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CASE BASED REVIEW

Family history of ochronotic arthropathy

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Abstract

Alkaptonuria is a rare autosomal-recessive disorder that produces accumulation of homogentisic acid in body fluids. The accumulation in collagen tissues, mainly in the joint cartilage, produces ochronotic arthropathy. We report two clinical cases of one brother and sister with alkaptonuria and ochronotic arthropathy diagnosed in old age. In the first case, the patient is diagnosed by musculoskeletal involvement with long-term low back pain with other associated manifestations that made this pathology suspected. In the second case, the patient comes due to osteoporosis and other associated fractures and with the family history and the rest of the clinic, the appropriate complementary tests were performed and the diagnosis is established. It is unknown if there is consanguinity in these patients between parents or ancestors. It is an infrequent pathology that is often diagnosed intraoperatively. Despite the poor efficacy of medical treatment, it would be advisable to make an early diagnosis to avoid accumulation of the pigment and accelerated joint destruction and deposition in other locations. Owing to its prevalence, it is difficult to find a significant number of patients to search for new treatments that are intended to correct the enzyme deficit and not only to modify the elimination.

Keywords Ochronotic arthropathy · Alkaptonuria · Ochronosis · Osteoporosis

Introduction

Ochronotic arthropathy is a musculoskeletal manifestation in patients with alkaptonuria. Alkaptonuria is a rare autosomal-recessive disorder with a prevalence lower than 1:200,000 that is increased in Dominican Republic and Slovakia, around 1:19,000 [1–3]. It was first described by Garrod in 1902, being the first disease recognized to follow classic Mendelian-recessive inheritance [2, 4, 5]. This metabolism error is due to the deficiency of the homogentisate 1,2-dioxygenase homogentisic acid 1,2 dioxygenase (HGD). Due to this, homogentisic acid (HGA) cannot be converted to maleylacetoacetate and it accumulates in body fluids and then being converted in benzoquinones that are finally converted to melanin-like pigments that deposit in collagen tissue [6, 7].

The accumulation of homogentisic acid causing ochronosis occurs mainly at the level of the articular cartilage, in addition there is accumulation in tendons, heart valves and in the prostate besides depositing in other tissues. All this can cause more accelerated degenerative pathology and arthritis at the joint, spontaneous tendon rupture, valvular heart disease, and prostatic pathology in the form of lithiasis and prostatitis [8–11]. In many patients, it is asymptomatic until more advanced ages, being able to be diagnosed by dark urine or occasionally during a joint replacement surgery.

In the ochronotic arthropathy, symptoms usually begin around the third or fourth decade with low back pain and stiffness and can subsequently extend to the thoracic spine causing limitation for thoracic expansion. The axial clinic

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usually begins insidiously although it may debut abruptly due to the rupture of the nucleus pulposus [11–15]. The described peripheral arthropathy is mainly degenerative in which destruction of the articular cartilage occurs in an accelerated way although joint inflammation can also be produced. The arthritis showed inflammatory synovial fluid with absence of calcium pyrophosphate crystals (CPPD) although CPPD arthropathy can precipitate episodes of arthritis in patients with ochronosis [16, 17]. The involvement occurs predominantly in weight-bearing joints, such as the knees and hips, while the involvement of small joints in the hands is uncommon [11]. As we have already mentioned, tendon deposition is also relatively frequent, which can lead to calcifying tendonitis or spontaneous rupture. Pigmentation of the sclera or auditory pavilion are typical and can help diagnosis in the presence of arthropathy [11, 18, 19]. The purpose of this work is to describe two cases of ochronosis, an infrequent disease, focusing on musculoskeletal involvement in two patients who are first-degree relatives.

Case 1

A 71-year-old male patient attended the Rheumatology Department in November 2002 with a 10-year history of chronic low back pain, diagnosed with ankylosing spondylitis in another center. No family history of interest was known. Like other personal history, he presented benign prostatic hyperplasia, recurrent nephritic colic, and sleep apnea. Upon arrival, the patient was being treated with NSAIDs and low back pain persisted, with great limitation for trunk flexion. In addition, he presented right coxalgia for a few months and occasionally bilateral gonalgia without associated swelling.

In the examination, we found axial stiffness with trunk flexion limitation and decreased range of movement of both hips, being painful with the opening maneuvers. Crepitus was present in both knees with active movement with no associated swelling. Sclerae pigmentation and a skin lesion in the right temporal region suggesting a melanocytic nevus were observed. Blood test with study of HLA-B27 and radiographic study of pelvis, lumbar spine, and both knees were requested. The HLA study was negative and the blood count, liver enzymes, renal function, and acute phase reactants were within normal limits. Upon suspicion, urine mass spectrometry was performed, showing a high intensity peak of HGA.

