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Case Report

Hypercalcemia due to Adrenal Insufficiency. A Case Report and Literature Review

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Abstract

Severe hypercalcemia is a frequently seen and treated condition in hospitalized patients. Life threatening hypercalcemia is usually seen with malignancy and requires administration of iv bisphosphonates, calcitonin and aggressive hydration with normal saline. Primary hyperparathyroidism due to parathyroid adenoma or hyperplasia is another common cause of hypercalcemia, usually managed in ambulatory settings and usually requires surgical intervention. But adrenal insufficiency is a rare cause of severe life-threatening hypercalcemia. Its investigation and management are quite different from the other well-known etiologies of hypercalcemia. Awareness about this condition is helpful as it can help diagnose and manage it early and effectively. We present one such case here.

Introduction

Hypercalcemia has been reported to be a rare complication of adrenal insufficiency [1]. This association has been documented in literature but is oftentimes underdiagnosed and rarely recognized. Long-term use of corticosteroids leads to hypothalamic pituitary/adrenal axis suppression [1]. We present here a case of a 49-year-old female admitted to the Hospital Medicine service for hypercalcemia and acute renal failure associated with a constellation of symptoms including nausea, vomiting, confusion, weakness and dizziness. She underwent extensive investigation and was ultimately diagnosed with corticosteroid withdrawal induced adrenal insufficiency as the culprit of her hypercalcemia.

Case Description

A 49-year-old female with a history of Cushing's disease status post pituitary resection (and adrenal insufficiency secondary to resection), type 2 diabetes mellitus, hypothyroidism, polycystic ovarian syndrome presented to the Emergency Department with 1-week history of nausea, vomiting, confusion, weakness and dizziness. Her vitals at admission were blood pressure 127/84 mm/Hg, heart rate 120 beats per minute, respiratory rate 28/minute, temperature: 36.6°C, SpO2: 89%. Preliminary work up with BMP showed hypercalcemia with serum calcium of 14.1 mg/dl and acute kidney injury with serum creatinine of 1.75 mg/dl (baseline 0.8 - 0.9). She was also noted to be hyponatremic with sodium 129mEq/L, and hyperkalemic with potassium 5.6mEq/L. Further workup for her hypercalcemia can be seen in the table below (Table 1).

PTH	PTHrP	25 OH Vitamin D	1,25 dihydroxy vitamin D	Ionized Calcium	Serum Calcium (mg/dl) Trend
<6.0 Pg/ml	0.4	30 ng/ml	<8.0	7.34 mg/dl	14.1->13.5->12.7->12.2->11.0->10.4->9.9->10.0->8.9->8.5->8.2->7.6->7.7

Pre-admission BMP	Admission BMP	Discharge BMP	TSH	AM Cortisol
Na 142 mEq/L	Na 129 mEq/L	Na 137 mEq/L	0.7	1.8
K 4.2 mEq/L	K 5.6 mEq/L	K 3.9 mEq/L		
Cl 103 mEq/L	Cl 99 mEq/L	Cl 107 mEq/L		
HCO3 21 mEq/L	HCO3 16 mEq/L	HCO3 21 mEq/L		
Anion Gap 18	Anion Gap 15	Anion Gap 9		
BUN 14 mg/dl	BUN 26 mg/dl	BUN 18 mg/dl		
Creatinine 1.03 mg/dl	Creatinine 1.75 mg/dl	Creatinine 1.76 mg/dl		
EGFR 67 ml/min	EGFR 35 ml/min	EGFR 35 ml/min		
Calcium 9.9 mg/dl	Calcium 14.1 mg/dl	Calcium 7.7 mg/dl		
Glucose 128 mg/dl	Glucose 139 mg/dl	Glucose 91 mg/dl		

Extensive workup for hematological malignancy including CT chest, abdomen and pelvis with contrast and multiple myeloma workup returned negative.

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Given the negative workup detailed above for hypercalcemia, her history of pituitary resection with subsequent adrenal insufficiency, as well as her symptoms occurring shortly after a corticosteroid taper and her BMP showing mild hyponatremia and hyperkalemia (as seen with mineralocorticoid deficiency) the diagnosis of presumed adrenal insufficiency leading to severe hypercalcemia was eventually made.

She was hydrated aggressively with 0.9% normal saline and administered IV zoledronic acid and calcitonin (these medications were used on admission to lower her serum calcium as it was unclear initially as to what caused her such severe hypercalcemia). Serum calcium levels were closely monitored, and her serum calcium trended down to 7.7 mg/dl on the day of discharge (day 7). Regarding her corticosteroid taper for adrenal insufficiency, she was on hydrocortisone 15 mg in a.m. and 5 mg in p.m. prior to admission to the hospital. Due to her acute illness, she received stress dose steroids with an increase in her hydrocortisone dose to 50 mg IV every 8 hours. She was noted to hallucinate while on this increased dose and it was thus tapered down to oral hydrocortisone 30 mg a.m. and 20 mg p.m. at discharge. Steroid dosing recommendations were discussed in detail with the patient's primary Endocrinologis

Post Discharge BMP
Na 143 mEq/L
K 3.7 mEq/L
Cl 108 mEq/L
HCO3 23 mEq/L
Anion Gap 12
BUN 11 mg/dl
Creatinine 1.62 mg/dl
EGFR 39 ml/min
Calcium 8.3 mg/dl
Glucose 103 mg/dl

Discussion

Hypercalcemia is an electrolyte abnormality commonly encountered in the hospital. Hypercalcemia can be further stratified by severity such as mild (calcium of 10.5 –12 mg/dl), moderate (calcium of 12.1 – 14 mg/dl and severe (calcium of > 14 mg/dl), as was the case with this patient. Acute and severe hypercalcemia can lead to life-threatening complications such as cardiac arrhythmia, and if untreated can progress to obtundation and coma [2].

