CASE REPORT

A malignant cause of hypoglycaemia: a metastatic insulin-secreting pancreatic neuroendocrine carcinoma

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SUMMARY

Most cases of insulinomas are benign. We report a case of a malignant form of insulinoma. A 46-year-old man presented with behavioural changes associated with hypoglycaemia. Diagnostic work up revealed high serum insulin, high C-peptide and low glucose levels, compatible with endogenous hyperinsulinaemic hypoglycaemia. CT imaging of the abdomen revealed a pancreatic head mass and multiple liver masses. Biopsy of the pancreatic mass revealed a grade three pancreatic neuroendocrine carcinoma. Histological analysis of a liver mass showed that it was identical to the pancreatic mass, confirming its metastatic nature. The patient underwent distal pancreatectomy with en bloc splenectomy. There was persistence of hypoglycaemic symptoms after removal of the pancreatic mass, suggesting that the liver metastases were also functioning. Symptoms were controlled by diazoxide and octreotide long-acting release. The patient is already 1 year postsurgery with no recurrence of severe hypoglycaemia, and he has good functional capacity and has returned to his office job.

BACKGROUND

Severe hypoglycaemia is a medical emergency. It is usually as a result of medications being taken for diabetes. However, there are times when the cause is not related to medicine intake. Among patients without diabetes, one differential is an insulin-producing tumour. Most of these tumours are benign pancreatic lesions. We report a malignant insulin-producing tumour in a patient who received surgical and pharmacological treatment.

CASE PRESENTATION

A 46-year-old apparently well man was brought to the emergency room of another hospital for behavioural changes described as incoherent and inappropriate speech, hallucinations and inability to recognise family members. Capillary blood glucose was measured and found to be low. The patient was given intravenous dextrose with normalisation of his behaviour. Prior to this admission, he reported having to eat very frequently and would even be awaked at night by the urge to eat.

He had no diabetes and was not taking any medication to lower blood sugar levels. There was also no access to glucose-lowering medications as there was no diabetic in his household and he was not a health worker.

At presentation, he had no fever, weight loss, weight gain, anorexia, palpitations, cold sweats, hunger, abdominal pain nor jaundice.

He had no other medical illness. There was no similar illness in his family.

On physical examination, the patient's height was 170 cm and weight 77 kg, and he had a body mass index of 26.6 kg/m². He was ambulatory, awake, conversant and coherent. The only pertinent finding was a palpable non-tender epigastric mass. There was no jaundice. There was neither spider angioma, fluid wave, prominent superficial veins nor splenomegaly. He had no visible injection marks to indicate insulin administration. There was no hyperpigmentation to suggest primary adrenal insufficiency. There were no focal neurological deficits.

INVESTIGATIONS

An observed 72 h fast was planned. The patient developed symptoms of hypoglycaemia 6 h into the fast. Capillary blood glucose was low at 2.5 mmol/L (45 mg/dL). Venous blood was extracted, which revealed plasma glucose of 3.23 mmol/L (58.15 mg/dL), insulin of 95.12 µIU/mL and C-peptide of 1.16 nmol/L.

These findings suggested endogenous hyperinsulinaemic hypoglycaemia, which is defined as a plasma insulin concentration of ≥3 µIU/mL and C-peptide of ≥0.2 nmol/L when the fasting glucose is <3.05 mmol/L (55 mg/dL).¹ The plasma glucose of 3.23 mmol/L may have been 0.18 mmol/L higher than the diagnostic cut-off but the insulin and C-peptide levels could be considered inappropriately way above the diagnostic cut-off values, being elevated 32× and 6×, respectively.

Serum cortisol at the time of hypoglycaemia was 12.2 µg/dL (329.4 nmol/L).

Complete blood count was normal. Serum creatinine was 95 µmol/L (N: 58–110) with mild hypokalaemia at 3.1 mmol/L (N: 3.6–5.1). Corrected serum calcium was normal at 2.30 mmol/L.

Liver enzymes were elevated 2–3 times normal, with aspartate aminotransferase (AST) at 81 IU/L (N: 15–41) and alanine aminotransferase (ALT) at 195 IU/L (N: 17–63). Albumin was slightly low at 33 g/L (N: 35–48) and alkaline phosphatase was elevated at 152 IU/L (N: 38–126). Total bilirubin was normal at 7.2 µmol/L (N: 5.1–20.5).

Triphasic CT scan of the abdomen (figure 1) revealed a calcified lobulated mass anterior to the

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Figure 1 Contrast-enhanced abdominal CT scan showing a calcified pancreatic mass (arrow) and multiple peripherally-enhancing masses in the liver (arrowheads).

body and tail of the pancreas, with evidence of strong enhancement on postcontrast scan. The lesion showed an area of necrosis. A clear cleavage plane from the pancreas was not evident. There were also hypodense masses scattered throughout the liver parenchyma, with rapid irregular enhancement at the periphery on the arterial phase of the scan. The largest lesion on the left lobe measured 6.75×8.09 cm, while the largest on the right lobe was 4.87×5.35 cm. There was rapid washout of the contrast material in the portal venous and delayed phases of the scan.

