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Ochronosis – a rare metabolic disease

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ABSTRACT

Alkaptonuria is a rare disorder, an autosomal recessive condition with genetic determinism and hereditary transmission, having a prevalence of 1 per 1 million population in USA. The pathogenesis includes the deficiency of the homogentisate 1,2-dioxygenase (HGD) enzyme, an intermediary enzyme in phenylalanine and tyrosine catabolism. Mutations in HGD gene leads to deficient levels of functional HGD and an excess of homogentisic acid (HGA). Although HGA is rapidly excreted by the kidneys, it slowly accumulates in various tissues. Due to HGA oxidase deficiency, HGA turns into melanin-like pigment which determines: alkaptonuria, accumulation in the connective tissues, in the joints, or can make cardiovascular and genitourinary deposits. The chronic accumulation of HGA destroys the affected tissue, leading to the characteristic black-blue colour and to clinical symptoms of alkaptonuria. The aim of this paper is to investigate the particularities of rheumatic manifestations in a rare metabolic disease and to support the correct diagnosis.

A 58-year-old male patient was admitted to our clinic in 2019 for bilateral knee and left shoulder pain. In 2008 he was diagnosed with polyarticular ochronosis having dorsal and lumbar pain, mixed scapulohumeral pain, lumbar intervertebral disk calcifications; at that time, a diagnosis of ankylosing spondylitis or Forestier disease was excluded. At the current admission, the patient has been thoroughly reassessed to obtain a proper diagnosis and to determine the severity of the disease. The ochronotic axial damage caused important differential diagnosis problems with ankylosing spondylitis.

Pigment deposition in the eyes, ears and skin does not cause problems to patients, but cardiovascular and genitourinary deposition leads to important complications. Kinetotherapy and NSAIDs are beneficial for pain symptoms. There is no specific medication for stopping the disease progression.

Conclusions. Ochronosis is a rare disease which can cause a lot of problems regarding a proper diagnosis and treatment. When differential diagnosis with AS is difficult, the HLA-B27 genotyping is recommended. Final diagnosis is based on qualitative and quantitative urinary tests. The treatment includes only symptomatic drugs such as NSAIDs and kinetotherapy to improve joint mobility and muscle toning.

Keywords: ochronosis, alkaptonuria, ankylosing spondylitis

INTRODUCTION

Alkaptonuria is a rare, autosomal recessive metabolic disorder caused by homogentisic acid (HGA) oxidase deficiency, the only enzyme capable of catabolizing HGA. It is known that HGA is an intermediary metabolite in phenylalanine and tyrosine catabolism. The gene responsible for this defect codifies the 445-amino acid homogentisate 1,2-dioxygenase (HGD) enzyme mapped to chromosome 3q21-q23 [1-6]. Over 90 different mutations in the HGD gene have been found [4,6]. A loss of 99% in HGD activity is required to cause the symptoms of the disease. HGD deficiency leads to the accumulation of HGA and the production of oxidized products such as benzoquinone acetate acid (BQA). Both HGA and BQA generate specific blue-black coloration of the cartilage, followed by degeneration, inflammation and calcification of tendons, ligaments, intervertebral discs, large joints and an increased bone resorption [7]. The role of interleukin 6 (IL-6) in the pigmentation process of chondrocytes has been demonstrated [8]. The affected connective tissues become fragile over time, leading to degenerative changes and osteoarthritis (OA) [9]. HLA-DR7

