Refractory Hypercalcemia in a Patient with End Stage Renal Disease

Sir,

Patients with chronic kidney disease (CKD) are immunocompromised and prone to develop chronic infections such as tuberculosis. PTH-independent hypercalcemia occurs in 20% of the tuberculosis subjects due to the increased activity of ectopic 25(OH) D-1alpha-hydroxylase (CYP27B1) present in the macrophages and decreased degradation of 1,25(OH) $_2$D.[1] 1,25(OH) 2D has been shown to increase the expression of the receptor activator of nuclear factor kappa ligand (RANKL), thus increasing the osteoclast activity.[2] Long-standing hypercalcemia can cause nephrocalcinosis, nephrolithiasis, diabetes insipidus, and soft-tissue calcification. Denosumab, a RANKL inhibitor, is an excellent option for refractory hypercalcemia in the setting of low creatinine clearance or in patients on hemodialysis. We describe a 50-year-old man with end-stage renal disease (ESRD) who presented with disseminated extrapulmonary tuberculosis and refractory hypercalcemia that was successfully managed with denosumab.

Our patient is a 50-year-old farmer, non-smoker, presented with generalized fatigue, high-grade fever, and weight loss of 1-month duration. He was thin, febrile, emaciated (BMI: 18.5 kg/m^2) and on examination had an enlarged single firm left supraclavicular lymph node 2 cm × 2 cm in size. In the background, the patient had a history of recurrent renal stone disease and hypertension for the last 10 years. He was detected to have CKD with a serum creatinine of 3.5 mg/dL 3 years ago. Six months before the present admission, he was diagnosed with primary hyperparathyroidism with lab parameters showing creatinine of 5.5 mg/dL, serum calcium 12.5 mg/dL, serum phosphorus 2.5 mg/dL, and iPTH 1275 pg/mL with multiple coalescent adenomas on imaging for which he underwent left-side parathyroidectomy. Postoperative calcium and PTH levels got normalized. The patient was not on any calcium/vitamin D supplement after surgery. The biopsy showed follicular adenoma without any granulomas.

Evaluation in the present admission revealed anemia (hemoglobin 6.8 gm/dL), ESR 98 mm/h, creatinine 14 mg/dL, serum calcium 13.8 mg/dL, serum phosphorus 4.9 mg/dL, and a iPTH of 66 ng/mL, thus ruling out tertiary hyperparathyroidism [Table 1]. An iPTH value of 66 ng/mL is low for a patient with CKD5. In view of PTH-independent hypercalcemia and elevated 1,25 (OH)$_2$ levels, possibilities such as tuberculosis, cryptococcosis histoplasmosis, and lymphoma were considered. Serum and urine electrophoresis, free light chain assay, and skeletal survey were normal. Contrast-enhanced CT scan showed enlarged necrotic mediastinal lymph nodes [Figure 1a] and extensive vessel wall calcification in the abdominal arteries. Dual-energy absorptiometry (DEXA) scan showed osteoporosis with a T value of −3.0 in both the hip and lumbar spine. Skin tuberculin test was strongly positive. The kidneys were shrunken, with bilateral multiple renal calculi. Excision biopsy done from the left supraclavicular lymph node revealed extensive necrosis bound by

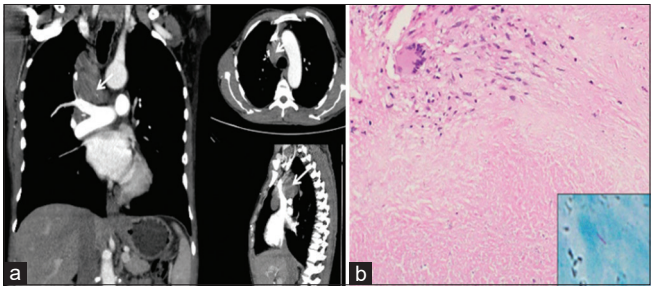

Figure 1: (a) Coronal (left), axial (upper right), and sagittal (lower right) images of CECT thorax showing enlarged superior mediastinal lymph node with the central non-enhancing area (white arrow) suggestive of necrosis. (b) Histopathology of the excised supraclavicular lymph node showing few epithelioid cell granulomas with scattered Langhans types of giant cells (H and E, 400×). Inset shows acid fast bacillus (Ziehl Neelson stain, 1000×)

Table 1: Laboratory parameters at admission and at 1-month follow-up

	At presentation	1 month post Denosumab
Hemoglobin (13.5-17.5 g/dL)	6.9	8.1
Serum Calcium (8.6-10.3 mg/dL)	13.8	9.2
Ionized calcium (1.05-1.37 mmol/L)	1.94	1.3
Serum phosphorus (2.5-4.5 mg/dL)	4.92	4.2
Serum protein (6.3-8.3 g/dL)	5.32	5.4
Serum Albumin (3.5-5.2 g/dL)	2.37	2.6
Alkaline phosphatase (50-150 IU/L)	99	121
25 (OH) vitamin D (<30 ng/ml – deficiency)	40	32
1,25 (OH)$_2$ vitamin D (18-64 pg/mL)	115	
Parathyroid hormone (15-65 pg/mL)	66	88
Angiotensin Converting Enzyme (0-40 ug/L)	65	

epithelioid histiocytes and giant cells with the presence of acid-fast bacilli [Figure 1b]. It was later confirmed by Gene Xpert as Mycobacterium Tuberculosis.

The patient was initially managed with low calcium hemodialysis (dialysate calcium of 1.25 mmol/L) through a non-tunneled right internal jugular vein catheter, calcitonin nasal spray (for 72 h), and dexamethasone 4 mg BD for 2 weeks. Bisphosphonate could not be administered in view of reduced GFR. He was started on a 4-drug anti-tubercular drug regimen. He had persistent hypercalcemia with serial calcium values of more than 12 mg/dL even after 4 weeks of ATT. Denosumab 60 mg infusion was given once. Post a single dose of denosomab, his hypercalcemia resolved. He was maintained on twice-weekly hemodialysis with monthly monitoring of calcium, phosphate, alkaline phosphatase, 25(OH) vitamin D, and PTH levels. He underwent primary fistula and arterio-venous graft failure in both upper limbs likely due to compromised and calcified vessels. Follow-up at 6 months revealed serum calcium of 9.6 mg/dL with improved weight and appetite.

Our patient initially had PTH-mediated hypercalcemia due to primary parathyroid adenoma followed by PTH-independent hypercalcemia caused by disseminated tuberculosis. Denosumab, though not FDA approved, is commonly used for the treatment of hypercalcemia due to primary hyperparathyroidism.[3] Few case reports also mention the use of denosumab for tuberculosis-related hypercalcemia.[4] Hypocalcemia can occur following denosumab injection and requires close monitoring. Kyohei *et al.* in a recent cohort study showed that denosumab was equally effective in HD versus non-HD patients; however, the risk of hypocalcemia is significantly higher in dialysis patients.[5] It is likely that in the future, denosumab might become the first-line choice for the management of hypercalcemia in ESRD patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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