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Case Report

Occult insulinoma after oesophagectomy for oesophageal cancer-diagnostic challenges

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ABSTRACT

Hypoglycaemia in the post-operative period is mainly iatrogenic (related to anti-hyperglycaemic drugs), but can be explained by an endogenous hyperinsulinemic state. In the context of previous gastrointestinal surgery, a form of dumping syndrome can mask hypoglycaemia from an underlying cause, such as an insulinoma. The authors present a clinical case of a male patient who underwent oesophageal surgery for an oesophago-gastric junction adenocarcinoma and developed hypoglycaemic symptoms in the post-operative period, caused by an undiagnosed insulinoma. This case report portraits the diagnostic investigation of a hypoglycaemia state in the post-operative period, narrowing to the workup of an endogenous hyperinsulinemic hypoglycaemia and provides a summary of insulinoma's treatment. An insulinoma should always be considered in a patient with endogenous hyperinsulinemic hypoglycaemia, even with a history of oesophago-gastric surgery.

Keywords: Oesophageal cancer, Dumping syndrome, Endogenous hyperinsulinemic Hypoglycaemia, Insulinoma

INTRODUCTION

Hypoglycaemia in the post-operative period is mainly iatrogenic (related to antihyperglycaemic drugs), but can also be a consequence of reduced nutritional intake, sepsis, hormone deficiency (such as hypothyroidism or hypocortisolism), non-islet cell tumour or endogenous hyperinsulinism.[1]

Dumping syndrome (DP) is a common complication of oesophago-gastric surgery. Symptoms of late dumping syndrome usually occur between 1 to 3 h after a meal and are primarily the manifestations of hypoglycaemia.[2] In the context of previous gastrointestinal surgery, a form of dumping syndrome can mask hypoglycaemia from an underlying cause, such as an insulinoma.[3]

Insulinoma is the most frequent functioning form of pancreatic neuroendocrine neoplasm (NEN). Its incidence is estimated at 4 per million people a year.[4] Although rare, it's the most common cause of hyperinsulinemic hypoglycaemia, usually occurring in the fasting state but occasionally in the postprandial period.[1] The diagnosis of insulinoma is based on biochemical tests (with measurement of plasma glucose, insulin, C-peptide and proinsulin) and imaging tests (such as CT, MRI and PET scan).[5] Recently, PET scan with ^{68}Ga-DOTA conjugated peptides (such as ^{68}Ga-DOTA-NOC) brought an improvement in diagnosis of insulinoma, for its high

affinity for type 2, 3 and 5 somatostatin receptors which are present in pancreatic neuroendocrine tumours; however, ^{68}Ga-DOTA-exendin-4 PET-CT-targeting glucagon-like peptide 1 receptor (GLP-1R) is considered the most sensitive diagnostic tool but it's not available in all centers.[6,7]

The authors present a clinical case of a male patient who underwent oesophageal surgery for an oesophago-gastric junction adenocarcinoma and developed hypoglycaemic symptoms only in the post-operative period, caused by an undiagnosed insulinoma.

This case demonstrates an uncommon presentation of an insulinoma (following oesophageal surgery) and its diagnostic challenge, due to the similarities with dumping syndrome. Indeed, insulinoma remains an important diagnosis to exclude in both post-prandial or fasting hyperinsulinaemic hypoglycaemia.[3]

CASE REPORT

A 65-year-old male patient was referred to our oesophageal cancer reference center, with a diagnosis of oesophago-gastric junction (EGJ) adenocarcinoma (Siewert I). His past medical history included vocal cord malignancy (submitted to laryngectomy and cervical radiotherapy in 1994) related to previous tobacco abuse. The patient was asymptomatic and the diagnosis was made with a biopsy during a screening upper endoscopy. No metastasis or other pathologic findings were found on pre-operative studies (thoraco-abdominopelvic computed tomography-TAP-CT and ^{18}F-fluorodeoxyglucose positron-emission tomography CT-^{18}F-FDG PET-CT).

Our patient underwent a minimal invasive radical subtotal oesophagectomy (Ivor-Lewis). In post-op period, he developed thoracic empyema that was percutaneously drained and was discharged on postoperative day 10, without further complications. Histology revealed oesophageal adenocarcinoma (pT2N0M0).

One month after hospital discharge, the patient presented to the emergency room with fasting severe symptomatic hypoglycaemia (35 mg/dL), which was corrected with intravenous dextrose (Whipple's triad), and dysphagia. The patient had no history of abdominal pain or diarrhea. He was admitted to the general surgery ward with the presumptive diagnosis of food intake impairment/late DP. Despite endoscopic confirmation of anastomotic patency and a strict nutritional control, the patient maintained asymptomatic fasting hypoglycaemic episodes and was transferred to the endocrinology ward.

