Macrophage Activation in Lupus Nephritis: An Unknown Cause of Severe Hypercalcemia

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ABSTRACT

A Hispanic male in his 20s presented to the hospital with altered mental status and severe hypercalcemia. During his hospitalization, he developed clinical deterioration requiring intubation and ICU transfer. Initial work-up revealed low PTH and PTHrP levels, along with elevated vitamin D 25-OH and 1,25-OH levels. He developed progressive acute kidney injury, and a kidney biopsy later confirmed macrophage activation syndrome (MAS) in a background of type III lupus nephritis. His hypercalcemia resolved following pulse methylprednisolone therapy. Once clinically improved, the patient reported recent use of vitamin D supplementation. After excluding other causes of non-PTH-dependent hypercalcemia with elevated 1,25-OH vitamin D, MAS was determined to be the driver of increased 1-alpha hydroxylase activity, exacerbated by exogenous vitamin D. This is the first reported case of severe hypercalcemia due to MAS from lupus nephritis, compounded by vitamin D supplementation.

KEYWORDS: Hypercalcemia; Systemic Lupus Erythematosus; Macrophage Activation Syndrome' 1,25-hydroxyvitamin D

INTRODUCTION

Hypercalcemia is a common entity, with over 90 percent of cases due to primary hyperparathyroidism or malignancy.[1] Although rare, systemic lupus erythematosus (SLE) has been reported as a cause of hypercalcemia, potentially linked to parathyroid hormone-related protein (PTHrP) production and cytokine release, though the exact mechanism remains unclear.[2,3]

Macrophage activation syndrome (MAS) is a hyperinflammatory condition characterized by excessive cytokine production, leading to macrophage and T-cell activation, hemophagocytosis, and life-threatening multi-organ dysfunction.[4] MAS can be triggered by systemic inflammatory disorders, including SLE. Activated macrophages produce 1,25-dihydroxyvitamin D through unregulated 1-alpha hydroxylase activity, a mechanism previously noted in granulomatous diseases.[1,5] This dysregulation, especially when combined with high vitamin D stores, can result in hypercalcemia.

We report the first known case of a 22-year-old Hispanic male with SLE complicated by severe lupus nephritis, presenting with altered mental status due to hypercalcemia found to be secondary to MAS coupled with recent vitamin D supplementation.

CASE PRESENTATION

A Hispanic male from the Dominican Republic in his 20s, who immigrated to the United States one year prior, with ongoing work up for possible SLE, presented to the hospital after an acute change in mental status. On arrival, the patient was hemodynamically stable, but somnolent and oriented only to person and place. No focal deficits were present on the neurological exam. Due to deteriorating mental status, he required transfer to the Intensive Care Unit (ICU). There, he was found to have severe hypercalcemia of 15.9 mg/dL.

DIAGNOSTIC ASSESSMENT

Initial calcium was 15.9 mg/dL followed by 13.5 mg/dL after IV fluids. Ionized calcium was 1.46 mmol/L. Hypercalcemia workup revealed Parathyroid hormone (PTH) of 1.6 pg/mL (reference 15–65 pg/mL), 25-hydroxyvitamin D of 129 ng/mL (30–100 ng/mL), 1,25-dihydroxyvitamin D of 190 pg/mL (24.8–81.5 pg/mL), free light chains ratio unremarkable. White blood count was 15 10e3/µL, potassium 6.2 mEq/L, sodium 128 mEq/L, lactate 2.7 mmol/L, and procalcitonin of 1.6 ng/mL. His kidney function revealed Cr of 1.59 (increased from a baseline of 0.9). Cerebrospinal fluid analysis and brain MRI were unremarkable. Investigation of the AKI revealed a positive ANA 1:1280, positive dsDNA, and a low C3/C4 concerning for a primo diagnosis of SLE. Eventually, due to worsening AKI, a kidney biopsy revealed lupus nephritis, with immunofluorescence significant for full house deposition (presence C3, C1a and all major immunoglobulins: IgG, IgA, and IgM) with a strong predominance of C1q, consistent with type III lupus nephritis. There was also evidence of MAS secondary to lupus with interstitial kidney involvement.

