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Case Review

Hypercalcaemia with undetectable parathormone levels

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A 54 year old woman had unintentional weight loss of 12-19 kg with nausea, abdominal discomfort, and constipation over 2-3 months. She presented acutely with profuse vomiting for three days. She was taking venlafaxine 150 mg/day for bipolar disorder, she smoked (40 pack years), consumed little alcohol, and had no family history of disease. On examination, she was dehydrated, her blood pressure was 106/74 mm Hg, pulse 122 beats/min and regular, and her temperature was 37.2°C. She had a smooth symmetrical goitre with no retrosternal extension or lymphadenopathy, and mild abdominal tenderness. Systems examination was normal. She underwent blood tests, the results of which were normal for renal function, alkaline phosphatase, total protein, globulin, and protein electrophoresis. Abnormal blood test results are shown in **table 1**.

Chest radiography and computed tomography scans of the abdomen and pelvis were normal.

Table 1 Abnormal blood test results

Test	Result	Reference range
Potassium	3.0 mmol/L	3.5-5.3
Adjusted calcium	3.02 mmol/L	2.20–2.60
Phosphate	1.06 mmol/L	0.8-1.5
Parathyroid hormone (PTH)	<0.4 pmol/L	1.3-9.3
Alanine transaminase (ALT)	256 IU/L	<50
Free thyroxine (FT4)	63.3 pmol/L	9.2-21
Free triiodothyronine (FT3)	>46.1 pmol/L	2.6-5.7
Thyroid-stimulating hormone (TSH)	<0.02 mU/L	0.3-4.4
TSH receptor antibody (TRAb)	>40 IU/L	<0.9
Vitamin D	37 nmol/L	>50
Angiotensin-converting enzyme (ACE)	64 U/L	8-52

Questions

1. **What are the possible causes of this patient's hypercalcaemia?**

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2. **What is the most likely diagnosis?**
3. **How would you treat this patient?**

1. What are the possible causes of this patient's hypercalcaemia?

Print answer

This patient has non-PTH mediated hypercalcaemia (low PTH, high adjusted calcium).

Causes include:

- Malignancy (eg lung, breast, kidney, skin, multiple myeloma, lymphoproliferative disorders)
- Granulomatous disorders (eg sarcoidosis, tuberculosis)
- Drugs - e.g. vitamin D and vitamin A toxicity, thiazide diuretics, calcium supplements causing milk alkali syndrome, vitamin A
- Endocrine disorders (eg, thyrotoxicosis/hyperthyroidism, phaeochromocytoma, hypoadrenalism, VIPoma)
- Immobilisation

Online answer

This patient has non-PTH mediated hypercalcaemia (low PTH and high adjusted calcium levels).

In PTH mediated hypercalcaemia, PTH levels are inappropriately raised, ie, detectable, and within or above the reference range. In non-PTH mediated hypercalcaemia, PTH is below the reference range or undetectable. The causes of both are summarised in **table 2**.

Table 2 A summary of the causes of PTH mediated and non-PTH mediated hypercalcaemia

PTH mediated hypercalcaemia	Non-PTH mediated hypercalcaemia
Primary hyperparathyroidism • Adenoma • Hyperplasia • carcinoma	Malignancy • multiple myeloma • lymphoproliferative disorders • lung • breast • kidney • skin
Familial benign hypocalciuric hypercalcaemia	
Tertiary hyperparathyroidism	Granulomatous disease • Sarcoidosis • tuberculosis
Drugs • lithium	Endocrine disorders • Thyrotoxicosis/hyperthyroidism/Graves disease • Pheochromocytoma • Hypoadrenalism • VIPoma
Ectopic PTH production resulting from malignancy (rare)	Drugs • Vitamin D toxicity • Thiazide diuretics • Calcium supplements (causing milk-alkali syndrome) • Vitamin A toxicity • calcium and calcitriol or vitamin D analogues for chronic renal failure
	Immobilisation

Adapted from Minisola et al.[1]

Primary malignancies (eg, lung, breast, kidney, skin) cause hypercalcaemia by producing PTH related peptide (PTHrP), and by causing bone destruction. PTHrP produces similar effects to PTH, ie, increases gut and renal tubular calcium absorption, and activates osteoclast bone resorption—all causing an increase in serum calcium. Secondary malignancies cause bone destruction by producing osteoclast activating cytokines and PTHrP locally.[2] Rarely, malignancies (eg, lymphoproliferative disorders) may cause hypercalcaemia by increasing vitamin D3 (by activating the 1-α-hydroxylase enzyme), or causing ectopic PTH production (ovarian, small cell, and squamous lung cancers).

