CLINICAL VIGNETTE

Bilateral Hand Arthritis in a Patient with Hemochromatosis and Persistent Ferritinemia

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Introduction

Classic hereditary hemochromatosis is an autosomal recessive disease, most commonly associated with C282Y mutation and among those of Northern European descent, which predisposes toward iron dysregulation and organ disease. The liver, heart, skin, and endocrine organs may be impacted. Secondary osteoarthritis can occur with hemochromatosis, with some studies reporting radiologic evidence of arthropathy in over 80% of patients with histologically proven genetic hemochromatosis.[1]

Joint pathology in hemochromatosis closely resembles osteoarthritis with regards to synovitis, synovial hyperplasia, osteophyte formation and joint space narrowing, although there may be neutrophil invasion of synovial tissue, particularly associated with haemosiderin deposition,[2] and erosive disease[3] reminiscent of inflammatory arthritides such as rheumatoid arthritis. Radiographically, osteoarthritic changes and hook-like osteophytes of the second and third metacarpophalangeal joints and chondrocalcinosis are typically observed.[4] Discerning between hemochromatosis and inflammatory arthritis can at times present a diagnostic challenge, with one study finding the C282Y allele frequency overrepresented in patients with undifferentiated arthritis as compared to healthy controls.[5]

Case Description

A 71-year-old Caucasian female was referred to the rheumatology clinic for concerns regarding hand pain. Her medical history was pertinent for seizure disorder on carbamazepine, hypothyroidism, fatty liver disease, osteopenia, and hemochromatosis diagnosed two years prior to presentation, with elevated ferritin (6,804 ng/mL), iron (>200 mcg/dL), and homozygous C282Y mutation of the HFE gene. Transferrin saturation was incalculable. On review of old records, iron elevation was also present in four years prior to diagnosis (194 mcg/dL). Older labs were not available. She also reported bilateral knee replacement surgeries, with pathology reports consistent with osteoarthritis, within the past eleven years.

She was unable to tolerate weekly phlebotomy, and 500 cc blood draws every other week were initiated. Despite almost a year of therapy, she had persistent ferritinemia between 3000-4000 ng/mL, and phlebotomies were gradually increased to 500 cc weekly, four weeks on, one week off, over the following year. Ferritin levels trended down, but remained elevated between 1000-2000 ng/mL. Given persistent ferritin elevation and complaints of chronic hand pain, an underlying inflammatory arthritis was suspected, and she was referred to Rheumatology for additional evaluation.

In rheumatology, she reported gradual onset and intermittent hand and wrist pain and deformity, ongoing for approximately ten years, with metacarpophalangeal joint enlargement and one hour of morning stiffness. She denied acute episodes of joint heat, redness and swelling. Review of systems was pertinent for livedo reticularis and repeated hand trauma related to sports, but was otherwise nonfocal. Her physical examination demonstrated mild tenderness, soft tissue swelling and bony hypertrophy of the second and third metacarpophalangeal joints (Figure 1). There was wrist tenderness without effusion. Serological testing was negative for antinuclear antibody, rheumatoid factor and cyclic citrulline antibody. Sedimentation rate was low. Hand x-rays were obtained (Figure 2), with severe second and third metacarpophalangeal joint space narrowing, subchondral cystic changes, and hook-like osteophyte formation. Her overall presentation was felt to be related to hemochromatosis arthropathy and immunosuppressing agents were deferred.

On follow-up, ferritin levels continued to decreased with ongoing phlebotomy and normalized at 106 ng/mL six months later.

Discussion

Hemochromatosis arthropathy can present a diagnostic challenge, particularly when there is severe symmetric arthritis, joint deformity and swelling, prolonged morning stiffness, and persistent ferritin elevation. Ferritin can be elevated as an acute phase reactant in autoimmune connective tissue disease, in addition to fatty liver disease and uncontrolled hemochromatosis, which can lead to further confusion.

Conversely, recognition of hemochromatosis arthropathy can potentially aid in the early diagnosis of hereditary hemochromatosis. A European cross-sectional prospective study determined that men with hemochromatosis complained of joint pain with earlier initial age of onset, as compared to those with primary hand osteoarthritis (48 years versus 58.4 years respectively). The gap was not as large among women with hemochromatosis (47.8 years versus 52.1 years), potentially owing to the later age of iron overload onset for women versus men. Pattern of joint involvement was also significantly different between

hemochromatosis and primary hand osteoarthritis, with more severe degenerative changes found in metacarpophalangeal joints in hemochromatosis arthropathy as compared to primary hand osteoarthritis.[6,7] Evaluations for early hand osteoarthritis with predominant metacarpophalangeal joint involvement should therefore prompt a thorough work-up for secondary causes of osteoarthritis.

