Parathyroid Hormone-Related Peptide (PTHrP) Secretion by Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Clinical Features, Diagnosis, Management, and Follow-Up

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Context: Only a small number of case reports has been published on patients with PTHrP-hypersecreting metastatic gastroenteropancreatic (GEP) neuroendocrine tumors (NETs).

Objective: The objective of this study was to evaluate the clinical, biochemical, and radiological features, management, and treatment outcome of patients with PTHrP-hypersecreting GEP-NETs.

Design: Retrospective case series.

Setting: Tertiary referral hospital.

Main Outcome Measures: Clinical, biochemical, and radiological features were measured, as well as response to therapy and survival.

Patients: Ten patients with PTHrP-secreting GEP-NETs (nine pancreatic and one unknown primary) with a median age of 50.4 years (range, 38.3–61.1) were studied. Multiple endocrine neoplasia type 1 patients were excluded.

Results: The median follow-up was 57.2 months (range, 11.6–204.5 mo). Median overall survival was 86.0 months. In total, 51 different treatment interventions and combinations were applied. In seven of the 10 patients, somatostatin analog (SSA) treatment resulted in a temporary normalization of serum calcium levels with a long-term response observed in two patients (up to 35.2 mo). Peptide receptor radiotherapy (PRRT) with radiolabeled SSAs induced long-term responses ranging from 9.0–49.0 months in four of six patients treated with PRRT.

Conclusions: Hypersecretion of PTHrP by metastatic GEP-NETs is very rare and seems to be exclusively associated with metastatic pancreatic NETs. PTHrP production has major clinical impact because poorly controllable hypercalcemia is associated with increased morbidity and mortality. The most successful treatment options for PTHrP-producing GEP-NETs are SSAs and PRRT using radiolabeled SSAs. Isotonic saline and bisphosphonates can be considered as supportive therapies. **(*J Clin Endocrinol Metab* 99: 3060–3069, 2014)**

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Abbreviations: CgA, chromogranin-A; GEP, gastroenteropancreatic; HHM, humoral hypercalcemia of malignancy; LAR, long-acting repeatable; MEN-1, multiple endocrine neoplasia type 1; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; NSE, neuron-specific enolase; $1,25(OH)_2D$, 1,25 dihydroxyvitamin D_3; 25(OH)D, 25-hydroxyvitamin D_3; PRRT, peptide receptor radiotherapy; RANK, receptor activator of nuclear factor κB; SD, stable disease; SSA, somatostatin analog; sst_2, somatostatin receptor subtype 2; t.i.d., three times a day; WHO, World Health Organization.

Hypercalcemia is a well-known paraneoplastic manifestation in patients with metastatic malignancies (1). Two types of hypercalcemia can be distinguished in patients with metastatic gastroenteropancreatic (GEP) and thoracic neuroendocrine tumors (NETs): local osteolytic hypercalcemia, and humoral hypercalcemia of malignancy (HHM) (2–5).

The first is the result of increased bone resorption by osteoclasts mediated by (metastatic) tumor cells, which are in direct contact with bone. The second is associated with the hypersecretion of PTH or PTHrP into the circulation by tumor cells (2–5). Increased extrarenal conversion of 25-hydroxyvitamin D_3 (calcifediol, calcidiol, 25-hydroxycholecalciferol [25(OH)D]) to 1,25 dihydroxyvitamin D_3 (calcitriol, 1,25-dihydroxycholecalciferol [$1,25(OH)_2D$]), as a result of increased activity of the enzyme 25(OH)D-1α-hydroxylase, generally does not occur in GEP-NETs (5).

Bone resorption by osteoclasts may be stimulated by PTH, PTHrP, and $1,25(OH)_2D$ and can subsequently cause hypercalcemia. A number of cytokines (such as IL-1α, IL-1β, IL-6, TNF, lymphotoxin, and TGF-α) also stimulate octeoclastic bone resorption either alone or in combination with PTHrP. Some of these cytokines have been linked to HHM. Besides stimulating osteoclast-mediated bone resorption, both PTH and PTHrP increase the reabsorption of calcium from the distal tubule, thus interfering with the ability of the kidneys to clear the filtered calcium load. Furthermore, PTH and PTHrP also increase $1,25(OH)_2D$ synthesis, which further contributes to a hypercalcemic state (5).

PTH and PTHrP show amino acid sequence homology at the amino terminus, where eight of the first 13 amino acids are identical. The consequent activation of the shared PTH/PTHrP receptor explains the ability of PTHrP to resemble PTH as an inducer of bone resorption, renal phosphate wasting, and hypercalcemia (6, 7).

