Case report

Long-term Survival in a Child with Malignant Insulinoma After Liver Transplantation

Moszczyńska E et al. Malignant Insulinoma and Liver Transplantation

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What is already known on this topic?
Insulinoma, especially malignant, is a very rare pancreatic neuroendocrine tumor in children. Insulinoma may be a part of multiple endocrine neoplasia type 1 and is very rare with von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis. Surgical resection remains the treatment of choice whenever possible. Diazoxide or somatostatin analogs can be used as an initial pre-surgical treatment or to achieve biochemical control in patients with unresectable tumors.

What does this study add?
Liver transplantation is one of the surgical treatment options for liver metastases, especially in young people, after primary pancreatic neuroendocrine tumor resection. Due to the sporadic presence of insulinoma in children, they should be treated in the multidisciplinary reference centre specialized in neuroendocrine tumors, equipped with modern treatment methods, providing surgical oncology, and with the participation of specialists in adult care.

Abstract
Insulinoma belongs to pancreatic neuroendocrine tumors and is immensely rare in children. The tumor leads to severe consequences of hypoglycemia caused by excessive insulin release. We report a pediatric patient with malignant insulinoma linked with liver transplantation due to metastases to this organ. A 13-year-old girl presented with symptoms of hypoglycemia due to hyperinsulinism. In computed tomography (CT), a polycyclic lesion in the head of the pancreas and enlarged lymph nodes were revealed. Modified Whipple's operation was performed, and histological examination confirmed pancreatic neuroendocrine tumor. CT of the body showed an enlarged liver with numerous metastases. Allogeneic liver transplantation was carried out successfully. Positron emission tomography-computed tomography (PET/CT) using 68Ga-DOTA-labeled somatostatin analogs at the age of 22 confirmed the complete metabolic remission. The patient currently remains under immunosuppressive and antiproliferative treatment. Multiple surgical interventions, liver transplantation combined with somatostatin analogs, and immunosuppressive medication could be effective in malignant insulinoma.

Keywords: Hypoglycemia, insulinoma, liver transplantation, children

Introduction
Insulinoma is an isolated, usually benign pancreatic neuroendocrine tumor (PanNET) with an extremely low prevalence (annual incidence of 4 in every 1 million persons). Although this pancreatic islet mass shows various symptoms, one of its main characteristics is the Whipple's triad which consists of fasting hypoglycemia (< 50 mg/dL), symptoms of hypoglycaemia, and the disappearance of the symptoms mentioned above after food intake. This condition may also be connected with multiple endocrine neoplasia type 1 (MEN-1) and very rarely with von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis (TS).

Once the tumor is found in the diagnostic process, the only medical procedure to be applied is surgical removal, which is used in over 90% of all recorded cases (1). However, it should be noted that the conventional examination can result in misdiagnosis, and the islet mass may not be detected at all.

