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The diagnostic challenge of hyperinsulinaemic hypoglycaemia: A report on two atypical cases

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ABSTRACT

*Objectives:*The authors describe 2 atypical cases of patients with hypoglycaemia, suspected for insulinoma.
Methods: The 2 reports are accompanied by a concise review of the literature.
Results: Patient 1 had a distal pancreatectomy performed for suspected insulinoma, and was diagnosed with a glucagonoma and beta-cell hyperplasia (nesidioblastosis). To the authors's knowledge, co-existing glucagonoma and nesidioblastosis had not been previously reported. Patient 2 was diagnosed with a benign insulinoma and 5 years later with metastatic disease.
Conclusion: The authors conclude that insulinomas are rare entities which often present a diagnostic and therapeutic challenge. In such cases, patient referral to tertiary multidisciplinary centers is recommended.

LEARNING POINTS

- Insulinomas, originating from the pancreatic beta-cells, are the most common disease for hyperinsulinaemic hypoglycaemia in adults. Diagnosis is made by a 72-hour fasting test revealing decreased plasma glucose (<2.2 mmol/l), increased insulin, C-Peptide and/or proinsulin, and symptoms of hypoglycaemia that are compensated by glucose infusion (Whipple's triade).
- Glucagonomas cause glucose intolerance, diabetes, weight loss, and migratory necrolytic erythema; diagnosis requires demonstration of an inappropriately elevated s-glucagon (diagnostic at levels above 500-1000 pg/ml).
- Adult nesidioblastosis, a rare form of abnormal islet cell proliferation arising from the pancreatic ductal epithelium, affects approximately 4% of adults with hyperinsulinaemic hypoglycaemia; when radiological studies do not show a pancreatic mass, nesidioblastosis should be suspected.

KEYWORDS

Hyperinsulinaemic hypoglycaemia, insulinoma, glucagonoma, malignant insulinoma, nesidioblastosis.

INTRODUCTION

Pancreatic neuroendocrine tumours (pNET) are rare tumours with an annual incidence of < 1 per 100.000[1]. Seventy percent (%) of pNETs are non-functioning and insulinomas and gastrinomas are the most common tumours among functioning pNETs[2]. Insulinomas, originating from the pancreatic beta-cells, cause hyperinsulinaemic hypoglycaemia in adults. Diagnosis is made by a 72-hour fasting test which reveals decreased plasma glucose (<2.2 mmol/l), increased insulin, C-Peptide and/or proinsulin, and symptoms of hypoglycaemia that are compensated by glucose infusion (Whipple's triade). More than 90% of insulinomas are solitary and have a benign behaviour[1,3]. About 50% of insulinomas are < 1 cm[3], and pre-operative tumour localization may represent a clinical challenge. Non-invasive techniques often fail to localize small tumours, and in the majority of cases, several diagnostic tests are necessary.

CASE REPORT 1

In 2011, a 59-year-old Caucasian woman was admitted to our NET Centre after episodes of loss of consciousness and seizure. Blood glucose was 1.6 mmol/l (normal range [NR] 4-7 mmol/l); plasma insulin (p-insulin) 400 pmol/l (NR 10-125 pmol/l); C-peptide 6000 pmol/l (NR 265–

1026 pmol/l); and plasma glucagon (p-glucagon) 119 pg/ml (NR < 60 pg/ml). A fasting test was positive. Computer tomography (CT) and Magnetic Resonance Imaging (MRI) (*Fig. 1*) demonstrated a 2 cm cystic lesion in the pancreatic tail. At CT and endoscopic ultrasonography (EUS), a further lesion in the body of the pancreas was suspected. Octreotide scintigraphy showed no pathological uptake. Selective intra-arterial calcium stimulation with hepatic venous sampling demonstrated a moderate increase of p-insulin following calcium injection into the splenic artery, suggesting an insulinoma in the pancreatic tail. Intraoperative ultrasound demonstrated a lesion in the pancreatic tail, and a distal pancreatectomy was performed. Pathological examination revealed a 1.7 cm neuroendocrine cystic tumour in the pancreatic tail and diffuse pancreatic beta-cell hyperplasia.

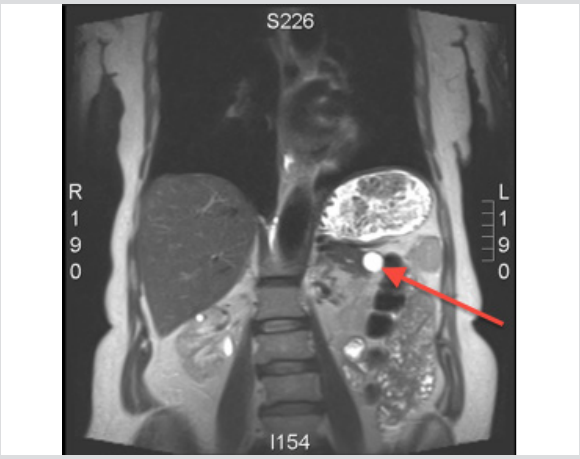

Figure 1: Abdominal magnetic resonance imaging (MRI) showing hypervasular neuroendocrine tumour of 2 cm in the pancreatic tail.

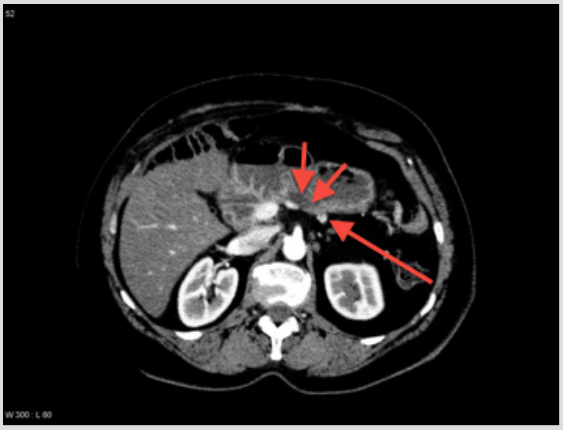

Figure 2: Abdominal computer tomography (CT) showing a hypervasular lesion less than 1 cm (long arrow) and a remaining part of the pancreas with a dilated pancreatic duct (short arrows).

