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Case Report

Coexistence of Ochronosis and Rheumatoid Arthritis

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Summary **We describe a 64-year-old female patient with ochronosis and rheumatoid arthritis. Magnetic resonance imaging of the spinal column disclosed the destruction of vertebral disks, and a bony bridging in Th12 to L2. In addition, we observed joint space narrowing in the wrists as well as among the carpal bones, positive rheumatoid factor and the presence of rheumatoid nodules, in which the histological findings were compatible with those of rheumatoid arthritis. The coexistence of these two diseases has not yet been previously reported. Pre-existing ochronotic arthropathy might have masked the manifestation of rheumatoid arthritis and made the diagnosis of rheumatoid arthritis rather difficult.**

Key words **Rheumatoid Arthritis, Ochronosis, Alkaptonuria.**

INTRODUCTION

Alkaptonuria is an inborn error of the metabolism of tyrosine and phenylalanine which is inherited in an autosomal recessive manner. The occurrence of alcaptonuria ranges from 1/100,000 to 1/1,000,000 (1). In patients with alcaptonuria, homogentisic acid oxidase is absent from the liver and kidney, and the excretion of homogentisic acid into the urine is usually characterized by a darkening of the urine (alcaptonuria) as well as the presence of pigmentation in the ear, axilla, sclera and upper respiratory tract (ochronosis) (2-4). When such patients enter their late 30's, up to 50% of them suffer from spondylosis and arthropathy, usually beginning with backache prior to the onset of joint symptoms. The deposition of homogentisic acid is most prominent in the cartilage (2,4,5). Histologically, the synovial membrane is thickened with a proliferation of synovial lining cells and infiltrated mononuclear cells, while numerous pigments are mounted in the synovial tissue and cartilage (2,4,5). We encountered a patient with alcaptonuria and ochronosis, also complicated with rheumatoid arthritis (RA) (6). Since the association of ochronosis and RA is quite rare, we herein present this case.

CASE REPORT

In June 1992, a 64-year-old woman visited our outpatient clinic complaining of pain in both shoulders, left knee, lumbar spine which started in her late 40's, as well as pain in both hands and wrists. Since the age of 56, she had been suffering from pain and the swelling of both wrists, metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints and her left knee.

The family history revealed that the patient's parents had a consanguineous marriage (Fig. 1). Her mother, grandmother and younger brother of her mother were diagnosed as having rheumatoid arthritis; however, the diagnosis of RA was not based on any definite findings such as evident joint destruction on X-ray films or the presence of rheumatoid factor.

A physical examination showed a bilateral brown pigment in the sclera and a blue-black pigmentation of the ear cartilage. Morning stiffness in the hands lasted for 30 minutes; the grip strength of the hands, as measured by a sphygmomanometer, was 136 mmHg (normal>260 mmHg). The patient's bilateral shoulders, wrist, MP and PIP joints, and knees were swollen and painful. She also had nodules around the olecranon of both elbows.

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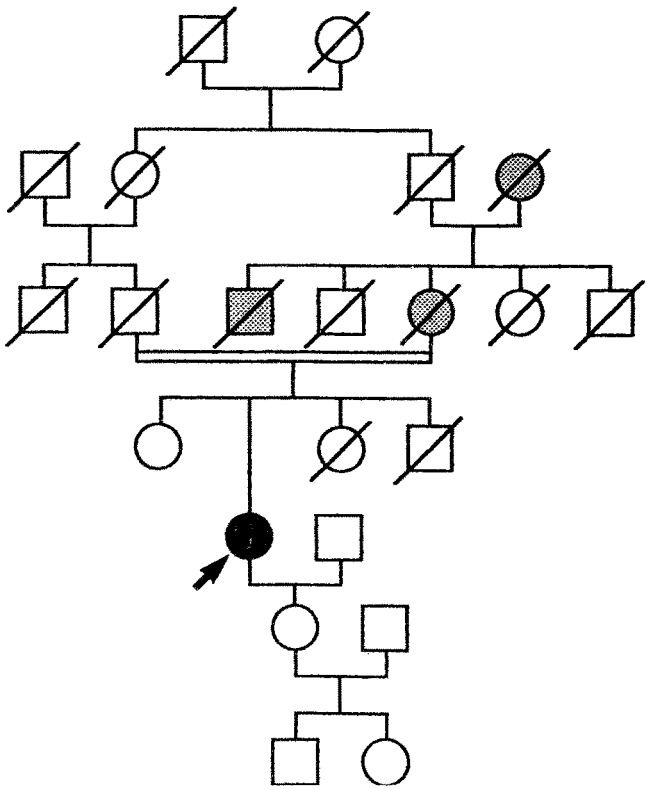


