Hypercalcemia in Two Patients With Sarcoidosis and *Mycobacterium avium intracellulare* Not Mediated by Elevated Vitamin D Metabolites

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Abstract: *Introduction:* To describe 2 unusual cases of hypercalcemia due to granulomatous diseases with normal vitamin D metabolites and no other ready explanation for the hypercalcemia. *Methods:* We present the clinical, laboratory and pathologic findings of 2 patients with hypercalcemia and review previous reports of hypercalcemia in granulomatous diseases without elevated vitamin D metabolites. *Results:* Hypercalcemia was described in various granulomatous diseases including sarcoidosis, tuberculosis, berylliosis, leprosy and, rarely, in fungal infections. Elevated serum level of vitamin D or its metabolites was linked to the pathogenesis of hypercalcemia in these disorders. The authors present the clinical, laboratory and pathologic findings in 2 patients who presented with hypercalcemia and normal vitamin D metabolites with no other ready explanation for the hypercalcemia. The first patient was diagnosed with *Mycobacterium avium,* whereas the second patient was found to have sarcoidosis. *Conclusion:* Although hypercalcemia in granulomatous diseases has been attributed to be mediated by elevated vitamin D metabolites, there have been several case reports that documented normal values of active vitamin D metabolites. This report illustrates the regulatory feedback mechanisms of vitamin D synthesis and introduces the term "inappropriately normal" vitamin D metabolites levels in light of low levels of parathyroid hormone.

Key Indexing Terms: Granulomatous diseases; Vitamin D; Hypercalcemia; Sarcoidosis; Mycobacterial diseases; *Mycobacterium avium*. **[Am J Med Sci 2011;342(4):336–340.]**

Hypercalcemia has been described in patients with most granulomatous disorders.[1] Sarcoidosis, in which hypercalcemia is seen in approximately 10% of patients,[1] has been studied as the prototype for these disorders, where enhanced 1-α hydroxylation of 25 hydroxyvitamin D to its potent active form, 1, 25 dihydroxyvitamin D has been thought to play the major role in causing hypercalcemia.[2]

The relationship between vitamin D and sarcoidosis was first recognized by Harrel and Fisher[3] in 1939 when they noted that a vitamin D-rich diet can exacerbate hypercalcemia in patients with sarcoidosis. Fifteen years later, Albright et al[4] postulated that homeostasis of calcium in sarcoidosis is similar to conditions seen with vitamin D intoxication. This was attributed to increased 25-hydroxyvitamin D 1-α hydroxylase activity. Although the principal site for this enzyme is in the proximal renal tubular epithelial cells, hypercalcemia has been reported in an anephric patient with sarcoidosis.[5] In addition, a number of studies have documented the production of 1, 25 $(OH)_2$ vitamin D from sample tissues of pathological lymph nodes or cultured alveolar macrophages in patients with sarcoidosis.[6,7] Together, these data provide strong evidence of extrarenal 1-α hydroxylation in patients with this disorder.

Although the renal 1-α hydroxylase is under stringent regulation by parathyroid hormone (PTH), calcium, phosphorus and 1, 25 $(OH)_2$ vitamin D itself,[8] the 1-α hydroxylase in activated macrophages does not respond to the same feedback mechanisms, resulting in abnormally elevated levels of 1, 25$(OH)_2$ vitamin D and calcium.[8] Although this lack of feedback control has been thought to be the exclusive etiology of hypercalcemia in granulomatous diseases, many reports continued to document normal levels of active vitamin D metabolites as a unique phenomenon. In this study, we report 2 cases of hypercalcemia in granulomatous diseases [*Mycobacterium avium intracellulare* (MAI) and sarcoidosis] with normal vitamin D metabolites, which illustrate the principle of "relative" excess 1, 25 $(OH)_2$ vitamin D levels to be sufficient to mediate hypercalcemia in these disorders. Also reviewing the literature, we found other less common mechanisms of hypercalcemia in granulomatous disorders.

CASE 1

A 33-year-old Hispanic male with a 1-year history of human immunodeficiency virus (HIV) infection presented with lethargy, fever and diarrhea. An endocrinology consultation was requested for a serum calcium level of 6.8 mg/dL (normal: 9–10.3), and corrected calcium level for albumin was 8.8 mg/dL with albumin of 1.5 g/dL (normal: 3.2–4.8). Further testing revealed 25 (OH) vitamin D <7 ng/mL (reference: 20–57), 1, 25$(OH)_2$ D of 17 pg/mL (reference: 15–75) and intact PTH (iPTH) of 24.7 pg/mL (normal: 14–72). Alkaline phosphatase was 629 U/L (normal: 45–129), whereas alanine transferase and aspartate aminotransferase were at 61 U/L (normal: 12–49) and 49 U/L (normal: 12–34), respectively. Medical history was also significant for genital herpes simplex virus, esophageal candidiasis and sickle cell trait. CD4 count was 1% (normal: 32–71%) and HIV viral load was 435,000 copy/mL. Medications were Emtricitabine/Tenofovir, Lopinavir/Ritonavir, Bactrim, Ethambutol and Valacyclovir. Hypocalcemia was thought to be due to vitamin D deficiency, and treatment was initiated with Ergocalciferol 50,000 units po weekly, elemental calcium 333 mg as calcium citrate combined with vitamin D_3 200 IU twice daily. Three weeks later, the patient developed hypercalcemia with serum calcium = 12.1 mg/dL and albumin 2 g/dL (corrected calcium for albumin 13.7 mg/dL). iPTH was <2.5 pg/mL, PTH-related peptide (PTHrP) <2.5 pg/mL, and 25 (OH) vitamin D was 42 ng/mL, whereas 1, 25$(OH)_2$ D was 53 pg/mL. Alkaline phosphatase was 220 U/L, whereas alanine transferase and aspartate aminotransferase were normal at 17 U/L and 12 U/L, respectively. Serum

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protein electrophoresis (SPEP) and bone survey were normal. Chest and abdomen computed tomography showed mediastinal and paraaortic lymphadenopathy. Fine needle aspiration of lymph nodes showed chronic inflammation with MAI.