DIFFERENTIAL DIAGNOSIS

Endogenous hyperinsulinaemic hypoglycaemia secondary to an insulin-producing malignant pancreatic tumour with liver metastases.

TREATMENT

To address the hypoglycaemia while awaiting surgery, the patient was given intravenous saline with 10% dextrose and advised to eat frequently.

On exploratory laparotomy, there was a 5×4 cm hard mass in the pancreatic body and multiple bilobar liver masses. Ascites and carcinomatosis were absent. The surgical team proceeded with distal pancreatectomy with en bloc splenectomy (figure 2) and liver biopsy. The liver masses were deemed unresectable and non-surgical modalities were planned for these.

Figure 2 Surgically removed en bloc specimen showing the tumour (T), distal pancreas (P) and spleen (S).

Histopathological analysis of the pancreatic mass using H&E stain showed a monotonous or uniform population of small blue tumour cells with round nuclei, and a scant to moderate amount of eosinophilic granular cytoplasm (figures 3 and 4). The liver biopsy showed identical results, confirming the metastatic nature of the liver masses (figure 5). Tumour was also seen in 3 of 14 peripancreatic lymph nodes. Immunohistochemical stain was positive for synaptophysin and chromogranin (figure 6A, B), confirming its neuroendocrine nature. Immunohistochemical staining for insulin was, likewise, positive (figure 6C). The proliferation index Ki-67 was positive in 5–10% of cells in the pancreatic tumour and in 20–30% of cells in the liver mass (figure 7). Based on the WHO 2010 classification, this tumour would be classified as a grade 3 (G3) neuroendocrine carcinoma, with this group being defined as having >20 mitoses/10 high power field (HPF) and 3–20% Ki-67 index.²

OUTCOME AND FOLLOW-UP

Postoperatively, the patient continued to have symptomatic hypoglycaemic episodes, which were addressed by intravenous glucose and oral intake of carbohydrates. This suggested that the liver masses were also producing excessive amounts of insulin. Insulin and C-peptide levels were no longer measured postoperatively as we still attributed the hypoglycaemia to excessive insulin secretion by the liver metastases.

The patient was started on oral diazoxide 100 mg three times a day. However, he developed bipedal oedema for which the dose was reduced to 50 mg three times a day.

He was also started on octreotide 10 mg long-acting release (LAR) intramuscular gluteal injections once a month. While on diazoxide and octreotide, he no longer experienced symptomatic hypoglycaemia even after an overnight fast. He recovered from surgery with good functional capacity, and even returned to his job.

Transarterial chemoembolisation (TACE) and radiofrequency ablation (RFA) were also offered to the patient, but he did not consent to these, cognisant of the risk of liver failure, as his liver lesions were multiple and bilobar in distribution.

Seven months after the initial surgery, a repeat abdominal CT scan showed persistence of the liver masses with no recurrent tumour in the pancreatic bed.

Figure 3 Photomicrograph showing the tumour (T) in the upper portion, composed of a uniform population of small blue cells, and normal pancreatic tissue (P) on the lower portion (H&E stain, ×100 magnification).

Figure 4 Photomicrograph of the pancreatic tumour showing round cells with prominent nuclei and a scant to moderate amount of eosinophilic granular cytoplasm. A mitotic figure can be seen (arrow) (H&E, ×1000 magnification).

Because of the splenectomy, the patient also received vaccinations against *Streptococcus pneumoniae*, *Haemophilus influenzae* b and *Neisseria meningitidis*, postoperatively.

DISCUSSION

This patient satisfied the Whipple's triad: (1) signs and symptoms compatible with hypoglycaemia, (2) documentation of low blood sugar levels, and (3) relief of signs and symptoms after administration of exogenous glucose.

He was considered to have endogenous hyperinsulinaemic hypoglycaemia because of the finding of excessively high plasma insulin and C-peptide levels when blood sugar level was low.

Differential diagnoses for endogenous hyperinsulinaemic hypoglycaemia include sulfonylurea intake, insulin antibodies, non-insulinoma pancreatogenous hypoglycaemia and insulinomas. Insulinomas could either be benign or malignant.

This patient did not have access to sulfonylurea as he was not a diabetic, nor was any member of his household. He was not a healthcare worker, who might have had knowledge of its effect. A sulfonylurea assay could have been carried out to confirm this but it was not available in this country. This, together with

Figure 5 Photomicrograph of a liver mass showing a similar uniform population of round cells, with prominent nuclei and a scant to moderate amount of eosinophilic granular cytoplasm. There are several mitotic figures (arrows) seen (H&E, ×1000 magnification).

