Diagnosis of pancreatic focal nesidioblastosis assisted by dual-nuclide tracer positron emission tomography/computed tomography: A case report

GUANGWEN ZHU[1], LITING XIE[2] and XIANWEN HU[3]

Departments of [1]Endocrinology and [2]Gynaecology, Zunyi Hospital of Traditional Chinese Medicine, Zunyi, Guizhou 563000; [3]Department of Nuclear Medicine, The Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, P.R. China

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Abstract. Nesidioblastosis is a rare cause of hyperinsulinemic hypoglycemia in adults and its clinical features are similar to those of insulinoma with recurrent hypoglycemic attacks. The present study reports the case of a 48-year-old man who visited the Affiliated Hospital of Zunyi Medical University (Zunyi, China) with a 5-year history of recurrent hypoglycemic symptoms such as dizziness and palpitations. Abdominal magnetic resonance imaging (MRI) showed a mass of ~1.2x1.0 cm in the head of the pancreas, which was suspected to be an insulinoma. For confirmation, the patient underwent both fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and gallium-68-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-teraacetic acid-d-Phel-Tyr3-Thr8-OC (^{68}Ga-DOTATATE) positron emission tomography/computed tomography (PET/CT), which showed a moderately increased uptake of ^{18}F-FDG but no uptake of ^{68}Ga-DOTATATE in the corresponding lesion. The patient subsequently underwent surgery to remove the lesion, which was pathologically confirmed as a pancreatic nesidioblastosis. This case showed that nesidioblastosis should be considered a differential diagnosis for insulinoma and that dual nuclear tracer PET/CT imaging is helpful for differentiating between the two. If conventional imaging techniques such as ultrasound, CT and MRI cannot identify the cause of hypoglycemia in future cases, dual-nuclide tracer PET/CT imaging should be considered.

Correspondence to: Dr Xianwen Hu, Department of Nuclear Medicine, The Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Huichuan, Zunyi, Guizhou 563003, P.R. China
E-mail: huxw56@sohu.com

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Introduction

Nesidioblastosis refers to the diffuse proliferation of insulin-secreting cells in the pancreatic duct epithelium and was first reported by Laidlaw in 1938 (1). According to the extent of pancreatic involvement, nesidioblastosis can be divided into focal nesidioblastosis, which is characterized by nodular hyperplasia, and diffuse nesidioblastosis, which involves the whole pancreas (2). Nesidioblastosis, part of the disease spectrum of non-insulinomatous pancreatic hypoglycemia syndrome, is the most common cause of hyperinsulinemic hypoglycemia in infants and children, but is rare in adults, accounting for only 0.5-7% (3,4). The clinical manifestations and biochemical examination results of nesidioblastosis and pancreatic islet cell tumor are similar. The initial symptoms are mainly dizziness, cold sweating, accompanied by overeating, easy hunger, combined with repeated consciousness disorders, memory loss, and decreased reaction ability. Both have a history of hypoglycemic coma, typical Whipple triple syndrome, and symptoms can be alleviated by eating multiple meals, taking oral sugar water, or intravenous glucose, but repeated attacks (2). Specific imaging features for pancreatic nesidioblastosis are limited in the literature, and pancreatic nesidioblastosis is often misdiagnosed as insulinoma, especially the nodular type (5). Most adult patients with focal nesidioblastosis require surgery. However, a uniform standard for surgical resection is lacking (6). The present study reports a case of hypoglycemia due to nesidioblastosis diagnosed using dual-nuclide tracers, fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and gallium-68-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-d-Phel-Tyr3-Thr8-OC (^{68}Ga-DOTATATE), in positron emission tomography/computed tomography (PET/CT).

Case report

A 48-year-old man with a 5-year history of dizziness, palpitations, sweating, limb tremors, pale complexion, disturbance of consciousness, and even coma in the morning on an empty stomach, presented to the Affiliated Hospital of Zunyi Medical University (Zunyi, China) in May 2021 due to reoccurrence and worsening of the aforementioned over the past 2 days.

