Syndrome of Inappropriate Antidiuresis Associated with Pancreatic Neuroendocrine Tumor: Case Report

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Case Report

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Abstract

Background

Functional pancreatic neuroendocrine tumors (pNETs) rarely produce vasopressin. To the best of our knowledge, only one case of an ADH-producing pNET has been reported thus far. Here, we report a case of pNET producing vasopressin in a 78-year-old man with hyponatremia.

Case presentation

The patient presented with anorexia 4 years ago, and the lowest serum sodium level was 121 mmol/L. Upon admission, serum osmolality was 277 mOsm/kg·H₂O, urine osmolality was 465 mOsm/kg·H₂O, urine sodium level was 82.5 mmol/L, and 24-hour urine sodium level was 140.25 mmol. There was no evidence of adrenal insufficiency or hypothyroidism. Syndrome of inappropriate antidiuresis (SIAD) was diagnosed on the basis of laboratory and clinical findings. The serum sodium level was maintained within the normal range after the oral administration of tolvaptan 7.5 mg. ⁶⁸Ga-tetraazacyclododecanetetraacetic acid–DPhe1-Tyr3-octreotate positron emission tomography-computed tomography (⁶⁸Ga-DOTATATE PET-CT) showed a high uptake lesion measuring approximately 1 cm in diameter in the pancreatic body, and the possibility of the pNET was considered. The patient underwent surgery, and the immunohistochemical study showed that the tumor cells were positive for somatostatin receptors 2 (SSTR2) and vasopressin. The patient was weaned from tolvaptan post-surgery, and low-dose corticosteroids were started due to signs of relative adrenal insufficiency, which was probably related to heart failure and surgery. Serum sodium level was maintained within the normal range.

Conclusions

This case illustrates the potential ectopic production of vasopressin resulting in SIAD in pNETs, highlighting the adoption of ⁶⁸Ga-DOTATATE PET-CT and vasopressin immunohistochemical staining in the evaluation of the etiology of SIAD.

Background

Hyponatremia, defined as serum sodium level < 135 mmol/L, is the most common electrolyte abnormality observed in clinical practice[1]. It is estimated that hyponatremia occurs in up to 15–30% of cases in hospitalized patients[1]. Acute, severe hyponatremia exacerbates patients' conditions and is associated with increased mortality[2, 3]. Furthermore, recent studies suggest that hyponatremia contributes to cognitive decline[4] and an increased risk of falls and fractures[5, 6], especially among the elderly.

One of the main causes of hyponatremia is SIAD[7], formerly named as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[8]. SIAD results from an inappropriate release of antidiuretic hormone (ADH, also called vasopressin) release or an increased renal response to ADH[9, 10], which leads to excessive reabsorption of water and dilutional hyponatremia. Conditions that may cause SIAD include:

1) ectopic ADH secretion by malignant tumor cells, e.g., small cell lung cancer; 2) increased production of ADH-like substances by the hypothalamus, secondary to trauma, infection, or tumors; 3) infectious lung disease, including tuberculosis, pneumonia, and fungal infection, etc.; and 4) drugs stimulating the secretion of ADH, including cytotoxic drugs, anesthetics, and interferons. A pancreatic neuroendocrine tumor (pNET) is a type of neuroendocrine tumor (NET) that originates in the pancreas. A functional pNET may produce a variety of hormones, including insulin, gastrin, vasoactive intestinal polypeptide, glucagon, somatostatin, growth hormone-releasing hormone, and adrenocorticotrophic hormone (ACTH) [11, 12]. However, only one case of SIAD with the pNETs has been reported so far, in which the pNET produced insulin and ADH[13].

Herein, we report an unusual case of a pNET ectopically producing ADH that led to SIAD, which was confirmed by vasopressin immunohistochemical staining of the pathological examination.

Case Presentation

A 78-year-old man was referred to our department of endocrinology and metabolism for recurrent episodes of hyponatremia on July 5, 2019. The patient presented with anorexia approximately 4 years ago, and the patient's laboratory test results from the local hospital indicated hyponatremia, which was resolved after symptomatic treatment. The patient later experienced 3 subsequent episodes of anorexia in the past 4 years, during which laboratory tests consistently indicated hyponatremia. The lowest serum sodium level was 121 mmol/L. He was not on any medication known to induce SIAD. He did not have a familial history of NET. Upon admission, his blood pressure was 144/74 mmHg, pulse rate 60 beats per minute, respiratory rate 22 breaths per minute, and temperature 36.4 °C. He was alert with normal skin elasticity. Physical examinations of his heart and lungs were unremarkable. The abdomen was soft, without tenderness, and with normal bowel sounds. There was no edema in the lower limbs.

