Iron Synovitis in Hemochromatosis Associated Arthropathy - A Great Mimicker

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Secondary hemochromatosis is a condition generated by defects in the iron metabolism such as elevated intestinal iron absorption and increased iron stores in tissues and organs. The current case report presents a 35-year-old female admitted for inflammatory pain of the left ankle, second and third right MCP joints and right sternoclavicular joint associated with Celsian clinical signs, subcutaneous edema and loss of articular function. The patient is known with beta thalassemia major, secondary hemochromatosis and chronic hepatitis C as a consequence of repeated blood transfusions. We pleaded for the existence of a HC-A associated with microcrystalline calcium pyrophosphate dehydrate crystal deposition (CPPD) disease associated with secondary osteoarthritic changes.

Keywords: beta thalassemia, hemochromatosis, arthropathy, iron stores

Secondary hemochromatosis is a condition generated by defects in the iron metabolism such as elevated intestinal iron absorption and increased iron stores in tissues and organs [1].

Acquired iron overload may be determined by iron-loading anemias such as beta-thalassemia major, aplastic anemia, chronic hemolytic anemia, parenteral iron overload due to red blood cell transfusions or long term hemodialysis and chronic liver disease [2].

This pathology has complex manifestations affecting mostly the skin, liver, pancreas, heart, thyroid, spleen and joints. Arthralgia is one of the most commonly encountered symptoms of this disease and it can occur in any segment, with the second and third metacarpophalangeal joints (MCP) being the most frequently affected [1, 3]**.** Also, the arthropathy due to hemochromatosis can affect other joints such as wrists, knees, hips, shoulders or ankles [4].

Experimental part

We present the case of a 35-year-old female admitted in the Department of Rheumatology for inflammatory pain of the left ankle, second and third right MCP joints and right sternoclavicular joint associated with Celsian clinical signs, subcutaneous edema and loss of articular function. The patient is known with beta thalassemia major, therapeutic splenectomy at the age of 2, secondary hemochromatosis and chronic hepatitis C as a consequence of repeated blood transfusions. Other significant pathologies include autoimmune thyroiditis with positive antithyroperoxidase antibodies, therapeutic ovariectomy due to an abundant menstruation which accentuated the anemia and severe secondary osteoporosis. The patient's family history was relevant considering her grandfather, father and mother all had beta thalassemia minor. The patient also experienced two other previous episodes of acute arthritis, following a viral respiratory infection, accompanied by fever, elevated inflammatory tests and liver enzymes, a serum creatinine of 2 mg/dL and uric acid of 10 mg/dL, partially remitted after the administration of non-steroidal anti-inflammatories and anti-pyretics.

The clinical examination revealed skin hyper-pigmentation, swollen and painful left ankle, second and third MCP of the right hand and right sternoclavicular joint with increased local heat and decreased mobility, subcutaneous edema extended to the proximal half of the calf, dactylitis of the second and third fingers of the right hand and hepatomegaly with the inferior margin reaching the antero-superior iliac crest.

The biological profile at admission revealed an intense inflammatory process with ESR 75 mm/hr and CRP 6.90 mg/dL, elevated liver enzymes with ALT 85 U/L and AST 42 U/L, a ferritin recorded level of over 2000 mcg/mL, a mild anemia with hemoglobin levels of 11.14 g/dL and hematocrit 34.04%, leukocytosis of 14.86 x 10^3/mcL, normal values for serum creatinine and uric acid. Immunology tests showed a positive rheumatoid factor with a value of 22.32 UI/mL, negative anti-citrullinated protein antibodies (ACPA), absent Chritidia Luciliae, negative Extractable Nuclear Antigens screening, negative BCR/ABL p190 and p210 genes and borderline low levels of C3 complement (fig. 1).

The musculoskeletal ultrasonography (MUS) examination of the left ankle displayed a distension of the

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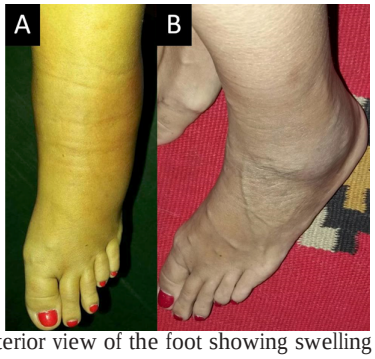

Fig. 1. A - Anterior view of the foot showing swelling of the ankle and subcutaneous edema, B - Lateral view of the foot showing swelling of the ankle

joint capsule due to the presence of a third degree synovial proliferation within the anterior recess of the tibiotalar joint, a second degree synovial proliferation within the talonavicular joint, moderate proliferative tenosynovitis of the tibialis posterior, flexor digitorum longus and severe tenosynovitis of flexor hallucis longus tendons, medial perimalleolar subcutaneous edema and a disrupted cortical bone with multiple erosions. MUS of the hand identified dactylitis of the second and third fingers of the right hand, with synovitis, tenosynonovitis, subcutaneous edema, cortical bone irregularities consistent with osteophytes at the second and third MCP joints bilaterally, focal hyperechoic spots of calcifications within the triangular fibrocartilage of the wrist. Furthermore, the MUS examination also revealed severe synovial proliferation in the right sternoclavicular joint fig. 2).

