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Case Report

Clinical, Radiographic and Echocardiographic Findings in a Patient with Ochronosis

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Abstract: Hereditary alkaptonuric ochronosis is an autosomal recessive metabolic disorder that affects approximately one in one million individuals. The most common clinical features are homogentisic aciduria, pigmentation of cartilages and other connective tissues, ochronotic arthritis and cardiovascular ochronosis. We report a case of ochronosis which has all these clinical features mentioned above. We detected homogentisic acid in the patient's plasma and urine sample by using a high-performance liquid-chromatographic method. The patient was HLA-B27 negative. The case was evaluated with both conventional radiography and helical CT. The main characteristic manifestations of ochronotic arthritis were observed in conventional radiographs. We also obtained Ray-Sum and maximum intensity projections (MIP) images of ankylosed ochronotic spine of our patient. Such images of an ochronotic patient were not encountered in the literature. Echocardiographic examination revealed thickening of the right coronary cusp which may be related to ochronotic calcific deposition, along with coaptation deficiency and slight aortic regurgitation (grade I–II). No other abnormalities concerning the other valves and ventricular function were detected.

Keywords: Cardiovascular ochronosis; Ochronotic arthritis; Ochronosis

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Introduction

Alkaptonuria is a rare hereditary metabolic disorder characterised by deficiency of the enzyme homogentisic acid oxidase [1]. This enzyme deficiency leads to elevated levels of homogentisic acid in the body, and a portion of the homogentisic acid is excreted in the urine and imparts a characteristic black discoloration upon oxidation. In addition, a polymer derived from homogentisic acid is deposited in the connective tissues of the body, causing a pathological pigmentation known as ochronosis [2]. The major clinical manifestations of alkaptonuric ochronosis are related to deposition of ochronotic pigment in the affected organs. While it primarily involves the larger joints of the body, including the spine, the cartilage of the ear, conjunctival stroma, episclera, genitourinary system and cardiovascular system can also be affected [3, 4].

We report a case of ochronosis with involvement of the musculoskeletal and cardiovascular systems and review the literature on the subject.

Case Report

A 53-year-old man was admitted to our clinic in March 1997, complaining of low back, shoulder and knee pain. He had suffered from numerous episodes of inflammatory low back pain and stiffness in the previous 16 years. Although he had noticed darkening of his urine for the past 10 years, the diagnosis of alkaptonuria had not been made. He denied having had psoriasis, inflammatory bowel disease, uveitis, conjunctivitis or urethritis.

On physical examination, the most prominent features were brown pigmentation of the cartilage of both ears

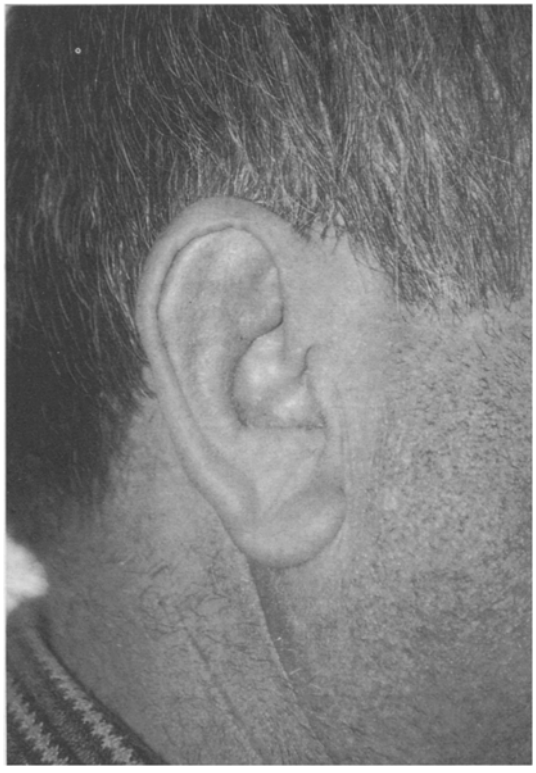


Fig. 1. Brown pigmentation of the ear cartilage can be seen in this ochronotic patient.