Radiography of the spine evidenced diffuse narrowing of the lumbar intervertebral spaces with osteophytosis, calcification, and vacuum phenomenon of the intervertebral discs and facet arthrosis (Fig. 1). The pelvis showed important loss of joint space of both hips (predominantly on the right hip) and sacroiliac joints with asymmetric signs of joint space narrowing, osteophytosis and subchondral sclerosis (Fig. 2). Furthermore, osteophytosis and subchondral sclerosis in the symphysis pubis were also found. Exeresis of the skin lesion was performed, showing intraepidermal melanocytic nevus with brownish pigment deposition compatible

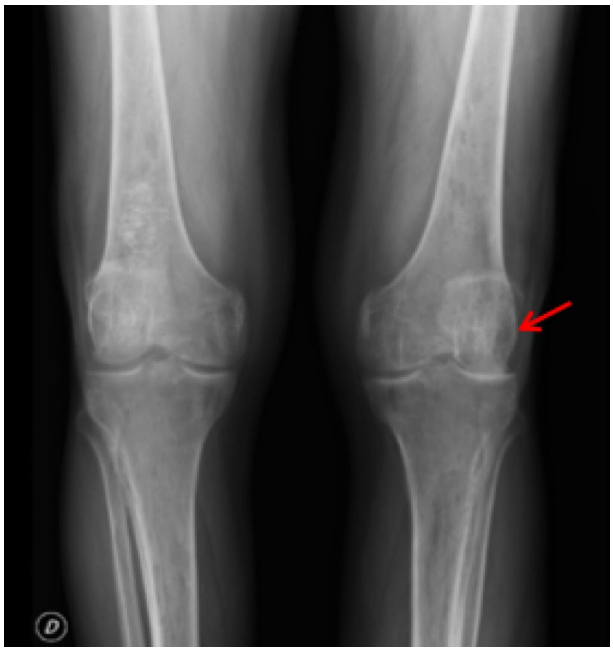

Fig. 1 (Case 1). Circle: Calcification and vacuum phenomenon in intervertebral discs. Arrow: Diffuse narrowing of the lumbar intervertebral spaces with osteophytosis

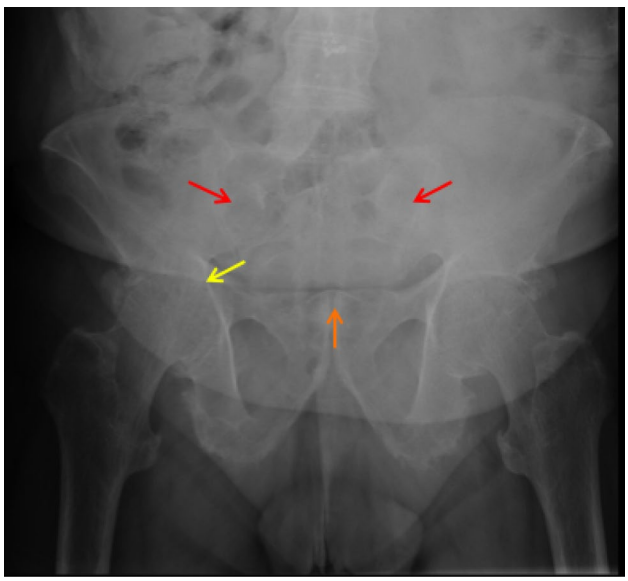

Fig. 2 (Case 1). Red arrow: Subchondral sclerosis with asymmetric joint space narrowing. Yellow arrow: Narrowing of joint space with superior migration of the right hip. Orange arrow: Osteophytosis and subchondral sclerosis in symphysis pubis

with homogentisic acid. A transthoracic echocardiogram was performed without signs of valve calcification.

Owing to the radiological findings and his symptoms, the patient was referred to the Trauma and Orthopedic Surgery department and a total right hip arthroplasty was performed. Macroscopically, a brownish pigment was found in the cartilage of the femoral head. Considering all these findings, it was decided to start treatment with vitamin C (at a dose of 10 g a day, divided into four doses according to the dosage administered in other previous studies [20]) to decrease the conversion of HGA in its intermediaries, dietary restriction, and physical therapy with associated NSAIDs (Ibuprofen 600 mg/8 h). The patient is currently being monitored every 3 months in outpatient Rheumatology consultations and in subsequent follow-up by the Trauma and Orthopedic Surgery Department.

Case 2

A 68-year-old female patient was admitted to our unit in February 2019 referred by her primary care doctor for osteoporosis with associated fractures. As the only family history of interest, the patient reported that her brother (Case 1) was diagnosed with alkaptonuria with ochronotic arthropathy and was being followed up by our service. The patient's past medical history consisted of a distal radius fracture in March 2018, olecranon and patella fracture in October 2018 after accidental fall from her own height. No other medical history of interest was reported. For more than 10 years, the patient has had low back pain that responded partially to NSAIDs and for approximately 1 year, left gonalgia that has been increasing in the recent months without associated swelling.

