Int J Clin Exp Med 2017;10(11):15666-15671
www.ijcem.com /ISSN:1940-5901/IJCEM0059751

Case Report

Hypoglycemia as the onset manifestation of Somatostatinoma: a case report and review of the literature

Wei Zhang[1,3*], Guoji Yang[2*], Hongwei Li[3], Hanmin Wang[1], Yumei Jin[4], Haobin Chen[5], Weiwen Chen[1,3], Joseph A Bellanti[6], Song Guo Zheng[3,7]

Departments of [1]Endocrinology and Rheumatology, [4]MRI, [5]Pathology, [3]Workstation for Academicians and Experts of Yunnan Province, Qujing Affiliated Hospital of Kunming Medical University, 655000 Yunnan, China; [2]Department of Hepatobiliary Surgery, The Second People's Hospital of Qujing, 655000 Yunnan, China; [6]Department of Pediatrics and Microbiology-Immunology, Georgetown University Medical Center, Washington, DC, USA; [7]Division of Rheumatology, The Pennsylvania State University, College of Medicine, 500 University Drive, Hershey, PA 17033, USA. [*]Equal contributors.

Received June 18, 2017; Accepted September 8, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Somatostatinoma is a rare pancreatic tumor characterized by diabetes mellitus, cholelithiases, and diarrhea. Although hypoglycemia is a distinctively unusual manifestation of the condition, most patients are symptomatic at the time of diagnosis. However, since the tumor is slow growing and symptoms are often not present for several years before diagnosis, the disease is often quite advanced by the time, patients seek medical attention and preoperative diagnosis is therefore often difficult. We reported a 30-year-old man who presented with hypoglycemia, hypersomnia and hyperinsulinemia. Magnetic resonance imaging (MRI) demonstrated a low-density mass in the head of the pancreas suggestive of a malignancy that was definitively identified as a somatostatinoma by immunohistochemical staining of a biopsy specimen.

Keywords: Somatostatinoma, hypoglycemia, hyperinsulinemia, hypersomnia

Introduction

Pancreatic neuroendocrine tumors (P-NETs) are neoplasms that arise from the hormonal producing Langerhans cells of the pancreas, known also as the pancreatic islet cells. The most recently updated WHO classification for gastrointestinal neuroendocrine tumors dates back to 2011 [1]. P-NETs are a rare group of tumors, occurring with an incidence of 1 in 100,000 individuals and represent approximately 1-2% of all pancreatic neoplasms [2]. Somatostatinomas are a rare subset of P-NETs that usually arise in the pancreas (55%) or duodenum/jejunum (44%) [3]. In 1977, Larsson et al., [4] reported the first cases of somatostatinoma. We reported a young man with hypersomnia, hypoglycemia and hyperinsulinemia diagnosed as insulinoma reoperatively and definitively identified as a pancreatic somatostatinoma by immunohistochemical staining of a biopsy specimen.

Case report

A 30-year-old man was admitted to the Qujing First Hospital in 2016 for evaluation of recurrent episodes of prolonged somnolence occurring over the previous 3 years. Initially, 6 years prior to his current evaluation, the patient presented with muscle weakness and early morning dizziness upon arising, unassociated with tremor,palpitations, perspiration or numbness. His symptoms improved or disappeared after-breakfast. Hypoglycemia was subsequently diagnosed with extremely low levels of blood glucose (2.1 mmol/L) occurring 3 to 4 times a day. Over the past 3 years he presented with prolonged somnolence and extreme difficulty in arousal from sleep and the hypersomnia was attributed to hypoglycemia. The above mentioned symptoms occurred every 1-2 months and were associated with an inability to concentrate, and mild memory impairment. There was no family history of malignancy or other comorbidities including diabetes mellitus.

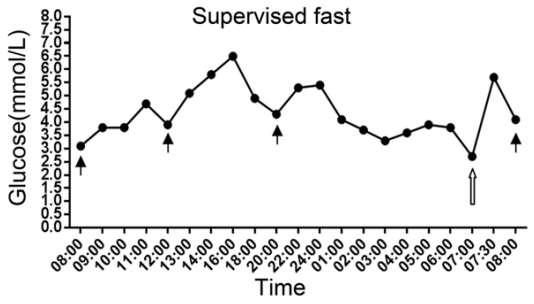

Figure 1. Point-of-care glucose trend during supervised fast. Our patient's point-of-care glucose was monitored during hospital admission and showed a rapid decline to 2.7 mmol/L at 7:00 pm. Black arrows: food time. White arrow: oral glucose solution at 50% concentration.

