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CASE REPORT

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A case of insulinoma diagnosed postpartum with hypoglycemic symptoms that were masked during pregnancy

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Abstract

The diagnosis of insulinoma in perinatal women can be difficult, as hypoglycemic symptoms may be masked by pregnancy-associated insulin resistance. In addition, when multiple insulinomas are observed, it is necessary to consider the possibility not only of MEN1, but also of insulinomatosis.

KEYWORDS

hypoglycemia, insulin resistance, insulinoma, insulinomatosis, pregnancy

1 | INTRODUCTION

Insulinoma is a rare pancreatic neuroendocrine tumor characterized by fasting hyperinsulinemic hypoglycemia. We report the case of a 34-year-old woman with insulinoma whose hypoglycemic symptoms were masked during pregnancy, because of increased insulin resistance; they manifested in the postpartum period.

Although insulinoma is a rare neuroendocrine tumor of the pancreas (annual incidence of four cases per million persons per year), it is the most common cause of endogenous hyperinsulinemic hypoglycemia in adults and is slightly more common in women.[1] In general, its occurrence in women during pregnancy or after delivery is considered exceptional. However, previous reports in the English literature have shown that insulinoma can occur during pregnancy [2-16] or the postpartum period,[2,14,17-23] especially immediately after delivery.[2,18,19,23] In these cases, hypoglycemic symptoms were masked during pregnancy and manifested in the postpartum period. It was postulated that increased insulin resistance masked the hypoglycemic symptoms during pregnancy, and postpartum elimination resulted in their appearance. We here report a case of a 34-year-old woman with insulinoma whose hypoglycemic symptoms were apparent immediately after delivery.

2 | CASE REPORT

A 34-year-old multiparous Japanese woman, in the early stages of pregnancy with her third child, experienced cold sweats in the fasting state that were relieved by food intake. Although

the symptoms improved during the gestational period, a 50 g oral glucose tolerance test for gestational diabetes, conducted in the second trimester, revealed a plasma glucose level of 45 mg/dL after glucose loading. However, parameters such as the immunoreactive insulin (IRI) level were not tested for. No further investigation was conducted. In the 38th week of gestation, the patient successfully delivered a healthy female infant, although she had gained 17 kg in weight (from 51 to 68 kg) during the pregnancy. Two weeks after delivery, she presented with recurrent cold sweats and confusion during fasting, and was transferred to the emergency department of the admitting hospital with impaired consciousness. The patient was found to be in a state of acute hypoglycemia (plasma glucose level, 36 mg/dL; normal range: 70-109 mg/dL) with nonsuppressed insulinemia (IRI, 6.8 μU/mL; normal range: 5.0-10.0 μU/mL, C-peptide immunoreactivity (CPR), 0.79 ng/mL; normal range: 1.40-4.40 ng/mL). Magnetic resonance imaging (MRI) of the pituitary was performed to rule out the possibility of Sheehan's syndrome or lymphocytic hypophysitis, because of impaired consciousness in woman at postpartum. However, no suspicious findings such as empty sella or swollen pituitary gland, nor any obvious pituitary adenoma was observed. Abdominal dynamic computed tomography (CT) showed enhanced nodules with diameters of 13 and 6 mm in the tail of the pancreas during the early phase (Figure 1); the patient was referred to our hospital for further evaluation.

There was no family history of multiple endocrine neoplasia (MEN) or previous usage of glucose-lowering agents. The patient was 160.0 cm tall, with a body weight of 66.0 kg; her BMI was 25.8 kg/m^2. Other than mild obesity, there were no abnormal findings on physical examination. Laboratory findings on admission are shown in Table 1. Her serum cortisol level was within the normal range, and the insulin autoantibody test was negative (Table 1). Meanwhile, she showed an elevated intact parathyroid hormone (PTH) level, with both normocalcemia (adjusted serum calcium level, 8.9 mg/dL; normal range: 8.5-10.2 mg/dL) and normophosphatemia (Table 1), indicating early-stage primary hyperparathyroidism (pHPT). However, Tc-99m sestamibi/single-photon emission computed tomography (SPECT) scanning was not conducted because she was breastfeeding. A prolonged (5-h) period of supervised fasting confirmed hypoglycemia (plasma glucose level, 43 mg/dL) accompanied by insulinemia (IRI, 3.83 μU/mL; CPR, 1.01 ng/mL; proinsulin immunoreactivity, 41.0 pmol/L) and impaired ketogenesis (β-hydroxybutyrate level, 17.2 μmol/L) (Table 2). Furthermore, 1 mg intravenous glucagon increased her blood glucose level from 43 to 96 mg/dL at the end of the fast. Thus, we clinically diagnosed the patient with insulinoma.

