An unusual case of malignancy-related hypercalcemia

Objective: To report the case of a 28-year-old woman who presented with hypercalcemia (total calcium = 4.11 mmol/L), elevated parathyroid hormone (PTH) 24.6 pmol/L, normal parathyroid hormone-related peptide 7.8 pg/mL, and a 63 mm × 57 mm, poorly differentiated neuroendocrine carcinoma (small-cell type) pancreatic mass with liver metastases.

Investigations and treatment: Hypercalcemia was acutely managed with intravenous fluids, pamidronate and calcitonin. Investigations for multiple endocrine neoplasia type 1 and parathyroid adenoma were initiated. The identified neuroendocrine tumor was treated with cisplatinum/etoposide chemotherapy.

Results: The pancreatic mass (56 mm × 49 mm) and metastases decreased in size with chemotherapy and calcium levels normalized. Eight months later, calcium increased to 3.23 mmol/L, PTH increased to 48.2 pmol/L, and the pancreatic mass increased in size to 67 mm × 58 mm. The patient was given a trial of cinacalcet but was unable to tolerate it. Chemotherapy was restarted and resulted in a decrease in the pancreatic mass (49 mm × 42 mm), a reduction in PTH levels (16.6 pmol/L), and calcium levels (2.34 mmol/L).

Conclusion: Ectopic PTH secreting tumors should be considered when there is no parathyroid related cause for an elevated PTH. Recognizing the association between PTH and hypercalcemia of malignancy may lead to an earlier detection of an undiagnosed malignancy.

Keywords: hypercalcemia of malignancy, parathyroid hormone, parathyroid hormone related-peptide, neuroendocrine tumor

Introduction

Hypercalcemia is a common metabolic disorder with multiple etiologies, of which primary hyperparathyroidism is the most common cause. Hypercalcemia can occur at any age but occurs most often in patients over the age of 50. It is most commonly due to either a single adenoma or hyperplasia of the parathyroid gland. Hypercalcemia may also be part of a hereditary syndrome (multiple endocrine neoplasia [MEN1] or multiple endocrine neoplasia type 2A [MEN2A]) particularly when identified in children or young adults. Parathyroid lesions are routinely identified with 99 mTc-Sestamibi scintigraphy scans and often successfully treated with surgical resection.

Hypercalcemia is also a well-established paraneoplastic condition that is associated with many malignancies and may occur through a number of different mechanisms (Table 1). In 1941, Albright was first to suggest that humoral factors secreted by cancer cells caused bone resorption and impaired renal calcium excretion. Parathyroid hormone (PTH) was originally thought to be the humoral factor that caused hypercalcemia of malignancy, however, in 1987 PTH-related peptide (PTHrP) was found to be the primary
mediator associated with malignancy-induced hypercalcemia.\textsuperscript{5–8} In such cases, patients often have suppressed PTH levels, metabolic alkalosis and low 1,25 dihydroxyvitamin D levels.\textsuperscript{9}

Since the discovery of PTHrP, there have been only rare cases of ectopic production of PTH by neuroendocrine tumors reported in the literature.\textsuperscript{10–26} In contrast to PTHrP-secreting tumors, patients with elevated PTH levels are often found to have normal PTHrP levels, hyperchloremic acidosis and elevated 1,25 dihydroxyvitamin D levels.\textsuperscript{9}

We present a rare case of malignancy associated hypercalcemia secondary to ectopic PTH. We will review previously reported cases of PTH-secreting tumors, discuss the differences in biochemical findings between humoral causes of hypercalcemia,\textsuperscript{27–31} and possible treatment options for management of hypercalcemia caused by PTH secreting tumors.

**Case report**

**Background**

A previously healthy 28-year-old presented to hospital with a 2-week history of nausea, fatigue, abdominal pain, and weight loss. Initial laboratory investigations showed severe hypercalcemia (Ca =4.11 mmol/L, N=2.20–2.52 mmol/L) and acute renal failure (creatinine =215 µmol/L, N=35–88 µmol/L). Other laboratory investigations are summarized in Table 2. An electrocardiography (ECG) showed a normal sinus rhythm of 74 beats per minute and a corrected QT interval of 395.

