The Management of Resistant Hypercalcaemia Secondary to Cancer of Unknown Primary and Presenting with Pancreatitis

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Abstract: We present a 31-year-old female who presented to the general surgical take with epigastric pain associated with a raised amylase and corrected calcium on admission. Computed tomography confirmed acute pancreatitis and also demonstrated a 15 cm liver tumour. She was subsequently diagnosed with cancer of unknown primary with liver metastases. The patient's pancreatitis symptoms improved with conservative management, but her calcium proved quite resistant to basic measures. Further input was sought from the medical on-call endocrinology and oncology teams to help manage this patient's hypercalcaemia, which included pamidronate, zolendronate, and denusomab, but ultimately it only improved significantly following chemotherapy. This case to our knowledge is the only one of its kind and highlights the importance of early multidisciplinary team involvement across specialties to help manage complex patients.

Keywords: hypercalcaemia; pancreatitis; cancer of unknown primary; positron emission tomography

1. Introduction

Untreated hypercalcaemia can be life threatening. The most common cause of hypercalcaemia due to non-parathyroid hormone (PTH) dependent causes is malignancy [1]. Hypercalcaemia occurs in up to 30% of patients with malignancy [2]. Cancers of unknown primary (CUP) are typically aggressive cancers and account for approximately 3–5% of cancer diagnoses [3].

Severe pancreatitis is a life-threatening condition, of which hypercalcaemia is an uncommon cause, with a reported prevalence of just 1.5–13% [4]. The majority of severe pancreatitis is secondary to PTH-dependent causes. The management of both of these conditions in combination with CUPs can provide a challenge for clinicians and are best treated using a multidisciplinary approach.

We present a young woman admitted under general surgery for treatment of pancreatitis who had a significant refractory hypercalcaemia to normal measures of treatment. We sought input from four other specialties to help manage her hypercalcaemia, which was later found to be due to CUP metastasising to the liver. To our knowledge this is the only documented case of its kind.

2. Case Presentation Section

A 31-year-old female presented to general surgery with a one-day history of epigastric pain and polydipsia on a background of four weeks' history of intermittent vomiting and malaise. She had no history of previous similar episodes. Her past medical history included epilepsy and asthma. Her medications were lamotrigine and salbutamol. She was a current smoker of 10 pack-years. She had no significant family history.

On examination, she had generalised abdominal tenderness with epigastric guarding. Murphy's sign was positive.

Blood tests revealed a white cell count of 16.5×10^9/L (3.5–9.5×10^9/L), C-reactive protein of 56.5 mg/L (<5 mg/L), amylase of 226 IU/L (28–100 IU/L), and adjusted calcium of 3.19 mmol/L (mmol/L)

A computed tomography (CT) scan confirmed acute pancreatitis and identified a large 15 cm tumour, which almost entirely replaced the left lobe of the liver and infiltrated the left branch of the portal vein.

Further blood tests on day two of admission revealed an adjusted calcium of 4.09 mmol/L (2.2–2.6 mmol/L), PTH of 0.8 pmol/L (1.6–6.9 pmol/L), phosphate of 0.52 mmol/L (0.8–1.5 mmol/L), cortisol and thyroid stimulating hormone were normal.

Magnetic resonance imaging (MRI) scan of the liver performed on day two also demonstrated the large tumour replacing the lateral left lobe of the liver (Figure 1). There was a further small lesion within the caudate lobe consistent with another tumour. Two further small abnormalities were present in the right lobe of the liver, one of which was suspicious of being a third tumour. The MRI features were not suggestive of hepatocellular carcinoma. No gallstones were present.
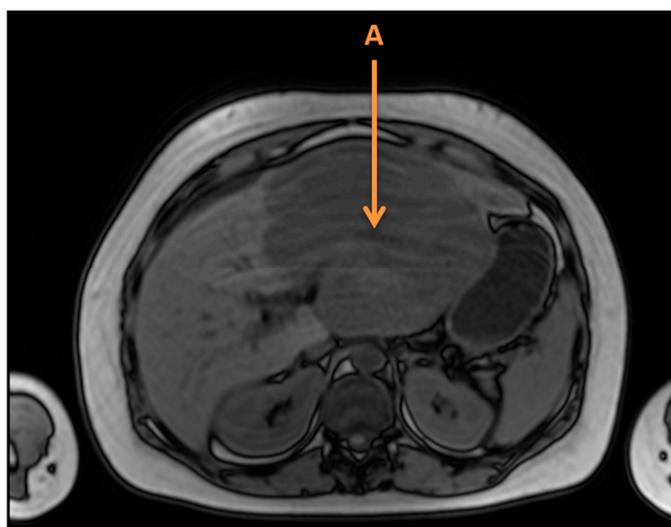

Figure 1. Axial reconstruction. T1 magnetic resonance imaging of abdomen and pelvis showing a large mass in the left lobe of the liver. (**A**): Tumour.

