Refractory hypercalcaemia secondary to localised gastrointestinal stromal tumour

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ABSTRACT

Gastrointestinal stromal tumours are a rare form of intra-abdominal neoplasm derived from mesenchymal tissue, typically presenting with abdominal pain, anaemia or bleeding into the bowel or abdominal cavity. Hypercalcaemia is an unusual complication, having been documented in only seven previous patients, all of whom had advanced metastatic disease. We present a case of treatment-resistant hypercalcaemia in a patient with non-metastatic gastrointestinal stromal tumour, which resolved following excision of the tumour.

KEYWORDS

Gastrointestinal stromal tumours – Gastrointestinal stromal tumour hypercalcaemia

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Case report

A 50-year-old male taxi driver presented with a one-month history of generalised abdominal pain associated with nausea, anorexia and unintentional weight loss of approximately 8 kg. The abdominal pain was constant and was exacerbated by bowel movements, and not relieved with simple analgesia. He also complained of polyuria and polydipsia, which had progressed gradually over six months, and mild lower back pain. His medical history was unremarkable with the exception of idiopathic sinus tachycardia, for which he took bisoprolol. On initial assessment, he was noted to be underweight but haemodynamically stable. Examination revealed a large mass in the lower abdomen that was tender on palpation but with no signs of peritonism. Bloods tests showed a normocytic anaemia (haemoglobin 106 g/l, mean corpuscular volume 85.5 fl), raised inflammatory markers (C-reactive protein 61 mg/l) and hypercalcaemia (adjusted Ca^{2+} 3.67 mmol/l), with normal liver and renal function and no other electrolyte abnormalities. Parathyroid hormone (PTH) was appropriately low at 1.1 pmol/l.

The patient was admitted to hospital and computed tomography of the chest, abdomen and pelvis was performed, which showed a large heterogeneous intraperitoneal mass in the lower abdomen, with extension into the pelvis (Fig 1). The mass measured 15 × 12.5 × 10 cm with appearance suggestive of a gastrointestinal stromal tumour (GIST) and a blood supply derived from the right colic

branches of the superior mesenteric artery. There was no evidence of metastasis. Myeloma screen and magnetic resonance images of the spine were normal.

A transcutaneous biopsy of the mass was taken and preliminary histology suggested a probable GIST. The case was discussed at the upper gastrointestinal multidisciplinary team meeting and the patient was scheduled to undergo laparotomy and excision of the mass the following week. Adjusted calcium levels were persistently raised throughout this period, despite aggressive intravenous fluid therapy and treatment with pamidronate. On the day prior to the procedure, the patient's haemoglobin dropped from 94 g/l to 68 g/l on routine blood tests and two units of packed red blood cells were transfused preoperatively. The operation revealed a large mass arising from the small bowel and a large volume of blood in the abdominal cavity. A further four units packed red blood cells were transfused intraoperatively and the tumour was removed successfully with no immediate complications.

The patient made a good recovery with prompt resolution of his symptoms. His calcium levels returned to normal within 24 hours and remained so until his discharge 12 days later. He was commenced on a three-year regimen of adjuvant imatinib and he remains well with no adverse effects and no signs of recurrence. Final histology confirmed a GIST, with tissue staining positive for the KIT proto-oncogene markers CD117 and DOG1 and negative for intracellular parathyroid hormone.

Discussion

GISTs are cancers of mesenchymal origin arising in the gastrointestinal tract, thought to be derived from the interstitial cells of Cajal in the myenteric plexus.¹ Despite being the most common single type of sarcoma, the absolute incidence is relatively low at around 10 per million in the UK, accounting for just 1% of all gastrointestinal malignancies.² GISTs can occur at any point along the gastrointestinal tract, but most frequently affect the stomach (50–60%) and small intestine (30–35%). Malignant potential is variable, with metastatic disease present in 10–20% of cases at presentation and subsequently affecting nearly half of those who initially present with localised disease.⁵ The understanding and treatment of GIST was advanced by the discovery of mutations in the KIT proto-oncogene, present in up to 80% of tumours⁴ and platelet-derived growth factor receptor- α (PDGFRA).⁵ KIT and PDGFRA encode tyrosine kinase receptors (TKR); mutations typically affect the transmembrane or extracellular domains of these receptors, leading to dysregulated dimerisation and constitutive activation of oncogenic signalling pathways. The use of TKR inhibitors such as imatinib has improved outcomes in advanced cases.⁶

