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Published in:
Pancreatology

DOI:
10.1016/j.pan.2019.12.017

Publication date:
2020

Document version:
Accepted manuscript

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Citation for published version (APA):

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Occult insulinoma, glucagonoma and pancreatic endocrine pseudotumour in a patient with multiple endocrine neoplasia type 1

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Dear Editor,

In multiple endocrine neoplasia type 1 (MEN1), the tumour penetrance by the age of 50 years reaches 30-70% in the neuroendocrine pancreas and duodenum (1) and hyperinsulinaemic hypoglycaemia (HH) caused by an insulinoma is rarely the first manifestation of MEN1. In a study of 160 MEN1 patients under the age of 21 years, 10% debuted with insulinomas, the youngest being five years old (2). We wish to highlight the diagnostic challenges in young patients with insulinoma and MEN1, exemplified by an
exceptional patient report of an adolescent with an occult insulinoma, which only could be visualised and curatively resected after eight months of search despite repeated, multimodality diagnostic imaging.

The patient, a 14-year-old female, presented with a one-year long history of unrecognized hypoglycaemia symptoms. She had normal growth and puberty with regular menstruations. By fasting test, plasma glucose was 1.7 mmol/L; blood ketones 0.3 mmol/L. At plasma glucose 2.5 mmol/L, p-insulin was 158 pmol/L (ref. 18-173) pmol/L, establishing the diagnosis of HH. Genetic testing revealed a novel *MEN1* frameshift mutation, NM_130799: c.1391dupC, p.(Ala465GlyfsTer66) in the proband, her two elder sisters and their father. The patient's father had no history of hypoglycaemia, but during a surgery for perforated gastric ulcer and was diagnosed with hyperparathyroidism and Zollinger-Ellison syndrome with extremely elevated p-gastrin as a feature of MEN1. Two older siblings of the proband had no disease history at time of diagnosis, but both developed hyperparathyroidism and had surgery for non-functioning PNETs. A deceased grandmother on the paternal side had undergone a subtotal pancreatectomy in 1948 due to several episodes of hypoglycaemia, and parathyroid gland surgery due to hypercalcaemia.

The proband had no other biochemical MEN1-related abnormalities at the time of initial presentation. An MRI scan of her brain revealed a 5-6 mm pituitary microadenoma. At the time of HH diagnosis, diazoxide (9 mg/kg/d) and octreotide (8 mcg/kg/d) were unsuccessful, prompting continuous intravenous glucagon (2 mcg/kg/h) in addition to i.v. glucose (1-2 mg/kg/min) to ensure normoglycaemia. Endoscopic ultrasound (EUS) of the pancreas was normal. An $^{68}$Ga-DOTA-NOC PET/CT scan during iv glucose only showed a small focal process in the head of the pancreas (Figure 1a). The process was resected (Figure 1b) and perioperatively stained positive for synaptophysin. However, hypoglycaemia returned soon after surgery, resulting in renewed dependence on i.v. glucagon and central venous infusion of glucose 20%. Based on postoperative immunohistochemical staining of the lesion, the diagnosis of a 4 mm glucagon-positive pancreatic neuroendocrine tumour (PNET) was made (Figure 2a, b, and c). Consistently,
analysis of a blood sample drawn before surgery revealed extremely high plasma glucagon levels of 1000 (ref. 5-20) pmol/L.

A repeat $^{68}$Ga-DOTA-NOC-PET/CT scan without medication failed to identify a pancreatic focus. A subsequent $^{18}$F-DOPA-PET/CT scan showed two small foci in the uncinate process of the pancreas with a maximal standardised uptake value (SUV) ratio of 1.50. This led to a second pancreatic surgery with resection of a part of the pancreatic head and a modified Roux-en-Y procedure. Frozen section showed an area with hyperplastic islet cells. At postoperative microscopy with immunohistochemistry, one glucagon-positive microadenoma (2 mm) and several smaller microadenomas (<1 mm) were found. The blood glucose levels only remained stable for a week, after which hypoglycaemia returned with the need for continuous iv glucagon 1.8-3.7 mcg/kg/h. No tumour was detectable by repeat $^{68}$Ga-DOTA-NOC-PET/CT or $^{18}$F-DOPA-PET/CT, why the girl was transported to the Netherlands for a $^{111}$In-exendin-SPECT scan during iv glucose, which identified increased uptake of $^{111}$In-exendin in the remaining head of the pancreas close to the common bile duct (Figure 1c). A third operation with a modified Whipple’s procedure was performed with removal of the remaining part of the pancreatic head, duodenum, gallbladder and common bile duct. Unfortunately, only a 0.2 mm glucagon-positive neuroendocrine microadenoma was found, together with a lesion measuring 5 mm, consisting of fibrosis, inflammation and pronounced aggregation of islets of Langerhans (Figure 2 d, e, and f). We termed this lesion an “endocrine pseudotumour”, according to the impression of a PNET in the preoperative $^{111}$In-exendin-SPECT scan. No insulinoma was identified in this resected specimen.