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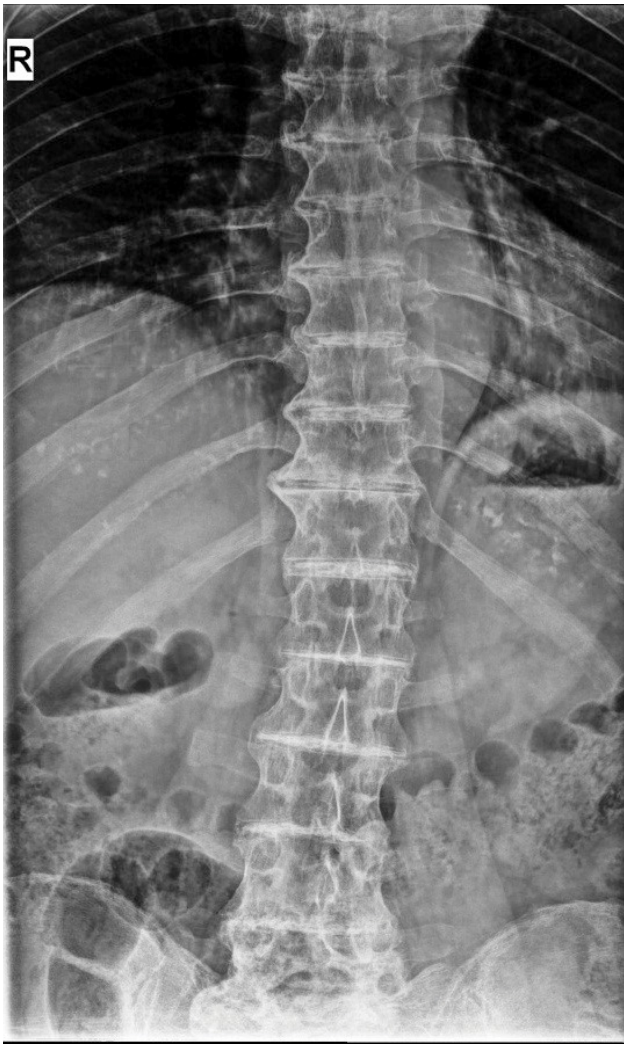

FIGURE 1. X-ray of the dorsal and lumbar spine (2008). The image shows intervertebral discs calcifications, bone bridges between dorsal vertebras

antigen was found in patients with alkaptonuria, being included in the genetic predisposition of these cases [10].

CASE PRESENTATION

The 58-year-old male patient was first admitted to our clinic in May 2008 for low back pain and quasi-permanent bilateral knee and shoulder pain. He was diagnosed with polyarticular ochronosis according to X-ray modifications (lumbar intervertebral disk calcifications) and a positive urine test (Figure 1). At that time, a differential diagnosis with ankylosing spondylitis (AS) and Forestier disease was made.

In 2019, he was admitted for reassessment. Personal medical history revealed that in May 2012 the patient had a total right hip arthroplasty for secondary ochronotic hip OA.

The clinical examination revealed: bilateral blue-black pigmentation of the eyes and of the ear cartilage; anterior projection of the cephalic extremity; a flattened thoracic cage followed by abdominal breathing; dorsal kyphosis; paravertebral lumbar muscular contracture; a significant limitation in the mobility in the whole spine; negative sacroiliac joint maneuvers; limited mobility in the knees, shoulders and hips (Figure 2).

The biological parameters revealed no inflammatory syndrome, discrete normochromic, normocytic anemia, hyposideremia and a normal urinary test. But, macroscopically, the urine colour has changed after being left for two hours in open air.

Taking this fact into consideration, the urine alkalization test was made. In the laboratory of the