Laboratory findings on admission showed hyponatremia (128 mmol/L; normal, 136–145), glucose 5.5 (normal 3.6–5.8) mmol/L, blood urea nitrogen (BUN) 1.4 (normal, 2.5–7.1) mmol/L, uric acid (UA) 141 (normal, 140–414) μ mol/L, creatinine 58 (normal, 62–133) μ mol/L. Serum osmolarity was 277 (normal 275–305) mOsm/kg·H₂O, urine osmolarity 465 (normal 600–1000) mOsm/kg·H₂O, urine sodium 82.5 mmol/L, and 24-hour urine sodium 140.25 mmol. Other laboratory findings are presented in Table 1. Repeated measurements of morning cortisol levels were 157.54 and 411.09 (normal 137.95–689.75) nmol/L, respectively. The 24-hour urinary cortisol level was 0.10 (normal 0.09–0.30) μ mol/24 h. Renin and aldosterone levels were decreased. Adrenal computed tomography (CT) findings were normal. A diagnosis of SIAD was made on the basis of laboratory and clinical findings. Normal serum sodium levels were maintained for a week after the oral administration of tolvaptan 7.5 mg. Head magnetic resonance imaging (MRI) did not show any signs of central nervous system disease. Positron emission tomography-CT (PET-CT) using ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) was unremarkable. However, ⁶⁸Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate (DOTATATE) PET-CT displayed a DOTATATE high uptake lesion, measuring approximately 1 cm in diameter in the pancreatic body (Fig. 1),

which was indicative of pNET. Furthermore, non-enhanced and enhanced MRI of the upper abdomen revealed a small nodule in the body of the pancreas, which was consistent with pNET (Fig. 2).

Table 1
Blood lipids and hormone levels during hospitalization of the patient

Category	Date	Reference range	Values
TP (g/L)	July 5, 2019	63–82	62
Alb (g/L)	July 5, 2019	35–50	31
Glo (g/L)	July 5, 2019	20–40	31
TC (mmol/L)	July 6, 2019	3.59–5.17	5.23
TG (mmol/L)	July 6, 2019	0.57–1.71	1.76
HDL-C (mmol/L)	July 6, 2019	0.80–2.20	0.52
LDL-C (mmol/L)	July 6, 2019	1.33–3.36	3.95
FT3 (pmol/L)	July 6, 2019	2.63–5.70	2.48
FT4 (pmol/L)	July 6, 2019	9.01–19.05	11.78
TSH (μIU/mL)	July 6, 2019	0.35–4.94	2.914
8:00am cortisol (nmol/L)	July 6, 2019	137.95-689.75	157.54
ACTH (pmol/L)	July 6, 2019	0.00-10.12	6.07
8:00am cortisol (nmol/L)	July 10, 2019	137.95-689.75	411.09
ACTH (pmol/L)	July 10, 2019	0.00-10.12	7.46
hour urinary cortisol (μmol/24 h)	July 10, 2019	0.09–0.30	0.10
renin(recumbent position, uIU/ml)	July 8, 2019	2.8–39.9	1.7
aldosterone (recumbent, nmol/L)	July 8, 2019	0.08–0.65	< 0.03
renin(recumbent, uIU/ml)	July 15, 2019	2.8–39.9	0.6
aldosterone (recumbent, nmol/L)	July 15, 2019	0.08–0.65	< 0.03
renin(standing, uIU/ml)	July 17, 2019	4.4–46.1	< 0.5
aldosterone (standing, nmol/L)	July 17, 2019	0.08–0.98	0.06
TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ACTH, Adrenocorticotrophic Hormone			

The patient underwent laparoscopic-assisted middle segment pancreatectomy and pancreatic-gastric anastomosis on July 31, 2019. Pathology confirmed pancreatic neuroendocrine tumors (G2, Fig. 3).

Karyokinesis was rare. The Ki-67 index was greater than 3%. Immunohistochemistry showed positivity for CgA, Syn, CD56, CK, somatostatin receptors 2 (SSTR2) and vasopressin (NB110-65214, Neurophysin II/Arg-vasopressin Antibody, Novus Biologicals) (Fig. 4), in the tumor cells, indicating that this was an ADH-producing pNET.

The patient developed heart failure and hyponatremia in the postoperative period, with serum sodium level of 134 mmol/L. Relative adrenal insufficiency was suspected, and intravenous fluids and oral corticosteroids were initiated. The serum sodium level normalized (142 mmol/L) 5 days after 50–100 mg of hydrocortisone treatment daily. The corticosteroid was gradually tapered. Upon the last follow-up 17 months after surgery, the patient is in good condition, taking methylprednisolone 4 mg QOD, and has been free of anorexia or hyponatremia episodes. Owing to the outbreak of coronavirus disease 2019 (COVID-19), the patient has not visited our hospital for recent follow-up.

