**68Ga-DOTATATE PET/CT imaging for insulinoma in MEN1 patient with endogenous hyperinsulinemic hypoglycemia**

A case report

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**Abstract**

**Rationale:** Multiple endocrine neoplasia type 1 (MEN1) syndrome is a rare and complicated disease that is associated with several endocrine tumors. Here, we report a case of MEN1 associated with insulinoma, parathyroid, and pituitary tumors by 68Ga-DOTATATE positron emission tomography/computed tomography (PET/CT).

**Patient concerns:** A 49-year-old woman presented with intermittent hypoglycemia for more than a year and developed indistinct consciousness without an apparent trigger.

**Diagnoses:** Biochemical results showed abnormally high serum insulin and parathyroid hormone levels. She underwent an Abdominal magnetic resonance imaging revealed a small nodule in the uncinate process of the pancreas, but it did not clarify the nature of the small nodule. Pituitary magnetic resonance imaging scan revealed a micropituitary tumor, and parathyroid imaging showed no abnormalities. 18F-FDG PET/CT showed no apparent abnormal 18F-FDG uptake in the whole body. In contrast, 68Ga-DOTATATE PET/CT imaging showed pathological radiotracer uptake in the pancreatic uncinate process, accompanied by mild radiotracer uptake in the pituitary gland, and no apparent abnormal radiotracer uptake in the parathyroid area.

**Interventions:** The patient underwent echoendoscopy for pancreatic uncinate process lesions and surgical resection.

**Outcomes:** Histological analysis was suggested of insulinoma of pancreatic neuroendocrine tumor, the Ki-67 index was low (only 1% being positive).

**Lessons:** This case demonstrates that 68Ga-DOTATATE can be used for the detection of MEN1-related tumors and preoperative localization of small and low-grade insulinomas by PET/CT.

**Abbreviations:** CT = computed tomography, GLP-1 = glucagon-like peptide-1, MEN1 = multiple endocrine neoplasia type 1, MRI = magnetic resonance imaging, PET/CT = positron emission tomography/computed tomography, pNET = pancreatic NET, PTH = parathyroid hormone, SSTR = somatostatin receptor.

**Keywords:** 18F-FDG, 68Ga-DOTATATE, insulinoma, MEN1, neuroendocrine tumor, PET/CT

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary disease with autosomal dominant inheritance. MEN1 is characterized by the development of several endocrine tumors in a single individual; the most common are tumors of the parathyroid gland, pituitary gland, and neuroendocrine tumors (NETs) in the pancreatic islets.\(^{[1,2]}\) The diagnosis of MEN1 needs to meet one of the following criteria: the development of 2 or multiple MEN1-related endocrine neoplasms (including intrapancreatic tumor, parathyroidoma, pituitary adenoma, and others), the appearance of MEN1-related neoplasms in first-degree relatives for 1 patient with MEN, and testing for MEN1 gene mutation in a patient who may be asymptomatic and has not yet abnormal
findings. Pancreatic insulinoma is a typical functioning pancreatic NET in MEN1 that causes endogenous hyperinsulinemic hypoglycemia.

Imaging is of paramount importance for the diagnosis of MEN1-associated tumors. Normally, conventional imaging (such as US, CT, or MR) can offer detailed anatomical features and aggressive expansion of tumor cells; however, the small size of NETs makes it difficult to detect the primary tumors or their metastases using conventional anatomic imaging. Considering that anatomic imaging patterns are not able to describe the peculiar characteristics of endocrine tumors, they suggested that the diagnostic sensitivity and accuracy of functional imaging are better than those of conventional anatomic imaging. The combined ⁶⁸Ga-SSA (somatostatin analog)/¹⁸F-FDG positron emission tomography/computed tomography (PET/CT) imaging has received particular attention because its potential application can reflect the molecular biological characteristics of MEN1-related NETs from the expression level of somatostatin receptor (SSTR) and the level of glucose metabolism, respectively.

Herein, we report a rare case of MEN1 associated with insulinoma due to intermittent hypoglycemia for more than 1 year, and without a family history, which was successfully diagnosed by means of a novel tool of ⁶⁸Ga-DOTATATE PET/CT.

2. Case report
A 49-year-old woman presented with intermittent hypoglycemia for more than a year, and without a family history, which was successfully diagnosed by means of a novel tool of ⁶⁸Ga-DOTATATE PET/CT.

Figure 1. Upper row (A–D): MR study of the uncinate process of the pancreas. Lower row (E–G): MR study of the pituitary. (A) A small nodule with slightly low signal on T1WI. (B) Identical signal on T2WI. (C) Slightly high signal intensity on DWI. (D) The lesion was with minimal enhancement. (E–G) Identical signal on T1WI and slightly low signal on T2 in the right lower pituitary, the enhanced scan revealed a hypointense lesion. MR = magnetic resonance, T1WI = T1-weighted imaging, T2WI = T2-weighted imaging.
3. Discussion

Insulinomas account for 10% to 30% of pancreatic tumors in MEN1-associated patients; in other words, they can also be said to be insulin-secreting cells that are tumors on β-islet cells.\(^1\) The primary manifestations are insulinomas in 10% of MEN1-associated patients, and there a few insulinoma patients are accompanied by MEN1.\(^1\) The most common types of functioning pNETs are insulinomas, which usually appear as solitary
and small tumors. Accurate preoperative localization for insulino- 
amas is widely accepted, since some small insulinosmas may not be found during surgery. Nevertheless, preoperative localiza- 
tion of insulinosmas is a difficult clinical problem because of 
their small size and close resemblance to surrounding tissue. For 
MEN1 surveillance and screening, some clinical guidelines gen-
erally advise the anatomical localization of NETs in conjunction 
with clinical characteristics and biochemical results. However, 
there is little data and a lack of consensus guidelines on the 
most precise methods for screening patients with MEN1-related 
tumors, and patients may present with metastases as soon as 
they are diagnosed.

