

CASE REPORT

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Peptide receptor radionuclide therapy controls inappropriate calcitriol secretion in a pancreatic neuro-endocrine tumor: a case report

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Abstract

Background: Hypercalcemia of malignancy is not uncommon in patients with advanced stage cancer. In rare cases the cause of the hypercalcemia is excessive production of calcitriol, the active form of vitamin D. Although inappropriate tumoral secretion of calcitriol is typically associated with lymphomas and some ovarian germ cell tumors, we present a case of calcitriol overproduction-induced hypercalcemia due to a pancreatic neuroendocrine tumor. The high expression of somatostatin receptors on this neuroendocrine neoplasm opened up the opportunity to treat the patient with radiolabelled somatostatin analogs, which successfully controlled the refractory hypercalcaemia and calcitriol levels. This case documents a rare finding of refractory hypercalcaemia of underlying malignancy due to a calcitriol-producing pancreatic neuroendocrine tumor, responding to peptide receptor radionuclide therapy (PRRT).

Case presentation: A 57 years-old patient presented with back pain, general discomfort, polydipsia, polyuria, fatigue and recent weight loss of 10 kg. Clinical examination was normal and there was no relevant medical history. Biochemical evaluation showed hypercalcemia with markedly increased calcitriol levels. CT-thorax-abdomen and ultrasound guided biopsy revealed a pancreatic neuroendocrine tumor with multifocal liver metastases, suggesting that excessive overproduction of calcitriol by this neuroendocrine tumor was the cause of the refractory hypercalcemia. The patient was eligible for PRRT. Four cycles of ¹⁷⁷Lu-DOTATATE PRRT resulted in a morphological response and a normalization of serum calcium levels, confirming the hypothesis of a calcitriol producing pancreatic neuroendocrine tumor. Progression of liver metastases warranted further therapy and temozolomide-capecitabine was started with morphological and biochemical (serum calcium, calcitriol) stabilization.

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Conclusion: Although up to 30–40% of gastroenteropancreatic neuroendocrine tumors are known to be functional (i.e. producing symptoms associated with the predominant hormone/peptide secreted), calcitriol secreting pancreatic neuroendocrine tumors are very rare. However, treatment with PRRT resulted in normalization of calcium and calcitriol levels, strongly supporting the hypothesis of a calcitriol-producing pancreatic neuroendocrine tumor.

Keywords: ^{177}Lu -DOTATATE, PRRT, Calcitriol, Neuroendocrine tumor, Pancreas, Vitamin D, Hypercalcemia

Background

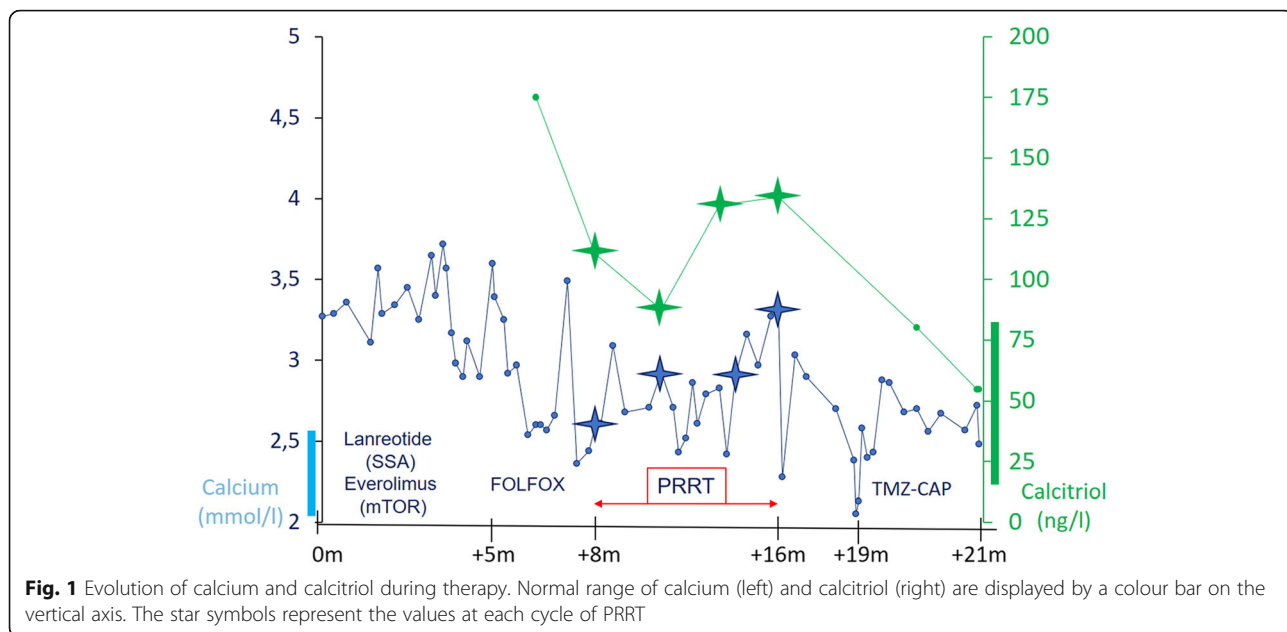
Hypercalcemia without elevated parathyroid hormone (PTH) level is most frequently due to an underlying neoplasm [1, 2]. This so called hypercalcemia of malignancy (HCM) is a common finding, affecting up to 44% of cancer patients [3, 4] and is most often associated with advanced tumor stages [4]. Up to 80% of HCM are caused by systemic secretion of PTH-related Peptide (PTHrP) [1, 3] which mimics the function of PTH: increasing kidney calcium reabsorption, stimulating the maturation of osteoclast precursors and increasing bone resorption [5]. Extensive osteolysis accounts for about 20% of the cases of HCM [1, 6]. In rare cases (<1%) the cause of the hypercalcemia is an excessive production of calcitriol (1,25-dihydroxyvitamin D), due to an ectopic overexpression of 1-alpha-hydroxylase [1, 7, 8]. The latter is common in lymphomas and in some ovarian germ cell tumors [1]. However, we report it in a grade 2 pancreatic neuroendocrine tumor (pNET).