The patient had been admitted to other hospitals several times, and no imaging tests, including CT and magnetic resonance imaging (MRI), had been performed except for abdominal ultrasound, which did not reveal any suspicious positive lesions. Moreover, the symptoms of hypoglycemia were relieved each time a glucose solution was administered, so the patient did not pay much attention to the condition. The patient had no history of hepatitis, tuberculosis, surgery or other illnesses. The patient's family members were healthy and had no genetic or tumor history. No positive signs were found on a general physical examination. A laboratory examination revealed that the serum insulin level had increased to 219.3 μIU/ml (normal reference value, 2.6-24.9 μIU/ml) and the blood glucose level had decreased to 1.79 mmol/l (normal reference value, 3.9-6.1 mmol/l). Moreover, the fasting C-peptide level significantly increased to 6,440 pmol/l (normal reference value, 370-1,470 pmol/l). Abdominal MRI (Siemens Sensation 3.0T MR Scanner; Siemens AG) was performed with the following scanning parameters: For T1-weighted imaging (T1WI), repetition time (TR) at 100 msec and echo time (TE) at 2.46 msec; and for T2WI, TR at 1,400 msec and TE at 81 msec; the scanning layer thickness was 6 mm and layer spacing was 1 mm; contrast enhanced scanning was performed by intravenous injection of 0.1 mmol/kg gopentate meglumine. Analysis of the results revealed an abnormal signal shadow in the pancreatic head (Fig. 1).

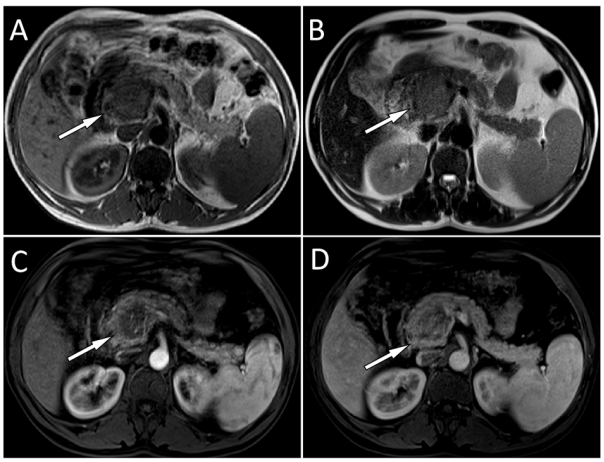

Figure 1. Abdominal magnetic resonance imaging showed an abnormal signal shadow of ~1.2x1.0 cm in the head of the pancreas (arrows), with (A) a slightly low signal on T1WI and (B) equal signaling on T2WI. On contrast-enhanced T1WI, the signaling of the lesion was slightly weaker than that of the peripheral normal pancreatic parenchyma in the (C) arterial and (D) venous phases. WI, weighted imaging.

