CASE REPORT

Malignant hypercalcaemia related to parathyroid hormone-related peptide (PTHrP) secretion from a metastatic pancreatic neuroendocrine tumour (NET)

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Accepted 9 March 2017

SUMMARY

A 54-year-old woman presented to our centre with acute abdominal pain and vomiting. Routine blood tests showed severe hypercalcaemia (>4 mmol/L). Serum parathyroid hormone (PTH) was suppressed. CT scan detected a pancreatic mass and some liver lesions, initially suspicious for metastatic pancreatic adenocarcinoma. Liver biopsy however revealed the presence of a well-differentiated, grade 1, metastatic neuroendocrine tumour (NET) where prognosis is considerably better. Serum PTHrP was raised, indicating paraneoplastic hypercalcaemia, most likely secondary to the pancreatic NET. Following injection of a short-acting somatostatin analogue octreotide, serum PTHrP levels normalised within 24 hours, causing a rapid drop of serum calcium below the lower limit of normal and an immediate compensatory rise of serum PTH. Ongoing treatment with long-acting somatostatin analogues together with replacement with calcium carbonate, vitamin D3 and once weekly alendronic acid resulted in stable normal adjusted calcium levels over a 3-month follow-up period.

BACKGROUND

Hypercalcaemia is a common finding in patients with systemic malignancies¹ and can be related to osteolysis in patients with metastatic bone involvement, immobilisation and dehydration.² Malignancy-associated severe hypercalcaemia can also result from excess production of PTHrP, which is known as humoral hypercalcaemia of malignancy (HHM).^{3–4} HHM in patients with pancreatic NET is extremely rare.⁵ In contrast to a previously published case,⁵ our patient exhibited an immediate and sustained response to treatment with somatostatin analogues (short-acting octreotide 200 mcg intramuscular; followed by long-acting Lanreotide LAR 120 mg deep SC once monthly), thus preventing further episodes of life-threatening hypercalcaemia.

CASE PRESENTATION

A 54-year-old woman with no significant medical history was referred for urgent endoscopy for dysphagia and weight loss, when she was noted to be acutely confused and ataxic. History at that time indicated a rapid onset of nausea and vomiting and poor coordination for ~2 weeks. Some upper abdominal pain was also reported. There was no weakness or loss of sensation, but the patient mentioned intermittent paraesthesia in her fingers. On examination at admission, Glasgow Coma Scale

(GCS) was 14. Tone, power and sensation were normal in upper and lower limbs, although gait was ataxic and the patient showed bilateral impaired coordination in the upper and lower limbs. Her abdomen was soft with some epigastric tenderness,

Figure 1 Key biochemical markers. Changes in serum-adjusted calcium (normal range 2.10–2.58 mmol/L) (A), parathyroid hormone (PTH) (normal range 1.1–4.2 pmol/L) (B) and parathyroid hormone-related peptide (PTHrP) (normal range <1.9 pmol/L) (C) over a 140 day observation period. Asterisk indicates start of non-specific treatment for hypercalcaemia (rehydration and pamidronate disodium infusion); Down arrow indicates start of treatment with short-acting somatostatin analogues (Octreotide 200 mcg SC; followed by ongoing treatment with long-acting somatostatin analogues (Lanreotide Autogel 120 mg once monthly per deep subcutaneous injection).

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To cite: Symington M, Davies L, Kaltsas G, *et al.* *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2017-219692

and there was a palpable liver edge to 4 cm below the rib cage. She was therefore admitted for further investigations.

INVESTIGATIONS

A CT head for investigation of acute confusion showed no acute pathology. Serum-adjusted calcium was excessively raised at 4.01 mmol/L, together with suppressed serum PTH (figure 1A and B). Serum creatinine was acutely raised from previously normal to 122 µmol/L, reflecting dehydration related to severe hypercalcaemia. Treatment with rehydration and pamidronate disodium infusion transiently normalised serum-adjusted calcium to 2.44 mmol/L, but this effect was short lived, with serum-adjusted calcium levels raising again to 2.8 mmol/L within 18 days (figure 1A). Endoscopy that was undertaken to investigate weight loss and gastrointestinal symptoms showed mild oesophagitis only.

CT thorax, abdomen and pelvis revealed a 4 cm×5 cm lobulated soft tissue lesion within the tail of the pancreas and multiple liver lesions, the largest being 8.2 cm in diameter. This CT also showed a lesion in the right breast that on biopsy and subsequent surgical removal revealed a synchronous 24 mm, grade 3, hormone receptor triple negative, invasive, ductal breast carcinoma, pT2 pN0 (0/3) pMx; with no relation to the pancreatic NET. A liver biopsy showed a metastatic well-differentiated pancreatic NET with positive neuroendocrine markers synaptophysin, chromogranin A and CD56 and a low Ki-67 proliferative index <1% (grade 1).

