Humoral hypercalcemia of malignancy presenting after oncologic surgery

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CASE PRESENTATION

A 59-year-old Caucasian woman presented to our hospital for biopsy of a rectal mass and diverting colostomy. Four months earlier, she had developed rectal pain and bleeding. Colonoscopy had revealed a large rectal mass; pathology was consistent with a neuroendocrine carcinoma. A labeled octreotide scan was positive in the area of the tumor and the para-aortic lymph nodes, but did not show hepatic or bony involvement.

Laboratory values, obtained 3 days before surgery, are shown (Table 1).

The patient had a history of mild asthma. She denied any prior personal or family history of malignancy, nephrolithiasis, parathyroid or other endocrine disease. Her listed medications included sustained release oxycodone 20 mg b.i.d., ibuprofen 400 mg t.i.d. p.r.n., montelukast 10 mg p.r.n., and zolpidem 10 mg p.r.n.

Exploration of the abdomen revealed a large mass and enlarged lymph nodes along the iliac vessels. Diverting sigmoid colostomy and repeat biopsy were performed without complications. Pathology was consistent with a large cell neuroendocrine carcinoma with ulceration and focal infiltration.

The patient did well in the perioperative period, requiring no blood products and remaining hemodynamically stable on maintenance intravenous (i.v.) fluids 0.45% saline at 100 ml/h. She tolerated advancement of her diet within 24 h and required no nasogastric suctioning. However, 2 days after her surgical procedures, laboratory values were notable for a plasma calcium of 12.5 mg/dl and an elevated venous CO_2 of 31 meq/l consistent with a mild metabolic alkalosis. The plasma phosphate was low. Over the next week, these metabolic abnormalities became more exaggerated, prompting the involvement of the renal consult service (Table 2).

On specific questioning, the patient admitted to recent and regular use of calcium carbonate antacids before her hospitalization to treat symptoms of acid reflux. She had self-administered 1500 mg calcium carbonate antacid on the day of her surgery but denied ongoing intake since that one dose. In addition to maintenance fluids, her only medications were cefazolin 1 g i.v. every 8 h for three total doses, metronidazole 500 mg i.v. every 8 h for three total doses, i.v. morphine sulfate 2 mg every 4 h as needed, and ondansetron 2 mg i.v. every 6 h as needed. Metoprolol per OS 25 mg twice a day had been started on post-operative day (POD) 3 for elevated blood pressure.

Examination revealed a thin, fatigued-appearing Caucasian woman with a flat affect. Vital signs were temperature 98.2 F, blood pressure 151/87 mm Hg, pulse 67 bpm, respiratory rate 18 bpm with room air oxygen saturation of 98%. Mucous membranes were moist. Neck exam revealed a normal-sized thyroid gland and no neck masses. Jugular venous pressure was estimated at 6 cm H_2O. Lungs were clear to auscultation. Heart sounds were regular with a II/VI systolic ejection murmur. The abdomen was soft with active bowel sounds. The colostomy looked healthy. There were no rashes, joint tenderness, or edema. There were no focal neurological findings and the patient was alert and oriented.

Initial differential diagnosis of the hypercalcemia and metabolic alkalosis included milk-alkali syndrome from ongoing (surreptitious) antacid ingestion, humoral hypercalcemia of malignancy (HHM) due to parathyroid hormone-related peptide (PTHrP), osteolytic hypercalcemia due to unrecognized bone metastases or primary hyperparathyroidism, either isolated or within the syndrome of multiple endocrine neoplasia 1. She was felt to have mild intravascular volume contraction in the setting of hypercalcemia with exacerbation of her alkalosis.