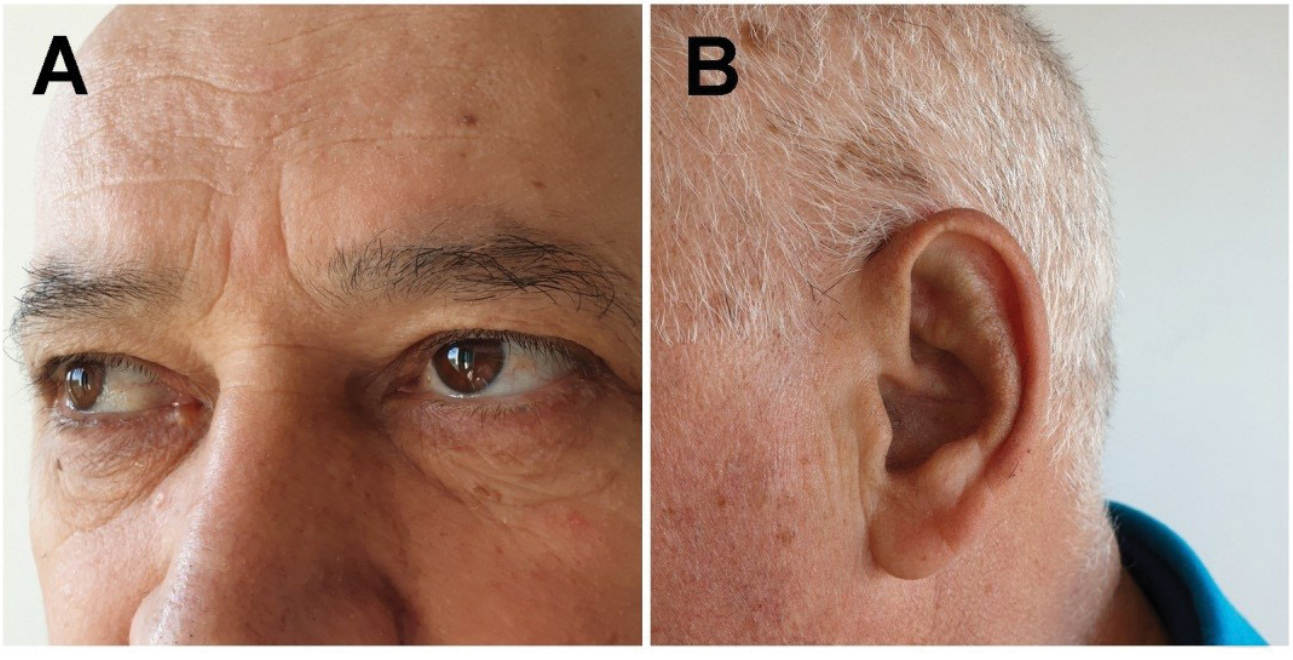

FIGURE 2. Clinical aspects of the patient: (**A**) Hyperpigmentation of the lower eyelids; (**B**) Hyperpigmentation of the antihelix

