

Hypercalcemia in a patient with autoimmune polyglandular syndrome

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Abstract

Hypercalcemia is a rare condition in patients with autoimmune polyglandular syndrome (APS-1), usually characterized by hypoparathyroidism and hypocalcemia, and it can develop due to simultaneous adrenal insufficiency. We present a case of severe hypercalcemia in a patient with APS-1, found to have adrenal insufficiency secondary to steroid non-compliance.

Introduction

Hypercalcemia is one of the most common electrolyte disturbances. The pathogenesis of hypercalcemia is usually multifactorial with the most common cause in the outpatient setting being primary hyperparathyroidism. As a result, hypercalcemia is rarely seen in patients with hypoparathyroidism, except in the setting of excessive vitamin D therapy. Adrenal insufficiency is a much less common cause of hypercalcemia and its mechanism is poorly understood. We present a case of a young woman with hypoparathyroidism who presented with hypercalcemia secondary to adrenal insufficiency.

Case Report

A 26-year-old woman known to our clinic presented to the emergency department (ED) with a total serum calcium of 13.4 mg/dL and an ionized serum calcium of 6.4 mg/dL. She had a history of Autoimmune Polyglandular Syndrome Type I (APS-I) manifested by hypoparathyroidism, adrenal insufficiency, and premature ovarian failure. At baseline, she was maintained on cortisone acetate, fludrocortisone, calcium carbonate, vitamin D, calcitriol, and ethinyl estradiol/norelgestromin transdermal patch. Due to poor compliance, her serum calcium was usually in the range of

6.5-8.5 mg/dL, and she had multiple prior admissions to the hospital for hypocalcemia.

During the month prior to this presentation, the patient had been admitted to another hospital on three occasions with hypercalcemia with serum calcium levels ranging from 11-15 mg/dL; each time she was treated with intravenous fluids. On the day of this current presentation, the patient complained of intermittent chest pain, shortness of breath, blurry vision, weakness, fatigue, and constipation. She was sent to our ED where she was again found to be hypercalcemic with a serum calcium of 13.4 mg/dL. There was also evidence of acute on chronic renal failure with a blood urea nitrogen (BUN) of 33 mg/dL and serum creatinine of 2.6 mg/dL (baseline 24 and 1.5 mg/dL, respectively). Further initial laboratory results are shown in Table 1. Systolic blood pressure (SBP) dropped to 70-80 mmHg in the ED and she was treated with intravenous fluids (6 L of 0.9% saline) and hydrocortisone (100 mg IV). SBP increased to 100-110 mmHg (her baseline), calcium decreased to 9.7 mg/dL and creatinine decreased to 2.2 mg/dL. A chest computed tomography scan did not show evidence of sarcoidosis or underlying malignancy. The patient was admitted to the hospital and was given additional intravenous fluids and stress doses of hydrocortisone (100 mg IV every 8 h). She was then transitioned back to maintenance doses of cortisone acetate and fludrocortisone. Calcium carbonate and calcitriol were gradually restarted as well. At the time of discharge, serum calcium was 7.2 mg/dL, BUN was 27 mg/dL, and creatinine was 1.6 mg/dL.

Two weeks after discharge, outpatient laboratory testing showed that her serum calcium increased again to 13 mg/dL and she was sent back to the ED. On presentation, she had a blood pressure of 80/65 mmHg, heart rate of 155/min, and temperature of 36.5° C. Her serum calcium was 14.5 mg/dL, ionized calcium was 6.7 mg/dL, and phosphorus was 4.2 mg/dL. She also again had acute on chronic renal failure with a BUN of 37 mg/dL and creatinine of 2.3 mg/dL; additional initial laboratory results on the second admission are shown in Table 2. Given the elevated adrenocorticotropic hormone (ACTH) and undetectable serum cortisol found on this admission, the hypercalcemia was suspected to be due to adrenal insufficiency secondary to non-compliance with glucocorticoid replacement. She was admitted to the hospital and again treated with intravenous fluids and hydrocortisone. Following treatment, serum calcium decreased to 10.3 mg/dL and renal function returned to baseline. She was discharged again on calcitriol, calcium carbonate, cortisone acetate, and fludrocortisone.

Following discharge, non-compliance was confirmed by her pharmacist who reported she

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had not been filling any of her prescriptions regularly, and had missed many months of refilling the cortisone acetate. For ease of compliance, her glucocorticoid treatment regimen was changed from cortisone acetate (twice daily dosing) to prednisone (once daily dosing). Since then, she has been filling her prescriptions regularly and her serum calcium has remained in the low-normal range.

