

Adrenal Insufficiency Presenting as Hypercalcemia

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Adrenal insufficiency occurring in a patient in the surgical intensive care unit is not an unusual event.¹ Prompt recognition and management of adrenal insufficiency are critical to patient recovery and survival. Although it is an infrequent presenting sign of adrenal insufficiency, hypercalcemia is a well-recognized complication of the disorder.^{2,3} Hypercalcemia has been reported to occur not only with primary hypoadrenalism but also with secondary hypoadrenalism.³ This report describes a 45-year-old woman whose postoperative course was complicated by adrenal insufficiency that presented as hypercalcemia. The article also reviews the pathophysiology, differential diagnosis, and management of hypercalcemia secondary to adrenal insufficiency.

CASE PRESENTATION

A 45-year-old woman with a history of hypothyroidism underwent exploratory laparotomy for distal colonic obstruction. She had a sigmoid colectomy with colostomy and resection of a portion of her small intestine for the management of a diverticular mass. There was no evidence of malignancy. Her postoperative course was complicated by infection and septic shock that resulted in multiple surgical procedures for exploration and débridement around the colostomy site. She also developed pseudomonas pneumonia and candidemia and remained ventilator dependent.

She received total parenteral nutrition, without calcium. At the time of admission for the surgery, her ionized calcium level was 4.8 mg/dL (normal range, 4.7–5.2 mg/dL); however, 3 weeks after her admission, she developed ionized hypercalcemia. Her serum intact parathyroid hormone (PTH) level was only 7 pg/mL (normal, 10–65 pg/mL), and her serum ionized calcium level was 6.8 mg/dL (eventually peaking at 7.6 mg/dL). The inorganic phosphorus level was 4.0 mg/dL (normal range, 2.5–4.5 mg/dL). However, her phosphorus level exceeded the upper limit of normal on 3 occasions while she was hypercal-

cemic, the highest level being 5.4 mg/dL when her ionized calcium level was also 5.4 mg/dL. Other laboratory data while the patient was hypercalcemic are shown in [Table 1](#).

During the hypercalcemic period, the patient's sodium level remained in the normal range, but her potassium level increased from high-normal levels to frank hyperkalemia. Initially, her renal function was normal. However, her blood urea nitrogen level increased to 30–33 mg/dL (normal, 6–20 mg/dL), and her serum creatinine level increased to 1.5–1.6 mg/dL (normal, 0.5–1.1 mg/dL) while she was hypercalcemic. A stimulation test with 250 µg of corticotropin (ACTH) administered intravenously was indicative of at least partial adrenal insufficiency ([Table 2](#)).

The patient was treated with stress doses of intravenous hydrocortisone. Her ionized calcium level decreased to 5.5 mg/dL within 2 days. A computed tomography scan of her abdomen obtained during this period did not reveal any visible pathology of her adrenal glands. Before further diagnostic work-up could be performed, the overwhelming sepsis took its toll. The patient died despite aggressive management.

DISCUSSION

Adrenal insufficiency is a well-known complication of sepsis¹; however, it can also occur during the postoperative period without sepsis.⁴ The incidence of adrenal insufficiency among patients who received care in a surgical intensive care unit for more than 14 days has been reported at 6%.⁵ Although it is not a common presenting

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Table 1. Initial Laboratory Test Results While the Case Patient Was Hypercalcemic

Variable	Result	Reference Range
Ionized calcium	6.8 mg/dL	4.7–5.2 mg/dL
Intact PTH	7 pg/mL	10–65 pg/mL
Inorganic phosphorous	4 mg/dL	2.5–4.5 mg/dL
25-Hydroxyvitamin D	< 5 ng/mL	15–57 ng/mL
1,25-Dihydroxyvitamin D	5 pg/mL	15–75 pg/mL
Thyroid stimulating hormone	4.88 µIU/mL	0.4–3.6 µIU/mL
T ₄	3.2 µg/dL	4.5–11.5 µg/dL
T ₃ Uptake	1 unit	0.7–1.2 unit
Free thyroxine index	3.2	5–12

PTH = parathyroid hormone; T₃ = triiodothyronine; T₄ = thyroxine.

feature of adrenal insufficiency, hypercalcemia is a well-recognized complication of the disorder.

Clinical Presentation

In the critically ill patient with or without sepsis, adrenal insufficiency can present as catecholamine-resistant hypotension, hyponatremia, hyperkalemia, hypoglycemia, and hypercalcemia.¹ In patients with overwhelming sepsis, hypotension may be caused by multiple factors. However, it is difficult to explain the hyperkalemia and hypercalcemia in the case patient on the basis of sepsis alone. Adrenal insufficiency may also occur transiently in critically ill patients. Severe inflammation of the adrenal glands may result in low serum cortisol levels. These levels increase when inflammation decreases.⁶

Pathophysiology

In adrenal insufficiency, there is reduced calcium removal by the kidneys and increased calcium input into the circulation.⁷ Hypovolemia resulting from adrenal insufficiency and a consequent reduction in the glomerular filtration rate (GFR) result in a reduction in the amount of calcium filtered at the glomerulus, as well as an increase in proximal tubular reabsorption of calcium and sodium.⁷ Reduced GFR and the level of filtered calcium normalize with volume repletion. However, this effect does not reverse the increased input of calcium into the circulation.