When the MRI results were combined with the patient's clinical manifestations of hypoglycemia, and increased insulin and C-peptide levels, an insulinoma was suspected. To confirm this hypothesis, the patient underwent PET/CT (Biograph mCT PET/CT scanner; GE Healthcare). According to the patient's weight, ^{18}F-FDG was injected intravenously at 0.12 mCi/kg and ^{68}Ga-DOTATATE was injected intravenously at 0.05 mCi/kg. ^{18}F-FDG PET/CT was performed 24 to 48 h before the ^{68}Ga-DOTATATE PET/CT. The patient underwent imaging 45-60 min post-intravenous injection of the tracers. The scanning range was from the top of the skull to the middle of the femur. CT scanning was performed first using the following parameters: Tube voltage, 120 kV; tube current, 119 mA; and layer thickness, 5 mm. PET scanning was performed immediately after the completion of CT scanning. The 3-dimensional acquisition mode was 2.0 min/bed, with 6 to 7 beds. The lesion of the pancreatic head had moderate ^{18}F-FDG uptake, but no ^{68}Ga-DOTATATE uptake (Fig. 2). Consequently, the initial diagnosis of an insulinoma was rejected, as insulinomas usually express somatostatin receptor type 2 and are characterized by strong uptake of ^{68}Ga-DOTATATE, while ^{18}F-FDG is usually absent or has mild uptake (7). After communicating with the patient and obtaining consent, the patient underwent a duodeno-sparing pancreaticocephalic focus excision and pancreaticojejunostomy (Roux-en-Y anastomosis) with laparoscopic guidance under general anesthesia in June 2021. The excised lesion tissues were sent for postoperative pathological examination. For hematoxylin-eosin staining, the specimen was fixed with 10% neutral formalin, dehydrated at room temperature for ~24 h and paraffin embedded. Next, 3- to 4-μm thick sections were stained with hematoxylin-eosin (Fuzhou Maixin Biotech. Co., Ltd.), and viewed at x400 magnification under an optical microscope. The staining revealed a diffuse distribution of round or oval cells of varying sizes in the islets with deeply stained nuclei (Fig. 3), suggesting nesidioblastosis. The patient was treated with cefuroxime (1-2 g per dose, twice a day, 7 days in total) anti-inflammatory therapy 1 week after surgery, during which time hypoglycemia did not develop. The serum insulin, blood glucose and C-peptide values returned to normal after surgery (Fig. 4). The most recent follow-up was conducted in November 2023 (routinely followed up every 6 months), and the patient currently has a good prognosis with no symptoms of hypoglycemia, such as dizziness, palpitations or sweating.

Discussion

Insulinoma is the most common cause of adult hyperinsulinemic hypoglycemia, while nesidioblastosis is a rare cause, accounting for only 0.5-5% of cases (5). The pathogenesis of adult nesidioblastosis is unknown, but possible causes include β-cell dysfunction, genetic variation located on chromosome 11, and growth factor (insulin-like growth factor receptorl receptor-α and transforming growth factor-β receptor 3) production and/or increased expression of its receptors (8-10). There is overlap between the clinical manifestations of nesidioblastosis and insulinoma, the initial symptoms of which are dizziness, chronic obstructive pulmonary disease, sweating, overeating, and increased hunger; in addition to the above symptoms, both insulinoma and neidioplastoma can be accompanied by recurrent consciousness disorders, memory loss, and decreased responsiveness (11). Both tumors may present with the classic Whipple's triad of periodic coma and psychiatric symptoms, usually with daily episodes on an empty stomach or after exertion; episodes of a blood glucose level <2.8 mmol/l and the rapid disappearance of symptoms after oral or intravenous glucose administration are indicative (12). Moreover, the biochemical findings of nesidioblastosis and insulinoma are similar in that, during the onset of clinical symptoms, both can be detected as decreased blood glucose values and abnormally

