Case Report

Hypercalcemia and Lytic Bone Lesions Masquerading Inflammatory Arthritis

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Abstract

Hyperparathyroidism is a complex clinical syndrome characterized by dysfunction in the metabolism of bone, calcium and phosphorus. Rheumatologic manifestations are common amongst patients with hyperparathyroidism.

We report a 50-year-old woman with hypercalcemia, lytic bone lesions and inflammatory arthritis of both hands that were not resolved after parathyroidectomy.

Laboratory evidence of elevated erythrocyte sedimentation rate, positive C-reactive protein (CRP) and high titers of anti-CCP and rheumatoid factor was diagnostic of rheumatoid arthritis (RA) according to European League Against Rheumatism criteria. Eventually, with the concomitant diagnoses of hyperparathyroidism and RA, she was treated with methotrexate and hydroxychloroquin.

Hyperparathyroidism may present with rheumatologic manifestations, leading to an initial misdiagnosis. Furthermore, attention to this fact that hypercalcemia is not commonly associated with RA, and rather suggestive of a concomitant disorder, is crucial to the diagnosis of hyperparathyroidism in RA patients with hypercalcemia.

Keywords: Hypercalcemia, hyperparathyroidism, musculoskeletal symptoms, rheumatoid arthritis

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Introduction

Hyperparathyroidism is a complex clinical syndrome characterized by dysfunction in the metabolism of bone, calcium and phosphorus. It is typically a sporadic disease, but may present as a familial syndrome in 5% of the cases.[1] Occasionally, it may be asymptomatic or have an atypical presentation.[2] The disease most often presents in postmenopausal women and mostly in the sixth decade of life.[2] The prevalence among the general population has been reported 3/10000, a figure which decreases annually beyond the age of 75 years.[3–4] In such cases, screening for osteoporosis and hypercalcemia helps in the detection of hyperparathyroidism. The incidence of the disease is influenced by environmental, nutritional and iatrogenic factors, although the exact relationship is unknown.[1]

Hyperparathyroidism is associated with increased secretion of parathyroid hormone (PTH), hypercalcemia, and hypophosphatemia. Hyperparathyroidism is the most common cause of hypercalcemia. However, there are also normocalcemic forms of the disease associated with reduced bone density.[5–6] Common clinical manifestations include renal stones, bone pain, myopathy, muscle atrophy, involvement of the gastrointestinal system in the form of peptic ulcer disease and pancreatitis, and a wide range of neurologic manifestations from depression to coma.[3,7] It may be associated with rheumatologic manifestations such as arthralgia, myalgia, and sinovitis.[8] Patients may initially present with polyarthritis, mimicking rheumatoid arthritis (RA). The most frequently involved joints in patients with hyperparathyroidism are the knees, wrists, interphalangeal joints and shoulders. Such manifestations are observed in half the cases of primary hyperparathyroidism.[2,9]

Erosive arthritis may develop in metacarpophalangeal and radiocarpal joints, which may present as non-inflammatory erosions, leading to the collapse of subchondral bone and changes in the joint cartilage. In contrast to RA, the majority of erosions are on the ulnar side of the joint, there is no joint space narrowing, and the proximal interphalangeal joints are less involved.[10–11] Intra- and peri-articular erosions of the head of the humerus bone without calcium deposition in the joint as uncommon form of shoulder involvement have been described. In this form, patients are typically asymptomatic. Myalgia is the most common rheumatologic complaint and when accompanied by pain in the shoulder girdle in the elderly, it may be erroneously diagnosed as polymyalgia rheumatica. Occasionally, patients may complain of fatigue, which, as in secondary hyperparathyroidism, is associated with osteomalacia and osteomalacia-like myopathy.[4]

Hyperparathyroidism has been reported to be associated with pseudogout in 30% of cases, as well as with hyperuricemia and gout.[12] However, the concomitant finding of hyperparathyroidism and RA is not common. There are a few case reported with the concomitant diagnosis of rheumatoid arthritis and hyperparathyroidism in literature,[13–15] but when an inflammatory arthritis is present in a patient with hyperparathyroidism, RA should be strongly considered. Likewise, hypercalcemia in a patient with RA raises the diagnosis of hyperparathyroidism as the most common cause.[12] It is important to differentiate the classic symptoms and signs of RA from the rheumatoid arthritis-like presentation of hyperparathyroidism. Furthermore, considering the fact that hy-