In this case, the diagnosis of hemochromatosis arthropathy was made on the basis of second and third metacarpophalangeal joint changes typical for hemochromatosis, in addition to low sedimentation rate, and negative serologies for etiologies such as rheumatoid arthritis and systemic lupus erythematosus. Calcium pyrophosphate deposition disease and manual labor arthropathy can also potentially cause similar metacarpophalangeal changes, although these etiologies can be easily excluded with a thorough patient history, and upon reviewing radiographs for chondrocalcinosis.[8] Pathology reports obtained from the patient's prior knee replacement surgeries were consistent with osteoarthritis and there was no mention of hemosiderin deposition.

The management of hemochromatosis arthropathy is similar to that of primary hand osteoarthritis, and can include topical or oral analgesics, joint protection, orthotics, and hand exercises. Patients may need evaluation with a hand surgeon for severe arthritis. Treatment of hemochromatosis includes phlebotomy and iron chelation therapy.

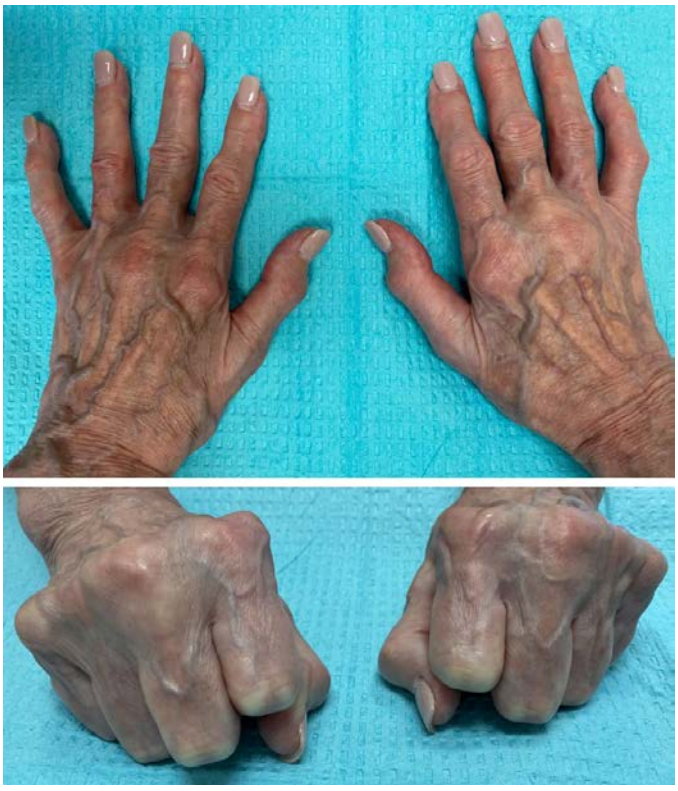

Figure 1. Photograph of the bilateral hands demonstrating joint enlargement, most notable in the second and third metacarpo-phalangeal joints, and proximal interphalangeal joints.

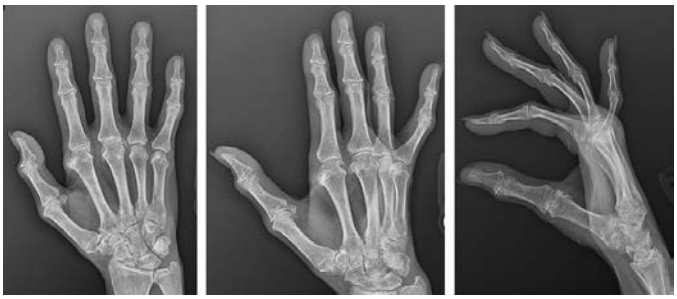

Figure 2. Posteroanterior, oblique, and lateral right hand series demonstrating second and third metacarpophalangeal joint space narrowing, subchondral cystic changes, and hook-like osteophyte formation. There are osteophytes present in the interphalangeal joints, radiocarpal joint space narrowing, and cystic changes to the carpal bones consistent with osteoarthritis. There is no chondrocalcinosis appreciated.

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