**Treatment and investigations**

Following therapy with intravenous (IV) fluids, pamidronate disodium (60 mg IV), and calcitonin (200 units twice daily), her serum calcium improved to 2.82 mmol/L within 3 days. Further investigations revealed an elevated serum PTH level at 24.6 pmol/L (1.6–9.3 pmol/L, intact PTH immunometric assay) and a high circulating 1,25 dihydroxyvitamin D level at 229 pmol/L (29–193 pmol/L) (Figure 1 and Table 2). This raised the possible diagnoses of primary hyperparathyroidism or MEN1. There was no family history of either of these disorders. Ongoing abdominal discomfort despite improvements in calcium levels resulted in a diagnostic

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**Table 1** A summary of the humoral causes and frequency of malignancy-related hypercalcemia with the associated biochemical findings

| Causes of hypercalcemia of malignancy | Local osteolytic hypercalcemia | PTH-rp | Calcitriol | Ectopic PTH |
|--------------------------------------|-------------------------------|--------|------------|-------------|
| **Hypercalcemia of malignancy**     |                               |        |            |             |
| Types of malignancy                 | Multiple myeloma              | Squamous cell carcinoma, RCC, breast, ovarian, bladder\textsuperscript{27} HTLV lymphoma/leukemia\textsuperscript{28} | Lymphoid tumors (Hodgkin’s lymphoma)\textsuperscript{27} | • Lung (small cell,\textsuperscript{16} squamous cell,\textsuperscript{17} not specified,\textsuperscript{18} bronchogenic carcinoma\textsuperscript{19}) • Ovarian\textsuperscript{19,21} • HCC\textsuperscript{16,17} • Thymus\textsuperscript{18} • Thyroid\textsuperscript{19} • Pancreas\textsuperscript{20,21} • TCC of the bladder\textsuperscript{22} • Metastatic neuroectodermal tumor\textsuperscript{23} • Nasopharyngeal rhabdomyosarcoma\textsuperscript{14} • Neuroendocrine tumor in the neck\textsuperscript{23} • Gastric carcinoma\textsuperscript{28} |
| Frequency of hypercalcemia of malignancy | 20%                           | 80%    | Less than 1% | Less than 1% |
| Mechanism of action                 | Cytokines, chemokines\textsuperscript{27} | Stimulates renal tubular reabsorption of Ca, stimulates osteoclast activity.\textsuperscript{29} Does not stimulate alpha-1- hydroxylase activity\textsuperscript{30} | Acts on intestines and kidneys to ↑ Ca absorption and reabsorption respectively\textsuperscript{27} | Increased absorption of calcium by stimulating the conversion of 25-OH vitamin-D to 1, 25-dihydroxyvitamin D. Increased osteoclast activity and renal reabsorption of Ca. Promotes phosphoturia.\textsuperscript{31} |
| Ca level                             | ↑(if renal failure)          | ↑      | ↑          | ↑           |
| PO4                                  | Normal↑                      | ↑      | ↑          | ↑           |
| PTH level                            | ↓                            | ↓      | Normal     | Normal      |
| PTH-rp level                         | Normal↑↑                     | ↑↑     | Normal     | Normal      |
| 1,25dihydroxyvitamin D               | Variable                     | ↑      | ↑          | ↑           |

**Abbreviations:** PTH-rp, parathyroid hormone related peptide; PTH, parathyroid hormone; HTLV, human T-lymphotropic virus type 1; HCC, hepatocellular carcinoma; TCC, transitional cell carcinoma; Ca, calcium; 25-OH vitamin D, 25-hydroxyvitamin-D; PO4, phosphate; RCC, renal cell carcinoma; ↑, high; ↑↑, very high; ↓, low; ↓↓, very low.
ectopic-PTH production

abdominal ultrasonography being performed, which showed a $6.0 \times 6.7 \times 8.0$ cm solid mass between the stomach and tail of the pancreas with multiple liver metastases. A computed tomography scan (CT-scan) showed a large $63 \times 57$ mm mass that was inseparable from the pancreas in the lesser sac infiltrating the splenic artery (Figure 2). An ultrasonography-guided core biopsy of the liver metastases revealed a poorly differentiated neuroendocrine carcinoma of the small-cell type consistent with the pancreas as the primary site of malignancy. Investigations to identify the source of PTH secretion including a CT-scan of the neck and 99mTc-sestamibi scintigraphy scan failed to find evidence of a parathyroid adenoma. Further staging investigations, including pituitary magnetic resonance imaging (MRI) and genetic testing for MEN1, were negative. A skeletal survey did not show any bony abnormalities and bone mineralization was normal throughout. A bone scan did not show any evidence of metastatic disease. The patient did not suffer any pathologic fractures. A bone density scan was not performed.

