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Case Report

Parathyroid Hormone–Related Peptide Secretion From a Pancreatic Neuroendocrine Tumor: A Rare Case Report of Severe Hypercalcemia

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ABSTRACT

Background/Objective: Hypercalcemia is a common occurrence associated with malignancy, due to a number of causes: (1) lytic bone metastases, (2) production of 1,25-dihydroxyvitamin D from lymphoma, and (3) parathyroid hormone–related peptide (PTHrP) secretion usually from solid tumors.
Case Report: A 56-year-old woman presented with symptoms of severe hypercalcemia. Investigations determined that this was due to PTHrP secretion from a pancreatic neuroendocrine tumor (pNET), a noted complication in 1.1% of pNET cases. Although unfit for curative therapy, the patient was treated with fluid replacement, bisphosphonates, calcitonin, and denosumab. After treatment, she had recurrent severe symptomatic hypercalcemia on several occasions despite adjunctive therapy with a somatostatin analog. Ultimately, the patient died as a result of refractory hypercalcemia.
Discussion: The hypercalcemia that is rarely associated with PTHrP secretion from pNETs is aggressive and often refractory to the usual medical treatment of hypercalcemia of malignancy. Effective treatment requires cytoreduction of the causative tumor. Denosumab, a receptor activator of nuclear factor kappa beta ligand inhibitor, has proven useful in some cases.
Conclusion: This challenging case highlighted the rare but potentially fatal association of pNET with hypercalcemia. Hypercalcemia was the main cause of mortality in an otherwise relatively indolent malignancy.

Introduction

Hypercalcemia is a frequent paraneoplastic finding, present in up to a quarter of oncology cases.[1] Approximately 80% of malignant hypercalcemia cases are driven by the secretion of parathyroid hormone (PTH)–related peptide (PTHrP) into the bloodstream.[2,3] The peptide acts upon parathyroid receptors in the bone and kidneys to increase the serum calcium levels.[4] PTHrP may be secreted by a solid tumor or as an overexpression of the standard gene product from a variety of epithelial- and mesoderm-derived tissues.[5] Malignancies are most frequently associated with increased PTHrP levels including breast and lung cancers.[6] Comparatively, few cases of hypercalcemia caused by PTHrP secretion are reported in pancreatic neuroendocrine tumors (pNETs).[7,8]

pNETs are relatively rare malignancies (incidence approximately 7/100 000) originating from neuroendocrine cells.[9] The ectopic hormones that they secrete shape the clinical syndrome of the patient. The incidence of hypercalcemia secondary to these tumors is low.[10] A retrospective study spanning 27 years in a European center indicated that only 2% of patients developed high calcium levels, approximately half due to increased serum PTHrP levels.[11] This report documents a case with this unusual finding.

Case Report

A 56-year-old woman presented to a hospital in Australia with lethargy, weight loss, and bony pain for 3 months. She had a past medical history of childhood rheumatic fever only. Examination indicated a cachectic woman with generalized weakness. There were no masses or lymphadenopathy on palpation. Both chest and abdominal examinations were benign. Blood tests showed a corrected calcium level of 18.0 mg/dL with significant acute kidney

Abbreviations: NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related peptide; SSA, somatostatin analog.

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Table
Reference Ranges

Blood test	Normal low	Normal high	Case
Calcium (mg/dL)	8.5	10.5	18.0
Creatinine (mg/dL)	0.6	1.1	3.2
Potassium (mEq/L)	3.5	5.2	3.3
PTHrP (pg/mL)	<12.3	<12.3	598.8
PTH (pg/mL)	9.4	66	8.5
Chromogranin A (μg/L)	0	102	119
25-Hydroxyvitamin D (ng/mL)	20	60	21.2
1,25-Dihydroxyvitamin D (pg/mL)	19	76	18

Abbreviations: PTH = parathyroid hormone; PTHrP = parathyroid hormone–related peptide.

injury; the serum creatinine level was 3.2 mg/dL having previously been within the normal range (Table). The patient was treated with aggressive fluid resuscitation (4 L of normal saline intravenously) for 24 hours; however, the calcium levels were slow to respond. Pamidronate 90 mg (a bisphosphonate) and calcitonin (100 units 3 times daily for 3 days) were subsequently administered, and intravenous fluids were continued. Several doses of furosemide were administered to manage fluid overload. After 96 hours, the serum calcium level remained increased at 12.5 mg/dL with associated symptoms; therefore, denosumab 120 mg was administered subcutaneously. This combination of treatment agents was effective in lowering the serum calcium levels to within the normal range.

