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Priyadarshini Balasubramanian, Deepak Kana Kadayakkara, Gregory Soloway, William Laskin, Sachin Majumdar

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Introduction: Necrotizing sarcoid granulomatosis (NSG) is a rare variant of sarcoidosis with pathologic features of necrosis and vasculitis that overlap with rheumatologic and infectious diseases. Hypercalcemia is occasionally the presenting feature of classical sarcoidosis occurring in 10–20% of patients, most commonly in association with pulmonary involvement. However hypercalcemia in NSG is less common and has not been previously described when NSG primarily affects the liver.

Case Report: We report a 65-year-old Caucasian female who presented with hypercalcemia and NSG of the liver without pulmonary involvement.

Conclusion: Hypercalcemia was mediated by 1, 25-vitamin D which was most likely produced by hepatic granulomas and it resolved rapidly with prednisone. Further, we describe the time-course for the resolution of hypercalcemia and other biochemical abnormalities with treatment, and suggest potential roles for monitoring 1, 25-dihydroxyvitamin D and ACE in guiding therapy.

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CASE REPORT

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Keywords: 1,25-Dihydroxyvitamin D, Hepatic granuloma, Hypercalcemia, Necrotizing sarcoid granuloma

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INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder classically observed in young African-American females of 25–40 years of age. However, it can occur in all races and age groups, with about 30% of cases in elderly patients [1]. In over 90% of cases sarcoidosis involves the lung, and hypercalcemia, occurring in 10–20% of patients, is rare in the absence of pulmonary involvement [2]. Necrotizing sarcoid granulomatosis (NSG) is an uncommon variant of sarcoidosis characterized by granulomas with necrosis and vasculitic changes [3]. Necrotizing sarcoid granulomatosis can mimic rheumatologic and infectious diseases, yet like classical sarcoid it primarily affects the lungs, though rarely it can present with extra-pulmonary manifestations. When extra-pulmonary involvement occurs the most commonly affected sites are the eyes and the central nervous system. Unlike classic sarcoidosis which is more common in African-American females,

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NSG is thought to be more prevalent in Caucasians. We present a case of calcitriol mediated hypercalcemia due to NSG of the liver in the absence of pulmonary involvement in an elderly Caucasian female.

CASE REPORT

A 65-year-old female presented to the hospital with a six-week history of headache, vomiting, weight loss, confusion and constipation. She denied fever, loss of appetite, cough, chest pain, visual disturbances or weakness.

Past medical history of the patient was remarkable for hypertension, depression and intra-ductal atypia of left breast s/p lumpectomy a year ago. Her medications at home included losartan, atorvastatin and quetiapine. She denied taking over the counter nutritional supplements. Physical examination of the patient was unremarkable.

Laboratory workup revealed a calcium level of 15.8 mg/dl (8.5–10.2 mg/dl), 25-hydroxyvitamin D 28 ng/ml (20–100 ng/ml), 1, 25-dihydroxyvitamin D (calcitriol) 119 pg/ml (20–62 pg/ml) and parathyroid hormone (PTH) of 7.3 pg/ml (7.5–53 pg/mL). Creatinine was 1.2 mg/dl, AST 126 U/L (14–36 U/L), ALT 156 U/L (9–52), and ALP 342 U/L (38–126 U/L). Chest X-ray was normal. The results indicated calcitriol-dependent hypercalcemia, and the diagnostic possibilities considered were malignancies (hematological cancers and solid tumors) and granulomatous disorders including tuberculosis and sarcoidosis. Computed tomography scan of the chest, abdomen and pelvis did not show evidence of malignancy or lymphadenopathy. Ultrasound of the liver showed normal echotexture with no focal lesions. A skeletal metastatic series was negative as were serum and urine protein electrophoresis. Upper gastrointestinal endoscopy with biopsies of stomach, duodenum, and distal esophagus were negative for malignancy, parasites and celiac disease. An angiotensin converting enzyme (ACE) level was 260 u/L (8–53 u/L).

With elevated liver enzymes, high ACE, and a negative malignancy workup, a liver biopsy was performed which showed necrotizing granulomas present in portal areas and in parenchyma. No GMS fungal elements or AFB-positive organisms were identified. Reticulin stain showed normal liver plates and iron stains were negative. The PAS with diastase failed to identify organisms but highlighted lipofuscin within Kupffer cell granulomas associated with necrotic hepatocytes consistent with the necrotizing variant of sarcoidosis, of NSG, as shown in (Figure 1).

The patient was started on 20 mg/d of prednisone and improved symptomatically along with significant reductions in calcium, calcitriol, ALP, liver enzymes, and ACE levels as depicted in (Figure 2). Serum calcium and calcitriol normalized within one week of starting steroids, ALP took at least one month to normalize, and liver enzymes and ACE declined significantly yet remained

elevated. Calcitriol correlated with hypercalcemia and responded rapidly to steroid therapy with suppression maintained at low doses, which permitted rapid tapering while minimizing side effects. Angiotensin converting enzyme levels declined yet their persistent elevation appeared to reflect a more sensitive measure of disease activity with less clinical impact.

