CASE REPORT

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Ochronotic arthropathy: case report and review of the literature

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Abstract Alkaptonuria is an inherited metabolic disorder which is associated with various systemic abnormalities and related to the deposition of homogentisic acid pigment in connective tissues. These pigmentary changes are termed “ochronosis”. We describe two patients with ochronotic arthropathy who presented with progressive and advanced degenerative changes in the lumbo-sacral spine. The literature, differential diagnosis and management of this rare condition are reviewed in this article. Management is usually conservative, but replacement surgery may be offered for severely affected major joints.

Résumé L'ochronose est une manifestation musculo-squelettique de l'alkaptonurie due à un désordre métabolique qui accompagne diverses anomalies systémiques et associé au dépôt de pigments acides homogénétiques dans les tissus congénitifs. Nous décrivons deux cas d'arthropathie présentant des douleurs progressives et des symptômes de dégénérescence avancée de la région lombo-sacrée. Cet article inclut la bibliographie, les diagnostics différentiels et le traitement de cette maladie rare. La thérapie classique est toujours d'actualité, mais l'implantation de prothèses peut être offerte dans des cas d'atteintes sévères des articulations majeures.

Introduction

Ochronosis was first described and so named by Virchow in 1866 as a post-mortem finding. He observed pigmentation of certain tissues in the body with granules which appeared black (ochre) in colour under the microscope, hence the name ochronosis.

The basic defect is absence of the enzyme homogentisic oxidase which is transmitted as an autosomal recessive trait. This enzyme normally oxidises homogentisic acid to malylacetoacetic acid, and the defect results

in a progressive accumulation of the substrate. There is no protein deficiency or other overt biochemical or hormonal abnormality.

Pigment deposition occurs in the affected joints in articular cartilage and also in peri-articular, collagen-rich ligaments and menisci. The tissues become black, lose elasticity and develop poor resistance to mechanical strain. Small blackened fragments of cartilage are dislodged into the joints where they become embedded into the synovial membranes. The spine and larger peripheral joints, most commonly the knees, are mainly involved and affected persons experience progressive disability, pain, and stiffness.

Pattern of presentation

Ochronosis generally presents in adults, although the disorder may be identified in childhood. With ageing, patients show increasing problems and joints which are particularly affected are the spine, knees, hips, and shoulders. The relentless development of the arthropathy is a characteristic feature and in some instances the articular involvement progresses rapidly, resulting in severe crippling by middle age. Affected males appear to have more problems than females, possibly due to their higher level of physical activity. A pathognomonic feature of ochronosis is darkening of the urine with exposure to air. A diagnostic test involves the addition of reducing substances such as glucose to the urine, which immediately darkens.

Distinguishing features of ochronotic arthropathy

The articular symptoms and signs of ochronotic arthritis (OCA) may resemble those of rheumatoid arthritis, notably chronic painful swelling and limitation of function of the joints. The radiological features are degenerative changes with loss of joint space and subchondral bone sclerosis. Osteophytic changes are not as evident as in

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Table 1 Screening tests for reducing substance in urine (Clinitest tablet (Ames Division, Miles Lab, Indiana, USA))

Reagent	Urine amount	Reaction
Copper sulphate sodium hydroxide	1 ml	Dark brown in minutes
Silver nitrate (5 ml)	0.5 ml	Immediate black coloration

osteoarthritis (OA). Spinal involvement usually presents with chronic low back pain (LBP) and stiffness. Radiography reveals widespread disc degeneration, compression and narrowing, with dense calcification. The pattern of involvement differs from that of degenerative joint disease (DJD) in that dorsolumbar changes predominate, as compared to lumbo-sacral in DJD. Non-articular manifestations include pigmentation of the pinna of the ears, sclera and nasal cartilae. Less common manifestations include aortic valve calcification and stenosis, and renal and prostatic stones.