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Table 1 | Laboratory values 3 days before surgery

	BWH unit	SI unit	Normal range	SI normal range
Na	135 mmol/l	135 mmol/l	136–142 mmol/l	136–142 mmol/l
K	3.5 mmol/l	3.5 mmol/l	3.5–5.0 mmol/l	3.5–5.0 mmol/l
Cl	99 mmol/l	99 mmol/l	98–108 mmol/l	98–108 mmol/l
CO_2	27 meq/l	27 mmol/l	23–32 mmol/l	23–32 mmol/l
BUN	9 mg/dl	3.2 mmol/l	9–25 mg/dl	3.2–8.9 mmol/l urea
Cr	0.5 mg/dl	44 μmol/l	0.7–1.3 mg/dl	50–110 μmol/l
Glucose	87 mg/dl	4.8 mmol/l	54–118 mg/dl	3.0–6.6 mmol/l
Albumin	3.7 g/dl	37 g/l	3.7–5.4 g/dl	40–60 g/l
Calcium	10.3 mg/dl	2.57 mmol/l	8.8–10.5 mg/dl	2.20–2.58 mmol/l
Alkaline phosphatase	75 U/l	75 U/l	36–118 U/l	36–118 U/l

BUN, blood urea nitrogen.

Table 2 | Postoperative development of hypercalcemia and metabolic alkalosis

	POD0	POD1	POD3	POD4	POD5	POD6	POD7
CO_2 BWH (23–32 meq/l) SI (23–32 mmol/l)	30	31	31	32	30	32	33
Calcium BWH (8.8–10.5 mg/dl) SI (2.20–2.58 mmol/l)	11.4	10.8		12.5	12.3	13.5	14.9
Ionized calcium BWH/SI (1.13–1.32 mmol/l)				1.74		1.81	1.82
PO_4 BWH (2.4–5.0 mg/dl) SI (0.77–1.61 mmol/l)							2.1

POD, post-operative day.

Table 3 | Laboratory values after initiation of high-rate saline intravenous fluids

	POD8	POD9	POD10	POD11	POD12	POD13
CO_2 BWH (23–32 meq/l) SI (23–32 mmol/l)	26	30	32	32	29	28
Creatinine BWH (0.7–1.3 mg/dl) SI (50–110 μmol/l)	0.6	0.6	0.6	0.7	0.6	0.6
Calcium BWH (8.8–10.5 mg/dl) SI (2.20–2.58 mmol/l)	12.3	12.7	11.8	12.0	10.1	10.1
Ionized calcium BWH/SI (1.13–1.32 mmol/l)	1.71	1.53		1.49	1.38	
PO_4 BWH (2.4–5.0 mg/dl) SI (0.77–1.61 mmol/l)			$<$assay	1.1	1.2	1.4

POD, post-operative day.

She was advised against any further intake of antacids. Intravenous fluids were changed on POD 8 to 0.9% normal saline at 250 ml/hr. Her urine output increased to more than 5 l/day. Despite this aggressive fluid resuscitation, her plasma calcium and venous CO_2 remained elevated. On POD10, the rate of i.v. fluids was increased to 350 ml/h. On POD11, she was noted to have developed worsening hypertension and mild peripheral edema. Furosemide i.v. 10 mg boluses were added with mild improvement in her metabolic profile (Table 3). Amlodipine per OS 5 mg twice a day was added to treat the persistent systolic and diastolic hypertension. On POD 13, additional test results returned (Tables 4 and 5).

DIAGNOSIS

(1) Rectal large cell neuroendocrine carcinoma.
(2) HHM with metabolic alkalosis, induced by surgical manipulation of the tumor.

CLINICAL FOLLOW-UP

The patient received treatment with one dose of pamidronate 60 mg i.v. and had her i.v. fluids slowly tapered as plasma calcium improved. She was discharged on POD 15 with plasma calcium 8.6 mg/dl and phosphate 1.4 mg/dl. Since discharge, she has not returned to our hospital. No further follow-up on her care is available.

DISCUSSION

Humoral hypercalcemia of malignancy

Hypercalcemia has been reported to occur in up to 20–30% of patients with a malignancy at some time during the course of their disease.[1] A previous review of hypercalcemia associated with malignancy found its detection to signify a very poor prognosis, with approximately 50% of patients dying within 30 days.[2]

HHM accounts for approximately 80% of the hypercalcemia cases caused by malignancy.[3] The majority of the other 20% cases are owing to local osteolytic liberation of calcium (e.g., in multiple myeloma) and, much more rarely, 1,25 OH vitamin D production by lymphomas or ectopic PTH secretion.[4] HHM has been reported with a wide range of tumor cell types, most often with squamous cell, breast, and renal carcinomas.

