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Case Report

INSULINOMA MANIFESTING EARLY POSTPARTUM: CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Objective: Insulinomas are insulin-producing neuroendocrine tumors. Insulinomas presenting during pregnancy and the early postpartum period are very rare.

Methods: A 33-year-old woman with hypoglycemia early postpartum is described. Abdominal computed tomography and endoscopic ultrasound showed 2 lesions of the pancreas. An ^{11}C-5-hydroxy-L-tryptophan (^{11}C-HTP) positron emission tomography-computed tomography (PET-CT) scan demonstrated additional uptake in lymph nodes and liver, suggesting malignant insulinoma. Six months after pylorus-preserving pancreatoduodenectomy and excision of liver and lymph node metastases, tumor progression was noted on repeated ^{11}C-HTP PET-CT scans without recurrent hypoglycemia. She was enrolled in a clinical trial and was randomized for dual pan-class I phosphoinositide 3-kinase inhibitor and mammalian target of rapamycin inhibitor treatment, on which there was no tumor progression during 21 months follow-up. A systematic search of PubMed and Medline with the search strategy 'insulinoma AND pregnancy' OR 'insulinoma AND postpartum' was performed to identify English-, Dutch-, and German-language publications. All publications about (malignant) insulinoma during pregnancy and in the early postpartum period (≤3 months postpartum) were reviewed in addition to the described case report.

Results: Insulinoma manifesting during pregnancy or early after delivery has been described in 31 cases, including only 3 cases of malignant insulinoma. Management of malignant insulinoma requires an individualized approach; optimal medical treatment is evolving.

Conclusion: The usefulness of ^{11}C-HTP PET-CT in the diagnosis of malignant insulinoma was demonstrated in the present case. Hypoglycemia may particularly become manifest in the postpartum period when insulin action increases consequent to decreased levels of placenta-derived counterregulatory hormones after delivery. **(AACE Clinical Case Rep. 2015;1:e230-e239)**

Abbreviations:
^{11}C-HTTP = ^{11}C-5-hydroxy-L-tryptophan; **CT** = computed tomography; **EUS** = endoscopic ultrasound; **MEN-1** = multiple endocrine neoplasia type 1; **mTOR** = mammalian target of rapamycin; **MRI** = magnetic resonance imaging; **PET-CT** = positron emission tomography-computed tomography; **SRS** = somatostatin-receptor scintigraphy

INTRODUCTION

Insulinomas are insulin-producing neuroendocrine tumors arising from the pancreatic β-cells. The incidence of insulinomas is estimated to be 4 per 1 million persons per year, of which 5 to 10% show malignant degeneration. Median age of presentation was reported to be 47 years, with 59% being women (1). Insulinoma presenting during pregnancy or in the postpartum period is considered to

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be very rare. In this study, we report a case of malignant insulinoma manifesting in the early postpartum period and provide a systematic review of the literature.

CASE REPORT

A 33-year-old Caucasian woman (G2P1A1) who had experienced a normal pregnancy and an uncomplicated delivery (40 weeks; 0 days) was referred to the emergency department 6-days postpartum because of excessive sweating, dizziness, and confusion during breastfeeding. Her medical history was uneventful except for an unspecified collapse 1 year before pregnancy. She did not use any medication. Weight gain during pregnancy was approximately 8 kg, with a body weight change from 60 to 68 kg. The new-born was a healthy girl with a weight of 2.920 kg (standard deviation score: −0.7, according to the World Health Organization child growth standards). At hospital arrival, the patient's capillary plasma glucose level was 1.7 mmol/L (31 mg/dL). Her symptoms disappeared immediately after taking dextrose orally, and the plasma glucose level increased to 6.1 mmol/L (110 mg/dL). During 24 hours of observation, the patient recovered completely, her glucose level remained normal, and she was discharged.

