Case Report

Non-insulinoma Pancreatogeneous Hypoglycemia Syndrome with False-Positive Somatostatin Receptor Scintigraphy: A Case Report and Review of Literature

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Non-insulinoma pancreatogeneous hypoglycemia syndrome (NIPHS) is a rare cause of hypoglycemia in adults. The cause of NIPHS is diffuse hyperinsulinism. As a result, computed tomography (CT) of pancreas, endoscopic pancreatic ultrasonography (EUS), and somatostatin receptor scintigraphy (SSRS), which are usually performed to locate an insulinoma, are not able to diagnose NIPHS. Moreover, SSRS can give a false-positive result. In this case report, we introduce a 22-year-old Thai woman who presented with fasting and postprandial hyperinsulinemic hypoglycemia. Accordingly, an insulinoma was suspected. She underwent several studies to locate the lesion. Pancreatic CT and EUS failed to locate a lesion; however, SSRS showed a faint focus of increased uptake at the pancreatic head. The suspected insulinoma was not identified during a first operation. Thereafter, other diagnostic methods were performed in an effort to locate the suspected insulinoma, including selective arterial calcium stimulation test. The result of the selective arterial calcium stimulation test was negative. Intraoperative ultrasonography during a second operation also failed to locate a tumor. Finally, a pancreatic head resection was performed according to SSRS result, yet capillary blood glucose levels did not increase after resection. In response, a 95% pancreatectomy was performed. The pathology report was consistent with diffuse hyperinsulinism. This report emphasizes that SSRS can give false positive result in NIPHS.

Keywords: *Hypoglycemia, Insulinoma, Non-insulinoma pancreatogeneous hypoglycemia syndrome, Somatostatin receptor scintigraphy*

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Insulinoma is the most common cause of adult-onset endogenous hyperinsulinemic hypoglycemia; whereas, nesidioblastosis, which also known as persistent hyperinsulinemic hypoglycemia of infancy, is the main cause of hypoglycemia in children[1]. A number of adult onset nesidioblastosis cases have been reported. The first case series in adult nesidioblastosis was reported in 1981[2]. A new syndrome called non-insulinoma pancreatogeneous hypoglycemia syndrome (NIPHS) was then proposed in 1999 as a new moniker for this unique disorder[3]. This syndrome is characterized by patients that present with postprandial hypoglycemia, normal prolonged fasting test, and negative preoperative localization for insulinoma. The pathologic appearance of NIPHS resembles nesidioblastosis. In this report, we present a rare case of NIPHS with focal uptake of somatostatin receptor scintigraphy at the pancreatic head that mimics insulinoma.

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Case Report

A 22-year-old Thai female had recurring episodes of palpitations, sweating, and tremulousness for two years. These symptoms developed a few hours after meals twice a week during the first year, and then every day in both fasting and postprandial states during the second year. She recognized that her symptoms were improved by taking food, so she ate meals frequently. This caused her to gain 15 kilograms in body weight. She was admitted to a provincial hospital after being found unconscious in the morning with a capillary blood glucose level of 20 mg/dl. After receiving 50 grams of dextrose intravenously, she regained consciousness. However, she still had left hemiparesis and right homonymous hemianopia.

Magnetic resonance venography revealed an occlusion in the entire left transverse sinus and a filling defect at the posterior part of the superior sagittal sinus. She was diagnosed with a cerebral venous sinus thrombosis, and an anticoagulant was prescribed. She was then transferred to our institute (the largest tertiary referral hospital in Thailand) for further investigation of hypoglycemia. Her family history was negative for hypoglycemia-related tumors.

Physical examination revealed an obese patient with body mass index (BMI) of 35.3 kg/m^2, right homonymous hemianopia, and left facial palsy. All other systems were normal. Laboratory results showed normal kidney and liver function. Her glycosylated hemoglobin level was 5.3%. The day after admission, she had an episode of sweating and palpitations in the morning after fasting overnight for seven hours. Blood samples were taken every 15 minutes, three times during the episode. Results showed low plasma glucose concentrations (48, 43, and 46 mg/dl), high plasma insulin levels (61.7, 39.7, and 43.7 µU/ml), and normal cortisol responses (26.5, 21.8, and 25.1 µg/dl), respectively (Table 1).