Investigations

After hypoglycaemic drugs were excluded and in the absence of a sepsis or other critical illness, a workup was made during a spontaneous hypoglycaemia with measurement of plasma glucose, insulin, anti-insulin antibodies, C-peptide, TSH, T4, cortisol, ACTH, growth hormone and insulin grow-factor (IGF) concentrations. Plasma insulin and C-peptide levels were elevated (17 µUI/mL and 4, 6 ng/mL, respectively) and plasma glucose was low (50 mg/dL), consistent with endogenous hyperinsulinemic hypoglycaemia (EEH). An autoimmune hypoglycaemic state was excluded since insulin antibodies were negative. Thyroid hormone function and ACTH/cortisol/growth hormone and IGF plasma concentrations were normal.

The patient was treated with diazoxide and an abdominal CT scan with intravenous contrast was repeated, looking for an insulinoma, a 21x19 mm nodular lesion was now apparent on the pancreatic neck (Figure 1). ^{68}Ga-DOTA-NOC PET CT confirmed the diagnosis of insulinoma (Figure 2).

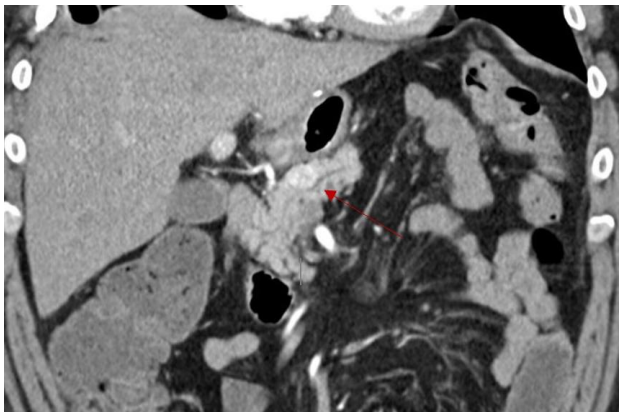

Figure 1: Abdominal CT scan with intravenous contrast (coronal view) of a 21x19 mm nodular lesion (not seen on previous studies; pointed with arrow) compatible with insulinoma.

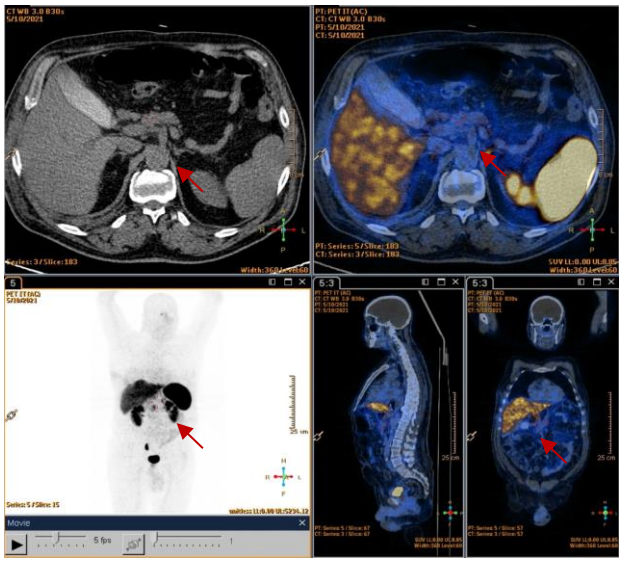

Figure 2: ^{68}Ga-DOTA-NOC PET CT of a heterogeneous uptake on pancreatic neck (SUV max: 8,7) (pointed with arrows), compatible with insulinoma.

Treatment and outcome

Given the imagiological confirmation of insulinoma, the patient underwent a laparotomic distal pancreatectomy with splenic preservation. In the postoperative period a grade B pancreatic fistula was found, leading to an intra-abdominal collection that was percutaneously drained.

On gross examination of the surgical specimen there was a 15x10x14 mm nodular lesion of the pancreas, formed by pale tissue with soft consistency and haemorrhagic areas. Histological examination showed a grade 1 neuroendocrine pancreatic tumour (neoplastic cells expressed Ck cam 5.2, chromogranin, synaptophysin, insulin and amyloid; Ki 67 <3%) (Figure 3).

