Endocrinology, Diabetes & Metabolism CASE REPORTS

S D N De Silva and others | Hypercalcaemia due to adrenal insufficiency

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Glucocorticoid-induced adrenal insufficiency: an uncommon cause of hypercalcaemia

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Summary

Long-term use of exogenous glucocorticoids leads to the suppression of the hypothalamic–pituitary–adrenal axis. Therefore, if the glucocorticoid is withdrawn abruptly, patients will develop adrenal insufficiency. Hypercalcaemia is a rare but well-known complication of adrenal insufficiency. However, hypercalcaemia is a rare presentation of glucocorticoid-induced adrenal insufficiency (GI-AI). A 62-year-old patient with a past history of diabetes mellitus, ischaemic heart disease, stroke, hypertension and dyslipidaemia presented with polyuria, loss of appetite, malaise and vomiting for a duration of 2 months. His ionized calcium level was high at 1.47 mmol/L. Intact parathyroid hormone was suppressed (4.3 pg/mL) and vitamin D was in the insufficient range (24.6 ng/mL). Extensive evaluation for solid organ or haematological malignancy including contrast-enhanced CT chest, abdomen, pelvis, multiple myeloma workup and multiple tumour markers were negative. His synacthan-stimulated cortisol was undetectable thus confirming adrenal insufficiency. His adrenocorticotrophic hormone level was 3.82 pg/mL (4.7–48.8) excluding primary adrenal insufficiency. His MRI brain and other pituitary hormones were normal. Further inquiry revealed that the patient had taken over-the-counter dexamethasone on a regular basis for allergic rhinitis for more than 2 years and had stopped 2 weeks prior to the onset of symptoms. Therefore, a diagnosis of GI-AI leading to hypercalcemia was made. The patient was resuscitated with intravenous fluids and replacement doses of oral hydrocortisone were started with a plan of prolonged tailing off to allow the endogenous adrenal function to recover. His calcium normalized and he made a complete recovery.

Learning points:

- Long-term use of glucocorticoids leads to the suppression of the hypothalamic–pituitary–adrenal axis.
- If the glucocorticoid is withdrawn abruptly, patients will develop adrenal insufficiency which is known as glucocorticoid-induced adrenal insufficiency.
- Adrenal insufficiency should be considered in the differential diagnosis of parathyroid hormone-independent hypercalcaemia.
- A thorough clinical history is of paramount importance in arriving at the correct diagnosis.

Background

Hypercalcaemia could be due to parathyroid hormone (PTH)-dependent or -independent mechanisms. Primary hyperparathyroidism is the commonest cause of PTH-dependent hypercalcaemia. Neoplasms are the commonest cause of PTH-independent hypercalcaemia and generally, this is due to PTH-related peptide (PTHrP) secreted by a wide variety of solid organ and haematological neoplasms. 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) produced by lymphomas or benign granulomatous diseases like sarcoidosis also can cause hypercalcaemia. Malignancies metastasizing to bone or arising from bone or bone marrow such as multiple myeloma can cause hypercalcaemia due to

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the production of a variety of growth factors and cytokines other than PTHrP. Drugs like hydrochlorothiazide, lithium, foscarnet, excess vitamin A and endocrinopathies like hyperthyroidism and acromegaly and other causes like milk-alkali syndrome and prolonged immobilization also can cause hypercalcaemia (1). Adrenal insufficiency is a rare cause of PTH-independent hypercalcaemia. We present a patient who presented with adrenal insufficiency and hypercalcaemia after abrupt withdrawal of exogenous steroids which were taken by him inadvertently without medical advice.

