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Case report

Hemochromatosis simulating rheumatoid arthritis: a case report[☆]

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ARTICLE INFO

Article history:

Received on 4 December 2011

Accepted on 14 May 2013

Keywords:

Arthritis rheumatoid

Hemochromatosis

Point mutation

ABSTRACT

This is a report of a patient who had a previous diagnosis of rheumatoid arthritis, non-erosive, rheumatoid factor negative, that despite the therapeutic approach presented progressive worsening of the articular and general condition. After extensive research, she had a diagnosis of hemochromatosis. Joint symptoms are common manifestations in hemochromatosis. The arthropathy of hemochromatosis may resemble inflammatory arthropathy mimicking RA, particularly in the most common sites as 2nd and 3rd metacarpophalangeal. Radiologically are observed decreased joint space, subchondral sclerosis, cyst formation and chondrocalcinosis. Treatment with disease modifying drugs for rheumatoid arthritis tend to worsen the clinical picture, since the liver is the major site of deposition of iron in hemochromatosis and these medications are known to be hepatotoxic. Phlebotomy treatment for hemochromatosis is apparently ineffective in reversing the articular manifestations, which requires the association with iron chelating drugs. Due to the apparent difficulty in differentiating between the two diseases, a screening profile of iron in patients with rheumatoid arthritis with atypical progression is necessary.

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Hemocromatose simulando artrite reumatoide: relato de caso

RESUMO

Este é um relato de uma paciente que teve diagnóstico prévio de artrite reumatoide, não erosiva, fator reumatoide negativo, que apesar da terapêutica instituída apresentava piora progressiva do quadro articular e do estado geral. Após extensa investigação, apresentou diagnóstico de hemocromatose. Sintomas articulares são manifestações frequentes na hemocromatose. A artropatia da hemocromatose pode assemelhar-se a artropatias inflamatórias imitando a AR, particularmente nos sítios mais comuns, como 2ª e 3ª metacarpofalangeanas. Radiologicamente são observadas diminuição do espaço articular, esclerose

Palavras-chave:

Artrite reumatoide

Hemocromatose

Mutação puntual

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doi:10.1016/j.rbre.2014.02.009

subcondral, formação de cistos e condrocalcinoses. O tratamento com drogas modificadoras de doença para artrite reumatoide tende a piorar o quadro clínico, uma vez que o fígado é o principal sítio de depósito de ferro na hemocromatose e essas medicações são sabidamente hepatotóxicas. O tratamento com flebotomia para hemocromatose é aparentemente ineficaz na reversão das manifestações articulares, sendo necessária a associação com medicações quelantes de ferro. Devido à dificuldade aparente de diferenciação entre as duas patologias, faz-se necessária uma triagem no perfil do ferro em pacientes com diagnóstico de artrite reumatoide com evolução atípica.

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Introduction

Hemochromatosis (HC) is a disorder of iron metabolism characterized by increased intestinal iron absorption and progressive deposition in organs and tissues, resulting in injury and functional impairment, particularly the liver, pancreas, heart, joints and pituitary.¹ It affects more often males in the fourth and fifth decade. Schumacher, in 1964, was the first to recognize the relationship between HC and arthritis.² Although arthritis in the second and third metacarpophalangeal (MCP) joints is often observed as a typical finding of HC, virtually all joints can be affected, with signs and symptoms of osteoarthritis.^{3,4} Sometimes, it can be observed in intermittent arthritis leading to misdiagnosis of rheumatoid arthritis.⁵

Rheumatoid arthritis (RA) is a symmetric, progressive, autoimmune, chronic inflammatory polyarthritis of unknown cause that affects about 1% of the adult population. It is most common in women between the fourth and sixth decades.

This paper aims to report a case of HC with a diagnosis of RA.

Case report

Female patient, 56 years old, white, married, born in Minas Gerais, residing in Sao Paulo, homemaking, complaining of joint pain in hands and knees associated with morning stiffness greater than 1 h. At the physical examination, synovitis was observed in the right (R) and left (L) 2nd proximal interphalangeal (PIP) joints and in the 2nd and 3rd MCP R and L, wrists, knee (R) and sternoclavicular joint (L). Radiography (RX) of hands, knees and feet revealed diffuse bone thinning with space preserved in the hands; prominent tibial spine, subchondral cysts, osteophytes and reduced joint space in knees; the laboratory analysis showed an increase of transaminases – ALT: 207 (n = 7-35 U/L), AST: 127 (n = 8-33 U/L) and increased ESR: 41 (n = 0-10 mm), with no other changes, including serology. RA was suspected, and the patient was treated with chloroquine 250 mg/day and steroid depot at the time of appointment. In addition, abdominal ultrasound was requested, due to increase of transaminases, with normal results.

