An uncanny case of paraneoplastic calcitriol mediated hypercalcaemia

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Summary
A 77-year-old female patient with a history of treated breast cancer and a recently diagnosed laryngeal cancer presented with severe hypercalcaemia associated with suppressed parathyroid hormone (PTH) levels. Her initial investigations included 25-hydroxy vitamin D levels, short synacthen test, bone scan, myeloma screen and thyroid function tests which were within normality. A computerised tomography (CT) scan showed some right lung apical fibrotic changes. Her PTH-related peptide (PTHrP) was normal and sarcoidosis was also excluded. Her previous and current malignancies were thought to be unlikely behind her hypercalcaemia. Her 1,25-dihydroxy vitamin D (calcitriol) levels were found to be elevated. Her hypercalcaemia was initially managed with intravenous fluids and intermittent bisphosphonates infusions which would transiently reduce her calcium levels. Steroid treatment was initiated which improved her hypercalcaemia; however, the calcium levels rebounded on tapering the steroids down, a pre-requisite prior to a positron emission computerised tomography (PET-CT) scan to determine the source of the excess calcitriol production. This was cancelled following an emergency admission with marked hypercalcaemia and acute renal and liver injury. A contemporary CT scan showed a right apical lung mass with hepatic lesions suggestive of a disseminated lung primary. The histology obtained from a liver biopsy was compatible with metastatic small-cell lung carcinoma. Unfortunately, her clinical condition deteriorated further and she did not survive. To the best of our knowledge, this is the first report in the literature describing calcitriol-mediated hypercalcaemia due to a small-cell lung cancer.

Learning points
- Paraneoplastic hypercalcaemia may manifest even without overt detection of the primary cancer.
- The workup for paraneoplastic hypercalcaemia should be meticulous.
- Both bisphosphonates and steroids are useful in the initial management of calcitriol-mediated hypercalcaemia, but the definitive management is the treatment of the cause.

Background
Hypercalcaemia secondary to a malignant pathology is up to four times more common in patients with advanced, stage IV cancer than in those with an early neoplasia, and it is usually associated with poor prognosis when detected with an average of 25–52 days survival rate (1). Although a number of mechanisms have been described to explain this paraneoplastic manifestation, its aetiology might not be exclusively mediated by the tumour and other potential causes behind this presentation should be excluded. Isolated calcitriol-mediated hypercalcaemia is rare and identifying its aetiology in patients with current or previous history of cancer can present a significant diagnostic challenge as highlighted in our case report. It is even more uncommon that two histologically different tumours, i.e. squamous cell carcinoma of the larynx and small-cell lung cancer, develop in such a short time span adding complexity to our case. Coordinating care across multiple specialities and secondary care centres also
presents its own challenges especially during the Covid-19 pandemic.

Case presentation

A 77-year-old lady was referred to endocrinology with severe hypercalcaemia, with an adjusted calcium (adj. Ca) of 3.24 mmol/L (normal range: 2.20–2.60 mmol/L) 6 months after she completed treatment for a locally invasive squamous cell carcinoma of the larynx (T4 N0 M0). This consisted of a successful total laryngectomy and thyroidectomy with post-operative radiotherapy administered in May 2020. The right superior parathyroid gland was preserved.

She had a previous history of T2 N2 Mx ER/PR (+) breast cancer diagnosed in 2006, treated with right-sided mastectomy (no reconstructive silicone implant in situ), adjuvant radio-chemotherapy and 5 years of Tamoxifen, and was then deemed disease free. Additional past medical history included obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease stage 3 and multiple duodenal ulcers (Zollinger–Ellison syndrome excluded). She was a former smoker having stopped at the age of 40 with a 30 pack-year history of cigarette smoking and was on no regular medications that could cause hypercalcaemia.