There is reasonable doubt about whether PTHrP has an important role in the daily maintenance of calcium homeostasis. Under physiological conditions, circulating levels of PTHrP are considerably lower than PTH levels. Nevertheless, PTHrP is essential for the development of adult tissues and has a number of physiological functions. PTHrP is widely expressed in mesenchymal tissues—including cartilage, many epithelial tissues, skeletal and heart muscle, distal renal tubules, hair follicles, brain, and placenta (6, 7).

PTHrP hypersecretion may be associated with highly malignant tumors (such as squamous cell carcinomas, breast carcinomas, renal cortical carcinomas, and the adult T-cell leukemia syndrome) but also with a variety of less aggressive NETs (6–8).

In patients with primary pancreatic, lung, or thymus NETs presenting with hypercalcemia in combination with elevated circulating PTH levels, primary hyperparathyroidism as part of multiple endocrine neoplasia type 1 (MEN-1) syndrome should be considered (9).

Only a few case reports of non-MEN-1 patients with metastatic GEP-NETs presenting with hypercalcemia as a result of PTHrP hypersecretion have been described in the literature. These show that investigational protocols, treatment management, and management of unusual complications vary considerably between patients and institutions (9–15).

We have, therefore, analyzed in a tertiary referral center the clinical, biochemical, and radiological features in all metastatic GEP-NET patients with PTHrP hypersecretion who presented with symptoms and signs of HHM.

Patients and Methods

Patients

We studied the medical records of 10 patients with PTHrP-hypersecreting GEP-NETs who were treated between 1986 and 2013 in the Erasmus University Medical Center (Erasmus MC), Rotterdam, The Netherlands. Patients diagnosed with the MEN-1 syndrome were excluded.

All GEP-NET patients treated in the Erasmus MC, Rotterdam (as described in the present manuscript), gave written informed consent before inclusion in the studies, which were approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam.

Analysis of clinical and pathological data, laboratory parameters, and imaging findings was performed, and information on surgical and nonsurgical treatments was collected.

During this study, the PTH assay had changed over time (see *Assays* below). Also, new treatment options were introduced, such as the clinical availability of different radiolabeled somatostatin analogs (SSAs) and the introduction of denosumab. The development and clinical introduction of multireceptor subtype-specific SSAs, like pasireotide, has potentially improved efficacy of SSA treatment in GEP-NET patients (16–18).

Diagnosis of GEP-NET

Diagnosis of GEP-NET was made on the basis of serological markers (chromogranin-A [CgA]; neuron-specific enolase [NSE]), pathological elevations of circulating, hypersecreted neuroendocrine hormones or peptides (19), and imaging according to international protocols and standards (20, 21) in combination with histological confirmation according to current guidelines (22, 23).

Diagnosis of PTHrP hypersecretion

The diagnosis of PTHrP-hypersecreting NETs was based on persistent hypercalcemia and (almost) completely suppressed plasma PTH levels in combination with elevated plasma PTHrP levels. Patients with low but detectable PTH levels, absent data on PTHrP levels, and bone metastases were excluded from the analysis. Patients taking pharmacological doses of 25(OH)D or $1,25(OH)_2D$ at baseline were excluded as well.

Table 1. Patient Demographics and Biochemical Results in 10 Patients With PTHrP-Hypersecreting NETs

Case No.	Age, y	Sex	Primary	Metastases	Tumor Grade	ENETS Stage	Presentation	Symptoms	Calcium, mmol/L[a]	PTHrP, pmol/L	25(OH)D, nmol/L	1,25(OH)$_2$D, pmol/L	CgA, μg/L	NSE, μg/L
1	41.1	M	Pancreas	L	ID	IV	Syn	A, N	2.99	2.6–6.0	118	87	ID	6.5
2	58.3	M	Pancreas	L, LN	1	IV	Meta	A, N, V, PA, O, Fa, D	3.64	2.9–5.2	77	104	19 445	222.2
3	40.0	F	Pancreas (VIP)	L, LN	ID	IV	Syn	A, N, V, Fa, P	3.33	2.3	40	133.9	63	20.5
4	52.9	M	Pancreas	L, B	3	IV	Syn	PD, PU, Fa, C	3.35	2.0–2.6	52	263.9	8486	15.2
5	61.1	M	Pancreas	L	1–2	IV	Syn	A, PU, Fa	2.89	5.4–16.3	60	150.7	377	12.1
6	60.8	M	Unknown	L	2	IV	Syn	A, N, V, PA, PD, PU, Fa, C	3.42	2.5	29	>220	ID	14.3
7	38.3	M	Pancreas	L	1	IV	Syn	A, N, V, PA	2.67	2.5	ID	ID	96	28.2
8	42.2	F	Pancreas	L, LN	ID	IV	Syn	A, PD, PU, Fa, MW, C	3.53	3.1	95	275.2	259	15.8
9	51.3	F	Pancreas	L	ID	IV	Syn	A, V, N	2.93	3.4	65	268.7	53	9.4
10	49.5	F	Pancreas	L, LN	1	IV	Meta	A, N, PA, PD, PU, Fa	3.57	1.8	24	299.5	49	7.3
Reference ranges									2.20–2.65	0.0–1.5	50–120	38–183	27–94	0.0–16.2

