

# Endocrine paraneoplastic hypercalcemia in a patient with pancreatic neuroendocrine neoplasm

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Endocrine paraneoplastic hypercalcemia occurs in up to 10% of patients with neoplasms, and the most common cause is the tumor secretion of parathyroid hormone-related peptide (PTHrP).<sup>1</sup> Neuroendocrine neoplasms (NENs) may produce several types of peptides, however, paraneoplastic hypercalcemia in NENs is exceedingly rare.<sup>1–4</sup>

In October 2018, a 35-year-old white woman with NEN-associated severe hypercalcemia was referred to our endocrinology department. A month earlier she had been admitted to another hospital due to an acute confusional state. At that time, she reported poor appetite, occasional nausea, vomiting, indigestion, and a 5 kg weight loss in the last 12 months. Gastroscopy and brain computed tomography (CT) were unremarkable. However, ultrasound of the abdomen showed numerous hyperechoic, solid formations in the liver and a hypoechoic, solid lesion in the tail of the pancreas. Total body CT scan confirmed the presence of multiple metastases, up to 40 mm in diameter, in both lobes of the liver and a lesion 20 mm in diameter in the pancreatic tail. Moreover, enlarged lymph nodes with a maximum diameter of 18 mm in the left subdiaphragmatic area were found. Histopathologic examination of the liver biopsy specimen revealed well-differentiated NEN, Ki67 index 10%. Immunohistochemistry was positive for CD56, synaptophysin, panCK, and chromogranin A. Laboratory evaluation showed hypercalcemia (4.92 mmol/l; reference range [RR], 2.15–2.5 mmol/l) and acutely raised serum creatinine (254.3 µmol/l; RR, 44–80 µmol/l). Treatment with intravenous saline, loop diuretics, corticosteroids, and bisphosphonates was introduced. When the patient arrived at our facility, biochemical tests of calcium metabolism showed persistent hypercalcemia (3.87 mmol/l), hypophosphatemia (1.7 mg/dl; RR, 2.3–4.7 mg/dl),

increased activity of total alkaline phosphatase (315 U/l; RR, 37–98 U/l) and its bone-type isoenzyme (83.4 µg/l; RR, 3–19 µg/l), a low level of 25-hydroxyvitamin D (18.6 ng/ml; RR, 20–80 ng/ml) with a normal level of 1,25-dihydroxyvitamin D (28.40 pg/ml; RR, 25–86.5 pg/ml), and low parathyroid hormone level (<3 pg/ml; RR, 10–62 pg/ml). Based on the results, we suspected PTHrP-related hypercalcemia, which was confirmed by a markedly elevated serum concentration of PTHrP (38 pmol/l; RR, <1.3 pmol/l). Moreover, we found a high level of chromogranin A (193.2 ng/ml; RR, <84.7 ng/ml), slightly elevated gastrin level (123 pg/ml; RR, 13–115 pg/ml), and normal level of serotonin (227 nmol/l; RR, 138–1080 nmol/l). Somatostatin receptor scintigraphy revealed strong expression of somatostatin receptors in the primary tumor and metastases (Krenning score 4). We continued the therapy of hypercalcemia with intravenous isotonic saline, furosemide, corticosteroids, and bisphosphonates, and initiated treatment with short- and long-acting somatostatin analogs (SSA) (FIGURE 1A). Due to insufficient control of hypercalcemia despite the treatment, we administered 4 cycles of peptide receptor radionuclide therapy (PRRT) with a lutetium-177 (<sup>177</sup>Lu)-based probe linked to the somatostatin analog octreotate ([<sup>177</sup>Lu]Lu-DOTA-TATE) and referred the patient for a distal pancreatectomy and splenectomy with simultaneous radiofrequency ablation of the liver metastases (FIGURE 1A). Histopathologic examination of the primary lesion of the pancreatic tail showed NEN grade 2 according to the 2019 World Health Organization grading system with Ki67 index 15%.<sup>4</sup> After the treatment, we observed improvement in the clinical condition, normalization of calcium, phosphorus, and parathyroid hormone (PTH) levels, full recovery of renal function, and reduction of the PTHrP level (FIGURE 1A). Moreover, follow-up CT

