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CASE REPORT

Bone Marrow Sarcoidosis: Hiding Within an Evaluation of Hypercalcemia

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Abstract

Patients with granulomatous disease often have widespread pulmonary and extrapulmonary disease. In the absence of this, a search of the pulmonary, renal, hepatic, ocular, and bone marrow is warranted in the setting of hypercalcemia with unexplained elevated 1,25-dihydroxyvitamin D, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). We present a case of hypercalcemia and a decline in renal function in a patient with bone marrow sarcoidosis. A 45-year-old woman was admitted to the hospital after hypercalcemia, acute kidney injury, and pancytopenia were found on a routine outpatient lab. She was discharged after improvement with IV fluids. She had interval worsening of hypercalcemia and was readmitted within a week for pamidronate treatment. Imaging and labs were concerning for sarcoidosis, but bronchoscopy with biopsy was nondiagnostic. Eventual bone marrow biopsy confirmed evidence of granulomas. Her condition improved with prednisone over 3 months and ultimately, azathioprine. Non-parathyroid hormone-mediated hypercalcemia should be thoroughly worked up for a source to rule out malignancy and to diagnose treatable causes such as sarcoidosis. Sarcoidosis may not present in its traditional pulmonary pattern, necessitating further diagnostic measures such as a bone marrow biopsy.

1. Introduction

Hypercalcemia is caused by primary hyperparathyroidism and malignancy in 90% of cases.[1] When both are ruled out, other causes must be investigated. One such alternative diagnosis is sarcoidosis. While recent data suggest that disease incidence is highest in Sweden, data collection and analysis methods vary globally, proving it hard to make direct comparisons between countries.[2] Within the US, the incidence and prevalence of the disease are significantly higher in the African-American population in comparison to those of European, Latin-American, and Asian descent.[3] The presentation of sarcoidosis can vary significantly, but 95% of those affected have an element of lung involvement.[4] Symptoms are often vague, but can include any constellation of cough, shortness of breath, fatigue, malaise, fever, rash, vision changes, or arthralgias. Workup generally consists of a complete metabolic panel (CMP), a complete blood count (CBC), and urinalysis (UA). Although hypercalciuria is more often seen in sarcoidosis than hypercalcemia is, a 24-h urine calcium is not necessary to make the diagnosis.[5] Various other tests such as 1,25-dihydroxyvitamin D, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are often elevated but are non-specific. Given that the presence of bilateral hilar lymphadenopathy can be as high as 75–90% amongst sarcoidosis patients, a chest radiograph should be obtained. In most cases, a high-resolution CT chest image is subsequently completed due to superior characterization of the extent of lymphadenopathy.[6] Although there is no definitive diagnostic test for sarcoidosis, the combination of compatible clinical and radiographic findings with the exclusion of other similarly presenting diseases may suffice. Asymptomatic bilateral hilar lymphadenopathy can be simply monitored for resolution. Classical symptoms of Lofgren syndrome, which include fever, an erythema nodosum rash, acute arthritis, and hilar lymphadenopathy, may also suffice for diagnosis and not require further testing.[7] Other exceptions that do not require tissue sampling include the presence of

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lupus pernio or Heerfordt's Syndrome.[8] Ultimately, most cases will require histological evidence of noncaseating granulomas. This is often done via bronchoscopy with endobronchial or transbronchial lung biopsy. In the absence of lung pathology, multiple organ systems should be surveyed. Bone marrow involvement is only thought to be present in roughly 4% of cases.[4] This is in the form of bone marrow granulomas, seen on bone marrow biopsy.