Discussion And Conclusions

In this case, SIAD due to pNET ectopically producing ADH was clinically suspected and confirmed by pathology, highlighting the adoption of ^{68}Ga -DOTATATE PET-CT and vasopressin immunohistochemical staining in the evaluation of etiology of SIAD.

Hyponatremia is mainly an abnormality of water balance with a relative excess of body water compared to the total sodium content in the body[14]. Sodium ions are the main component of osmotic pressure in the extracellular fluid. The main physiological mechanism of regulating serum osmotic pressure are thirst, as well as ADH released by the pituitary[14]. ADH is a polypeptide synthesized by the supraventricular nucleus and paraventricular nucleus of the hypothalamus and secreted by the posterior pituitary gland. The main reaction of the kidney to vasopressin is the increase in the water permeability of the kidney's collecting tubules. Hyponatremia is usually related to a disorder of ADH that governs water balance[14].

SIAD is one of the important causes of hyponatremia, especially in the elderly. SIAD was firstly described by William B. Schwartz when he found that two patients with bronchogenic carcinoma had severe, unexplained hyponatremia and increased renal sodium excretion[8]. Dr. Schwartz believed that this was due to inappropriate secretion of ADH, which should have been completely stopped in the presence of obvious hyponatremia and decrease in plasma osmotic pressure, so the disease was first named SIADH[8]. Further studies showed inappropriate ADH secretion may occur as follows: 1) ADH synthesized by the supraventricular nucleus and paraventricular nucleus of the hypothalamus and released by the posterior pituitary gland; 2) ectopic ADH secretion; 3) missense mutation in V2 vasopressin receptor (V2R) causing constitutive activation of V2R and the patient's SIAD-like clinical manifestation[15].

The essential features for SIAD diagnosis are as stated below[16]: 1) decreased effective serum osmolarity ($< 275 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$); 2) urine osmolarity $> 100 \text{ mOsm/kg}\cdot\text{H}_2\text{O}$ during hypotonicity; 3) no clinical signs of hypovolemia (no orthostasis, tachycardia, decreased skin turgor, or dry mucous

membranes) or hypervolemia (no edema or ascites); 4) urine sodium > 40 mmol/L with normal diet; 5) normal thyroid and adrenal function; 6) no recent use of diuretics. In our patient, the diagnosis of SIAD was based on the results of laboratory findings combined with clinical signs and symptoms. The patient had normal head MRI findings, thyroid function test results, and glomerular filtration rate. Thus, central nervous system disorders, hypothyroidism, and renal diseases were ruled out from the possible causes of hyponatremia.

As shown above, the ^{68}Ga -DOTATATE PET-CT and immunohistochemistry of vasopressin provided key information in our case. Therefore, it is essential to conduct the vasopressin immunohistochemical staining for patients who could have ADH-producing NETs. ^{68}Ga -DOTATATE PET-CT is a functional imaging modality used to assess well-differentiated NETs[17], which is an effective tool for locating primary tumors in NETs patients with unknown primary tumors[18]. Ga-DOTATATE has the highest affinity for SSTR2, which tends to be most overexpressed in NETs[19]. It has become the preferred imaging method for initial diagnosis, patients inclined to receive peptide receptor radionuclide therapy, and localization of unknown primary tumors[17]. Moreover, a prospective study showed that ^{68}Ga -DOTATATE PET-CT changed the treatment of 33 patients (66%) among 50 patients who underwent this imaging procedure[20]. Thus, for staging and monitoring of NETs, ^{68}Ga -DOTATATE PET-CT should be considered as it is usually related to changes in treatment[20].

As far as we know, there is only one case of the ADH-producing pNET reported so far. Omalkhaire M. Alshaikh et al.[13] reported on a 52-year-old man presenting with intermittent abdominal pain. Initial findings showed a suspicious mass in the hilum of the spleen. Further, CT of the abdomen showed that the pancreas/spleen mass had increased to 7.6 cm. At that point, the blood glucose level was 6.5 mmol/L and serum sodium level was 132 mmol/L. Core biopsy confirmed a NET originating from the pancreas. The pathology of the NET was positive for pancreatic polypeptide and insulin. Four years later he developed hypoglycemia accompanied by inappropriately elevated proinsulin and insulin levels. Laboratory findings showed that serum osmolality was 250 mOsm/kg and urine osmolality was 140 mOsm/kg, which were consistent with SIAD. The autopsy was diffusely positive for vasopressin which was not observed in the original biopsy. In this patient, the ADH-producing feature of the pNET was confirmed by the autopsy, when he died of the disease nearly 9 years after the initial diagnosis. This suggests that early diagnosis of the cause resulting in hyponatremia is difficult in clinical practice.