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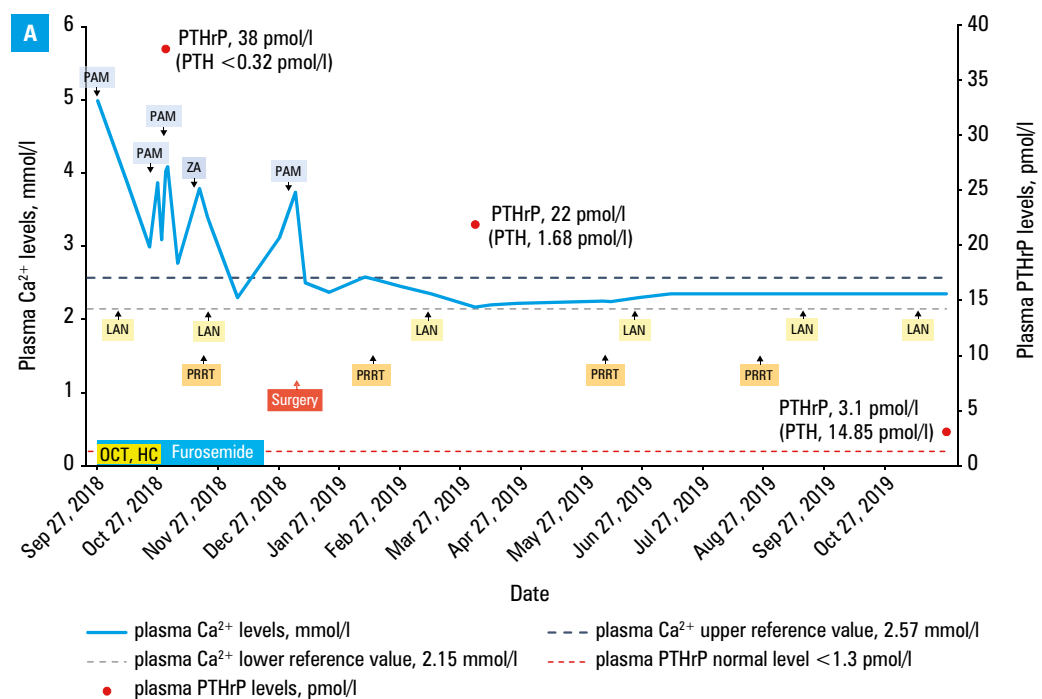
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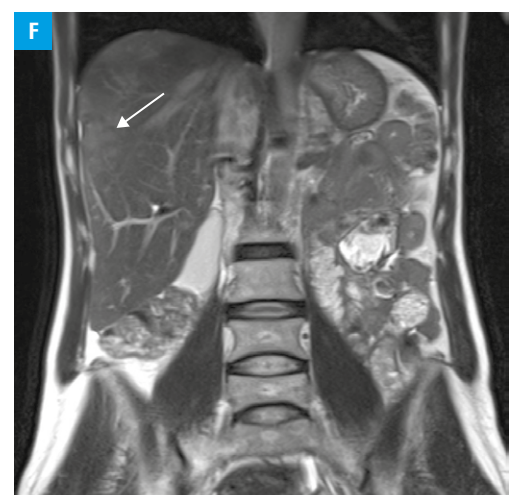
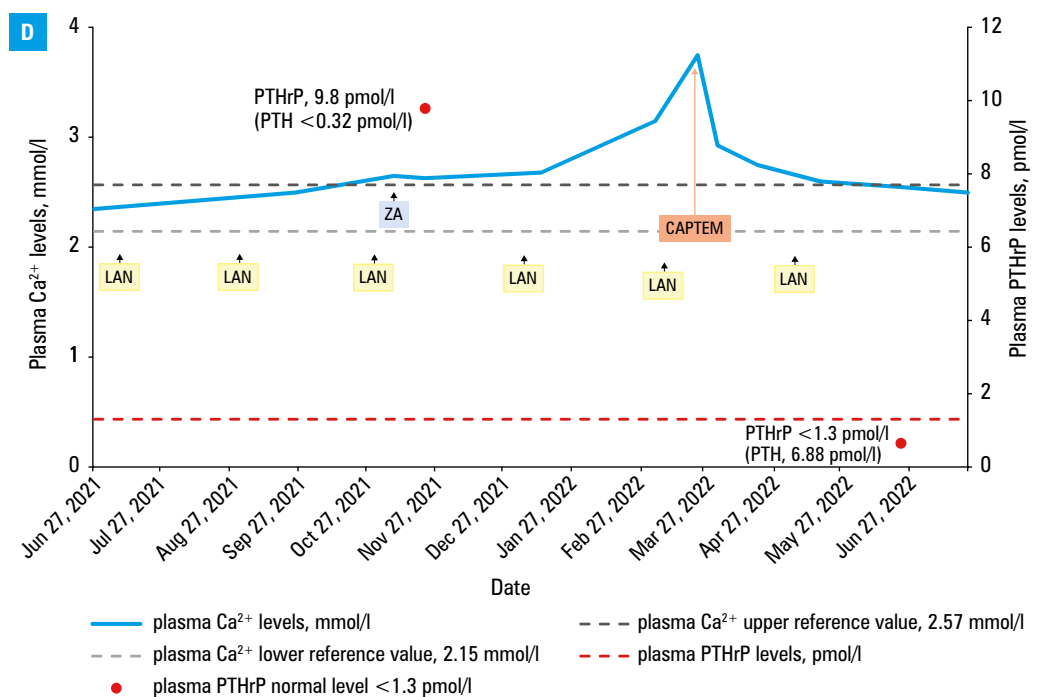