Because she repeatedly experienced hypoglycemic symptoms, which could be controlled by the administration of dextrose, she was readmitted to the hospital for further evaluation. An adequately reacting, healthy, lean young woman with normal vital signs and unremarkable findings at physical examination was seen. The neurologic examination revealed no abnormalities. Laboratory studies showed a normal blood count. Serum electrolytes, as well as liver and renal function tests, were unremarkable. We initiated a formal prolonged fasting test. After fasting for only 3 hours, the patient experienced symptomatic hypoglycemia with a venous plasma glucose of 1.9 mmol/L, which coincided with an increased insulin level of 27.6 mU/L and a C-peptide level of 1.2 pmol/L (Chemiluminescence Microparticle Immuno Assays for Architect 2000i, Abbott Laboratories Diagnostics Division, Abbott Park, IL; cutoff values endogenous hyperinsulinemia for insulin ≥3 mU/L and for C-peptide ≥200 pmol/L, respectively) (2). Symptoms were relieved after glucose ingestion. Sulfonylureas (glibenclamide, gliclazide, glimepiride, and tolbutamide; high-performance liquid chromatography-diode array detector system) were undetectable in a serum sample, which essentially ruled out the deliberate use of this class of drugs. Therefore, these laboratory findings indicated that hypoglycemia was consequent to endogenous hyperinsulinemia. There was no laboratory evidence for thyroid dysfunction or adrenal insufficiency. Genetic testing for multiple endocrine neoplasia type 1 (MEN-1) syndrome on peripheral blood leukocyte DNA was negative.

A dual-phase computed tomography (CT) scan of the pancreas showed a 2.5-cm large, irregular, and hypervascular mass in the head of the pancreas and a second, smaller hypervascular focal lesion just dorsal of the uncinate process. Furthermore, an undefined lesion close to the left adrenal gland was observed. An endoscopic ultrasound (EUS) confirmed the large irregular lesion in the pancreatic head and an additional lesion in the pancreatic body. ^{111}Indium-pentetreotide somatostatin-receptor scintigraphy (SRS) showed abnormal uptake in the head of the pancreas but could not identify other tumor locations. An ^{11}C-5-hydroxy-L-tryptophan (^{11}C-HTP) positron emission tomography (PET)-CT scan showed HTP accumulation in the head of the pancreas, in at least one lymph node and in the laterodorsal part of the right liver lobe (Fig. 1). These findings were consistent with metastatic insulinoma. The patient underwent an exploratory laparotomy with pylorus-preserving pancreaticoduodenectomy (i.e., a procedure in which the stomach and a small rim of the first portion of the duodenum are spared) (3), local excision of a subcapsular liver metastasis from segment 6, and excision of multiple lymph nodes from the mesentery of the colon and jejunum. The histopathologic diagnosis was a pT3N1M1, grade 2, pancreatic neuroendocrine tumor (World Health Organization 2010 classification) (4). Mitotic count was 4 per 10 high-power fields on the pancreatic tumor. The Ki-67 proliferation index was 2.9%. Immunostaining for insulin and chromogranin A was positive. The tumor had progressed to peripancreatic fat tissue and was present in 2 of the 10 resected lymph nodes, as well as in the liver.

The hypoglycemic periods resolved after surgery. A postoperative fasting test revealed a plasma glucose level of 3.3 mmol/L and an insulin concentration of 2.3 mU/L after a 72-hour fast. An ^{11}C-HTP PET-CT scan performed 6 months postoperatively revealed recurrence of retroperitoneal lymph node metastases (Fig. 2), although she remained free of symptomatic hypoglycemia.

