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***Case Report***

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# Hemochromatosis Arthropathy in Heterozygous HFE H63D Mutation Without Iron Overload- An Entity Less Commonly Touched

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## Abstract

Human homeostatic iron regulator protein gene (HFE gene) H63D mutations even when homozygous are rarely associated with iron overload. These mutations, independent of iron status, are associated with calcium pyrophosphate dihydrate crystal deposition disease (CPPD) leading to arthropathy even for heterozygotes. The arthropathy does not respond to iron depletion. We report a case of a 62-year-old male with chronic generalized arthralgias with no evidence of iron overload or elevated inflammatory markers with characteristic radiographic hook-like osteophytes suggestive of hemochromatosis arthropathy. Further, he was found to be a carrier of HFE H63D mutation. Recognition of the association can help guide goal directed management.

**Keywords:** Calcium pyrophosphate dihydrate crystal deposition disease, Hereditary hemochromatosis, HFE H63D mutation, Pseudogout, İron overload.

## INTRODUCTION

CPPD crystal deposition disease is also called as pseudogout. Pseudogout commonly occurs in elderly individuals. Occurrence of pseudogout in a young or a middle-aged individual suggests secondary etiology such as hemochromatosis [1]. Hemochromatosis leads to decreased clearance of calcium pyrophosphate crystals from the synovial fluid. As a result, these individuals may develop any presentation of CPPD such as chondrocalcinosis, acute pseudogout, and classic polyarthropathy with hook-like osteophytes most prominent in the second and third metacarpophalangeal (MCP) joints [1-3]. It is recommended that young individuals presenting with atypical osteoarthritis involving the MCP joints should undergo screening for secondary causes including hemochromatosis with serum iron studies. [1-4].

## CASE REPORT

A 62-year-old male with a past medical history of hypertension, coronary artery disease, hyperthyroidism, chronic obstructive pulmonary disease on long term home oxygen was evaluated in the clinic for generalized arthralgias. He reported chronic generalized myalgias, neck pain, diffuse arthralgias involving elbows, knees, hips, second metacarpophalangeal joints, first carpometacarpal joints with associated morning joint stiffness lasting less than 30 minutes of a duration of one year. A complete review of systems was otherwise unremarkable with no constitutional symptoms of weight loss, skin changes, Raynaud's phenomenon. He had no personal history of diabetes mellitus. His family history was notable for an unknown type of arthritis in father and maternal grandfather with no known family history of hemochromatosis. His social history was notable for daily cigarette smoking, occasional alcohol use, and no illicit drug use. Vitals signs were stable. His physical examination revealed tenderness but no swelling or local skin changes over second metacarpophalangeal joints and carpometacarpal joints bilaterally.

Laboratory workup revealed no evidence of iron overload or any elevation in inflammatory markers. *[Table 1]* Plain radiographs of hands revealed characteristic hook-like osteophytes over second to fourth

metacarpophalangeal joints bilaterally, and at right distal radioulnar joint but no evidence of chondrocalcinosis. This was suspicious for hemochromatosis arthropathy. *[Figure 1]*

Deoxyribonucleic acid (DNA) analysis of human homeostatic iron regulator protein gene (HFE gene) was performed by polymerase chain reaction (PCR) amplification followed by restriction enzyme digestion analyses. A single copy of H63D hereditary hemochromatosis (HH) mutation was identified. C282Y and S65C mutations were negative. He was diagnosed to have an HFE H63D carrier state with no evidence of iron overload.

He had no indication for phlebotomy as there was no evidence of iron overload. He was conservatively managed with activity modification and physical therapy for his arthropathy based on his treatment preferences. He will be followed closely in the outpatient setting for further monitoring.

**Table 1:** Laboratory workup findings

| Test | Result | Reference Range |
|---|---|---|
| Ferritin | 115 ng/ml | 30-400 ng/ml |
| Total Iron Binding Capacity | 288 ug/dl | 250-450 ug/dl |
| Serum Iron | 66 ug/dl | 38-169 ug/dl |
| Iron Saturation | 23% | 15-55% |
| Hemoglobin | 17.6 g/dl | 13.0-17.7 g/dl |
| Serum Creatine Kinase | 59 U/L | 41-331 U/L |
| Intact Parathyroid Hormone | 28 pg/ml | 15-65 pg/ml |
| Vitamin B12 | 248 pg/ml | 232-1245 pg/ml |
| Antinuclear antibodies (ANA) | Negative | Negative |
| C- Reactive Protein | 4 mg/ml | 0-10 mg/ml |
| Cyclic Citrullinated Peptide antibodies IGG/IGA | 7 units | 0-19 units |
| Hepatitis C Antibody | <0.1 S/CO Ratio | 0-0.9 S/CO Ratio |
| Rheumatoid Factor | 11.1 IU/ML | 0-13.9IU/ML |
| Erythrocyte sedimentation rate (ESR) | 9 mm/h | 0-30 mm/h |
| Serum uric acid | 4 mg/dl | 3.7-8.6 mg/dl |