Hypercalcaemia of multiple myeloma is also mediated through cytokines and occurs in 30% of cases. Most patients with normal renal function in multiple myeloma will adapt to the increased calcium load and not develop hypercalcaemia.

In granulomatous disorders and some lymphomas, activated 1-α-hydroxylase causes vitamin D3 overproduction which increases renal and gastrointestinal absorption of calcium.

Hypercalcaemia occurs in approximately 20% of patients with thyrotoxicosis, and is uncommon, asymptomatic, and mild in Graves' disease.[4] The hypercalcaemia of Graves' disease is caused by FT3 mediated osteoclast activation, increasing bone turnover and transfer of calcium from bone to serum.[3] Rising calcium levels will suppress PTH through a negative feedback mechanism and PTH will be low or undetectable. Although calcium absorption from the intestines is reduced and renal calcium excretion is increased in thyrotoxicosis,[5] FT3 stimulated osteoclast activation results in a net increase in calcium levels, and hypercalcaemia.

2. What is the most likely diagnosis?

Print answer

Hyperthyroidism due to Graves' disease, causing non-PTH mediated hypercalcaemia.

Classical features of Graves' disease include tachycardia, weight loss, a smooth symmetrical goitre, and high TRAb levels. The patient also presented with relatively uncommon features of Graves' disease: hypercalcaemia with normal serum phosphate, and biochemical evidence of hepatitis. The hypercalcaemia of Graves' disease is caused by FT3 mediated osteoclast activation, increasing bone turnover and transfer of calcium from bone to serum.

Online answer

Hyperthyroidism due to Graves' disease causing non-PTH mediated hypercalcaemia.

Classic clinical features of Graves' disease include tachycardia, weight loss, a smooth symmetrical goitre, and high TRAb levels. This patient also presented with two relatively uncommon features of Graves' disease: hypercalcaemia with normal serum phosphate (resulting from absent PTH, and phosphate conservation by thyroid hormones) and biochemical evidence of hepatitis. In 15%-76% of people with Graves' disease, liver enzymes are abnormal.[7] This results from thyroid hormone or drug induced liver damage (eg, by thionamides), concomitant autoimmune liver disease; and heart failure, singly or in combination.

TRAb (detectable in 90%-95% of patients with Graves' disease) stimulates the TSH receptor, increasing serum thyroid hormone levels.

If renal function is not impaired, normal serum phosphate and hypercalcaemia are good indicators of non-PTH mediated hypercalcaemia. Phosphate is low in PTH-mediated hypercalcaemia because PTH is phosphaturic (eg, in primary hyperparathyroidism).

In thyrotoxicosis, high FT3 levels activate mitochondrial induced liver apoptosis,[8] and the liver vasculature fails to keep up with increased cellular oxygen demands. A mild increase of the transaminases therefore occurs.

3. How would you treat this patient?

Print answer

Immediate management involves rapid rehydration with intravenous normal saline infusion (to increase glomerular filtration and calcium excretion) and intravenous bisphosphonates (to inhibit osteoclast activation.)

Next, treat the hyperthyroidism with oral thionamides after warning the patient about side effects, especially neutropenia and liver toxicity. If thionamides are unsuitable or there is relapse, consider radioiodine or thyroidectomy with lifetime levothyroxine.

Online answer

Treatment involves:

1. *Rehydration*—Vomiting and renal salt/water wasting (hypercalcaemia induced nephrogenic diabetes insipidus) can substantially deplete volume in hypercalcaemia. Rehydration increases glomerular filtration and excretion of calcium. Infusion rates are guided by age, severity of hypercalcaemia, and the presence of heart or renal compromise. Recommended regimens using 0.9% normal saline are (a) 200-300 ml/hour initially, adjusted to maintain a 100-150 ml/hour urine output; (b) 3-4 L daily; (c) 1-2 L bolus followed by 200-250 ml hourly.