Therefore, insulinoma was suspected, and localization studies were performed, including pancreatic computed tomography (CT) and endoscopic pancreatic ultrasonography (EUS). These investigations were unsuccessful at localizing any lesion. Somatostatin receptor scintigraphy (SSRS) was then performed (Fig. 1a). SSRS showed a faint focus of increased uptake at the posterior aspect of the pancreatic head. SSRS results indicated presence of neuroendocrine tumor. Accordingly, our patient was diagnosed with insulinoma and scheduled for surgery.

Table 1. Laboratory results during hypoglycemic episode

Time after symptoms (minute)	Plasma glucose (mg/dl)	Plasma insulin (µU/ml)	Plasma cortisol (µg/dl)
0	48	61.7	26.5
15	43	39.7	21.8
30	46	43.7	25.1

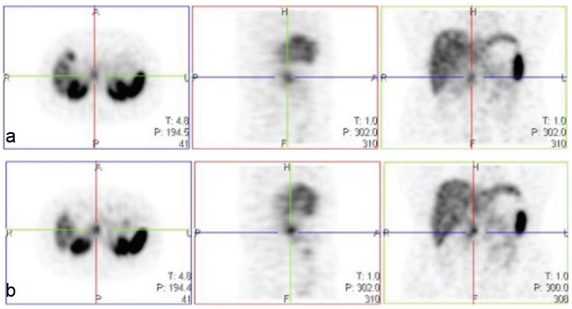

Fig. 1 The first SSRS shows a faint focus of increased uptake at the posterior aspect of the pancreatic head (a). The second SSRS shows greater isotope uptake than the first SSRS at the same location (b).

Intraoperative ultrasonography and careful palpation of the pancreas failed to detect insulinoma; therefore, a pancreatectomy was not performed. After discharge, she received advice to eat frequently. However, she still had mild to moderate hypoglycemic symptoms, and her body weight increased from 94 to 104 kilograms in 10 months. To localize the suspected insulinoma, she was admitted for reinvestigation. CT pancreatic protocol did not reveal any pancreatic mass. Selective arterial calcium stimulation test was performed with negative result (Table 2).

SSRS with SPECT/CT, which was performed 13 months after the first scan, revealed a hot focus at the pancreatic head, similar to the patient's previous investigation. However, this lesion had greater isotope uptake than the previous SSRS (Fig. 1b).

After a deliberative discussion that included the patient, a well-experienced pancreatic surgeon, and our team of endocrinologists, the patient underwent a second exploratory laparotomy. Once again, intra-

Table 2. Negative response of plasma insulin to selective arterial calcium stimulation

Artery	Plasma insulin level (µU/ml)					Ratio* (peak/baseline)
	0 second	20 seconds	40 seconds	60 seconds	120 seconds	
Gastroduodenal	71.60	107.90	112.70	112.30	111.20	1.57
Superior mesenteric	86.60	85.37	94.72	91.74	135.00	1.56
Proximal splenic	80.70	89.00	118.00	103.10	81.30	1.46
Mid-splenic	71.41	104.00	111.40	109.10	106.00	1.56
Proper hepatic	95.48	82.90	71.54	116.10	101.00	1.23

* A 2-fold increase in plasma insulin level after calcium stimulation indicates a positive arterial calcium stimulation test.

