right leg pain	No pigmentation	Ochronotic pigment (+) in the urine	Decalcification, narrowing of disc spaces, little calcification	Unavailable	Multiple prolapsed discs	Minimal back pain, no leg pain
	30/F	Low back pain, left leg pain	Discoloration of nasal and ear cartilages	Homogentisic acid (+) in the urine, urine turns dark after waiting	Unavailable	L4-5 disc protrusion	Unavailable	No leg pain
Farzannia et al.,[14] 2003	28/M	Lumbago, right leg pain	Discoloration of sclera and darkening of nose	Homogentisic acid (+) in the urine	Unavailable	Unavailable	L5-S1 disc protrusion	No back or leg pain
	36/M	Low back pain, left leg pain	Discoloration of nasal and ear cartilages and fingernails	Homogentisic acid (+) in the urine	Unavailable	L5-S1 disc protrusion, osteophytes, vacuum phenomenon	Unavailable	Mild back pain, no leg pain
Gürkanlar et al.,[15] 2006	45/M	Low back pain, left leg pain	Discoloration of nasal and ear cartilages	Homogentisic acid (+) in the urine, urine turns dark after waiting	Narrowing of disc spaces, osteophytes, calcification	Protrusions, osteophytes, vacuum phenomenon, facet degenerations	Degenerative changes, narrowing of disc spaces, L4-5 disc herniation	No back or leg pain
Present case	45/M	Low bac pain, left leg pain	No pigmentation	Increased HGA excretion in the urine	Narrowing of disc spaces, osteophytes	Unavailable	L3-4 disc protrusion	Mild back pain, no leg pain

M: male; F: female

phenomenon and diffuse degenerative changes are the typical radiological findings. Surgical results are satisfactory for all patients. Discoloration of the skin, sclera or cartilages tissues and darkening of the urine were not observed in our patient's re-examination unlike the other cases. Additionally, no disc calcification has been observed on radiologic examination.

Alkaptonuric patients may be treated supportively, but there is as yet no proven effective treatment or prophylaxis. Localizing the recombinant HGD to its normal location in liver cells would seem to be the best strategy.[19] If necessary, corrective surgical procedures such as disc removal or decompression of the spinal cord have been helpful in this group of patients.[11-15] The early recognition and prompt treatment of the complications is important in order to decrease the morbidity, especially in patients with no other signs of alkaptonuria. Therefore, the spine surgeons should keep in mind the metabolic disorders such as alkaptonuria in the differential diagnosis of degenerative disc disease.

Conflicts of Interest: No conflicts declared.

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