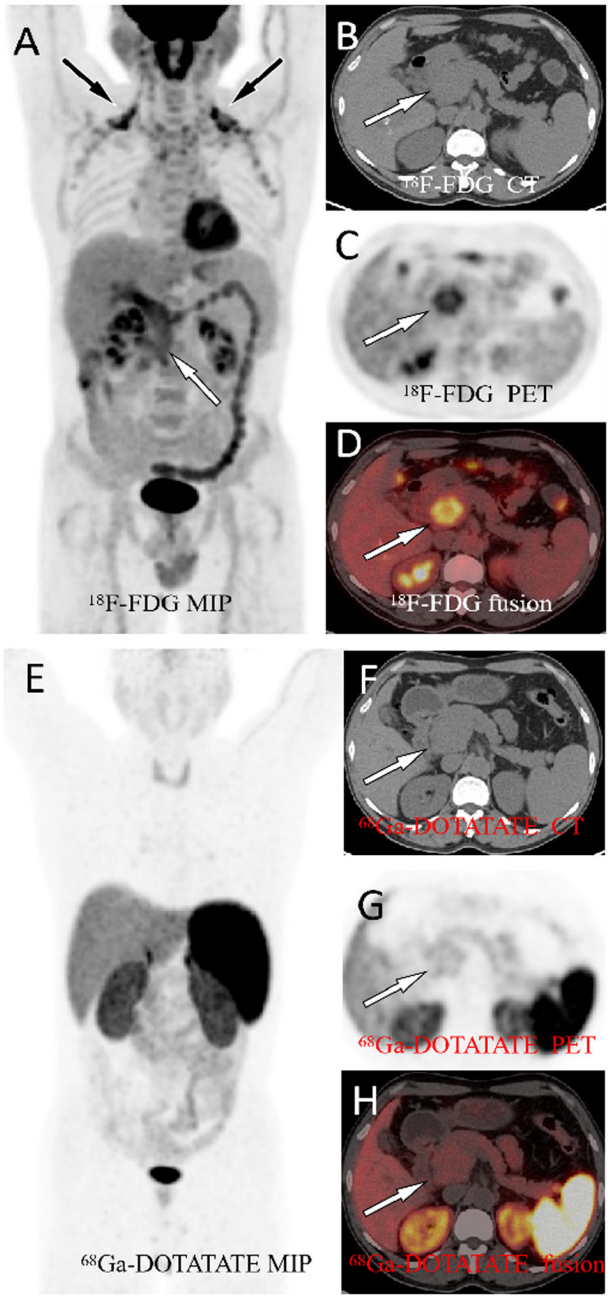

Figure 2. (A) MIP showing ^{18}F-FDG uptake in the lesion in the pancreatic head region (white arrow). Moreover, symmetrical non-specific inflammatory uptake was observed bilaterally in the neck (black arrows). An axial examination revealed that the volume of the pancreatic head increased with moderate focal ^{18}F-FDG uptake (arrows), with a maximum standardized uptake value of 4.2 [(B) CT; (C) PET; and (D) PET/CT fusion) However, ^{68}Ga-DOTATATE uptake was not observed in the corresponding areas [(E) MIP; (F) CT; (G) PET and (H) PET/CT fusion). ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; MIP, maximum intensity projection; ^{68}Ga-DOTATATE, gallium-68-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-d-Phel-Tyr3-Thr8-OC.

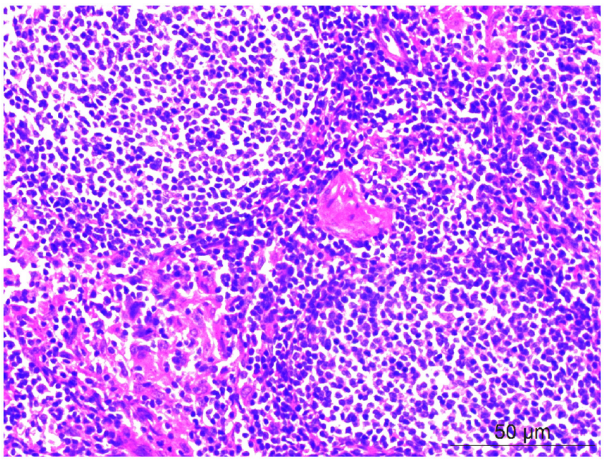

Figure 3. Hematoxylin-eosin staining showed a diffuse distribution of round or oval enlarged β cells in the pancreatic islets, with deeply stained nuclei and abundant clear cytoplasm; x400 magnification.

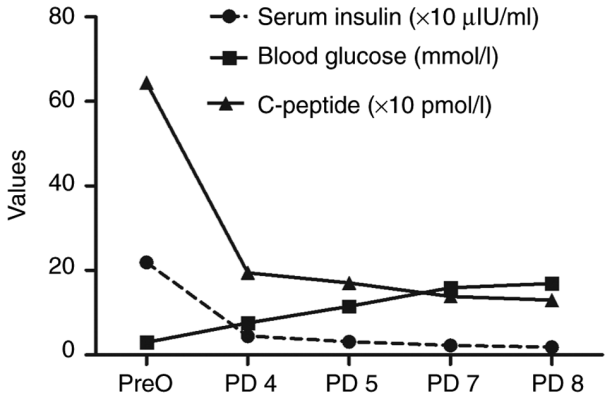

Figure 4. Preoperative and postoperative changes in blood glucose, insulin and C-peptide levels. preO, preoperative; PD, postoperative day.

high insulin and C-peptide levels, making the differential diagnosis of the two relatively difficult (5). The patient in the current study presented with recurrent symptoms of hypoglycemia, such as dizziness, palpitations, sweating, tremors of the limbs, pallor, impaired consciousness and coma, which were relieved with oral glucose. At symptom onset, the patient's insulin and C-peptide levels were significantly elevated, consistent with report in the literature (5).