Table 3. Capillary blood glucose during second operation

Time	Capillary blood glucose (mg/dl)	Glucose infusion rate (g/hour)
Before surgery	168	10
Before pancreatic head resection	153	10
After pancreatic head resection	158	10
15 minutes after pancreatic head resection	183	10
30 minutes after pancreatic head resection	176	10
60 minutes after pancreatic head resection	137	10
After 95% pancreatectomy	210	10
30 minutes after 95% pancreatectomy	221	10
60 minutes after 95% pancreatectomy	290	10

operative pancreatic ultrasonography (US) failed to localize a tumor. According to the result of the SSRS, a duodenal-preserving pancreatic head resection was performed. Nevertheless, capillary blood glucose levels did not increase, and she still required intravenous glucose 10 g/hour after pancreatic head resection (Table 3). Accordingly, a 95% pancreatectomy was performed, which resulted in complete resolution of the patient's hypoglycemia.

Pathologic examination demonstrated increased density of the pancreatic islets (Fig. 2a). These islet cells showed enlarged nuclei and conspicuous nucleoli with positive immunostaining for insulin (Fig. 2b, c). These microscopic features were consistent with diffuse hyperinsulinism.

After discharge, our patient did not have any recurrence of hypoglycemia symptoms and lost 10 kilograms in body weight within three months. However, she developed diabetes mellitus that requires lifelong insulin treatment and steatorrhea that required pancreatic enzyme administration.

Discussion

In most cases, hyperinsulinemic hypoglycemia in adults is caused by insulinoma. Only 1.5 to 5% of cases are caused by NIPHS[4]. NIPHS was proposed in 1999 to characterize patients that present with postprandial hypoglycemia, normal prolonged fasting test, negative preoperative imaging study for localized insulinoma, and positive insulin response to intra-arterial calcium stimulation. In addition, pathological reports of NIPHS show islet cell hypertrophy, islet cell hyperplasia, and nuclear pleomorphism, all of which are compatible with nesidioblastosis[3].

Making a preoperative diagnosis of NIPHS is very problematic because clinical manifestation and initial investigation of insulinoma and NIPHS may overlap. Both insulinoma and NIPHS have hyperinsulinemic hypoglycemia and may have negative preoperative imaging studies. As a result, most previous case reports of NIPHS were diagnosed after surgery because they were initially diagnosed as insulinoma[5,6]. There are, however, some differences in clinical presentation between insulinoma and NIPHS. The majority of NIPHS cases have hypoglycemic symptoms within four hours after meal and negative prolonged fasting test[3,7] while the majority of insulinoma cases have fasting hypoglycemia and positive prolonged fasting test[8]. A small proportion of insulinoma and NIPHS cases have the same clinical presentation of fasting hypoglycemia and positive prolonged fasting test[6,9], this matching the presentation of our patient.

Preoperative localization studies for insulinoma, such as CT, MRI, EUS, and SSRS are normally negative in patients with NIPHS, due to diffuse islet cell pathology without definite mass lesion. However, our patient had positive SSRS at pancreatic head, which supported the preoperative

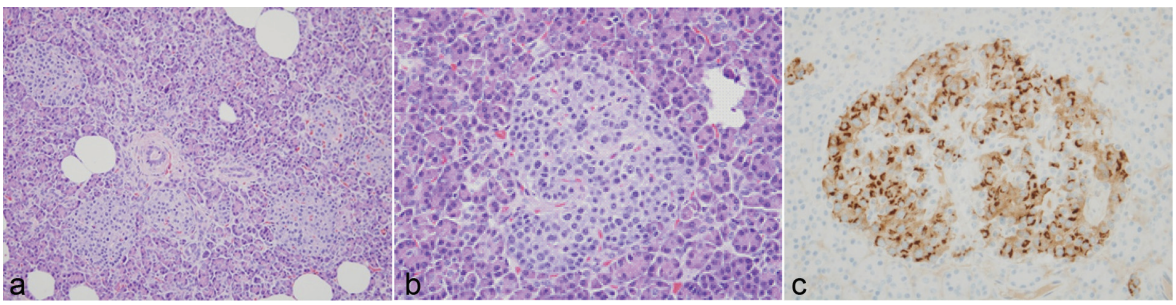

Fig. 2 a) Microscopic examination demonstrating increased density of pancreatic islets, b) Islet cells showing enlarged nuclei and conspicuous nucleoli, c) Islet cells with positive immunostaining for insulin.

