Ochronosis: a case of severe ochronotic arthropathy

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Abstract

Ochronosis involves primarily the large cartilaginous joint surfaces, ribs, intervertebral discs, ear cartilage etc. We report on a 52-year-old woman with typical alkaptonuric ochronosis with dark urine, blue-black pigmentation of the auriculae and hands, spondylarthropathy and severe hip and shoulder joints involvement. The differential diagnosis of this rare condition is discussed with a review of the literature.

Introduction

Ochronosis (alkaptonuria) is a rare autosomal recessive metabolic disorder.[1] Ochronosis occurs from a deficiency of enzyme homogentisic acid oxidase leading to accumulation of homogentisic acid (HGA), which is oxidized, polymerized, and deposited in connective tissues, causing characteristic pigmentation.[2] The major clinical manifestations of alkaptonuric ochronosis are related to deposition of ochronotic pigment in the affected organs. The skeletal system is predominantly involved, although other systems, including cardiovascular, urinary and auditory systems, may also be affected.[3]

We report not only the radiologic and clinical findings of the lumbar spine but also the involvement of hip and shoulder joints, which is rarely seen in ochronosis.

Case Report

A 52-year-old female was admitted to our outpatient clinic with progressive pain in the left hip joint for the last one and half month. She had right shoulder pain. She had suffered from numerous episodes of inflammatory low back pain and stiffness in the previous 10 years. Although she had noticed darkening of her urine, the diagnosis of alkaptonuria had not been made.

On physical examination, the most prominent features were brown pigmentation of the cartilage of both ears and the face (Figure 1).

She had stiffness of the lumbodorsal spine with pain on extension. Her right shoulder movements were also painful and limited. The Fabere and sacroiliac compression tests were positive on the left. Laboratory investigations, including assessment of urinalysis, a complete blood cell count, rheumatoid factor, erythrocyte sedimentation rate, liver function tests and other blood chemistry values yielded normal results. A pelvic sonography was also normal. The patient had no history of renal stones. The patient's Urine color was normal when voided but turned black over variable periods spontaneously (Figure 2).

Lateral views of the thoracic and lumbar spine plain radiographs (Figure 3) 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. The antero-posterior and oblique views of radiographs of the sacroiliac joints were interpreted as normal. The magnetic resonance imaging (MRI) of the right shoulder showed severe degenerative changes with narrowing of the right shoulder joint space (Figure 4). Severe degenerative changes were present on the MRI of her left hip (Figure 5).

Based on cardiac investigations, an alkaptonuria-associated degenerative valve defect with aortic, mitral and tricuspid valve insufficiency was diagnosed. We did not perform a biochemical analysis to determine whether the level of homogentisic acid was elevated but diagnosed the disease based on histopathological and clinical examinations.

Discussion

Ochronosis is a rare disorder of tyrosine metabolism inherited as an autosomal recessive trait with an incidence of 1/200,000.[4]

The disease often goes unrecognized until middle life; it becomes evident only in the third and fourth decades of life. An explanation as to why it cannot be recognized until middle life is that there is an effective second line clearance mechanism from the kidneys. With ageing, the efficiency of the process decreases and the steady level of plasma HGA slowly rise. This development accelerates the accumulation of HGA over time.[3] The excess homogentisic acid causes dark discoloration of the connective tissues, also known as ochronosis. The skeletal system is predominantly involved, although the other systems, including cardiovascular, urinary and auditory systems, may also be affected.[3]

How HGA accumulation leads to ochronosis and arthropathy has not yet been fully understood. Various theories have been put forward, however. Ochronotic pigment accumulates in the muscles, tendons, ligaments and hyaline cartilage comprising connective tissue. The HGA collecting in the tissues may act as a chemical irritant, leading to joint degeneration and inflammation. It is likely that HGA attaches physically to connective tissues and affects the macromolecular structure and the interactions between them. Other views are that HGA leads to degeneration of oxidant products. Benzochinon acetate that forms with HGA oxidation binds to collagen diagonal bonds and impairs the connective structure. In addition, free radicals forming as a result of oxidation affect the development of tissue damage and trigger the inflammatory process. Finally, clinical findings regarding damage in connective tissue are now emerging.[5]

Our patient has had complaints for ten years. In 20% of cases, alkaptonuria is diagnosed before one year of age, while in 80% the mean age at the time of diagnosis is 29. In general, the severity of the disease progresses after the age of 30 and more rapidly in men than in women.[6] The diagnosis of alkaptonuria is usually based on the detection of degenerative joint disease, ochronosis of the connective tissues and the darkening of urine after alkalinisation. In addition, alkaptonuria may be associated with nephrolithiasis, which develops at a mean age of 64[6] and could be the leading symptom. Our patient had no history of renal stones. Her pelvic sonography was normal. Clinical findings include the pigmentation of the ear cartilage and the sclera of the eyes, which only occur after the age of 30 and are very variable in appearance.[6] The symptoms of ochronotic arthropathy begin with low-back pain and stiffness. Later, the process extends to the thoracic spine, and followed in

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the ensuing 10 years by involvement of the knees and later the shoulders and hips after these spinal changes.[7] In rare cases, the small joints of the hands, wrists, and elbows are affected. Affected persons experience progressive disability, pain and stiffness.[3] By the age of 55 years, 50 % of patients with alkaptonuria have undergone at least one joint replacement.[6] A black meniscus with a complicated tear can be the first finding of ochronosis before vertebral involvement. The characteristic arthroscopic findings may be premonitory signs of ochronosis without other systemic manifestations.[8]

The radiographic abnormalities of ochronotic arthropathy are found in both spine and the extraspinal joints. The lumbar spine is affected initially, followed by the dorsal and cervical regions.[9] The radiological appearances are of a degenerative joint disease with loss of joint space, pronounced sclerosis, small cysts, periarticular calcification and mild osteophytosis.