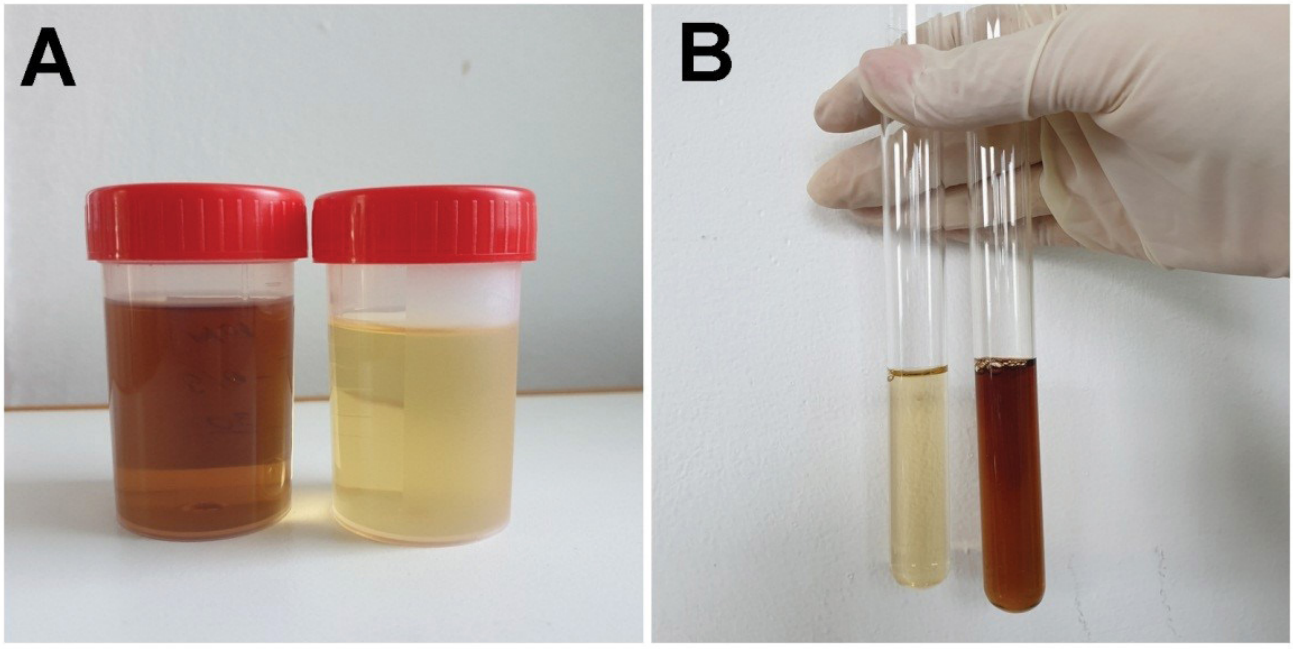

FIGURE 3. Modifications in the urine colour: (**A**) Urine samples before and after being left in open air; the urine became dark brown; (**B**) Urine discoloration after adding NAOH; the specific brown colour