Case presentation

This 62-year-old patient had been independent and in his usual health until November 2020 when he developed five to six episodes of watery loose stools per day. This lasted for 3 days. He also had loss of appetite, malaise, vomiting and increased frequency of urination. There was no fever. Despite settling of diarrhoea he had persistent loss of appetite and ill health. He also developed constipation. He had an episode of altered behavior and disorientation lasting 2 weeks in December 2020. This improved after intravenous fluid resuscitation at the hospital. In February 2021, he was found to have high serum calcium levels and was admitted to our ward for further evaluation. He did not have any cough or haemoptysis. There was no back pain or any difficulty in passing urine. He did not have skin rashes or heat intolerance.

He was a diagnosed patient with diabetes mellitus for 20 years on oral hypoglycaemic agents with satisfactory glycaemic control. He had a past history of ischemic heart disease with episodes of acute coronary syndromes in 1990 and 1994. He had bilateral lower limb numbness suggestive of diabetic peripheral neuropathy but no documented history of nephropathy or retinopathy. He was also a diagnosed patient with hypertension and dyslipidaemia on treatment. He was not on any drug associated with hypercalcaemia. He was not a smoker and had alcohol only occasionally. There was no family history of hypercalcaemia or neck surgeries.

On admission he was afebrile. He did not have overt signs of Cushing's syndrome such as suprascapular fat pad, dorsal fat pad or purple striae. There were no palpable lymph nodes or neck lumps. He was not pigmented and there were no rashes suggestive of erythema nodosum or lupus pernio. His pulse rate was 96 b.p.m. with supine blood pressure of 130/80 mmHg and standing blood pressure of 100/60 mmHg. Cardiac auscultation was normal and there was no evidence of pleural effusions or masses on respiratory examination. There was no organomegaly or any palpable lumps on abdominal examination and digital rectal examination was normal with a normal prostrate. The testicular examination also was normal. On neurological examination, there was length-dependent sensory predominant peripheral neuropathy mainly affecting joint position sense and vibration sense.

Investigation

His basic investigations (Table 1) revealed evidence of renal impairment and hypercalcaemia with normal phosphorus levels. Vitamin D was in insufficient range. Spot urine calcium to creatinine ratio showed hypercalciuria. He had not recently taken any calcium-containing preparations or vitamin D and there was no biochemical evidence of thyrotoxicosis. Intact PTH (iPTH) level was measured using Advia Centaur XP automated immunoassay analyzer which showed suppressed iPTH level. Malignancy was considered to be the most probable cause in this patient with PTH-independent hypercalcaemia and a prolonged history of generalized ill health and loss of appetite. Therefore, extensive evaluation was performed to exclude solid organ malignancy and plasma cell disorder. However, contrast-enhanced CT chest, abdomen, pelvis did not show any evidence of malignancy or lung or liver involvement suggestive of sarcoidosis. Multiple tumour markers including β human chorionic gonadotrophin, prostate-specific antigen, alpha-fetoprotein, carcinoembryonic antigen and CA 19-9 were negative. The blood picture did not show any evidence of haematological malignancy and lactate dehydrogenase, urine for Bence Jones Protein, serum protein electrophoresis and skeletal survey were negative. Chest X-ray was normal, and sputum for acid-fast bacilli, sputum GeneXpert MTB/RIF assay and Mantoux test were negative. Serum angiotensin-converting enzyme level was normal.

At this point, his serum 9:00 h random cortisol was found to be undetectable. A short synacthan test was carried out and still serum cortisol was undetectable confirming adrenal insufficiency. Adrenocorticotrophic hormone (ACTH) level was suppressed thus making primary adrenal insufficiency unlikely. Furthermore, his pituitary–gonadal and pituitary–thyroid axis, serum prolactin and MRI pituitary were normal thus excluding pituitary pathology. At this point, further questioning revealed that he had taken oral dexamethasone 2 tablets (1 mg) twice daily over the counter for few years to help his allergic rhinitis and had stopped in November 2020. Therefore, a diagnosis

Table 1 Summary of baseline investigations.