Physical examination of the patient revealed a dorsolumbar kyphoscoliosis, crepitus in both knees with active movement with no swelling and sclerae pigmentation (Fig. 3). To complete the study, we requested blood test with bone metabolism markers, HLA-B27, and acute phase reactants, revealing that all parameters were within normal limits. In addition, a selective bone densitometry was requested (last in 2015) showing a lumbar spine T-score of − 3.9 and a femoral neck of − 4.2. Dorsal, lumbar, knees, and pelvis radiographs were performed. Dorsal and lumbar radiograph showed calcification of the discs, narrowing of the intervertebral space, osteophytosis, and lumbar scoliosis. In both sacroiliacs, a decrease in joint space with associated subchondral sclerosis was observed. The radiograph of both knees presented a decrease in joint space with impingement of the external compartment of the left knee (Fig. 4) and loss of bilateral femoropatellar space with calcification in the distal femur in the right knee. Urine mass spectrometry was performed and showed a high intensity peak of HGA. A transthoracic echocardiogram revealed calcification of the aortic valve that caused mild valve stenosis without other valve involvement.

Due to the described findings, it was decided to start treatment with intravenous zoledronic acid (5 mg annually in a single dose) and calcifediol (0.266 mg per month) together with physical therapy and analgesic treatment associated. The patient is currently being monitored by the Trauma and Orthopedic Surgery department to assess possible intervention of the left knee. In this case, it does not require a close follow-up since the arthropathy is not as severe and is well controlled with analgesic treatment and is followed up

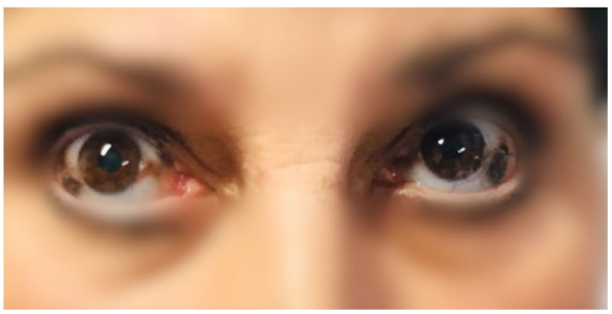

Fig. 3 (Case 2) Sclerae pigmentation

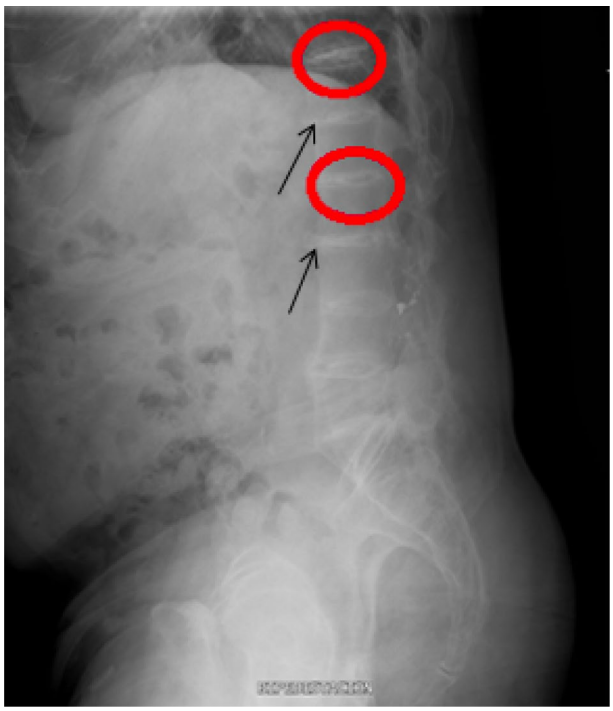

Fig. 4 (Case 2) Decrease in joint space with impingement of the external compartment of the left knee and loss of bilateral femoropatellar space with calcification in the distal femur in the right knee

every 5 months with annual administration of treatment for osteoporosis.

Search strategy

We searched MEDLINE for English-language sources using the following keywords: ochronosis, ochronotic arthropathy, alkaptonuria and then we used advanced search to combine osteoporosis and ochronosis. Preference was given to sources published within the past 10 years. Since we found many results (542) with the search for the term alkaptonuria due to the multitude of articles that collect all the associated manifestations, we decided to narrow the search with the term ochronotic arthropathy, finding 215 articles. To analyze the most recent articles, we focused our search on the last 5 years finding 33 results. Of all the previously analyzed, we focused mainly on those who comment on aspects related to musculoskeletal manifestations without focusing excessively on the surgical approach. We also checked the references in the retrieved articles.

