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Proceedings of UCLA Health

Title

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Journal

Proceedings of UCLA Health, 22(1)

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Publication Date

2018-09-24

CLINICAL VIGNETTE

Too Much of a Good Thing

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Clinical Case

A 47-year-old man who had been in good health, was found to have an elevated serum creatinine of 5.65 mg/dL on routine physical examination prompting hospital admission. The patient was not seeing a health care provider regularly and had unremarkable past medical history except for gonorrhea treatment 3 months prior and a recent sinus infection treated with a course amoxicillin/clavulanate. He had no specific complaints but on review of systems, reported mild increased urinary frequency over the past two months and increased thirst for the past week. On occasion he had taken ibuprofen for body aches. He also took a number of supplements including creatine, multivitamin, "Assault" power drink, beta-prostate, tribulus, yohimbe and Vitamin D. Family history was significant for diabetes and hypertension. There was no personal or family history of kidney disease. He denied smoking, alcohol or illicit drug use. He exercised regularly and worked in a department store.

The patient's exam included normal vital signs. Pertinent findings included dry mucous membranes, soft 2/6 systolic murmur, clear lungs, soft, non-tender, non-distended abdomen, no edema in extremities, normal neurologic exam and no rash.

Laboratory evaluation was significant for sodium of 134, potassium of 4.9, chloride of 94, bicarbonate of 28, BUN of 60, creatinine of 5.65, glucose of 102, calcium of 12.1, magnesium of 2.0, phosphorus of 4.5. Hemoglobin was 11.7 with normal white blood cell count and platelet count. Liver enzymes were normal. Albumin was 3.3. Urinalysis showed pH of 7, specific gravity of 1.006, trace leukocyte esterase, small blood, 4 red blood cells and 3 white blood cells. Urine eosinophils were positive. Spot urine protein to creatinine ratio was 0.38 grams. Urine microscopy showed rare white blood cells, rare non-dysmorphic red blood cells, 1 white blood cell cast, rare fragmented granular casts and no red blood cell casts. Renal ultrasound showed echogenic but normal sized kidneys, normal intrarenal Doppler wave forms, no hydronephrosis, and normal post-void residual.

A hypercalcemia work-up showed intact PTH of 7.5, Vitamin D 25-OH level of 184 and ionized calcium of 1.77. Other serologies including PTHrp, Quantiferon gold, ACE level, Coccidioides IgG/IgM, Vitamin A level, Hemoglobin A1c, and SPEP/UPEP were all negative or normal. Of note, HIV test returned positive. Chest CT scan was significant for mild scattered bronchiectasis, old granulomatous disease with calcified right upper lobe nodules and a partially calcified right precarinal node. An

echocardiogram revealed an LVEF of 55-60% with mild aortic sclerosis.

Our differential diagnosis for patient's renal insufficiency included pre-renal state from hypercalcemia-induced polyuria, acute tubular necrosis from hypercalcemia and associated nephrocalcinosis, and/or acute interstitial nephritis from the multiple herbal supplements and recent antibiotic use.

A renal biopsy showed significant acute tubular injury with focal tubular rupture, diffuse calcification in tubular epithelial cells and interstitium, scant focal interstitial nephritis and no chronic changes. The cause of our patient's hypercalcemia was vitamin D intoxication from excessive dietary supplementation resulting in acute kidney injury from acute tubular necrosis related to hypercalcemia.

Discussion

Vitamin D is a pro-hormone which plays an important role in many bodily functions, most importantly in calcium homeostasis and bone mineral metabolism. Recent studies show its role extending to such areas as cell differentiation, inhibition of cell growth and immune modulation.¹ Much attention has focused on the treatment and management of vitamin D deficiency, which has become a global problem.¹⁻³ Many studies estimate at least 50-60% of the elderly in North America have low vitamin D levels.¹ However, more recently, hypervitaminosis D, or vitamin D toxicity, a rare but serious condition, has become an ever-increasing consequence.^{2,3} There are two major forms of vitamin D: vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is obtained from dietary sources or converted from 7-dehydrocholesterol in the skin when exposed to ultraviolet B radiation. Vitamin D2 is found in plants and is consumed in fortified foods or supplements. Both forms of Vitamin D are hydroxylated in the liver to 25-hydroxyvitamin D, which requires further hydroxylation in the kidney to form 1,25-dihydroxyvitamin D (calcitriol). Calcitriol is the active form of vitamin D, which acts in an endocrine manner to regulate calcium metabolism, mainly by mobilizing calcium from the skeleton and increasing intestinal calcium absorption.²⁻⁴

There are many causes of vitamin D toxicity. Since vitamin D is a fat-soluble vitamin, excessive supplementation is one of the leading causes of vitamin D toxicity, especially in today's

environment of widespread vitamin D fortification of foods and drinks. Another leading cause is iatrogenic vitamin D toxicity from over-administration of high doses of vitamin D. Less common but equally important causes include primary hyperparathyroidism, MEN I & II syndrome, malignancies such as Hodgkin's and Non-Hodgkin's lymphoma, and granulomatous diseases like sarcoidosis and tuberculosis.^{1,3}

The clinical manifestations of vitamin D toxicity are varied and mostly due to hypercalcemia. Often, patients present with fatigue, weight loss, abdominal pain, polydipsia, anorexia, and constipation. After a few days or weeks, patients can develop bone pain, persistent headaches, irregular heartbeat, muscle and joint pain, frequent urination, and kidney stones.^{1,3}

The diagnosis of symptomatic vitamin D toxicity includes: 1) Elevated serum and urine levels of calcium, 2) Clinical manifestations of hypercalcemia, 3) Reduced serum intact parathyroid hormone and 4) Serum 25(OH)D3 level > 100 ng/mL.¹

Management of vitamin D toxicity is manifold, most importantly being dietary restriction of calcium intake and aggressive hydration. Decreased oral intake of fluids and increased renal sodium loss perpetuates the volume depleted state. This then exacerbates the hypercalcemia by increasing sodium reabsorption in the thick ascending limb of the loop of Henle. Thus, volume repletion with isotonic sodium chloride solution is the most effective short-term treatment for hypercalcemia. A loop diuretic can sometimes be added once the patient is euvoletic, which helps block sodium and calcium reabsorption in the thick ascending loop of Henle. Attention must be paid to replete ongoing sodium, potassium, chloride and magnesium losses if prolonged sodium chloride and loop diuretic therapy is instituted. In addition to hydration, discontinuation of vitamin D is necessary. Since vitamin D is stored in fat, vitamin D intoxication usually persists for weeks after stopping vitamin D ingestion. Studies have shown that such patients are responsive to glucocorticoids. When given in doses of 100 mg/day of hydrocortisone, most patients' serum calcium levels normalize in several days. Some hypothesize prednisone may help reduce plasma calcium levels by reducing intestinal calcium absorption but studies are still needed to further elucidate the exact mechanism.¹ Bisphosphonates are another useful adjunctive therapy since the direct effect of calcitriol is increasing bone resorption.^{1,5}

Conclusion

Our patient was immediately treated with intravenous normal saline at 250 cc/hr. He also received calcitonin 4 units/kg subcutaneously for total 4 doses, titrated to repeat ionized calcium levels. He was then started on prednisone 40 mg daily for planned 3-4 week tapered course as well as bisphosphonate infusion once serum creatinine had improved. Over the next few days, his serum creatinine slowly improved to 2.25 and his ionized calcium also improved to 1.36. Unfortunately, he left against medical advice on day 4 of hospitalization and remains lost to follow up.

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Submitted August 6, 2018