Unexplained hypoglycemia in adult non-diabetic patients requires thorough clinical and laboratory workups (13). In patients with suspected hypoglycemia, a 4- to 6-h oral glucose tolerance test and a 72-h fasting test, and routine monitoring of blood glucose, serum insulin and C-peptide levels are required to identify pancreatic hyperinsulinemic hypoglycemia (11). Owing to its rarity, imaging studies of nesidioblastosis have been poorly reported, resulting in cases of false-negative pancreatic nesidioblastosis on both CT and MRI due to isointense or isosignal patterns with a normal pancreatic parenchyma (14,15). However, typical insulinomas may show significant round or oval enhancement on contrast CT/MRI, which lasts longer and can still be seen in the portal phase, thus aiding the differentiation from nesidioblastosis, but smaller insulinomas may also be undetectable (16). The current case was isointense to the normal pancreatic parenchyma on CT; however, on contrast-enhanced T1WI, the lesion was slightly less isointense than the normal pancreatic parenchyma signal, which was slightly inconsistent with the MRI findings of nesidioblastosis reported in the literature and differed from the obvious enhancement of insulinomas. The main advantage of

Table I. Comparison of the clinical features and imaging findings of nesidioblastosis and insulinoma.

Parameters	Nesidioblastosis	Insulinoma	(Refs.)
Symptoms	Both conditions can present with hypoglycemic symptoms, such as dizziness, palpitations, sweating, trembling limbs, paleness and disturbance of consciousness		(11)
Prevalence	More common in infants and children, while less common in adults	More common in adults	(3,4)
Imaging features			
CT	Isodense, usually cannot be displayed	Isodense or low-density nodules, with significant enhancement on contrast-enhanced CT	(13,14)
MRI	T1WI shows equal or slightly low signal, and T2WI shows equal or slightly higher signal	T1WI shows low signal and T2WI shows high signal	(15)
PET/CT	Mildly increased ^{18}F-FDG uptake, with no ^{68}Ga DOTATATE uptake	No or mild increase in ^{18}F-FDG uptake, strong uptake of ^{68}Ga-DOTATATE	(16-18)
Pathological features	Microscopic visualization of multiple β-cells with enlarged and deeply stained nuclei and abundant transparent cytoplasm, the normal spatial distribution of various cell types in the pancreatic islets and the absence of endocrine cell proliferative activity	Tumor cells may be arranged as flowery bands or gyrus, acinoid or Daisy clusters, solid masses, or diffuse sheets. Different pathological grades of insulinoma showed different cell atypia, among which G1 grade cell atypia was low, G3 grade cell atypia was high	(3,20,24)

CT, computed tomography; ^{18}F-FDG, fluoro-18 fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; WI, weighted imaging; ^{68}Ga-DOTATATE, gallium-68-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceticacid-D-Phel-Tyr3-Thr8-OC.

nuclear medicine is that different radiopharmaceuticals can be synthesized for targeted imaging based on receptors expressed in the lesion. ^{18}F-FDG PET/CT, a common functional imaging technique, has been widely used in the localization, differential diagnosis, staging and post-treatment response assessment of a variety of primary tumors; however, it has shown limited value in the diagnosis and differential diagnosis of neuroendocrine tumors, including insulinoma (17).