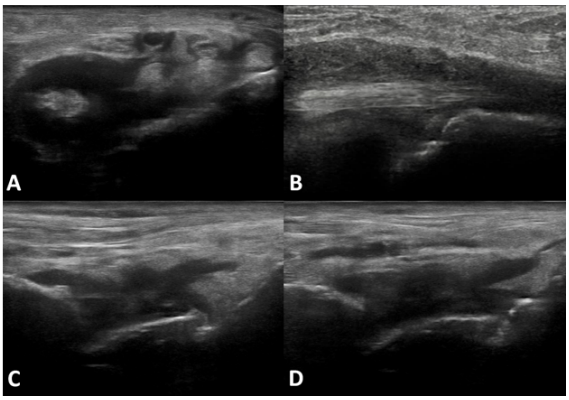

Fig. 2. A, B-Longitudinal and transversal section of the medial compartment of the ankle showing a third degree proliferative tenosynovitis of the flexor hallucis longus tendons

The knee radiograph showed a modified bone structure with fascicular architecture, a diffuse osteosclerosis area of approximately 7/2 cm situated in the external supracondylar compartment of the left knee. The hand radiograph revealed narrowing of the distal interphalangeal joint space, juxta-articular osteoporosis, cubital deviation of the second and third fingers and a modified bone structure with fascicular aspect at the wrist, changes consistent with hemochromatosis associated arthropathy (HC-A) (fig. 3).

We performed an ultrasound guided needle biopsy of the synovial tissue from the left tibiotarsal joint. The tissue samples were stained with Hematoxylin and Eosin and Perls' Persian blue for histological assessment. The results showed proliferative synovitis with iron deposits in the synovial lining and macrophages (fig. 4).

During hospitalization, the patient was administered pulse corticosteroid therapy with methylprednisolone for

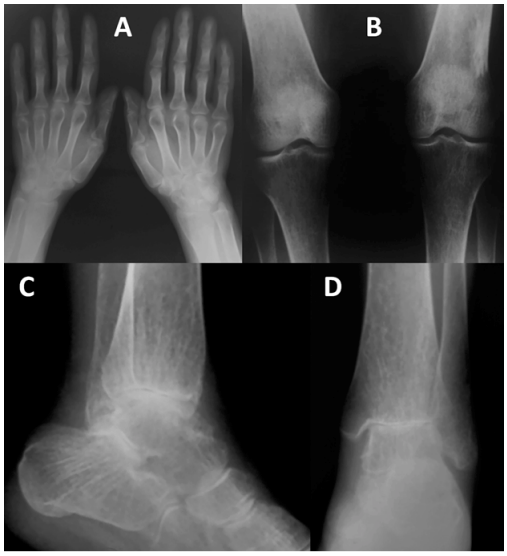

Fig. 3. A- Hand X-ray showing narrowing of the distal interphalangeal joint space, juxta-articular osteoporosis, cubital deviation of the second and third fingers and a modified bone structure with fascicular aspect at the wrist. B- Knee X-ray showing a modified bone structure with fascicular architecture, a diffuse osteosclerosis area of approximately 7/2 cm situated in the external supracondylar compartment of the left knee. C- Lateral X-ray of the foot showing narrowing of the joint spaces and fascicular aspect of the calcaneus. D- Anterior X-ray of the ankle showing narrowing of the joint spaces and fascicular aspect of the tibia

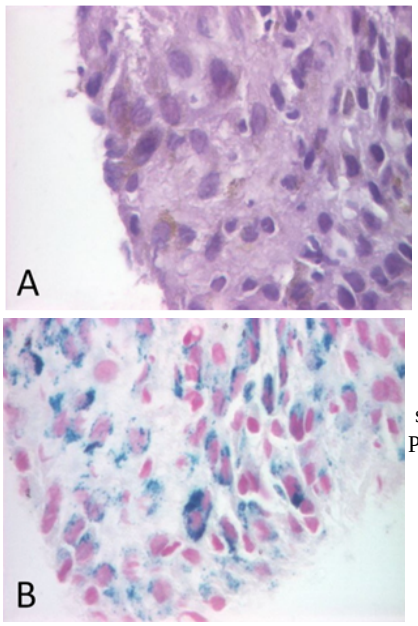

Fig. 4. A -Hematoxylin and Eosin staining showing golden brown hemosiderin deposits. B- Perls' Prussian blue staining showing bluish Perls positive pigment.

