Parathyroid hormone-related peptide in pancreatic neuroendocrine tumours associated with hypercalcaemia

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Background

Hypercalcaemia is a common paraneoplastic syndrome. In the context of pancreatic neuroendocrine tumours, it is occasionally caused by secretion of parathyroid hormone-related peptide (PTH-rP).

Case outlines

Two patients are reported in whom persistent hypercalcaemia was traced to a large neuroendocrine pancreatic tumour hypersecreting PTH-rP. Resection of the tumour reduced serum levels of calcium and PTH-rP transiently in each case until the patient developed bulky metastatic disease. A 33-year-old woman remained hypercalcaemic after the removal of all four hyperplastic parathyroid glands had rendered circulating parathormone levels undetectable. Radical distal pancreatectomy was followed over the next 4 years by operative debulking of liver metastases, multiple hepatic artery embolisations, octreotide injections and repeated admissions for intravenous fluid and biphosphonate therapy. A 41-year-old man presented with hypercalcaemia as well as features of somatostatinoma syndrome. Symptomatic improvement after radical distal pancreatectomy was short-lived, and hepatic artery embolisation failed to control his rapidly progressive disease.

Discussion

Malignant hypercalcaemia associated with a neuroendocrine pancreatic tumour hypersecreting PTH-rP is difficult to treat and can be life-threatening. Aggressive surgical treatment is recommended initially, while somatostatin analogues and hepatic artery embolisation are alternative therapeutic options for metastatic disease.

Keywords

pancreatic neuroendocrine tumour, hypercalcaemia, parathormone, parathyroid hormone-related peptide.

Introduction

Pancreatic neuroendocrine tumours are uncommon malignancies originating from the neural crest cells, with an annual incidence of five cases per million population. Up to 75% of these tumours are functioning [1], i.e. they secrete various biologically active peptides responsible for specific clinical syndromes [2]. The remainder (at least 25%) are non-functioning. They tend to behave more aggressively, but as their growth is generally indolent, all neuroendocrine tumours carry a much better prognosis than ductal carcinoma of the pancreas [1].

The rare hypersecretion of parathyroid hormone-related peptide (PTH-rP) by islet cell tumours produces hypercalcaemia, which greatly complicates the patient's clinical course [3–5]. There are 31 reported cases of PTH-rPoma in the world literature. This paper reports another two patients with malignant hypercalcaemia due to excessive PTH-rP production by pancreatic neuroendocrine tumours. The clinical details of the second patient have been described previously [6], but the immunohistochemistry has now been reviewed in the light of the first case.

Case no. 1

A 33-year-old woman presented in August 1995 with left upper quadrant pain and a palpable abdominal mass associated with symptomatic hypercalcaemia (3.2 mmol/L, normal 2.1–2.6 mmol/L) but a normal serum level of parathormone (PTH) (2.8 pmol/L, normal 1.10–6.80 pmol/L). She was treated with intravenous fluids and pamidronate. Computed tomography (CT) scan revealed an 11.5-cm mass arising from the tail of the pancreas with three liver deposits and nephrocalcinosis (Figure 1).

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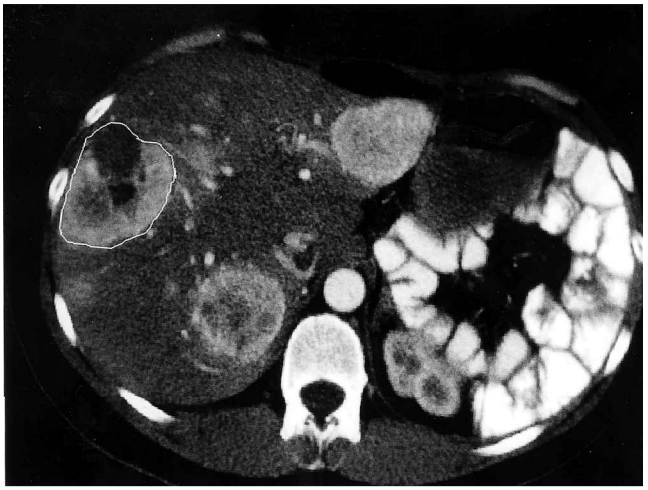

Figure 1. *Case no. 1: computed tomography showing the presence of three liver metastases.*

Angiography (Figure 2) and CT-guided biopsy confirmed the typical appearance of an endocrine tumour of the pancreas. Ultrasound scan of the neck revealed two masses of 4 mm and 5 mm in diameter located inferior to the right and superior to the left thyroid lobe respectively. A diagnosis of multiple endocrine neoplasia type I (MEN I) was made, but removal of all four (hyperplastic) parathyroid glands failed to cure the hypercalcaemia. Her postoperative PTH levels became undetectable, while serum PTH-rP was elevated at 4.0 pmol/L (normal <0.5 pmol/L).