Additional blood tests were performed to determine the cause of hypercalcemia including PTH (8.5 pg/mL), vitamin D (21.2 ng/mL), 1,25-dihydroxyvitamin D (18 pg/mL), and a myeloma screen (no monoclonal bands identified). None of these investigations indicated abnormal results (Table) apart from a slightly low 1,25-dihydroxyvitamin D level. The PTHrP level was 598.8 pg/mL. As renal function improved, imaging was performed. Computed tomography showed a large hypervascular neoplastic mass at the tail of the pancreas measuring 45 × 55 mm and multiple hypervascular lesions in both lobes of the liver in keeping with metastases (Fig. 1). Fine needle aspiration of the pancreatic lesions for cytology was performed using endoscopic ultrasound (the liver lesions were considered too vascular for safe biopsy). Microscopic analysis revealed atypical cells in cohesive diffuse sheets but also in groups with some rosette-like formations, consistent with a pNET. The tumor was positive for CD56 (a phenotypic marker of natural killer cells), chromogranin, and synaptophysin. The cellular proliferative index (Ki-67) was 7%, consistent with a grade II neuroendocrine tumor (NET). The patient was discharged from hospital pending a medical oncology referral and community monitoring of the calcium levels. Because of family ties, she returned to her native country of New Zealand several days after discharge. She was referred to local oncology services where she commenced monthly injections of subcutaneous octreotide. Before treatment, her chromogranin A and 24-hour urinary 5-hydroxyindoleacetic acid levels were 119 μg/L (mildly increased) and 6.7 mg (normal), respectively. Her case was referred to the National Neuroendocrine Tumor forum to consider peptide receptor radionuclide therapy (PRRT). The recommendation was to continue octreotide and consider PRRT if there was evidence of further disease progression on interval imaging.

She tolerated octreotide well, and after 2 months of treatment, the chromogranin A level was stable (122 μg/L). However, 4 months later, the patient was admitted to hospital with symptoms of nausea and worsening lethargy. The serum calcium and potassium levels upon admission were >20 mg/dL and 3.3 mEq/L, respectively. Electrocardiography again showed J[12] and U waves (Fig. 2). The patient was treated with intravenous rehydration, zoledronate, and calcitonin. She remained in hospital for 5 days until the serum levels normalized. An interval staging computed tomography showed an increase in the size of the pNET and liver metastases, and the chromogranin A level increased to 230 μg/L. No bone metastases were identified. DOTATATE positron emission tomography was planned. Her dose of long-acting octreotide was increased from 30 mg monthly to 60 mg monthly. The patient was hospitalized once again a month later, this time presenting with increasing drowsiness. She had been rapidly declining at home with deteriorating oral intake. The calcium level once again increased at >20 mg/dL. On examination, a Glasgow Coma Scale score of 14 was noted. Despite aggressive therapy, the serum calcium level did not respond. After discussions with family, the decision was made not to continue with active treatment and commence palliative care. The patient passed away the following day.

Highlights

- Hypercalcemia due to secretion of PTHrP is rarely associated with pancreatic neuroendocrine tumors
- High serum calcium levels may be refractory to standard medical treatment
- Denosumab, a monoclonal antibody to a receptor activator of nuclear factor kappa beta ligand, can be effective

Clinical Relevance

This case report is of clinical relevance as an example of the presentation and treatment of severe hypercalcemia. It highlights the different pathologic mechanisms of hypercalcemia associated with malignancy. The challenges presented in managing such a case and various treatment approaches are described. Novel options for treatment are also mentioned.

Discussion

Hypercalcemia in patients with pNETs is rare.[10,11] Here, we report a case of a pNET associated with increased PTHrP levels, resulting in symptomatic hypercalcemia. Her electrocardiography showed the characteristic J waves (also known as Osborne waves) seen in hypothermia and severe hypercalcemia. It also showed U waves associated with the coexistent hypokalemia. The mechanism for this is that the hypercalcemia leads to deactivation of the chloride-sodium-potassium cotransporter in the ascending limb of the loop of Henle. In turn, this causes urinary losses of sodium, potassium, magnesium, and calcium. Hypovolemia results from an inability to concentrate urine.[13] To our knowledge, this is the first case in New Zealand described in the literature. The largest case series described involves 6 cases of gastroenteropancreatic NETs,[8] of which 4 were pNETs (1 of which was a pNET associated with multiple endocrine neoplasia type 1). In each of these cases, liver metastases were present; however, all except 1 involved low-grade tumors, and it was noted that hypercalcemia was not present until months to years after diagnosis. It seemed that the levels of PTHrP increased over time with progression of the pNET until the magnitude was sufficient to cause hypercalcemia. All cases were treated with standard intravenous fluids and bisphosphonates; however, hypercalcemia tended to be refractory, and cytoreduction of the tumor was necessary to lower the calcium levels. Treatment of the disease with somatostatin analogs (SSAs) and chemoembolization of the liver metastases resulted in improvement in