2. Case presentation

A 45-year-old white woman with a history of treated astrocytoma was admitted to the hospital after hypercalcemia and acute kidney injury were revealed on a routine outpatient lab. Bloodwork was notable for a calcium of 13.2 (8.4–10.6) and a creatinine of 2.3 (0.5–1.2); both were previously normal eight months prior. She reported taking vitamin D 2000 units and 400 mg of calcium daily, but denied excess dairy intake or calcium carbonate use. She had experienced 6 weeks of malaise, poor appetite, and urinary frequency. She denied any bone pain or symptoms of kidney stones. Chest x-ray was unremarkable. No acute kidney changes were seen on renal ultrasound, but hypoechoic lesions in the spleen were noted. Her parathyroid hormone (PTH) and 25-vitamin D levels were low-normal at 32.8 (18.4–88) and 29.7 (30–50) respectively. Serum protein electrophoresis (SPEP) was normal. Her CBC had a white blood cell (WBC) count of 4100 (4500–10,300), hemoglobin (Hb) 10.7 (12–16), and platelets 147K (150–500K). She was discharged after 2 days with mild improvement in her calcium and creatinine after receiving IV fluids. Her parathyroid hormone-related protein (PTH-rP) returned low, but the 1,25-vitamin D was markedly elevated at 112 (19.9–79.3). On follow-up with the endocrinology clinic 4 days later, repeat labs showed a calcium of 15 and a creatinine of 2.1, prompting hospital readmission. Her calcium improved to 10.1 after receiving pamidronate and IV fluids. Further testing was notable for an ESR of 47 (0–20) and a CRP of 2.4 (0–0.5). CT imaging aligned with suspected sarcoidosis with hilar and retroperitoneal lymphadenopathy, as well as splenomegaly. Endobronchial ultrasound-guided biopsy of hilar lymph nodes did not reveal any granulomas. Oncology follow-up was suggested to rule out lymphoma. A nuclear bone scan was without abnormalities. A bone marrow biopsy revealed multiple noninfectious granulomas, consistent with sarcoidosis. Her condition improved with prednisone and azathioprine treatment. The prednisone was tapered over the span of months with improved lab results, allowing her to continue on just azathioprine.

3. Case discussion

This case highlights an extensive workup of hypercalcemia with vague symptoms. Though nonspecific, elevated ESR, CRP, and 1,25-dihydroxyvitamin D levels should raise concern for sarcoidosis in the setting of non-PTH mediated hypercalcemia. Even when lung involvement is not confirmed, other organ systems should be investigated for granulomas if the clinical suspicion for sarcoidosis remains high. It is possible that bone marrow involvement is more common than reported, as it may go under-reported given most patients do not receive a bone marrow biopsy. A full history that includes symptoms of both intrathoracic and extrathoracic manifestations of sarcoidosis can be integral to the diagnosis, as symptoms are often insidious in nature.[9] Common findings in bone marrow sarcoidosis include cytopenias, lymphadenopathy, and hypersplenism; all of which were present in this patient.[10] Although there is no randomized trial to definitively compare treatment modalities of bone marrow sarcoidosis, steroids appear to be the preferred method of treatment amongst published cases.[11] When a patient progresses or does not respond to steroids, other options include various immunosuppressants such as azathioprine, methotrexate, or adalimumab.[9,12] The combination of prednisone and azathioprine was successful in the treatment of the patient discussed. It should also be noted that no demographic population should be ruled out based on lower disease prevalence, as cases vary greatly in backgrounds.

4. Conclusions

In conclusion, hypercalcemia can be a prominent presenting factor of various pathologies, sarcoidosis being one of them. Though lung involvement is to be expected in most cases of sarcoidosis, the workup should not be limited to the lungs if clinical suspicion remains high. Sarcoidosis symptoms are very often vague, so there should be a low threshold for having it on the differential. Though the reported presence of bone marrow infiltration of sarcoidosis is thought to be as low as 4%, the true incidence may be higher due to the fact that patients do not routinely receive a bone marrow biopsy as part of their evaluation. Not every patient with sarcoidosis should undergo this type of testing, however it should remain on the radar of clinicians.

Disclaimers

A poster presentation of this case was presented at the Ascension Saint Thomas Resident Research Day 2023 in Nashville, TN (5/5/2023).

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Conflicts of interest

None to report.

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