Upon returning in consultation, no significant clinical improvement was observed. The laboratory workup showed a negative rheumatoid factor, normalization of transaminases and reduction of ESR; AST 23, ALT, 25, VHS 21. At this time, a diagnosis of erosive RA with negative rheumatoid factor was

established. Methotrexate (MTX) 15 mg/week was prescribed. After 6 months, the patient returns with the same clinical and laboratory findings. The patient presented grayish blemishes, bruises and small dilated vessels in the lower limbs (LL), in association with arthritis. We chose to increase the dose of MTX to 20 mg/week, with no clinical response. Because of skin changes and no response to treatment with DMARD and corticosteroid, we chose to investigate the patient profile of iron, with the following findings: Iron: 224 (n = 37-170 µg/dL), iron binding capacity: 244 (n = 250-450 µg/dL), transferrin saturation: 91.8 (n = 20-60%), ferritin: 2140 (n = 11.1-264 ng/mL), RBC unchanged; AST, 53; ALT, 83, ESR, 17; hemochromatosis was hypothesized. Magnetic resonance imaging of the liver with iron deposits was requested, with alteration: 250 µmCl/g (n = 36 µmCl/g); and the C282Y and H63D mutation in HFE gene survey resulted in a mutated homozygous genotype for C282Y and absence of H63D mutation, with confirmation of the diagnosis.

At this time, MTX was discontinued and the corticosteroid was gradually suppressed, and the patient was referred to the hematology service, where she is being followed and treated with phlebotomy sessions and an iron chelator (deferoxamine).

Currently, after 8 phlebotomy sessions the patient only shows synovitis in 2nd and 3rd PIP D and E, and intermittent episodes of joint pain in knees, without morning stiffness. Laboratory workup: Fe, 234; transferrin saturation, 57%, ferritin, 975, AST 38, SGPT, 44; RBC unchanged.

Discussion

Familial hemochromatosis is the most common autosomal recessive hereditary disease, with a prevalence of approximately 1:400 in the European population, and is often underdiagnosed as a cause of arthropathy. This disease is caused by a mutation in the HFE gene located on chromosome 6.⁶ HFE protein binds to the transferrin receptor, diminishing the receptor affinity to FE ion, thereby interfering in its metabolism.^{1,3} Two mutations in the HFE gene were identified: one resulting in the substitution of cysteine at 282 position by tyrosine (C282Y), and the other resulting in the substitution of histidine at position 63 by aspartic acid (H63D).

It has been shown that most patients with clinical manifestations of HC are homozygous for C282Y mutation, as observed in the case of our patient, and about 5% are C282Y/H63D heterozygous.^{4,5} Recent studies have revealed that the prevalence of C282Y mutation in patients with RA did not dif-

fer from the control population.^{7,8} Moreover, H63D mutation is more frequent in RA population *versus* healthy controls.⁸ However, in contrast to C282Y mutation, H63D mutation is not associated with iron metabolism.^{2,8}

Joint symptoms are common manifestations in HC (about 30% of patients), which are sometimes reported as the first symptom of the disease, similar to that observed in our patient. Typically, 2nd and 3rd MCP are involved, but other joints such as wrists, knees, hips, shoulders and ankles may also be affected^{9,10}. Radiologically, decreased joint space, subchondral sclerosis, cyst formation and chondrocalcinosis are observed. Treatment with phlebotomy for HC is apparently ineffective in reversing the joint manifestations and, in some patients, progression of these symptoms with decreased levels of iron have been described.¹¹ Our patient initially presented clinical improvement after the implementation of phlebotomy therapy.

The arthropathy of hemochromatosis may resemble rheumatoid arthritis, because one of its manifestations may be a symmetrical arthritis in MCP; rheumatoid factor can be positive; ferritin, a marker of iron overload, can be increased in other inflammatory conditions such as RA.¹² Thus, diagnostic difficulties may arise in differentiating between RA and HC arthropathy, which will delay a proper treatment.

The clinical treatment of patients with HC and an early diagnosis of RA are difficult because 83% of the patients exhibit liver involvement – and the liver is one of the major sites of iron deposition. At the same time, many DMARDs used in the treatment of RA have high hepatotoxicity. Furthermore, it has been demonstrated that DMARDs, as MTX, can increase serum iron levels.¹³ On the other hand, iron is known to catalyze oxidative reactions, with subsequent formation of hydroxyl radicals and lipid peroxidation, which can cause inflammation and tissue damage.

Furthermore, it has been shown that iron stimulates DNA synthesis in synovial cells, with an additive effect on cell proliferation, together with cytokines such as IL-1 β and TNF- α . These findings emphasize the role of iron as a modulator of disease activity in RA. The hypothesis would be that the patient's treatment with MTX would result in an increase in serum iron levels, activating a latent HC and leading to the exacerbation of joint manifestations.¹⁴ This was observed in our patient, who suffered clinical worsening of the joint picture after the introduction of MTX.

Due to the high prevalence of RA and HC in the general population, this fact reinforces the usefulness of the screening for HFE gene mutation in patients with RA with atypical development of the disease, as well as in patients with undifferentiated arthritis.

Conflicts of interest

The authors declare no conflicts of interest.

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