Abbreviations: L, liver; B, bone; LN, lymph nodes; Meta, metachronous; Syn, synchronous; ID, insufficient data; A, anorexia; D, dehydration; N, nausea; V, vomiting; PA, poor appetite; O, obstipation; PU, polyuria; PD, polydipsia; Fa, fatigue; MW, muscle weakness; C, cerebral symptoms; P, palpitations; VIP, vasoactive intestinal polypeptide. No patients showed symptoms or signs of dehydration, ileus, bone pain, and hypertension.

[a] Serum calcium values were corrected for albumin.

Assays

PTH and PTHrP were measured in all patients. Assays were performed in the endocrine laboratory of the Erasmus MC, Rotterdam, The Netherlands. PTHrP was measured in EDTA-plasma containing aprotinin using the PTHrP IRMA Kit (Mitsubishi Kagaku Iatron, Inc). After centrifugation, plasma was stored at −80°C until assayed. The Immulite 2000XPi (Siemens Diagnostics) was used until 2012, and afterward the Vitros ECIQ (Ortho Clinical Diagnostics) was used for measurements of plasma PTH levels. CgA and NSE assays were performed in the Department of Clinical Chemistry of the Erasmus MC. CgA in serum was measured using a solid-phase, two-site IRMA assay (Cisbio Bioassays). NSE in serum was measured using an electrochemiluminescence immunoassay on an immunoassay analyzer (Roche Diagnostics).

Disease progression and response to therapy

Disease progression and response to therapy of hypercalcemia were assessed using three parameters: 1) radiological documentation of progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (24); 2) progression of clinical symptoms (such as weight loss and symptoms related to hypercalcemia); and 3) worsening of relevant biochemical markers (for example, uncontrolled hypercalcemia, not responsive to treatment).

Statistical analysis

Overall survival was analyzed using Kaplan-Meier methods. Log-rank testing was used to determine whether there was a statistically significant difference between the mortality in the normocalcemic pancreatic NET patient group and the group of hypercalcemic GEP-NET patients with PTHrP hypersecretion. Calculations were performed using Statistical Package for Social Sciences software, version 21.0 (SPSS Inc).

Results

Between 1986 and 2013, after exclusion of MEN-1 patients, 895 new patients with GEP-NETs were seen in our center. This series included 295 patients with pancreatic NETs. Eighteen patients presented with, or developed, hypercalcemia.

Baseline data and presenting symptoms

Between 1986 and 2013, a total of 10 patients (six men and four women) were diagnosed with a PTHrP-hypersecreting GEP-NETs. The demographic and biochemical characteristics of these 10 patients are listed in Table 1. Patients had a median age of 50.4 years (range, 38.3–61.1 y) at diagnosis of the GEP-NETs. The median follow-up was 57.2 months (range, 11.6–204.5 mo).

Almost all patients (90%) had primary pancreatic PTHrP-hypersecreting NETs, and only one patient was diagnosed with a metastatic GEP-NET of unknown primary.

All patients had developed ENETS/NANETS stage IV disease (Table 1) (25, 26). Main tumor metastatic localizations were liver (100%), lymph nodes (40%), and bone (10%). Tumor grading was available in six of 10 GEP-NETs (60%): four GEP-NETs (40%) were classified as well-differentiated (grade 1), one GEP-NET (10%) was classified as moderately differentiated (grade 2), and one GEP neuroendocrine carcinoma (NEC) (10%) was classified as poorly differentiated (grade 3).

All patients had OctreoScan-positive lesions. Currently, three of the 10 patients are still alive and in active follow-up. The primary causes of death included disease progression with uncontrollable hypercalcemia (n = 4), cause of death unknown/referred to another hospital (n = 2), and septicemia probably caused by cholangitis (n = 1).

Interventions

Information regarding therapeutic interventions for PTHrP hypersecretion, treatment response, and duration is listed in Table 2.