**FIGURE 1** **A** – a chart showing serum calcium levels and parathyroid hormone–related peptide (PTHrP) levels during the treatment; **B** – multiple liver metastases on an axial computed tomography (CT) scan from the hepatic arterial phase following intravenous contrast administration in April 2019. One of the largest metastases, 24 mm in diameter, was located in the 7th segment of the liver (arrow); **C** – an axial CT scan from the hepatic arterial phase following intravenous contrast administration in November 2019, showing partial regression of metastatic foci. The largest metastatic lesion located in the 7th segment of the liver was then 20 mm in diameter (arrow). Abbreviations: CAPTEM, temozolomide and capecitabine; HC, hydrocortisone; LAN, lanreotide; OCT, octreotide; PAM, pamidronate; PRRT, peptide receptor radionuclide therapy; PTH, parathyroid hormone; ZA, zoledronic acid

scans showed a marked reduction in the tumor mass in the liver and withdrawal of adenopathy (**FIGURE 1B** and **1C**). After 22 months of the disease stability on SSAs only, we observed a recurrence of symptoms, hypercalcemia (**FIGURE 1D**), increase of the PTHrP level, and tumor progression (**FIGURE 1E**). The patient was started on chemotherapy with temozolomide and capecitabine (CAPTEM), with satisfactory control of her metastatic disease (**FIGURE 1D** and **1F**). She remains under the care of an endocrinology and oncology outpatient clinic. Despite the CAPTEM and long-acting SSA therapy, she takes vitamin  $\text{D}_3$  in a prophylactic dose of 2000 IU daily, metformin due to pancreatogenic diabetes, and timonacil for metastatic liver disease.

Hypercalcemia of malignancy may be due to bone metastases or paraneoplastic secretion of humoral factors. According to the literature,

pancreatic NENs producing PTHrP are the most common cause of humoral hypercalcemia in NENs.<sup>1,2</sup> Ectopic secretion of PTH or 1,25-dihydroxyvitamin D by NENs has also been reported.<sup>1</sup> It should be highlighted that hypercalcemia associated with NENs may also result from primary hyperparathyroidism as a manifestation of multiple endocrine neoplasia type 1 syndrome.<sup>3,4</sup> Therefore, a complete evaluation of calcium metabolism in NEN patients with hypercalcemia is mandatory. Emergency management of NENs paraneoplastic hypercalcemia should focus on lowering calcium levels. Based on a literature review, long-term control can only be achieved by the treatment of the underlying tumor, specifically surgery, when possible, SSAs, and PRRT with [ $^{177}\text{Lu}$ ]Lu-DOTA-TATE.<sup>2</sup> Regarding second-line treatment, CAPTEM chemotherapy appears to be an effective approach,



**FIGURE 1** **D** – a chart showing serum calcium levels and PTHrP levels in the period of the tumor recurrence; **E** – tumor progression seen on a coronal magnetic resonance imaging (MRI) scan of the liver performed in February 2022, depicted on T2-weighted images obtained with the half-Fourier acquisition single-shot turbo spin-echo technique. At that time, the largest metastatic lesion of the 7th segment of the liver was up to 60 mm in diameter (arrow). Moreover, new metastatic lesions appeared in both lobes of the liver. The lymph nodes were not enlarged (not shown). **F** – a coronal, T2-weighted MRI scan of the liver performed in July 2022, showing regression of the metastatic foci. The largest lesion of the 7th liver segment was 42 mm × 31 mm in diameter (arrow); other liver metastases were comparable in size or slightly smaller. Abbreviations: CAPTEM, temozolomide and capecitabine; LAN, lanreotide; PAM, pamidronate; PRRT, peptide receptor radionuclide therapy; PTH, parathyroid hormone; ZA, zoledronic acid

which may prolong survival in patients who have a well-differentiated, metastatic NEN and who have progressed on previous therapies.<sup>5</sup> Subsequent measurements of the hormone produced by NEN after therapeutic intervention with radiologic testing allow for determining the response to the therapy or the tumor recurrence.<sup>3,4</sup>

## ARTICLE INFORMATION

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**CLINICAL IMAGE** Hypercalcemia in pNEN

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