Diagnosis

Ochronosis features in the differential diagnosis of atypical LBP, especially in adults without systemic manifestations of joint disease or infection. Initially, only a single, or a few large joints may be involved. The severity of the radiological changes is often out of proportion to the clinical symptoms and the age of the patient.

The differential diagnoses of chronic ochronotic LBP in the adult male includes disc prolapse, infection such as tuberculosis, brucellosis or fungal, and ankylosing spondylitis.

Diagnostic confirmation in ochronotic arthropathy is not difficult; a fresh urine sample mixed with a drop of

reducing agent darkens rapidly and urinary screening tests can be readily undertaken using one of the formats shown in Table 1. Specific quantitative determination of homogentisic acid in urine is available using gas chromatography and mass spectrometry.

Case presentations

Patient I – MM

A 39-year-old maintenance technician was referred to the orthopaedic clinic for assessment of progressive chronic LBP that interfered with his work. Lower back pain and stiffness had begun two and a half years previously, and was more noticeable in the morning and during prolonged squatting. The back pain generally improved with activity as the day progressed. The patient had also noticed occasional darkening of his urine.

There was no relevant family history and on examination, no other abnormality was found apart from some dark pigmentation of the right ear lobe. Musculoskeletal assessment revealed stiffness of the lumbo-dorsal spine, with pain on flexion.

Radiographic skeletal survey revealed changes that were predominant in the spine and extended from the lower dorsal region (Fig. 1). MRI showed diffuse loss of intervertebral disc height, mainly in the lower dorsal and upper lumbar regions, with heterogeneous intensity on T₁ and its loss in T₂. Multilevel, severe disc protrusions were seen at the L₃₋₄, L₄₋₅ and L_{5-S1} disc spaces (Fig. 2). The hip joints had superior acetabular sclerosis and early narrowing. The shoulders, hands, knees and wrists were radiographically normal.

Fig. 1a, b Frontal (a) and lateral radiographical (b) views of the lumbar spine of patient 1. These show calcification of the disc space and narrowing, with maximal involvement in the upper lumbar spine. The changes are far more advanced than would be expected for the patient's age

Fig. 2 Sagittal T₁ and T₂ weighted magnetic resonance images of patient 1. These show diffuse loss of intervertebral disc height mainly in the lower dorsal and upper lumbar regions. The disc spaces showed heterogeneous intensity on T₁ and its loss on T₂. Multilevel severe disc protrusions were evident at the L₃₋₄, L₄₋₅ and L_{5-S1} disc spaces

Fig. 3 Lateral and anteroposterior radiographs of the lumbar spine of patient II. Pronounced spondylsclerosis, disc calcification and narrowing of disc spaces are seen, together with a focal upper lumbar scoliosis, convex of the left

Fig. 4 Lateral magnetic resonance images in patient II. The sagittal T_1 and T_2 weighted views show diffusely narrowed disc spaces with loss of normal hyper-intensity due to calcification. Multilevel disc protrusions are present at L_{2-3} , L_{4-5} and L_5-S_1 . There is also a retrolisthesis of L_3 with respect to L_4 and loss of normal spinal curvature

Fig. 5 Antero posterior radiograph (AP) of the left shoulder of patient II showing pronounced narrowing of the joint space with some accompanying subchondral sclerosis

Fig. 6 Standing AP radiograph of the knees of patient II. Early loss of joint space, and subchondral sclerosis are more pronounced on the left side; minimal osteophytosis is present

Laboratory investigations, including the erythrocyte sedimentation rate, were normal. A urine sample tested with silver nitrate and ammonium hydroxide produced rapid, deep brown discoloration which confirmed the diagnosis of ochronosis.

Following diagnosis and counselling the patient changed his occupation. He also began a physiotherapy program which, with occasional use of simple analgesics, helped to control his symptoms.

Patient II – HQ

A 48-year old male was referred for assessment of progressive chronic LBP and shoulder pain. The LBP and stiffness had begun 9 years previously and more recently he had experienced symptoms in both shoulders, predominantly on the left side. He also complained of pain and stiffness in his fingers and occasionally in his knees. There were no other symptoms and no relevant family history.