Case presentation
A 13-year old girl with no prior medical history was admitted to the District Hospital with weakness, paleness, profuse sweat, balance impairment, and hypoglycaemia (35 - 43 mg/dL). Loss of consciousness and seizures were not observed. An intravenous glucose infusion was applied. Abdominal magnetic resonance imaging (MRI) revealed a polycyclic, heterogeneous mass with visible cystic areas just below the lobus caudatus of the liver and in the direct vicinity of the pancreatic uncinate process.
The patient was transferred to the Endocrinology Department where no abnormalities were detected in the initial examination. However, hypoglycaemia (27 mg/dL) was identified, without acetonuria and with a correct hyperglycaemic response after the glucagon test with the marked level of insulin and C-peptide during hypoglycaemia 90.9 μU/mL and 3.86 ng/mL, respectively (Tab. 1). The results pointed to endogenous hyperinsulinism. Subsequently, an intravenous infusion of 10% glucose and orally taken diazoxide (daily dosage 5 mg/kg, divided into three equal doses every 8 hours) was administered. Due to side effects such as weight gain, recurrent headaches, and hirsutism, diazoxide treatment was stopped. Considering the possibility of the MEN-1 syndrome, the prolactin, insulin-like growth factor 1 (IGF-1), calcium, and parathyroid hormone (PTH) were marked, and these results were correct. Also, the genetic test for MEN-1 syndrome did not confirm the diagnosis. Positron emission tomography-computed tomography (PET/CT) showed only one mass with high metabolism of fluorine-18-L-3,4-dihydroxyphenylalanine (18F-DOPA) in the head of the pancreas (Fig. 1.1D), whereas the CT scan revealed a polycyclic lesion in the head of the pancreas and metastases to the liver and lymph nodes (Fig. 1.1A). The patient underwent a modified Whipple's operation based on the clinical picture and performed tests. Histopathological examination of the sample collected during the procedure showed pancreatic neuroendocrine tumor - PanNET G2 with Ki67 labeling index 16% (Fig. 1.4A) and mitotic account 10 mitoses/2mm² (Fig. 1.3C), and with metastases to the liver and three peripancreatic lymph nodes. Immunohistochemical examination revealed the expression of cytoplasmic insulin, chromogranin, and syneaptophysin in neoplastic cells. In addition, the tumor cells were positive for somatostatin (Fig. 1.5C) and focally for insulin (Fig. 1.5D).

The post-operative hypoglycaemia occurred and was successfully treated with somatostatin analogs (SSAs: 130 mg of octreotide LAR, intramuscular injection every four weeks). Two months after the operation, a CT of the body was performed. It showed an enlarged liver with numerous metastases (Fig. 1.1B-C). PET/CT using 68Ga-DOTA-labeled somatostatin analogs imaging revealed nine focal points of pathological radiomarker's intensification in both liver lobes. As a result, allogeneic liver transplantation (LT) was carried out, and sirolimus was applied. PanNET G2 was then found in histopathological examination of the liver and metastatic lymph nodes. Thirteen months after the graft, the immunosuppressive treatment was modified to tacrolimus due to cytomegalovirus (CMV) infection. After four years from diagnosis, 68Ga-DOTA PET/CT revealed two metastatic foci (Fig. 1.2A-D).

The patient had a laparotomy to remove the metastasis mentioned above: the paraaortic lymph node bundle and the small lymph node between the left adrenal gland, renal artery, and aorta. Histopathological examination confirmed metastatic foci neuroendocrine tumor in the paraaortic lymph nodes (NET G2). The result of 68Ga-DOTA-labeled somatostatin analogs PET/CT is currently (at the age of 22) negative for the active neoplastic disease with an increased expression level of somatostatin receptors, which means complete metabolic remission is maintained. At present, after three operations, the patient has been in remission for over six years, taking immunosuppressive medication (mycophenolate mofettol) due to liver transplantation and anti-proliferation treatment (somatostatin analog and rapamycin).

Written informed consent was obtained from the patient.

**Discussion**

Insulinoma is an uncommon neuroendocrine tumor of the pancreas characterized by autonomous insulin secretion by islet beta cells indiscriminately of glycaemia. At diagnosis, the median age is 47 years (2); however, it may occur in all age groups. Insulinomas are usually solitary, sporadic benign tumors, and less than 10% are malignant (3,4). Moreover, about 10% of insulinomas are associated with MEN-1 (2). The most characteristic finding is fasting hyperglycaemia, often after exercise or prolonged fasting. Sympathoadrenal activation symptoms can be observed, including palpitations, tremors, and sweating. Severe hypoglycaemia can cause neuroglycopenic symptoms, such as slurred speech, cognitive impairment, or seizures. The suspicion of insulinoma is confirmed by Whipple's triad and inappropriate elevated blood insulin levels with hypoglycaemia during the fasting test. Establishing a diagnosis of an insulinoma requires demonstrating inappropriately high insulin, proinsulin, or C-peptide levels during hypoglycaemia in a fasting test. Furthermore, after intravenous glucagon administration, beta-hydroxybutyrate levels below 2.7 mmol/l and glycaemia above 25 mg/dL (1.4 mmol/l) help establish the diagnosis (5).

