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Hypercalcaemia secondary to hypophysitis and cortisol deficiency: another immunotherapy-related adverse event

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Summary

Hypercalcaemia is a common complication seen in malignancy, frequently due to paraneoplastic parathyroid hormone-related peptide production or osteolytic bony metastases. We present a 58-year-old female with immunotherapy-mediated hypophysitis causing secondary cortisol deficiency resulting in severe glucocorticoid-responsive hypercalcaemia. Whilst hypophysitis is a well recognised adverse event in those receiving immunotherapy for advanced malignancy, it does not typically present with hypercalcaemia. The mechanism responsible for hypercalcaemia due to hypocortisolaemia has not been fully elucidated although hypotheses include the effects of volume depletion and thyroxine's action on bone. Prompt treatment with glucocorticoids caused an improvement in the patient's symptoms and corrected her hypercalcaemia which later returned after an attempted glucocorticoid wean. With the increasing uptake of immunotherapy, clinicians should be aware of this unusual presentation of immunotherapy-related hypophysitis and secondary hypocortisolaemia which can be life-threatening if the diagnosis is delayed.

Learning points

- Immunotherapy can cause inflammation of the pituitary gland resulting in secondary hypocortisolaemia, which can, though rarely, present as hypercalcaemia.
- Secondary hypocortisolaemia requires prompt recognition and treatment with glucocorticoids. Glucocorticoid replacement leads to rapid clinical and biochemical improvement in these patients.
- The differential diagnosis for glucocorticoid-responsive hypercalcaemia extends beyond granulomatous disorders (e.g. sarcoidosis, tuberculosis) to adrenocorticotrophic hormone and cortisol deficiency, particularly in patients receiving immunotherapy.
- Hypocortisolaemia can lead to hypercalcaemia through various proposed mechanisms. Low serum glucocorticoids are associated with reduced blood volume, thus reducing renal calcium excretion. In addition, without glucocorticoid's inhibitory action, thyroxine appears to drive calcium mobilisation from bone.

Background

Cancer cells can manipulate different immune checkpoint pathways that lead to immune system evasion. Since their approval in 2011, immune checkpoint inhibitors (ICIs) have revolutionised cancer management but, due to their toxicities, have often required specialist input from a range of different medical disciplines, including endocrinology. These monoclonal antibodies interrupt inhibitory signalling pathways and promote immune-mediated tumour cell destruction (1). The introduction of ipilimumab (an anti-cytotoxic T-lymphocyte antigen-4 antibody (anti-CTLA-4)) in 2011 was soon followed by various anti-PD-1 (programmed cell death protein 1) and

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anti-PD-L1 (programmed death-ligand 1) therapies, with efficacy seen in a range of different cancers (1). Due to the inhibition of the normal physiological barriers against autoimmunity, immune-related adverse events (irAEs) are a common occurrence in those receiving immunotherapy (1). Endocrine irAEs are increasingly encountered with around 10% of patients developing endocrine adverse effects (2), with endocrinologists therefore increasingly involved in the management of these patients.

Inflammation of the pituitary gland (hypophysitis) is an irAE which can be life-threatening if left untreated and can occur in up to 10% of those receiving anti-CTLA-4 therapies and <1% of those on single-agent anti-PD-1 therapies (3). Hypophysitis can often present with non-specific symptoms such as headache, lethargy and appetite loss, with an MRI brain scan for diagnosis often being of low yield (3). The patterns of anterior pituitary hormone deficiencies differ in patients but most commonly present as isolated adrenocorticotrophic hormone (ACTH) deficiency resulting in secondary hypocortisolaemia (3). Early recognition of this condition is crucial, with management involving lifelong glucocorticoid replacement therapy.

In 5% of presentations of primary hypocortisolaemia (adrenal insufficiency), hypercalcaemia may be present (4). The cause of this is considered multifactorial including reduced renal perfusion (and thus impaired calcium excretion) (5) and the loss of cortisol inhibition of thyroxine-mediated calcium mobilisation from bone (6). Hypercalcaemia in malignancy is most common secondary to paraneoplastic parathyroid hormone-related peptide (PTHrP) production or osteolytic metastases (7). However, immunotherapy-mediated hypophysitis is another important cause given its responsiveness to glucocorticoids and potential life-threatening consequences if the diagnosis of hypocortisolaemia is delayed. We present an unusual case of delayed onset immunotherapy-mediated hypophysitis resulting in secondary hypocortisolaemia and glucocorticoid-responsive severe hypercalcaemia.