Table 1. 75 g anhydrous glucose OGTT test

Test	Result (reference range)
C-peptide (0 min)	2.95 ng/mL (0.8-4.2)
C-peptide (30 min)	8.51 ng/mL
C-peptide (60 min)	8.81 ng/mL
C-peptide (120 min)	7.29 ng/mL
C-peptide (180 min)	3.82 ng/mL
Insulin (0 min)	22.69 uIU/mL (3.21-16.32)
Insulin (30 min)	51.4 uIU/mL
Insulin (60 min)	40.1 uIU/mL
Insulin (120 min)	17.1 uIU/mL
Insulin (180 min)	9.2 uIU/mL
Glucose (0 min)	2.78 mmol/L (3.89-6.11)
Glucose (30 min)	3.99 mmol/L (6.11-10)
Glucose (60 min)	6.46 mmol/L (6.11-10)
Glucose (120 min)	5.74 mmol/L (3.9-7.8)
Glucose (180 min)	3.13 mmol/L (2.87-6.67)

Physical examination revealed a body mass index (BMI) of 26.9 kg/m^2. The neurological evaluation was within normal limits and no tenderness or palpable masses were detected on abdominal examination. Fingertip blood glucose testing revealed low nocturnal and early morning blood glucose concentrations which could be reversed from hypoglycemic to normoglycemic concentrations by the oral administration of a 50% glucose solution (**Figure 1**).

Laboratory test results including blood cell counts, blood biochemistry, coagulation four indices, thyroid function, gonadal function, anti-nuclear antibody, insulin antibody, as well as AFP, CEA and all other tumor markers were all within normal levels. Serum hormone levels (calcitonin, prolactin, intact parathyroid hormone, growth hormone, cortisol, and ACTH) were normal. In order to identify the etiologic cause of the hypoglycemia, a 75 g anhydrous glucose oral glucose tolerance test (OGTT) wasperformed (**Table 1**). The results revealed a low glucose level (2.78 mmol/L) at baseline, with a corresponding level of insulin 22.69 uIU/mL (3.21-16.32), C-peptide 2.95 ng/mL (0.8-4.2), and insulin index (insulin/glucose) = 8.2.

Although enhanced abdominal computed tomography (CT) scanning demonstrated no obvious abnormalities (**Figure 2**), magnetic resonance imaging (MRI) revealed a tumormass in the uncinate process of the pancreas measuring 17 mm × 11 mm × 12 mm in diameter (**Figure 3**) with no dilatation of the biliary ducts or the main pancreatic ducts. There was no evidence of metastasis found in lymph nodes or other organs. Brain CT scanning demonstrated ischemic findings in the anterior frontal and superior cerebral regions. Based upon the findings of hypoglycemia, hyperinsulinemia, and the MRI, apre-surgical diagnosis of insulinoma was entertained. Although measurements of plasma somatostatin concentrations are sometimes useful in making a preoperative diagnosis of somatostatinoma, these were not included in the diagnostic evaluation of this patient since the other parameters were so conclusive.

Gross and histological examination of a biopsy specimen of the pancreatic head mass obtained after surgery revealed the following. The gross morphology of the specimen displayed a solitary, well-demarcated, hard mass scattered with gray-red nodules. Hematoxylin eosin (HE) staining revealed typical features of a pancreatic somatostatinoma with a clearly demarcated tumor tissue border. Tumor cells had a trabecular and sheet-like architecture. Cell nuclei were round to ovoid and showed vesicular nuclei with diminished meiotic clarity. Individual cells were characterized by prominent eosinophilic cytoplasm and prominent nucleoli. Intercellular regions contained scattered blood sinuses, and few cytoplasmic translucent tissue cells (**Figure 4**).

Immunohistochemistry staining showed that many of the tumor cells were positive for somatostatin (SS), synaptophysin (Syn), chromogranin A (CgA), and CD56 (**Figure 4**). However,

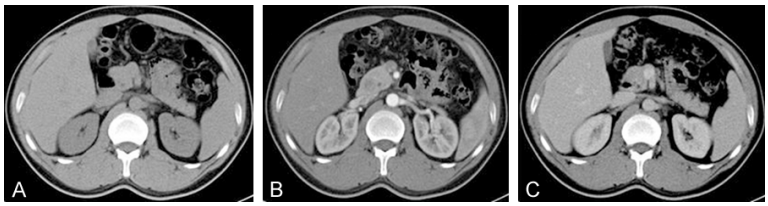

Figure 2. Results of CT of the abdomen. CT scanning demonstrated no obvious abnormalities (A, CT thin scan. B, CT enhancing scan, arterial phase. C, CT enhancing scan, portal vein phase).