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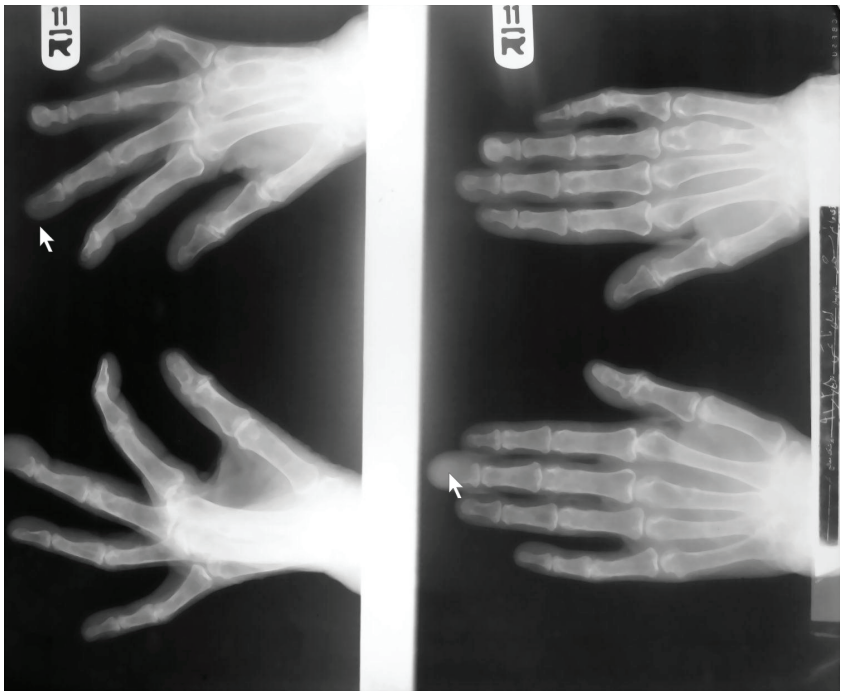

Figure 1. Osteopenia and Brown tumor in the fingers and metacarpals.

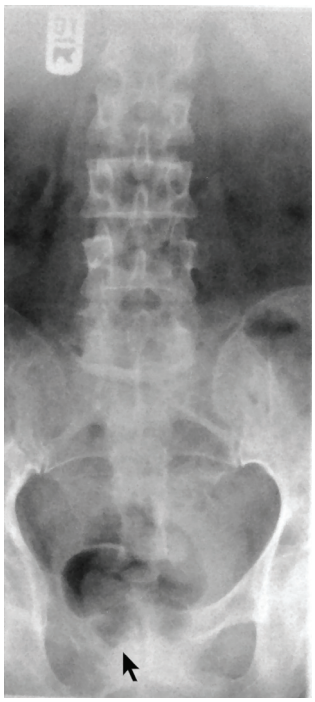

Figure 2. Brown tumor of the pubic bone.

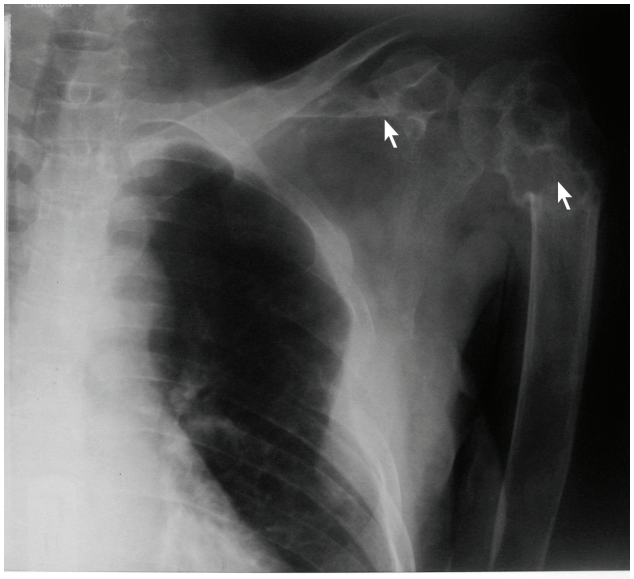

Figure 3. Fracture of the neck of the humerus.

percalcemia is not a typical finding in RA would possibly lower the chances of missing a concomitant diagnosis of hyperparathyroidism.

The following is a patient with the clinical manifestations of hypercalcemia and RA, which eventually led to the concomitant diagnoses of hyperparathyroidism and RA.

Case Report

A 50-year-old woman presented to the emergency department complaining of general malaise, diffuse musculoskeletal pain, and morning joint stiffness of more than one hour duration for a period of approximately one year. The patient had received analgesic treatment with relative improvement in symptoms. However, over the course of her illness, she had experienced increased myalgia and generalized musculoskeletal pain. In addition, the patient gave a several-month history of swelling of the knees, wrists and the metacarpophalangeal (MCP) joints associated with morning stiffness exceeding one hour plus low grade fever. Gradually, she had also developed occasional nausea and vomiting and increased urine volume together with anorexia, constipation, and weight loss of 3–4 kilograms over a two-month period. A significant finding in the patient's medical history over the few months before admission was that of multiple fractures which had occurred in the

left humerus bone, clavicle, and ribs and the pelvis (Figures 1–3). The patient had received outpatient treatment for epigastric pain and dyspepsia several times. However, the past medical history was unremarkable for diabetes, dyslipidemia, heart disease. She had no history of trauma.

On examination, increased size of the 3rd distal phalanx of the left hand and the 4th of the right hand was noticed. Arthritis was detected in the knee joints and both wrists, and the proximal interphalangeal joints of both hands in a symmetric fashion. No organomegaly or lymphadenopathy was detected.