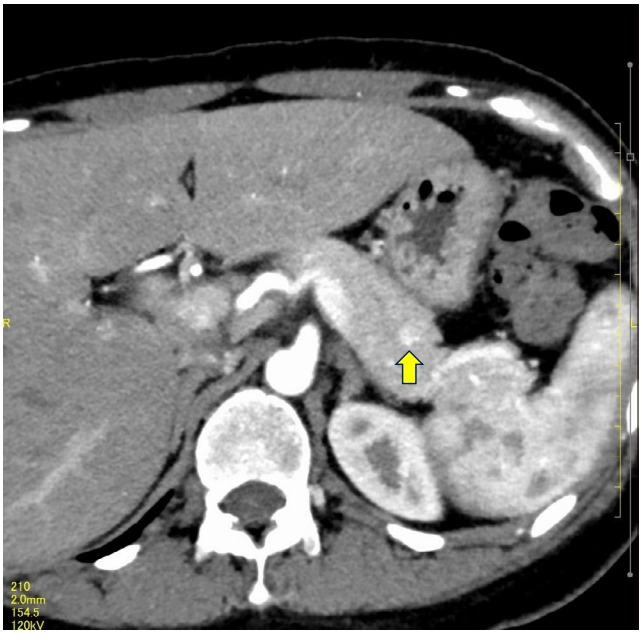

FIGURE 1 Contrast-enhanced computed tomography of the pancreas. An enhanced nodule (diameter of 13 mm) in the tail of the pancreas was revealed by contrast-enhanced computed tomography during the early phase (yellow arrow)

We performed a selective arterial calcium injection (SACI) test to localize the insulinoma. Sampling from the hepatic vein following selective arterial calcium loading was performed in the order of the superior mesenteric artery, gastroduodenal artery, proper hepatic artery, and splenic artery. An at least twofold increase in the IRI level 30-60 seconds after injecting the calcium was considered significant.[24] Consequently, calcium-induced insulin secretion was observed with stimulation in the superior mesenteric artery and splenic artery (Table 3). The IRI level was high both before and after injecting calcium into the proper hepatic artery; the level was not significantly increased after the injection and decreased gradually. There was a decrease in the IRI over time after calcium loading in the gastroduodenal artery. These results indicated that insulinomas were localized to both the head and the tail of the pancreas. To detect the lesions in the pancreatic head suggested by the SACI test, we performed endoscopic ultrasonography (EUS), which has high sensitivity for detecting insulinomas, including microadenomas in the head and body of the pancreas.[25] EUS revealed 13.0-, 9.5-, and 9.2-mm round hypoechoic nodules in the tail of the pancreas, compatible with pancreatic neuroendocrine tumors (NETs). However, no nodules suspected as NETs were found in the head or body of the pancreas. In addition, we observed no intense uptake on somatostatin receptor scintigraphy, in pancreatic or metastatic lesions. From these results, we concluded that insulinomas targeted for surgery were present only in the pancreatic tail.

One month after the diagnosis, the patient underwent laparoscopic distal pancreatectomy. Interestingly, histopathological examination identified more than 20 tumors, including macroadenomas (≥5 mm), microadenomas (<5 mm), and small insulin-expressing monohormonal endocrine cell clusters (IMECCs) (<1 mm), as also reported by Anlauf