Test	Value	Reference range
Serum creatinine	1.9 mg/dL	0.5–1.1
HbA1c	6.4%	<7%
Serum-ionized calcium	1.47 mmol/L	1.10–1.30
Serum total calcium (albumin corrected)	13.2 mg/dL	8.2–10.3
Serum phosphorus	3.8 mg/dL	2.47–4.63
Serum magnesium	1.4 mg/dL	1.58–2.55
ALP	78 U/L	40–150
$25(OH)_2D$	24.6 ng/mL	30–100 (sufficiency)
iPTH	4.8 pg/mL	18.4–80.1
Spot urine calcium to creatinine ratio	0.54 mg/mg	<0.2
TSH	3.0 mIU/L	0.55–4.78
fT4	1.0 ng/dL	0.89–1.76
9:00 h cortisol	<13.79 nmol/L (Undetectable)	118.6–618
Short synacthan test (0, 30, 60 min)	<13.79, <13.79, <13.79 nmol/L (Undetectable)	Stimulated cortisol > 550 nmol/L at 30 min or 60 min
ACTH	3.4 pg/mL	4.7–48.8
Total testosterone	483.9 ng/dL	241–827

ALP, alkaline phosphatase; ACTH, adrenocorticotropic hormone; fT4, free thyroxine;.Ipth, intact parathyroid hormone; TSH, thyroid-stimulating hormone.

of glucocorticoid induced adrenal insufficiency (GI-AI) causing hypercalcaemia was made.

Treatment

As the initial management step fluid resuscitation was carried out with intra venous 0.9% saline. He was observed for features of fluid overload. He was also started on intravenous hydrocortisone 50 mg 6 hourly and was later converted to replacement doses of oral hydrocortisone (10 mg, 5 mg and 5 mg). This dose was gradually tailed off over 6 months allowing his endogenous cortisol axis to recover.

Outcome and follow-up

His total calcium gradually came down and by discharge, it was 8.5 mg/dL (Figure 1). Serum creatinine came down to 0.9 mg/dL. All his symptoms completely improved. He was started on vitamin D 2000 IU daily and magnesium supplementation was given. Magnesium improved to 1.7 mg/dL. In 2 months of follow-up, his ACTH level had increased to 10.64 pg/mL showing recovery of the hypothlamo-pituitary-adrenal axis. DEXA scan was arranged to assess his bone mineral density as he had been on long-term steroid therapy.

Discussion

Exogenous steroid therapy is a well-known cause of hypothalamic–pituitary–adrenal axis suppression. The exact dose and duration of steroid therapy that causes adrenal suppression is a matter of debate. However, when prednisolone is given at a dose of 5 mg or more per day for a duration of 3 weeks or more, clinically significant suppression of hypothalamo–pituitary–adrenal axis is likely to occur and abrupt withdrawal can precipitate adrenal insufficiency (2). When high-dose steroid therapy is given even a 5-day course can cause adrenal suppression (3). Even high-dose inhaled steroid therapy and topical steroid therapy can cause adrenal suppression (4). A study conducted among young healthy subjects showed that 70% had suppression of cortisol levels with dexamethasone doses less than 0.5 mg. However, cortisol suppression was not observed even with 1 mg of dexamethasone in two

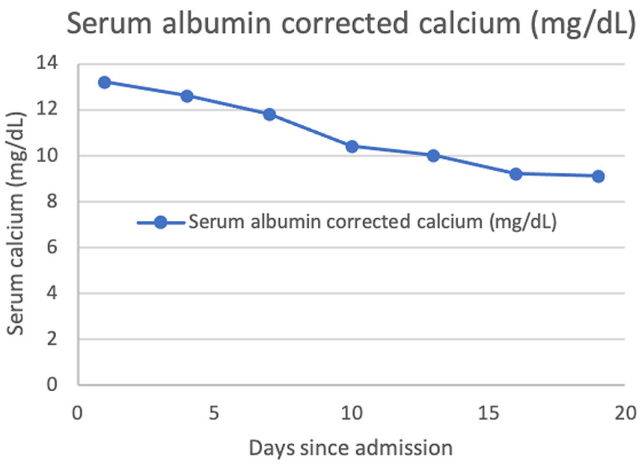

Figure 1
Serum albumin-corrected calcium change during admission.

subjects (5). Recovery of adrenal function usually occurs 3–6 months after steroid withdrawal, although it can take up to 3 years. Gradual tapering of steroid dose is important to prevent adrenal insufficiency in these patients.