TREATMENT

The patient was started on methylprednisolone 1 mg/kg on hospital day 2 due to concern for lupus nephritis. Given persistent hypercalcemia, he was given calcitonin 200 mg subcutaneously on hospital days 4 and 5, then started on calcitonin 200 mg every eight hours for six doses. Bisphosphonates and aggressive IV fluid resuscitation were avoided given the patient's acute kidney injury. After type III lupus nephritis was confirmed, he completed a five-day course of methylprednisolone 1 g daily.

OUTCOME AND FOLLOW-UP

Mental status slowly improved, and vitamin D levels trended down (vitamin D 25 hydroxy 69 ng/mL and vitamin D 1,25 50.7 pg/mL) on hospital day 6. Unfortunately, the patient developed hemorrhagic shock due to a large left retroperitoneal hematoma and hemoperitoneum after kidney biopsy. After multiple surgical interventions for bleeding source control and a massive transfusion protocol (received 14 units of red blood cell products), he ultimately improved and was transferred out of the ICU again. His calcium levels normalized after the second day of steroid pulse therapy. When the patient was stable and extubated, he endorsed vitamin D supplementation.

DISCUSSION

Hypercalcemia is a common finding, with primary hyperparathyroidism and malignancy accounting for approximately 90% of cases.[1] The other 10% of causes are diverse, including vitamin D intoxication, granulomatous disorders, medications, and thyrotoxicosis.[1] Systemic lupus erythematosus is a rare and not fully understood cause of hypercalcemia.[2,3] One of the mechanisms that has been proposed is that there is an excessive PTHrP or presence of autoantibodies against PTH receptors that drive the hypercalcemia.[2,3] Another proposed mechanism is that the cytokines released by active SLE such as interleukin (IL)-6, IL-1 and prostaglandin E directly stimulate osteoclast bone resorption leading to hypercalcemia.[2,3] Xu et al presented a literature review of hypercalcemia and lupus nephritis and of the 17 patients they reviewed with SLE and hypercalcemia, 14 had active SLE, 3 patients had elevated PTHrP, and five had lupus nephritis.[3] Out of all the 17 patients, the hypercalcemia responded to glucocorticoids in 11 of them. In their recent review of rare causes of hypercalcemia, Motlaghzadeh et al mentioned SLE in several cases, most of them due to elevated PTHrP.[1] In our case, PTHrP was negative.

MAS is a life-threatening complication of inflammatory conditions, occurring in the setting of activated macrophages and hemophagocytic histiocytes causing multiple organ dysfunction.[4] This condition was initially reported in a patient with systemic juvenile idiopathic arthritis, later described in multiple other systemic inflammatory disorders, including SLE. Recognition of MAS is challenging as there is no diagnostic test or criteria that differentiates it from other systemic inflammatory conditions.[4] As it has been described in other conditions such as granulomatous diseases, activated macrophages are able to produce 1,25-dihydroxyvitamin D due to unregulated expression of 1-alpha-hydroxylase.[1,5] There has not been any established relationship between MAS and hypercalcemia in the literature. We believe that our patient's hypercalcemia was likely due to MAS, given the findings of the kidney biopsy results and his elevated levels of 1,25-hydroxyvitamin D, adding to the fact of no other identifiable cause (such as granulomatous disease). The over-expression and unregulated activity of 1-alpha-hydroxylase due to the activated macrophages in MAS could explain the rapid conversion of the patient's 25-OH-vitamin D to active 1,25-hydroxyvitamin D, leading to his severe hypercalcemia. The kidney biopsy revealed findings consistent with MAS, and the decrease in serum 1,25-dihydroxyvitamin D and calcium after treatment of the lupus nephritis with pulse dose steroids support our theory. Moreover, the successful treatment of MAS in the setting of a lupus flare with steroids has been previously described in the literature.[6]

Most cases of 1,25-dihydroxyvitamin D induced hypercalcemia improve with glucocorticoids as seen in our case.[1] Glucocorticoids are the therapy of choice for patients with 1,25-hydroxyvitamin D mediated hypercalcemia, as they inhibit 1-alpha-hydroxylase.[7] Patients usually have a favorable response within a week of initiating steroids.

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