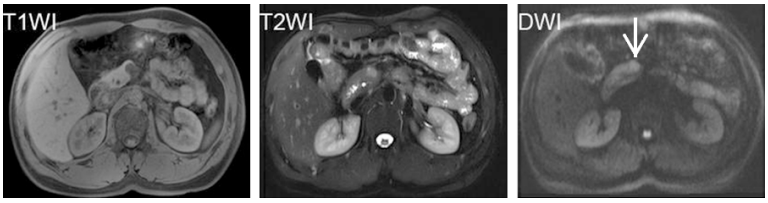

Figure 3. Results of MRI of the abdomen. T1-weighted image (T1WI) demonstrated a mass that was uniformly low in signal intensity, and T2-weighted image (T2WI) demonstrated high signal intensity in the uncinate process of the pancreas measuring 17 mm × 11 mm × 12 mm in diameter, some small cystic degeneration were in the mass. Diffusion weighted imaging (DWI) demonstrated a bit limited dispersion (white arrow).

there was negative staining for insulin, pancreatic polypeptide (PP), glucagon, CK7, and CK8 (**Figure 4**). Approximately 5-8% of the cell population were Ki-67 positive, suggesting a low proliferative activity of the tumor cells. Based on the 2012 ENETS Consensus Guidelines, these findings indicate that the classification of this malignancy is consistent with a pancreatic somatostatinoma G2 [3].

After a six-month follow-up, the postoperative course of this patient has progressed well. The surgical resection has been associated with complete resolution of the hypersomnia and associated symptoms. Blood glucose monitoring has shown consistent maintenance of normoglycemic concentrations suggesting normalcy of pancreatic islet cell function. Fortuitously, the patient has not required adjuvant chemotherapy and has shown no signs of local recurrence or distant metastatic tumor spread at his latest follow-up visit.

Discussion

Somatostatinomas are rare neoplasms that originate from the delta cells (δ-cells or D cells), the somatostatin-producing cells, found in the stomach, intestine and the pancreatic islets. Of all these sites of origin, pancreatic somatostatinomas are among the rarest [2]. Their obscure symptoms and diminutive size are often responsible for an unfortunate delay in diagnosis.

Symptoms of somatostatinoma

The somatostatinoma syndrome includes the following comorbidity entities, diabetes-mellitus (63-90%), cholelithiases (65-90%), and diarrhea (35-90%) [3]. The syndrome is a well described but poorly recognized condition, primarily because most tumors are asymptomatic. The present report describes this diagnostic dilemma in a patient with the characteristic findings of hypersomnia, hypoglycemia, and hyperinsulinemia but with no distinctive features on imaging examinations. Although the patient was initially diagnosed with MRI as an insulinoma, pancreatic somatostatinoma could only be appropriately diagnosed by postoperative histopathological examination. Similar to patients described in published reports [5, 6], the delay in diagnosis of somatostatinoma in our patient was not only due to the slow tumor growth but also to the non-specific nature of the clinical manifestations.

Imaging of somatostatinoma

Since there are no significant differences between somatostatinoma and insulinoma when measured by MRI (**Table 2**) [7], the use of MRI presents difficulty to accurately diagnose a particular type of pancreatic neuroendocrine tumor. On the other hand, endoscopic ultrasound (EUS) offers a better image tool for the early diagnosis of these tumors. For example, Anderson *et al*. [8] showed that EUS had an overall sensitivity and accuracy of 93% for pancreatic neuroendocrine tumors. Their results support the use of EUS as a primary diagnostic modality in the evaluation and management of patients with neuroendocrine tumors of the pancreas. Nonetheless, the more detailed characteristics