In January 1996 the enormous pancreatic tumour was removed by means of distal pancreatectomy *en bloc* with spleen and adherent stomach. In addition, the largest of the liver metastases was injected with alcohol. Immediately postoperatively her serum calcium returned to normal (2.2 mmol/L). Histological examination showed a malignant neuroendocrine tumour, with nests of polygonal cells and a focal trabecular and glandular pattern. Infiltration into the splenic parenchyma, prominent lymphatic involvement and vascular invasion were noted. Immunohistochemical staining was positive for PTH-rP (Figure 3) as well as neuron-specific enolase (NSE), synaptophysin, chromogranin and somatostatin. It was negative for pancreatic polypeptide, insulin, gastrin, glucagon and vasoactive intestinal polypeptide (VIP).

The patient remained well and normocalcaemic for 18 months until nausea and vomiting developed and recurrent hypercalcaemia was found; hepatic artery embolisation failed to improve matters. PTH-rP level at that time was 1.6 pmol/L. In June 1998 she underwent removal of most of the liver mass via an extended right hepatectomy, plus a metastatic nodule attached to the splenic flexure of colon. Reoperation for reactive haemorrhage was followed by staphylococcal pneumonia requiring percutaneous tracheostomy, but eventually she was discharged home in good health at 6 weeks.

The patient continued to have symptomatic and intractable hypercalcaemia, requiring frequent admissions for intravenous rehydration and biphosphonate therapy. Repeat transcatheter embolisation of hepatic metastases in September 1998 was more successful than before in controlling this problem until August 1999, when multiple bony metastases (spine, pelvis: Figure 4) were treated with external beam radiotherapy to control pain. Serum PTH-rP measurement (April 2000) remained elevated at 2.2 pmol/L. Slow-release octreotide was started to control

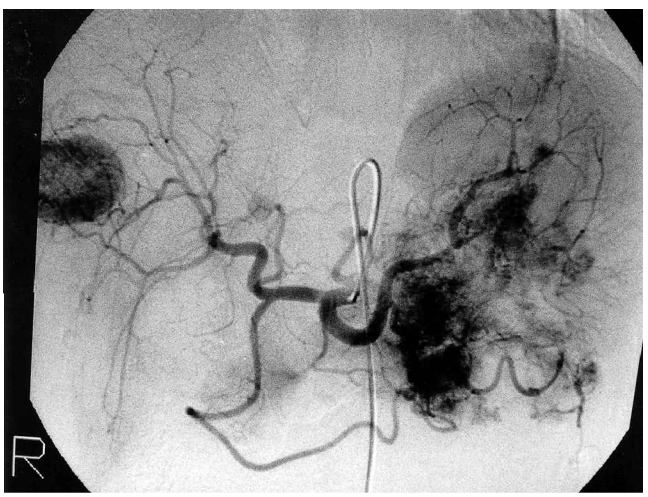

Figure 2. *Case no. 1: coeliac angiogram showing the 'blush' of a large tumour in the body of the pancreas plus one liver metastatic deposit.*

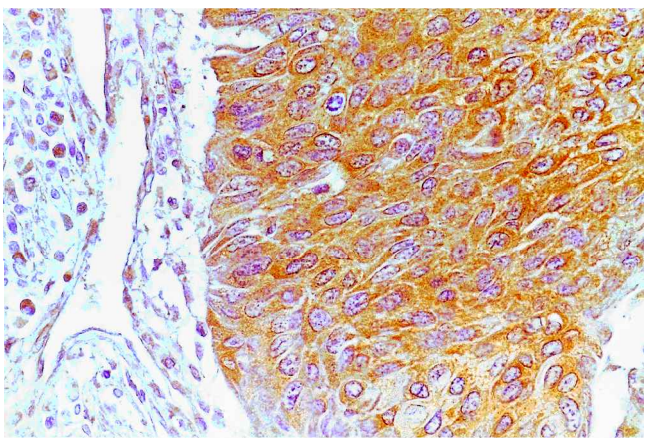

Figure 3. *Case no. 1: photomicrograph of the pancreatic tumour showing an acinus and its adjacent duct, with positive (brown) staining for PTH-rP (original magnification ×400).*