Calcium may also be released from bone in patients with adrenal insufficiency. However, in one study, there

Table 2. Case Patient's Results from a Standard Corticotropin Stimulation Test*

Timing of Sample	Serum Cortisol
Baseline	7.9 µg/dL
30 Minutes	12.9 µg/dL
60 Minutes	14.5 µg/dL

*250 µg of corticotropin administered intravenously.

was no evidence of increased osteoclast activity; in this study, bone histology suggested that bone remodeling in the trabecular bone surfaces was less than normal, and the authors postulated that there was either an increase in nontrabecular bone resorption or an increase in calcium transport out of the interstitial bone fluid by quiescent lining cells.⁸ Also, there are glucocorticoid receptors in bone. Glucocorticoid treatment reduces the influx of calcium into circulation. It is possible that physiologic amounts of glucocorticoids are necessary for acquisition and preservation of the differentiated state in osteoblasts.

However, there may be other factors involved in the pathophysiology of adrenal insufficiency. It has been postulated that bone in the hypoadrenal state is thyroxine dependent, and hypercalcemia can develop only in the presence of thyroid hormone.³ Increased absorption of calcium from the gastrointestinal tract is unlikely to be the cause of hypercalcemia in adrenal insufficiency.⁹ Studies performed on adrenalectomized dogs did not show any difference in the incidence of hypercalcemia when the animals were fed calcium-rich or calcium-free diets.

Differential Diagnosis

In addition to adrenal insufficiency, the differential diagnosis of hypercalcemia in the case patient includes primary hyperparathyroidism, underlying malignancy (with or without parathyroid hormone-related protein [PTH-rp]), hypervitaminosis D (secondary to granulomatous diseases or other causes), parenteral nutrition, thyrotoxicosis, immobilization, and critical care hypercalcemia. In the case patient, the intact PTH level was low, ruling out primary hyperparathyroidism. Also, there was no evidence of malignancy; if PTH-rp were the cause of her hypercalcemia, one would expect phosphaturia¹⁰ and a low or low-normal serum phosphorus level. The case patient had high-normal to frankly high levels of serum inorganic phosphorus during the hypercalcemic period. Additionally, her

25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were very low, and there was no evidence of granulomatous disease. Parenteral nutrition can cause hypercalcemia if the formula contains calcium or vitamin D.¹¹ However, hypercalcemia due to vitamin D usually occurs only after months of parenteral nutrition therapy. When parenteral nutrition containing vitamin D is the cause of hypercalcemia, the plasma 25-hydroxyvitamin D level is usually normal or high; again, however, in the case patient, the level was low. Moreover, the case patient had a history of hypothyroidism, and her thyroid function test results ruled out thyrotoxicosis as a cause of her hypercalcemia.

In young individuals, immobilization can cause hypercalcemia,^{12,13} which can be exacerbated by other high bone-turnover conditions (eg, Paget's disease, hyperparathyroidism, hyperthyroidism).² Hypercalcemia caused by immobilization is usually treated with and responsive to calcitonin or bisphosphonates.¹⁴ Immobilization could have played a role in worsening the case patient's hypercalcemia. Finally, critical care hypercalcemia is typically mild and may be associated with mild increases in PTH levels.¹⁵ The case patient experienced severe hypercalcemia.

Diagnosis

Adrenal insufficiency should be suspected in ill patients with hypercalcemia, especially when the cause of the hypercalcemia is not clear. The screening test for adrenal insufficiency is a standard stimulation test with 250 µg of ACTH.¹ This test has been used to study general adrenal function in critically ill patients.⁵ A dose of 250 µg of ACTH, however, has been shown to sometimes elicit a normal response even in patients with partial adrenal insufficiency.¹⁶ The case patient had a subnormal response to the test (Table 2).

Treatment

Unstable patients with adrenal insufficiency should be treated immediately with high-dose intravenous glucocorticoids.¹ Dexamethasone 4 mg should be administered intravenously after drawing blood samples for measurement of electrolyte, glucose, plasma cortisol, and ACTH levels. Isotonic saline should be administered intravenously to hypotensive patients. Glucose supplementation should also be provided. If there is clinical suspicion, one should not wait for laboratory results to start treatment. Alternatively, hydrocortisone 100 mg intravenous bolus initially, followed by 100 mg every 6 hours administered intravenously, may be used. Dexamethasone has the advantage of little or no interference with the laboratory measurements of cortisol

levels. Patients with primary adrenal insufficiency will require mineralocorticoid replacement. However, this treatment does not need to be started during acute management of adrenal insufficiency when the patient is receiving intravenous isotonic saline. If the hypercalcemia is secondary to adrenal insufficiency, the hypercalcemia will resolve with glucocorticoid therapy and fluid replacement. The cause of adrenal insufficiency should be evaluated. The glucocorticoid dose should be tapered to a physiologic dose over the next few days if the patient is stable.

CONCLUSION

Hypercalcemia in a critically ill patient may be the first sign of adrenal insufficiency. With regard to the case patient, the other signs of adrenal insufficiency either were not prominent or were partly masked by the case patient's concomitant illnesses. One should always consider the possibility of adrenal insufficiency when observing a case of hypercalcemia and perform an ACTH stimulation test. However, one should not wait for laboratory results to start treatment if there is clinical suspicion. Identification of the underlying hypoadrenal state and prompt treatment with glucocorticoids are critical to a favorable prognosis. Supportive measures such as maintenance of hydration are important as well. HP

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