Case presentation

A 58-year-old female with early breast cancer presented with a 3-week history of fatigue and confusion having recently completed 6 months of neoadjuvant chemoimmunotherapy (pembrolizumab (anti-PD-1) in combination with paclitaxel, then doxorubicin and cyclophosphamide). Other than a past hepatitis B infection for which she was on entecavir prophylaxis, her medical history was unremarkable. Examination demonstrated tachycardia (HR 126 bpm), hypotension (94/40 mmHg) and dry mucous membranes.

Investigation

Biochemistry (Table 1) revealed hypercalcaemia with corrected calcium 3.26 mmol/L (2.10–2.60) and elevated troponin of 319 ng/L (<16) with normal renal function. Serum parathyroid hormone (PTH) was appropriately suppressed at <0.4 pmol/L, PTHrP was undetectable (<4.2 pmol/L) and she had low 25(OH)-VitD3 of 16 nmol/L (50–140) and undetectable 1,25(OH)2-VitD3 of <12 pmol/L (60–120). There was no evidence of bony metastases on recent whole-body computed tomography (CT) scans. She was not taking any medications known to cause hypercalcaemia such as thiazides or lithium (8). Myeloma screen was negative and thyroid function tests indicated mild thyrotoxicosis which spontaneously resolved 3 weeks later, consistent with low-grade immunotherapy-induced thyroiditis (Table 1). Intravenous methylprednisolone (three doses of 1 g daily) was promptly administered due to concerns of immunotherapy-related myocarditis given haemodynamic compromise, elevated troponin concentration and interval reduction in left ventricular ejection fraction (LVEF) on trans-thoracic echocardiogram

Table 1 Baseline biochemistry results at initial presentation of hypercalcaemia.

Blood test	Result	Reference range
Corrected calcium, mmol/L	3.26	2.10–2.60
Phosphate, mmol/L	1.54	0.75–1.50
Magnesium, mmol/L	0.54	0.70–1.10
Intact PTH, pmol/L	<0.4	1.6–7.2
PTHrP, pmol/L	Undetectable	<4.2
25(OH)-VitD3, nmol/L	16	50–140
1,25(OH)2-VitD3, pmol/L	<12	60–210
eGFR, mL/min/1.73 m^2	>90	>60
Creatinine, µmol/L	64	45–90
Troponin I, ng/L	319	<16
TSH, mIU/L	0.03	0.40–4.00
Free T3, pmol/L	9	2.6–6
Free T4, pmol/L	23.2	9.0–19.0
ACE, nM/mL/m	101	20–70
Hb, g/L	105	115–165
Neutrophils, $\times 10^9$/L	2.6	2.0–8.0
Eosinophils, $\times 10^9$/L	1	<0.5
CRP, mg/L	17	<5

1,25(OH)2-VitD3, calcitriol; 25(OH)-VitD3, calcifediol; ACE, angiotensin-converting enzyme; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; free T3, free triiodothyronine; free T4, free thyroxine; Hb, haemoglobin; intact PTH, intact parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TSH, thyroid-stimulating hormone.

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(LVEF of 55%, having been 65% previously). These various cardiac abnormalities swiftly resolved following glucocorticoid administration. Due to the urgent glucocorticoid requirement, cortisol and ACTH levels were not assessed prior to methylprednisolone delivery.

Further investigation into the causes of her hypercalcaemia revealed a mildly elevated serum angiotensin-converting enzyme (ACE) concentration of 101 nM/mL/m (20–70). A CT chest scan identified multiple small scattered lung nodules and mediastinal lymph nodes, some of which had been present on previous PET imaging. A diagnosis of ICI-associated sarcoidosis was considered given these findings and the glucocorticoid-responsive nature of her hypercalcaemia. Formal rheumatology and respiratory consultation were subsequently sought, however, undetectable 1,25(OH)2-VitD3 concentration and non-significant pulmonary findings made the diagnosis less likely and so bronchoscopy was not performed. Quantiferon gold assay result was negative prior to commencing immunotherapy and she had no recent tuberculosis exposure.

Treatment

Following the administration of 3 days of i.v. methylprednisolone, this was stepped down to oral prednisolone 50 mg daily. There was a rapid reduction of serum calcium concentration to 2.46 mmol/L within 4 days of glucocorticoid commencement, alongside an improvement in symptoms. A gradual oral glucocorticoid wean was commenced over the following 2 months and during this time, outpatient monitoring of her biochemistry showed persistent normocalcaemia. Her prednisolone was then weaned down to 0 mg daily at which point she quickly developed fatigue and her serum calcium increased rapidly (Fig. 1). Upon increasing prednisolone to 25 mg daily, serum calcium quickly normalised after 3 days and her lethargy resolved. A repeat glucocorticoid wean to 0 mg daily 2 months later resulted in the recurrence of the hypercalcaemia which again promptly corrected on increasing the oral glucocorticoid dose.