3 consecutive days followed by low-dose oral methylprednisolone for one month, colchicine 1 mg per day and hydroxychloroquine 400mg per day, leading to the improvement of joint function and reduction of the swelling and pain. Considering the characteristics of the arthritis, the acute onset of the symptoms and the major Celsian clinical signs, we pleaded for the existence of a HC-A associated with microcrystalline calcium pyrophosphate dehydrate crystal deposition (CPPD) disease associated with secondary osteoarthritic changes.

Results and discussions

Beta thalassemia is an autosomal recessive disorder determined by a genetic deficiency in the beta-globin genes. The treatment for severe cases includes blood

transfusions in order to reduce the chronic anemia which can lead to an acquired iron overload, similar to our patient's clinical evolution [5]. The extensive iron deposits in the tissues and organs may lead to clinical and pathological characteristics comparable to those in hereditary hemochromatosis such as liver disease, diabetes, arthropathy and cardiomyopathy [6].

Several pathogenic mechanisms of joint involvement in hemochromatosis have been studied but without any conclusive results. Some of the proposed theories are: the promoter role of iron salts in the nucleation of calcium pyrophosphate crystals and the inhibition of their exclusion from the joint, the existence of other metabolic defects and the increase of serum levels of the parathyroid hormone [7].

Taking into consideration the relatively asymmetric joint involvement and the presence of tenosynovitis, a differential diagnosis between HC-A, psoriatic arthritis, spondyloarthritis and reactive arthritis is required. Common causes of reactive arthritis characterized by arthritis and tenosynovitis of the ankles consist of infections with Salmonella, Shigella, Yersinia Species and Chlamydia trachomatis while a less frequent cause is the infection with β-hemolytic group A streptococcus [8]. Due to the absence of psoriatic lesions, sacroiliac joint pain, negative HLA-B27 and negative tests for infections the diagnosis tends towards HC-A.

The association between the complex pathologies presented by the patient also requires differential diagnosis between HC-A, rheumatoid arthritis (RA) and hepatitis C virus-related arthropathy (HCV-A).

From the clinical point of view, the onset of HC-A typically involves the small joints of the hands, especially the second and third MCP joints. Other joints such as the shoulders, hips, knees and ankles may also be affected in the pathological process. The most common symptoms that occur are arthralgias, mainly after physical exercise, morning stiffness and the impossibility to flex the joint. Patients may also experience episodes of arthritis with joint swelling accompanied by erythema, local heat and pain during movement, probably as a consequence of calcium pyrophosphate dehydrate and iron deposition in the synovia, as observed in the situation of our patient [9].

Several characteristics can be taken into account when referring to the differential diagnosis between RA and HC-A: 1. Symmetrical inflammation of MCP joints accompanied by swelling is a clinical feature encountered in both pathologies. 2. A positive rheumatoid factor may be observed in RA but also in hemochromatosis [10]. 3. The production of ACPA is a highly specific immunopathological process in RA while in HC-A the inflammation can promote the citrullination of proteins. However, there is no immunological basis to support the process resulting in the absence of ACPA. 4. Osteophytes, erosions, narrowing of the joint space and subchondral cysts are characteristic changes in both RA and HC-A. 5. Serum ferritin can be elevated not only in hemochromatosis but also in inflammatory diseases such as RA [11]. 6. Ultrasound abnormalities like erosions, osteophytes, cartilage disruption, Grey Scale and Power Doppler synovitis and tenosynovitis are consistent with both RA and HC-A, but with varying frequency [12]. 7. Histological studies have focused on the presence of synovitis, ranging from low grade in HC-A to high grade in RA. Immunohistochemistry was also applied in order to evaluate the immune cell infiltration, showing the absence of B and T cell infiltrates in HC-A, compared to RA. Furthermore, in HC-A iron is mainly stored in chondrocytes and in the synovial lining layer [13].

To sum up, the difference between RA and HC-A is mainly highlighted by the histopathology report and the determination of ACPA serum levels.

In the present case, differentiating HCV-A and HC-A is primordial because both pathologies share several characteristics: the articular involvement is usually symmetrical, affecting mainly the small joints of the hand and the rheumatoid factor may be positive [14, 15]. In contrast with HC-A features, HCV-A may present positive serum levels of ACPA in 20-30% of the cases. Although some radiological similarities may be encountered in both diseases, the presence of erosions pleads for HC-A since the arthritis in HCV-A is non-deforming and non-erosive [15, 16].

Due to the therapeutic ovariectomy, our patient developed osteoporosis at a very young age, increasing the risk of complications such as decreased bone structure leading to bone fragility and a higher possibility of fractures [17]. In this case, treatment with glucocorticoids should involve a loading dose, followed by low sustainment doses with dose tapering in order to prevent the risk of bone fractures and other side effects [18].

Conclusions

Taking into consideration the particular aspects of the arthritis accompanied by the characteristic histopathologic examination we plead for the existence of an arthropathy in the context of secondary hemochromatosis with iron deposits in the synovia and a secondary arthrosis with calcium pyrophosphate dehydrate deposition, complications developed due to elevated serum ferritin levels.

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