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Case Report

Extrapancreatic insulinoma

ABSTRACT

A 38-year-old female presented with recurrent episodes of hypoglycemia for 5 years. On 72-h fast test, critical sample biochemistry was suggestive of endogenous hyperinsulinemic hypoglycemia. Both constrast-enhanced computed tomography and ^{68}Ga-DOTATATE positron emission tomography/computerized tomography (PET/CT) revealed no pancreatic lesion but showed a jejunal lesion suggestive of neuroendocrine tumor (NET) but not confirmatory of insulinoma. ^{68}Ga-Exendin-4 PET/CT showed intense uptake in the proximal jejunum, and this being a specific scan for insulinoma, confirmed it as an ectopic insulinoma. The patient attained normoglycemia after excision of this NET confirming it to be a case of ectopic insulinoma located in the jejunum. Although most insulinomas are located in the pancreas, rarely ectopic cases have been described in the spleen, perisplenic tissue, duodenohepatic ligament, adjacent to the ligament of Treitz, duodenum, and the jejunum. Functional scanning with ^{68}Ga-Exendin-4 PET/CT scan aids the localization of ectopic insulinoma.

Keywords: ^{68}Ga-Exendin-4 positron emission tomography/computerized tomography, ^{68}Ga-DOTATATE positron emission tomography/computerized tomography, ectopic jejunal insulinoma

INTRODUCTION

Insulinoma is a rare tumor with an incidence of four cases per million persons per year.[1] Although most insulinomas are located in the pancreas, rarely ectopic cases have been described in the spleen, perisplenic tissue, duodenohepatic ligament, adjacent to the ligament of Treitz, duodenum, and a single case in the jejunum.[2,3] Here, we report a rare case of ectopic insulinoma located in the jejunum.

CASE REPORT

A 38-year-old nondiabetic female presented with recurrent episodes of hypoglycemia for 5 years which used to abort after consuming food. In the past, she had to be hospitalized during one episode of severe hypoglycemia (random plasma glucose 40 mg/dl), requiring intravenous (i.v.) glucose for recovery.

She was subjected to 72-h fast test. Critical sample biochemistry (plasma glucose: 20.6 mg%; serum insulin: 23.50 μU/ml; C-peptide: 4.44 ng/ml; and β-hydroxybutyrate: 0.36 mmol/L) was suggestive of endogenous hyperinsulinemic hypoglycemia.

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Contrast-enhanced computed tomography (CECT) scan showed a pedunculated arterially enhancing lesion measuring 1.9 cm × 1.8 cm in the proximal jejunum but no evidence of pancreatic lesion [Figure 1]. Then, ^{68}Ga-DOTATATE positron emission tomography/computerized tomography (PET/CT) scan was done 60 min after i.v. injection of 3.0 mCi of ^{68}Ga-DOTATATE using a whole-body full-ring dedicated LYSO PET CT time of flight scanner. Images were acquired using three-dimensional PET protocol. Data were reconstructed using an iterative (row-action maximum likelihood algorithm) algorithm. Attenuation correction was done by using low dose CT with 50 mA and 120 KV. ^{68}Ga-DOTATATE PET/CT scan did not reveal any pancreatic lesion but showed a diffuse uptake in a jejunal mass (maximum standard uptake values [SUV_{max}] - 23) [Figure 2]. This somatostatin

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receptor (SSTR) expressing lesion on ^{68}Ga-DOTATATE PET/CT could have been a jejunal neuroendocrine tumor (NET) and not necessarily an insulinoma. To confirm insulinoma, we required a specific scan. Hence, the patient was subjected to ^{68}Ga-Exendin-4 PET/CT. After 67 min of i.v. injection of 3.2 mCi of ^{68}Ga-Exendin, the patient was scanned using a dedicated 16 slice PET CT. SUV were normalized to body weight obtained over the lesions. This showed focal single intensely increased tracer uptake (SUV_{max} 37.8) in the lesion measuring 1.9 cm × 1.8 cm in the proximal jejunum likely to be ectopic insulinoma [Figure 3]. The patient attained normoglycemia after excision of this NET, confirming it to be a case of ectopic insulinoma. Histopathological examination report of the excised tumor was confirmatory of NET [Figure 4].