TABLE 1 Laboratory data on admission

Urine		BUN	6.7 mg/dL	*Endocrinology*	
Glucose	(-)	Cr	0.61 mg/dL	FT3	3.17 pg/mL
Protein	(-)	UA	5.0 mg/dL	FT4	1.02 ng/dL
Ketone	(-)	Na	141 mEq/L	TSH	1.07 μIU/mL
Complete Blood Count		K	4.0 mEq/L	LH	9.51 mIU/mL
WBC	$4.9x10^3$ /μL	Cl	108 mEq/L	FSH	7.31 mIU/mL
RBC	$3.48x10^6$ /μL	Ca	8.3 mg/dL	PRL	11.5 ng/mL
Hb	10.8 g/dL	IP	3.9 mg/dL	Cortisol	5.44 μg/dL
Plt	$25.4x10^4$ /μL	CK	41 IU/L	ACTH	12 pg/mL
Blood Chemistry		CRP	<0.10 mg/dL	IGF-1	184 ng/mL
TP	5.9 g/dL	T-Chol	184 mg/dL	GH	8.35 ng/mL
Alb	3.4 g/dL	LDL-C	115.9 mg/dL	DHEA-S	150 μg/dL
AST	15 IU/L	HDL-C	51.9 mg/dL	Intact PTH	76.6 pg/mL
ALT	13 IU/L	TG	70 mg/dL	Gastrin	1.76 pg/mL
ALP	168 U/L	HbA1c	4.4%	Epinephrine	11.6 pg/mL
LDH	139 U/L	FPG	75 mg/dL	Norepinephrine	124.45 pg/mL
γ-GTP	10 U/L	Insulin antibody	<0.01 ng/mL	Dopamine	9.82 pg/mL

Abbreviations: ACTH, adrenocorticotropic hormone; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CRP, C-reactive protein; DHEA-S, dehydroepiandrosterone sulfate; FPG, fasting plasma glucose; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; Hb, hemoglobin; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LH, luteinizing hormone; Plt, platelet; PRL, prolactin; PTH, parathyroid hormone; RBC, red blood cell; TG, triglyceride; TP, total protein; TSH, thyroid-stimulating hormone; WBC, white blood cell; γ-GTP, γ-glutamyl transpeptidase.

TABLE 2 Prolonged supervised fasting test

Fasting time (hr)	**1**	**2**	**3**	**4**	**5**
PG (mg/dL)	62	79	54	45	43
IRI (μU/mL)	11.00	13.60	6.68	9.04	3.83
CPR (ng/mL)	1.41	1.29	1.13	1.20	1.01
Proinsulin (pmol/L)					41.0
β-Hydroxybutyrate (μmol/L)					17.2

Note: Significant hypoglycemia was observed after a 5-h fast, along with insulinemia and impaired ketogenesis.

Abbreviations: CPR, C-peptide immunoreactivity; IRI, immunoreactive insulin; PG, plasma glucose.

and colleagues,[26] in the tail of the resected pancreas; these findings indicated insulinomatosis (Figure 2). The largest tumor found in the pancreatic tail was 15 mm in diameter. All tumors were positive for CD56, synaptophysin, and insulin (Figure 3). The histopathological diagnosis was of NET G2 (Ki67 index, 4.6%), and pathological TNM stage was T1N0M0, Stage IA (UICC). Immediately after surgery, plasma glucose levels were normalized and hypoglycemic symptoms disappeared. Although MEN1 was suspected, the patient demonstrated early-stage pHPT in addition to insulinomas, sequencing of the *MEN1* gene revealed no mutations.

No hypoglycemia has been observed 1 year after surgery. However, the elevated PTH level associated with normocalcemia persisted, so Tc-99m SPECT scanning after breastfeeding is now being considered.

3 | DISCUSSION

Insulinoma is a rare pancreatic NET that is the most common cause of endogenous hyperinsulinemic hypoglycemia in adults.[1] Although its occurrence in women during pregnancy

TABLE 3 Selective arterial calcium injection test

Time after calcium injection (s)		0	30	60	90	120
IRI (μU/mL)	SMA	3.3	45.1	22.6	12.7	8.5
	GDA	1.7	24.5	113	180	153
	PHA	75.8	37.2	30.4	21.5	16.7
	SpA	1.6	16.2	6.9	4.6	3.1

Note: After abdominal arteriography, catheters were placed into the SMA, GDA, PHA, and SpA. Calcium gluconate (0.025 mEq/kg) was injected into each artery. Blood was sampled from a catheter placed in the right hepatic vein, and IRI levels were determined at 0 (baseline), 30, 60, 90, and 120 s after calcium injection. A twofold or greater increase in IRI within 60 s compared with baseline was considered positive.