Surprisingly, the tumour was immunohistochemically positive for glucagon, but negative for proinsulin and insulin. Plasma levels of insulin, C-Peptide, glucose, and glucagon normalized postoperatively, and have remained with the normal range ever since.

CASE REPORT 2

A 62-year-old Caucasian woman had distal pancreatomy performed in 1994 for insulinoma. The patient had recurrence of hypoglycaemia in 1999, and underwent re-resection of the left pancreas and a pancreatico-duodenectomy in 2004. However, hypoglycaemia persisted and an additional abdominal exploration and treatment with diazoxide, octreotide and norditropin were unsuccessful.

In 2005, the patient was referred to the NET Centre of Rigshospitalet. A fasting test was positive after 19 hours. EUS and a dedicated pancreatic CT revealed a 6 mm lesion in the bed of the resected pancreas (*Fig. 2*). Surgery was postponed as localization of a 6 mm-large tumour in a field of several previous interventions might be unsuccessful. Instead, chemotherapy with streptozotocin and 5-fluorouracil was initiated.

In the period 2007-2010, CT revealed unchanged lesion in the pancreatic bed. Due to persistent attacks of hypoglycaemia, minor residual pancreatic tissue was resected in 2010. Histology demonstrated multiple neuroendocrine islets, but no insulinoma. One year later, CT showed a 14 mm lesion in the pancreatic bed. A laparotomy was performed and a lymph node was resected, which contained neuroendocrine tissue, but further immunohistochemical evaluation was not possible due to an insufficient quantity of tissue. The patient was euglycaemic at the time of discharge but episodes of hypoglycaemia recurred. A 68Ga-DOTATOC-PET/CT and treatment with somatostatin analogues or everolimus were refused by the patient as symptoms had subsided since the last operation. Since the start of treatment, the patient has had few attacks of hypoglycemia.

DISCUSSION

Both cases described above demonstrated diagnostic and therapeutic challenges. In Case 1, the patient underwent 6 diagnostic tests, of which 4 disclosed the tumour. Surprisingly, the histological examination revealed a glucagonoma and nesidioblastosis – but no insulinoma. It is uncertain whether there was a causal relationship between the glucagonoma and nesidioblastosis, or it was a coincidential finding.

Glucagonomas originate from the alpha-2 cells of the pancreas and secrete glucagon, which causes glucose intolerance, diabetes, weight loss and migratory necrolytic erythema[4]. Diagnosis requires demonstration of an inappropriately elevated p-glucagon (diagnostic at levels above 500-1000 pg/ml). Of note, the patient was diagnosed with diabetes mellitus and had taken metformin until 2 weeks prior to admission; metformin was discontinued due to side effects, but did not have migratory necrolytic erythema. Preoperatively, p-glucagon was only slightly increased.

Adult nesidioblastosis, a rare form of abnormal islet cell proliferation arising from the pancreatic ductal epithelium, affects approximately 4% of adults with hyperinsulinaemic hypoglycaemia. The histopathological criteria include beta-cell hypertrophy, islet hyperplasia, and an increase in the beta-cell mass. The patients have elevated insulin and C-peptide levels. When radiological studies do not show a pancreatic mass, nesidioblastosis should be suspected. Most surgeons perform 60-80% distal pancreatectomy in patients with nesidioblastosis, which results in cure in about half on the patients.

Cases of endogenous hyperinsulinaemic hypoglycaemia due to nesidioblastosis after gastric-bypass surgery have been described, as well as coexisting nesidioblastosis and insulinoma. To our knowledge, this is the first reported case of a glucagonoma associated with secondary symptomatic nesidioblastosis.

Case 2 also presented a diagnostic challenge and illustrates the need for long-term follow-up of insulinoma patients. The patient was initially diagnosed with a benign insulinoma, and presented 5 years later with metastatic disease.

The annual incidence of malignant insulinoma is 0.1 cases per million. Most patients with malignant insulinoma have lymph node or liver metastasis and a median survival of 23 months compared to 124 and 70 months of those with localized and regional disease, respectively[2]. The median disease-free survival after curative resection is 5 years. In Case 2, concurrent nesidioblastosis is likely, since an increased number of islet cells were found in the surgical specimens.

The primary treatment of benign or malignant insulinomas is surgery, if resection of all or the majority of the tumor burden can be achieved[5]. If surgery is not possible, anti-tumoural treatments include somatostatin analogues, chemotherapy, everolimus, sunitinib, and radionuclide treatment. Treatment of persistent hypoglycemia is a challenge, but the m-TOR inhibitor everolimus may prevent episodes of hypoglycemia.

CONCLUSION

Insulinomas are rare and often present both diagnostic and therapeutic challenges. Referral to specialised NETcentres with a multidisciplinary approach is recommended.

REFERENCES

1. Halfdanarson TR, Rubin J, Farnell MB, Grant CS, et al. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer.* 2008;**15**:409-27.
2. Falconi M, Bartsch DK, Eriksson B, Kloppel G, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology.* 2012;**95**:120-34.
3. Jensen RT, Cadiot G, Brandi ML, de Herder WW, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology.* 2012;**95**:98-119.
4. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology.* 2008;**135**:1469-92.
5. Knigge U, Hansen CP. Surgery for GEP-NETs. *Best Pract Res Clin Gastroenterol.* 2012;**26**:819-31.