Excess PTHrP secretion by the pancreatic NET was suspected to be the driving factor for the patient's life-threatening hypercalcaemia and raised circulating PTHrP concentrations were

confirmed in a subsequent blood test (figure 1C), along with raised levels of plasma chromogranin A (352 pmol/L; upper limit of normal (ULN) 61 pmol/L), chromogranin B (2503 pmol/L; ULN 161 pmol/L) and gastrin (46 pmol/L; ULN 41 pmol/L).

Contrast MRI confirmed three arterial enhancing lesions in the liver and a primary lesion in the pancreas (figure 2A and B). A somatostatin receptor scintigraphic (SRS) octreotide scan showed an avid tail of pancreas mass and three large, up to 8 cm, avid lesions in the liver, in further agreement with a diagnosis of a well-differentiated metastatic pancreatic NET (figure 2C). Notably, the 24 mm breast tumour was negative on SRS octreotide scan, further supporting that PTHrP excess was caused by the pancreatic NET rather than the breast tumour.

Following injection of somatostatin analogues, serum-adjusted calcium dropped within 72 hours and declined further below normal to 1.81 mmol/L over the next 8 days, causing mild symptoms of hypocalcaemia including tingling. This responded well to replacement with two times per day combined calcium carbonate 1.5 g and colecalciferol (vitamin D3) 1400 units, resulting in stable adjusted calcium <2.31 mmol/L.

No further complications of hypercalcaemia were identified after resolution of initial neurological symptoms and normalisation of renal function tests. There was no suspicion of renal calculi on imaging and ECG was normal, including the QT interval.

DIFFERENTIAL DIAGNOSIS

Initial differentials included a metastatic pancreatic carcinoma. The breast lesion was found to be a synchronous primary

Figure 2 Imaging. Coronal MRI images of the upper abdomen in arterial phase, showing three large enhancing lesions in the liver segments 3, 5/6 and 7/8, measuring 5.5, 7.8 and 8.2 cm, respectively (A and B) and two smaller lesions in segments 6/7 and 6 peripherally; and the 4.4 cm enhancing primary lesion in the tail of the pancreas (B). (C) Images from a SRS octreotide scan 4 and 24 hours following intravenous administration of octreotide, with evidence for a markedly avid SRS avid lesion in the pancreatic tail and three markedly avid lesions in the liver, involving both lobes. SRS, somatostatin receptor scintigraphy.

malignancy. An initial differential included a metastasis from the pancreatic tumour, which was ruled out by histological investigation.

TREATMENT

Acute treatment was given for the raised calcium including intravenous fluids and pamidronate disodium infusion. Following histological diagnosis of a well-differentiated metastatic pancreatic NET with suspected paraneoplastic PTHrP secretion, treatment with somatostatin analogues was started (short-acting octreotide 200 mcg intramuscular; followed by long-acting Lanreotide LAR 120 mg deep SC once monthly). Oral bisphosphonates (alendronic acid 70 mg weekly PO) were started to reduce the risk of hungry bones syndrome, which can result from a rapid increase in bone formation following removal of PTHrP excess. Initial supportive treatment with oral calcium and vitamin D3 preparations was needed due to immediate and dramatic reduction of adjusted calcium levels following a single injection of short-acting somatostatin, with adjusted calcium dropping to 1.81 mmol/L and a compensatory immediate raised of PTH to 19.3 pmol/L. The observed rapid correction of PTHrP and serum calcium levels after the first injection of somatostatin analogues strongly suggested that severe hypercalcaemia was related to paraneoplastic PTHrP secretion from the pancreatic NET, rather than the synchronous breast cancer that did not express any neuroendocrine markers. This assumption was further supported by the raised NET biomarkers chromogranin A and B in circulating blood, sampled after 10 hours of overnight fasting; and the fact that the relatively large breast lesion was negative on SRS octreotide scan. After replacement with calcium and vitamin D3, serum-adjusted calcium and PTH normalised, whereas PTHrP remained below the measurement limit in follow-up blood tests over 3 months. Time lines of key biochemical markers are presented in [figure 1](#).

The synchronous primary breast carcinoma (pT2, 25 mm tumour) was treated with wide local excision and adjuvant chemotherapy with FEC-100, Carboplatin and Docetaxel, 4+4 cycles/6 months. Radiotherapy is planned as a further measure.

For the pancreatic NET, the patient will be considered for further treatment after chemotherapy for the breast cancer. This may include distal pancreatectomy for the pancreatic primary, especially in case of possible pressure symptoms. The hepatic masses are unlikely amenable for surgical resection, but palliative reduction of tumour mass may include consideration of transhepatic embolisation (TAE) of the large liver lesions. Chemotherapy treatment with streptozocin or biological treatment options (Sunitinib or mTOR inhibitors; and possibly peptide receptor radionuclide therapy (PRRT)) will be further considered.