DISCUSSION

The diagnosis of hypoglycemia is usually established when venous plasma glucose is <55 mg/dl and is supported by the presence of Whipple's triad (symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms or signs after the plasma glucose level is raised).[4] In a seemingly well nondiabetic individual, etiological factors of hypoglycemia include endogenous hyperinsulinism due to either a β-cell tumor (insulinoma), nesidioblastosis or autoimmune hypoglycemia.

Insulinoma is a rare tumor with an incidence of four cases per million persons per year.[1] It usually arises from pancreatic islet β-cells and is the most common (~25%) functioning pancreatic NET.

Ectopic insulinoma is an extremely rare (~2%) entity whose diagnosis should be suspected when a biochemically confirmed insulinoma is not localized in the pancreas.[5] These tumors are usually located in the duodenal wall, although other locations such as the spleen, perisplenic tissue, duodenohepatic ligament, and surrounding tissues of the pancreas have been reported.[2,3] Ectopic insulinomas usually develop in the ectopic pancreas also referred to as heterotopic, accessory, or aberrant pancreas, an anatomical

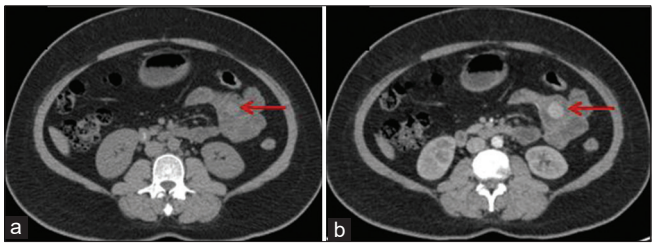

Figure 1: Contrast-enhanced computed tomography of the abdomen showing pedunculated arterially enhancing lesion measuring 1.9 cm × 1.8 cm in the proximal jejunum (↑); with 47 Hounsfield units on unenhanced image (a) and 103 Hounsfield units on contrast-enhanced image (b)

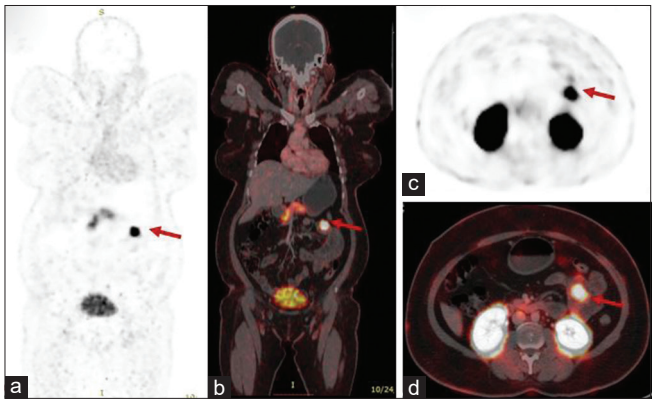

Figure 3: ^{68}Ga-Exendin-4 positron emission tomography/computerized tomography scan showing intensely increased tracer uptake (SUV_{max} 37.8) in the lesion measuring 1.9 cm × 1.8 cm in proximal jejunum (↑) in coronal (a and b) and axial (c and d) view. (b and d) Represent fusion images. SUV_{max}: Maximum standardized uptake value

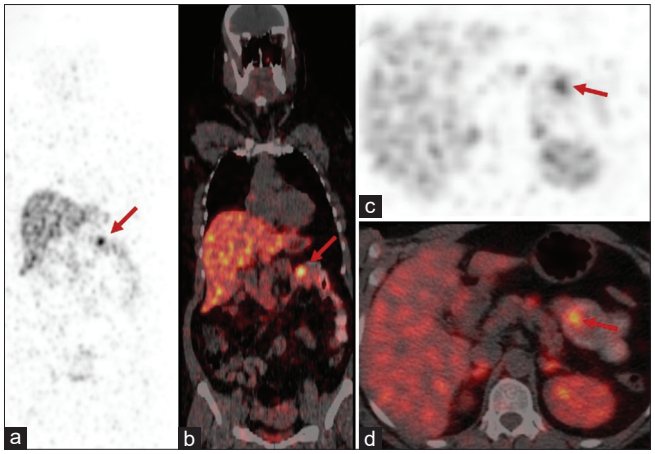

Figure 2: ^{68}Ga-DOTATATE positron-emission tomography/computerized tomography scan showing diffuse tracer uptake (SUV_{max} 23) in the jejunal area (↑) in coronal (a and b) and axial (c and d) view. (b and d) Represent fusion images. SUV_{max}: Maximum standardized uptake value

