Severe hypercalcemia unmasked by Vitamin D in a patient with sarcoidosis

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ABSTRACT

Severe hypercalcemia is uncommon in clinical practice and is usually due to primary hperparathyroidism or malignancy. We present a patient who presented with severe hypercalcemia with renal failure; further evaluation of which revealed the diagnosis of sarcoidosis. This case is presented in view of the rarity of presentation of sarcoidosis with hypercalcemic crisis.

Key words: Hypercalcemia, renal failure, sarcoidosis, Vitamin D

Introduction

Hypercalcemia is a commonly diagnosed medical condition picked up during routine blood chemistry screening. Severe hypercalcemia (calcium >15.0 mg/dL) is usually due to primary hyperparathyroidism in the outpatient setting and malignancy in the inpatient setting. We present a patient who presented with severe hypercalcemia with renal failure; further evaluation of which revealed the diagnosis of sarcoidosis. This case is presented in view of the rarity of presentation of sarcoidosis with hypercalcemic crisis.

Case Report

A 53-year-old lady, detected to be diabetic and hypertensive for 7 years presented with h/o generalized weakness, poor appetite, and constipation of 1 month. She had lost about 1-2 kgs in the preceeding month. There was no h/o fever, night sweats, proximal or distal muscle weakness, arthralgia, or rash. She was post-menopausal and had undergone total abdominal hysterectomy for dysfunctional uterine bleeding 8 years earlier. She denied any respiratory symptoms. Her medications included insulin, glimeperide, atenolol, and multivitamin. She had received two injections of Vitamin D 60,000 International Units (IU) 1 week apart for about a month before presentation elsewhere for suspected osteomalacia. On examination, she was thin built, had a blood pressure of 130/90 m of Hg, pulse rate of 86/min, and respiratory rate of 18/min. General physical examination was non-contributory and no peripheral lymphadenopathy could be appreciated. Systemic examination of the cardiac, respiratory, and abdominal evaluations was normal. Her investigations are summarized in Table 1. A thorough work-up was done to investigate the cause of hypercalcemia.

Ultrasound examination of the neck did not reveal any thyroid or parathyroid nodule. Serum electrophoresis was normal and mammogram was negative. Computed tomography abdomen was negative and did not show any lymphadenopathy. High resolution computerized tomography chest revealed reticulonodular shadows in both lung fields, one small paratracheal lymph node and two isolated pleural nodules. With clinical suspicion of sarcoidosis with associated renal failure, a renal biopsy was done and this revealed non-caseating granulomatous interstitial nephritis with features of acute tubular injury [Figure 1]. Patchy chronic interstitial nephritis was also noted. She was initially treated before the biopsy diagnosis with intravenous hydration, furosemide to increase renal calcium excretion, and one dose of calcitonin. A temporary reduction in serum calcium was noted to 13.4 mg/dL. Following the diagnosis of sarcoidosis, she was then

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Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.116325

Table 1: Laboratory investigations at admission

Value	Normal value	Patient value
Hb (gm/dL)	13-15	13.1
WBC count (cc/mm)	4000-10,000	9200
Platelet count (cc/mm)	1.5-3.5 lakh	2.85
Total protein (gm/dL)	5-8	5.8
Serum albumin (gm/dL)	3.5-5.5	2.1
Blood urea (mg/dL)	20-40	53
Serum creatinine (mg/dL)	0.8-1.2	2.3/1.9/1.7*
Serum potassium (mEq/L)	3.5-5.5	3.7
Serum calcium (mg/dL)	8.5-10.5	15.2/13.4/11.6/ 12.9/10.6/9.5*
Serum phosphorus (mg/dL)	2.5-4.5	2.8
Ionized calcium (mg/dL)	4-6	8.0
Serum PTH (IU/L)	9-65	9.79
1,25 dihydroxy vitamin D level	>30	70
Serum ACE level (U/L)	8-52	73
Serum TSH (IU/L)	0.5-4.5	2.53
24 h urinary calcium (mgs)	200-300	280

Hb: hemoglobin, WBC: white blood cell count, PTH: parathyroid hormone, ACE: angiotensin converting enzyme, TSH: thyroid stimulating hormone, *Depicts serial values after admission

started on betamethasone followed by oral prednisone at 1 mg/kg for 1 week, tapered to 0.5 mg/kg at discharge. This led to a gradual fall in calcium levels and some improvement in renal functions. Serum creatinine at last follow-up was stable at 1.5 mg/dL.