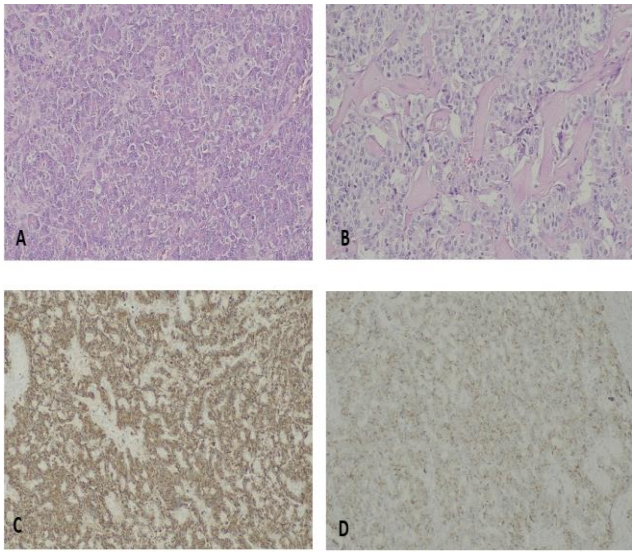

Figure 3 (A-D): Histological examination of the surgical specimen of a tumour formed by nests and trabeculae of monotonous cells with "salt and pepper" round nucleus (Panel A, H and E stain, 100x), with amyloid deposits (Panel B, H and E stain, 200x) and positive for synaptophysin (Panel C, 100x) and insulin (Panel D, 100x).

At three months follow-up the patient was asymptomatic, with normal glucose levels, without diazoxide or any additional medication and maintained adequate oral nutritional intake.

DISCUSSION

We report a case of an occult insulinoma, symptomatic only about one month after an Ivor-Lewis oesophagectomy for oesophageal cancer. By the time of diagnosis and staging of the oesophageal adenocarcinoma, the patient was asymptomatic and the pancreatic lesion was not found on the first CT or ^{18}F-FDG PET-CT scans.

Given the recent oesophageal surgery and the concomitant complaint of dysphagia, two main differential diagnoses were considered for the hypoglycaemic state of our patient-food intake impairment due to anastomotic stenosis and late DP.

Benign anastomotic stenosis are relatively frequent after oesophagectomy (10 to 56% in some series), mainly with cervical anastomosis; the prophylactic use of proton-pump inhibitors and endoscopic dilatation techniques have reduced the morbidity related to this complication.[8,9] In this case, this hypothesis was disregarded given the anastomotic patency proved by endoscopy.

DP is a known complication following upper gastrointestinal surgery, including oesophagectomy (with a reported incidence as high as 50%), but its symptoms are severe and persistent in only 10% of cases.[2,10] DP symptoms' are experienced after ingestion of a meal, as a consequence of rapid gastric emptying of food to the small intestine.[10] Early DP (within an hour, after the meal) is a consequence of a rapid passage of osmotically active particles into the small intestine, causing gastrointestinal and vasomotor symptoms; on the other hand, late DP (one to 3 hours after a meal) is attributed to reactive hypoglycaemia induced by a rise in insulin plasmatic levels.[10,11] The treatment of this complication relies mainly on dietary changes (smaller and more frequent meals, excluding liquids from meals, decreasing carbohydrate intake, preferring complex carbohydrates).[10] In our case, the patient still maintained fasting hypoglycaemic episodes even with strict dietary control and a further investigation was pursued; also, the hypoglycaemic profile (fasting rather than post-prandial) raised awareness for other causes.

After excluding other frequent hypoglycaemic causes in the post-operative period including exogenous administration of insulin/insulin secretagogue/other hypoglycaemic drugs (such as indomethacin, pentamidine, glucagon), sepsis and hormone deficiency, workup was directed towards finding of an EHH.

The diagnosis of EHH is biochemical and requires blood glucose <55 mg/dL, insulin ≥3 µUI/mL, C-peptide ≥0.6 ng/mL and proinsulin levels ≥5 pmol/L. When hypoglycaemic syndrome is severe these criteria can be evaluated on a fasting blood test; when the clinical or biochemical conditions are not clear, 72 hour fasting test remains the gold standard for diagnosis. C-peptide levels are important in order to exclude administration of exogen insulin as the cause of hypoglycaemia. Insulinomas are the most frequent cause of EHH; however, other causes must be considered: hypoglycaemia consequent to upper gastrointestinal surgery due to neisidioblastosis of pancreatic tissue-non insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) and insulin autoimmune hypoglycaemia.[1,12,7] As referred before, in our case insulin autoimmune hypoglycaemia was excluded and localisation/imagiological studies found a nodular

pancreatic lesion, pointing for an insulinoma rather than NIPHS as cause for this hypoglycaemic state.