Table 2. Therapeutic Interventions (n = 51) After Diagnosis of a PTHrP-Hypersecreting NET, Including Response and Duration of Response (n = 10)

TIs After Diagnosis of PTHrP Hypersecretion	No. of Patients	No. of TI	Calcium Response, n			Response Duration, mo	
			Normalization	Decrease	None	Normalization	Decrease
Total patients	10	51	27	16	8	0.1–49.0	0.03–1.5
NaCl 0.9%							
24-h	3	3		2	1		0.1–0.2
12-h (intervals)	1	1			1		
SSA							
Octreotide LAR 20 mg/4 wk[a]	1	1	1			35.2	
Octreotide IR	6	7	6	1		1.0–7.7	0.5
Bisphosphonates							
Single short iv infusion	2	4	1	2	1	2.3	0.2–0.4
Repetitive iv infusions	1	1	1			1.6	
Surgery (cytoreduction)							
Primary + metastases	1	1	1			28.2	
Embolization liver metastases	1	3	3			0.1–1.1	
Ethanol injections liver metastases	1	2	1		1	0.3	
PRRT							
^{177}Lu-octreotate (4 cycles)	2	2			2		
^{177}Lu-octreotate + Capecitabine (4 cycles)[b]	1	1	1			9.0	
^{90}Yt-octreotide (5 cycles)	1	1			1		
^{111}In-pentetreotide (4 cycles)	1	1	1			0.5	
Glucocorticoids	1	1		1			0.3
Sunitinib	1	1	1			5.2	
Denosumab	1	1		1			0.1
Combination therapies							
NaCl 0.9% + SSA IR	1	1		1			0.2
NaCl 0.9% + B iv	4	8	2	5	1	0.8–2.7	0.03–1.3
NaCl 0.9% + SSA IR + B iv	2	2	1	1		0.5	0.1
NaCl 0.9% + B oral + B iv repetitive	1	1	1			10.0	
SSA IR + B iv repetitive	1	1	1			1.2	
SSA LAR + B iv repetitive	1	1		1			1.5
SSA LAR + B iv + G	1	1	1				0.5
S + NaCl 0.9%	1	1	1			3.3	
D + NaCl 0.9% + SSA IR	1	1		1			1.5
PRRT ^{177}Lu-octreotate (4 cycles) + SSA IR	1	1	1			14.5	
PRRT ^{177}Lu-octreotate (6 cycles) + SSA LAR	2	2	2			33.3–49.0	

Abbreviations: TI, treatment intervention; IR, immediate release; B, bisphosphonate; G, glucocorticoid; S, sunitinib; D, denosumab.

[a] One patient switched from Octreotide LAR 20 mg/4 wk to Octreotide LAR 30 mg/2 wk.

[b] Capecitabine 1650 mg/m^2.

A total of 51 different therapeutic regimens, including combinations, were administered. Twenty-seven therapeutic interventions were able to normalize serum calcium levels at some stage. A decrease of serum calcium levels could be achieved with 16 therapeutic interventions, and with eight therapeutic interventions no serum calcium response was observed.

Short-term responses were obtained with iv isotonic saline (0.1–0.2 mo), bisphosphonates (0.2–2.3 mo), and embolization of liver metastases (0.1–1.1 mo).

Peptide receptor radiotherapy (PRRT) with radiolabeled SSAs had favorable effects on the hypercalcemia and plasma PTHrP levels with long-term responses ranging from 9.0 to 49.0 months in four of six patients. However, two of the six patients had worsening of hypercalcemia while still undergoing PRRT or directly after finalization of the PRRT. In seven of 10 patients, SSA treatment resulted in a temporary normalization of serum calcium levels (<7.7 mo). Two patients obtained a long-term response (up to 49 mo) with a combination of PRRT and SSA.

In the five patients who underwent PRRT with ^{177}Lu-octreotate, tumor stabilization (stable disease [SD]) ranged from 10 to 51 months. This SD was paralleled by normalization of serum calcium levels in three of five patients. In one patient who underwent PRRT with ^{177}Lu-

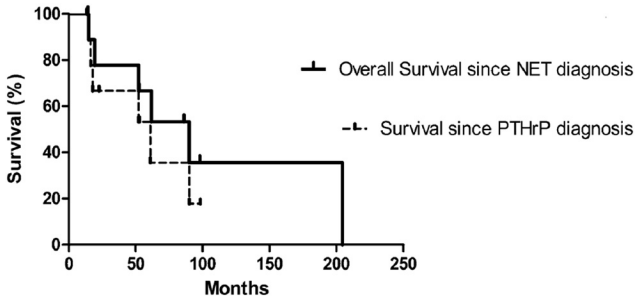

Figure 1. Survival Kaplan-Meier curve of 10 patients with plasma PTHrP-hypersecreting NETs: overall survival and survival since the diagnosis of PTHrP hypersecretion. Median overall survival was 86.0 months. Median survival since PTHrP diagnosis was 52.2 months.

octreotate (Table 1, patient 5), SD was 48 months, whereas the biochemical response lasted 15 months. In one patient (Table 1, patient 4), PRRT with ^{111}In-pentetreotide or ^{90}Yt-octreotide resulted in SD of 7 and 8 months, respectively, but this was not paralleled by a biochemical response. In the only patient treated with sunitinib (±isotonic saline) (Table 1, patient 5), SD was 13 months, and this was paralleled by normalization of serum calcium levels for 8 months.