Her hypercalcaemia was incidentally detected following the preoperative assessment performed prior to her laryngeal surgery (adj.Ca: 2.94 mmol/L). No historical calcium levels were found on previous records. Parathyroid hormone (PTH) levels were not obtained at that time. She received 30 mg of Prednisolone preoperatively to minimise laryngeal oedema. Post-operatively, her PTH was suppressed at <0.3 pmol/L (normal range: 1.3–9.3 pmol/L) with an adj.Ca of 2.67 mmol/L hence iatrogenic hypoparathyroidism was initially suspected. Calcium and alfacalcidol were initiated and promptly discontinued by the ear, nose and throat (ENT) surgical team when hypercalcaemia developed (adj.Ca: 2.79 mmol/L). She was a former smoker having stopped at the age of 40 with a 30 pack-year history of cigarette smoking and was on no regular medications that could cause hypercalcaemia.

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Investigations

Initial investigations included 25-hydroxy vitamin D levels, myeloma screen, short Synacthen test and liver and thyroid function tests, which were all within normality. A bone scan excluded metastatic bone disease. Paraneoplastic antibodies (anti-Yo/ anti-Hu/ anti-Ri/anti-Ma) were negative. Her PTH-related peptide levels, analysed in France due to technical laboratory issues in the UK, were also within the normal range. Her 1,25-dihydroxy vitamin D (calcitriol) levels were within the reference range too (57 pmol/L, normal range: 20–120 pmol/L). A mildly elevated angiotensin-converting enzyme level (ACE) (81 U/L, normal range: 20–70 U/L) and subtle right lung apical fibrotic changes and traction bronchiectasis reported on computerised tomography (CT) scans were the only positive findings identified (CT thorax arranged in June 2020 and repeated in February 2021). Consultations with respiratory, oncology and the ENT teams suggested that sarcoidosis, additional lung pathology or her previous malignancies were unlikely to be responsible for her biochemical picture.

Her calcitriol levels increased up to 155 pmol/L approximately 9 months after her initial endocrinology appointment hence a diagnosis of calcitriol-mediated hypercalcaemia of unknown origin was made. A positron emission computerised tomography (PET-CT) was planned however this required discontinuation of steroids to improve its accuracy and it was cancelled during an emergency admission to hospital with severe hypercalcaemia associated with renal and liver injury.

Treatment

Following her initial intravenous (iv) pamidronate infusion (30 mg), her calcium levels remained persistently elevated (adj.Ca: 2.76–3.75 mmol/L), requiring intermittent hospital admissions for iv rehydration and iv bisphosphonate therapy (iv pamidronate, doses 30–60 mg and one dose of 5 mg iv zolendronic acid), mostly arranged at her local district hospital, making overall management challenging. Dietitians adjusted her oral supplements and enteral feed to minimise exogenous calcium administration while improving her malnutrition. Her mobility slowly improved but not to baseline levels.

Cinacalcet was considered; however, she was unable to tolerate it due to nausea, vomiting and a burning sensation on her throat. A trial of 30 mg/day of Prednisolone was started which lowered her adj.Ca from 3.02 mmol/L to 2.52 mmol/L within 2 weeks. An attempt to slowly reduce the Prednisolone failed, since doses below 30 mg/day were ineffective in controlling her hypercalcaemia. Intravenous zolendronate (4 mg) was administered to prevent a calcium rebound while the steroids were tapered off prior her PET-CT to increase its accuracy.
Outcome and follow-up

She was urgently readmitted to hospital 2 weeks later with marked peripheral oedema, acute kidney and liver injury and severe hypercalcaemia. Her hypercalcaemia remained refractory (adj.Ca: 3.38–3.61 mmol/L) despite vigorous intravenous rehydration, forced diuresis, further zoledronate infusion (4 mg) and subcutaneous calcitonin (100 units thrice daily) (Fig. 1). Her cortisol levels were normal. An urgent CT scan (Fig. 2) showed a right apical lung mass associated with hilar and mediastinal lymphadenopathy with hepatic lesions suggestive of a disseminated lung primary (T1c N2 M1c). A liver biopsy was obtained; however, her clinical condition rapidly declined and she died within 48 hours. The combined immunohistochemistry (strong staining with TTF1, CD56, and chromogranin with Ki67 index of 60%) (Figs. 3, 4 and 5) and morphological appearances of her liver histology were consistent with metastatic small-cell carcinoma of the lung.