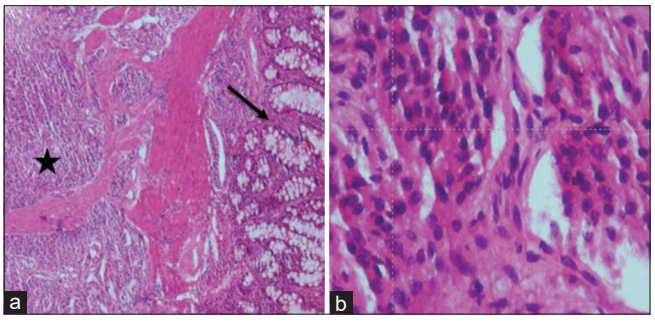

Figure 4: Hemotoxylin and eosin staining of tumor tissue under light microscopy showing jejunal mucosa (↑) with encapsulated tumor (star) in submucosa which is composed of sheets of monomorphic cells among blood vessels with stippled chromatin in nuclei and moderate eosinophilic cytoplasm with mitosis of <2/500 cells suggestive of neuroendocrine tumor Grade I (a and b) ([b] represents magnified view)

abnormality that represents the growth of pancreatic tissue outside of the pancreas, with no anatomic or vascular connection. Ectopic pancreas are reported in about 0.5%–15% of autopsies and in 1 of 500 abdominal surgeries and were mainly found in the stomach, duodenum, and jejunum.[2,3,6]

Four cases of ectopic insulinoma located in the duodenum and a case of malignant insulinoma located in the jejunum have been reported in the English literature.

Ectopic insulinomas represent challenging neoplasms with clinical implications mainly due to the difficulties in their preoperative diagnosis and localization. With the progress of nuclear medicine technologies, however, there is a better chance of detecting cases before the autopsy. In a recent study, ^{68}Ga-DOTATATE PET/CT identified most pancreatic insulinomas (9/10, 90%) compared with other modalities, including CT, magnetic resonance imaging (MRI), endoscopic ultrasound, and selective arterial secretagogue injection, this is because, ^{68}Ga-DOTATATE has a high affinity to SSTR 2 and SSTR 5, which are expressed in insulinomas in up to 80% of cases.[7]

It was later shown that targeting of the glucagon-like peptide-1 receptor (GLP-1R), which is highly expressed in insulinomas, using the specific ligand Exendin-4, is a much more sensitive method for localizing insulinomas with PET/CT, especially with high sensitivity for hidden small insulinoma.[8] In a recent study by Luo *et al.*, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of ^{68}Ga-Exendin-4 PET/CT in diagnosing insulinoma were 99.0%, 100%, 99.3%, 100%, and 98.3%, respectively.[9]

Theoretically, the sensitivity of CECT should be higher than that of functional scans because it is not biologically plausible to have a tracer uptake on the functional scan without a corresponding anatomical substrate on CT/MRI. However, for clinical relevance, suggestive lesions on CECT should not only escape an overlook but also be convincing enough to provoke therapeutic intervention. Functional scan, especially ^{68}Ga-Exendin-4 PET/CT, provides the specificity of uptake by highly expressed GLP-1Rs in insulinomas which confirms the diagnostic localization.

Arterial enhancement in CECT is another feature that gives additional support to the diagnosis of NETs.

In our patient, endogenous hyperinsulinemic hypoglycemia was proved on a 72-h fast test. Both CECT and ^{68}Ga-DOTATATE PET/CT revealed no pancreatic lesion but showed a jejunal lesion suggestive of NET but not confirmatory of insulinoma. ^{68}Ga-Exendin-4 PET/CT showed intense uptake in the proximal jejunum, and it being a specific scan for insulinoma, confirmed it as an ectopic insulinoma [Figure 3]. This case underscores the importance of functional scanning with 68Ga-exendin-4 PET-CT scan, which aided the localization of ectopic insulinoma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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