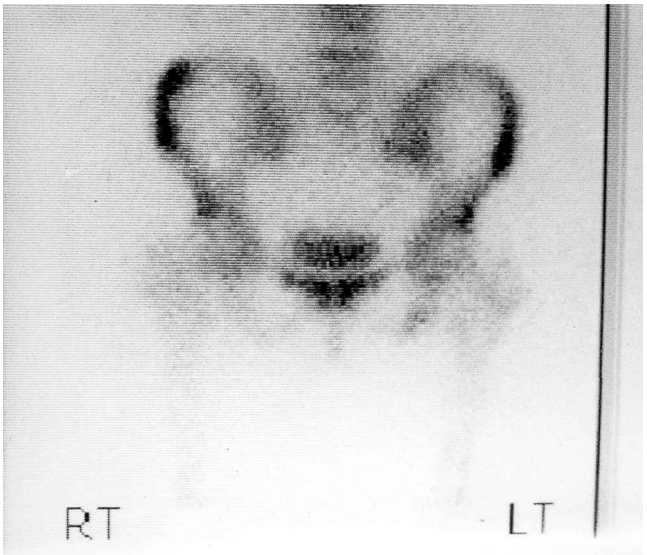

Figure 4. *Case no. 1: bone scan showing bony metastases in the pelvis.*

recurrent hypercalcaemia (3.35–3.21 mmol/L) plus two further hepatic artery embolisations during late 2000. Targeted octreotide therapy is now being considered since scintigraphy shows plentiful somatostatin receptors within the metastatic deposits.

Case no. 2

During an open cholecystectomy for gallstones, multiple liver metastases were discovered in a 41-year-old man. Biopsies showed neuroendocrine tumour and CT scan revealed a lesion in the pancreatic tail. Thereafter the patient declined conventional medical treatment and was lost to follow-up, but 4 years later he developed symptomatic hypercalcaemia (4.5 mmol/L) with undetectable serum PTH but elevated levels of PTH-rP (7.8 pmol/L) and somatostatin (774 pmol/L: normal <100 pmol/L). Hepatic artery embolisation produced only temporary control. One year later radical distal pancreatectomy was undertaken for a 20-cm tumour with *en bloc* excision of the spleen, left kidney, adrenal and colon. He recovered well with falls in PTH-rP (1.1 pmol/L) and calcium (2.8 mmol/L), but persistent elevation of somatostatin (1141 pmol/L). Histological examination showed typical features of a pancreatic neuroendocrine tumour with vascular invasion and lymph node involvement. Immunohistological staining was positive for NSE, chromogranin, somatostatin and PTH-rP. It was negative for pancreatic polypeptide, insulin and VIP. Four months postoperatively he developed seizures due to recurrent hypercalcaemia (and tumour) and died soon afterwards.

Discussion

Hypercalcaemia is one of the most frequent types of paraneoplastic syndrome [7,8]. Malignant hypercalcaemia can be classified as local osteolytic, resulting from bone resorption mediated by primary or metastatic tumour cells, or hormonal, mediated by humoral factors such as PTH-rP [8]. Hypercalcaemia associated with endocrine pancreatic tumours is commonly due to primary hyperparathyroidism, with elevated serum PTH levels as part of multiple endocrine neoplasia type I [9]. Hypercalcaemia is a rare feature of islet cell carcinoma of the pancreas, although many such patients have increased serum levels of PTH-rP with normal levels of PTH [3]; this combination discriminates between primary hyperparathyroidism and PTH-rPoma [3,10]. Both our patients presented with a neuroendocrine pancreatic tumour, hypercalcaemia and increased serum PTH-rP level. Immunohistochemical staining was positive in each case, and one patient (case no. 2) developed concomitant features of somatostatinoma (gallstones and mild diabetes).

PTH-rP is a single-chain peptide, and its amino terminal domain has considerable similarity to PTH [3]. The PTH-rP gene is located on human chromosome 12 and is thought to belong to the same gene family as PTH [11]. PTH-rP is expressed in response to a variety of physiological stimuli and acts as an autocrine, paracrine and endocrine peptide involving calcium translocation and/or signalling [12]. If PTH-rP is produced in excess, it exerts an endocrine effect by interacting with the classical bone and kidney PTH-receptor leading to the humoral hypercalcaemia of malignancy [13]. Serum PTH-rP level can be used as a tumour marker to indicate treatment effectiveness and disease progression (as in both our patients) [3].