Discussion

Hypercalcemia has been described in almost all granulomatous diseases such as sarcoidosis, berrylliosis, tuberculosis, and leprosy. Sarcoidosis is an idiopathic, multisystem, and granulomatous disease affecting people of all racial and ethnic groups. The incidence among African–Americans is approximately three times higher than in Whites. The reported peak incidence is between 20 and 39 years of age, however, a later presentation after the fourth decade has been described in Blacks.[1] The lung and the intra-thoracic lymph nodes are the main organ systems involved, however, sarcoidosis can involve every organ. The frequent extra-thoracic involvement sites are the peripheral lymph nodes, eyes, skin, and liver.[2] The initial symptoms at presentation can be respiratory (80%), fatigue (30%), weight loss (28%), fever (10-27%), and erythema nodosum (3-44%).[1] Renal involvement in sarcoidosis may be part of the systemic disease or may occur as an isolated involvement. Incidence of renal disease ranges from 7% to 27%.[3-5] Renal involvement may manifest as hypercalcemic nephropathy, granulomatous interstitial nephritis, glomerulonephritis, renal amyloidosis, or renal tubular dysfunction. Acute renal failure associated with hypercalcemia as presentating feature of sarcoidosis has been reported, however, it is rare.[6-11]

The most common cause of renal involvement in sarcoidosis is abnormality of calcium metabolism

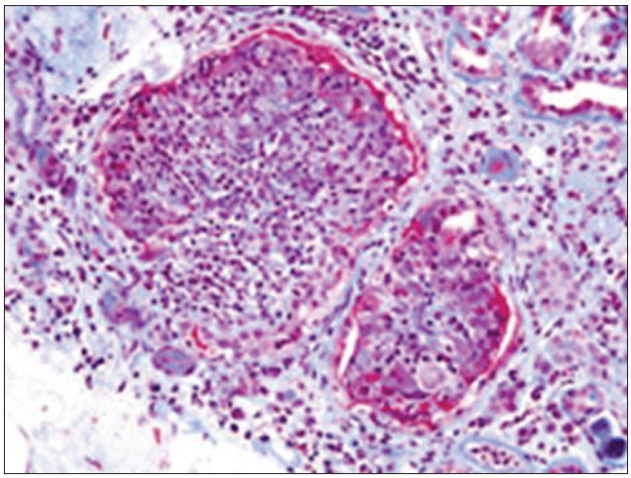

Figure 1: Renal Biopsy of patient showing non- caseating granuloma with chronic interstitial inflammation

secondary to increased synthesis of calcitriol or active Vitamin D 3 (1,25 Di-Hydroxy Vitamin D) by macrophages of the granulomatous lesion. Hypercalcemia is detected in more than 50% of patients, however, it is usually dependent on co-existing renal functional abnormality when the capacity of the kidney to excrete calcium is compromised. Nephrolithiasis and nephrocalcinosis may occur in 10% of patients.

Harrell and Fischer in 1939 first reported the occurrence of hypercalcemia in 6 out of 11 patients with sarcoidosis.[12] Subsequent studies in 1979 by Bell *et al.*,[13] first recognized that levels of 1.25 dihydroxy Vitamin D are elevated in patients with sarcoidosis. High levels of active Vitamin D3 due to intrinsic 1 α hydroxylase activity in macrophages is the most probable cause of hypercalcemia, but overproduction of bone resorbing cytokines and parathyroid-related peptide may also play a role.[14] Hypercalcemia in the setting of normal Vitamin D levels has also been described and the mechanisms that cause calcium to rise are not clearly understood.[15] Hypercalcemia has been reported to be unmasked after Vitamin D injections in patients with sarcoidosis.[16,17] Calcitriol-induced hypercalcemia can occur in sarcoidosis when macrophages are challenged with sudden availability of the substrate 25-OH–D.[18] Our patient also presented with severe hypercalcemia following two doses of parenteral Vitamin D.

Conclusion

We report a patient with biopsy proven sarcoidosis in whom severe hypercalcemia associated with renal failure was the unusual presenting feature. Sarcoidosis without pulmonary symptoms often poses a diagnostic challenge to the clinician and should arouse suspicion in non-parathyroid-dependant hypercalcemia.

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How to cite this article: Nayak-Rao S. Severe hypercalcemia unmasked by Vitamin D in a patient with sarcoidosis. Indian J Nephrol 2013;23:375-7.

Source of Support: Nil, **Conflict of Interest:** None declared.