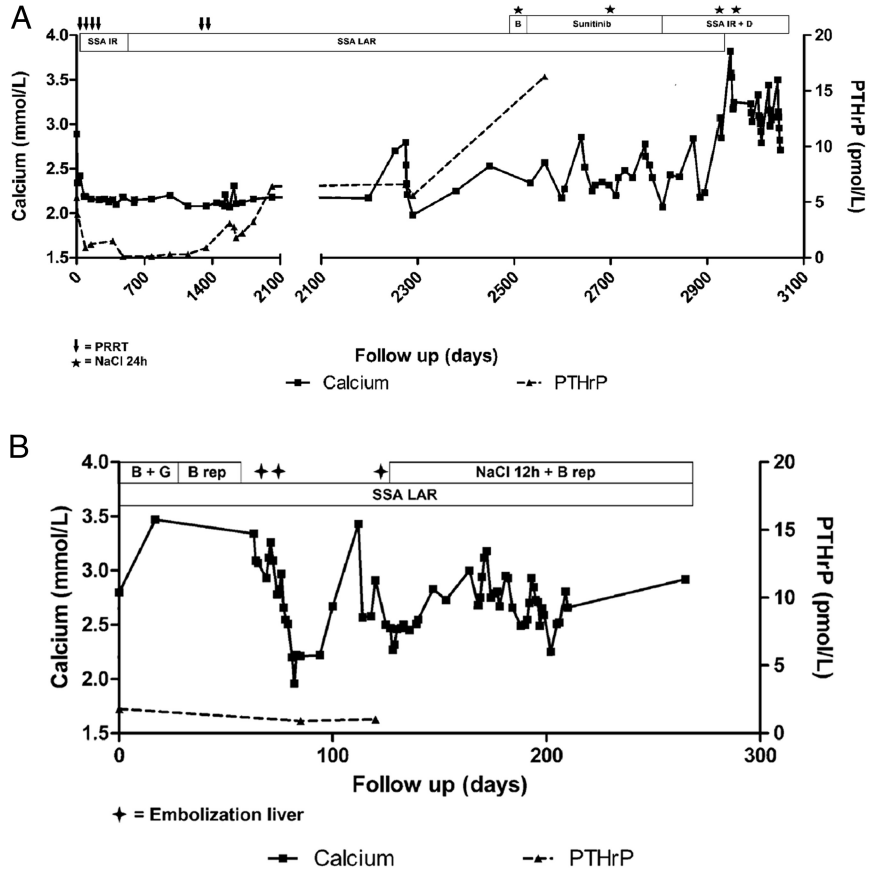

Figure 2. Serum calcium (corrected for albumin) and plasma PTHrP levels in the follow-up of two patients with PTHrP-hypersecreting pancreatic neuroendocrine tumors. A, Patient 5, pancreas NET with synchronous PTHrP secretion. B, Patient 10, pancreas NET with metachronous PTHrP secretion. IR, immediate release; B, bisphosphonate; D, denosumab; B rep, bisphosphonate repetitive iv infusions; G, glucocorticoids.

Prognosis

Median overall survival of our normocalcemic patients with pancreatic NETs (n = 277) was 161.8 months. Median overall survival of our 10 patients since the first diagnosis of GEP-NET was 86.0 months, and median survival of our 10 patients since the diagnosis of PTHrP hypersecretion was 52.2 months (see Figure 1). The overall survival in the patients with PTHrP hypersecretion was significantly shorter ($P = .002$) than in the group with normocalcemia.

Seven of 10 patients (70%) finally developed fatal progressive disease according to RECIST version 1.0 (24) in combination with uncontrollable elevated serum calcium levels and elevated plasma PTHrP levels.

Case Reports

This paper now reports in more detail two patients with pancreatic NETs with hypercalcemia due to excessive PTHrP hypersecretion. Patient 5 was diagnosed with a pancreatic NET with synchronous PTHrP secretion, and patient 10 was diagnosed with a pancreatic NET with metachronous PTHrP secretion. For both patients, more than one PTHrP measurement was available.

Patient 5 (Figure 2A)

A 61-year-old man was referred to the urologist for prostate hyperplasia (Table 1, patient 5). Subsequent imaging with computed tomography revealed pathological lesions in the pancreas and liver. The past medical history included type 2 diabetes and exocrine pancreatic insufficiency for which he received oral medication. Symptoms related to the hypercalcemia were involuntary weight loss, fatigue, and polyuria. His clinical condition was WHO-1.

