CASE REPORT

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

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What is already known on this topic?

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

What this study adds?

Long-term survival and even remission may be achieved in malignant insulinoma metastatic to the liver in young patients if treated appropriately in experienced centers. It may require repeated surgical procedures, close monitoring and modification of anti-rejection therapies together with continued treatment with SSAs.

Abstract

Insulinoma is one of the pancreatic neuroendocrine tumors (PanNET) and is exceptionally rare in children. The tumor leads to severe hypoglycemia caused by excessive insulin release. We report a pediatric patient with malignant insulinoma who underwent liver transplantation (LT) due to liver metastases of the insulinoma. A 13-year-old girl presented with symptoms of hypoglycemia due to hyperinsulinism. On computed tomography (CT), a polycystic lesion in the head of the pancreas and enlarged lymph nodes were revealed. A modified Whipple's operation was performed, and histological examination confirmed PanNET. CT also showed an enlarged liver with numerous metastases. Allogeneic LT was carried out successfully. Positron emission tomography-CT using ^{68}Ga-DOTA-labeled somatostatin analogs (SSAs) at the age of 22 years confirmed complete metabolic remission. The patient currently remains under immunosuppressive and anti-proliferative treatment. Multiple surgical interventions, LT combined with SSAs, and immunosuppressive medication proved effective in this case of metastatic 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 may exhibit a range of 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 these symptoms after food intake. This condition may be associated with multiple endocrine neoplasia type 1

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(MEN-1) and, very rarely, with von Hippel-Lindau syndrome, neurofibromatosis type 1, or tuberous sclerosis.

Once the tumor is found through the diagnostic process, the leading 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. Abdominal ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) can not localize these frequently small tumors. If these imaging techniques do not visualize the lesion other methods include positron emission tomography (PET)/CT or PET/MRI (2).

Case Report

A 13-year old girl with no prior unusual medical history was admitted to the District Hospital with weakness, paleness, profuse sweating, balance impairment, and hypoglycaemia (35-43 mg/dL). Loss of consciousness and seizures were not observed. An intravenous glucose infusion was applied. Abdominal MRI revealed a polycystic heterogeneous mass with visible cystic areas just below the lobus caudatus of the liver and in the immediate vicinity of the pancreatic uncinate process.

The patient was transferred to the endocrinology department where no abnormalities were detected on initial examination. However, hypoglycaemia (27 mg/dL) was identified, without urinary acetone and with a correct hyperglycaemic response after the glucagon test with the marked level of insulin and C-peptide during hypoglycemia of 90.9 μIU/mL and 3.86 ng/mL, respectively (Table 1). The results indicated endogenous hyperinsulinism.

Subsequently, an intravenous infusion of 10% glucose and oral diazoxide (daily dose 5 mg/kg, divided into three equal doses every 8 hours) was administered. Due to side effects, including weight gain, recurrent headaches, and hirsutism, diazoxide treatment was stopped. Considering the possibility of MEN-1, prolactin, insulin-like growth factor-1, calcium, and parathyroid hormone were measured, and these results were within normal ranges. Furthermore, the genetic test for MEN-1 syndrome did not support the diagnosis. PET/CT showed only one mass with high metabolism of fluorine-18-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) in the head of the pancreas (Figure 1.1D), whereas the CT scan revealed a polycystic lesion in the head of the pancreas and metastases to the liver and lymph nodes (Figure 1.1A). The patient underwent a modified Whipple's operation based on the clinical picture and test results. Histopathological examination of the sample material collected during the procedure showed PanNET G2 with Ki-67 labeling index 16% (Figure 1.4A) and mitotic count 10 mitoses/mm² (Figure 1.3C), and with metastases to the liver and three peripancreatic lymph nodes. Immunohistochemical examination revealed the expression of cytokeratin (Figure 1.5A), chromogranin (Figure 1.5B), and synaptophysin in neoplastic cells. In addition, the tumor cells were positive for somatostatin (Figure 1.5C) and focally for insulin (Figure 1.5D).

Post-operational hypoglycemia occurred and was successfully treated with somatostatin analogs (SSAs) (30 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 (Figure 1.1B, 1C). PET/CT using 68-gallium 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (^{68}Ga-DOTA)-labeled SSAs imaging revealed nine focal points of pathological intensification of the isotopic marker in both liver lobes. As a result, allogeneic liver transplantation (LT) was carried out, and sirolimus was given. PanNET G2 was then identified on histopathological examination of the liver and metastatic lymph nodes. Thirteen months after the graft, immunosuppressive treatment was modified to tacrolimus due to cytomegalovirus infection. Four years after diagnosis, ^{68}Ga-DOTA PET/CT revealed two metastatic foci (Figure 1.2A-2D).