Treatment course

After one round of chemotherapy treatment with cisplatinum (40 mg IV) and etoposide (160 mg IV), there was a decrease in the size of the pancreatic mass ($56 \times 49$ mm) and liver metastases. With shrinkage of the tumor, calcium and PTH levels also decreased (Ca $2.02$ mmol/L,

| Test                  | Result  | Normal range |
|-----------------------|---------|--------------|
| Sodium                | 137 mmol/L | 136–144 mmol/L |
| Potassium             | 4.4 mmol/L  | 3.6–5.1 mmol/L  |
| Chloride              | 97 mmol/L   | 101–111 mmol/L  |
| Bicarbonate           | 29 mmol/L   | 22–32 mmol/L    |
| Calcium               | 4.11 mmol/L | 2.23–2.58 mmol/L|
| Magnesium             | 0.84 mmol/L | 0.74–1.03 mmol/L|
| Phosphate             | 1.31 mmol/L | 0.78–1.53 mmol/L|
| Albumin               | 43 g/L      | 35–48 g/L       |
| Creatinine            | 215 mmol/L  | 35–88 mmol/L    |
| PTH (on admission)    | 24.6 pmol/L | 1.6–9.3 pmol/L  |
| PTH (prior to first round of chemotherapy) | 39.7 pmol/L | 1.6–9.3 pmol/L |
| TSH                   | 1.71 mU/L   | 0.3–5.60 mU/L   |
| ALT                   | 37 U/L      | 14–54 U/L       |
| AST                   | 47 U/L      | 15–13 U/L       |
| GGT                   | 82 U/L      | 6–34 U/L        |
| ALP                   | 103 U/L     | 38–126 U/L      |
| 24-hour urine calcium | 12.3 mmol/d | 2.5–7.5 mmol/d  |
| CK                    | 38 U/L      | 20–160 U/L      |
| Lipase                | 27 U/L      | 22–51 U/L       |
| Beta-hCG              | <1 IU/L     | 0–5 IU/L        |
| 25-OH Vitamin D       | 54 nmol/L   | >75 nmol/L      |
| 1,25 dihydroxyvitamin-D | 229 pmol/L | 29–193 pmol/L   |
| Serum protein electrophoresis | Normal | N/A |

Table 2 Investigations and results for 28-year-old previously healthy patient found to have hypercalcemia on presentation to hospital

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Figure 1 PTH, PO4 and calcium levels for case study.

Notes: Serum PTH, PO4, and Ca levels of a 28-year old, previously healthy patient with suspected ectopic production of PTH from a pancreatic neuroendocrine tumor on admission, following acute management of hypercalcemia and relative to the initiation of chemotherapy treatment.

Abbreviations: PTH, parathyroid hormone; PO4, phosphate; Ca, calcium.
At the request of the patient, chemotherapy was stopped after six cycles. Eight months later, she was readmitted with recurrent hypercalcemia (Ca 3.23 mmol/L). An abdominal CT-scan showed an increase in the size of the pancreatic mass (67 mm × 58 mm). Her serum PTH level was increased (48.2 pmol/L), whereas PTHrP levels were within normal limits (7.8 pg/mL, 1–15 pg/mL) (Figure 1). The patient was treated with IV fluids and multiple doses of bisphosphonates (zoledronic acid 4 mg, pamidronate disodium 60 mg) and given a trial of cinacalcet hydrochloride 30 mg twice daily. The patient was not able tolerate the cinacalcet for more than 2 days before it was discontinued because of worsening nausea. Chemotherapy was restarted with doxorubicin 74 mg IV, vincristine 1.8 mg IV, and cyclophosphamide 1480 mg IV. After the first cycle, her calcium levels normalized (2.34 mmol/L) and following the second cycle, her PTH level decreased to 16.6 pmol/L (Figure 1). A repeat CT scan of her abdomen also showed a reduction in the size of the pancreatic mass (49 mm × 42 mm) (Figure 2). Immunohistochemical staining of tissue from liver biopsy was done but failed to show evidence of PTH immunoreactivity within the tumor cells. Despite chemotherapy, the patient died 15 months after diagnosis from recurrent hypercalcemia. An autopsy was declined by her family.

Discussion
Pancreatic neuroendocrine tumors are uncommon, with an incidence of 1 per 100,000 patients per year. Among this type of malignancy, insulin-secreting pancreatic neuroendocrine tumors are the most common, followed by gastrinomas, glucagonoma, vasoactive intestinal peptide secreting tumors (VIPomas), and somatostatinomas. PTH-secreting pancreatic neuroendocrine tumors are rare, with the present case being only the third reported in the literature to date.