Discussion

Hypercalcaemia of malignancy is a paraneoplastic manifestation found in up to a third of solid tumours and haematological malignancies. Pathophysiologically, it is usually due to humoral secretion of PTHrP or 1,25-dihydroxy vitamin D (calcitriol), the development of osteolytic metastases with local cytokine release or infrequently, the ectopic production of PTH (1). Co-secretion of both PTHrP and calcitriol has been rarely described in non-small-cell lung carcinoma, non-Hodgkin’s lymphoma, seminomas, squamous cell carcinoma of the tongue, metastatic renal cell carcinomas and pancreatic neuroendocrine tumours (2); however, isolated calcitriol over-production is seldom seen in solid tumours especially in lung cancer, although it is well recognised in granulomatous conditions driven by the excessive production of 1-alpha hydroxylase in the activated macrophages within granulomas (3). The mechanism behind calcitriol-mediated hypercalcaemia in non-granulomatous conditions remains unclear although some reports have demonstrated the presence of 1-alpha hydroxylase enzyme in macrophages surrounding dysgerminomas and lymphomas and the activation of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D in vitro within both lymphoma and plasma cells (4). It usually carries a poor prognosis.

To the best of our knowledge, this is the first report in the literature describing calcitriol-mediated hypercalcaemia due to a small-cell lung cancer. It is rather unusual that two histologically different tumours, i.e., squamous cell carcinoma of the larynx and small-cell lung cancer present in such a short time span adding complexity to this case. It is possible our patient initially had microscopic lung changes difficult to identify on standard imaging. As her...
lung pathology progressed, her hypercalcaemia became more severe and refractory to treatment suggestive of increasing tumour mass and calcitriol production. Other potential causes contributing to her hypercalcaemia such as excessive exogenous calcium intake, vitamin D intoxication, sarcoidosis, prolonged immobility, metastatic bone disease, thyrotoxicosis, hypoadrenalism and PTHrP production were excluded.

Foreign body granulomas associated with calcitriol-related hypercalcaemia have been described in patients who have received cosmetic silicone or paraffin oil injections or in those with rupture of silicone implants (5). Our patient decided against reconstructive breast surgery with silicone implants following her right-sided mastectomy hence excluding this uncommon aetiology.

The typical biochemical pattern found in PTH-independent extrarenal calcitriol production is elevated calcitriol with suppressed native PTH levels. This results in increased intestinal calcium absorption leading to hypercalcaemia although a degree of bone resorption can contribute to the picture. If PTHrP co-secretion is identified, bone resorption will be further enhanced in addition to increased distal tubular calcium resorption and suppression of proximal tubular phosphate transport. Routine assays might not detect PTHrP and calcitriol levels should be tested if 25-hydroxy vitamin D levels are discordant with the clinical picture hence the importance of liaising closely with the local blood science department to coordinate these tests.

Calcitriol-induced hypercalcaemia is managed by treating the cause in conjunction with steroids since a favourable response with the latter is often seen (3, 6). Steroids inhibit both the activation of 25-hydroxy vitamin D and the resorption carried out by osteoclasts through

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**Figure 2**
CT scan of the chest showing the lesion in the upper lobe of the right lung.

**Figure 3**
TTF-1 staining on immunohistochemistry.

**Figure 4**
CD56 staining on immunohistochemistry.

**Figure 5**
Chromogranin staining on immunohistochemistry.
suppression of cytokine production by the tumour (7). The optimal, most effective steroid dose remains unclear and various empirical regimens have been described in the literature. Doses of 20–40 mg/day of prednisolone have been used (8). Intravenous hydration, bisphosphonates, calcitonin and denosumab are also supportive therapeutic measures that could be used in this context, although the long-term efficacy of calcitonin is limited by the development of early tachyphylaxis.

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

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Patient consent
Written consent was obtained from the next-of-kin of the patient for the publication of this report.

Patient’s perspective
It is my fervent wish that my wife’s death provides help to any afflicted in the same way as she was.

Author contribution statement
PM Shah contributed to the case discussion. S Saeed contributed to the case summary. S Gonzalez was the named clinician and contributed and reviewed the totality of this case report.

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