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Lumbar spinal stenosis associated with alkaptonuria. Case report

Tahir Yıldırım[1], Bilal Ertuğrul[1], Muhammet Çalık[2], Metin Kaplan[1]

[1] Department of Neurosurgery, Firat University Faculty of Medicine, Elazığ, TURKEY
[2] Department of Pathology, Firat University Faculty of Medicine, Elazığ, TURKEY

ABSTRACT

Alkaptonuria is a rare autosomal recessive metabolic disorder caused by a deficiency of the homogentisic acid oxidase enzyme. In this disease, degenerative changes occur in the intervertebral discs and connective tissue due to pigment accumulation. This report presents a 45-year-old female patient who developed multi-level lumbar spinal stenosis due to alkaptonuria and underwent surgical treatment. Clinical findings, radiological imaging, and characteristic pigment accumulation observed during surgery were discussed. In this patient with severe spinal stenosis unresponsive to conservative treatment, surgical decompression provided significant improvement in symptoms, while intraoperative black disc material and pigmented ligamentum flavum provided important clues for diagnosis. As spinal degeneration associated with alkaptonuria can be aggressive, these cases should be followed up regularly over the long term.

Keywords
Alkaptonuria, lumbar spinal stenosis, spinal degeneration

Corresponding author:
Tahir Yıldırım

Fırat University Faculty of Medicine, Elazığ, Turkey

dr.yildirim.nrs@hotmail.com

INTRODUCTION

Alkaptonuria is an autosomal recessive metabolic disorder. These cases involve a deficiency of the enzyme homogentisic acid oxidase, which plays a role in phenylalanine and tyrosine metabolism (1, 2). It manifests itself primarily as dark pigment accumulation (ochronosis) in cartilage and connective tissue (3). Over time, progressive degeneration also occurs in the spine and joints of these patients (4, 5).

The degeneration occurring in connective and cartilage tissue presents itself in patients mainly as widespread joint pain. Over time, back and neck pain accompany the patients' extremity complaints. Spinal instability and/or limited mobility may develop in relation to the severity of degeneration (6). Disc herniations, stenosis, and spondylolisthesis are spinal problems that can be seen in these patients (7, 8). This report presents a case of alkaptonuria in which the patient had previously undergone surgery for cervical and lumbar disc herniations and subsequently developed multi-level lumbar stenosis. The case was examined in terms of clinical, radiological, and surgical treatment, and the results were discussed.

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CASE PRESENTATION

A 45-year-old female patient who underwent surgery for lumbar disc herniation in 2013 and cervical disc herniation in 2017 was evaluated for progressive neurogenic claudication. On examination, no findings were observed except for hypoesthesia below the left knee. In addition to complaints of pain in her back and legs, the patient had neurogenic claudication that worsened after approximately 50 meters. Her medical history revealed that during her 2013 surgery for an extruded lumbar disc herniation at the L5-S1 level, dark pigment accumulation was observed in the disc material, leading to further investigation and a diagnosis of alkaptonuria. Similarly, dark pigment accumulation in the disc material was reported in the 2017 surgery performed for cervical disc herniation (Figure 1).

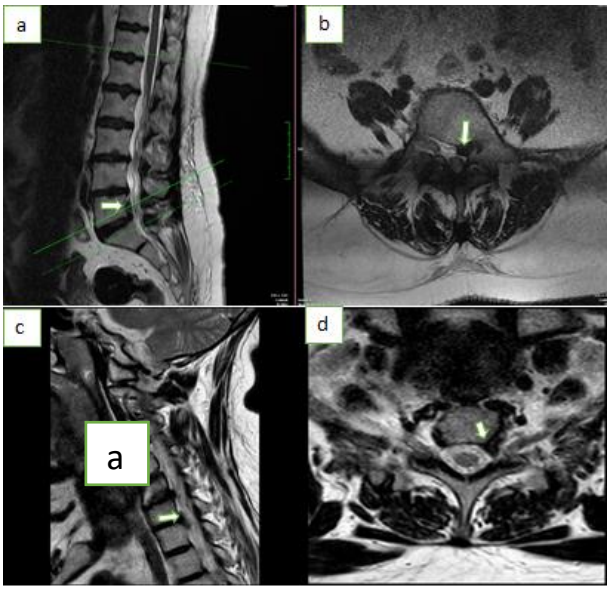

Figure 1. (a) Sagittal T2-weighted lumbar MRI showing an upwardly extruded lumbar disc herniation (*white arrow*), (b) axial T2-weighted lumbar MRI with a disc herniation compressing the left S1 nerve root (*white arrow*), (c) sagittal T2-weighted cervical MRI revealing an inferiorly migrated cervical disc herniation (*white arrow*), and (d) axial T2-weighted cervical MRI demonstrating a disc herniation impinging on the left cervical nerve root (*white arrow*).