Malignant insulinoma is extremely rare in a pediatric population, and metastases are mainly observed in the liver and regional lymph nodes (6). In the differential diagnosis of hypoglycaemia in children, the presence of acidaemia is essential. If non-ketotic hypoglycaemia is suspected, defects of ketogenesis, such as carmitine deficiency or beta-oxidation defects like medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) presenting with high free fatty acid and low insulin levels, should be considered (7). Given that congenital hyperinsulinism usually manifests in the neonatal period and that hypoglycaemia occurred at the age of 4 years in our patient, this diagnosis was very unlikely. Moreover, hypoglycaemia could be a manifestation of pituitary or adrenal deficiency and may also be observed during sulfonylureas or insulin treatment (5).

Localization of insulinoma is challenging and requires invasive and non-invasive imaging, though the sensitivities and specificities are not well documented in children. Most commonly used techniques include 3 phase CT, MRI, and endoscopic ultrasound (EUS) (5). The effectiveness of CT and MRI in detecting insulinoma in adults is estimated at 55 and 61% respectively (8).

Other diagnostic options include somatostatin receptor scintigraphy (SRS), though tumors often lack sufficient expression of somatostatin receptors, especially somatostatin receptor subtype 2 (SST2). However, certain insulinomas express the glucagon-like peptide 1 (GLP-1) receptor. If the imaging techniques mentioned above do not visualize the lesion, other methods, including PET/CT or PET/MRI using 68Ga-DOTA-labeled somatostatin analogs, 18F-DOPA PET/CT, or 68Ga-DOTA-exendin-4 PET/CT may be employed (5). These methods significantly improved the effectiveness of localizing insulinoma, indicated by some authors at above 90% (8,9).

Invasive regionalization procedures, including arterial stimulation and venous sampling (ASVS) or trans-portal venous sampling (THPVS), are currently less used because of the continuous development of imaging techniques (5).
Surgical intervention is the treatment of choice, which allows curing the disease. Insulinomas are typically removed by enucleation of the tumor. Rarely, tumors located in the head of the pancreas require a pancreaticoduodenectomy (Whipple's procedure) like our patient. Moreover, numerous liver metastases prompted the decision to perform liver transplantation, which was based on Milan's criteria (10). Thus far, several malignant, metastatic insulinoma cases in children, which required liver transplantation, have been published (11,12).

Medical management of insulinoma consists of the initial pre-surgical treatment or achieving biochemical control in patients with unresectable tumors. Diazoxide, which inhibits insulin secretion and enhances glycogenolysis, can be the first-line treatment. Side effects, such as sodium retention, edema, congestive heart failure, or hirsutism, are observed, though usually not severe. The addition of diuretics or benzothiadiazine, which improves the hyperglycaemic effect of diazoxide and reduces edema, should be considered. Glycaemic control can be achieved with calcium channel blockers, beta-adrenergic-receptor blocking drugs or glucocorticoids in selected patients (5). Somatostatin analogs are an important part of insulinoma therapy due to the inhibition of secretion of insulin and anti-proliferating effects. SSAs slow down the progression of the disease and reduce the size of the tumor (5). Despite incomplete resection after numerous surgical procedures, SSAs maintain remission in our patient.

For advanced, unresectable cases, other types of therapy like peptide receptor radionuclide therapy (PRRT), tyrosine kinase inhibitors (TKIs), and inhibitors of the mammalian target rapamycin (mTOR), or chemotherapy can still be used, especially in adults (5).

In conclusion, malignant insulinoma is a rare tumor in children. Surgical intervention remains the treatment of choice whenever possible. In case of incomplete resection or recurrence, multiple surgical interventions, pharmacological treatment, or chemotherapy should be considered. The risk of recurrence makes long-term follow-up mandatory. However, even with advanced, metastatic disease, current treatment options allow our patients to maintain complete remission for many years as in our patient.