Prednisone was tapered and stopped in eight months. One month after discontinuation of prednisone the calcium was 9.2 mg/dl, 1, 25 vitamin D 39 pg/ml, ACE 89 U/L, AST 52 U/L, ALT 36 U/L and ALP 102 U/L.

DISCUSSION

Sarcoidosis is a multisystem disease of unknown etiology with the pathological hallmark being the presence of non-caseating granulomas. The NSG is a rare and poorly understood entity characterized by granuloma with caseous necrosis making it difficult to distinguish from infectious conditions like tuberculosis. It was first described in 1973 by Liebow as sarcoid-like granuloma with vasculitis and necrosis, not caused by rheumatological or infectious diseases [3]. There is a controversy as to whether the entity is sarcoidosis with necrosis of the vessels, or a separate vasculitic disorder. Therefore, it is important to exclude other conditions to avoid unnecessary delay in treatment. Necrotizing

Figure 1: Biopsy of the liver. (A) Liver parenchyma showing granulomatous inflammation and necrosis (x200), and (B) Discrete sarcoid granuloma (x400). Acid-Fast Bacilli (AFB) and fungal stains were negative.

Figure 2: Graph showing angiotensin converting enzyme and calcitriol in response to prednisone.

sarcoid granulomatosis is thought to be more common in the lung with extra-pulmonary involvement being very rare, though when present the most commonly affected sites are the eyes and central nervous system [4]. While sarcoidosis is typically more common in African-American females, all of the 14 cases of NSG in a review published by Quaden et al. were Caucasians, of which 10 patients were females and 4 were males [5]. Therefore, one could postulate that NSG is more common in Caucasian females, and our case supports this hypothesis.

Necrotizing sarcoid granulomatosis of the liver with calcitriol mediated hypercalcemia has not been previously described. There are only two other cases of NSG of the liver described in literature. The clinical presentation was not described in one patient and the second patient did not have hypercalcemia associated with NSG of the liver [6]. Hypercalcemia in sarcoidosis and other granulomatous conditions appears to be mediated by elevated levels of circulating calcitriol resulting in increased intestinal calcium absorption [7]. Excessive calcitriol synthesis in sarcoidosis has been shown to originate from increased 1 α -hydroxylase activity in alveolar macrophages [8, 9]. Hence hypercalcemia is rare in the absence of pulmonary involvement. Our patient had no evidence of pulmonary involvement suggesting calcitriol production in extra-pulmonary granulomatous tissue such as the liver or GI tract, yet we cannot exclude the possibility of occult pulmonary disease.

Angiotensin converting enzyme has historically been used to monitor disease activity in sarcoidosis, but calcitriol has not. However, when hypercalcemia is the major clinical manifestation, calcitriol may be useful in guiding therapy, particularly as a more direct marker of disease activity whose responsiveness to treatment could foster rapid reductions in steroid dose, while providing reassurance of therapeutic effectiveness. In our case, when the prednisone dose was lowered, calcitriol levels remained stable, and this was helpful in deciding to proceed with tapering steroid doses and ultimately discontinuing treatment while providing reassurance that treatment remained effective and the disease was stable. Monitoring calcitriol also provided the potential to prevent symptomatic hypercalcemia when steroids were discontinued, particularly in the setting of persisting ACE elevations, because if calcitriol levels were to rise, one could consider resuming steroid treatment before significant hypercalcemia could occur. Angiotensin converting enzyme levels were useful indicators of disease activity, but were a step removed from the pathogenesis of hypercalcemia in comparison to calcitriol, yet changes could be informative in regards to disease activity, with rises in ACE potentially prompting closer monitoring or treatment consideration. Hence, we propose that monitoring calcitriol can help guide steroid therapy in the acute setting when sarcoidosis is associated with hypercalcemia, while ACE levels may be useful for chronic disease monitoring rather than treatment guidance.

Corticosteroids are the mainstay of treatment in sarcoidosis. Recommendations suggest 1 mg/kg/day of prednisone which can be tapered over several weeks to months, however required to lower calcium level may be much lower. Drugs like methotrexate, hydroxychloroquine or azathioprine may be used in steroid resistant cases or as steroid sparing agents. Prognosis is variable and depends on gender, race, age, organ involvement, the signs and symptoms at presentation. In the majority of patients, sarcoidosis stabilizes in the first two years of illness with treatment. There are no gold standard tests available to monitor the response to therapy.

CONCLUSION

We describe the first case of calcitriol-mediated hypercalcemia associated with necrotizing sarcoid granulomatosis (NSG) of the liver in the absence of pulmonary involvement. The NSG appears to be more common in Caucasian females and sarcoidosis can present with hypercalcemia without pulmonary involvement. Elevated calcitriol and angiotensin converting enzyme levels can be useful markers of disease activity and also potentially guide treatment. Calcitriol monitoring can help guide therapy by matching steroid dose with its relative effectiveness on suppression of hypercalcemia, while monitoring angiotensin converting enzyme can provide information on disease activity potentially altering longer term care needs of the patient. In this context, both measures have the potential to add precision to medical decision making in efforts to minimize side effects of therapies, gauge their effectiveness, and provide more specific information about disease activity to the clinician and patient.

Author Contributions

Priyadarshini Balasubramanian – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Deepak Kana Kadayakkara – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Gregory Soloway – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
William Laskin – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Sachin Majumdar – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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