Hypercalcaemia is the most common metabolic oncological emergency, affecting one-third of all cancer patients.⁷ However, hypercalcaemia is extremely rare in GIST patients, with only seven documented cases worldwide (Table 1).^{8–14} Reported cases have an age range of 45 to

Table 1

Case details	Demographics	Presenting features	Primary tumour	Metastatic spread	Mechanism of raised Ca^{2+}	Treatment
Oman, 2006 ^{8;a}	Male, 45 years	Not recorded	Pelvic mass, exact site not recorded	Peritoneum, liver	Unknown	Imatinib
Netherlands, 2007 ⁹	Female, 48 years	Abdominal pain, weight loss, anorexia, night sweats	Abdominal mass, exact site not specified	Peritoneum, omentum, mesentery, liver	Elevated PTHrP	IV fluids, pamidronate, imatinib
Malaysia, 2008 ¹⁰	Female, 65 years	Reduced GCS	Probably small bowel	Liver, abdominal wall	Unknown	IV fluids, furosemide
USA, 2013 ¹¹	Female, 52 years	Symptomatic hypercalcaemia	Pelvic mass, exact site not recorded	Peritoneum, liver, lung	Elevated calcitriol	Bisphosphonates, imatinib
Denmark, 2015 ¹²	Female, 70 years	Weight loss, fatigue, palpable abdominal mass	Duodenum ^b	Liver	Elevated calcitriol	IV fluids, calcitonin, prednisolone, zoledronate, imatinib
Japan, 2016 ^{13;a}	Male, 73 years	Not recorded	Small bowel	Peritoneum, possible gastric metastasis	Elevated PTHrP	IV fluids, imatinib, sunitinib, regorafenib, elcatonin, zoledronate, denosumab
USA, 2017 ¹⁴	Female, 77 years	Weakness, confusion	Unknown	Peritoneum, liver	Elevated calcitriol	IV fluids

^a Abstract only.

^b Location of primary tumour prior to recurrence.

GCS, Glasgow Coma Scale; IV, intravenous; PTHrP, parathyroid hormone-related peptide.

77 years and a gender distribution of five to two female to male. All previous patients had advanced disease at the time of presentation, with peritoneal or hepatic metastases. None were treated surgically, but rather with tyrosine kinase inhibitors and measures to reduce serum calcium. The underlying mechanism driving hypercalcaemia has been documented in five patients, with three found to have elevated levels of 1,25-(OH)₂-vitamin-D₃ (calcitriol), and two patients with elevated parathyroid hormone-related peptide (PTHrP). The specific cause was not found in this case. That the hypercalcaemia was driven by a GIST-dependent mechanism is supported by the lack of response to treatment prior to resection and the rapid and sustained normalisation of calcium levels postoperatively.

PTHrP is expressed by certain normal tissues and has autocrine, paracrine and endocrine activity, being able to bind to both PTHrP and PTH receptors. It is also expressed by many malignant cell types and has been positively associated with tumour growth and metastatic potential.¹⁵ Studies have found cytoplasmic PTHrP/PTH to be present in around 90% of GIST cells, which are also known to express PTHrP/PTH receptors, suggesting that PTHrP may have an autocrine role driving tumour growth and differentiation.¹⁶ Many cancer types also express ectopic 1 α -hydroxylase, the enzyme responsible for the renal conversion of 25-(OH)-vitamin-D₃ into calcitriol.¹⁷ However, hypercalcaemia driven solely by elevated calcitriol is rare in solid tumours, with the exception of lymphoma.¹² It has been suggested that hypercalcaemia may occur only when the disease is sufficiently advanced to allow these autocrine and paracrine signalling mechanisms to exert systemic metabolic effects.¹⁸ This is consistent with the advanced stage and tumour burden of previous cases. The large size of the primary tumour in this case could therefore explain the occurrence of hypercalcaemia, despite the lack of metastatic spread.

Summary

Hypercalcaemia in patients with GIST is a rare phenomenon and has been reported only in patients with advanced metastatic disease. The underlying mechanism is usually elevated serum calcitriol or PTHrP. This is the first reported case of hypercalcaemia in a GIST patient with

localised disease, which responded completely following surgical excision of the tumour.

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