Table 1. Blood samples results at first presentation

Parameters	Serum level	Reference range
Blood glucose (mg/dL)	27	70-99
Insulin (μIU/mL)	90.9	4-16
C-peptide (ng/mL)	3.86	0.5-2.0
β-hydroxybutyrate (mg/dL)	0.43	0.21-2.81
Lactates (mmol/L)	2.34	0.5-1.6
Glucagon test-blood glucose (mg/dL)	0'-35 5'-40 15'-61 30'-100	An increase in glucose of >25 mg/dL suggests an insulin-mediated etiology
Morning cortisol (μg/dL)	33.74	5-20
Prolactin (ng/mL)	23.10	5.18-26.53
IGF-1 (ng/mL)	384.0	183-850
Calcitonin (ng/L)	<0.9	0.5-7.8
Calcium (mmol/L)	2.41	2.10-2.55
Phosphorus (mmol/L)	1.22	0.95-1.75
PTH (pg/mL)	82.0	16-87
αFP (IU/mL)	2.61	<5
β-HCG (mIU/mL)	<0.03	<0.1
CgA (U/l)	9	2-18
NSE (μg/L)	13.7	<18.3

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

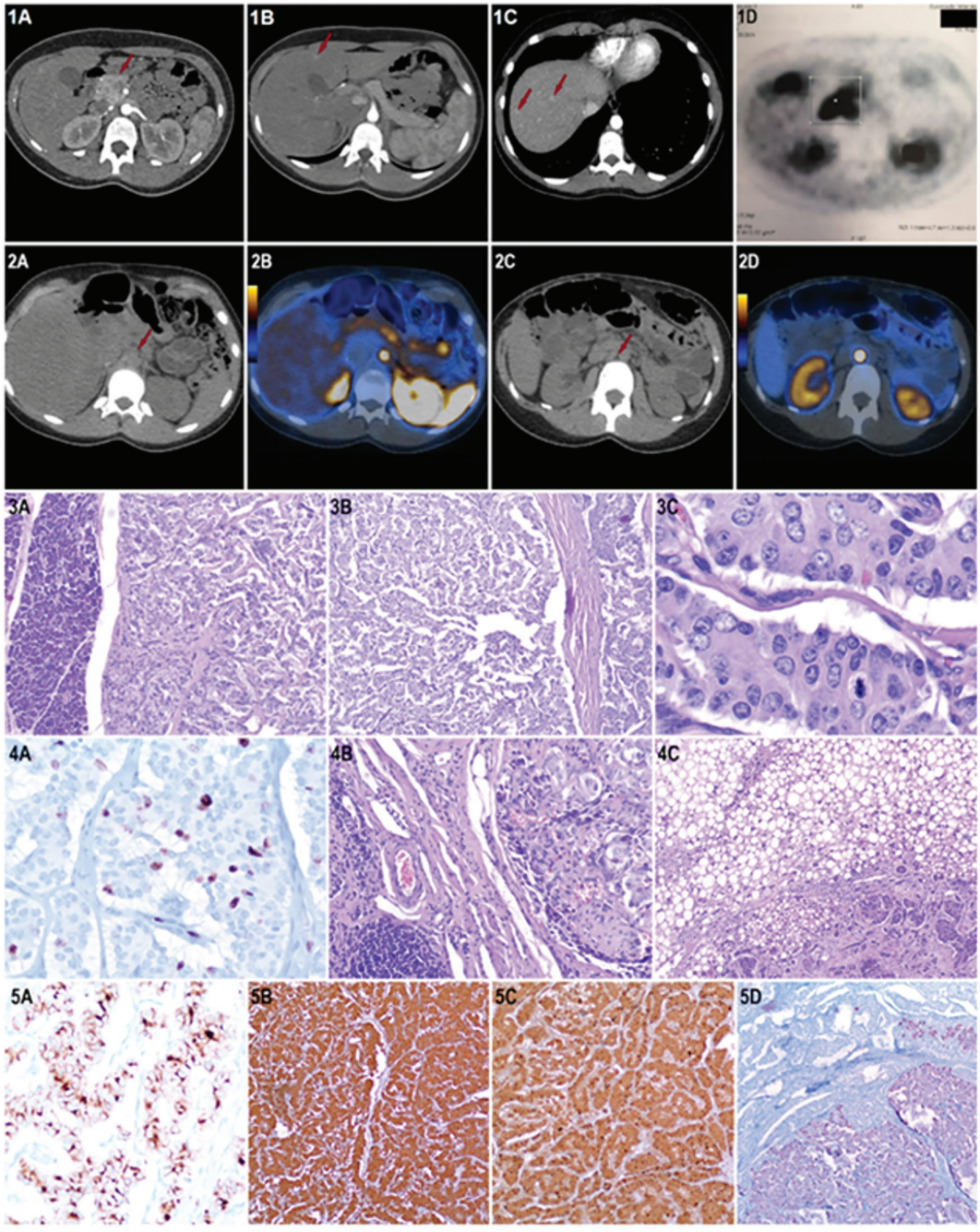

Figure 1. 1A-D: Imaging tests (CT, PET/CT) before (1A, 1D) and 2 months after (1B, 1C) excision of pancreatic neuroendocrine tumor. 1A: CT-a polycyclic lesion 27x36x43 mm in the head of the pancreas, widening of the pancreatic duct and enlarged lymph nodes in the hilum area of the liver (up to 14 mm) (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 mesenterium. 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, 2D: ^{68}Ga-DOTA PET/CT-between aorta and inferior vena cava on the level of L2 (red arrow). 3,4A-C: Hematoxylin and eosin 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 mm^2). 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 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