Fig. 1: Pedigree chart of a patient with ochronosis and rheumatoid arthritis.
The pedigree chart indicates the presence of a consanguineous marriage in her parents and suggests the prevalence of rheumatoid arthritis in her mother's pedigree. The daughter's urine did not show any homogentisic acid. One of the elder sisters is still alive, but the collection of urine and blood could not be made.
: proband, : suspected rheumatoid arthritis.

Laboratory tests disclosed a white blood cell count of 9,900/μl, haemoglobin of 8.8 g/dl, platelet of 62.9×10^4/μl, erythrocyte sedimentation rate of 74 mm at 60 min, CRP of 9.60 mg/dl, rheumatoid factor of 264 IU/ml (normal; less than 21 IU/ml) measured by laser nephelometry. HLA typing was A2, A11, Bw55(w22), Bw61(49), Cw1, DR4 and DR12 (5). The urine turned black on alkalinization. The gas chromatography/mass spectrometry of the urine showed a definite peak of homogentisic acid, but the serum showed no such peak.

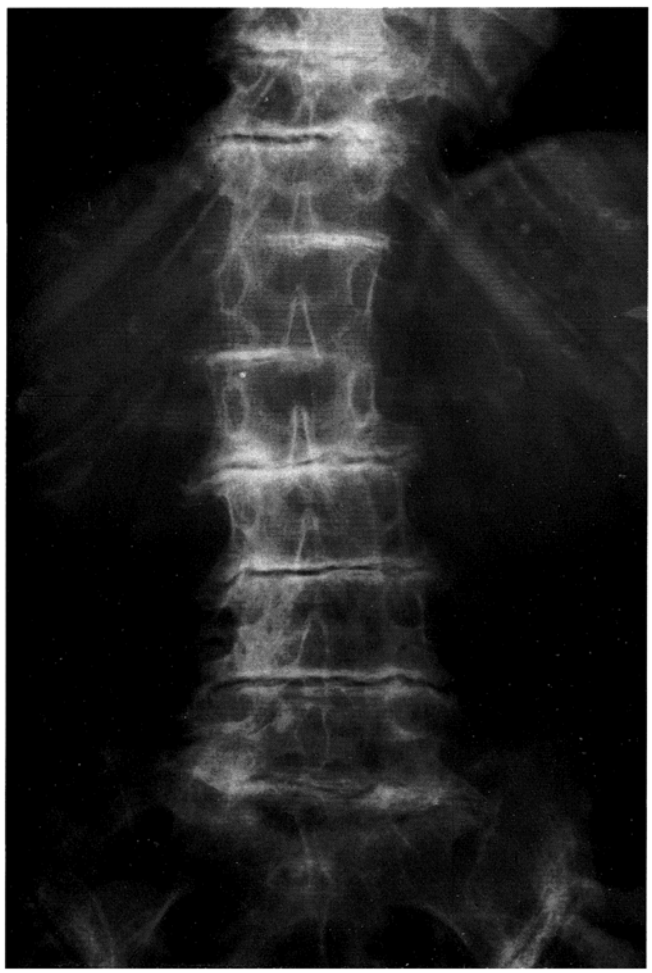
The synovial fluid of the right knee revealed a leukocyte count of 13,000/μl mostly composed of polymorphonuclear leucocytes, rheumatoid factor of 273 IU/ml, CH50 of less than 12 u/ml, total protein of 5.1 g/dl with 57.1% of albumin and decreased mucin content. Neither cytoplasmic inclusions in the mononuclear cells nor calcium pyrophosphate dihydrate crystals was found. A biopsy of the subcutaneous nodule on the right elbow showed that the specimen consisted of fibrous connective tissue with fibrinoid degeneration and mild proliferation of the lining cells with inflammatory cell infiltration. A labial salivary gland biopsy revealed neither lymphoid infiltration nor any deposition of ochronotic pigments.