Curative surgical treatment options were absent. Because improved control of hypoglycemia in patients with insulinoma treated with everolimus was described before, and because streptozocine/doxorubicine treatment would require hospitalization for several nights, we chose an oral treatment regimen (5,6). Therefore, the patient was enrolled in a randomized phase II study of the mammalian target of rapamycin (mTOR) inhibitor, everolimus, or BEZ235 in advanced pancreatic neuroendocrine tumors (NCT01628913). BEZ235 is a dual pan-class I phosphoinositide 3-kinase inhibitor and also an mTOR inhibitor. The patient was randomized for BEZ235 treatment, initially 2 times 400 mg per day. She experienced nausea and vomiting, for which the drugs were stopped temporarily. After complaints resolved, she has continued with a 25% reduced dose (300 mg 2 times daily) until now. She has been clinically stable since the start of treatment (April 2013 until present; 21 months). The lowest fasting plasma glucose level measured during BEZ235 treatment was 2.3 mmol/L (41 mg/dL) but increased to 5.1 mmol/L (92 mg/dL) at the

latest evaluation. Other monthly performed biochemical screening tests revealed serum transaminase elevations that normalized with continued treatment. Kidney function has remained normal to date (estimated glomerular filtration rate ranging between 64 and 111 mL/min/1.73 m^2). CT scans, assessed by Response Evaluation Criteria In Solid Tumors 1.0 criteria, were performed every 3 months and showed no tumor progression at the latest evaluation.

Approval of the Medical Ethical Committee of the University of Groningen was obtained, and the patient provided written informed consent.

Review of the Literature

We searched PubMed and Medline for English-, Dutch-, and German-language publications using the search strategy: 'insulinoma AND pregnancy' OR 'insulinoma AND postpartum.' In addition to the described case, we identified 30 case reports on insulinoma during pregnancy or at most 3 months postpartum, including 2 cases of malignant insulinoma (Table 1) (references are given in Supplementary Table 1, a-aa). Fourteen of the patients suffered symptoms during the first trimester of pregnancy. In 11 cases, hypoglycemic symptoms occurred in the early postpartum period. Five patients had symptoms during the second or the third trimester. In 29 patients, signs and symptoms were described repeatedly: weakness (5 patients), uncoordinated movements (8 patients), numbness in the limbs and/or the face (6 patients), confusion (11 patients), apathy (5 patients), seizures (8 patients), altered or loss of consciousness (16 patients), blurred vision (3 patients), or change in behavior/mood (8 patients). In 26 patients, hypoglycemia was sufficiently controlled with frequent meals and/or intravenous glucose until surgery. In 3 patients, drug treatment with diazoxide was initiated to treat hypoglycemia. Of the patients with insulinoma diagnosed during pregnancy, surgery was performed in 4 patients during the first trimester and in 2 patients during the second trimester. In 9 patients, surgery was postponed until after delivery because of sufficient glucose control and absence of maternal and fetal hazards. Three patients did not undergo surgery. Most of the patients showed good clinical outcome after removal of the insulinoma. Only 3 patients had residual neurologic manifestations after surgery (7-9). Two patients died because of hepatic/renal failure and severe sepsis, respectively (10,11).

This series of cases also included 2 cases of malignant insulinoma. First, Friedman et al (10) reported a patient suffering from ascites and liver metastases during pregnancy. As this patient died 10 days after delivery from hepatic failure, it could be argued that extensive hepatocellular damage had contributed to the hypoglycemia. The second patient was diagnosed after having severe hypoglycemia at 17 weeks of gestation. Imaging confirmed a mass in the pancreatic tail and liver metastasis. This patient was treated with the somatostatin analogue, octreotide, until caesarean section was performed at 34 weeks of gestation. Resection of the insulinoma was not performed because of diffuse liver metastases. Treatment with everolimus was started, but the outcome was not reported (12).