References

Figure 1. 1A-D. Imaging tests (CT, PET-CT) before (1A,1D) and 2 months after (1B,1C) excision of pancreatic neuroendocrine tumor. 1A. CT - a polycyclic lesion 27x36x43 mm in the head of the pancreas, widening of the pancreatic
duct and enlarged lymph nodes in the hilum area of the liver (up to 14mm) (red arrow). 1B-C. CT - metastases to the liver of the diameter reaching 2.5 cm and numerous lymph nodes (red arrow) in the area of adipose tissue of mesentery. 1D. PET/CT - the intensified uptake focus of $^{18}$F-DOPA in the head of the pancreas. 2A-D. $^{68}$Ga-DOTA PET/CT - two foci of increased somatostatin analogue uptake identified after 4 years from diagnosis. 2A-B. $^{68}$Ga-DOTA PET/CT - from the left side of the superior mesenteric artery (red arrow). 2C-D. $^{68}$Ga-DOTA PET/CT - between aorta and inferior vena cava on the level of L2 (red arrow). 3,4 A-C: Hematoxylin and Eosin (H&E) staining of tumor cells of pancreatic material collected during the first surgical procedure. 3A. The border region between tumor and pancreas. 3B. Trabecular architecture. 3C. Mitotic activity of neoplastic cells (10 mitoses/2 mm²). 4A. Ki67 labeling index of neoplastic cells (16%). 4B. The regional lymph node with metastases. 4C. The liver with steatosis and the presence of metastases. 5A-D. Immunochemical examination (IHC) of tumor cells of pancreatic material collected during the first surgical procedure. 5A. Tumor cells stained positive for cytokeratin. 5B. Tumor cells stained positive for chromogranin. 5C. Tumor cells stained positive for somatostatin. 5D. Tumor cells stained positive for insulin.
Table 1. Blood samples results before excision of pancreatic neuroendocrine tumor

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Serum level</th>
<th>Reference range</th>
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<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>27</td>
<td>70 - 99</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>90.9</td>
<td>4 - 16</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>3.86</td>
<td>0.5 - 2.0</td>
</tr>
<tr>
<td>β-hydroxybutyrate (mg/dL)</td>
<td>0.43</td>
<td>0.21 - 2.8</td>
</tr>
<tr>
<td>Lactates (mmol/L)</td>
<td>2.34</td>
<td>0.5 - 6.6</td>
</tr>
<tr>
<td>Glucagon test - blood glucose (mg/dL)</td>
<td>0' - 35</td>
<td>An increase in glucose of &gt; 25 mg/dl - an insulin-mediated etiology</td>
</tr>
<tr>
<td></td>
<td>5' - 40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15' - 61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30' - 100</td>
<td></td>
</tr>
<tr>
<td>Morning cortisol (µg/dL)</td>
<td>33.74</td>
<td>5 - 20</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>23.10</td>
<td>5.18 - 26.53</td>
</tr>
<tr>
<td>IGF-1 (ng/mL)</td>
<td>384.0</td>
<td>183 - 850</td>
</tr>
<tr>
<td>Calcitonin (ng/L)</td>
<td>&lt; 0.9</td>
<td>0.5 - 7.8</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.41</td>
<td>2.10 - 2.55</td>
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<tr>
<td>Phosphorus (mmol/L)</td>
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<td>0.95 - 1.75</td>
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<tr>
<td>PTH (pg/mL)</td>
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<tr>
<td>αFP (IU/mL)</td>
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<tr>
<td>βHCG (mIU/mL)</td>
<td>&lt;0.03</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>CgA (UI)</td>
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<td>2 - 18</td>
</tr>
<tr>
<td>NSE (µg/L)</td>
<td>13.7</td>
<td>&lt; 18.3</td>
</tr>
</tbody>
</table>

IGF-1 - insulin like growth factor 1, PTH - parathyroid hormone, αFP - α-fetoprotein, βHCG - β-human chorionic gonadotropin, CgA - chromogranin A, NSE - neuron-specific enolase