The high incidence of somatostatin receptors (SSR) on gastroenteropancreatic neuroendocrine tumors (GEP-NETs) provides imaging and therapeutic options. Somatostatin receptors overexpression is the basis of pharmacological treatment with non-radioactive somatostatin analogs (SSAs) (eg. Octreotide) [9]. SSAs can also be labelled with radionuclides [10–13]. Depending on the specific decay characteristics of the attached radionuclide, the compound can be used for diagnostic molecular imaging (eg. ^{68}Ga -DOTATATE) or targeted radionuclide therapy (eg. ^{177}Lu -DOTATATE). In case of inoperable/metastatic well-differentiated GEP-NETs, this so-called Peptide Receptor Radionuclide Therapy (PRRT) is an established treatment modality [14] whose role has been proven by the excellent results obtained in the randomized controlled NETTER-1 trial [15]. Furthermore, up to 30–40% of the GEP-NETs are known to be functional (i.e. causing symptoms mediated by excessive hormone/peptide secretion) [16], and evidence is accumulating that PRRT is valuable in controlling these functional neuroendocrine tumor syndromes [17–22]. This case documents a rare finding of refractory hypercalcaemia of underlying malignancy due to a calcitriol-producing pancreatic neuroendocrine tumor, responding to peptide receptor radionuclide therapy (PRRT).

Case presentation

A 57 years-old male patient presented with back pain, general discomfort, polydipsia, polyuria, fatigue and recent weight loss of 10 kg. Clinical examination was normal and there was no relevant medical history. Biochemical evaluation showed hypercalcemia (2,85 mmol/L; normal: 2.15–2.55 mmol/L) with slightly lowered PTH levels (14,2 ng/L; normal 14,9–56,9 ng/L) excluding hyperparathyroidism. CT-thorax-abdomen and ultrasound guided biopsy revealed a pNET with multifocal liver metastases as well as some small bone lesions. The Ki-67 index was 15 to 20% compatible with a grade 2 tumor. PTHrP was normal and although our patient had some osteodense skeletal metastases, these bone lesions alone could not explain his marked hypercalcemia. However, markedly increased calcitriol levels up to 134.3 ng/L (normal: 20.0–80.0 ng/L) were detected. We hypothesized that overproduction of this active form of vitamin D by the pNET was the cause of the HCM.

Initial treatment with lanreotide, a non-radioactive SSA, and everolimus, an inhibitor of mammalian target of rapamycin (mTOR), resulted in morphologically stable disease, but there was no effect on the hypercalcemia nor on the associated symptoms. The patient was evaluated for treatment with PRRT. In the meantime, therapy with FOLFOX chemotherapy was started. ^{68}Ga -DOTATATE scan revealed intense SSR expression in the pancreatic lesion as well as strong uptake in the liver metastases and the skeletal metastases. All malignant lesions had an uptake intensity above the spleen (Krenning score grade 4) [23]. ^{18}F -FDG-PET/CT showed strong hypermetabolism in some of the liver metastases (metabolic grade 3) [24]. There were no ^{18}F -FDG + / SSR - mismatched lesions. Evaluation of the renal function showed no contraindication for therapy. Four cycles of PRRT with ^{177}Lu -DOTATATE were given, with a treatment interval of 8 weeks up to a cumulative activity of 29.6 GBq. Three months after the final cycle, the initially refractory serum calcium levels had normalized and the associated symptoms disappeared (Fig. 1), confirming the hypothesis of a calcitriol secreting pNET. Although there was a clear morphologic response (Figs. 2 and 3), some liver lesions showed an increase in ^{18}F -FDG uptake compared with baseline (Fig. 3). Because of these signs of metabolic progression, the patient was