In the series described here, fetal outcome was generally satisfactory, and 20 of the neonates were born at term. Birth weight was reported in 21 cases and ranged from

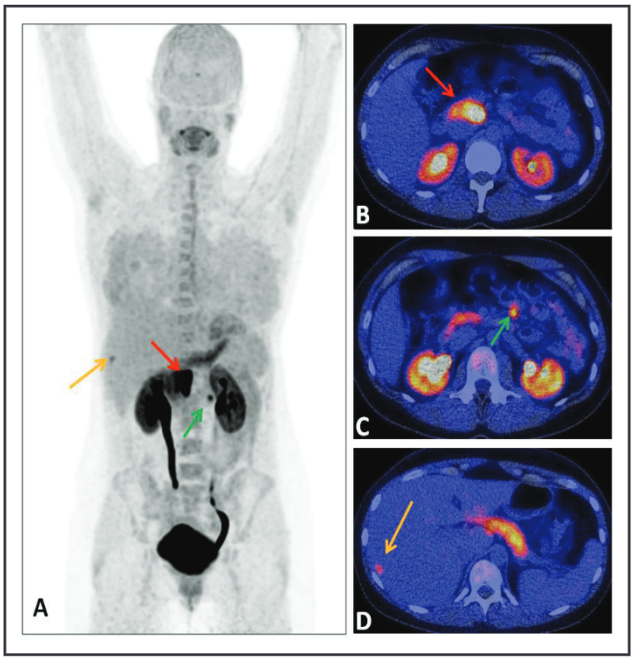

Fig. 1. Baseline ^{11}C-5-hydroxy-l-tryptophan positron emission tomography (PET)-computed tomography (CT) scanning. (*A*) Coronal image and (*B*, *C*, *D*) transaxial fused PET-CT images. Red arrow: primary lesion in head of the pancreas. Green arrow: mesenterial lymph node metastasis. Yellow arrow: liver metastasis.

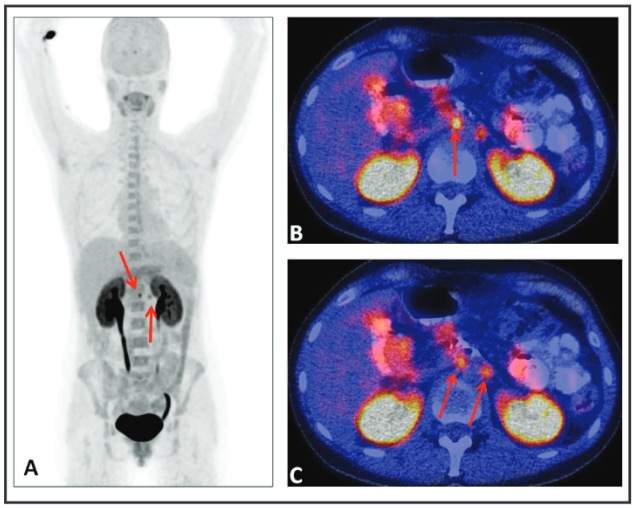

Fig. 2. ^{11}C-5-hydroxy-l-tryptophan positron emission tomography (PET)-computed tomography (CT) scanning 6 months after surgery, showing recurrent disease with retroperitoneal lymph node metastases (red arrows). (*A*) Coronal image, (*B*, *C*) transaxial fused PET-CT images.

1.80 kg (twins) to 4.15 kg (mean birth weight, 3.15 kg). Weight for gestational age was infrequently reported. One infant died at 22 weeks of gestation (13).

DISCUSSION

The unusual occurrence of hypoglycemic manifestations shortly after delivery led us to perform a comprehensive literature search on insulinoma cases manifesting during pregnancy and in the early postpartum period. Apart from the presently described case, a limited number of 30 cases of insulinoma during pregnancy or in the postpartum period has been reported to date, including only 2 cases of a malignant insulinoma.

It is recommended to evaluate the underlying cause of hypoglycemia only in patients with Whipple's triad (i.e., signs and symptoms consistent with hypoglycemia, coinciding with low plasma glucose concentration, and relief of these symptoms in response to glucose raising measures) (2,14). A prolonged fasting test is advised to evaluate whether hypoglycemia is due to endogenous hyperinsulinemia. In the present case, we unequivocally demonstrated endogenous insulin-mediated hypoglycemia only 3 hours after fasting.