An inoperable well-differentiated (grade 1) NET in the pancreatic body with multilobar liver metastases was diagnosed. Serum calcium levels were elevated, serum phosphate levels were reduced, and serum creatinine levels were within the reference range. Plasma PTH concentrations were undetectable, whereas plasma PTHrP levels were elevated (Table 1, patient 5). Serum levels of CgA were elevated, and serum levels of NSE

were within the reference range (Table 1, patient 5). ^{111}In-pentetreotide scintigraphy (OctreoScan) showed a scan-positive lesion in the pancreas and multiple liver lesions.

The patient started treatment with Octreotide IR, 50 μg three times a day (t.i.d.) sc, which was converted to octreotide long-acting repeatable (LAR) (20 mg/4 wk im). PRRT with ^{177}Lu-octreotate (cumulative dose, 43.9 GBq) was given in six cycles. The liver metastases showed regression (partial response), and the pancreatic lesion remained stable. This therapeutic approach also resulted in normalization of serum calcium levels. The octreotide therapy in combination with PRRT was capable of maintaining calcium levels within the reference range for a total period of 7 years (Figure 1A).

Seven years after the initial diagnosis of a PTHrP-secreting NET, tumor progression in combination with recurrence of hypercalcemia occurred (Figure 1A). The patient was treated with iv bisphosphonates (zoledronic acid, 4 mg), and serum calcium levels normalized again for almost 2 months (Figure 1A). Subsequently, treatment with sunitinib at a dose of 37.5 mg/d was started. Serum calcium levels normalized again for another 5 months (Figure 1A). At 91 months after the initial diagnosis, the serum calcium levels increased again, iv isotonic saline was given in combination with sunitinib at a dose of 37.5 mg/d, and serum calcium levels normalized for 3 months. After 94 months, all other treatment modalities were ineffective to normalize calcium levels. Intravenous isotonic saline and denosumab (60 mg sc) were both only able to lower the serum calcium levels slightly, and no response was seen after the renewed iv administration of 4 mg zoledronic acid. Also, the combination of iv isotonic saline and denosumab and octreotide IR (500 μg t.i.d. sc) was only able to slightly reduce, but not normalize, the serum calcium levels (Figure 1A). Meanwhile, the pancreatic NET and its metastases increased in size and number. Additionally, the patient underwent two cycles of ^{177}Lu-octreotate (data not shown); he is still alive, 100 months after the initial diagnosis, and presently has slightly increased serum calcium levels. His current clinical condition is World Health Organization (WHO)-2.

Patient 10 (Figure 2B)

A 49-year-old woman was diagnosed with a well-differentiated (grade 1) NET in the pancreatic head (Table 1, patient 10). Her past medical history was uneventful. She underwent a pancreaticoduodenectomy with curative intent. She was disease-free for 10 years. She subsequently developed lymph node and multilobar liver metastases for which she was treated with metastasectomy and ^{177}Lu-octreotate (44.3 GBq, given in six fractions).

Fifteen years after the diagnosis of the primary pancreatic NET, routine laboratory monitoring showed highly elevated calcium levels. Three months after the first diagnosis of hypercalcemia, the patient was admitted to our hospital with involuntary weight loss as well as nausea, poor appetite, polyuria, polydipsia, and persistent fatigue. Her clinical condition at that time was WHO-2.

Serum calcium concentrations were elevated, whereas serum phosphate and creatinine levels were within the reference range (Table 1, patient 10). Plasma PTH concentrations were undetectable, whereas plasma PTHrP levels were elevated (Table 1, patient 10). Serum levels of CgA and NSE were within the reference range (Table 1, patient 10). ^{99m}Tc bone scintigraphy showed no bone metastases.

The patient was treated with Octreotide LAR (20 mg/4 wk im) in combination with a single short iv infusion of bisphosphonates and dexamethasone. This combination therapy was only able to decrease serum calcium levels for 0.5 month.

After recurrence of the hypercalcemia in combination with elevated plasma PTHrP levels, monthly infusions with bisphosphonates were started in combination with Octreotide LAR (20 mg/4 wk im). This resulted again in a decrease in serum calcium levels for almost 2 months.

Five months after the initial diagnosis of the PTHrP hypersecretion, hepatic arterial embolization was performed because of tumor progression and recurrent hypercalcemia. The hypercalcemia normalized only for a short period of time (0.1–1.1 mo) after three hepatic arterial embolizations. The last treatment option tried in this patient was nightly iv isotonic saline in combination with furosemide and 4 mg zoledronic acid iv/4 wk. Nine months later, 18 months after the initial diagnosis of the PTHrP hypersecretion, the patient died of progressive disease and uncontrollable hypercalcemia.

Discussion

This study presents the clinical, endocrine, and laboratory features of a group of 10 successive patients with PTHrP-hypersecreting GEP-NETs who were evaluated and treated in a single tertiary referral center.