Humoral hypercalcemia is a rare complication of tumors of the gastrointestinal tract.[5] Sakata's[6] recent report of a case of HHM from a poorly differentiated colonic adenocarcinoma noted 20 prior cases of HHM associated with colonic

Table 4 | Endocrine test results

	BWH unit	SI unit	BWH normal range	SI normal range
PTH	5.0 pg/ml	0.55 pmol/l	10–65 pg/ml	1.1–7.2 pmol/l
25-Vitamin D	7 ng/ml	17 nmol/l	20–57 ng/ml	50–142 nmol/l
TSH	0.969 mIU/l	0.969 mIU/l	0.5–5.0 mIU/l	0.5–5.0 mIU/l
T4	9.9 μg/dl	127 nmol/l	5–11 μg/dl	64–152 nmol/l
PTHrP	6.4 pmol/l	6.4 pmol/l	0.0–1.5 pmol/l	00–1.5 pmol/l

PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TSH, thyroid-stimulating hormone.

Table 5 | Conversion of BWH to SI units

	BWH normal range	SI conversion	SI normal range
Na	136–142 mmol/l	1.0	136–142 mmol/l
K	3.5–5.0 mmol/l	1.0	3.5–5.0 mmol/l
Cl	98–108 meq/l	1.0	98–108 mmol/l
CO_2	23–32 mmol/l	1.0	23–32 mmol/l
BUN	9–25 mg/dl	0.357	3.2–8.9 mmol/l urea
Creatinine	0.7–1.3 mg/dl	88.4	50–110 μmol/l
Glucose	54–118 mg/dl	0.05551	3.0–6.55 mmol/l
Albumin	3.7–5.4 g/dl	10	40–60 g/l
Calcium	8.8–10.5 mg/dl	0.2495	2.20–2.58 mmol/l
Ionized calcium	1.13–1.32 mmol/l	1.0	1.13–1.32 mmol/l
Phosphate	2.4–5.0 mg/dl	0.3229	0.77–1.6145 mmol/l
Alkaline phosphatase	36–118 U/l	1.0	36–118 U/l
25-Vitamin D	20–57 ng/ml	2.496	50–142 nmol/l
PTH	10–65 pg/ml	0.11	1.1–7.15 pmol/l
PTHrP (ARUP)	0.0–1.5 pmol/l	1.0	0.0–1.5 pmol/l
TSH	0.5–5.0 mIU/l	1.0	0.5–5.0 mIU/l
T4	5–11 μg/dl	12.87	64–152 nmol/l

BUN, blood urea nitrogen; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; TSH, thyroid-stimulating hormone.

malignancy. Fujita[7] subsequently reported on a case of HHM associated with an adenosquamous carcinoma of the sigmoid colon, raising the number of previously reported cases in the English literature to 22.

Gastrointestinal neuroendocrine tumors are relatively uncommon tumors arising from the widely scattered enterochromaffin cells. These tumors, along with similar tumors originating from the lungs and thymus, have traditionally been defined as 'carcinoid tumors'. The majority are slow-growing (well-differentiated neuroendocrine tumors) and retain the ability to produce and secrete biologically active amines. The tumors may present with stereotypical clinical syndromes due to biological activity of these amine products.[8–10] Rarely, they may show aggressive behavior and become highly malignant (poorly differentiated neuroendocrine tumors or neuroendocrine carcinoma). Hypercalcemia is a rare complication of these tumors. A previous case report of hypercalcemia due to PTHrP secretion by a hepatic carcinoid found only 10 other cases of hypercalcemia associated with carcinoid tumors reported between 1966 and 1994.[11] Four additional cases of HHM due to PTHrP secretion by a carcinoid tumor or neuroendocrine carcinoma have been reported since this review, involving tumors of the stomach, bronchus, thymus, and pancreas.[12–15] In general, tumors that present with HHM are advanced and apparent, although this may not be the case with neuroendocrine tumors.[16]