The lumbar Magnetic Resonance Imaging (MRI) scan performed due to neurogenic claudication revealed significant lumbar degeneration and the presence of multi-level spinal stenosis (Figure 2). When compared to the previous lumbar MRI, it was observed that lumbar degeneration had significantly increased and progressed to severe spinal stenosis (Figures 1, 2).

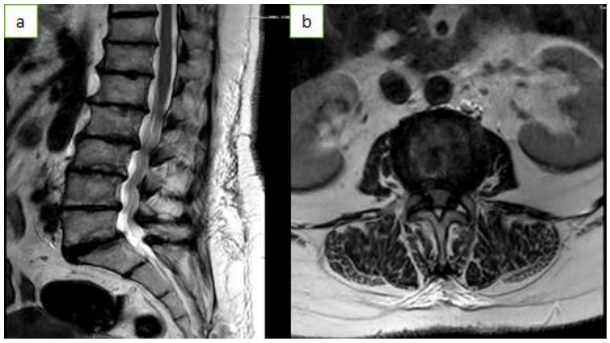

Figure 2. (a) Sagittal T2-weighted lumbar MRI showing narrowing of intervertebral disc spaces, multilevel osteophytic degeneration, spondylopathy, and grade 1 spondylolisthesis at the L5–S1 level, (b) axial T2-weighted lumbar MRI demonstrating spinal canal stenosis at the L2–L3 level.

Lumbar Computed Tomography (CT) revealed narrowing of the intervertebral disc spaces with a vacuum phenomenon, Schmorl's nodes, osteophytic spurs along the vertebral body margins, facet joint sclerosis, a defect in the pars interarticularis of L5, and Grade I spondylolisthesis at the L5-S1 level (Figure 3).

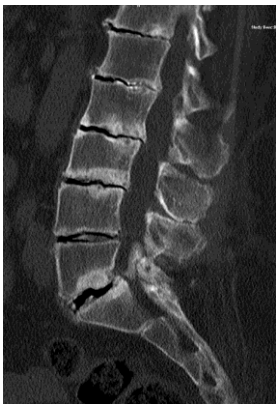

Figure 3. Sagittal lumbar CT; the calcification and narrowing of intervertebral disc spaces, Schmorl's node formations, osteophytic degeneration, spinal sclerosis, and grade 1 spondylolisthesis at the L5–S1 level are seen.

The patient, who had severe spinal stenosis and did not respond to conservative treatment, underwent surgery. During the surgery, bilateral partial hemilaminectomy and foraminotomy were performed at the levels where stenosis was observed. Spinal instrumentation was not performed because the patient did not want it. At these levels, dark pigment accumulation in the ligamentum flavum was seen accompanying degeneration of the flavum. Postoperatively, the

patient's pain and neurogenic claudication improved significantly. Pathological examination of tissue samples obtained during surgery reported the presence of brown pigment deposition and degeneration (Figure 4).

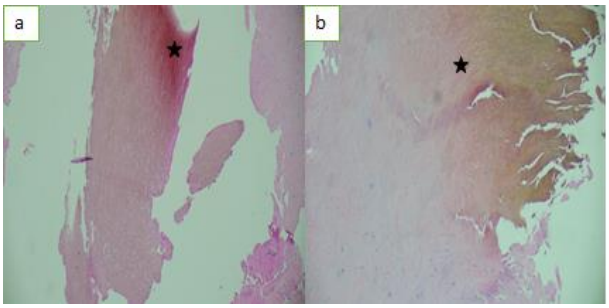

Figure 4. Microscopic examination of the ligamentum flavum shows brownish pigment deposition consistent with ochronotic degeneration due to homogentisic acid accumulation (stars). (a) H&E ×4, (b) H&E ×20.