Hypercalcemia associated with a high PTH level commonly results from a primary parathyroid disorder. This was initially suspected in our patient. However, the clinical and biochemical findings in our case provide evidence to suggest that this pancreatic neuroendocrine tumor was secreting ectopic PTH. In our patient, serum calcium and PTH levels were found to be elevated, and PTHrP remained in the normal range. Despite a number of imaging modalities, there was no evidence of a parathyroid adenoma or hyperplasia to explain the high PTH levels. Chemotherapy treatment led to a reduction of the pancreatic tumor, normalization of calcium levels, and a reduction in PTH levels.

Although paraneoplastic secretion of PTH is not commonly known to cause hypercalcemia of malignancy it has been described in association with a number of different malignancies (Table 3). In the few cases reported to date, it appears to be more common in males (11 of 17 cases reported) and predominantly affects those over the age of 60 (14 of 17 cases). This is only the second case report of ectopic PTH production in a patient under the age of 30.

As summarized in Table 3, a number of techniques have been reported in the literature as being used to confirm the diagnosis of hypercalcemia secondary to ectopic PTH production. Immunohistochemical staining for PTH in tissue samples from the liver metastases was attempted in our patient; however, these were negative. The negative results...
Table 3 A summary and description of the cases of ectopic production of PTH reported in the literature since the discovery of PTHrp

| Study                  | Age/sex | Primary malignancy                          | Method of PTH confirmation                                                                 | Treatment/outcomes                                                                 |
|------------------------|---------|----------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Yoshimoto et al10      | 70 M    | Small cell carcinoma of the lung             | Immunohistochemical staining, PTH mRNA                                                   | Patient died from refractory hypercalcemia                                      |
|                        |         |                                              | Gel filtration chromatography of tumor extract                                             |                                                                                   |
|                        |         |                                              | Tumor cell expression of PTH gene                                                       |                                                                                   |
| Neilsen et al11        | 71 M    | Squamous cell lung carcinoma                 | Immunohistochemical staining                                                             | Resection of lung tumor                                                            |
| Uchimura et al12       | 74 M    | Lung                                         | Immunohistochemical staining                                                             | Patient died 3 weeks after thoracotomy                                             |
| Weiss et al13          | 71 F    | Bronchogenic carcinoma                       | Technitium-99 sestamibi scan                                                             | Lobectomy                                                                         |
| Nussbaum et al14       | 74 F    | Ovarian carcinoma                            | Immunoradiometric assay; PTH mRNA; Tumor cell expression of PTH gene                     | Bilateral salpingo-oopherectomy/chemotherapy                                       |
| Chen et al15           | 37 F    | Small cell carcinoma of the ovary            | Immunohistochemical staining                                                             | Bilateral salpingo-oopherectomy/chemotherapy                                       |
| Koyama et al16         | 83 M    | HCC                                          | Venous sampling                                                                         | Transcatheter arterial embolization                                                |
| Mahoney et al17        | 72 M    | HCC                                          | Technitium-99 sestamibi scan; immunoradiometric assay and rapid assay                     | Transcatheter arterial embolization                                                |
| Rizzoli et al18        | 25 M    | Thymoma                                       | Immunohistochemical staining and PTH mRNA                                                | Thymic mass removed                                                               |
| Iguchi et al19         | 72 F    | Papillary adenocarcinoma of the thyroid gland | Technitium-99 sestamibi scan and immunohistochemical staining                           | Hemithyroidectomy                                                                 |
| Vacher-Coponat et al20 | 58 F    | Pancreas                                     | Technitium-99 sestamibi scan and venous sampling suprahepatic and peripheral vein         | Chemotherapy                                                                      |
| VanHouten et al21      | 74 F    | Pancreas                                     | Immunohistochemical staining and PTH mRNA                                                | Tumor unresectable. Patient died from refractory hypercalcemia and multiorgan failure |
| Eid et al22            | 73 M    | Transitional cell carcinoma of the bladder   | Transactivation of the PTH gene                                                          | Pelvic mass not resectable. Patient received palliative chemotherapy with poor response. The patient died a few weeks later. |
| Strewler et al23       | 69 M    | Metastatic neuroectodermal tumor             | Immunohistochemical staining                                                             | Patient died from recurrent hypercalcemia                                         |
| Wong et al24           | 62 M    | Nasopharyngeal rhabdomyosarcoma              | Tumor cell expression of PTH gene                                                       | Chemotherapy/radiation. Patient died from respiratory failure due to pneumonia      |
| Kandil et al25         | 73 M    | Neuroendocrine tumor in the neck             | Immunohistochemical staining                                                             | Resection of neck mass                                                            |
| Nakajima et al26       | 70 M    | Gastric carcinoma                            | Immunohistochemical staining/crude cytosolic fractioning from metastatic liver tissue    | Chemotherapy. Patient died from multi-organ failure                                |