GEP-NETs represent a heterogeneous group of relatively rare neoplasms with a distinct biological behavior (27). Recent epidemiological reviews show that the age-adjusted incidence of all GEP-NETs is 3.65, and for pancreatic NETs it is 0.43 (28). Our series of 895 new patients with GEP-NETs (295 patients with pancreatic NETs) included only 18 patients with hypercalcemia (2%) and 10 patients (1.1%) with proven PTHrP production, which demonstrates that PTHrP-hypersecreting GEP-NETs are extremely rare.

Only seven studies, reporting a total of 20 patients with PTHrP-hypersecreting pancreatic NETs, have been published (9–15). Our series is, therefore, the largest published single-center case series.

In our study, we have only included patients with low to undetectable PTH levels. Although very rare, we might, therefore, have missed patients presenting with combined ectopic PTH and PTHrP hypersecretion. Ectopic PTH secretion by NETs and NECs has been described in only a few case reports (29–31). Combined ectopic PTH and PTHrP hypersecretion has been suggested in a patient with a non-neuroendocrine lung carcinoma (32), but a patient with a pancreatic NEC described by VanHouten et al (31) presented with both elevated PTH and elevated PTHrP levels.

Our management of patients with PTHrP-hypersecreting GEP-NETs was aimed at long-term control and achieving normalization of serum calcium, preferably also paralleled by tumor stabilization or reduction, and finally prolongation of (progression-free) survival.

Resection of the primary pancreatic NET and its metastases was only feasible in one patient; this was followed by a decrease in plasma PTHrP and resulted in normalization of serum calcium levels for more than 2 years. However, in two other patients, hepatic artery embolization and ethanol injections of liver metastases with the intent to obtain significant tumor debulking were successful for a very limited period of time (less than 2 mo) or were unsuccessful.

Alternatively, hypercalcemia can be controlled by medical therapies such as iv isotonic saline, bisphosphonates, glucocorticoids, and SSAs.

The iv administration of isotonic saline corrects possible volume depletion due to hypercalcemia-induced urinary salt wasting and, in some cases, vomiting. Hypovolemia can exacerbate hypercalcemia by impairing the renal clearance of calcium (33). Our results show that iv isotonic saline should be considered as the standard supportive therapy in patients with PTHrP-hypersecreting NETs and hypercalcemia, but as monotherapy it has only limited effectiveness.

Bisphosphonates inhibit calcium release by interfering with the osteoclast-mediated bone resorption (34, 35). Because of the ability of PTHrP as an inducer of bone resorption, renal phosphate wasting, and elevated distal tubular reabsorption of calcium, bisphosphonates should theoretically be able to control serum calcium levels in patients with PTHrP-hypersecreting tumors and hypercalcemia (6, 7). A systematic review of bisphosphonates for HHM showed that, in general, bisphosphonates can normalize serum calcium levels in >70% patients; however, approximately 25% of cases with HHM are still resistant to bisphosphonate therapy (36). In our patients, bisphosphonates were only able to decrease, or normalize, serum calcium levels for a relatively short period of time (maximum, 2.3 mo), and therefore the clinical effectiveness of bisphosphonate monotherapy was limited.

As already stated, increased 25(OH)D-1α-hydroxylase activity has not been reported in GEP-NET patients. The activity of this enzyme can be successfully inhibited by glucocorticoids. It is, therefore, not surprising that glucocorticoid administration was ineffective in the control of hypercalcemia in our patients.

Gastrointestinal NETs express the somatostatin receptor subtype 2 (sst_2) in approximately 90% of the tumors and pancreatic NETs (with the exception of nonmetastatic insulinomas) in approximately 80% of the tumors (37).

The currently available commercial octapeptide SSAs show a high affinity for sst_2 and low-median affinities for somatostatin receptor subtypes 3 and 5 (sst_3 and sst_5) (38). These drugs are effective therapies for symptom control and control of tumoral hormone secretion in patients with GEP-NETs, achieving symptom control in up to 71% of patients and biochemical response in up to 51% (39–42).

In the present study, SSA treatment resulted in a temporary normalization of serum calcium levels in seven of 10 patients. Two patients obtained a long-term response (up to 35.2 mo).

The use of SSAs as antiproliferative agents in patients with GEP-NETs has been recently established. Sandostatin LAR (30 mg/mo im) resulted in a prolongation of time to progression from 8 to 16.3 months, as compared to placebo, in patients with metastatic NETs of the small intestinal tract (43). Lanreotide Autogel (120 mg/mo sc) in patients with GEP-NETs resulted in a prolongation of progression-free survival over placebo. Median progression-free survival was not reached with this drug vs 18 months with placebo (44).