diagnosis of insulinoma. A positive SSRS in patients with NIPHS has occasionally been reported[10-12]. Almost all patients with positive SSRS have focal uptake of somatostatin at various sites such as pancreatic head, pancreatic tail, or junction between head and tail of pancreas and negative results in other imaging studies. This was not the case, however, in a report by Przybylik-Mazurek et al that described a patient as having slightly increased uptake in the entire pancreas[13]. Some potential causes of false positive SSRS such as granulomatous disease, radiation inflammation, or accumulation of tracer at recent surgical site were not found in our patient[14]. Given that the sensitivity of SSRS for detection of insulinoma is approximately 50%[15], NIPHS should be considered if a patient presents with both postprandial hyperinsulinemic hypoglycemia and positive preoperative result from only SSRS.

Selective intra-arterial calcium injection into the major pancreatic arteries with hepatic venous sampling of insulin (intra-arterial calcium stimulation test, CaStim) has been reported to be the most sensitive preoperative localization tool for insulinoma[15,16]. Due to diffuse hyperinsulinism in NIPHS, CaStim usually has a positive result from multiple pancreatic arterial vessels[4,7]. However, CaStim can only be performed in tertiary care centers due to the complexity of the procedure. Although there have been no reports of false-negative results from CaStim in NIPHS, there have been some reports of false-negative CaStim results in localizing insulinoma[16,17]. For example, the National Institutes of Health of United State reported 11% false-negative results from CaStim in localization of insulinoma. The negative CaStim result in our patient may potentially be explained by anatomical variations.

Diagnosis of NIPHS is normally definitively confirmed by pathologic investigation. The exocrine parenchyma is normal. The endocrine pancreas is mainly characterized by presence of enlarged hyperchromatic nuclei with prominent nucleoli and abundant clear cytoplasm. Islet cells do not show increased proliferative activity. The number of islets per area may be increased in some patients[18]. While close association of islet cell clusters with ducts or ductulo-insular complexes is a distinctive feature of nesidioblastosis in infants, it is not a prominent feature in adults. Our case demonstrated typical pathologic features of NIPHS, including enlarged nuclei, prominent nucleoli of islet cells, islet cell hyperplasia, and no ductulo-insular complexes.

There is no universal recommendation for treatment of NIPHS. Degree of pancreatectomy ranged from distal to near total pancreatectomy, according to previous case reports. Degree of pancreatectomy correlates positively to not only the success rate, but also to the risk of diabetes[6]. Therefore, this procedure should be carefully discussed with potential outcomes being fully disclosed to the patient. Medical treatments, such as diazoxide, verapamil, and octreotide, should be considered when surgery fails[6,7,19]. In our patient, a 95% pancreatectomy was performed due to the unresponsiveness of capillary blood glucose levels to pancreatic head resection. Pancreatectomy resulted in successful reversal of her hypoglycemic symptoms.

Conclusion

Non-insulinoma pancreatogeneous hypoglycemia syndrome is a very rare disorder in adults. This case report profiles a patient that presented with both fasting and postprandial hypoglycemia and that had a false-positive SSRS result. This report emphasizes that a diagnosis of NIPHS should be considered in the postprandial hypoglycemic patient that has positive SSRS, negative CT, and negative EUS findings. Although intra-arterial calcium stimulation test was reported as positive in previous case reports, our patient's test result was negative.

What is already known on this topic?

Clinical presentation and initial investigation of non-insulinoma pancreatogeneous hypoglycemia syndrome usually overlap with insulinoma. In most cases, preoperative imaging studies give negative results due to diffuse hyperinsulinism.

What this study adds?

Somatostatin scintigraphy has low sensitivity for localizing insulinoma and sometimes gives a positive result in patients with non-insulinoma pancreatogeneous hypoglycemia syndrome.