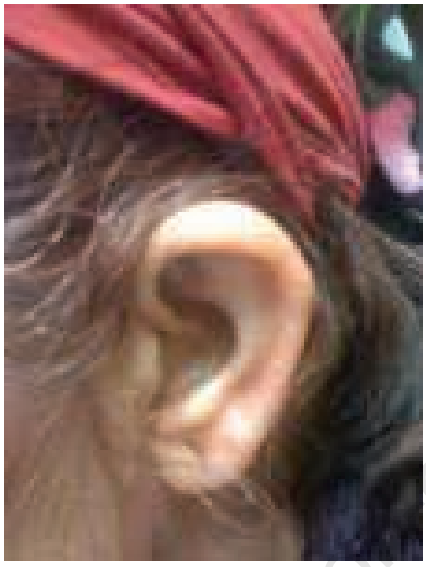

Figure 1. Brown pigmentation of the cartilage of both ears and the face.

Figure 2. Urine color turned black over variable periods spontaneously.

In the study of Aliberti *et al.*,[10] it was suggested that progressive osteoporosis and fragility fractures are prominent manifestations of ochronosis. The tissues lose elasticity and develop poor resistance to mechanical strain in ochronosis. Small blackened fragments of cartilage are dislodged into the joints where they become embedded into the synovial membranes.[3] In our case, lumbar spine was affected initially and many of the spinal and extraspinal radiological abnormalities were present. A presumptive diagnosis of ochronotic arthropathy is often suggested by radiographic examinations of the lumbar spine. As the radiologic features of ochronosis lead us to the diagnosis, features should be kept in mind.[11] They were also HLA-B27 negative.[12]

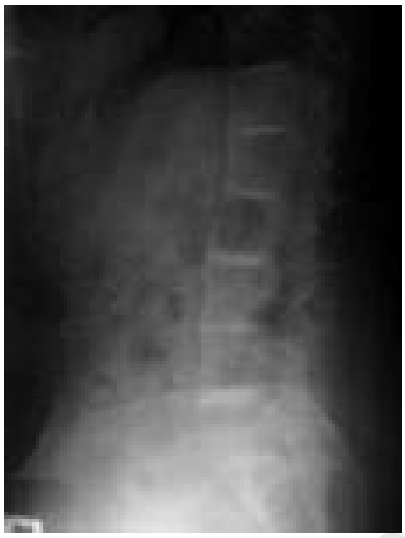

Figure 3. Typical wafer-like calcifications in the intervertebral discs, with narrowing of the disc spaces and osteoporotic rarefaction of the vertebral bodies on lateral views of the thoracic and lumbar spine plain radiographs.

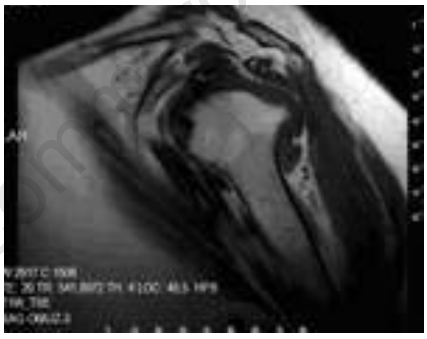

Figure 4. Severe degenerative changes with narrowing of the right shoulder joint space on magnetic resonance imaging of the right shoulder.

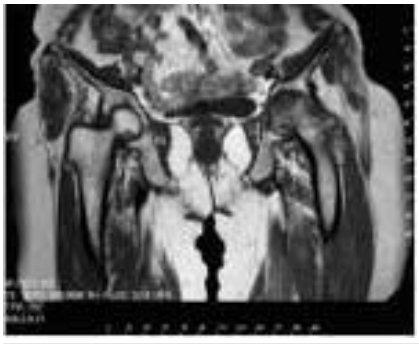

Figure 5. Severe degenerative changes seen on the magnetic resonance imaging of her left hip.

The differential diagnosis of this case mainly includes degenerative joint disease, ankylosing spondylitis, rheumatoid arthritis, and calcium pyrophosphate dihydrate (CPPD) crystal deposition disease. Discal calcification in the spine can also mimic hyperparathyroidism, hemochromatosis, amyloidosis, diffuse idiopathic skeletal hyperostosis (DISH), or surgical spinal fusion. The involvement of unusual articular sites with an unusual pattern of joint space loss, a typical presentation of degenerative arthropathy that was far more advanced than would be expected for the patient's age, and the nonsignificant history and laboratory findings except for the presence of HGA in the urine allowed the accurate diagnosis of ochronotic arthropathy.[13]

Conclusions

Ochronosis a metabolic disorder, though not life threatening, disability and pain forms the major complaint of these patients. General examination, local examination and radiological examination followed by biochemical tests help in confirming the diagnosis. Osteoarthritis can be treated symptomatically as for other osteoarthritis. Surgical intervention necessitates in advanced stages. Treatment with ascorbic acid (Vit. C) and dietary restrictions of food containing phenylalanine and tyrosine have proved to be successful in alleviating the symptoms.

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