Discussion

The clinical characteristics of the patients we describe (Table 1) are similar to those described in the literature. In our patients there is an accelerated degeneration of the articular cartilage affecting the axial skeleton and the weight-bearing joints. In our case, we objectified axial arthropathy with calcification of the vertebral discs with narrowing of the space and involvement at the sacroiliac level, which led to an erroneous diagnosis in the first case. Regarding peripheral involvement, it mainly occurs in the knees and hips, the clinic being subsequent to low back pain. In the hip, there is a superior migration of the femoral head with narrowing of the joint space that required arthroplasty and in the case of the knee, clamping of the external compartment of the knee, not requiring surgical intervention at the moment.

Another common manifestation that occurs in our patients is the pigmentation of the sclerae [11, 18], a patient also presented a nevus that contained HGA pigment. Neither patient had referred dark urine regularly, although the second case suffered some occasional episodes attributed to urinary infections. No spontaneous tendon ruptures or involvement of the Achilles tendon, long tendon of the biceps or supraspinatus has been described. The second case showed cardiac valvular involvement and in the first case a clear relationship between prostate pathology and the disease cannot be established.

The main objective in this disease, especially in patients with late diagnosis, is to minimize the damage of arthropathy, trying to reduce the accumulation of HGA in tissues.

Table 1 Clinical manifestations

Gender(Male/Female)	Age (years)	Age at diagnosis (years)	Urinary HGA	Axial involvement	Hip arthropathy	Knee arthropathy	Arthritis	Tendon affection	Arthroplasty	Sclerae pigmentation	Valvular calcification
M	71	53	3.0	++	++	+	–	–	+	+	–
F	68	67	3.2	+	–	++	–	–	–	+	+

+/− stand for presence (+) or absence (−) of the clinical manifestations in our patients

Dietary restriction has conflicting results in studies and seems to be more useful in patients diagnosed in childhood [21–23]. Vitamin C is used to modify the urinary excretion of HGA and can reduce the binding of this pigment to tissues [22–24]. The role of Nitisinone could be important in reducing the production of HGA and is being investigated [7, 25–28]. Currently, the basis of treatment is an early diagnosis, symptomatic treatment, physical measures and in cases with advanced arthropathy surgical replacement or arthroscopic treatment [15, 29].

As we have previously commented, the majority of articles on musculoskeletal involvement focus on the surgical approach, since ochronotic arthropathy is sometimes diagnosed intraoperatively or because it is the only treatment in most cases when the damage is advanced. This and the poor efficacy of medical treatment in most cases could be the reasons that could explain why most articles focus more on the surgical approach. In the most recent articles on ochronotic arthropathy, Wu et al. conducted a very comprehensive review of the literature on the musculoskeletal manifestations of the disease, in the form of early arthropathy, tendinopathy, and osteopenia/osteoporosis [30]. This article makes a similar approach to our case since it focuses on musculoskeletal involvement and reviews the literature on the types of involvement (joint, tendon, and bone mineral density) and the evidence that exists in medical treatment. In another article from the same year, Couto et al. comment on a case that is relatively frequently described in the literature, the intraoperative diagnosis of ochronotic arthropathy, a pathology that produces early arthropathy in these patients [31]. We believe that our case is of interest because it is a rare disease presented in two patients who are first-degree relatives, finding few cases in the literature since most of them are unique clinical cases due to the low prevalence. In both cases, a late diagnosis was made (in no case in childhood), which despite the fact that the response to medical treatment is not usually effective, could have required an earlier arthroscopic or surgical procedure.

In one of the cases, the diagnosis is made by joint involvement, as described above, in weight-bearing joints, in its case of axial predominance, knees and hips. In the second case, the diagnosis is suspected when presenting osteoporosis with associated arthropathy and the family history of her brother, so the study of this disease is carried out. Therefore, it is of interest because in both cases, the musculoskeletal involvement is described, being different in both cases (in one of them it has required surgical intervention and in the other it is evaluated for the future) and also they present other types of manifestations, such as cardiac valve and ocular involvement. Tendon involvement is not described in any of the cases. Despite the fact that medical treatment options are limited, since they cause a delay in the progression of the disease, early diagnosis is important for the surgical evaluation in earlier stages if necessary.

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Compliance with ethical standards

Conflict of interest We know no conflicts of interest associated with this publication, and there has been no financial support for this work that could have influenced its outcome.

Ethical statement All mandatory laboratory health and safety procedures have been complied with in the course of conducting any experimental work reported in the manuscript. We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. As Corresponding Author, I confirm that the manuscript has been read and approved for submission by all the named authors with subsequent modifications. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The publication is approved following the guidelines of the ethical committee of the University Hospital of Salamanca (CEIM Hospital Universitario de Salamanca. Ref: E.O. 19/743 EPA-OD 19 10/02/20).

Informed consent The patient involved agrees to include their clinical data for the publication of the case report.

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