Pregnancy has major effects on glucose homeostasis. These changes serve to meet the metabolic demands of the fetus, which is largely dependent on glucose as its source of energy (15-17). Several factors may contribute to explain why insulinoma is rarely diagnosed in pregnancy. First, fasting plasma glucose levels are lower during the first trimester because of increased insulin levels consequent to β-cell stimulation by estrogens and progesterone and because of enhanced insulin sensitivity in peripheral tissues (16,18). Therefore, possible symptoms of hypoglycemia during early pregnancy can readily be misinterpreted as being consistent with normal glucose homeostasis during pregnancy (17,19). Second, it is likely that the occurrence of hypoglycemia due to excessive insulin secretion is counteracted by a number of hormonal changes that occur during pregnancy. Insulin sensitivity decreases during the second and the third trimester of normal pregnancy, consequent to the production of human placental lactogen and placental growth hormone (20-22). The placenta may also produce leptin, a pro-inflammatory adipokine (20-22). Furthermore, insulin sensitivity is expected to decrease as a result of increased cortisol and possibly also prolactin levels (16). These factors could explain why only very few insulinoma cases have been reported during this phase of gestation. In the postpartum period, insulin sensitivity is quickly recovered, which could explain why the presently described patient developed severe hypoglycemic episodes shortly after delivery but not during pregnancy. In addition, breastfeeding could have triggered hypoglycemic episodes, as lactating women often have lower glucose levels than women who are not breastfeeding (23).

Neuroendocrine tumors are in general slowly growing processes (24). The influence of pregnancy on insulinoma growth as well as on its possible malignant degeneration is poorly understood. Increased levels of estrogens and progesterone during early pregnancy may stimulate hyperplasia and hypertrophy of pancreatic β-cells, possibly contributing to tumor growth (18,25).

The incidence of insulinomas in MEN-1 syndrome patients has been reported to be approximately 10 to 12%, with malignant tumors in about 12 to 20% of cases (26). National Dutch guidelines currently advocate the determination of *MEN-1* germline mutations in patients aged <35 years who present with 1 MEN-1 syndrome–associated tumor (Stichting Opsporing Erfelijke Tumoren; available at: www:oncoline.nl). Endocrine Society Clinical Practice Guidelines recommend performing genetic analysis in patients presenting with ≥2 MEN-1 syndrome–associated tumors (27). *MEN-1* gene mutations proved to be absent in the current patient. In the 2 previously described cases of malignant insulinoma, which manifested during pregnancy at 29 and 37 years of age, *MEN-1* gene mutations were also not reported.

To detect an insulinoma, a CT scan or magnetic resonance imaging (MRI) and EUS are currently recommended initial procedures, with sensitivities of 70 to 80% and higher than 90%, respectively (14,28,29). It is commonly advised to combine a CT scan or MRI with EUS, although the performance of EUS is dependent on the examiner's experience and has several pitfalls (28-31). Nuclear imaging studies are also frequently used to detect pancreatic neuroendocrine tumors (32). SRS with ^{111}In-pentetreotide can detect (metastatic) pancreatic neuroendocrine tumors with high sensitivity, but its sensitivity for insulinoma seems to be lower compared to other pancreatic neuroendocrine tumors. The sensitivity of SRS for insulinomas in general has been reported to be only 50 to 60% but could be higher in malignant insulinomas (33-36). In our case, SRS did not identify all tumor locations. This is possibly due to the limited spatial resolution of the gamma camera used for this imaging technique. More recently, several PET-based techniques have been introduced to visualize neuroendocrine tumors. Insulinomas are able to take up and decarboxylate amine precursors such as 5-HTP (37). The ^{11}C-HTP-PET scan may be superior to SRS, because it detects more and smaller malignant localizations more reliably (32). ^{11}C-HTP-PET imaging was found to be the most sensitive nuclear imaging procedure in detecting pancreatic neuroendocrine tumors compared to SRS and 3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine-PET, especially when combined with CT imaging (38). However, its diagnostic utility in detecting insulinoma awaits further study. Also, it should be noted that this imaging technique is not widely available. But in the presently described patient, the use of an ^{11}C-HTP PET-CT scan for pre-operative tumor staging was clinically relevant, as this imaging technique detected at least one lymph node metastasis and