Discussion

Alkaptonuria is an autosomal recessive metabolic disorder caused by a deficiency of the homogentisate 1,2-dioxygenase enzyme. This enzyme deficiency leads to the accumulation of homogentisic acid (HGA) in the body. Over time, HGA oxidizes, particularly in structures containing type 2 collagen, such as cartilage, connective tissue, and intervertebral discs, and converts into pigmented benzoquinone derivatives, which irreversibly bind to the tissue. Ochronotic pigment accumulation increases inter-fibrillar cross-linking and reduces tissue elasticity. Consequently, connective tissues become stiffened, brittle, and structurally compromised. (9, 10). Over time, this degenerative process in connective tissue leads to serious structural problems in the joints, and the clinical symptoms of patients are related to the severity of the degeneration (11). HGA accumulation has also been reported in the spinal region, causing similar degeneration (1, 12).

This degenerative process is particularly pronounced in the lower lumbar segments where axial loading is excessive. The structural deterioration in the connective tissue eventually leads to inadequate stabilization of the spine and increased loading on the posterior structures. This situation particularly increases the mechanical stress on the ligamentum flavum. In response to increased load and ochronotic pigment accumulation, elevated secretion of tissue inhibitors of metalloproteinase-2 (TIMP-2) results in hypertrophy of the ligamentum flavum (10, 13). Furthermore, the process associated with alkaptonuria in the intervertebral discs gradually disrupts the structure of the disc, facilitating the development of disc herniation (14). The resulting disc herniation further exacerbates the severity of spinal stenosis. In our case, there was a history of surgery for disc herniation at three levels: L5-S1, C6-C7, and C7-T1.

Although there were no specific findings related to alkaptonuria in the radiological diagnosis, findings indicative of segmental degeneration, such as narrowing of the disc space, calcification, vacuum phenomenon, osteophyte formation, endplate sclerosis, ligamentum flavum, and facet joint hypertrophy, can be observed on MRI and tomography (15, 16). These findings indicating segmental degeneration were also present in our case.

In most cases, degenerative changes associated with alkaptonuria become clinically apparent after the third or fourth decade of life. In most cases reported in the literature, the lumbar region is affected. Thoracic and cervical involvement has been reported more rarely (17, 18). Clinical symptoms and findings vary depending on the location and severity of the involvement. However, pain and limited mobility, as in our case, are the most common complaints in patients. In our case, both the lumbar and cervical regions were affected, and surgery for multi-level disc herniation and spinal stenosis had been performed at different times. With this feature, our report presents a unique example of how spinal degeneration related to alkaptonuria may pursue a particularly aggressive pattern.

Surgically, the distinctive dark blue-black coloration of degenerative disc material in patients with alkaptonuria is the most striking finding of the “black disc phenomenon.” In many cases, it has been reported that the nucleus pulposus fragments removed during discectomy are blackish in color and lighten in color upon contact with air (8, 19, 20). A similar appearance is also seen in the ligamentum flavum (9, 10). In our case, similar pigment accumulation in the ligamentum flavum was observed macroscopically and microscopically.

Since there is no definitive method to eliminate the underlying cause of alkaptonuria, treatment is limited to measures that support the control of

degenerative changes. Although protein (tyrosine-phenylalanine) restriction and vitamin C supplementation are recommended, nitisinone therapy, which reduces homogentisic acid production, has been reported to be beneficial in experimental studies (21, 22, 23). In cases with spinal involvement, surgical treatment can significantly improve patients' quality of life if there is severe pain and progressive neurological findings (18).

Conclusion

Although alkaptonuria is a rare disease, it should be kept in mind in the differential diagnosis of young patients with rapidly progressive, widespread spinal degeneration. Encountering black disc material and/or pigment accumulation in the ligamentum flavum during surgery is an important clue for alkaptonuria. In cases with advanced spinal stenosis that do not respond to conservative treatment, surgical intervention can significantly improve symptoms. Furthermore, it should be remembered that spinal degeneration associated with alkaptonuria, as in our case, can have an aggressive course, and such cases require periodic evaluation for spinal complications.

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