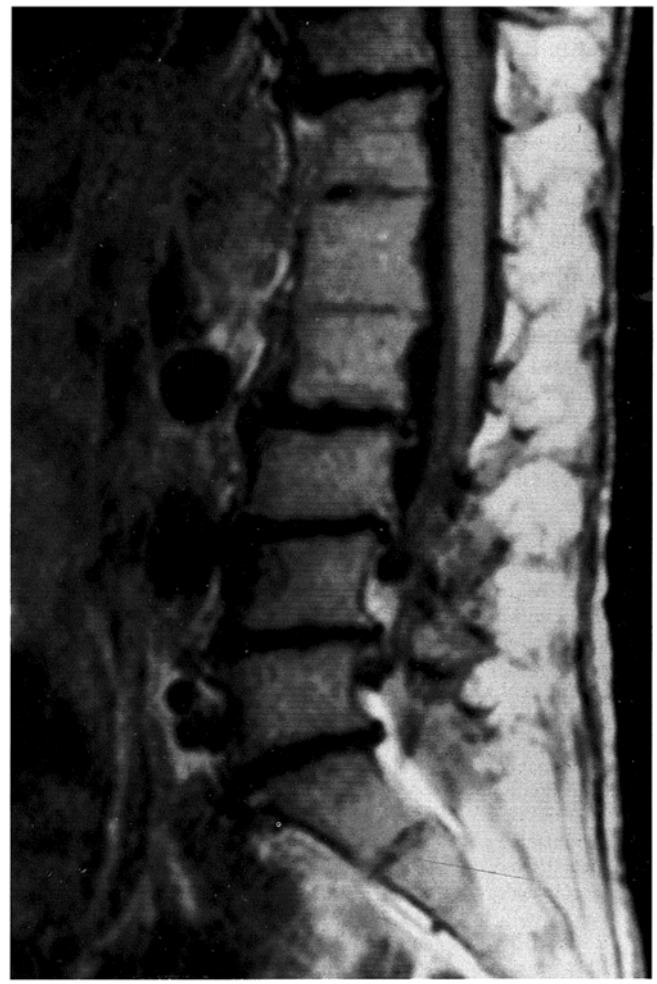
Bony bridging and osteosclerosis of the spine together with a marked narrowing of the intervertebral spaces from Th12 to L2 as well as an irregular surface of the intervertebral discs in L2-L5 were found in the spine (Figs. 2a, 2b). The shoulder and knee joints showed joint space narrowing, marginal osteophyte and a mild bone erosion. The hip, ankle and elbow joints were all normal. The sacroiliac joint indicated no fusion. Pubic symphysis showed a moderately narrow and irregular joint space. The plain X-ray films of the hands showed a mild space narrowing and osteopenia in both wrists and carpal joints (Fig. 2c). The MCP and PIP joints were almost normal.