A traditional imaging technique is used to detect and offer 
anatomical localization and staging of a tumor before sur-
gery, CT scans provides a wider view of tumor morphology, 
location, and extent of the tumor, whereas MR images with 
contrast enhancement can offer a better view of blood flow, 
availability, and diffusion restrictions. Previous studies have 
shown that approximately 10% of pNET have multi-
ple insulinosmas, which are generally associated with MEN1 
syndrome in the meantime. In general, it is difficult to locate 
small MEN1-associated tumors and to depict specific endo-
crine characteristics.

The distinctive increase in the incidence of NETs has been 
ascribed to improved diagnostic and pathological techniques 
over the last few decades. Compared with other conventional 
imaging patterns, functional imaging is a noninvasive imaging 
technique that distinguishes most insulinosmas. Studies have 
reported that 68Ga-exendin-4 PET/CT as a valuable and credible 
imaging technique to distinguish MEN1-associated insulino-
amas. In the detection of MEN1-associated benign insulinosmas, 
the sensitivity of PET/CT was 84.6% because of gluca-
gon-like peptide-1 (GLP-1) receptors are highly expressed in 
benign insulinosmas. Similarly, Sowa-Staszczak et al reported 
that the sensitivity and specificity of GLP-1 receptor 
imaging are 100% in patients with benign insulinosmas. 
There have been several studies on the diagnostic performance 
of 68Ga-DOTATATE PET/CT in patients with MEN1, and it is 
available for detecting MEN1-associated tumors. For 
insulinosmas, it is well established that SSTR2 densities are 
lower than other types of pNETs, which could, in combina-
tion with the small size of the lesion, lead to false-negative 
findings during SSTR imaging.

Wild et al showed that compared with benign insulino-
amas, the majority of malignant insulinosmas often lack GLP-1 
receptors but are more likely to express SSTR2 receptors. The Previous studies showed that only 36% of the malignant 
insulinosmas expressed GLP-1 receptors, when compared to 
benign insulinosmas. Zimmer et al reported SSTR scintigraphy 
showed low detection efficiency (<20%) in benign insulinosmas 
and a higher positive rate in 73% of malignant insulinosmas. 
Recent study has found that 68Ga-DOTATATE PET/CT pro-
vides better identification of insulinosmas (9/10, 90%) in com-
parison with other imaging modalities, 8 of 9 tumors had Ki-67 
of <2%, the diameter of insulinosma is about 0.7 to 2.5 cm, but 
sensitivity and accuracy of 68Ga-DOTATATE were not men-
tioned in benign and malignant insulinosmas, may be too little 
concerned with the number of cases.

Our case demonstrates MEN1-associated low-grade insul-
inosmas along with higher 68Ga-DOTATATE tracer uptake, 
which is significant in the proper diagnosis of MEN1-associated 
low-grade insulinosmas with SSTR expression. Pituitary MRI 
revealed a pituitary tumor with mild 68Ga-DOTATATE uptake, 
which may be related to small lesions and decreased SSTR2 
expression. Especially remarkable is that serum PTH was abnormally high in this patient, whereas 68Ga-DOTATATE and 
18F-FDG PET/CT parathyroid imaging showed no abnormality in the parathyroid region, probably due to the small size 
of the lesion at present; adenomas of the parathyroid should 
be watched carefully over her lifetime. For this patient, the 
treatment focused on insulinoma derived from the pancreatic 
uncinate process, and surgical resection was the preferred treat-
ment choice. The patient’s hypoglycemic symptoms disappeared 
after surgical resection.

Kornaczewski Jackson et al proposed that 18F-FDG PET/ 
CT could be helpful for MEN1 patients with pNETs with a 
higher malignant potential. We conducted a 68Ga-DOTATATE 
and 18F-FDG PET/CT scan, and the imaging results showed no 
apparent abnormal 18F-FDG uptake in the pancreatic uncinate 
process; thus, the possibility of MEN1-associated malignant 
insulinoas may be very small, and immunohistochemistry event-
ually confirmed this result.

In conclusion, we present a rare case of MEN1-associated 
tumors with low-grade insulinoma and parathyroid and pitu-
tary tumors, which showed MEN1 associated low-grade insul-
inosmas along with higher 68Ga-DOTATATE tracer uptake. 
68Ga-DOTATATE PET/CT imaging may be an available nuclear 
imaging tool for the detection of MEN1-related tumors and pre-
operative localization of small and low-grade insulinosmas by 
PET/CT.

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