A search of the world literature has revealed 31 previously reported patients [3–6,9,10,14–28] (Table 1), in whom endocrine pancreatic tumours have been associated with humoral hypercalcaemia of malignancy due to PTH-rP hypersecretion. As in our cases, these tumours show a predilection for young people (median age 44.5 years, range 8–77 years) and have an equal sex distribution (M:F = 15:17). They tend to be large (median diameter 10 cm); they arise within the tail of pancreas (53%), body (32%) or head (16%). They are slow-growing. From available data,

Table 1. *Details of 32 patients with neuroendocrine pancreatic carcinoma associated with hypercalcaemia*

Patient no.	Sex	Age (yr)	Size (cm)	Location	Metastases	Surgical resection	Other treatment	Reference no.
1	M	57	10	B	L	–	SZT	18
2	M	8	*	*	L	PP	–	19
3	F	62	*	*	L	–	SZT	20
4	F	60	10	T	L	–	5-FU+ SZT	4
5	M	41	14	H	L	PP	HAE	21
6	F	47	9	B	Nil	TP	–	22
7	M	44	*	*	L	*		23
8	F	37	5	T	L	–	SA	9
9	F	42	>10	B	L	–	SA	24
10	M	30	8	T	L	DP	–	5
11	F	60	>10	H	L	–	α-INF	5
12	M	45	12	T	Nil	DP	SZT	25
13	F	77	*	T	L	DP	SZT	26
14	F	47	11	T	L	DP	–	16
15	M	30	*	B	Nil	–	SZT	27
16	M	41	18	*	L	PP	–	15
17	M	43	15	B	L	DP	–	15
18	M	64	7	T	L, K, P, LN	–	Steroids	15
19	F	39	12	B	LN	PP	–	28
20	M	36	*	*	L, S	–	HAE	17
21	F	75	8	T	Nil	–	SA	10
22	F	45	3	H	L	W	SA	14
23	F	42	*	*	L, S	*		3
24	F	45	*	*	L	*		3
25	M	64	*	*	L	*		3
26	M	61	*	*	Nil	*		3
27	F	38	*	*	L	*		3
28	M	20	*	*	L	*		3
29	F	47	*	*	L	*		3
30	F	51	*	*	L	*		3
31	M	41	20	T	L, K, S, C,LN	DP	HAE	6
32	F	33	11	T	L, S, Bo, LN	DP	HAE, SA	†

H = head; B = body; T = tail; L = liver; S = spleen; K = kidney; C = colon; P = pleura; LN = lymph nodes; Bo = bone; PP = partial pancreatectomy; DP = distal pancreatectomy; TP = total pancreatectomy; W = Whipple's procedure; SZT = streptozotocin; 5-FU = 5-fluorouracil; α-INF = α-interferon; SA = somatostatin analogues; HAE = hepatic artery embolisation.

*Unknown.

†Case no. 1.

24 patients were alive at a median 6.9 year follow-up. For the other eight patients who died, the median survival time was 6.6 years. Metastatic spread (in 81% of patients) was usually to the liver (n=26) but also to the spleen (four), regional lymph nodes (four), left kidney (two) and (once each) bone, pleura and colon.

Management of the humoral hypercalcaemia of malignancy is aimed at the control of serum calcium, preferably by removal of the tumour [10], but alternatively by pharmacological means including forced diuresis and agents such as calcitonin, plicamycin, biphosphonates, gallium nitrate or glucocorticoids [29]. Pancreatectomy was feasible in 13 of 23 patients with available data, and resection was associated with decreased serum PTH-rP and serum calcium levels [5,6,16]. Palliative chemotherapy (streptozotocin, 5-fluorouracil, α-interferon, steroids) was given alone in six patients and after resection in two. Somatostatin analogues (octreotide, lanreotide) have recently been introduced and proved useful in one of our patients (case no. 1), as well as in another four reported cases [9,10,14]. Hepatic artery

embolisation offers another means of controlling hypercalcaemia related to liver metastases that was used in three patients [6,17]. Both our patients underwent resection of large cancers of the distal pancreas with resultant reduction in serum PTH-rP levels, and both had subsequent hepatic artery embolisation in an attempt to control the symptoms of recurrent disease. One patient is alive with multiple metastases, but the other died four months postoperatively from widespread disease.

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