Immunohistochemical staining

Figure 6 Immunohistochemical stain for chromogranin (A) and synaptophysin (B) are positive, confirming the neuroendocrine nature of the tumour (×400 magnification). Immunohistochemical stain for insulin is also positive, demonstrating that the tumour produces this hormone (C).

insulin antibodies and non-insulinoma pancreatogenous hypoglycaemia (NIPHG), are not compatible with the findings of multiple masses in the pancreas and liver.

Most insulinomas are benign, presenting as a solitary mass in the pancreas. This case is unique since the insulin-producing mass was malignant as evidenced by metastases to the liver. Immunohistochemical staining with insulin morphologically proved that the pancreatic mass and the liver metastasis produced insulin. Apart from the immunohistochemical staining, the finding of endogenous hyperinsulinaemic hypoglycaemia demonstrated the tumour's abnormal physiology.

Pancreatic endocrine tumours are rare with an estimated prevalence of 2.23/100 000 in 2005 and 2.69/100 000 in 2010. Estimates of annual onset incidence were 1.01/100 000 in 2005 and 1.27/100 000 in 2010. The majority are non-functioning. Among the non-functioning tumours, 20.89% to 38.2% are insulinomas.^{3 4}

Most insulinomas are benign. However, approximately 5.8% to 14.1% are malignant.^{5 6}

Malignant insulinomas have a poorer prognosis. In a study conducted in Brazil, 5-year survival of patients with malignant insulinomas was 16% compared to 100% for benign insulinomas.⁶ In a study carried out in the USA, 10-year survival of patients with malignant insulinoma was 29% compared to 88% for those with benign insulinomas.⁵

The aetiology of insulinomas is unknown but a case-control study in China found that residence in rural areas, family history of pancreatic endocrine tumour and other cancers, increase the odds of developing an insulinoma.⁷

Ki-67 Proliferation Index

5%-10% expression in
primary pancreatic tumour

20%-30% expression in
liver metastasis

Figure 7 Photomicrograph showing Ki-67 expression in the primary pancreatic tumour (A) and in a liver metastasis (B) (×400 magnification).

For our patient, the following strategies were employed: reduction of tumour mass by pancreatectomy followed by pharmacological measures to decrease insulin secretion by the functioning remaining liver metastases.

The primary tumour in the pancreas was excised. However, the liver metastases were found to be unresectable because of their multiplicity and bilobar involvement, risking liver failure if they were to be removed. TACE and RFA of the liver metastases were considered, but these were not pushed because of the risk of liver failure, as the metastases were present in both lobes of the liver, and these required multiple sessions to address all the metastases. Also, the patient opted for systemic pharmacotherapy over these invasive procedures.

For the pharmacological intervention, he was first started on diazoxide. This benzothiadiazine derivative binds to the sulfonylurea receptor (SUR) subunit of the K_{ATP} channel in the pancreatic β cells, causing the channel to remain open allowing entry of K ions into the cells, causing hyperpolarisation of the membrane and inhibiting insulin release.⁸ Its use in this patient was limited by the development of bipedal oedema, a known adverse effect.

Glucocorticoids may be used to increase blood sugar levels by antagonising insulin action. This class of drugs was avoided in this patient since he was already rendered immunocompromised by the splenectomy.

Octreotide is a somatostatin analogue that inhibits release of insulin by pancreatic β cells. Presence of SST2A receptor in insulinoma is associated with its efficacy.⁹ Gallbladder sludge and lithiasis are known adverse effects but these were not present in the patient, as seen on repeat CT scan. He was free of hypoglycaemic symptoms while receiving octreotide LAR and continued to tolerate it 1 year after the surgery.

Learning points

- Insulin-secreting tumours are a rare cause of hypoglycaemia. The majority of these are benign, but in this patient, a metastatic pancreatic neuroendocrine carcinoma was the cause.
- Liver metastases of this insulin-secreting pancreatic tumour were also functioning in the patient, as shown by persistence of hypoglycaemic episodes after removal of the primary pancreatic tumour.
- A combination of surgical and pharmacological interventions was performed to decrease the tumour bulk and to inhibit insulin secretion by the remaining tumour.
- Treatment with diazoxide and octreotide in this case may not have caused regression of the metastatic liver masses, but it did resolve the hypoglycaemia and greatly improved the patient's quality of life.

Systemic chemotherapy was considered but this was not pushed since the patient already had a good quality of life while on octreotide. Preservation of quality of life was a major consideration for this patient, cognisant of the toxic effects of chemotherapy.

Other options for treatment are inhibitors of the mammalian target of rapamycin pathway such as everolimus; antiangiogenic treatments such as sunitinib, pazopanib and sorafenib; and peptide receptor radionuclide therapy where radioisotopes such as yttrium and lutetium are coupled with somatostatin analogues so that these radionuclides are finally taken up by the cells expressing the somatostatin receptor.^{10 11}

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