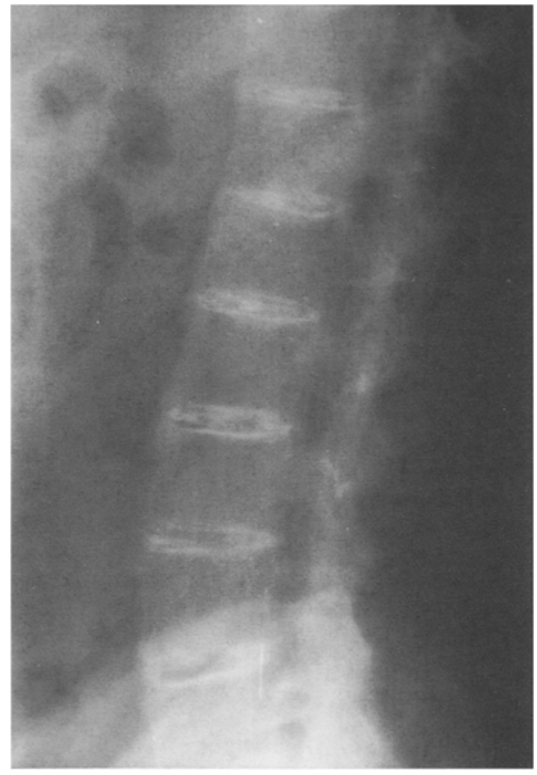


Fig. 2. A lateral radiograph of the lumbar spine showing typical wafer-like calcifications in the intervertebral discs.

(Fig. 1) and his postural deformity mimicking the findings of ankylosing spondylitis. A spine examination revealed marked restriction of both the thoracic and lumbar spine (modified Schober 1 cm). He had painful muscle spasm in the paravertebrals of the dorsolumbar spine and limitation of chest expansion to 2.5 cm. Peripheral joint examination revealed limited and painful movement of both the shoulders and knees. Blood pressure was 150/90 mmHg and the pulse was regular at 84 beats/min. A neurological examination was normal. We could not find any symptoms related to genitourinary and ocular involvement of ochronosis.

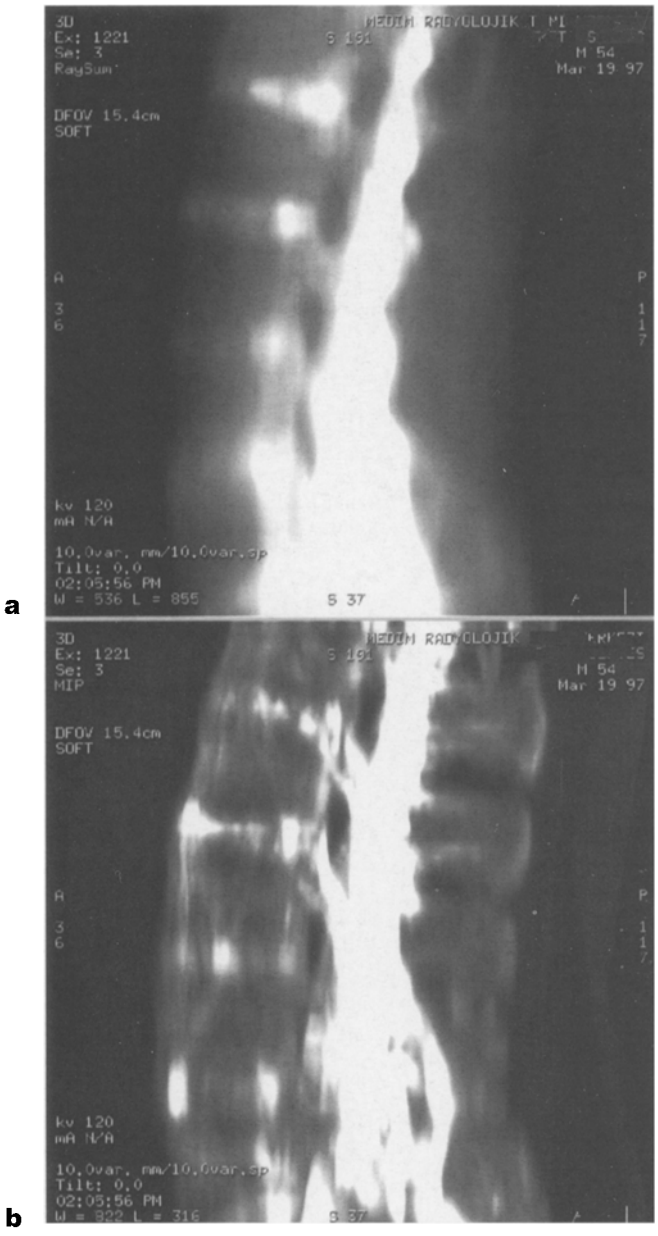
Laboratory tests revealed an erythrocyte sedimentation rate (ESR) of 18 mm/h. A complete blood count, serum proteins, urea and electrolytes were all within normal limits. We detected homogentisic acid in his plasma (44.3 μmol /l) and urine (25.0 mmol /24 h) by using a high-performance liquid-chromatographic (HPLC) method, which is a rapid, sensitive and specific technique for the diagnosis of alkaptonuria [5]. He was HLA-B27 negative. HLA-B27 typing was performed by flow cytometry using HLA-B27 specific monoclonal antibodies.