Discussion

Our patient presented with severe and symptomatic hypercalcemia, hypotension, and acute on chronic renal insufficiency. Her past medical history was complex and included hypoparathyroidism secondary to APS-1 and chronic kidney disease (CKD). However, none of these conditions are known to cause such drastic elevations in serum calcium and in fact are usually associated with hypocalcemia.^{1,2} It should be noted that although CKD can contribute to an elevated serum calcium, it was ruled out as the primary etiologic factor in this case as her serum parathyroid hormone level was low.³

The etiology of the marked hypercalcemia remained elusive until an elevated plasma ACTH level measured during her second admission implicated adrenal insufficiency as

the primary cause. Interestingly, only a handful of cases have been reported in which adrenal insufficiency has resulted in life-threatening hypercalcemia. Although a definitive mechanism for adrenal insufficiency related hypercalcemia has not yet been elucidated, a direct association has been noted in numerous cases.^{4,6} Moreover, as in this case, treatment with glucocorticoids has been observed to resolve hypercalcemia in patients with adrenal insufficiency.^{4,7,8}

Various mechanisms have been proposed to explain the causal relationship of adrenal insufficiency to hypercalcemia. One proposed mechanism is that the elevated calcium levels are due to an increase of calcium released from bone and is supported by the presence of marked hypercalciuria and urinary hydroxyproline excretion.⁹ However, the process is thought to be unrelated to the bone remodeling process; in fact, bone histology has shown that bone remodelling activity is actually reduced.¹⁰ Though the exact mechanism of this phenomenon remains unknown, increased osteoclastic bone resorption has been noted in hypercalcemic crises in the context of Addison's dis-

ease.¹¹ Moreover, the adrenal gland has recently been reported to produce a paracrine hormone called stanniocalcin, which reduces circulating calcium.^{12,13} Thus, in a state of adrenal insufficiency, there may be an influx of calcium into the circulation stemming from decreased stanniocalcin production. Furthermore, endogenous glucocorticoids also decrease intestinal calcium absorption via calcium channels in the duodenum, opposing the effects of vitamin D,^{14,15} and increase urinary calcium excretion.¹⁶ Thus the deficiency of endogenous glucocorticoid production in adrenal insufficiency may cause opposing effects and lead to hypercalcemia. In our patient, volume contraction was also a contributing factor (as evidenced by hypotension) which likely caused increased proximal tubular reabsorption of calcium and a reduction in calcium removal.^{8,17}

In the clinical setting, it is important to distinguish hypercalcemia secondary to adrenal insufficiency from that secondary to granulomatous disease and some lymphomas.¹⁸ These diseases are associated with an abnormal regulation of vitamin D metabolism, in which

there is an increased synthesis of calcitriol.¹⁹ Similarly, glucocorticoids are the drugs of choice in treating hypercalcemia due to these primary pathologies; their mechanism of action involves decreasing the endogenous production of the active form of vitamin D.²⁰ Treatment with glucocorticoids was similarly effective in correcting the hypercalcemia in our patient. However, the underlying pathogenesis for the hypercalcemia in our case was evidently different, as extensive evaluation for sarcoidosis and malignancy in our patient was negative.

In this case report, we discussed the occurrence of hypercalcemia in the setting of adrenal insufficiency in a patient with APS-I. While the mechanism by which adrenal insufficiency causes hypercalcemia remains unclear, this case illustrates the importance of considering adrenal insufficiency as a possible cause of unexplained hypercalcemia in a patient with multiple endocrinopathies.

Table 1. Initial laboratory results from the patient's first hospital admission.

Laboratory test	Result	Reference range
Total serum calcium	13.4 mg/dL	8.6-10.2 mg/dL
Ionized serum calcium	6.4 mg/dL	4.2-5.2 mg/dL
Phosphorus*	2.9 mg/dL	2.3-3.7 mg/dL
Serum albumin	3.0 g/dL	3.5-4.8 g/dL
Intact PTH	<2.5 pg/mL	14-72 pg/mL
PTH-related peptide	<1.1 pg/mL	0-4 pg/mL
1.25 (OH) ₂ Vitamin D	13 pg/mL	15-75 pg/mL
25-OH Vitamin D	13 ng/mL	30-80 ng/mL
ACE	52 U/L	9-67 U/L
TSH	0.83 µUI/mL	0.35-5.5 µUI/mL

*Level measured 9 h after all other labs drawn. PTH, parathyroid hormone; ACE, angiotensin converting enzyme; TSH, thyroid stimulating hormone.

Table 2. Initial laboratory results from the patient's second hospital admission.

Laboratory test	Result	Reference range
Total serum calcium	14.5 mg/dL	8.6-10.2 mg/dL
Ionized serum calcium	6.7 mg/dL	4.2-5.2 mg/dL
Phosphorus*	4.2 mg/dL	2.3-3.7 mg/dL
Serum albumin	3.6 g/dL	3.5-4.8 g/dL
Intact PTH	<2.5 pg/mL	14-72 pg/mL
1.25 (OH) ₂ Vitamin D	14 pg/mL	15-75 pg/mL
25-OH Vitamin D	15 ng/mL	30-80 ng/mL
Serum cortisol (2 PM)	<0.2 mcg/dL	3.0-16.7 µg/dL (PM range)
Plasma ACTH	496 pg/mL	6-58 pg/mL

*Level measured 2 h after all other labs drawn. PTH, parathyroid hormone; ACTH, adrenocorticotropic hormone.

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