Table 1
Thirty Cases of Insulinoma Diagnosed During Pregnancy or Early Postpartum

Case[a]	Age (years)	First symptoms	Imaging	Familial endocrine tumor syndromes	Benign/ malignant	Treatment	Maternal outcome
1 (a)	25	First trimester of gestation	-	-	Benign	Carbohydrate-rich meals; laparotomy postpartum	No residual symptoms
2 (a)	47	3 days postpartum	-	-	Benign	Glucose IV; laparotomy postpartum	Several residual neurologic defects
3 (b)	35	13 days postpartum (2nd pregnancy), 9 days postpartum (3rd pregnancy)	-	-	Benign	Glucose IV; laparotomy and removal of insulinoma after second pregnancy	No symptoms after removal
4 (c)	37	First trimester of gestation	-	-	Benign	Glucose IV; laparotomy at 12 weeks gestation	No symptoms after removal
5 (d)	21	First trimester of gestation	-	-	Benign	Anticonvulsants, prednisolone, diazoxide, glucose IV; laparotomy at 12 weeks gestation	Aphasia and mental "slowness"
6 (e)	33	First trimester of gestation	US & CT: 2-cm lesion in pancreatic head	-	Benign	Glucose IV, carbohydrate-rich diet; laparotomy at 17 weeks of gestation	No symptoms after removal
7 (f)	19	First trimester of gestation	CT: unremarkable; angiography: lesion (1.8 × 2.6 cm) in pancreatic tail	-	Benign	Glucose IV, high-carbohydrate diet, frequent feeding; distal pancreatectomy during 1st trimester	No residual symptoms 3 years later
8 (g)	24	First trimester of gestation	CT: unremarkable; angiography: tumor blush in body of pancreas	-	Benign	Frequent high-carbohydrate feedings, laparotomy postpartum	No residual symptoms
9 (h)	24	First trimester of gestation	US & CT & angiography: unremarkable	-	Benign	Glucose IV, diazoxide; laparotomy postpartum	Right hemiparesis, mild affective disorder
10 (i)	37	Third trimester of gestation	US: multiple hypodense defects in liver parenchyma; pancreas could not be adequately visualized	-	Malignant	Glucose IV, glucose-rich fluids; caesarean section in week 34 of gestation because of fetal distress: multiple nodules in liver confirmed	Died postoperative because of progressive hepatic failure
11 (j)	41	First trimester of gestation	CT & angiography: unremarkable	-	-	Frequent feeding; laparotomy postpartum	No residual symptoms
12 (k)	24	2 days postpartum	CT & angiography: unremarkable	-	Benign	Glucose IV; laparotomy postpartum	No residual symptoms
13 (l)	26	Second trimester of gestation	CT & angiography: tumor (2 cm) in pancreatic tail	Positive family history of MEN-1 syndrome	Benign	Glucose IV, frequent feeding; laparotomy postpartum	No residual symptoms
14 (m)	25	First trimester of gestation	US: unremarkable	-	Benign	Laparotomy in 1st semester	No residual symptoms
15 (n)	30	First trimester of gestation	-	-	Benign	Anticonvulsants, glucose IV, frequent meals; diagnosed at autopsy	Died 2 weeks after delivery (at 22 weeks) from severe sepsis
16 (o)	24	First trimester of gestation	US: unremarkable, MRI: lesion in pancreatic tail; US: nodular hypo-echoic lesion (1.1 × 1.4 cm)	-	Benign	Glucose IV, fractionated meals, exploratory laparotomy with removal of distal pancreas (2nd trimester), second laparotomy with resection tumor (postpartum)	No residual symptoms
17 (p)	26	Second trimester of gestation	CT: lesion (1 cm) in pancreatic tail; US, angiography, octreotide scan and vein sampling: unremarkable	-	Benign	Glucose IV, laparotomy after delivery	No residual symptoms
18 (q)	25	First trimester of gestation	US & EUS: unremarkable	-	Benign	Laparotomy at 17 weeks of gestation	No residual symptoms
19 (r)	36	1 day postpartum	CT: tumor (1.5 cm) in pancreatic head	-	Benign	Glucose IV, high-carbohydrate diet; laparotomy postpartum	No residual symptoms