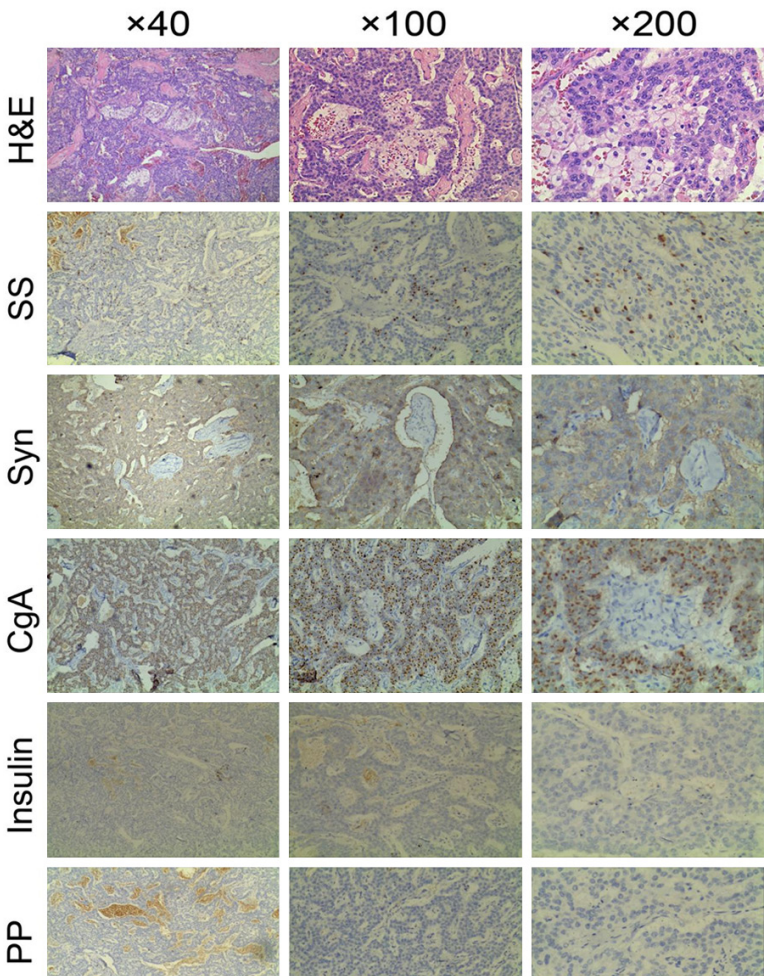

Figure 4. Histologic features of the pancreatic somatostatinomas. HE staining of the pancreatic somatostatinomas. The immunohistochemistry results of pancreatic somatostatinoma. Such as somatostatin (SS), synaptophysin (Syn), chromogranin A (CgA), insulin and pancreatic polypeptide (PP).

of these pancreatic neuroendocrine tumors when diagnosed by EUS is still unknown.

Pathology of somatostatinoma

Immunohistochemistry continues to remain the singular essential modality for the diagnosis of the somatostatinomas. It provides verification of hormonal production, validation of cell types, and a specific differential tool to distinguish the somatostatinomas from other P-NETs [9]. In addition, Immunohistochemistry using antibodies CgA, Syn, CD56, CK7 and CK8 helps to distinguish pancreatic neuroendocrine tumors from other diseases. Staining all samples for insulin, in addition to glucagon, SS and PP should be performed to determine their full hormone expression profiles. The calculation of mitotic index and Ki-67 are optional ancillary diagnostic measurements that can be employed in the assessment of the degree of invasion.

Current treatment

Surgical resection for removal of the primary tumor is not only the main treatment for the somatostatinomas but, currently, is also the only curative option. A successful outcome, however, depends on the stage of the disease [10]. Patients with pancreatic tumors < 2 cm with no metastatic tumor generally have spontaneous good long-term life expectancy [11]. However, most patients need adjuvant chemotherapy. Many kinds of chemotherapeutic drugs can be chosen. The response rate (RR) was 39% in advanced P-NET with Streptozocin plus Fluorouracil and Doxorubicin [12]. On the other hand, because of toxicity, such as hair loss, nausea, hematologic toxicity, and renal dysfunction, the widespread usage of this drug has been limited [13]. Strosberg *et al*. [14] investigated the efficacy of oral temozolamide plus capecitabine therapy andfound that the objective RR of this drug combination was 70% with an overall 2-year survival (OS) rate of 92%. In a study by Yao *et al*. [15], the median progression of free survival was 11.0 months with everolimus compared to 4.6 months with placebo. In addition to surgery, routine blood glucose monitoring and annual follow-ups should be included in the management algorhythym for these patients.