Abbreviations: PTH, parathyroid hormone; HCC, hepatocellular carcinoma; mRNA, messenger ribonucleic acid; PTHrp, parathyroid hormone related peptide; M, male; F, female.

may have been due to the quality of biopsy, the immunohistochemical staining antibody that was used, differences between metastatic tissue and primary malignancy, ectopic hormone production being restricted to a subpopulation of tumor cells, or structural differences between the ectopic and the natural form of the hormone not detected with immunohistochemical staining. A biopsy of the primary pancreatic mass was not performed as the procedure was not in the best interest of the patient. The cancer diagnosis was obtained from the biopsy of the liver metastases and therefore tissue from the primary tumor was not available for PTH staining.

Although PTH mRNA was not available at our center, other authors have successfully demonstrated ectopic PTH production by comparing PTH mRNA sequencing from tumor extracts to PTH mRNA from parathyroid tissue using northern blot analysis.9,14,18,21 Despite the lack of immunohistochemical staining or PTH mRNA to confirm ectopic production of PTH, the reduction in tumor burden and improvements in calcium and PTH levels with chemotherapy provides good evidence of PTH secretion from this neuroendocrine tumor.

Outcomes with ectopic PTH secretion are variable, as described in Table 2. In almost half of the studies reported,
patients succumbed to their disease shortly after diagnosis. Resistant hypercalcemia resulted in only transient improvements with standard therapy for hypercalcemia such as fluids and bisphosphonates reported in some cases of ectopic PTH secretion.\textsuperscript{10,20,21} Our patient had a similar course prior to the second course of chemotherapy, wherein the patient required weekly dosing of intravenous bisphosphonates and large amounts of IV fluids to maintain calcium levels at a reasonable albeit elevated level. A positive prognosis and long-term management of hypercalcemia in ectopic PTH secretion appears to be limited to resection of the malignancy or treatment with chemotherapy. There have been cases of hepatocellular carcinoma with a tumor producing intact PTH described where hypercalcemia was successfully controlled through transcatheter arterial embolization.\textsuperscript{16,17}

Another option for management of severe or resistant hypercalcemia caused by hyperparathyroidism may be cinacalcet. Cinacalcet is a calcimimetic that increases the sensitivity of the calcium-sensing receptor (CaSR) and has been shown to reduce both calcium and PTH levels in other forms of hyperparathyroidism.\textsuperscript{34} Cinacalcet was tried in our patient, but unfortunately it was not tolerated because of inducing severe nausea and vomiting. We are not aware of any other case reports where this therapy has been used to treat ectopic PTH secretion.

The benefit of cinacalcet may extend beyond the calcium lowering effects. The CaSR is known to be expressed in a number of tissues not classically considered to play a role in calcium regulation.\textsuperscript{35} Recent studies have found that CaSR expression and activity in various tissues correlates with both malignancy proliferation and suppression. In breast and prostate cancer, increased expression and activity of CaSR may facilitate bone metastases.\textsuperscript{36,37} In contrast, parathyroid carcinomas have been associated with decreased or absent expression of the CaSR.\textsuperscript{38} Animal studies have demonstrated that cinacalcet leads to both activation and increased expression of the CaSR, suppression of parathyroid hyperplasia and reduced PTH secretion in rodents with secondary hyperparathyroidism.\textsuperscript{39} It is possible that the CaSR may also play a role in ectopic-PTH producing malignancies, and that cinacalcet may have the potential benefit of suppressing the proliferation of PTH-secreting tumor cells. Although further research is required, the potential role of the CaSR to influence tumor growth and suppression presents a novel and important target for investigation of new malignancy therapies.

**Conclusion**

Hypercalcemia of malignancy resulting from ectopic production of PTH, although not common, should be considered when PTH levels are significantly elevated and there is no evidence of a parathyroid-related cause. Recognizing the association between elevated PTH levels and hypercalcemia of malignancy may prevent unnecessary parathyroid or exploratory neck surgeries and also could possibly lead to the early detection of an undiagnosed malignancy. More research is needed to determine whether there is a role for calcimimetics in treating resistant hypercalcemia secondary to ectopic PTH production and on the potential for suppressing tumor growth in these circumstances.

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**Disclosure**

The authors report no conflict of interest in this work.

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