Outcome and follow-up

Endocrinology consultation was sought and consideration was given to immunotherapy-mediated ACTH deficiency given the glucocorticoid-responsive nature of her hypercalcaemia and low likelihood of a granulomatous disorder as the cause. A short synacthen test to confirm the requirement for long-term glucocorticoid replacement was subsequently performed whilst she was on a stable dose of prednisolone 5 mg daily and >24 h after her last prednisolone dose. Baseline ACTH (<5.0 ng/L) and cortisol (<28 nmol/L) were undetectable with submaximal peak cortisol of 56 nmol/L (≥500) 1-h post-synacthen administration confirming ACTH and cortisol deficiency. No other dynamic pituitary tests were performed and an insulin tolerance test was deemed unsafe given her undetectable baseline cortisol. Further dynamic investigations such as CRH stimulation test were deemed unnecessary given undetectable ACTH at baseline. The remainder of the pituitary panel was unremarkable with post-menopausal range follicle-stimulating hormone (64.8 IU/L), luteinizing hormone (23.5 IU/L) and oestradiol (<100 pmol/L) as well as normal prolactin (269 mIU/L), thyroid-stimulating hormone (1.62 mIU/L) and fT4 (11 pmol/L).

Our patient continues to be followed up by medical oncology and endocrinology and remains very well, with persistent normocalcaemia with a daily dose of 5 mg oral prednisolone. Given the diagnosis of cortisol deficiency, our patient will require lifelong glucocorticoid replacement as well as ongoing biochemical monitoring and follow-up.

Discussion

This unusual case highlights the importance of considering ACTH and cortisol deficiency (secondary hypocortisolaemia) as a potential life-threatening yet treatable cause of glucocorticoid-responsive hypercalcaemia in patients with malignancy, receiving ICI immunotherapy. Within the overall population, primary hyperparathyroidism and malignancy account for most cases (90%) of hypercalcaemia (4), but low PTH and PTHrP concentrations and lack of bony metastases on recent whole-body CT imaging eliminated these causes in our patient, respectively. Given the glucocorticoid-responsive nature of her hypercalcaemia and the mildly elevated serum ACE concentration, sarcoidosis was considered as a differential. However, sarcoidosis was deemed unlikely given her CT chest scan findings, undetectable 1,25(OH)2-VitD3 concentration and the outcomes of respiratory and rheumatology consultations. The patient also had a negative quantiferon gold assay result prior to commencing immunotherapy, making tuberculosis less likely. Hypocortisolaemia is a rare cause of hypercalcaemia (9). Given our patient's immunotherapy exposure, the glucocorticoid-responsive nature of her hypercalcaemia, reproducible recurrence of hypercalcaemia with cessation of prednisolone, exclusion of granulomatous disorders and results of her short