2. *Bisphosphonates*—Pamidronate and zoledronic acid infusions inhibit osteoclast activation. Zoledronic acid is superior to pamidronate in efficacy and duration of response. Both 4 mg and 8 mg (given as 15 minute infusions) are superior to 90 mg of pamidronate (2 hour infusion).[11] Zoledronic acid reduces calcium slightly more quickly and normalises calcium in 80%-100% in less than three days. A second dose, if necessary, can be given after eight days. Calcitonin, loop diuretics, and corticosteroids have a limited role. Denosumab is a relatively new osteoclast inhibiting human monoclonal antibody against RANK-L; its clinical utility is uncertain.[1]
3. *Thionamides*—Treating Graves' disease is important for controlling symptoms, hypercalcaemia, and liver injury. Thionamides (CBZ or MMI) are recommended as first line treatment. CBZ is started 40 mg/day (given once or twice/day). Graves' disease will be controlled in about 4-6 weeks—the time taken to deplete intrathyroidal iodine stores and thyroid hormones. Dose titration is preferred (dose reduction every 4-6 weeks to the lowest effective dose of 5-10 mg/day, titrating dose against thyroid hormone response). This regimen is used for 12 months minimum (without benefit beyond 18 months). Some recommend a "block and replace" regimen—CBZ 40 mg/day, adding levothyroxine 100-125 µg/day when biochemically euthyroid and the combination usually continued for 6-9 months, with subsequent switch during the remaining period to low dose CBZ only. There is no advantage to either regimen in terms of recurrence.[12] Drugs for hyperthyroidism, thyrotoxicosis, and Graves disease (eg thionamides–carbimazole, methimazole, propylthiouracil) can cause liver dysfunction and hepatitis-like features.[9 10]
4. If after stopping thionamides Graves' disease relapses, definitive treatment with radioiodine or thyroidectomy is usually indicated, followed by lifelong replacement therapy with levothyroxine.[12]

Learning points:

- In non-PTH mediated hypercalcaemia, PTH is below the reference range or undetectable. In PTH mediated hypercalcaemia, PTH levels are inappropriately raised, ie, detectable, and within or above the reference range.
- In Graves' disease, hypercalcaemia with normal serum phosphate results from absent PTH and phosphate conservation by thyroid hormones.

Patient outcome

The patient responded well to rehydration with 0.9% saline, 60 mg pamidronate and potassium chloride infusions, and CBZ 40 mg/day (**table 3**). Thereafter, liver enzymes and

calcium remained normal persistently. She had a total thyroidectomy because her hyperthyroidism was not controlled, despite 18 months of high dose CBZ (she declined radioiodine). She remains euthyroid on lifelong levothyroxine (75 µg/day).

Table 3 Patient outcome on treatment

Investigation	At admission	Day 6	Reference range
Adjusted calcium (mmol/L)	3.02	2.50	2.20-2.60
Alanine transaminase (IU/L)	256	49	<50
FT4 (pmol/L)	63.3	27.4	9.0–19.1
FT3 (pmol/L)	>46.1	13	2.6-5.7

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- Lakdasa Premawardhana has received funding from the World Bank for a study examining "The emergence of thyroid autoimmunity following universal salt iodisation" (completed and data analysed and presented in Sri Lanka).
- LP has contributed to educational events for the European Federation of Laboratory Medicine and Clinical Chemistry in Amsterdam, March 2017, and on the topics "thyroid testing during acute illnesses" and "anomalous thyroid results in clinical practice" for the Sri Lanka Medical Association in Colombo, July 2017.
- Ilaria Muller has received an early career grant from the Society for Endocrinology (SfE), UK.
- IM has contributed to educational events on the topics "thyroid autoimmunity and breast cancer" for the 15th International Thyroid Congress (ITC) in Orlando, Florida, USA, 2015; on the topics "alemtuzumab-induced thyroid autoimmunity" for the British Thyroid Association (BTA) annual meeting in London, May 2017; and on the topics "alemtuzumab-induced thyroid autoimmunity" for the European Thyroid Association (ETA) annual meeting in Belgrade, Serbia, Sep 17. She received expenses from these companies for these events and a Society for Endocrinology (SfE) Travel Grant to attend the Society for Endocrinology (SfE) meeting in Harrogate, UK, 6-8 November 2017.

Patient consent obtained.

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