Abbreviations: GDA, gastroduodenal artery; IRI, immunoreactive insulin; PHA, proper hepatic artery; SMA, superior mesenteric artery; SpA, splenic artery.

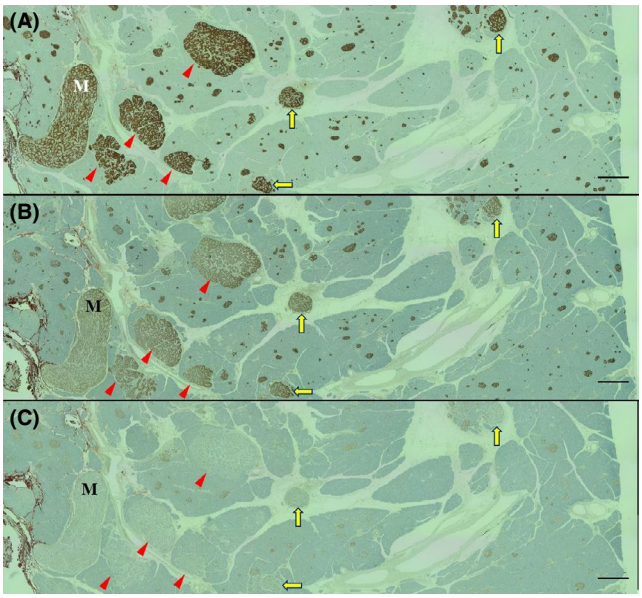

FIGURE 2 Insulin-expressing monohormonal endocrine cell clusters in the resected pancreas. Immunohistochemical analysis revealed various neuroendocrine tumors stained with insulin, including macroadenomas (≥5 mm, M), microadenomas (<5 mm, red arrowheads), and insulin-expressing monohormonal endocrine cell clusters (<1 mm, yellow arrows) in the resected pancreas. These tumors did not exhibit glucagon staining. A: Synaptophysin (brown) immunostaining. B: Insulin (brown) immunostaining. C: Glucagon (brown) immunostaining. Scale bar = 1000 μm. Magnification: ×8

or after delivery is considered exceptional, in the English literature, 25 cases of insulinoma during the perinatal period have been reported to date [2-23] (Tables 4 and 5). To the best of our knowledge, this is the first report of a Japanese case of insulinoma with hypoglycemic symptoms in the postpartum period and diagnosed with insulinoma. The patient initially showed hypoglycemic symptoms during early pregnancy. However, the symptoms abated during the gestational period and finally disappeared. Intriguingly, symptoms reappeared immediately after delivery. This was thought to be due to increased insulin resistance during pregnancy, which elevated the blood glucose level and masked the hypoglycemic symptoms associated with insulinoma, as in previous cases.[2,14,15,17-20,22]

Insulinoma is generally difficult to diagnose, even during early pregnancy, when there is no apparent increase in insulin resistance; there are several possible reasons for this. First, blood glucose levels in women during the first trimester tend to be low, because elevated estrogen levels increase both insulin secretion and insulin sensitivity.[21] Second, the various symptoms associated with hypoglycemia, such as cold sweats, dizziness, weakness, and poor concentration, are similar to those of hyperemesis gravidarum in pregnant women.[27]

As pregnancy progresses, maternal insulin resistance increases. This is due to the increased secretion of hormones such as human placental lactogen (hPL) and tumor necrosis factor (TNF)-α from the placenta, to maintain glucose supply to the fetus by increasing maternal circulating glucose levels.[28,29] Consequently, hypoglycemic symptoms may be attenuated during pregnancy in patients with insulinoma.

Interestingly, previous reports noted insulin resistance in patients with insulinoma,[30-33] despite the manifestation of hypoglycemic symptoms. Furthermore, Bar and colleagues also observed reduced insulin activity at its receptor in a case of insulinoma.[34] Intriguingly, insulin resistance in insulinoma cases has been reversed after surgical resection.[32,33] Although it is presumed that insulin resistance in cases of insulinoma functions primarily to maintain normal blood glucose levels, its pathophysiological significance remains unclear.