The girl remained asymptomatic for two months, after which the HH recurred. At this time, both the $^{18}$F-DOPA PET/CT and an $^{68}$Ga-DOTATATE (SUV 1.60) together with an MRI of the pancreas showed a process in the tail of the pancreas (Figure 1d). A left-sided resection of 20 mm of the pancreas was performed, and a 10 mm insulinoma was identified (Figure 2 g, h, and i). Eight months after the first diagnosis of HH, fasting and postprandial blood tests finally showed normal values. During the follow-up, until the girl turned 18 years old, primary hyperparathyroidism developed, successfully treated with subtotal parathyroidectomy.
A clinically significant glucagonoma has, to the best of our knowledge, never been reported in children or adolescents before. In adults, glucagonomas constitute 3% of the PNETs in MEN1 (1). The glucagonomas are usually large at presentation (>5 cm) and have a worse prognosis than other functioning pancreatic PNETs, as 50-80% of glucagonoma patients have metastases. Our patient did not present symptoms of hyperglucagonaemia despite a highly elevated glucagon level from her glucagonoma and no glucagonoma metastases were detected. Hyperglucagonaemia in MEN1 patients does not always result in clinically significant hyperglycaemia, which was also the case in our patient. However, the observed worsening of the hypoglycaemia after the resection of the glucagonoma suggested a counter-balancing effect of the glucagonoma on the insulinoma-induced hypoglycaemia. Co-existence of glucagonomas and insulinomas have been reported in adults with MEN1 (3).

A total of eight scans and four pancreatic surgeries were performed on our patient, before the insulinoma was identified and removed, eight months after her first admittance. Preoperative imaging of PNETs remains a challenge with non-optimal sensitivity and specificity of the different imaging techniques because of either small tumour size or lack of tracer targets. In a recent report on 80 patients with insulinoma, 17.5% were undetectable by conventional imaging (4). CT and MRI scans are usually considered the first- and second-line investigations used to locate and define the stage of PNETs (5). Reports on the diagnostic performance of imaging modalities are often hampered by small numbers of patients. The overall reported average sensitivity of CT and MRI in diagnosing insulinomas is 73% and 93%, respectively (5). EUS has a high reported average sensitivity (90 %) (5), but only 40 % of paediatric insulinomas are successfully diagnosed by use of EUS (6).

In our patient, neither EUS nor intraoperative palpation led to tumour identification. On the other hand, ¹⁸F-DOPA PET/CT succeeded to detect the insulinoma and was confirmed by ⁶⁸Ga-DOTA-TATE PET/CT and MRI. ⁶⁸Ga-DOTA-NOC PET/CT moreover identified what postoperatively turned out to be a glucagonoma in our first scan. Detection of a glucagonoma with ⁶⁸Ga-DOTA-NOC PET/CT has previously been described in one adult (7). ⁶⁸Ga-DOTA-peptides bind with high affinity to somatostatin receptors (SSRs), especially SSR2, which is highly expressed in PNETs with the exception of benign
insulinomas. $^{68}$Ga-DOTA-NOC PET/CT had a sensitivity of 26% to 90% for the localisation of insulinomas (8).

The $^{111}$In-exendin-SPECT scan takes advantage of exendin, a glucagon-like-peptide-1 (GLP1) analogue, which binds to the GLP1-receptors on pancreatic islet cells. Benign insulinomas have a very high density of GLP1-receptors, which explains the very high sensitivity (up to 100%) of the technique in diagnosing benign insulinomas (9). The lesion identified in our patient by $^{111}$In-exendin-SPECT was therefore expected to represent an insulinoma but showed to be an endocrine pseudotumour. Inflammatory pseudotumours are known in the setting of autoimmune pancreatitis and may mimic malignant pancreatic tumours at imaging (10). We speculate that the endocrine pseudotumour in our patient had developed due to surgery-induced inflammation with destruction of exocrine cells, thereby leading to the development of fibrosis and accumulation of islets of Langerhans. The islets of Langerhans are robust compared to the surrounding exocrine cells in pancreatitis. To the best of our knowledge, our patient report represents the first description of an endocrine pseudotumour leading to the preoperative suspicion of PNET in the literature. Such endocrine pseudotumours are, however, important to recognise, if possible preoperatively, especially in combination with an occult insulinoma. Our patient report highlights the need for improved imaging techniques of PNETs. A novel, promising alternative introduced at our institution with successful detection of focal HH lesions down to 3 mm in diameter in infants is intraoperative high frequency ultrasound (IOUS) (11), which is now also used in nonvisible insulinomas in adults (4). Among other novel imaging modalities, $^{68}$Ga-exendin-4 PET/CT (12) and PET combinations with MRI seem promising. Such modalities were, however, not available for our patient at the time of diagnosis.

Conservative treatment may be advocated when imaging procedures fail to identify a clear-cut pancreatic tumour in wait for tumour growth, but this should be balanced against the risk of metastases, side effects, and quality of life during problematic conservative treatment. Improved imaging techniques are warranted.

**Ethics:** Informed consent was obtained from the patient and family members for the publication.

**Disclosures:** Funding was not obtained for this study. The authors have nothing to disclose.
References


Figure 1. Imaging and surgery of a 14-year-old MEN1 patient with glucagonoma, endocrine pseudotumour and insulinoma.

a) $^{68}$Ga-DOTA-NOC PET/CT showing the glucagonoma in the head of pancreas. b) Surgical resection of a glucagonoma. c) $^{111}$In-Exendin 3 SPECT suspicious of an insulinoma in the remaining part of the pancreatic head. d) $^{18}$F-DOPA PET/CT scan showing the insulinoma in the tail of pancreas.
Figure 2. Histological findings.