A CT of the thorax was performed on day nine of admission to stage disease. The lungs were clear. There were no significant mediastinal or axillary nodes and no bony abnormality was seen.

Myeloma screening, hepatitis serology and chromogrannin A were negative. A breast examination did not identify any palpable masses or axillary lymphadenopathy. A parathyroid-related protein (PTHrP) was also requested, however this was not available at our institution.

Positron emission tomography (PET) fluourodeoxyglucose (FDG) scan was performed on day 21 of admission. The large lesion replacing the left lobe of the liver and two adjacent lesions were both found to be metabolically active. There was suspicion of a further lesion in the right lobe of the liver. However, there was no evidence of metabolically active extrahepatic disease.

Ultrasound-guided biopsy supported a metastatic lesion consistent with poorly differentiated carcinoma with basaloid features and excluded hepatocellular carcinoma or poorly differentiated neuroendocrine carcinoma.

Following discussion with the on call medical team, hypercalcaemia was initially treated with intensive intravenous fluids with five litres prescribed over the first 24 h. There was a good initial response to fluid therapy (Figure 2, square) and the adjusted calcium dropped to 3.52 mmol/L over two days. On day 5 of admission, serum calcium began to rise again and 60 mg intravenous pamidronate (Figure 2, diamond) was given, as advised by endocrinology services.
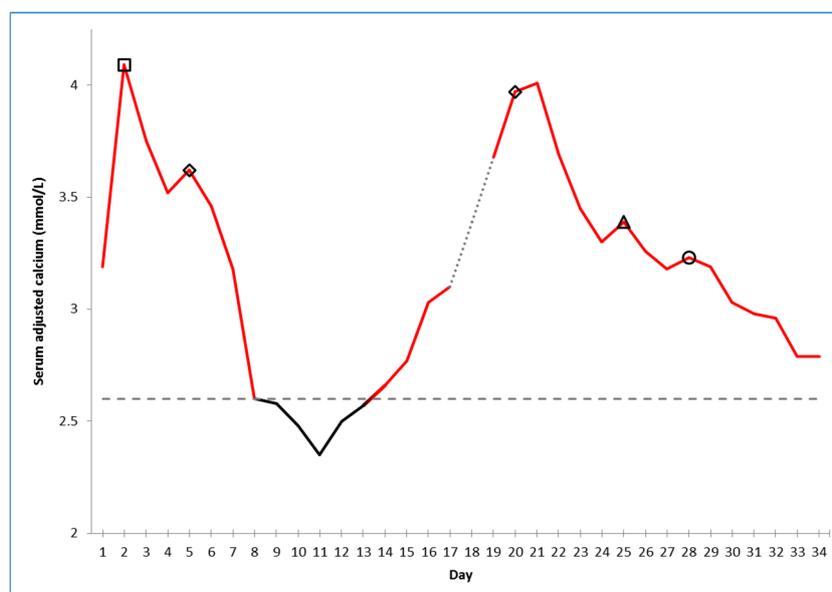
Figure 2. Graphical representation of adjusted calcium in response to medical therapies. Square, initiation of fluid therapy. Diamond, 60 mg intravenous pamidronate. Triangle, 5 mg intravenous zolendronate. Circle, 120 mg subcutaneous denusomab.

Initially, pamidronate therapy was effective in reducing the adjusted calcium level. After six days, adjusted calcium levels began to rise again sharply and repeat pamidronate was prescribed (Figure 2, diamond). After a delay in effect (where adjusted calcium rose above 4 mmol/L), repeated pamidronate therapy was only partially effective, with calcium levels rising four days after the second dose. Further discussion was held with endocrine and oncology services and zolendronate therapy was advised. Administration of 5 mg intravenous zolendronate (Figure 2, triangle) lowered the levels slightly; however, just two days later, the adjusted calcium again rebounded upwards.