Based on the above findings, it is not unreasonable to suggest that, when women with insulinoma become pregnant, hypoglycemic symptoms may easily be masked by the conspicuous insulin resistance associated with pregnancy. Moreover, the present patient exhibited significant weight gain during pregnancy. This was presumably associated with the insulinoma, which also contributed to the increase in insulin resistance and masking of hypoglycemic symptoms during pregnancy.

What should the course of action be if a pregnant woman, unlike the present case, has symptomatic hypoglycemia with insulinemia, suspected to be insulinoma? In such a setting, current diagnostic and therapeutic approaches raise several concerns. First, the prolonged supervised fasting test, which is the most important endocrinological examination for diagnosis of insulinoma, is invasive for both the mother and the fetus. Second, imaging studies such as CT, MRI with contrast agents, and EUS, which are essential for localization and staging of insulinoma, are also invasive. Surgery is the only curative treatment for insulinoma and is recommended in all cases.[35] However, surgery during pregnancy should be

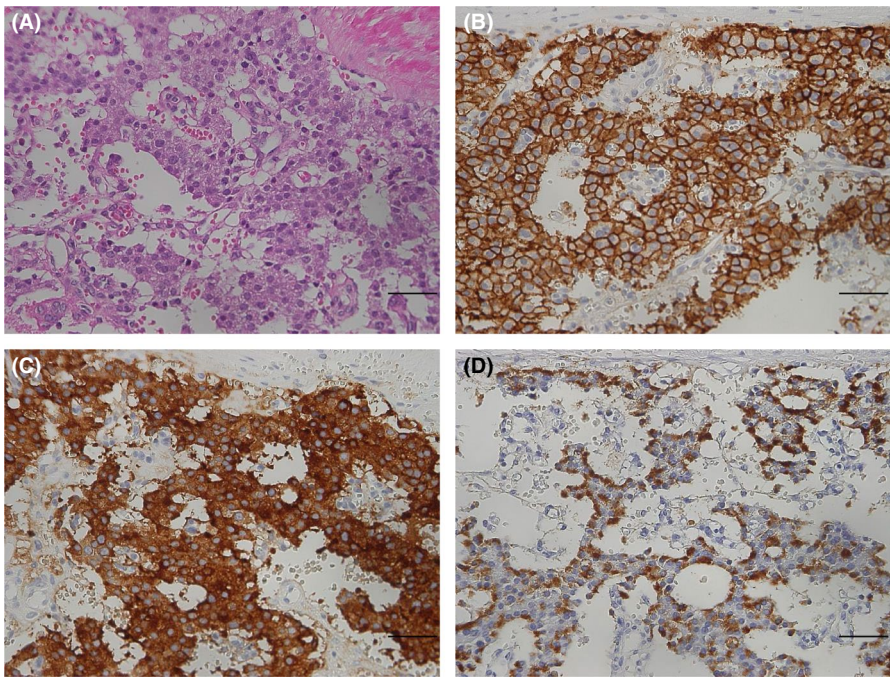

FIGURE 3 Immunohistochemical analysis of the largest insulinoma. A: Hematoxylin-eosin staining. B: CD56 (brown) immunostaining. C: Synaptophysin (brown) immunostaining. D: Insulin (brown) immunostaining. Bar = 50 μm. Magnification: ×800

avoided whenever possible, as it increases risks to the mother and fetus.[36] Although there have been several previous reports of successful surgery in pregnant women with insulinoma [3-5,16] (Table 4), the surgery should usually be scheduled after birth, or as late as possible after the fetus has reached a suitable age (ie, after 28 weeks),[36] unless hypoglycemic symptoms are progressive or the tumor is suspected to be malignant.