Lateral views of the thoracic and lumbar spine plain radiographs (Fig. 2) showed typical wafer-like calcifications in the intervertebral discs, with narrowing of the disc spaces and osteoporotic rarefaction of the vertebral bodies. Marginal discal ossification and narrowing of the apophyseal joints simulating the findings of ankylosing spondylitis were also observed. Narrowing of the intervertebral disc spaces and anterior osteophytosis were observed on the radiographs of his cervical spine. The antero-posterior and oblique views of radiographs of the sacroiliac joints were interpreted as normal. Radiographs of the shoulders showed moderate degenerative changes with narrowing of the right shoulder joint space. Mild degenerative changes were present on the radiographs of his knees and symphysis pubis.

Besides conventional radiography, axial helical computed tomography (CT) was also used to evaluate the lumbar spine of the patient. This enabled us to reconstruct the sagittal images using Ray-Sum and maximum intensity projection (MIP) techniques (Fig. 3). Increased density of the intervertebral disc spaces and apophyseal joints due to calcification and intense sclerosis was detected on both the Ray-Sum and MIP images. We have not encountered such images of an ochronotic patient in the literature.

An echocardiographic examination revealed thickening of the right coronary cusp, which may be related to ochronotic calcific deposition, along with coaptation deficiency and slight aortic regurgitation (grades I–II). No other abnormalities concerning the other valves and ventricular function were detected.

His 47-year-old sister had brown pigmentation in her ears. She had the complaint of pain in her low back and knees. His 34-year-old brother had blue pigmentation of his ear cartilage and also low back pain. We have not



a

b

Fig. 3. (**a**) Ray-Sum and (**b**) maximum intensity projection (MIP) images. Both images reveal increased density of the intervertebral disc spaces and apophyseal joints due to calcification and intense sclerosis.

documented these siblings, but we detected homogentisic acid in their plasma and urine samples. They were also HLA-B27 negative.

Discussion

Hereditary alkaptonuric ochronosis is an autosomal recessive metabolic disorder that affects approximately one in one million individuals, but the incidence is higher in inbred populations [3]. We observe consanguineous marriages frequently in some regions of our country. The parents of our patient were consanguineous and an example of these marriages. The incidence of this disease is not known exactly in our country but we think that it could be higher than we expect.

The clinical manifestations of alkaptonuric ochronosis usually become evident by the fourth decade of life and may be progressive. Ochronotic arthritis is the most common clinical feature of ochronosis. The radiographic manifestations of ochronotic arthritis can be divided into spinal and extraspinal abnormalities. Many of the spinal and extraspinal radiological abnormalities were present in our patient.

Generally, the characteristic manifestations of spinal abnormalities include widespread discal calcification, disc space narrowing, vertebral osteoporosis and small osteophytosis. The radiographic findings of ochronotic arthritis may resemble the abnormalities seen in ankylosing spondylitis. Syndesmophytes are usually thin and vertically oriented in ankylosing spondylitis, but in ochronosis there is broad band-like ossification of the large segments of the intervertebral discs [6]. Nevertheless, the coexistence of these two conditions in the same patient has been reported [7,8].

Osteoarthritis must also be kept in mind in the differential diagnosis of ochronotic arthritis, because extraspinal abnormalities such as joint space loss, mild osteophytosis, small cystic lesions and tendon abnormalities are all observed in both diseases. These abnormalities are particularly more frequent in the hips, shoulders, knees, sacroiliac joints and symphysis pubis [6].

There are some reports alleging a link between alkaptonuria and the histocompatibility antigen HLA-B27 [6, 8]. Moreover, it was claimed that an HLA-B27 positive patient with ochronosis may develop a more severe axial involvement, resembling that of ankylosing spondylitis [9]. In contrast, our patient was HLA-B27 negative though he had severe clinical and radiographic findings of ochronotic arthritis simulating ankylosing spondylitis. However, some HLA-B27 negative cases of ochronosis have been reported [7,10], similar to our patient.

A variety of cardiovascular abnormalities caused by the deposition of polymerised homogentisic acid in the cardiovascular system have been described in ochronosis. The most prominent deposits in the heart are usually present at the bases and anuli of the aortic and mitral valves. Ochronotic pigment may also be deposited in the pulmonic valves and endocardium, and in the walls of arteries and veins. The only functionally significant valve lesion reported appears to be aortic stenosis. Several cases of documented aortic stenosis associated with alkaptonuric ochronosis have been reported [11,12]. On the other hand, O'Brien et al. [13] found no increase in the frequency of either aortic stenosis or coronary artery disease in a large series of patients. The echocardiogram of our patient did not reveal aortic stenosis though there was calcification and thickening of the right coronary cusp. It was recommended to the

patient that he should be evaluated periodically by echocardiography in order to detect earlier any new cardiac involvement.

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