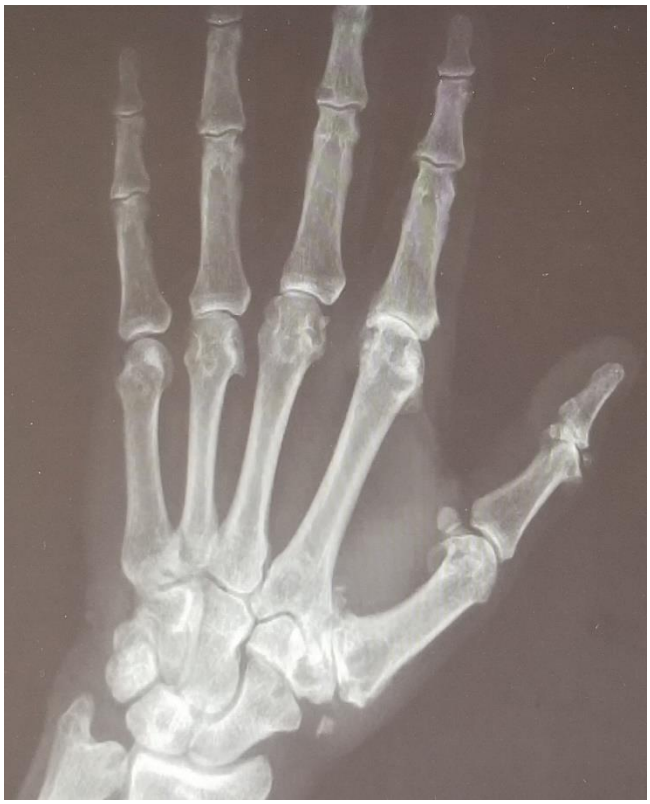

**Figure 1:** X-ray of left-hand anteroposterior view showing hook-like osteophytes

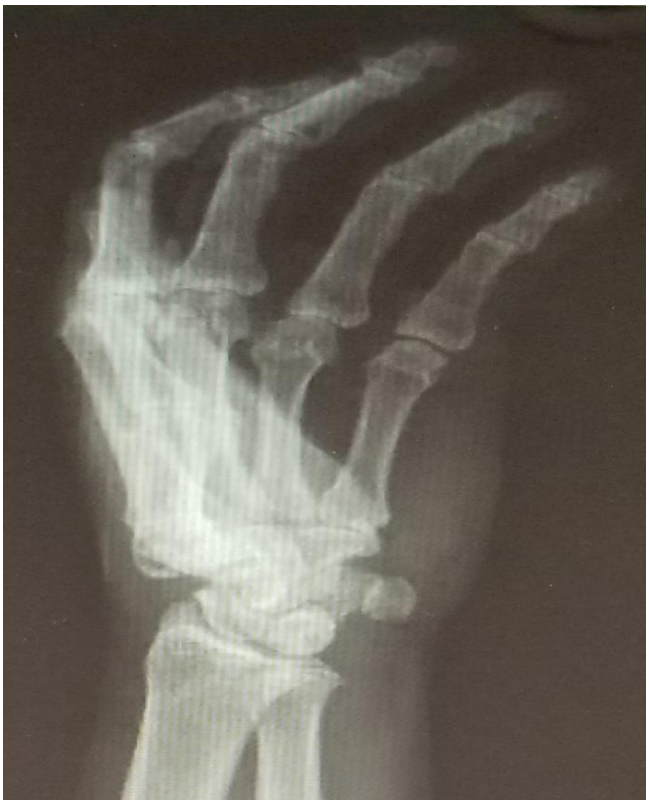

**Figure 2:** X-ray of left-hand lateral view showing hook-like osteophytes

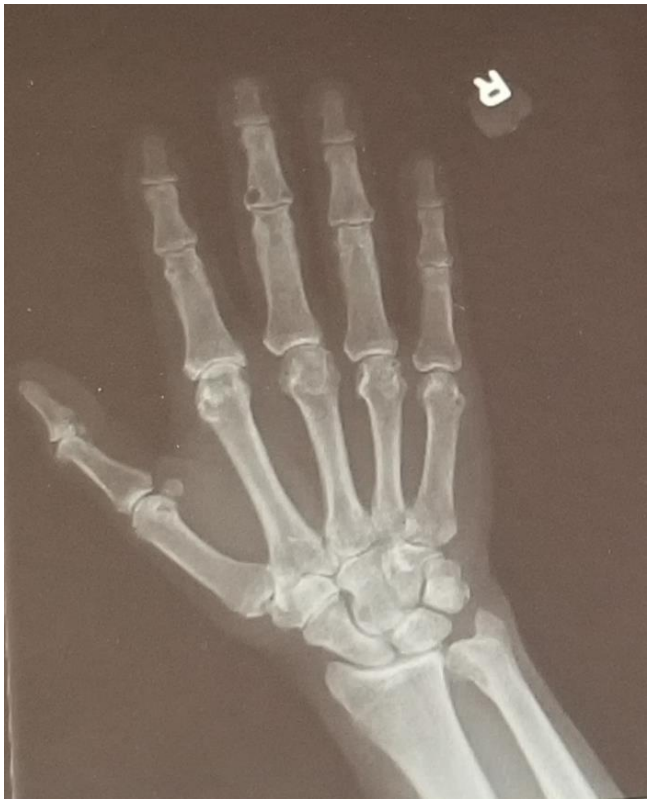

**Figure 3:** X-ray of right-hand anteroposterior view showing osteophytes

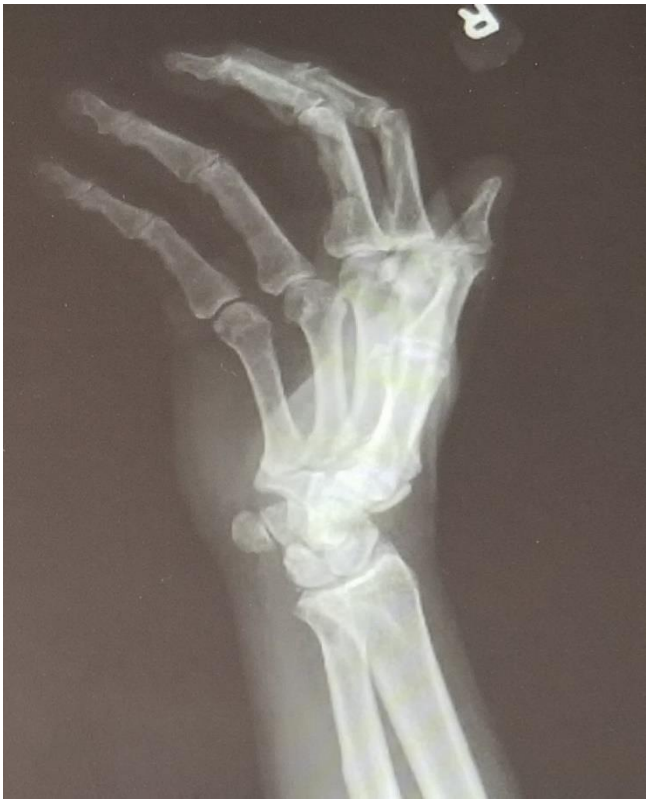

**Figure 4:** X-ray of right-hand lateral view

**DISCUSSION**

Radiological findings in hemochromatosis related arthropathy include subchondral sclerosis and cysts, joint space narrowing, and hook-shaped osteophyte formation in the metacarpophalangeal joints [1,4,5]. The presence of early onset arthropathy should raise a suspicion for secondary causes and such patients should undergo screening for the same [5]. The H63D genetic mutation may lead to arthropathy even in heterozygotes as was noted in our patient. Osteoarthritis that involves the MCP joints may be found in hemochromatosis. The H63D related arthropathy usually does not respond to iron depletion therapy. Treatment is usually supportive with symptom control for the arthropathy with anti-inflammatory agents [1,4,6].

**CONCLUSION**

The presence of a mutation of H63D, even heterozygous, may lead to arthropathy and may not have features of overt iron overload. The identification of classic radiographic feature of hook-like osteophytes especially in the second and third metacarpophalangeal joints suggests H63D related arthropathy. The presence of arthropathy in relatively young-aged or middle-aged should lead to a screening for secondary etiology.

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**Conflicts of interest**

The authors declared no conflict of interest.

**Note**

Verbal informed consent was obtained from the patient to publish their anonymized information.

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