Insulinomas are functioning NEN and more than 99% are located in the pancreas. They originate from the neuroendocrine islet cells or multipotent stem cells of the pancreas and produce insulin independently of glucose level's stimuli; as pointed before, they are the most common cause of EEH syndrome.[12] The main clinical manifestations of insulinomas are hypoglycaemia-related symptoms. They should be suspected in patients with autonomic and/or neuroglycopenic symptoms or signs, blood glucose <55 mg/dL and resolution of those symptoms or signs after the plasma glucose concentration is raised.[1] This Whipple's triad defines the pathognomonic presentation of this disease.[12,13]

One of the curious findings in our case is the appearance of the insulinoma-related symptoms only after oesophagectomy. This could be explained by two theories: first, the expectable decreased oral intake after this type of surgery lowered the patient's normal glucose plasmatic concentration that were not compensated with a reduced insulin production, leading to a symptomatic hypoglycaemia; second, the change in the gastrointestinal architecture contributing to a rapid gastric emptying could induced a further rise in insulin secretion by the normal pancreatic ß-cells (due to a higher incretin secretion), besides the autonomous insulin production by the insulinoma.

The other interesting fact was that the first CT study was unable to detect the insulinoma. This could be explained because typical imaging protocol used to stage hypovascular tumors-such as an adenocarcinoma-only includes a portal venous phase acquisition after intravenous contrast administration whereas a hyper-vascular lesion-such as an insulinoma-is better depicted in an early arterial (pancreatic) phase.

In our literature review, we found only one case of an occult insulinoma and a coexisting oesophageal carcinoma[14], which shows the rarity of this clinical scenario. In that report, the carcinoma of the oesophagus (with lymph node and hepatic metastasis) didn't show increased radioactivity on ^{68}Ga-DOTA-exendin-4 PET-CT (contrary to the insulinoma), being found by ^{18}F-FDG PET-CT. ^{68}Ga-DOTA-exendin-4 PET-CT is a PET tracer targeting GLP-1R, which is highly overexpressed on benign insulinoma cell surface. Most insulinomas are benign and usually very small (<2 cm), making it difficult to localize with the current imaging techniques, such as CT scans.[7] According to a metanalysis, ^{68}Ga-DOTATATE PET-CT is clinically equivalent or superior to octreotide imaging and should be used when available (which is not the case in on our country).[15]

Medical treatment for insulinomas can be used for preventing hypoglycaemia in insulinomas with unknown location or previously to surgical intervention. Possible choices, besides intravenous glucose infusion, are diazoxide, somatostatin analogues (SSA), everolimus and glucocorticoids.[12,13] Diazoxide is used as a first-line treatment for glycaemic control in patients with insulinomas preoperatively but also in cases of persistent hypoglycaemia after surgery.[12] It also can be used safely and effectively, on a long term basis, when it cannot be localized or removed surgically and SSA represent a good alternative, specially used in patients who cannot undergo surgical intervention and when diazoxide is not recommended due to adverse effects or inefficacy.[12,16-18] In cases of malignant insulinoma, SSA can also be considered first-line treatment because of their anti-proliferative effect. Everolimus can be used for refractory hypoglycaemia and glucocorticoids are only used when better pharmacological options were not available.[12]

Surgery is still the ideal treatment for patients with insulinoma, controlling symptoms of hypoglycaemia, with an overall cure rate up to 98%.[7] Given that insulinomas are usually solitary, well-capsulated, small and benign in more than 90% of cases, enucleation of the tumour is the ideal surgical approach, minimizing the risk of exocrine and endocrine insufficiency associated with an anatomic resection.[19] However, the proximity of the pancreatic lesion to the Wirsung duct made an enucleation not feasible in our case and we performed a distal pancreatectomy with splenic preservation.

Besides the diagnostic challenge in this case, there were also technical concerns during the surgical procedure, as we needed to preserve the gastric blood flow to the gastric tube (assured by the right gastroepiploic artery, a branch of the gastroduodenal artery). In fact, the integrity of the gastroduodenal artery could be jeopardized during pancreatic dissection and was a main concern in this case. This challenge (in addition to adhesions from previous oesophageal surgery) made a laparoscopic approach not feasible.

CONCLUSION

In summary, this case report illustrates an uncommon presentation of an insulinoma and the diagnostic challenges due to the time of presentation (after oesophago-gastric surgery), reminding us to always consider this entity in a patient with endogenous hyperinsulinemic hypoglycaemia.

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