The laboratory tests were normal for blood sugar levels, serum creatinine, uric acid and liver function tests. However, the finding of hypercalcemia (12.4 mg/dL) and a phosphorus level in the lower normal range (2.7 mg/dL) was followed by a test for serum PTH levels, which was inappropriately high (2347 pg/dL). The serum uric acid and vitamin D levels were in the normal range (41 ng/dL). The patient had an elevated ESR of 56 mm/h and positive CRP.

On bone mineral densitometry, the patient was reported to have osteoporosis in the lumbar vertebrae (T-score = -2) and the femoral neck (T-score = -2.5). A complete abdominal and pelvic ultrasound exam yielded no significant finding.

Considering the elevated PTH levels, a sestamibi scan confirmed the presence of a parathyroid adenoma, which was reconfirmed on histological examination following surgical resection. Based on the European League Against Rheumatism Criteria, the patient received a score of more than six based on multiple large and small joint involvement, high anti-cyclic citrullinated peptides (anti-CCP) and rheumatoid factor (RF) levels, and abnormal ESR and CRP, which indicates RA diagnosis.[11]

Ultimately, the patient underwent treatment for RA after parathyroidectomy with 400-mg daily doses of hydroxychloroquine and 10 mg of methotrexate per week with improvement in joint symptoms, musculoskeletal pain and the resolution of the patient's fever one month after parathyroidectomy.

Discussion

Primary hyperparathyroidism is a common endocrine disorder which is characterized by hypercalcemia, renal stones, and bone disease.[1] The diagnosis is made with an inappropriately high serum PTH level in the presence of hypercalcemia. Phosphorus levels are typically low, but may be normal with kidney disease.

In the present case, increased PTH levels, hyperclacemia and hypophosphatemia together with bone involvement in the form of lytic bone lesions called Brown tumor, and multiple fractures in humerus bone, clavicle, rib and pelvis were suggestive of hyperparathyroidism. Secondary hyperparathyroidism due to low serum vitamin D levels was ruled out with a normal serum 25-hydroxyvitamin D concentration (41 ng/dL).[16] In this patient, polyarthritis and laboratory data persistent after parathyroidectomy were not justified with the course of hyperparathyroidism.

Rheumatologic manifestations are common amongst patients with hyperparathyroidism. In a study, more than half of the patients (53%) with hyperparathyroidism had musculoskeletal symptoms for twelve months prior to the diagnosis of their disease. Of these, 26% had consulted a rheumatologist or orthopedist, their most common symptom being myalgia followed by arthritis, arthralgia, and erosive synovitis.[8] Hyperparathyroidism may also cause osteoporosis and pathologic bone fractures. Biwates reported rheumatoid-like erosions in the metacarpal bones and the styloid process of the ulnar bone in patients with hyperparathyroidism.[15] These changes could be the result of acute synovitis and effusion caused by subchondral bone collapse due to hyperparathyroidism.[15]

However, radiologic evidence of joint space narrowing of the metacarpophalangeal and proximal interphalangeal joints are suggestive of RA. The typical subperiosteal bone resorption on the radial side of fingers is found in a minority of patients with hyperparathyroidism. Bone erosions in hyperparathyroidism are mostly shaggy in appearance and are distributed in the radiocarpal, radioulnar, MCP, and distal interphalangeal joints rather than the PIPs. Other radiologic features in favor of hyperparathyroidism include Brown tumors and cystic changes in bones.[15]

In this case, symptoms such as myalgia, arthralgia, and arthritis may be observed in patients with hyperparathyroidism, yet laboratory evidence of elevated ESR, positive CRP, and high titers of anti-CCP and RF were diagnostic of rheumatoid arthritis. Also, polyarthritis did not resolve after parathyroidectomy. Therefore, the concomitant diagnoses of hyperparathyroidism and RA were made.

In a study by Kennedy, hyperparathyroidism was reported to be the most common cause of hypercalcemia in RA. This finding was later confirmed by a study conducted between the years 1987 and 1988 on 5000 patients with RA. Other causes of hypercalcemia in patients with RA included the use of thiazide diuretics, cancer, immobility, vitamin D toxicity, and chronic liver disease. These studies demonstrated that the etiologies for hypercalcemia in patients with RA are similar to those of the general population and hypercalcemia in RA was not, as previously thought, a complication of RA.[17]

Finally, the aim of the present case report with concomitant occurrence of hyperparathyroidism and rheumatoid arthritis was to highlight the fact that hyperparathyroidism may present with rheumatologic manifestations, leading to an initial misdiagnosis. Furthermore, attention to the fact that hypercalcemia is not associated with RA, and rather suggestive of a concomitant disorder, is crucial to the correct diagnosis of hyperparathyroidism in RA patients with hypercalcemia.

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Mount Tochal is at an elevation of 3,933 m, in the Alborz mountain range in northern Tehran, Iran.
(*photo by: M. H. Azizi MD, August 2015*)