Parathyroid hormone related peptide

PTHrP was recognized in the late 1980s as the primary mediator of HHM.[17–19] The peptide has since been found to have protean cellular expression, acting in a variety of endocrine, paracrine, and autocrine systems both in embryologic development and adult physiology (Table 6).[20] PTHrP is a 139–173 amino acid protein with N-terminal homology to parathyroid hormone (PTH). Of the first 13 amino acids, eight are identical to PTH. This homology is responsible for the activation of a common G protein-coupled receptor, the PTH/PTHrP or PTH1 receptor.[21] Beyond this region, the amino acid sequences of PTH and PTHrP have little in common. Diagnosis of PTHrP-mediated hypercalcemia is confirmed by assay measurement of the protein. The assay used in the diagnosis of this case was an immunoradiometric assay that identifies the first 86 amino acid sequence of PTHrP. The assay does not crossreact with any fragments of human PTH and has a detection threshold of 0.3 pmol/l[22] (ARUP Laboratories, Salt Lake City, Utah)

PTHrP produces hypercalcemia through its combined effects on bone and kidney. In bone (similar to PTH), the peptide stimulates osteoblasts to increase their expression of receptor activator of nuclear factor kappa B ligand, which, through binding to receptor activator of nuclear factor kappa receptors on osteoclasts, upregulates osteoclastogenesis and osteoclast activity.[23] PTHrP-induced bone resorption dramatically increases the pool of free calcium. Both PTHrP and

Table 6 | Normal PTHrP physiology

Tissue	Expression	Action
Cartilage	Embryo	Chondrocyte proliferation, endochondral bone formation
Mammary gland	Embryo	Development of epithelial rudiment and branching structure
	Adult	May regulate maternal calcium homeostasis
Tooth	Embryo	Osteoclast resorption of alveolar bone for tooth eruption
Skin	Adult	Basal keratinocyte proliferation, antagonist of differentiation and apoptosis
Hair	Adult	Antagonist of anagen phase of hair growth
Central nervous system	Adult	Protection of cerebellar granular cells against glutamate-triggered calcium neurotoxicity
Placenta	Adult	Regulation of placental–fetal calcium gradient

PTHrP, parathyroid hormone-related peptide.

PTH act upon the kidney through their common PTH1 receptor, producing similar effects on calcium and phosphate handling. The patient described here had hypercalcemia *and* hypophosphatemia, as is commonly seen in primary hyperparathyroidism. The peptides' other actions, however, are not identical. Experimental infusion with the homologous N-terminal peptide fragments of PTHrP and PTH produces similar increases in calcium reabsorption, cyclic AMP excretion, and phosphaturia.[24,25] However, infusion with whole PTHrP leads to a drop in urinary bicarbonate excretion rather than the increase in urinary bicarbonate produced by PTH.[26] This conservation of bicarbonate may explain the metabolic alkalosis associated with PTHrP-induced hypercalcemia. In contrast to this, primary hyperparathyroidism is associated with a hyperchloremic metabolic acidosis.

Management of humoral hypercalcemia of malignancy

Acute management of PTHrP-mediated hypercalcemia (as with all types of hypercalcemia) includes aggressive volume resuscitation followed by measures to increase calcium excretion and decrease its further liberation from bone.[4] Most patients with HHM are dehydrated and have a lowered glomerular filtration rate due to a combination of poor PO intake of fluids and renal water wasting (hypercalcemia induces a reversible nephrogenic diabetes insipidus). Thus, unless there is an obvious contraindication such as heart failure or severe renal failure, high volumes of normal saline should be prescribed, for example 200–500 ml/h. Volume expansion increases glomerular filtration rate, leading to more filtration of calcium. Furthermore, normal saline has a calciuretic effect. The patient's volume status and urine output should be frequently assessed on such fluid therapy. Only after the patient is well volume expanded, should loop diuretics be prescribed. Loop diuretics further increase renal calcium excretion but have the potential to exacerbate volume depletion and cause electrolyte abnormalities such as hypokalemia.