PET/CT: positron emission tomography/computed tomography

The patient had a laparotomy to remove these metastases, including the the paraaortic lymph node bundle and the small lymph node between the left adrenal gland, renal artery, and aorta. Histopathological examination confirmed metastatic foci of neuroendocrine tumor in the paraaortic lymph nodes (NET G2).

The result of ^{68}Ga-DOTA-labeled SSAs PET/CT is currently, at the age of 22 years, negative for active neoplastic disease with an increased expression level of somatostatin receptors, which indicates complete metabolic remission is maintained. At present, after three operations, the patient has been in remission for over six years, taking immunosuppressive medication (mycophenolate mofetil) due to liver transplant and anti-proliferative treatment (SSA 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 regardless of glycaemic status. At diagnosis, the median age is 47 years (2) but it may occur in any age group. 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 hypoglycemia, often after exercise or prolonged fasting. Sympathoadrenal activation symptoms may be evident, including palpitations, tremors, and sweating. Severe hypoglycemia can cause neuroglycopenic symptoms, such as blurry vision, cognitive impairment, or seizures.

The suspicion of insulinoma is based on Whipple's triad and inappropriately elevated blood insulin levels with hypoglycemia during the fasting test. Establishing a diagnosis of an insulinoma requires demonstrating inappropriately high insulin, proinsulin, or C-peptide levels during hypoglycemia in a fasting test. Furthermore, after intravenous glucagon administration, beta-hydroxybutyrate levels below 2.7 mmol/L and glycemia 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 hypoglycemia in children, the presence of acidemia is essential. If non-ketotic hypoglycemia is suspected, defects of ketogenesis, such as carnitine 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 hypoglycemia occurred at the age of 13 years in our patient, this diagnosis was very unlikely. Moreover, hypoglycemia may be a manifestation of pituitary or adrenal deficiency and may also be observed during sulfonylurea or insulin treatment (5).

Localization of insulinoma is challenging and requires both invasive and non-invasive imaging, though the sensitivities and specificities are not well documented in children. The most commonly used techniques include 3-phase CT, MRI, and endoscopic ultrasound (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, although tumors often lack sufficient expression of somatostatin receptors, especially somatostatin receptor subtype 2. However, certain insulinomas express the glucagon-like peptide-1 receptor. If the imaging techniques mentioned above do not visualize the lesion, other methods, including PET/CT or PET/MRI using ^{68}Ga-DOTA-labeled SSAs, ^{18}F-DOPA PET/CT, or ^{68}Ga-DOTA-exendin-4 PET/CT may be employed (5). These methods significantly improved the effectiveness of localizing insulinoma, reported by some authors to be >90% (8,9). Invasive regionalization procedures, including arterial stimulation and venous sampling or trans-hepatic portal venous sampling, are currently less used because of the continuous development of imaging techniques (5).

Surgical intervention is the treatment of choice, which permits a cure. Insulinomas are typically removed by enucleation of the tumor. Rarely, tumors located in the head of the pancreas require a pancreaticoduodenectomy (Whipple's procedure), as in the presented patient. Moreover, numerous liver metastases prompted the decision to perform LT in the present case, based on Milan's criteria (10). To date, several malignant, metastatic insulinoma cases in children, which required LT, 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, may be the first-line treatment. Side effects, such as sodium retention, edema, congestive heart failure, or hirsutism, are observed, though these are usually not severe. The addition of diuretic 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). SSAs are an important part of insulinoma therapy due to their 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 maintained remission in our patient.

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

Conclusion

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 may facilitate maintenance of complete remission for many years, as in the presented patient.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: Elżbieta Moszczyńska, Arnika Wydra, Klaudia Zasada, Marta Baszyńska-Wilk, Dorota Majak, Anna Śliwińska, Wiesława Grajkowska, Concept: Elżbieta Moszczyńska, Arnika Wydra, Design: Elżbieta Moszczyńska, Arnika Wydra, Data Collection or Processing: Elżbieta Moszczyńska, Arnika Wydra, Klaudia Zasada, Marta Baszyńska-Wilk, Dorota Majak, Anna Śliwińska, Wiesława Grajkowska, Analysis or interpretation: Elżbieta Moszyczńska, Arnika Wydra, Literature Search: Elżbieta Moszczyńska, Arnika Wydra, Writing: Elżbieta Moszcyńska, Arnika Wydra.

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