PRRT with ^{177}Lu-octreotate can not only result in a reduction in tumor size and prolongation of overall and progression-free survival, but can also lead to an improvement in symptoms. PRRT with ^{177}Lu-octreotate resulted in complete and partial remissions of metastatic GEP-NETs in 2% and 28% of patients, respectively. Also, symptoms improved in 40–70% of patients (45–47).

In patients treated with PRRT using ^{177}Lu-octreotate, mean serum calcium levels decreased significantly (48). However, the underlying mechanism for this process could not be elucidated (48). Hypoparathyroidism, 25(OH)D deficiency, renal insufficiency, pseudohypoparathyroidism, and low calcium intake could be excluded (48). The potential decrease of serum calcium levels in patients with PTHrP-hypersecreting tumors occurring after PRRT with ^{177}Lu-octreotate is, therefore, an extra advantage of this therapy.

In our series, PRRT also had favorable effects on the hypercalcemia and plasma PTHrP levels, with long-term responses ranging from 9.0–49.0 months in four of six patients. However, two of six patients had worsening of hypercalcemia while still undergoing PRRT, or directly after finalization of the PRRT. Tumor stabilization with PRRT was paralleled by normalization of serum calcium values in three of five patients treated with ^{177}Lu-octreotate.

Seven of the 10 patients developed progressive disease, and this was paralleled by an increase of plasma PTHrP and serum calcium levels. However, not only did the hypercalcemia worsen; the intervals between the treatments and treatment responses shortened as well. Worsening of hypercalcemia, therefore, generally reflected disease progression.

A possibly effective new treatment option for PTHrP-induced hypercalcemia might be the sc administration of denosumab. The human monoclonal antibody denosumab specifically binds the receptor activator of nuclear factor κB (RANK) ligand, blocks the binding of RANK ligand to RANK, and thereby reduces the formation, function, and survival of osteoclasts, which results in decreased bone resorption (35).

In one of our patients, monotherapy with denosumab was not very effective, and calcium levels only slightly decreased for 0.1 month. The combination of denosumab with iv isotonic saline and Octreotide IR (500 μg t.i.d. sc) was able to reduce serum calcium levels for a longer period of time (1.5 mo).

New antitumor treatment options are needed for patients with metastatic GEP-NET presenting with, or developing, PTHrP hypersecretion to prevent recurrence of hypercalcemia and thereby to improve survival of patients with metastatic PTHrP-hypersecreting GEP-NETs.

Clinical trials testing two new targeted antitumor therapies, everolimus and sunitinib, have subsequently led to the recent approval of these two drugs by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of inoperable, progressive, grade 1 and 2 pancreatic NETs (49, 50).

In one of our patients, monotherapy with sunitinib (37.5 mg/d) resulted in normalization of serum calcium levels for 5.2 months. After recurrence of hypercalcemia, iv isotonic saline was given in combination with sunitinib, and normocalcemia was achieved for another 3.3 months.

A study with anti-PTH immunotherapy in a patient with metastatic parathyroid carcinoma induced tumor shrinkage accompanied by hormonal, biochemical, and clinical improvements (51). Anti-PTHrP immunotherapy could be explored as another potentially interesting treatment option in patients with PTHrP-hypersecreting GEP-NETs.

A large international cohort study looked at survival and TNM staging for pancreatic NETs. A cumulative survival of approximately 83% at 5 years and 74% at 10 years was shown (52). In our study, the 5- and 10-year survival of patients with PTHrP-hypersecreting pancreatic NETs was approximately 70% and <40%, respectively. This suggests that PTHrP hypersecretion is associated with a worse survival. This is most probably due to complications of HHM in combination with tumor progression and/or suggests that PTHrP production occurs in a subset of GEP-NET patients with a worse clinical course.

We conclude that, although increased hypersecretion of PTHrP by metastatic GEP-NETs is very rare, it has major clinical impact because, apart from the poorly controllable hypercalcemia, it is also a bad prognostic sign. Paraneoplastic PTHrP production in patients with GEP-NETs seems to be exclusively associated with metastatic pancreatic NETs. The most successful treatment options for PTHrP-producing GEP-NETs are SSAs and PRRT using radiolabeled SSAs. Isotonic saline and bisphosphonates are generally used and can be recommended as a supportive therapy.

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R.A.F., W.W.d.H., R.C.S.v.A., D.J.K., and K.K. collected the data and wrote the manuscript. K.K. performed the data analysis/statistics and data registry. Y.B.d.R. was in charge of the laboratory measurements performed in the Erasmus MC, Rotterdam, The Netherlands. F.H.v.N. performed histological confirmation of the GEP-NET, including immunohistochemistry. R.A.F., W.W.d.H., D.J.K., and their coworkers were responsible for the treatment and follow-up of patients.

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