CASE 2

A 48-year-old white male was evaluated in endocrine clinic for hypercalcemia noted 4 months prior. Maximum serum calcium level was 12.2 mg/dL (ranged from 10.9 to 12.2) with concomitant iPTH of 6.6 pg/mL and albumin of 4g/dL. Corrected calcium for albumin was 12.2 mg/dL. PTHrP was <2 pg/mL, whereas 25 (OH) vitamin D was 42 ng/mL (reference: 20–57) with 1, $25(OH)_2$ D of 23 pg/mL (reference:15–75). Medical history was significant for congestive heart failure, hypertension, paroxysmal atrial fibrillation, hypothyroidism, gout and renal insufficiency (glomerular filtration rate = 60 mL/min). Medications: Allopurinol, Amiodarone, Isosorbide dinitrate, Hydralazine, Carvedilol, Warfarin and Levothyroxine 50 μg daily. The patient was not consuming antacids or vitamin D. There was no paraprotein detected on SPEP or urine protein electrophoresis (UPEP). A bone marrow aspirate showed a normocellular pattern with noncaseating granulomas consistent with sarcoidosis. Angiotensin converting enzyme and alkaline phosphatase levels were both normal. Hypercalcemia responded to treatment with tapering dose of prednisone and patient remained eucalcemic thereafter.

METHODS

The measurements of 25(OH) vitamin D was done using Diasorin Chemiluminescent, whereas 1, $25(OH)_2$ D was measured by RIA at ARUP laboratories at University of Utah, Salt Lake City, Utah.

LITERATURE REVIEW

A PubMed literature search was performed, with the limits to English and human and the use of the following terms "hypercalcemia AND mycobacterium avium," hypercalcemia AND mycobacterial diseases and "hypercalcemia AND granulomatous diseases" a total of 204 abstracts were reviewed. Of these, 124 were related to mycobacterial diseases, whereas the rest were related to different granulomatous disorders. As our focus was initially on the mycobacterial diseases, these articles were reviewed substantially and those who reported vitamin D level were included. For other granulomatosis disorders, only those who reported normal vitamin D were included in this review.

TABLE 1. Reported cases of hypercalcemia in mycobacterial diseases, cryptococcus, coccidiomycosis and pneumocystis jiroveci pneumonia

References	Disease	Ca (mg/dL)	Alb (mg/dL)	PTH	PTHrP	25 D	1, 25 D	Other Tests
Delahunt and Romeril[9]	*Mycobacterium avium*	11.8	2.4	↓ ↓	.	.	↑ × 2.5	.
Lin et al[10]	*Mycobacterium haemophilum*	11.9	.	↓	↑	N 2Q	↑ × 2.5	.
Playford et al[11] (two cases)	*Mycobacterium avium*	14.6	.	↓ ↓	.	.	N 4Q	.
		13.2	.	↓ ↓	↓	N 4Q	↑ × 1.8	.
Choudhary and Rose[12]	Disseminated tuberculosis	↑	.	.	.	.	↑ × ?	.
Ko et al[13]	Miliary tuberculosis	10.7	2.4	↓ ↓	.	N 2Q	↑ × 1.3	↑ ALK
Uchiyama-Tanaka and Mori[14]	*Mycobacterium avium*	11.0	.	↓ ↓	.	.	N 2Q	Bence-Jones –ve
Aly et al[15]	*Mycobacterium avium*	13.3	.	N	.	.	N 1Q	SPEP –ve
Newell and Nelson[16]	*Mycobacterium avium*	10.8	2.9	N	.	.	.	↑ ALK
Ferrand et al[17]	Disseminated tuberculosis	12.1	.	↓	.	.	.	↑ ALK, SPEP –ve
Nielsen and Andersen[18]	*Mycobacterium marinum*	↑	2.7	↓ ↓	.	↓	↓	SPEP –ve
Ali et al[19]	*Cryptococcus neoformans* and *Coccidioides immitis*	13.3	2.3	↓ ↓	↓	N 1Q	N 4Q	
Parker et al[20]	Coccidiomycosis	12.2	3.2	↓ ↓	.	N 4Q	↓ ↓	↑ Calcitonin
Westphal[21]	Coccidiomycosis	13.4	.	↓ ↓	.	.	↓	↑ ALK
Shahnaz[22]	Pneomocystis jiroveci pneumonia	17.2	2.7	↓ ↓	↓	.	N 2Q	N ALK

N, normal; Q, quartile; example N2Q, normal within the second quartile; Ca, calcium; Alb, albumin; 25 D, 25(OH) vitamin D; 1, 25 D, 1, $25(OH)_2$ vitamin D; ALK, alkaline phosphatase; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; . (period), no data.