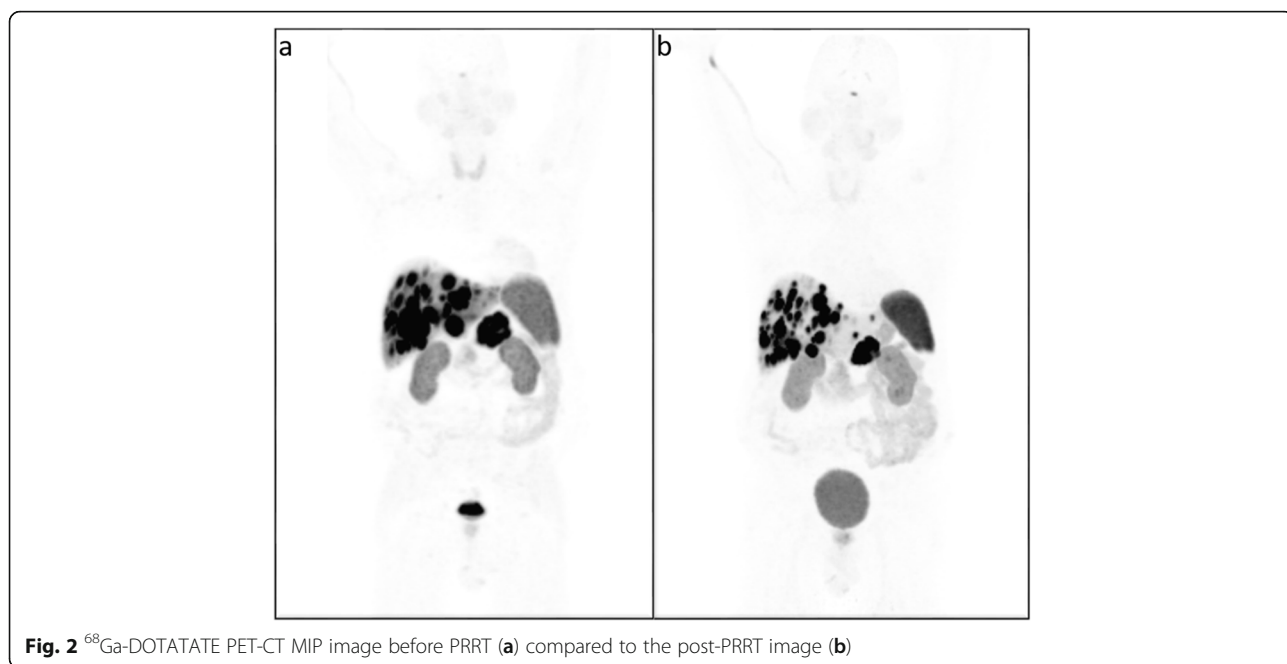


started on temozolomide-capecitabine, which resulted in continued morphological disease stabilization as well as continued normal serum calcium and calcitriol.

Discussion and conclusion

Hypercalcemia without elevated PTH level is most frequently due to HCM. However, the normal PTHrP values and the absence of osteolytic bone metastases, ruled out PTHrP production and skeletal osteolysis respectively. Instead, the strongly elevated calcitriol levels suggested a third, more rare cause of HCM: calcitriol

overproduction-induced hypercalcemia due to a pNET. To the best of our knowledge, only 2 other cases have described calcitriol-producing pNETs [25, 26], both in a metastatic setting. In the case report of Zhu et al. [25] biochemical disease stabilization was obtained using a combination of temozolomide-capecitabine as well as a 4-weekly regimen of octreotide. The case report of Van Lierop et al. [26] documented disease control after hemihepatectomy. In our case, initial therapy with lanreotide and everolimus had no effect on the hypercalcemia nor on the associated symptoms, so we opted to treat the



