A case of refractory hypercalcemia due to a pancreatic neuroendocrine tumor misdiagnosed as an adenocarcinoma

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Background

- ✓ Hypercalcemia is a well-described paraneoplastic manifestation encountered in a variety of malignancies.
- ✓ It is rarely the initial feature of a neuroendocrine tumor.

Objective

- ✓ To report a case of metastatic pancreatic neuroendocrine tumor (NET) presenting with a refractory hypercalcemia and initially misdiagnosed as an adenocarcinoma of the pancreas.
- ✓ To illustrate some of the complexities pertaining to the diagnosis of a pancreatic NET and the challenges in the management of an associated hypercalcemia caused by parathyroid hormone related protein (PTHrP) hypersecretion

Patients and Methods

- ✓ A 67-year-old woman presented with asthenia and weight loss and was found to have severe hypercalcemia.
- ✓ Laboratory evaluation demonstrated high calcium levels associated with low serum parathyroid hormone (PTH) levels. Despite an initial low PTH-rP level, nephrogenous cAMP was elevated consistent with PTH-rP related hypercalcemia
- ✓ Work up revealed a pancreatic tumor associated with liver and splenic metastases but no bone metastases. Biopsy of the liver metastases was in favor of an adenocarcinoma and appropriate chemotherapy was initiated.
- ✓ Despite the stability of the pancreatic tumor, the associated hypercalcemia was **refractory** to:
  - Corticosteroids
  - Bisphosphonates
  - Calcitonin
  - Denosumab
- ✓ Because of the indolent progression of the tumor and in view of the persistent hypercalcemia, slides of the pancreatic tumor were reviewed, and complementary immunohistochemistry was performed.
- ✓ The results contradicted the initial diagnosis and were compatible with a well **differentiated neuroendocrine tumor**.
- ✓ Additional staining was **positive for PTHrP** confirming the ectopic secretion of this hormone by the tumor.

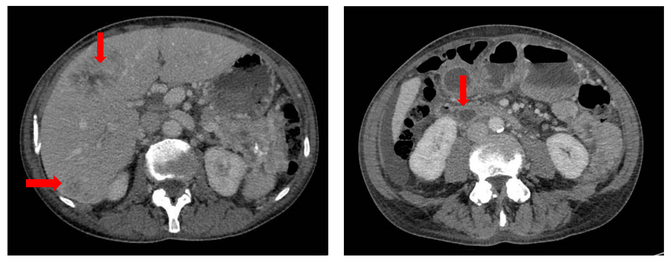
Patients and Methods

- ✓ **Chemoembolization of the liver metastases** was performed and treatment with **somatostatin analogues** (SSA) was introduced allowing a good but transient control of the hypercalcemia. This phenomenon of tachyphylaxis, after a few months of therapy with SSAs, has been described in some patients with NETs.
- ✓ Due to the rise of calcium levels, the patient was referred for **vectorized internal radiation therapy (Lutetium Lu 177 dotatate)** which also transiently controlled her hypercalcemia.

Biochemical Analysis on Admission

Parameter	Value	Reference range
Creatinine (µmol/L)	58	55-100
Glucose (mmol/L)	5.9	3.8-6.1
Sodium (mmol/L)	139	136-135
Potassium (mmol/L)	4.1	3.7-5.2
Albumin (g/L)	40.5	38-52
Total serum calcium (mmol/L)	3.5	2.2-2.6
Phosphate (mmol/L)	1.03	0.8-1.45
Alkaline Phosphatase	105	30-136
25(OH)D (ng/ml)	17	30-100
1,25(OH)D	NA	NA
PTH (ng/L)	6	15-65
PTHrP (pmol/L)	<1.3	<1.3
Urine calcium (mmol/24 hrs)	7.7	2.25-6.25
Urine créatinine (mmol/24 hrs)	7.6	5.3-13.3

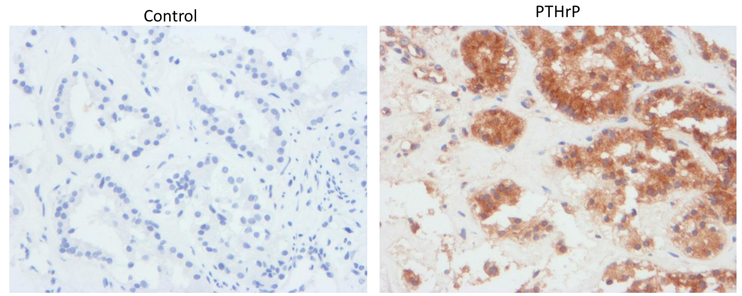
Abdominal CT SCAN on admission



Nephrogenous cAMP secretion and bone mineral workup

Parameter	Creatinine Clearance	Serum total calcium	Serum ionized calcium	Urinary calcium excretion	TRCa/GFR	Plasma phospha te	TmPi	Serum cAMP	Urinary cAMP	N cAMP	PTH
Unit	ml/min	mmol/L	mmol/L	mmol/mmol creatinine	µmol/dl GF	mmol/l	mmol/l	mmol/l	mmol/l	nmol/100ml GF	pg/ml
Fasting values	115	3.13 ↗	1.77 ↗	1.09 ↗	6.21 ↗	0.68	0.51 ↓	33	1.29 ↗	4.05 ↗	9
Range		2.09-2.52	1.15-1.32	0.04-0.37	0.35-2.58	0.82-1.39	0.76-1.62		0.16-0.55	0.59-1.99	11-57

PTHrP immunohistochemistry



PTHrP immunohistochemistry showed diffuse cytoplasmic expression in tumor cells

Conclusions

- ✓ Herein, we report a case of pancreatic neuroendocrine tumor with hypercalcemia as a presenting feature initially misdiagnosed as an adenocarcinoma of the pancreas.
- ✓ Hypercalcemia was refractory to all therapy and was only transiently controlled with SSA and Lutathera despite the stability of her underlying disease.
- ✓ This case highlights the challenges in diagnosing and controlling hypercalcemia due to PTHrP hypersecretion in patients with NETs.
- ✓ Furthermore, it underlines the importance of reconsidering the initial diagnosis in front of an unusual course of the disease.

The authors declare no conflict of interest