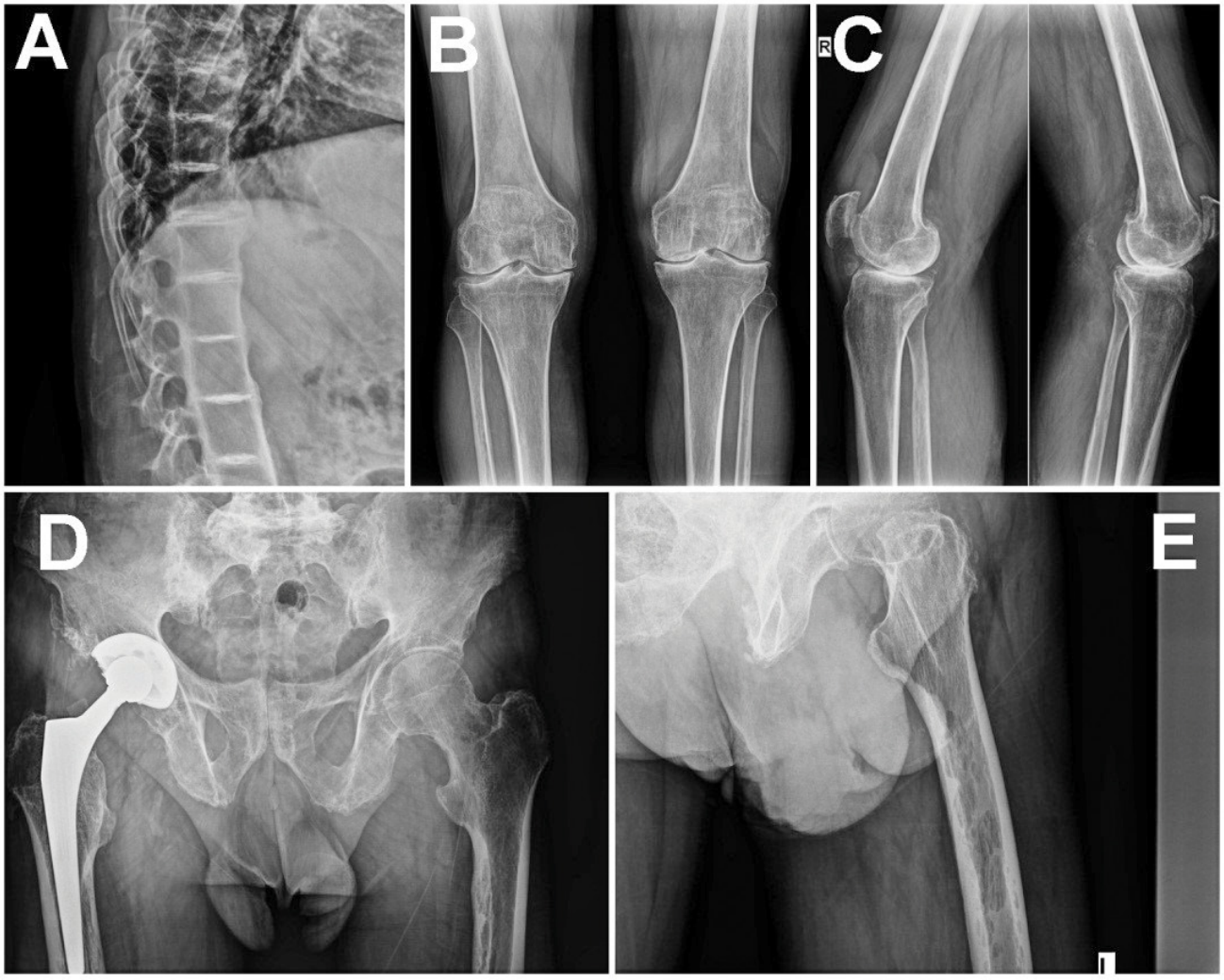

FIGURE 4. X-rays of the patient (2019): (**A**) X-ray of the dorsal-lumbar spine which shows disk calcifications and posterior longitudinal ligament ossifications; (**B**) and (**C**) Anteroposterior and lateral X-rays of the knees: space narrowing, subchondral sclerosis, marginal osteophytosis; (**D**) Pelvis X-ray: normal position of prothesis at the level of the right hip; (**E**) Left femur X-ray: fibrous dysplasia

Department of Organic Chemistry, Faculty of Chemistry "Al. I. Cuza" University Iasi, 10 drops of 10%NaOH solution were added to 20 ml urine. The qualitative measurement of the organic acids in urine was positive for HGA and the urine sample turned brown (Figure 3).

The quantitative reaction of HGA has been also performed, the urine sample being sent to Mayo Clinic, Minnesota, USA. The result confirmed a HGA excretion significantly higher (1932 mmol/mol creatinine) than reference ranges (< 1.1).

Multiple X-rays were performed. Dorsal kyphosis, ossification of the posterior longitudinal ligament, lower thoracic and lumbar intervertebral disk calcifications were seen. Knee X-rays revealed advanced bilateral tibiofemoral OA and bilateral patellofemoral OA with calcifications in the right quadriceps tendon enthesis. In addition, bilateral knee ultrasound sustained the advanced OA modifications. The orthopedic examination recommended bilateral knee arthroplasty. Pelvis X-ray showed a narrowed right sacroiliac joint space with microgeodes and condensation extended in the bone; a narrowed left sacroiliac joint space; right hip prosthesis; greater trochanter osteoporosis; transparent, well-defined lesions in the proximal femoral diaphysis for which radiological monitoring was recommended (Figure 4).

To make the differential diagnosis with AS, a HLA-B27 test was performed. The result was negative.

Corroborating clinical and paraclinical data, the following final diagnoses were made: ochronotic spondyloarthropathy (ochronotic SpA), left ochronotic hip OA, right hip arthroplasty, bilateral ochronotic scapulohumeral OA, bilateral ochronotic knee OA and bilateral femoral fibrous dysplasia.

The patient received non-steroidal anti-inflammatory drug treatment (NSAIDs) and physical therapy with a favorable outcome. He was discharged with the recommendation to continue the NSAIDs treatment and kinetotherapy exercises. Also, we recommended monitoring the cardiovascular and renal complications.

DISCUSSIONS

Literature data about ochronotic arthropathy is limited (only a thousand case reports published) [11]. The characteristic clinical tripod of this metabolic defect is formed by: ochronosis, urinary HGA excretion and ochronotic arthropathy [12,13].