Insulinoma usually occurs as a solitary mass, but multiple insulinomas are seen in about 10% of cases, most often in association with MEN1.[37] There have been three previous reports of pregnant women presenting with multiple tumors.[9,13,15] The sequencing of the *MEN1* gene was validated in one of the three cases, but no mutations were observed (Table 4). Similarly, our case had multiple insulinomas and early pHPT, suggesting MEN1; however, no mutations were observed in the *MEN1* gene. Anlauf and colleagues proposed a multicentric type of insulinoma disease called "insulinomatosis," which exhibits early recurrent hyperinsulinemic hypoglycemia, mainly affects relatively young women, and is histopathologically characterized by IMECCs in the pancreas. They also stated that insulinomatosis differs from solitary sporadic and MEN1-associated insulinomas.[26] In the present case, histopathological examination confirmed not only the large insulinomas observed on CT and EUS, but also various other tumors, including macroadenoma, microadenoma, and IMECCs in the resected pancreas. These findings are consistent with the term "insulinomatosis" proposed by Anlauf and colleagues. However, our case showed early pHPT, indicating possible MEN1. Although this is inconsistent with previous reports, few studies on insulinomatosis have been conducted to date, so further clinical and histopathological validation of insulinomatosis is needed. Iacovazzo and colleagues reported a disease-causing mutation in the β-cell–enriched V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA) transcription factor. They identified a p. Ser64Phe *MAFA* gene missense mutation in 25 individuals from two unrelated families who presented with diabetes mellitus or insulinomatosis.[38] None of the family members of our patient had diabetes or hypoglycemia, and the cause of insulinomatosis remains unclear.

Moreover, we should discuss another important point in considering whether this case is MEN1 or not. As mentioned above, the patient showed an elevated PTH level with normocalcemia. In this setting, we need to consider the possibility not only of normocalcemic pHPT, but also of secondary hyperparathyroidism, especially induced by vitamin D deficiency. However, in our case, we did not evaluate serum 25-hydroxyvitamin D, which is crucial for the diagnosis of vitamin D deficiency, because pHPT is also known to exhibit decreased serum 25-hydroxyvitamin D levels due to increased conversion of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D by increased circulating PTH levels.[39] On the other hand, vitamin D deficiency has been reported to be prevalent in postpartum Japanese women.[40] We therefore consider that we should have confirmed whether the elevated PTH level in this case was normalized by short-term vitamin D supplementation, that is, whether it was vitamin D deficiency.[41,42] Considering the convincing evidence of insulinoma in the current case, we consider that the patient is possible MEN1, and the elevated PTH level could be normocalcemic pHPT associated with MEN1 rather than secondary hyperparathyroidism by vitamin D deficiency.

In conclusion, this is the first report of a Japanese case of insulinoma where hypoglycemic symptoms were masked

TABLE 4 Previous cases of insulinoma diagnosed during pregnancy

Cases/ Ref.	Age (years)	Manifestation of symptoms	pHPT	Extrapancreatic NET	Family history	*MEN1* mutation	Number of the tumor	Treatment	Gestational age at delivery	Fetal outcome	Birth weight (g)	Maternal outcome
1/(2)	25	12 W	N/A	N/A	N/A	N/A	N/A	CHD, laparotomy (Po)	Term	LB	N/A	NRS
2/(3)	37	8 W	N/A	N/A	N/A	N/A	N/A	IVG, laparotomy (12 W of G)	Term	LB	3,500	NRS
3/(4)	21	1st Tr	N/A	N/A	N/A	N/A	Single	Anticonvulsants, IVG, corticosteroids, diazoxide, laparotomy (12 W of G)	Term	LB	2,400	Aphasia, mental slowness
4/(5)	33	7 W	N/A	N/A	N/A	N/A	Single	CHD, IVG laparotomy (17 W of G)	Term	LB	3,880	NRS
5/(6)	19	1st Tr	N/A	N/A	N/A	N/A	Single	CHD, IVG, laparotomy (1st Tr)	Terminated (1st Tr)	Terminated	N/A	NRS
6/(7)	24	10 W	N/A	N/A	N/A	N/A	Single	CHD, laparotomy (Po)	Term	LB	4,000	NRS
7/(8)	24	6 W	N/A	N/A	N/A	N/A	Single	IVG, diazoxide, laparotomy (Po)	Term	LB	3,500	Hemiparesis, affective disorder
8/(9)	37	33 W	N/A	Hepatic nodules	N/A	N/A	Multiple	IVG, liver exploration during CS	35 W (CS)	LB	2,050	Died after CS due to hepatic failure
9/(10)	41	1st Tr	N/A	N/A	N/A	N/A	Single	CHD, laparotomy (Po)	36 W	LB	2,780	NRS
10/(11)	26	16 W	Hypercalcemia	N/A	pHPT in 2 relatives	N/A	Single	CHD, IVG, laparotomy (Po)	Term	LB	3,033	NRS
11/(12)	30	16 W	N/A	N/A	N/A	N/A	N/A	Anticonvulsants, CHD, IVG	Fetal death (22 W)	Fetal death	N/A	Died after delivery from severe sepsis
12/(13)	26	6 W	N/A	N/A	N/A	N/A	Multiple	CHD, IVG, laparotomy (Po)	Term	LB	3,602	NRS
13/(14)	22	2 M	N/A	N/A	N/A	Negative	Single	CHD, laparoscopy (Po)	Term	LB	2,600	NRS
14/(15)	29	35 W	None	None	N/A	Negative	Multiple	IVG, diazoxide, laparotomy (Po)	Term	LB	2,800	NRS
15/(16)	36	2nd Tr	N/A	N/A	N/A	N/A	Single	CHD, laparotomy (21 W of G)	Term	LB	3,570	NRS