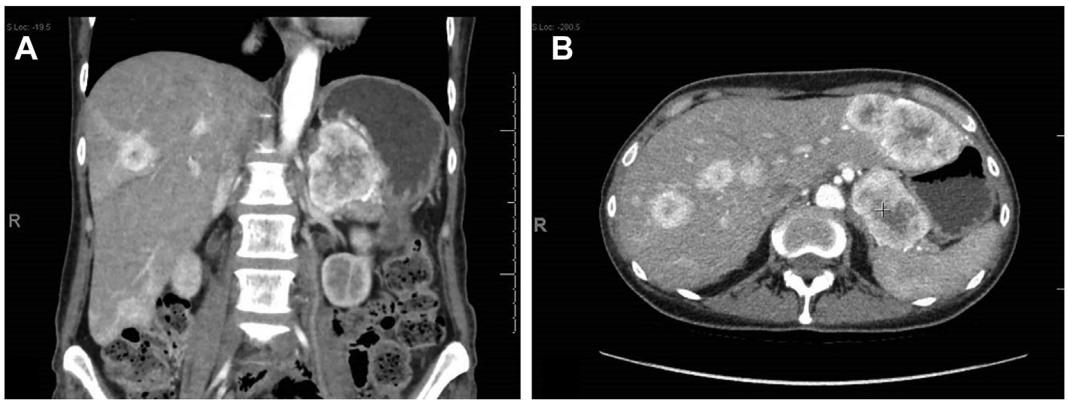

Fig. 1. Computed tomography with contrast demonstrating the pancreatic neuroendocrine tumor in the tail of the pancreas and numerous liver metastases. *A*, Coronal section. *B*, Axial section. These images were taken 6 months after diagnosis.

