Alkaptonuria – Case report*

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20143052

Abstract: Alkaptonuria, also called endogenous ochronosis, is a rare metabolic autosomal recessive disorder. It occurs by complete inhibition of homogentisic acid oxidase enzyme having its deposition in various tissues. Male patient, 52 years old, sought medical help complaining about progressive appearance of hyperchromic papules on the lateral edge of the second finger of both hands for 02 years. He also complained about darkening of urine, sperm and underwear. Incisional biopsy of second hand finger and test for homogentisic acid in the urine results were positive. The findings are compatible with the diagnosis of alkaptonuria. Given these findings, treatment was initiated, followed-up by other specialties and he was advised to avoid certain foods.

Keywords: Alkaptonuria; Homogentisic acid; Ochronosis

INTRODUCTION

Alkaptonuria, also called endogenous ochronosis, is a rare metabolic autosomal recessive disease, which affects 1:1,000,000 people. Alkaptonuria usually occurs in adults, starting after the age of 30.¹ It is a condition which is present at birth, but is associated to morbidity years later.² It arises from total inhibition of homogentisic acid oxidase enzyme.³ Its excess is deposited mainly in cartilaginous tissue, mucous, skin, bone surface and internal cardiac structures, as well as excreted in biological solutions (urine, sweat and semen). The main complications of alkaptonuria are valvular calcifications and osteoarthritis, mainly in the joints of the cervical spine, besides dark pigmentation of skin, cartilage, sclera and other connective tissues.³ Its diagnosis is done through the association of clinical history, histopathological exam and dosage of homogentisic acid in the urine.³

CASE REPORT

Male patient, 52 years old, sought medical assistance complaining about progressive appearance of hyperchromic papules on the lateral edge of the second finger of both hands for 2 years. He also complained about darkening of urine, sperm and underwear for 20 years with recent worsening. He is obese and hypertensive, currently using enalapril. He already underwent some orthopedic procedures, such as: knee arthroscopy, lumbar spine arthrodesis and achilles tendon tenorrhaphy two, eight and fifteen years ago, respectively. According to his family history his sister presented “Coca-Cola color” in her diapers, during early childhood.

At the dermatological examination: grayish spot in the sclera, grayish blue papules on the bilateral extensor surface of second finger, periurethral hyperpigmentation, generalized chromonychia (Figures 1 and 2). Radiography of vertebral column showed calcification of lower and lumbar intervertebral discs, reduction of disc spaces and posterior arthrodesis with metal rod (Figure 3).

With the goal of clarifying the diagnosis an incisional biopsy of the second finger papule was performed as well as test for homogentisic acid in urine, which resulted positive.

The histopathological exam evidenced hyperkeratosis, hypergranulosis, irregular acanthosis, basophilic fibrilar elastotic degeneration of collagen in the upper dermis (Figure 4). At higher magnification fractured and degenerated collagen fibers with deposit of ochre pigment in clusters can be observed (Figure 5).

These findings were compatible, therefore, with endogenous ochronosis or alkaptonuria. Given these results, treatment with vitamin C 500 mg twice a day was started together with monitoring by other specialties such as orthopedics, ophthalmology and cardiology. The patient was advised to avoid diets rich in phenylalanine, tyrosine and protein.
DISCUSSION

Endogenous ochronosis is a rare metabolic autosomal recessive disorder with total deficiency of homogentisic acid oxidase enzyme. It arises from the inhibition of this enzyme, in a more localized form, by several substances such as: phenol, resorcinol, mepacrine and mercury.

The homogentisic acid is part of the metabolic pathway of phenylalanine and tyrosine. The deficiency of the enzyme that metabolizes it (homogentisic acid oxidase) leads to its accumulation, that will be polymerized in a melanin-like pigment that presents high affinity for connective tissue, especially cartilage, resulting in an ochre color (for this reason it carries the name of ochronosis).1

In children, its main symptom is the darkening of the urine after a long period of rest or in contact with the environmental or alkali air, as well as blackened spots in babies’ diapers, whereas in adults, after the fourth decade of life, the main manifestation is osteoarthritis, followed by changes in eyes, ears, skin and in the genitourinary, cardiovascular and musculoskeletal systems, which are well described in the chart below (Chart 1).1,2,3

The deposition of pigment in alkaptonuria is observed in joints that suffer great pressure, like in the lumbar column and large articulations. This occurs because the ochronosis pigment has high affinity for the collagen fibers of articulations.4,5

The diagnosis is done through the clinical history and from changes in coloration of urine in environmental or alkali air and confirmed by dosage of homogentisic acid in urine, which is the gold standard.6

The description of dermoscopy in endogenous ochronosis was not found in any of these articles; however, the description of dermoscopy of a lesion by exogenous ochronosis, in which it is possible to visualize blackened blue dots obstructing hair follicles was observed in an article.7
Up to the present moment, there is no pharmacological treatment which cures the disease. For the articular lesions the use of non-steroidal anti-inflammatory drugs is recommended, associated with the practice of physical exercises and physical therapy. In some cases, a surgery will be necessary for substitution of large articulations. There must be restricted intake of proteins, mainly phenylalanine and tyrosine aminoacids. Another important measure is to utilize a super dose of vitamin C, in the dosage of 500mg twice a day, for it presents an antioxidant effect which prevents the oxidation of the homogentisic acid. Nitisone (not yet available in Brazil), a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, acts by diminishing the production and urinary excretion of homogentisic acid. However, its long-term use is still unknown, as well as its adverse effects.

The follow-up with other specialties is needed as follows: cardiology with electrocardiogram, for possible rhythm alterations; echocardiography to observe calcification of the aortic and mitral valve; thorax computed tomography to observe calcification of coronary arteries; orthopedics for the study of the musculo-skeletal system, in addition to monitoring by an ophthalmologist and otolaryngologist, to observe visual acuity and auditory acuity, respectively.

Alkaptonuria is a still frequently subdiagnosed disease, of difficult management in spite of increasing multidisciplinary study and monitoring through complementary exams. However, it is possible to observe an increase in case reporting and research about alkaptonuria in recent times, making the diagnosis and support that must be offered to these patients easier.

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How to cite this article: Craide FH, Fonseca JSBM, Mariano PC, Fernandez NM, Castro CGC, Mene YSL. Alkaptonuria – Case report. An Bras Dermatol. 2014;89(5):799-801.