Adrenal insufficiency is a well-known cause of hypercalcaemia. Primary as well as secondary adrenal insufficiency can cause hypercalcaemia. Opioid-induced secondary adrenal insufficiency (6), bilateral adrenal histoplasmosis induced primary adrenal insufficiency (7) and lymphocytic hypophysitis-induced secondary adrenal insufficiency (8) have been reported to be associated with hypercalcaemia which responded to treatment with physiological doses of hydrocortisone. However, only a handful of cases have been reported of hypercalcaemia due to adrenal insufficiency precipitated by abrupt withdrawal of exogenous steroids. Montoli et al reported a patient who was on long-term steroid therapy after a renal transplant (9). She developed Addisonian crisis and hypercalcaemia 1 week after complete withdrawal of steroids. Bhatti et al reported a patient who inappropriately orally administered topical preparation of clobetasol (10). Two weeks after sudden withdrawal he presented with Addisonian crisis and hypercalcaemia. Ahn et al reported a patient who presented with adrenal insufficiency, hypercalcaemia and acute kidney injury (11). She had a past history of intra-articular steroid injections. Therefore, the possibility of GI-AI leading to hypercalcaemia was considered. Both first and second patients had suppressed PTH and ACTH suggestive of PTH-independent hypercalcaemia and secondary adrenal insufficiency respectively.

Hypercalcaemia has been reported in 8.4% of patients with idiopathic Addison's disease (12). Hypercalcaemia occurs in adrenal insufficiency due to reduced calcium removal by the kidney and increased calcium entry into the circulation. Adrenal insufficiency causes a state of volume depletion. This results in reduced glomerular filtration due to reduced renal blood flow and reduced filtration of calcium at the glomerulus. Reabsorption of calcium and sodium at the proximal tubule is increased due to volume depletion. Intravenous fluid therapy corrects hypovolemia and improves renal clearance of calcium thus reducing calcium levels (13).

In patients with adrenal insufficiency and hypercalcaemia, increase in osteoclastic bone resorption was not demonstrated in trabecular bone (9). Therefore, the exact mechanism of increased calcium entry into the blood is not known. Adrenal insufficiency can also cause increased activity of renal 1-alpha-hydroxylase enzyme which converts $25(OH)_2D$ to its active form $1,25(OH)_2D$. Active vitamin D will increase intestinal and renal absorption of calcium thus increasing serum calcium. Stanniocalcin is a paracrine hormone secreted from the adrenal gland (14). Studies conducted in stanniocalcin 2 knocked-out animals have shown hypercalcaemia (15). However, there is insufficient evidence on the role of stanniocalcin in adrenal insufficiency-induced hypercalcaemia in humans.

We could not measure PTHrP level and $1,25(OH)_2D$ level in this patient since these investigations are not available in our setting. However, we did an extensive workup to exclude other causes of PTH independent hypercalcaemia.

Abrupt withdrawal of long-term steroid therapy can result in adrenal insufficiency and symptomatic hypercalcaemia. This is an important albeit rare cause of hypercalcaemia that needs to be borne in mind whenever a patient is evaluated for hypercalcaemia. A thorough and detailed clinical history is of paramount importance in arriving at a correct diagnosis and no sophisticated investigation can replace it.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case reported.

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Patient consent
The patient has provided written consent for publication of this case.

Author contribution statement
S D N D was a part of treating team and did literature search and wrote the manuscript, P K was the primary physician who managed the patient and reviewed the manuscript. M A was a part of the treating team and reviewed the manuscript. All authors read and approved the final manuscript.

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