Various disorders have been implicated in causing hypercalcemia, however hyperparathyroidism and malignancy account for a greater than 90% of cases [2]. Malignancy is often the common cause of hypercalcemia in the inpatient setting and hyperparathyroidism is the most common cause in the ambulatory setting [4]. Less frequent causes include hypervitaminosis of vitamin D, sarcoidosis, medications (such as thiazide diuretics, lithium, calcium carbonate supplements). Non-parathyroid hormone disorders which can cause hypercalcemia include thyrotoxicosis, acromegaly, pheochromocytoma, and adrenal insufficiency [4]. Adrenal insufficiency leading to hypercalcemia is very rarely seen [2]. The patient described in this case had adrenal insufficiency due to a pituitary tumor resection for her ACTH dependent Cushing syndrome. In combination with the otherwise negative standard workup for her hypercalcemia and improvement of symptoms and labs with replacement of corticosteroids, the rare but well documented diagnosis of hypercalcemia induced by corticosteroid insufficiency/adrenal insufficiency was made.

Untreated acute hypercalcemia can lead to life-threatening cardiac arrhythmias [4]. The prevalence of hypercalcemia in patients with adrenal insufficiency is close to 6.5% - 8.4% [4].

The exact mechanism of hypercalcemia in patients with adrenal insufficiency is not well described. Possible mechanisms include increased bone resorption due to increased sclerostin levels in adrenal insufficiency [6], increased proximal tubular calcium reabsorption, increased binding of calcium to serum proteins and hypovolemia due to adrenal insufficiency leading to hemoconcentration resulting in hypercalcemia [4]. Adrenal insufficiency increases the activity of the renal 1-alpha-hydroxylase enzyme which converts 25(OH)2D to its active form 1,25(OH), which increases the intestinal and renal absorption of calcium. Chronic opioid use can also lead to secondary adrenal insufficiency which is often overlooked [4]. Sarcoidosis is one condition where adrenal insufficiency and hypercalcemia are seen together [4]. A paracrine hormone named stanniocalcin is secreted from the adrenal gland which prevents the efflux of calcium from skeletal tissue into circulation. Adrenal gland impairment decreases the levels of stanniocalcin resulting in hypercalcemia [7].

When there is clinically significant hypercalcemia along with hyperkalemia, hyponatremia and symptoms indicative of adrenal insufficiency due to HPA axis suppression commencing work with serum AM cortisol and cosyntropin stimulation test will be helpful [4].

Adrenal Insufficiency is a life-threatening condition with clinical manifestations resulting from relatively low production of glucocorticoids, sometimes also accompanied by deficiency of mineralocorticoids and adrenal androgens. Adrenal insufficiency can be primary or secondary. Primary adrenal insufficiency results from destruction of adrenal glands because of autoimmune adrenalitis (Addison's disease), tuberculosis, hemorrhage, or primary or metastatic cancer. Secondary adrenal insufficiency is due to interference of synthesis of adrenal cortisol when regions along the hypothalamic–pituitary–adrenal (HPA) axis are affected. Glucocorticoid withdrawal leads to secondary adrenal insufficiency. Chronic glucocorticoid use suppresses the hypothalamic pituitary axis. HPA axis suppression may cause atrophy of the adrenal glands, but they may still be able to secrete enough steroids required for physiological requirements [5].

Hypercalcemia is seen in ~5.5%–6.0% of Addison's disease patients [7]. Long-standing hypercalcemia and hypercalciuria leads to nephrogenic diabetes insipidus, nephrolithiasis, nephrocalcinosis, tubular atrophy with interstitial fibrosis and chronic kidney disease [7]. Hypercalcemia decreases the glomerular filtration rate directly by causing renal vasoconstriction and volume contraction which can lead to acute kidney injury [7]. Aggressive hydration with normal saline will improve the glomerular filtration rate and filtered calcium level. Correcting adrenal insufficiency with oral steroids can restore normal calcium levels rapidly.

Conclusion

This case describes a rare case of hypercalcemia induced by adrenal insufficiency from rapid taper of glucocorticoids. Long-term use of corticosteroids leads to suppression of the hypothalamic pituitary adrenal axis. In cases of parathyroid hormone independent hypercalcemia, as was the situation with our patient, adrenal insufficiency should be considered in the differential diagnosis. The exact dosing and duration of corticosteroid

treatment that causes adrenal suppression leading to hypercalcemia is unclear [1]. Correcting cortisol deficiency with oral steroids will restore normal serum calcium levels.t.

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