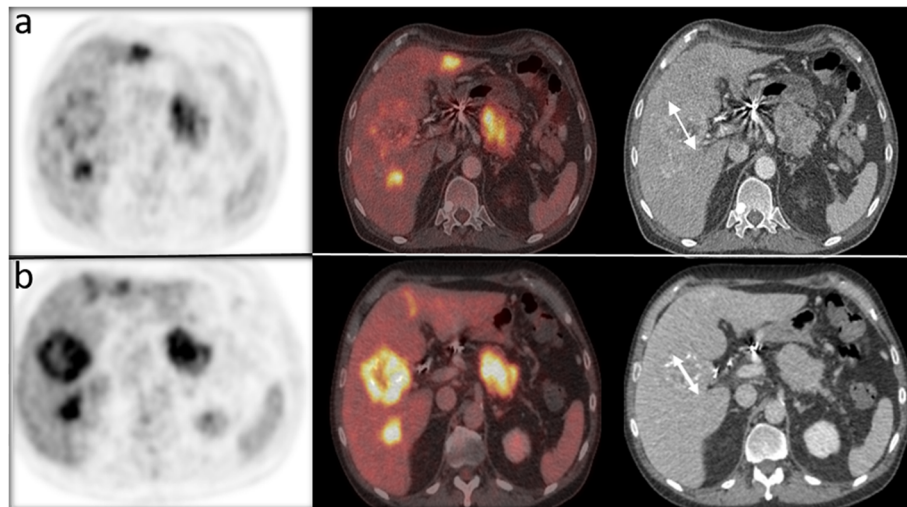


Fig. 3 ^{18}F -FDG-PET/CT transverse images before PRRT (row **a**) compared to post-PRRT images (row **b**). Some liver lesions showed an increase in ^{18}F -FDG uptake compared with baseline (left and middle images), although there was a morphologic therapy response on the CT images (right images) with new calcifications and a decrease in diameter (white arrow)

patient with PRRT as PRRT can reduce hormonal secretion by functioning NETs.

^{68}Ga -DOTATATE scan revealed intense SSR expression in the pancreatic lesion, the liver metastases and the rare skeletal metastases. Strong hypermetabolism in some of the liver metastases, suggested increased aggressiveness in those lesions [27]. However, no mismatched (^{18}F -FDG + / SSR -) lesions were detected, so there was no significant dedifferentiation which would be a contraindication for treatment with PRRT [28]. Since PRRT response is observed months after first administration (between 3 to 12 months or even later), the fluctuating calcium levels during PRRT treatment were probably caused by a combination of the symptomatic treatment with hydration and forced diuresis and the PRRT effect. However, a marked decrease in serum calcium as well as a morphological therapy response were observed three months after completion of PRRT, in line with the PRRT response kinetics. The biochemical and morphologic alterations after PRRT make it highly likely that calcitriol decreased concomitantly, although it was not measured between the end of PRRT and the start of chemotherapy and was only confirmed to be normal after additional chemotherapy. Although no ex-vivo biochemical proof of overexpression of 1-alpha-hydroxylase was available, our findings strongly support the hypothesis of a calcitriol-producing pNET and demonstrate for the first time the potential role of PRRT in controlling inappropriate tumoral secretion of calcitriol. This is in line with other data documenting successful PRRT treatment of different kinds of secreting NETs, proving PRRT to be a valuable asset in controlling functional neuroendocrine tumor syndromes.

Neuroendocrine neoplasms are known to be functional in up to 30–40% of the cases, but calcitriol secretion by a pNET has only rarely been described. However, treatment with PRRT resulted in normalization of calcium and calcitriol levels, strongly supporting the hypothesis of a calcitriol-producing pancreatic neuroendocrine tumor.

Abbreviations

PTH: Parathyroid hormone; HCM: Hypercalcemia of malignancy; PTHrP: PTH-related Peptide; pNET: Pancreatic neuroendocrine tumor; SSR: Somatostatin receptor; GEP-NETs: Gastroenteropancreatic neuroendocrine tumors; SSA: Somatostatin analog; DOTATATE: DOTA-(Tyr3)-octreotate; PRRT: Peptide receptor radionuclide therapy; CT: Computed tomography; mTOR: Inhibitor of mammalian target of rapamycin; FOLFFOX: Oxaliplatin 5-fluorouracil leucovorin; ^{18}F -FDG: ^{18}F -Fluorodeoxyglucose; PET: Positron emission tomography

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Authors' contributions

All authors have read and approved the manuscript. TD: was involved in diagnosis and clinical treatment of the patient. MH, KVL, CMD, EVC, CV: were involved in the PRRT treatment of the patient. MH, CMD: initial draft. All: reading and providing input towards final version of the manuscript. All marked agreement on final version.

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Patient was treated in routine medical care. Patient consented to routine clinical care.

Consent for publication

Patient provided written consent for publication of his case details and medical images.

Competing interests

The authors have no conflict of interest to disclose.

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