Potential conflicts of interest

None.

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ภาวะน้ำตาลในเลือดต่ำจากเนื้องอกตับอ่อนที่ไม่ใช่อินซูลิโนมาและให้ผลบวกลวงจากการตรวจด้วยสารโซมาโตสแตติน: รายงานผู้ป่วยและการทบทวนวรรณกรรม

ลักขณา ปรีชาสุข, อนัญญา พงษ์ไพบูลย์, ธาดา คุณาวิศรุต

ภาวะน้ำตาลในเลือดต่ำจากเนื้องอกตับอ่อนที่ไม่ใช่อินซูลิโนมาพบได้น้อยมากในผู้ใหญ่ เนื่องจากภาวะดังกล่าวมีการหลั่งอินซูลินมากกว่าปกติเกิดขึ้นทั่วทั้งตับอ่อน การตรวจเพื่อค้นหาเนื้องอกด้วยการตรวจเอกซเรย์คอมพิวเตอร์ การตรวจอัลตราซาวด์ และการตรวจด้วยสารเภสัชรังสีชนิดโซมาโตสแตตินมักให้ผลลบ ผู้นิพนธ์ได้รายงานผู้ป่วยที่มาพบแพทย์ด้วยอาการน้ำตาลในเลือดต่ำทั้งในช่วงก่อนและหลังอาหารและตรวจพบระดับอินซูลินในเลือดสูง ผลเอกซเรย์คอมพิวเตอร์และอัลตราซาวด์ของตับอ่อนไม่พบเนื้องอก แต่การตรวจด้วยสารโซมาโตสแตตินให้ผลบวกที่ตับอ่อนส่วนต้น จึงให้การวินิจฉัยเบื้องต้นเป็นโรคเนื้องอกอินซูลิโนมา ศัลยแพทย์ตรวจไม่พบก้อนเนื้องอกจากการคลำตับอ่อนและอัลตราซาวด์ในห้องผ่าตัด ผู้ป่วยจึงไม่ได้รับการผ่าตัดตับอ่อนในการผ่าตัดครั้งแรก เนื่องจากผู้ป่วยยังคงมีอาการน้ำตาลต่ำอยู่ตลอดจึงได้รับการตรวจเพิ่มเติมเพื่อหาเนื้องอกโดยการตรวจระดับอินซูลินในเลือดหลังจากฉีดสารแคลเซียมเข้าหลอดเลือดแดงที่เลี้ยงตับอ่อน โดยการตรวจนี้ยังคงให้ผลลบ การตรวจด้วยสารโซมาโตสแตตินครั้งที่ 2 ให้ผลบวกที่ตำแหน่งเดิมกับการตรวจครั้งแรก ในการผ่าตัดครั้งที่ 2 ศัลยแพทย์ยังคงตรวจไม่พบก้อนเนื้องอก จึงได้ทำการตัดตับอ่อนส่วนต้นตามผลการตรวจโซมาโตสแตติน แต่ระดับน้ำตาลของผู้ป่วยไม่เพิ่มขึ้น ศัลยแพทย์จึงผ่าตัดเพิ่มด้วยการตัดตับอ่อน 95 เปอร์เซ็นต์ ผลตรวจทางพยาธิวิทยาของผู้ป่วยเข้าได้กับภาวะน้ำตาลในเลือดต่ำจากเนื้องอกตับอ่อนที่ไม่ใช่อินซูลิโนมา รายงานผู้ป่วยรายนี้ชี้ให้เห็นว่าควรนึกถึงภาวะเนื้องอกตับอ่อนที่ไม่ใช่อินซูลิโนมาในผู้ป่วยที่มีอาการน้ำตาลต่ำในช่วงหลังอาหารและการตรวจเพื่อหาเนื้องอกให้ผลบวกเฉพาะการตรวจโซมาโตสแตตินซึ่งเป็นการตรวจที่อาจให้ผลบวกลวงในภาวะดังกล่าวได้