Abbreviations: CHD, carbohydrate diet; CS, cesarean section; G, gestation; IVG, intravenous glucose infusion; LB, live born; M, months; MEN1, multiple endocrine neoplasia 1; N/A, not available; NET, neuroendocrine tumor; NRS, no residual symptoms; pHPT, primary hyperparathyroidism; Po, postpartum; Tr, trimester; W, weeks.

TABLE 5 Previous cases of insulinoma diagnosed postpartum

Cases/Ref.	Age (years)	Manifestation of symptoms	pHPT	Extrapancreatic NET	Family history	*MEN1* mutation	Number of the tumor	Treatment	Gestational age at delivery	Fetal outcome	Birth weight (g)	Maternal outcome
1/(2)	47	3 D Po	N/A	N/A	N/A	N/A	N/A	IVG, laparotomy	Term	Terminated	N/A	Neurologic deficit
2/(17)	35	13 D Po	N/A	N/A	N/A	N/A	N/A	IVG, laparotomy	Term	LB	N/A	NRS
3/(18)	24	2 D Po	N/A	N/A	N/A	N/A	Single	IVG, laparotomy	Term	LB	4,150	NRS
4/(19)	36	1 D Po	N/A	N/A	N/A	N/A	Single	CHD, IVG, laparotomy	Term	LB	N/A	NRS
5/(20)	35	3 W Po	N/A	N/A	None	N/A	Single	Laparotomy	Term	LB	3,660	NRS
6/(14)	35	3 M Po	N/A	N/A	N/A	N/A	Single	CHD, antiepileptic drug, laparotomy	36 W	LB Twins	1,800/1,900	NRS
7/(14)	35	26 D Po	N/A	N/A	N/A	N/A	Single	IVG, laparoscopy	Term	LB	3,170	NRS
8/(21)	21	8 D Po	None	None	None	N/A	Single	Laparoscopy	Term	LB	3,635	NRS
9/(22)	38	3 W Po	N/A	N/A	N/A	N/A	Single	Laparotomy	Term	LB	3,180	NRS
10/(23)	34	2 D Po	None	None	None	N/A	Single	Laparoscopy	Term	LB	N/A	NRS

Abbreviations: CHD, carbohydrate diet; D, days; IVG, intravenous glucose infusion; LB, live born; M, months; MEN1, multiple endocrine neoplasia 1; N/A, not available; NET, neuroendocrine tumor; NRS, no residual symptoms; pHPT, primary hyperparathyroidism; Po, postpartum; W, weeks.

during pregnancy by increased insulin resistance. In the differential diagnosis of hyperinsulinemic hypoglycemia in women, it should be noted that pregnancy can mask hypoglycemic symptoms in this manner. Hypoglycemia recurrence and the appearance of other endocrine tumors should be checked for in the current case.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

TA and Y. Takeda: contributed to diagnosis and treatment of the patient and draft of the manuscript. MT: contributed to pathological diagnosis and draft of the manuscript. TT, AS, RB, MS, HK, HS, AA, and Y. Takiyama: contributed to diagnosis and treatment of the patient. KI: contributed to surgical treatment. SY: contributed to pathological diagnosis. All authors: read and approved the final version of the manuscript.

ETHICS STATEMENT

Written informed consent for publication was obtained from the patient.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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