OUTCOME AND FOLLOW-UP

Following initiation of treatment with once monthly SC somatostatin analogue injections, adjusted serum calcium levels remained lower end of normal over a 3-month follow-up period. Treatment is currently focused on the breast carcinoma. For the pancreatic NET, the patient currently continues on treatment with once monthly long-term somatostatin analogue injections and monitoring via the Specialist NET service, with further treatment options being considered as outlined above.

DISCUSSION

Hypercalcaemia is a well-documented paraneoplastic phenomenon. It is more widely reported being secreted by breast cancer or squamous cell lung cancer⁶ and has only rarely been reported

in NET.^{3 7} In the few cases where PTHrP secretion and hypercalcaemia have been documented in metastatic pancreatic NET, controlling hypercalcaemia has typically been challenging.^{3 5} PTHrP causes hypercalcaemia because it shares the same N-terminal end as parathyroid hormone and therefore it is able to bind to the type 1 PTH receptor and thus imitate many of the actions of PTH, including increased bone resorption and calcium reabsorption in the kidneys.⁸ This can lead to severe and life-threatening low PTH hypercalcaemia.

Hypercalcaemia in this context is often difficult to control, and this type of dramatic response to a single agent (somatostatin analogue) is rarely seen. The histological diagnosis of a pancreatic NET as the cause of paraneoplastic PTHrP secretion allowed initiation of a tailored and highly effective treatment plan. Hypercalcaemia in a patient with malignancy is often an end-stage complication treated palliatively, but it is important to remember that prognosis in patients with well-differentiated pancreatic NET with metastatic liver is considerably better, with reported average survival of some 7 years⁹ based on 12 years data; as compared with short-term survival of several months only in patients with metastasised pancreatic adenocarcinoma.¹⁰ Cases with metastatic pancreatic NET and survival up to 125 months with good quality of life have been reported.^{9 11-16}

Patient's perspective

Previously to all of this starting, I had been completely well and had even been on holiday 2 weeks previously to my hospital admission, with no concerns. I then became progressively unwell over a period of about 10 days, with vomiting, indigestion pain and poor coordination. I was admitted to hospital and diagnosed with hypercalcaemia. Once a pancreatic mass had been identified on a scan it was a scary thing to hear. However, we had some hope that there was a chance the mass was a neuroendocrine tumour, something we had never heard of but understood may mean my survival chances would be better. Knowing how well I had been recently we were hopeful this was the case and fortunately my diagnosis was very quickly confirmed to be a neuroendocrine tumour. I immediately met the NET team and the specialist nurse explained everything. The relief of the diagnosis was huge for me and my husband as there seemed to be a number of treatment options available to me. There was still the problem of my high calcium and of the breast lump that had been seen on one of my scans. The calcium immediately responded to my somatostatin injections for my NET, so much so that I started a number of other tablets to maintain my calcium levels and keep them stable. It was then a slightly difficult period while the breast lump was investigated to find out if it was related to the NET or a separate cancer. It is very rare to have two simultaneous cancers but it turns out in my case that was the result. It has been difficult being treated for two separate cancers at the same time due to the need to ensure that the treatments are coordinated. I have now had surgery on my breast and have started chemotherapy. I am continuing with my somatostatin and calcium stabilising drugs and fortunately my neuroendocrine tumour is stable and treatment for this will be decided once my breast cancer treatment is complete. I am happy to be part of a case report as I know my diagnosis is rare and this may create more awareness of the disease.

Learning points

- ▶ Neuroendocrine tumours (NETs) are a relatively rare but important differential in patients with pancreatic lesions. It is crucial to establish a diagnosis, ideally histologically, as there is currently effective, specific treatment for well-differentiated NET. Owing to the nature of the disease, the prognosis is greatly different from pancreatic adenocarcinoma.
- ▶ Severe hypercalcaemia can be caused by excess PTHrP secretion, with the key hint being low serum PTH concentrations in the presence of raised calcium levels. While initial resuscitation with fluid and pamidronate is important, somatostatin can be a very effective treatment in patients with NET-related PTHrP excess.
- ▶ Patients can have synchronous primary malignant tumours and although metastatic disease needs to be considered, histological diagnosis remains a key aspect to establish an appropriate and effective management plan.

Acknowledgements Helga Perry, Electronic Systems & Resources Librarian at University Hospitals Coventry and Warwickshire NHS Trust, provided support with manuscript preparation, editing and proof reading.

Contributors MS and MOW wrote the manuscript. LD supported the clinical care for the patient and has reviewed the manuscript. GK had provided important intellectual input and has reviewed the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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