(Continued on next page)

Table 1
Thirty Cases of Insulinoma Diagnosed During Pregnancy or Early Postpartum

Case[a]	Age (years)	First symptoms	Imaging	Familial endocrine tumor syndromes	Benign/ malignant	Treatment	Maternal outcome
20 (s)	26	First trimester of gestation	MRI & CT: lesion in pancreatic tail	-	Benign	Glucose IV, frequent meals; laparotomy postpartum	No residual symptoms
21 (t)	35	21 days postpartum	CT, abdominal US, intra-arterial calcium stimulation: unremarkable	No family history of neuroendocrine tumors	Benign	Laparotomy postpartum	No residual symptoms
22 (u)	34	14 days postpartum	US & EUS: inhomogeneity in pancreatic body; MRI: mass (1.7 × 1 cm) in pancreatic body; pathologic intra-arterial calcium stimulation	Negative testing for *MEN-1* gene mutations	Benign	Glucose IV, frequent meals; laparotomy postpartum	No residual symptoms
23 (v)	35	3 months postpartum	CT & angiography: unremarkable	-	Benign	Frequent carbohydrate ingestion, phenytoin, laparotomy, and removal of mass at junction of pancreatic head and body	No residual symptoms
24 (v)	35	26 days postpartum	CT & EUS & intra-arterial calcium stimulation: unremarkable	-	Benign	Glucose IV, laparoscopy, and enucleation of an 8-mm tumor in the pancreatic tail	No residual symptoms
25 (v)	22	First trimester of gestation	MRI: cystic mass (2.5 cm) in pancreatic tail; EUS: cystic mass (1.2 × 2 cm) and solid hypo-echoic lesion (1.7 × 1.5 cm)	Negative testing for *MEN-1* gene mutations	Benign	Enteral feeding because of hyperemesis gravidarum with high carbohydrates; laparoscopy postpartum	No residual symptoms
26 (w)	29	Third trimester of gestation	US, spiral CT, MRI, and somatostatin receptor scintigraphy: unremarkable; EUS: tumor (6 × 7 mm) in pancreatic head, confirmed by intra-operative US	Negative testing for *MEN-1* gene mutations	Benign	Glucose IV, diazoxide, laparotomy, pancreaticoduodenectomy, and cholecystectomy postpartum	No residual symptoms
27 (x)		4 days postpartum	MRI: lesion (1.2 cm) in pancreatic head, pathologic intra-arterial calcium stimulation	Negative testing for *MEN-1* gene mutations	Benign	Frequent carbohydrate meals, glucose IV, laparotomy with tumor resection	No residual symptoms
28 (y)	42	3 weeks postpartum	CT, MRI, and DOTATOC-PET: unremarkable; EUS: 13-mm lesion in pancreatic tail	-	Benign	Glucose IV, tumor resection by laparoscopic enucleation	No residual symptoms
29 (z)	21	8 days postpartum	CT: nodular lesion (2 cm) in pancreatic head	Negative testing for *MEN-1* gene mutations	Benign	Laparotomy with tumor resection	No residual symptoms
30 (aa)	29	Second trimester of gestation	US: multiple hypo-echoic round-shaped liver lesions; CT: 2-cm hypo-enhanced mass in pancreatic tail; MRI: multiple T2-hyperintense lesions	-	Malignant	Treatment with octreotide until 34 weeks of gestation; then caesarean section; postpartum start everolimus	