Bisphosphonates block osteoclast action on bone and are the mainstay of treatment for hypercalcemia associated with malignancy. Indications for bisphosphonate treatment in HHM include symptomatic hypercalcemia and plasma calcium >12 mg/dl (3 mmol/l).[4] Pamidronate and zolendronate are the most commonly used bisphosphonates in the USA; additional agents such as clodronate are available elsewhere. These drugs must be given i.v. but are generally well tolerated. Importantly, the plasma calcium does not start to fall until about 48 h after their administration. Hence, therapy with bisphosphonates should be started early and interim therapies such as aggressive resuscitation with normal saline should be pursued. There are two difficulties with the use of bisphosphonates in renal failure: firstly, bisphosphonates are renally excreted, so lower dosing is required; secondly, bisphosphonates can exacerbate renal failure.[27–29] Practical measures we use in our center include dose adjustment as per the manufacturers' guidelines, administration at half the normal infusion rate and concomitant administration of normal saline. In our (unpublished) experience, exacerbation of renal failure is rare. It is important to note that bisphosponates are the most effective drugs at controlling hypercalcemia; therefore, they will in many cases ultimately improve acute renal failure.

Calcitonin is still occasionally used in the initial treatment of HHM (it works within hours) but its calcium-lowering effects are limited. Octreotide has been used with variable success in treating HHM associated with neuroendocrine tumors.[11,13] A monoclonal antibody to PTHrP has been successful in treating hypercalcemia in HHM animal models, but results in humans have not been published.[30] Finally, the occasional cancer patient with hypercalcemia may require hemodialysis against a low calcium concentration dialysate. Hemodialysis is reserved for patients who have severe hypercalcemia and presumed irreversible renal failure (as opposed to the mild–moderate prerenal failure described above) and poor tolerance of i.v. normal saline.

Hypophosphatemia is commonly associated with HHM, as described in our case. Causes include the phosphaturic effect of PTHrP, poor food intake, and loop diuretics. Intravenous phosphate should not be prescribed in this setting because it can induce severe hypocalcemia, acute renal failure, and seizures.[31] Low dose per OS phosphate is appropriate but the plasma calcium and the plasma calcium $\times$ phosphate product should be closely monitored.

The ultimate therapy of HHM is that which specifically treats the cancer. Gastrointestinal neuroendocrine carcinomas may be cured if surgical resection is possible. As mentioned above, octreotide and octreotide analogs have been used with some success in controlling the growth of

neuroendocrine carcinomas.[11,13] Palliative radiation and chemotherapy with cisplatin and etoposide may reduce symptoms and prolong survival of patients with poorly differentiated neuroendocrine malignancies such as our case.[32–34]

Finally, it should be noted that not all cases of hypercalcemia in cancer patients will be associated with the malignancy. Evaluation of hypercalcemia in these patients should carefully consider not only HHM but also causes such as previously undiagnosed primary hyperparathyroidism, hyperthyroidism, or granulomatous disease, impaired calciuresis due to thiazide diuretics, and surreptitious intake of calcium-containing antacids or vitamin D.[4]

SUMMARY

We report a case of hypercalcemia of malignancy due to PTHrP that manifested after surgical manipulation of a rectal neuroendocrine carcinoma. Clinical presentation was remarkable for hypercalcemia and metabolic alkalosis, resistant to aggressive volume resuscitation. Initial differential diagnosis included the milk–alkali syndrome and hyperparathyroidism, either primary or related to MEN1, with volume contraction. These diagnoses were subsequently excluded and the patient's PTHrP level returned to more than four times the upper range of normal values. Despite volume expansion and measures to increase calciuresis, the hypercalcemia and alkalosis in our case resolved only after i.v. bisphosphonate treatment. Our case illustrates that hypercalcemia associated with metabolic alkalosis is not always due to the milk–alkali syndrome; HHM should also be considered in the differential diagnosis, particularly in patients with known neoplasia.

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