Following further discussion with endocrinology and oncology, the decision was made to trial a single 120 mg dose of subcutaneous denusomab (Figure 2, circle). This resulted in stabilisation of serum adjusted calcium levels below 3 mmol/L, though they remained elevated.

The results of imaging and histopathology investigations were discussed in the departmental multi-disciplinary team (MDT) meeting and the decision was made to refer the patient to the care of the carcinoma of unknown primary (CUP) MDT for further investigation and management

Following discharge from general surgical services, the patient remained an inpatient under oncology services for a further week. Hypercalcaemia was managed with zolendronate. She remained hypercalcaemic, though levels under 3 mmol/L were accepted by the team providing she remained asymptomatic.

She began palliative chemotherapy (epirubicin, cisplatin, and capecitabine) for CUP under oncology outpatients shortly after discharge, having been investigated for both breast and cervical cancer. Ultimately, it was chemotherapy that resolved the hypercalcaemia. Whilst the hypercalcaemia improved (2.45 mmol/L), there was only a partial response on the tumour size as per the response evaluation criteria in solid tumours criteria. She sought a second opinion from another tertiary centre and had an attempted curative liver resection which was unsuccessful and came back to our trust for palliative chemotherapy. The patient died 14 months following her initial admission.

3. Discussion

The patient was found to be hypercalcaemic on admission, which was persistent and refractory to treatment. The causes of hypercalcaemia can broadly be divided into PTH-dependent and non-PTH-dependent causes. PTH-dependent causes comprise primary and tertiary hyperparathyroidism of

various aetiologies. Meanwhile, the most common non-PTH-dependent cause is malignancy. Other PTH-independent causes include drugs (thiazide diuretics, calcium, vitamin D, lithium, vitamin A, and PTH), renal failure, and endocrine disorders [1].

Hypercalcaemia occurs in up to 30% of patients with malignancy [2]. A recent systematic analysis of 37,442 cancer patients in the United Kingdom showed hypercalcaemia occurred in less than 1% [5]. Hypercalcaemia to the degree found in this patient is relatively uncommon. Less than 3% of patients with hypercalcemia of malignancy, in one study, had serum calcium levels over 4 mmol/L [6]. In carcinoma of unknown primary, moderate to severe hypercalcaemia (as seen in this case) occurs in 2–3% of patients [4].

Up to 80% of malignancy-related cases of hypercalcaemia are due to parathyroid hormone-related protein (PTHrP) secretion—the so-called "humoral hypercalcaemia of malignancy" [2,7,8]. PTHrP is structurally similar to PTH and causes both hypercalcaemia (through increased renal tubular reabsorption of calcium and activation of osteoclasts via receptor activator of nuclear factor kappa-B ligand) and hypophosphataemia (through urinary phosphate excretion) [7,9]. The presence of humoral hypercalcaemia of malignancy is a poor prognostic indicator [8]. PTHrP can be released by different types of cancer such as head, neck, breast, lung, and renal as well as haematological malignancies [10].

Rarely, ectopic PTH or 1-alpha-hydroxylase secretion by the tumour may be the cause [7,9]. Due to the absence of bone metastases in our case, PTHrP release is the presumed mechanism of hypercalcaemia, though this unfortunately could not be confirmed as our trust does not have the capacity to perform the assay. A summary of common conditions grouped be causes is summarised in Table 1.

Table 1. Adapted from Minisola [1]—Common causes of hypercalcaemia.

Causes	Conditions
Parathyroid hormone mediated	Sporadic (adenoma, hyperplasia, or carcinoma); Familial (multiple endocrine neoplasia 1, 2a, or 4, hyperparathyroidism jaw tumour syndrome, familial isolated hyperparathyroidism, familial hypocalciuria hypercalcaemia); Ectopic parathyroid hormone in malignancy (rare); "Tertiary" hyperparathyroidism.
Malignancy	Humoral hypercalcaemia of malignancy (parathyroid hormone related protein); Local osteolysis (cytokines, chemokines, parathyroid hormone related protein); Ectopic parathyroid hormone in malignancy (rare); Calcitriol related hypercalcaemia.
Vitamin D related	Granulomatous disease (for example, sarcoidosis, tuberculosis, berylliosis, coccidiodomycosis, histoplasmosis, leprosy, inflammatory bowel disease, foreign body granuloma); Vitamin D intoxication (vitamin D supplements, metabolites, or analogues).
Endocrine disorders	Thyrotoxicosis; Adrenal insufficiency; Pheochromocytoma; VIPoma (Verner–Morrison) syndrome
Drugs	Thiazide diuretics; Lithium; Milk–alkali syndrome (calcium and antacids); Vitamin A; Parathyroid hormone.
Other	Coexisting malignancy and primary hyperparathyroidism; Immobilisation; Acute renal failure; Chronic renal failure treated with calcium and calcitriol or vitamin D analogues; Renal transplant.