Abbreviations: CT = computed tomography; DOTATOC = Dota-d-Phe(1)-Tyr(3)-octreotide; EUS = endoscopic ultrasound/echo-endoscopy; IV = intravenous; MEN-1 = multiple endocrine neoplasia 1; MRI = magnetic resonance imaging; PET = positron emission tomography; US = ultrasonography.
[a]References (a-aa) are provided in Supplementary Table 1.

a liver lesion, which were not seen on the SRS and CT scans. Also, the ^{11}C-HTP PET-CT scan procedure demonstrated recurrence of disease 6 months postoperatively and guided us to start palliative medical treatment.

The preferred treatment option for insulinoma is pancreatic surgery, in selected cases, combined with symptomatic treatment with somatostatin analogs and/or diazoxide (Table 1) (39). The choice of the procedure is dependent on the characteristics of the tumor mass. Partial pancreatectomy or enucleation has the advantage of preserving the pancreatic parenchyma as much as possible (40). Laparoscopic resection has been advocated for insulinomas that are benign and small or located in the body or tail of the pancreas (41). Radical resection should be considered in case of multiple lesions or when the lesion is not well-capsulated, large, and located near the main pancreatic duct. Metastatic insulinoma should primarily be treated with extensive pancreatic surgery, including removal and/or radioablation of liver metastasis, if present (39,42,43). Postoperative management should aim at alleviating hypoglycemic symptoms if still present. In case of unresectable tumors or recurrence, systemic antiproliferative treatment is recommended. Treatment with cytotoxic therapy, such as combination regimens including streptozocin, show objective radiologic response rates and increase of progression-free survival (44). The CLARINET trial recently demonstrated that lanreotide improves progression-free survival in enteropancreatic neuroendocrine tumors, in support of the antiproliferative capacity of somatostatin analogues (45). Of note, insulinoma patients were not included in that trial. Furthermore, the RADIANT-3 trial recently showed promising results of treatment with the mTOR inhibitor, everolimus, in advanced pancreatic neuroendocrine tumors (46). In comparison with placebo, everolimus was associated with a 6.4-month prolongation of the median progression-free survival (46). In addition, sunitinib, an oral multitargeted tyrosine kinase inhibitor, has antitumor activity in pancreatic neuroendocrine tumors (47). Treatment with the radiolabeled somatostatin analogue, [177 Lu-DOTA 0, Tyr3] octreotate, also showed promising responses (48) and is currently being investigated in a phase 3 trial in comparison with octreotide (NETTER1, NCT01578239).

CONCLUSION

The presently described patient presented with symptomatic hypoglycemic episodes that manifested in the early postpartum period after an uncomplicated pregnancy due to malignant insulinoma. Metastatic disease was detected by ^{11}C-HTP PET-CT scan. Insulinoma manifesting during pregnancy or early after delivery has been described in only 30 cases to date, including 2 cases of malignant insulinoma. Hypoglycemia may particularly become manifest in the postpartum period when insulin action has been recovered, consequent to decreased levels of placenta-derived counterregulatory hormones after delivery.

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E.C. Gertje designed the study, collected and researched the articles, and wrote the manuscript. A.M.E. Walenkamp reviewed/edited the manuscript. A.W.J.M. Glaudemans was responsible for the imaging studies and reviewed/edited the manuscript. A.J.C. Ijtsma reviewed/edited the manuscript. K. Hoogenberg reviewed/edited the manuscript, and R.P.F. Dullaart designed the study and wrote the manuscript.

DISCLOSURE

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