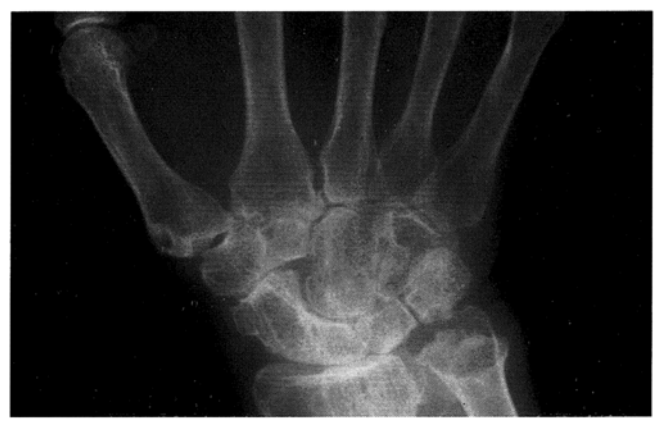
DISCUSSION

The patient suffered from alcaptonuria and ochronosis because of the increased urine excretion of the homogentisic acid as well as the deposition of brown pigment in the sclera and cartilages of the ear. Ochronosis is reportedly caused as a result of adverse reaction to drugs such as anti-malarial agents (7). There was, however, no evidence that our patient had been previously administered such drugs. Bone lesions of ochronotic spondylosis and arthropathy are of a degenerative nature and the radiographic findings in the joints are composed of the loss of joint space, the formation of osteophyte and joint destruction (2,4,5,8). Ochronotic arthropathy is commonly observed in the spine and large peripheral joints such as the shoulder, hip and knee (2,4,5). Bone changes in small joints, however, such as those in the hands and feet are unusual (2,4,5). The patient had symmetric arthritis involving hands and the space narrowing in carpal joint and wrist with mild osteopenia. The presence of symmetric polyarthritis, morning stiffness, joint destruction, rheumatoid factor and subcutaneous nodules supports the diagnosis of classical RA (6). Although the subcutaneous nodule of the patient was lacking in the central necrosis surrounded by palisading histiocytes, the histological findings of the patient were not contrary to those of rheumatoid nodules (6). Furthermore, synovial fluid from the knee joint had an inflammatory nature, which is compatible with that of RA (6). We, therefore, presented our case as the association of ochronosis with RA.

There have been a few reports on the association of ochronosis with connective tissue diseases such as chondrocarcinosis and ankylosing spondylitis (AS) (4,9-11).







Figs. 2a ↑, 2b ↗, 2c →: An X-ray film and magnetic resonance imaging of the spine as well as an X-ray film of both hands of the patient with ochronosis and rheumatoid arthritis.
Narrowing of the intervertebral spaces and irregular intervertebral discs, and bony bridging from Th12 to L2 are indicated on plain X-ray film(a) and magnetic resonance imaging(b). A mild space narrowing and osteopenia in both the wrist and carpal joints are observed, but the MCP and PIP joints are almost normal(c).

In our case, AS was ruled out by the absence of syndesmophyte resulting in the formation of a bamboo spine and vertebral body squaring, ankylosis of sacroiliac joint, whiskering at the ischial tuberosities and erosion at tendon insertions (12). In addition, pubic synchondrosis, which is commonly observed in AS, is not uncommon in patients with ochronosis (2,4,5). The pedigree chart of the patient indicates the presence of consanguinity and suggests the clustering of RA in the pedigree of the patient's mother. The patient did not have HLA-B27, which was reported to play some role in the asso-

ciation of AS with ochronosis, although this role is not as definite as the familial occurrence of AS (9,11,12).

The coexistence of ochronosis and RA has not been reported in the past 20 years in the world literature, while the occurrence of female patients with RA and AS has been reported to be 2.4/1,000 and 0.5/1,000, respectively (13). The occurrence of AS is much lower than that of RA. However, it has not yet been elucidated why the association of ochronosis and RA has never previously been reported. It has been reported that some patients with RA are free from rheumatoid factor and rheumatoid nodules. If our patient had been free from these two, then the diagnosis of RA might not have been made and symptoms based on rheumatoid inflammation might have been ascribed to those of ochronosis. Furthermore, if the disease onset of ochronosis had preceded that of RA as in our case, the coexistence of RA might have been masked by the ochronosis. It has been reported that the HLA class II antigens, such as HLA DR4 which our patient had, also play a significant role in the occurrence of RA (4). The HLA typing of the patient's relatives with arthritis, however, were not available since all had already died.

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