Initial treatment for hypercalcaemia of malignancy is with intravenous hydration with a normal saline, at rates of up to 300 mL/h after initial resuscitation. Following this, bisphosphonates are now first-line therapy. Their mechanism of action is to induce osteoclast apoptosis and reduce osteoclastic bone resorption and therefore they should be effective in both PTHrP-mediated and locally-osteolytic hypercalcaemia of malignancy due to bone metastases [7]. Pamidronate initially had beneficial effect in our patient. However, this was not prolonged and subsequent treatment with bisphosphonates was unsuccessful in controlling the hypercalcaemia.

Further management options include calcitonin, glucocorticoids (alone or in combination with calcitonin), and denosumab. Denosumab, a monoclonal antibody to RANKL is often effective in hypercalcaemia refractory to bisphosphonates [7]. Denusomab stabilised the serum calcium to below 3 mmol/L in this case but did not result in normalisation of calcium levels. Ultimately, the aim of management is to treat the underlying malignancy and only on instigation of chemotherapy did the patient's calcium finally normalise for a prolonged period.

PET fluorodeoxyglucose (FDG) was used in our trust to look for metabolically active areas and can detect various tumour types. The majority of neuroendocrine tumours tend to be metabolically inactive and thus FDG is not adequate in these cases [11]. Somatostatin receptor-based imaging techniques such as DOTA PET have been shown to be useful imaging tools in diagnosing neuroendocrine tumours [11]. ^{68}Ga-DOTATATE PET/CT has shown an even greater sensitivity for detecting neuroendocrine tumours at 80–100% [12].

CUPs are typically aggressive cancers, accounting for approximately 3–5% of cancer diagnoses [3]. CUPs can be divided into clinicopathological subsets based on a number of features including site, clinical features and histopathology, which help guide investigation and treatment [3]. Treatment is primarily with chemotherapy; however, depending on the subset, surgical and other targeted treatments may be offered [3].

Prognosis of CUPs is poor: an analysis of CUP patients with liver metastasis and histological diagnoses of either adenocarcinoma or undifferentiated carcinoma (as seen in our case), found median survival to be just 6–7 months [13].

In this case, hypercalcaemia caused the patient to present with acute pancreatitis. Hypercalcaemia is an uncommon cause of pancreatitis, which most frequently occurs secondary to hyperparathyroidism [14]. There are several proposed mechanisms for how hypercalcaemia causes pancreatitis. These include secretory blockade and stimulation of trypsinogen secretion, as well as mitochondrial dysfunction with resultant adenosine triphosphate depletion leading to acinar cell necrosis [15].

There are several case reports of pancreatitis secondary to hypercalcaemia of malignancy in the literature. These are frequently of neuroendocrine tumours [16,17], haematological malignancies [18–23] or solid cancers with bone metastasis [24–28]. There is a single documented case of acute pancreatitis secondary to hypercalcaemia related to cancer of unknown primary, however this was a neuroendocrine tumour, with bone metastases present [29]. To our knowledge there are no documented cases of pancreatitis secondary to CUP without bone metastases in the literature.

Multidisciplinary team (MDT) working was integral to this case. Formal MDT meetings have been demonstrated to improve survival and patient experience amongst cancer patients [30–32]. Furthermore, they provide an educational forum for MDT participants and for junior doctors [32]. From a general surgical perspective managing a pancreatitis patient is a common occurrence. It was evident very early in this patient's treatment that the pancreatitis was improving but her symptoms due to hypercalcaemia were not and further specialist involvement was required.

Due to the complicated nature of this case, not getting a specific tissue diagnoses made planning post treatment of the hypercalcaemia challenging; however, early involvement with oncology helped to not only manage the hypercalcaemia but also the patient in the long term. We fully advocate early involvement of medical specialties at the earliest relevant opportunity.

Consent: Consent was gained directly from the patient.

4. Conclusions

Management of pancreatitis can be further complicated when hypercalcaemia is the cause. Cancer of unknown primary can cause hypercalcaemic pancreatitis. Managing resistant hypercalcaemia requires a multidisciplinary approach.

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