New imaging techniques in nuclear medicine, including PET/CT imaging with ^{68}Ga-somatostatin receptors, such as ^{68}Ga-DOTATATE, and ^{68}Ga-glucagon-like peptide-1 (GLP-1) receptor analogs, such as ^{68}Ga-DOTA-exendin-4, can facilitate the localization and diagnosis of insulinoma to distinguish it from other tumors such as pancreatic cancer and pancreatic cystadenoma (7,17,18). Due to the high expression of somatostatin receptors, insulinomas show significant radioactivity uptake on ^{68}Ga-somatostatin receptor and ^{68}Ga-GLP-1 receptor analog PET/CT imaging (7,19). Compared with the aforementioned studies, the present study revealed that dual nuclear tracer PET/CT imaging may become a differential diagnostic method for the cause of hypoglycemia such as insulinoma and nesidioblastosis, as nesidoblasts do not express somatostatin receptors, resulting in no or only slight radioactive uptake on PET/CT imaging of ^{68}Ga-labeled somatostatin receptors. The patient's double-tracer PET/CT results showed moderate ^{18}F-FDG uptake but no ^{68}Ga-DOTATATE uptake, suggesting only a small possibility of insulinoma and that nesidioblastosis should be considered. The detailed comparison of the clinical features and imaging findings of nesidioblastosis and insulinoma are presented in Table I.

The current gold standard for nesidioblastosis diagnosis is based primarily on the histopathological diagnostic criteria proposed by Klöppel *et al* (3). The main criteria include the exclusion of insulinoma by visual, microscopic and immunohistochemical examination, including the microscopic visualization of multiple β-cells with enlarged and deeply stained nuclei, and abundant transparent cytoplasm, the normal spatial distribution of the various cell types in the pancreatic islets and the absence of endocrine cell proliferative activity. Secondary criteria included an increase in pancreatic islet number and size, lobulated or irregular islet structures, and multinucleated giant β cells. Primary criteria must be met for the pathological diagnosis of nesidioblastosis, and secondary criteria may not be present in all cases. The pathological examination of the patient in the present study showed a diffuse distribution of enlarged round or oval β cells in the pancreatic islets, with deeply stained nuclei and abundant clear cytoplasm consistent with the diagnosis of nesidioblastosis. Although a pathological diagnosis is the gold standard for nesidioblastosis, the present case suggested that dual nuclear

tracer PET/CT imaging is necessary, or even crucial, for the management of nesidioblastosis, as it can accurately locate the lesion and guide further puncture biopsy and treatment. However, ^{68}Ga-labeled somatostatin receptor PET/CT imaging can also produce false-negative results and cannot differentiate between normal pancreatic uptake, non-insulinomatous pancreatic hypoglycemia syndrome and postoperative gastric bypass hypoglycemia. In previous studies, patients affected by these conditions underwent selective intra-arterial calcium stimulation with hepatic venous sampling, which can increase the detection rate (19,20). In addition, the greater medical cost of dual-nuclide PET/CT imaging compared with MRI is another disadvantage, but it should still be considered if the patient's condition requires it.

In patients with nesidioblastosis and hypoglycemia, a low-carbohydrate diet and medications such as diazoxides, growth inhibitor analogs, calcium channel antagonists and α-glucosidase inhibitors may be considered first to improve the symptoms (21-23). Most adult patients require surgery, with one study revealing that total resection of the pancreatic lesion or subtotal pancreatectomy including the lesion has a 70% probability of normalizing blood glucose levels and an 8% risk of secondary diabetes (6). The blood glucose level of the present patient returned to normal soon after surgical removal of the lesion. At present, the patient has not experienced hypoglycemia such as dizziness, palpitations, or sweating again.

In conclusion, nesidioblastosis is a rare cause of hypoglycemia in adults and should be considered in the differential diagnosis of insulinomas. Dual-nuclide PET/CT tracers can help differentiate nesidioblastosis from insulinomas, both of which may present no or mild to moderate ^{18}F-FDG uptake. Insulinomas present with strong ^{68}Ga-DOTATATE uptake, whereas nesidioblastosis does not.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions

GZ, LX and XH conceived and designed the study. XH acquired, analyzed and interpreted the data. GZ and LX confirm the authenticity of all the raw data. GZ drafted the manuscript. XH critically revised the manuscript for intellectual content and approved the final version for publication. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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