Under most circumstances, the monism theory could help us to more accurately diagnose disease. However, hyponatremia is complicated, especially in elderly patients. In this patient, the ectopic production of ADH by the pNET, relative adrenal insufficiency, and the lack of aldosterone together resulted in hyponatremia.

The key factors that determine the management of SIAD are the severity, duration, and symptoms of hyponatremia[16]. Rapid treatment is suggested for patients with severe hyponatremia, as they can develop symptoms within 48 h[21]. The goal of the treatment, which includes 3% saline and furosemide, is to increase the serum sodium level by 1–2 mmol/L per hour. However, chronic hyponatremia should

not be corrected by more than 12 mmol/L over a period of 24 h; otherwise, it may lead to osmotic demyelination syndrome[16]. Fluid restriction is essential, regardless of whether hyponatremia is severe or chronic. A vasopressin-receptor antagonist, such as tolvaptan and conivaptan, is more recently used for the treatment of SIAD[22, 23]. For the elderly, low-dose tolvaptan (7.5 mg/day) for the treatment of SIAD was effective and safe[24]. If necessary, the dosage of tolvaptan can be increased to 15–30 mg/d.

There are several limitations to our case report. First, we did not measure the ADH level due to the lack of routine ADH serum analysis in clinical practice. Second, the assessment of adrenal function was insufficient before surgery, not involving tests such as the circadian adrenocortical rhythm and the ACTH stimulation. Third, we did not receive data on the patient's detailed serum sodium levels after discharge. Due to the influence of COVID-19 on the hospital environments as well as his advanced age, he was unable to visit our department, making follow-up visits difficult. However, we have learned that he is in good condition through telephone reports.

In conclusion, we reported a case with SIAD related to pNETs. The pNET was suggested by ^{68}Ga -DOTATATE PET-CT and confirmed by immunohistochemistry of vasopressin. This is a pNET ectopically producing ADH and leading to SIAD. Early diagnosis of the cause of hyponatremia is difficult, so the ADH-producing features of pNETs may go undetected in clinical practice. Our case highlights pNETs are possibly etiology of the hyponatremia. A systematic prospective study of SIAD should be conducted to clarify the true prevalence of this phenomenon.

Abbreviations

PNETs: pancreatic neuroendocrine tumors; SIAD: syndrome of inappropriate antidiuresis; SSTR2: somatostatin receptors 2; SIADH: inappropriate secretion of antidiuretic hormone; ADH: antidiuretic hormone; ACTH: adrenocorticotrophic hormone; BUN: blood urea nitrogen; MR: magnetic resonance; CT: computed tomography; PET-CT: Positron emission tomography-CT; ^{18}F -FDG: ^{18}F -fluorodeoxyglucose; DOTATATE: tetraazacyclododecanetetraacetic acid–DPhe1-Tyr3-octreotate; V2R: V2 vasopressin receptor

Declarations

Ethics approval and consent to participate

This study was approved by the medical research ethics committee of Tianjin Medical University General Hospital before study participation.

Consent for publication

Written informed consent was obtained from the patient for publication purposes.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JL obtained the clinical findings, reviewed the literature and prepared the figures. XZ wrote the initial manuscript and prepared the figures. QH obtained the clinical findings, reviewed and approved the manuscript. WF performed the immunohistochemical study of SSTR2 and vasopressin. ZW got the patient's history and built the timeline. HY performed the 18F-FDG PET-CT and 68Ga-DOTATATE PET-CT for the patients. QC was responsible for the diagnosis of the PET-CT. NL operated on the patient. DX made the pathological diagnosis for the patients. JC and ML obtained the clinical findings, reviewed and approved the manuscript, the figures, the diagnosis and supervised the manuscript.

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Availability of data and materials

The datasets used and/or analysis during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

Non-enhanced and enhanced magnetic resonance (MR) imaging of upper abdomen shows a small nodule in the body of the pancreas consistent with pNET

Figure 2

68Ga-DOTATATE PET-CT shows a DOTATATE high uptake lesion approximately 1 cm in diameter in the pancreatic body

Figure 3
 Pathology of the pancreatic neuroendocrine tumor (pNET)

Figure 4
 Positivity for SSTR2 (A) and vasopressin(B) in surgical specimen of tumor.

Supplementary Files

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