Alkaptonuria

Although the characteristic enzyme deficit prevents HGA conversion to maleylacetoacetate acid, plasma HGA is low, indicating a high renal clearance. The patient excretes high levels of HGA which, on air exposure, turns brownish-back due to the spontaneous oxidation and polymerization in an alkaline medium [14]. Besides glomerular filtration and tubular secretion, there is also mentioned a renal production of HGA [2]. During childhood, alkaptonuria is the only expression of the disease [12,15]. Sometimes, this urine specific colour may go unnoticed [16]. Our patient reported urine colour changes "since youth". The presence of HGA has to be confirmed by qualitative reactions based on the reducing properties of alkapton [12].

Sometimes, we can find dark-colored sweat staining or dark, black and blue earwax [12]. Our patient had dark earwax and brown sweat.

Ochronosis

HGA accumulates in collagen-rich connective tissues (sclera, cartilage, skin, tendons, ligaments, and large vessels intima) [17,18]. The human cartilage and tegument contain the HGA polyphenol oxidase enzyme. This enzyme catalyzes the oxidation of HGA to benzoquinone (benzoquinone acetic acid, benzoquinone acetate), which, by polymerization, turns into ochronotic pigment. It is irreversibly linked to collagen and causes blue-brown pigmentation [14,19]. Literature data describe sclera hyperpigmentation as the most frequent clinical finding, followed by conjunctival pigmentation [20]. Our patient has a bilateral blue-black pigmentation of the lower eyelids and ear cartilage (antihelix), but no sclera pigmentation.

For the final diagnosis, histological examination is not required. However, experimental evidence demonstrated the presence of serum amyloid A (SAA) in multiple ochronotic chondrocytes, classifying alkaptonuria as secondary amyloidosis. SAA in ochronotic chondrocytes is located in the cytoskeletal proteins (actin, vimentin and beta-tubulin) [21]. The accumulation of HGA in the cartilage leads to alteration of the cytoskeletal network [22]. Braconi et al. sustained that oxidative stress of HGA polymerization leads to protein oxidation, lipid peroxidation, inflammation and amyloid production in the affected tissues [23].

Ochronotic arthropathy

Over time, the disease leads to chronic joint pain and inflammation, especially at the spine level [16]. The involvement of the axial skeleton is characterized by a clinical picture similar to that found in AS: dorsal kyphosis, lumbar rectitude and bone bridges [14,24-26]. The accumulation of the ochronotic pigment will determine disc herniation [27,28]. It has been recently described that patients with myelopathy and ochronosis have pain and rigidity in the cervical or lumbar spine, hips and knees [29-33]. Inflammation, calcification, tendon

and ligament ruptures may also occur [34,35]. A complete Achilles tendon rupture with a non-traumatic calcaneal avulsion fracture was reported [36].

Pelvis and sacroiliac joints are affected in 35% of the cases of ochronotic arthropathy [6,37]. A simplified staging system of this disease based on the changes in the dorsal and lumbar spine was proposed [38].

In our patient, the differential diagnosis with AS was difficult due to bilateral radiographic sacroiliitis. But, the acute phase reactants were normal and the antigen HLA B27 was negative. There are studies which support the co-existence of ochronosis with AS or with the presence of HLA-B27 [39-42].

Kinetotherapy and NSAIDs are beneficial for pain symptoms. There is no specific medication for stopping the disease progression [6,43-45]. A successful approach using IL-1 antagonist drug was reported [46]. Nitisinone, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase used for patients with tyrosinemia type 1, proved no efficacy in SpA associated with ochronosis [47,48]. A proper disease management requires interdisciplinarity [42,44,49, 50].

Cardiovascular and genitourinary deposition can lead to severe complications. Patients can expect a normal life, but due to secondary OA, chronic pain or cardiovascular and renal involvement, they can develop a decreased quality of life [12].

CONCLUSIONS

Ochronosis is a rare disease which can cause a lot of problems regarding a proper diagnosis and treatment. When differential diagnosis with AS is difficult, the HLA-B27 genotyping is recommended. Final diagnosis is based on qualitative and quantitative urinary tests. The treatment includes only symptomatic drugs such as NSAIDs and kinetotherapy to improve joint mobility and muscle toning.

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