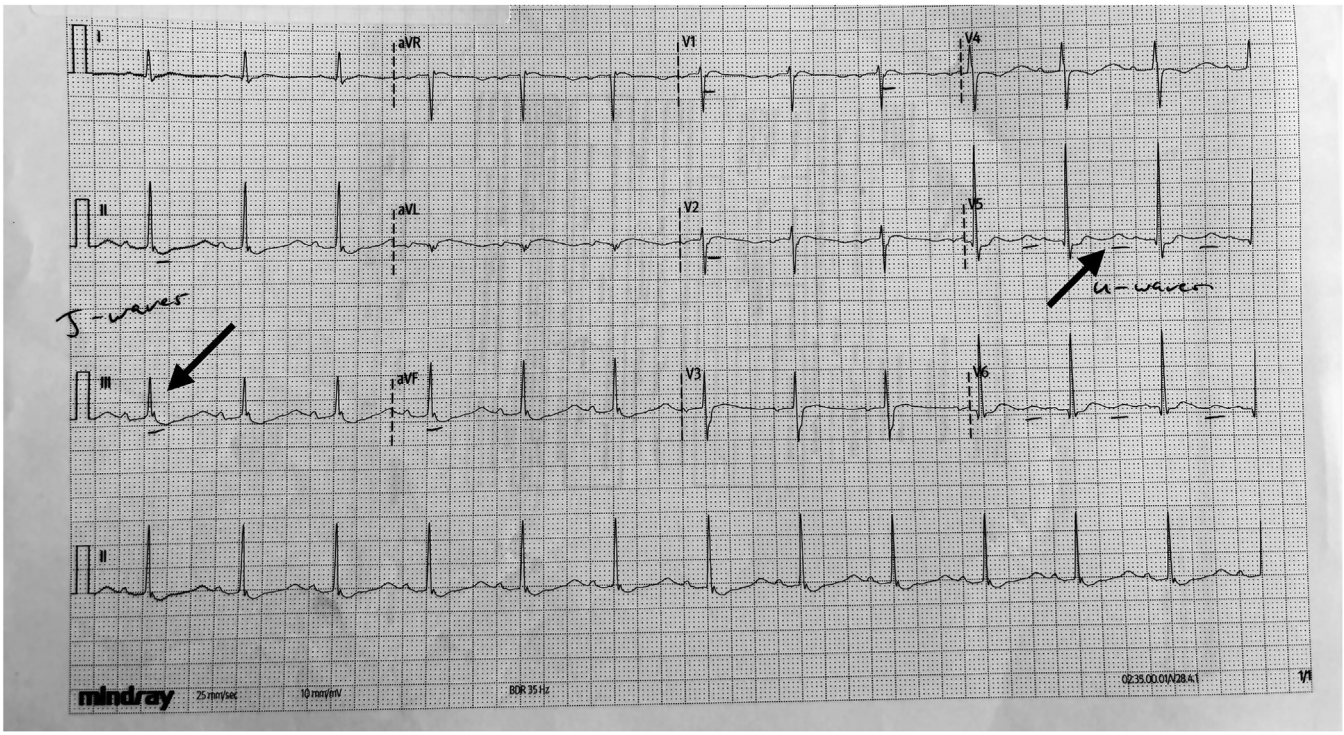

Fig. 2. Electrocardiography showing J (Osborne) and U waves associated with hypercalcemia and hypokalemia respectively. I, II, III, AVL, AVF, AVR, V1, V2, V3, V4, V5, and V6 are the names of the individual leads used in a 12 - lead electrocardiogram. They provide electrical impulse data from different anatomical sites on the heart.

the hypercalcemia in 2 of 3 cases, PRRT was successful in just 1 case, and chemotherapy was effective in controlling it in at least the short term in 2 of 3 cases. Another case report described a pNET with liver metastases associated with PTHrP secretion and severe hypercalcemia.[14] Surgical resection was declined. Hypercalcemia was first detected 4 years after diagnosis. Chemotherapy and SSA therapy did not control the hypercalcemia, nor did PRRT or systemic chemotherapy with conventional medical treatment for transarterial chemoembolization of the hepatic artery lead to an effective lowering of the hypercalcemia. Interestingly, this case went on to have brown tumors of the bone associated with the PTHrP but, at the time of the publication, had survived 6 years after the detection of hypercalcemia. PTHrP is produced in many tissues, and it has a wide range of actions and functions in an endocrine, paracrine, and intracrine manner. It is physiologically important in the fetus where it regulates calcium homeostasis mainly via production from the placenta. Many of its actions are paracrine in nature, playing a role in skeletal, tooth, skin, and hair development. It is also expressed in smooth muscle and involved in blood vessel, intestine, and bladder relaxation. It acts on the shared PTH/PTHrP receptor and exerts endocrine effects by increasing osteoclast activity and calcium resorption from bone and calcium reabsorption from the distal tubules in the kidneys. Denosumab, a monoclonal antibody to a receptor activator of nuclear factor kappa beta ligand, is an established treatment for osteoporosis and has been shown to be useful in the management of humoral hypercalcemia of malignancy. This monoclonal antibody lowers the serum calcium level by inhibiting osteoclast activity and is generally reserved for severe or refractory cases.[15-17] In New Zealand, it is available but publically funded in selected cases only. It has been used, to our knowledge, in

similar cases to ours and has successfully controlled severe hypercalcemia; however, frequent dosing (every 4-8 weeks) has been necessary (personal communication from E.O'Sullivan).

Treatment of neuroendocrine neoplasms is stratified according to origin, stage, and grade.[18] The goals are to control symptom and/or slow progression. Liver metastases can be resected or ablated via transarterial chemoembolization or radiofrequency ablation. In a grade II NET, systemic chemotherapy (streptozotocin/5-fluorouracil or capecitabine combined with temozolamide) can be used with unresected disease in patients whose cancers have progressed on SSAs for symptom control and an antiproliferative agent. Interferon alfa is seldom used as an adjuvant to SSAs for symptom control. Everolimus (a mammalian target of rapamycin inhibitor) and sunitinib (a tyrosine kinase inhibitor), although unfunded in New Zealand, have shown modest efficacy as targeted therapy to slow disease progression but with side effects and toxicity. Despite the available treatments, case reports indicate that hypercalcemia in this setting may be difficult to treat effectively.[19]

Conclusion

As with other malignancies, the primary method of maintaining the serum calcium level within the normal range is to treat the primary tumor.[17] However, in the acute setting, it may require several agents including denosumab to lower the calcium levels. Although rarely implicated, the PTHrP levels should be measured in patients with pNETs who present with increased calcium levels. In situations where the PTHrP level increases, clinicians should be aware of the possibility of refractory hypercalcemia requiring aggressive treatment with multiple agents to control it.[8]

Disclosure

The authors have no conflicts of interest to disclose.

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