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Case study

Alkaptonuria: A rare cause of recurrent severe back pain in the emergency department

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ABSTRACT

We report a 45 year-old male patient who presented to the emergency department of Hamad General Hospital with recurrent severe low back pain. Clinical examination revealed characteristic deposition of blue-brownish pigment in the sclera and ear. X-ray revealed diffuse intervertebral disc calcification. Alkaptonuria was suspected and the diagnosis was confirmed by detection of high levels of homogentisic acid in the urine.

Keywords: Alkaptonuria, homogentisic acid (HGA), back pain, dark urine, ochronosis

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INTRODUCTION

Alkaptonuria is a rare autosomal recessive disorder, which results from deficiency of the enzyme homogentisic acid oxidase (HGO), which in turn leads to accumulation of high levels of homogentisic acid (HGA) in the connective tissue and urine. The genecoding HGA was located to chromosome 3q21-q23.[1] The metabolic disorder does not reduce the normal life span of the patients; however there is a high rate of disability, especially later in life.[2]

CLINICAL FEATURES

These result from increased HGA and its oxidation by products, i.e., benzoquinones. These by products lead to darkening of the urine on standing; pigmentation (ochronosis) of cartilage and other connective tissues, and nearly always arthritis.[3] Ochronotic arthritis is the initial and most common connective tissue feature of long-standing alkaptonuria. The joint disease begins in the fourth or fifth decade of life. Joint symptoms progress, and if arthritis develops it may result in ankylosis. The chronic pain may prompt a knee, hip or shoulder replacement before the age of 55, on average. Tendon and ligament ruptures occur frequently,[4] and acute hip destruction has been reported.[5]

Clinically, alkaptonuria resembles ankylosing spondylitis,[6] and back pain is the symptom that usually brings patients to the hospital for an official diagnosis of alkaptonuria.[7] This condition may also lead to kyphosis and scoliosis.[3] Disc prolapse is rare in alkaptonuria; nevertheless, it has been reported.[8]

Because of degenerative changes in the coronary arteries and cardiac valves, careful assessment before surgery is needed,[9] and even annual echocardiograms are recommended at the age of 40. Aortic valve replacement may be needed if stenosis becomes severe. The deposited pigment may be apparent in the ear and sclera usually by the third decade of life.[1] Renal stones appear in 16 percent of cases, by a mean age of 64.[1] Characteristically, patients pass urine that becomes dark on standing.

DIAGNOSIS

The condition can be diagnosed easily if the patient has musculoskeletal symptoms and any classic signs of alkaptonuria, i.e., pigmentation of sclera and ear, passing of urine that darkens upon standing, and calcification of intervertebral discs. In one study, diagnosis was determined by dark urinein 55% and chronic joint pain in 45% of cases.[10] The radiographic changes in the case of alkaptonuria are almost pathognomonic.[11] The earliest finding is loss of disk height. Degeneration of the intervertebral discs leads to dense calcification of the remaining disc material.

This progresses at variable rates to fusion of the vertebral bodies. On occasion, the intervertebral disc can rupture.[12] The diagnosis of alkaptonuria can be made with reasonable certainty from the changes in the lumbar spine alone, as viewed through X-ray. Occasionally, free intra-articular bodies are found. Both MRI and X-ray can discover the typical changes inherent to alkaptonuria, such as narrowing of articular spaces, calcifications of the discs, osteophytes, multiple disc protrusions and reactive sclerosis, which is prominent in dorso-lumbar spine. Nevertheless, MRI was found to be more accurate for individualizing spine lesions and recognizing changes such as thickness of the anterior longitudinal ligament.[13]

Detection of high levels of HGA in the urine will establish the diagnosis. Treatment with brewers' yeast, tyrosinase, insulin, adrenocortical extract, vitamin B_{12}, cortisone, and phenylbutazone have failed to reduce plasma levels of HGA. In a retrospective study, six patients with alkaptonuria on self-imposed protein restriction had the same daily urinary HGA production as patients who had no protein-restrictions. The role of vitamin C is questionable. In 2002, two patients with alkaptonuria were treated with nitisinone—up to 1.4 mg twice aday—and as a result their daily urinary excretion of HGA fell by at least 69 percent.[14] Joint replacements should be considered primarily for pain relief rather than for improved range of motion. Liver transplantation, performed for hepatitis B-related cirrhosis, has been reported to remove alkaptonuria,[15] and a renal transplant for diabetic nephropathy may have provided some HGO activity to the recipient.[16]

CASE REPORT

We report a 45 year-old Indian male patient who presented with increasing lower back pain two weeks prior to his visit. He had a history of mild back pain for five years. The frequency of pains had increased over the last two years, and for two weeks the pain was severe enough to bring the patient to the emergency department. He denied any history of trauma, fever, skin rash, but he had occasional mild pain affecting both knees. The patient also denied any chest or abdominal pain; sore mouth or eyes, or

reduced acuity of vision. Physical examination revealed a well-looking patient who was not jaundiced or pale, but who had brown-bluish discoloration of the sclera (Figure 1) and brown discoloration of the