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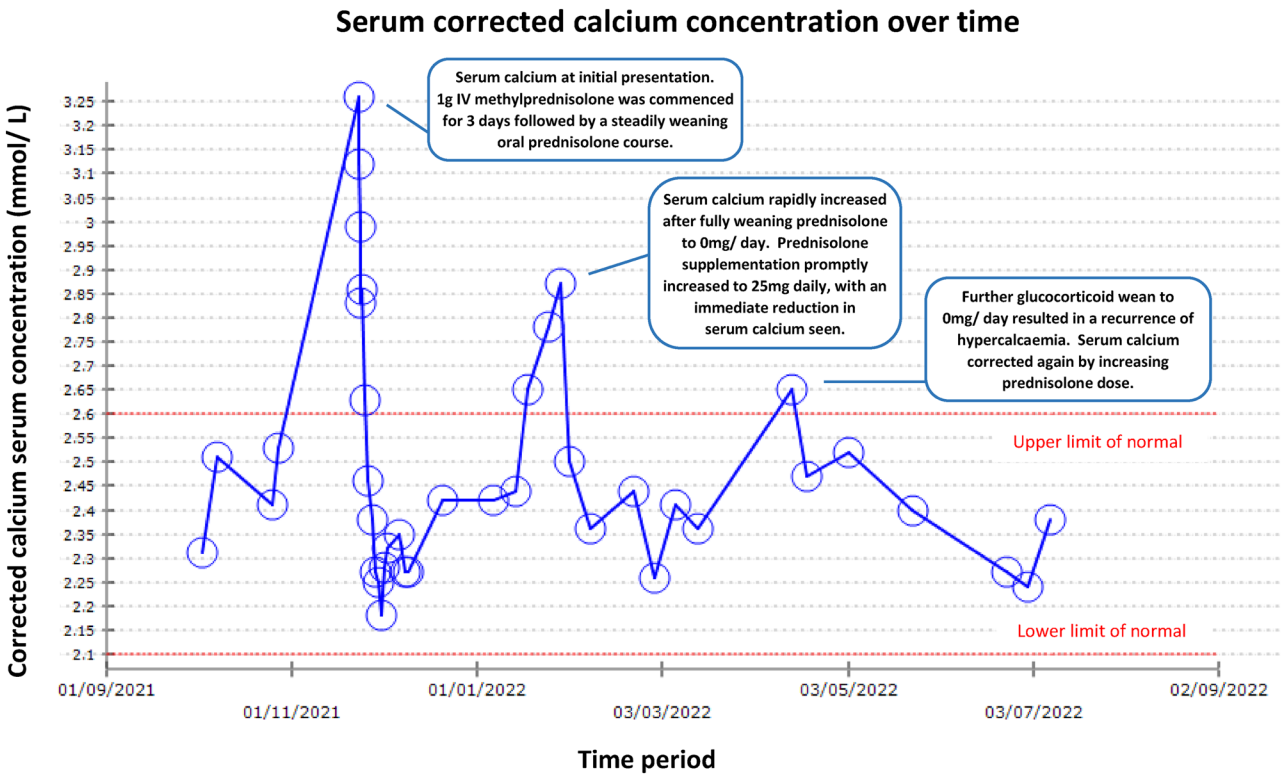

Figure 1
Serum calcium concentration from initial presentation to present day.

synacthen test and anterior pituitary hormone panel, the most likely diagnosis was hypercalcaemia secondary to isolated ACTH deficiency (secondary hypocortisolaemia) induced by immunotherapy. A low serum cortisol and ACTH concentration at initial presentation would have helped confirm this diagnosis; however, concerns for myocarditis and cardiac compromise prompted urgent treatment with i.v. glucocorticoids (10).

The potential aetiology for hypercalcaemia in patients with hypocortisolaemia is considered multifactorial. Volume depletion, as a consequence of hypocortisolaemia, results in a reduction in renal perfusion and this reduces calcium glomerular filtration and causes greater calcium reabsorption in the proximal tubule (6). This mechanism may have been implicated in our case, given that initial fluid resuscitation was associated with a small reduction in the serum calcium concentration. Despite glucocorticoid receptors being present in bone, the mechanism by which glucocorticoid deficiency influences calcium flux from bone remains unclear (11). The rise in calcium is not thought to be due to increased osteoclastic activity, based on bone biopsy evidence in a small case series (11). It has previously been shown that adrenalectomised dogs develop hypercalcaemia only in the presence of an intact thyroid gland (12). Thyroxine appears to facilitate calcium mobilisation from bone, with glucocorticoids inhibiting this action (6). Thus, the replacement of glucocorticoid deficiency may reduce bone calcium mobilisation and help return the patient to normocalcaemia. A final mechanism could include the role of stanniocalcin, a paracrine hormone secreted by the adrenal gland (13). Evidence in mice suggests an increased risk of hypercalcaemia in a stanniocalcin gene knockout mouse model (14), but there is currently insufficient evidence characterising the role of stanniocalcin in human physiology (15).

This case highlights the importance of considering immunotherapy-mediated hypophysitis and secondary hypocortisolaemia as a potential life-threatening condition in patients with malignancy. Delays in diagnosis due to the lack of awareness of this clinical entity and inappropriate cessation of glucocorticoids could lead to worse patient outcomes. Although delayed onset immunotherapy-induced hypophysitis is a rare cause of hypercalcaemia, the increasing uptake of immunotherapy may increase the frequency of this presentation and so clinical suspicion is warranted.

Declaration of interest
A M. Menzies has served on advisory boards for Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Roche, Pierre-Fabre and QBiotics. The remaining authors have no multiplicity of interest to disclose.

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Patient consent
Written informed consent for publication of their clinical details was obtained from the patient.

Author contribution statement
AMM was the primary treating physician for the patient with SRM, SK and AY assisting in the patient's care. SRM and SK drafted the manuscript and AY and AMM critically reviewed the manuscript. All authors approve of the final version of the manuscript.

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