Examination revealed dark bluish pigmentation on the radial border of his index and little fingers together with localised pig-

mentation of the sclerae of both eyes. Musculoskeletal assessment revealed marked stiffness in the dorsal-lumbo spine with diffuse tenderness in the mid-lower back. Movement of the pelvis gave rise to back pain. Examination of the knees revealed peri-articular thickening and 5°–120° of flexion with diffuse crepitus. Movement of the shoulders was associated with marked crepitus on the left side and limited elevation and rotation. Both hips showed slight limitation of rotation. The joints of the hands were not affected but the mid-tarsal joints of the feet were thickened. Radiographs of the lumbar spine revealed a mild scoliosis convex to left, narrowing of the disk spaces throughout the dorso-lumbar region with extensive disc calcification, and secondary degenerative changes at the area of maximum deformity (Fig. 3). All these features were compatible with an ochronotic arthropathy.

The sagittal T₁ and T₂ weighted MRI images revealed extensive disc space narrowing with loss of the normal hyperintensity due to calcification. Multilevel disc protrusions were noted at L₂₋₃, L₄₋₅, and L_{5-S1}. There was also retrolisthesis of L₃ with respect to L₄ and loss of normal curvature (Fig. 4).

Radiographs of the left shoulder showed marked narrowing of the joint space with some accompanying subchondral sclerosis, without osteophytosis (Fig. 5). Knee radiographs revealed early loss of joint space, which was more pronounced on the left side; subchondral sclerosis and minimal osteophytosis were present (Fig. 6). Radiographs of the hand showed symmetrical bilateral narrowing of the distal interphalangeal joints of the fifth digits.

Laboratory investigations, including assessment of rheumatoid factor and the erythrocyte sedimentation rate, yielded normal results. The urine tested positive for reducing substances.

Physiotherapy was carried out, together with education for a home exercise program, and strengthening exercises for the spine and knees were taught. Surgical replacement of the left shoulder was discussed as a possible future option for treatment.

Discussion

Persons with ochronosis (alkaptonuria) are usually asymptomatic until the 4th decade. Thereafter the condition progresses as a symptomatic arthropathy. The first clinical manifestation of alkaptonuria is often a change of urine colour but the diagnosis may be delayed until joint symptoms develop. Both of our patients presented with progressive spinal symptoms in early middle age.

An explanation as to why it takes so many years to develop ochronotic arthropathy, even though alkaptonuria is present at birth, is that there is an effective second line clearance mechanism for the accumulation of homogentisic acid. This process involves the renal tubular excretion system which efficiently secretes homogentisic acid (HA) as it does other organic acids. For this reason, an adult with alkaptonuria, on a regular diet, secretes several grams of homogentisic acid per day. Renal clearance of HA is maintained very effectively in youth. With ageing, the efficiency of the process decreases and the steady level of plasma HA slowly rises. This development accelerates the accumulation of HA over time.

The radiological appearances are of a degenerative joint disease with loss of joint space, pronounced sclero-

sis, small cysts, peri-articular calcification and mild osteophytosis. The extent of the radiographical changes are usually out of proportion of the age of the affected person, as evident in the radiographs of the spine of both our patients.

A key patho-physiological question remains unanswered. How does the metabolic defect lead to the connective tissue degradation of ochronotic arthritis? The pathogenesis may be simple. Benzoquinone acetic acid, derived from oxidation of homogentisic acid, may inhibit the enzyme lysine hydroxylase and thereby reduce the cross-linkage of collagen fibres. This would enhance fibre vulnerability to stress and shearing injury, leading to connective tissue failure, cartilage erosion, and progressive degenerative changes. If this sequence or a similar one were confirmed, a theoretical approach to preventive therapy might be to protect the lysyl hydroxylase by suitable reducing agents.

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