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Case Report

A case report on sarcoidosis: the great-mimicker

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ABSTRACT

Sarcoidosis is a rare multi-systemic disease of idiopathic etiology with a low incidence and the hallmark histologic feature of non-caseating granulomas. Sarcoidosis can involve any organ system. Thus, the manifestations at presentation are highly variable. Our case features a 55-year-old female who presented with complaints of abdominal pain, anorexia, weight loss, and a history of infrequent dry cough with lymphoma, tuberculosis, and lung carcinoma, the initial differentials in mind. In due course, investigations revealed bilateral renal calculi and hypercalcemia, which eventually led to the diagnosis of sarcoidosis. Hypercalcemia and renal dysfunction in sarcoidosis are relatively rare, affecting less than 10% of patients at presentation. In its acute phase, the consequences of hypercalcemia are reversible, and its prompt treatment subsequently reduces the risk of irreversible renal dysfunction, highlighting the importance of strong suspicion for a disease like sarcoid - the Great Mimicker.

Keywords: Anorexia, Granuloma, Hypercalcemia, Renal calculi, Sarcoidosis

INTRODUCTION

Sarcoidosis is a rare multi-systemic disease of idiopathic etiology with the hallmark histologic feature of non-caseating granulomas.1 Incidence of sarcoidosis is as low as 1-2 per 100,000 population among Southeast Asians, in contrast to approximately 70 per 100,000 population among African-Americans.2 Involvement of the lungs is seen in approximately 95% of cases, followed by skin and lymph node involvement.1 Among extrapulmonary manifestations, skin lesions, uveitis, liver or splenic involvement, peripheral and abdominal lymphadenopathy, and peripheral arthritis are the most frequent, with a 25-50% prevalence.3 However, hypercalcemia and renal dysfunction are relatively rare, affecting less than 10% of patients.3 The diagnosis of sarcoidosis is based on three main criteria: a compatible presentation, the evidence of non-caseating granulomas on histological examination, and the exclusion of any alternative diagnosis.3 Our case features a 55-year-old female who presented with complaints of abdominal pain, anorexia, weight loss, and a history of infrequent dry cough with initial differentials of lymphoma, tuberculosis, and lung carcinoma in mind. Investigations revealed bilateral renal calculi and hypercalcemia, which eventually led to the diagnosis of sarcoidosis - the Great Mimicker.

CASE REPORT

A 55-year-old lady presented to the medicine outpatient clinic with abdominal pain, anorexia, and weight loss for the past two months. Her abdominal pain was insidious in onset, diffuse, dull aching, with associated intermittent constipation, nausea, and anorexia. She also lost 2.5 kg of body weight over the past two months and had an associated history of infrequent dry coughs over the past month. However, there was no history of fever, night sweats, pedal edema, urine abnormalities, contact with a

tuberculosis patient, or any other notable abnormality. She was recently diagnosed with type-2 diabetes mellitus two months back and was prescribed oral anti-diabetic agents for it. On examination, she seemed lethargic with a low body mass index of 17.5 kg/m2 and pallor, with normal vitals and no notable systemic findings. Even abdominal examination revealed no organomegaly, tenderness, or any other specific clue to guide diagnosis. With this clinical picture, tuberculosis, lymphoma, and lung carcinoma were the initial differentials in mind.

Initial investigations revealed anemia of chronic disease with a hemoglobin of 9.6 g/dl, high serum ferritin (450 ng/dl), low serum iron (24 mcg/dl), total iron binding capacity (190 mcg/dl), and transferrin saturation levels (12.6%). The patient had raised serum creatinine (1.6 g/dl) and reduced eGFR (38 ml/min/1.73 m2) with normal urine examination findings. Albumin: Globulin ratio was decreased (Albumin=3 g/dl, Globulin 4.5 g/dl), and serum calcium levels were grossly elevated (14 mg/dl).

Further investigations conducted, given the renal derangement and abnormal serum calcium, revealed low parathormone (8.3 pg/ml) and 25-hydroxy vitamin D levels (18 ng/ml), ruling out any parathyroid gland abnormalities. An abdominal ultrasound revealed the presence of bilateral renal calculi with normal-sized kidneys, preserved cortico-medullary differentiation, and no evidence of post-renal obstruction. Thus, abdominal ultrasound and renal function test suggested a pre-renal cause of renal dysfunction. A Chest X-ray showed bilateral hilar fullness, which eventually became immensely pivotal in reaching the diagnosis of this case. Hilar fullness and hypercalcemia immediately raised the suspicion of sarcoidosis, albeit the presentation was not classical. To evaluate her along the lines of sarcoidosis, a contrast-enhanced computed tomography (CECT) of the thorax, subsequently, a bronchoalveolar lavage (BAL), alongside serum angiotensin-converting enzyme (ACE) assay was performed.