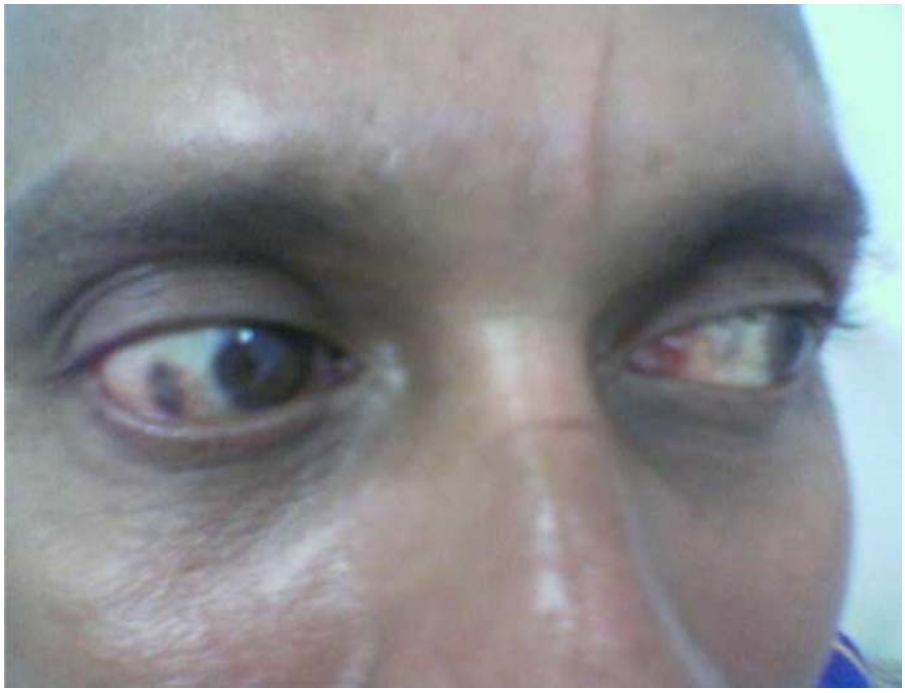

Figure 1. Ochronotic pigment in sclera.

ear. Joints showed no signs of arthritis or deformity. In the spine, flexion was limited and painful as was as lateral bending. The rest of the examination was unremarkable. The investigations revealed the following: complete blood count, electrolytes, liver function test, renal profile, ESR, C reactive protein, uric acid, protein electrophoresis. All results were normal. Urinalysis revealed protein 1+. Urine for homogentisic acid was positive. ECG was normal. X-ray of lumbosacral spine revealed diffuse intervertebral calcification (Figure 2).

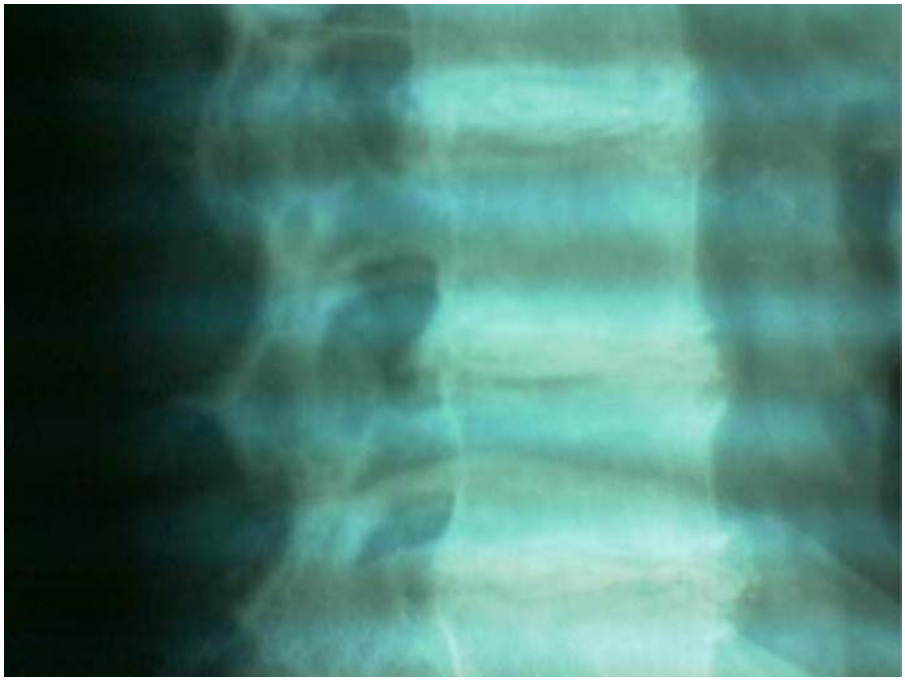

Figure 2. Intervertebral disc calcification.

DISCUSSION

This was the first case of alkaptonuria to be reported in Qatar. Although it can lead to variety of symptoms—for example, chest pain due to degenerative changes in the coronary arteries and valves or abdominal pain due to renal stones—patients typically present with back pain, which was the case with this patient. The condition resembles ankylosing spondylitis.[6,7] This patient has mild joint pain affecting both knees, which could be explained by the fact that arthritis begins in the fourth or fifth decade, so he could have just begun to have joint symptoms.

The patient denied passing dark urine, and this could be explained by the fact that patients usually pass urine which looks normal but turns dark on standing. X-ray evidence of diffuse intervertebral disc calcification pointed to diagnosis because this is almost pathognomonic for the condition.[11] This led us to look for characteristic pigmentation of the sclerae. The condition was subsequently confirmed by finding HGA in the urine. Although intervertebral disc calcification can be seen in many other conditions—e.g., degenerative spodylosis, pseudogout, ankylosing spondilitis, juvenile chronic arthritis, haemochromatosis, gout, diffuse skeletal hyerostosis, idiopathic and following spinal fusion[17]—the presence of characteristic pigmentation of the sclerae and urine, as well as the finding of HGA in the urine has led us to confirm the diagnosis (Figure 3). Despite the fact that it is a rare

Figure 3. Fresh and standing urine of the same patient.

condition, it could still be seen in our busy emergency department, as patients usually present with back pain, a very common complaint.[18] The condition can be diagnosed easily if a high index of suspicion is maintained. Properly diagnosed, the patient given diclofenac sodium 50 mg, three times daily, muscadol tablet (paracetamol) 450 mg and orphenadrine 35 mg, twice daily, and ascorbic acid, 500 mg daily, will benefit and show a good response.

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