In conclusion, pancreatic somatostatinoma is a rare disease. The absence of recognizable clinical features usually delays a definitive and early diagnosis. The current case is not associated with the distinct clinical manifestations of hormone alterations seen in the classic disease. Although, MRI is a better diagnostic tool than

Table 2. MRI features of the neuroendocrine tumors

Type	Location	Signal intensity (pre-Gad)	Enhancement pattern	Enhancement intensity
Insulinoma	Multifocal or Tail	T1 low/T2 high	Homogeneous or Heterogeneous	Moderate
Somatostatinoma	Tail	T1 low/T2 high	Heterogeneous	Moderate

CT, a combination of both MRI and EUS are more helpful for detecting the location and size of the tumor mass. However, the ultimate correct diagnosis is dependent upon pathology and immunohistochemistry examinations. When clearly diagnosed, a surgical resection is the singular recommended treatment that may lead to a therapeutic cure.

Acknowledgements

This work was supported by grant from the Department of Science and Technology of Yunnan Province-Kunming Medical University Basic Research (2017FE467(-105)) and project from the Workstation for Academicians and Experts of Yunnan Province.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Weiwen Chen, Department of Endocrinology and Rheumatology, Qujing Affiliated Hospital of Kunming Medical University, 655000 Yunnan, China; Department of Workstation for Academicians and Experts of Yunnan Province, Qujing Affiliated Hospital of Kunming Medical University, 655000 Yunnan, China. E-mail: 30620765@qq.com; Dr. Song Guo Zheng, Department of Workstation for Academicians and Experts of Yunnan Province, Qujing Affiliated Hospital of Kunming Medical University, 655000 Yunnan, China; Division of Rheumatology, The Pennsylvania State University, College of Medicine, 500 University Drive, Hershey, PA 17033, USA. E-mail: songguozheng2013@yahoo.com

References

[1] Scoazec JY, Couvelard A and pour le reseau T. [The new WHO classification of digestive neuroendocrine tumors]. Ann Pathol 2011; 31: 88-92.

[2] Asa SL. Pancreatic endocrine tumors. Mod Pathol 2011; 24 Suppl 2: S66-77.

[3] Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R; Barcelona Consensus Conference participants. ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95: 98-119.

[4] Larsson LI, Hirsch MA, Holst JJ, Ingemansson S, Kuhl C, Jensen SL, Lundqvist G, Rehfeld JF and Schwartz TW. Pancreatic somatostatinoma. Clinical features and physiological implications. Lancet 1977; 1: 666-668.

[5] Mori Y, Sato N, Taniguchi R, Tamura T, Minagawa N, Shibao K, Higure A, Nakamoto M, Taguchi M and Yamaguchi K. Pancreatic somatostatinoma diagnosed preoperatively: report of a case. JOP 2014; 15: 66-71.

[6] Williamson JM, Thorn CC, Spalding D and Williamson RC. Pancreatic and peripancreatic somatostatinomas. Ann R Coll Surg Engl 2011; 93: 356-360.

[7] Semelka RC, Custodio CM, Cem Balci N and Woosley JT. Neuroendocrine tumors of the pancreas: spectrum of appearances on MRI. J Magn Reson Imaging 2000; 11: 141-148.

[8] Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH and Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000; 95: 2271-2277.

[9] Hackeng WM, Hruban RH, Offerhaus GJ and Brosens LA. Surgical and molecular pathology of pancreatic neoplasms. Diagn Pathol 2016; 11: 47.

[10] Bilici A. Advances in the management of unresectable or metastatic pancreatic neuroendocrine tumors: chemotherapy, targeted therapy, hormonal treatment, and future directions. Asian Pac J Cancer Prev 2015; 16: 2151-2159.

[11] Jensen RT, Berna MJ, Bingham DB and Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. Cancer 2008; 113: 1807-1843.

[12] Prakash L, Bhosale P, Cloyd J, Kim M, Parker N, Yao J, Dasari A, Halperin D, Aloia T, Lee JE, Vauthey JN, Fleming JB and Katz MH. Role of Fluorouracil, Doxorubicin, and Streptozocin therapy in the preoperative treatment of localized pancreatic neuroendocrine tumors. J Gastrointest Surg 2017; 21: 155-163.

[13] Khagi S and Saif MW. Pancreatic neuroendocrine tumors: targeting the molecular basis of disease. Curr Opin Oncol 2015; 27: 38-43.

[14] Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J and Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011; 117: 268-275.

[15] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Oberg K; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364: 514-523.