The CECT revealed multiple enlarged mediastinal and hilar lymph nodes and bilateral centrilobular nodules. The fluid from BAL turned out to be lymphocytic with an increased CD4: CD8 ratio (3.1:1). A transbronchial lung node biopsy was performed and subjected to acid-fast staining, tissue cartridge-based nucleic acid amplification test (CBNAAT) and histopathological examination (HPE). While CBNAAT and acid-fast staining were negative for tuberculosis, HPE revealed non-necrotizing epitheloid granulomas with minimal lymphocytic cuff (Figure 1). Also, serum ACE levels were high (108 U/l). Thus, based on the findings of HPE, elevated CD4:CD8 ratio, serum ACE levels, hypercalcemia, and exclusion of other plausible causes, a diagnosis of sarcoidosis was made, with prompt initiation of specific treatment. The mainstay of the treatment was oral prednisolone, which was started at an initial dose of 1 mg/kg/day and was continued for six weeks, during which there was symptomatic relief. Upon re-evaluation, renal function was restored, hypercalcemia resolved, and there was regression of perihilar lymph nodes. We gradually tapered the dose over the next six weeks, and finally, the patient is now on a maintenance dose of 10 mg of oral prednisolone for a year. She is currently on follow-up and doing well so far.

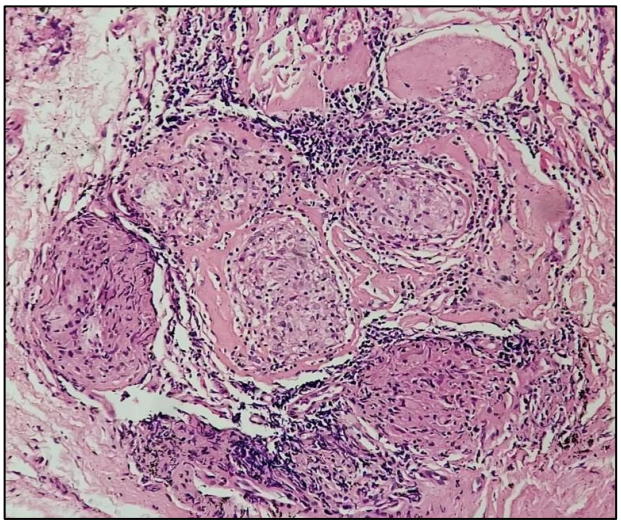

Figure 1: Hematoxylin-eosin stained histopathology section (400X) from a transbronchial lung biopsy include lung parenchyma containing carbon laden macrophages with nodular pattern of non-necrotizing granulomata composed of epitheloid cells having abundant eosinophilic cytoplasm and minimal lymphocytic cuff (naked granuloma).

DISCUSSION

Sarcoidosis is a rare granulomatous multi-systemic disease with idiopathic etiology.[1] It can virtually involve any organ, and thus, the characteristics and the symptoms at presentation of sarcoidosis vary highly. However, hypercalcemia and renal dysfunction at presentation in a case of sarcoidosis, as seen in this patient, are extremely rare and have relatively limited cases reporting the same.[2]

The largest up-to-date study, from a single center involving 1606 patients, reported that hypercalcemia appears in only about 6% of sarcoidosis patients.[4] However, a multi-centric study involving 736 patients reported the incidence of sarcoidosis-associated hypercalcemia of only 3.7%.[5] Primary hyperparathyroidism and malignancies are responsible for about 80-90% of all cases of hypercalcemia.[6] Therefore, an elderly presenting with abdominal pain, anorexia, and weight loss accompanied by hypercalcemia may invariably mislead a physician to investigate extensively for malignancies to no avail sometimes, as it could've been so in this case. Furthermore, the mechanism of hypercalcemia in sarcoidosis is understood to be due to the increased activity of 1α-hydroxylase that causes autonomous production of 1,25-dihydroxy vitamin D by granuloma macrophages.[7] Consequently, this condition typically leads to elevated levels of 1,25-dihydroxy

vitamin D. However, in this case, the levels of 25-dihydroxy vitamin D were inappropriately low (18 ng/ml), reflecting low levels of 1,25-dihydroxy vitamin D, which emphasizes that sarcoidosis-related hypercalcemia may not always be due to raised 1,25-dihydroxy vitamin D levels, and instead suggest other unknown mechanisms at play, the understanding of which could shine some light onto the poorly understood pathogenesis of sarcoidosis.[7]

The evidence of renal dysfunction added more to the peculiarity of this case. In context, cases of sarcoidosis presenting with renal failure are rare. The available epidemiological data are on small case series involving up to 60 patients. As a result, the exact incidence of renal sarcoidosis is still unknown.[8] A recently conducted meta-analysis found that renal dysfunction was detected in only 7% of patients with sarcoidosis.[9] In the acute phase, the renal consequences of hypercalcemia are reversible, and nephrolithiasis may be the presentation of sarcoidosis in only about 3-4% of cases.[8] Recent studies suggest hypercalcemia itself may be the primary cause of renal dysfunction. Additionally, it may contribute to tubular damage and acute kidney injury (AKI) due to vasoconstriction of the afferent arterioles.[10,11] However, in the acute phase, the consequence of hypercalcemia is reversible, making prompt treatment all the more essential.

CONCLUSION

Sarcoidosis is a multi-systemic disorder, which may have atypical presentations and is rightly called the 'great-mimicker' as it can present in innumerable ways, drawing a list of differentials that may sometimes be exclusive of sarcoidosis itself. It should also be noted that sarcoidosis-related hypercalcemia is not always due to raised 1,25-dihydroxy vitamin D levels, and there may be other mechanisms at play that call for further research that would bridge the existing lacunae. Given the reversibility of AKI due to sarcoid-related hypercalcemia, it becomes essential to have a high index of suspicion to diagnose and initiate timely treatment.

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