Pancreatic Vasoactive Intestinal Peptide Polypeptide-secreting Tumor With a Good Prognosis: a Case Report and Review of the Literature

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Case Report

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Abstract

Background: Pancreatic vasoactive intestinal polypeptide secreting tumor is a rare pancreatic endocrine tumor, which has high rate of misdiagnosis because of its rarity. We are always seeking for some novel treatment methods, constantly summarizing experience and lessons, and improving the diagnosis.

Case presentation: Here we report the case, a 48-year-old female patient was admitted to the hospital for 2 years with recurrent diarrhea. The computerized tomography scan of the upper abdomen demonstrated a 27 mm×31 mm space-occupying lesion in the tail of the pancreas. Electrolyte results suggest hypokalemia and elevated serum vasoactive intestinal peptide levels. After evaluating the condition, consider surgical removal of the pancreatic tail and active symptomatic treatment. Postoperative pathological biopsy was diagnosed as pancreatic neuroendocrine tumor, serum potassium recovered, serum VIP value decreased, and diarrhea stopped. After 8 years of follow-up, all indicators were normal and the prognosis was good.

Conclusions: We hope to draw the attention of clinicians from this situation in order to increase the correct rate of disease diagnosis and improve the prognosis.

Background

Vasoactive intestinal polypeptide-secreting tumor (VIPoma) is a neuroendocrine tumor that autonomously secretes vasoactive intestinal peptide (VIP) to induce a series of clinical features, including watery diarrhea, hypokalemia and achlorhydria, with an incidence of approximately one in ten million ¹. VIPoma originates from pancreatic endocrine cells, 80% of which are more common in the pancreas, especially in the tail. Approximately 20% of VIPoma occur outside the pancreas, such as the intestine, esophagus and sympathetic ganglia. Most of them have metastasized at the time of diagnosis and have a poor prognosis ². However, here, we report a retrospective case over 8 years in which a VIPoma patient was completely cured by surgery with a good prognosis and summarized the characteristics of VIPoma and effective therapy to improve clinicians' understanding of the disease.

Case Presentation

A 48-year-old female patient was admitted to our hospital in 2013 for "repeated diarrhea for 1 year". The patient developed watery diarrhea, yellow and loose stools, 3 to 4 times every day, with little volume, no abdominal pain and bloating, but intermittent attacks for 2 years. She was diagnosed with "chronic gastroenteritis" in many hospitals and improved after treatment with symptomatic supportive treatment. During the period, her condition was intermittent, and the frequency of diarrhea became 10 times every day with large-volume diarrhea (over 1 L/day), without mucus, pus and blood in the stool, accompanied by nausea, vomiting, acid reflux, no hematemesis, and melena. She was admitted with "chronic colitis" to our hospital and had lost 5 kg in weight since the onset of the disease. Extensive serological examination showed that blood serum potassium was low at 2.34 mmol/L, but serum VIP was high at 260.6 pg/ml

(Fig. 1). Hormone levels, including glucagon and insulin, and tumor indicators such as CA19-9 and CA125 were normal (Table 1). Upper abdominal computerized tomography (CT) and enhanced CT showed that a mass of 27 mm×31 mm was detected in the tail of the pancreas adjacent to the spleen and stomach, but no clear evidence of local infiltration (Fig. 2) and no obvious mucosal lesions were found by gastroscopy or colonoscopy. Endoscopic ultrasonography (EUS) showed that a circular hypoechoic area of 2.55 cm×3.32 cm was visible in the tail of the pancreas with clear boundaries, and no abnormalities of the head and body of the pancreas or pancreatic duct were observed. The distribution of blood vessels was clear, and a stripe blood flow signal was detected in the low echo area (Fig. 3). Based on the clinical symptoms as well as CT and EUS images, pancreatic vasoactive intestinal peptide tumor was highly suspected. Therefore, the somatostatin analog octreotide 0.1 mg was injected subcutaneously every 12 hours for diagnostic treatment, resulting in diarrhea that was immediately and significantly reduced. However, watery diarrhea recurred after octreotide was stopped. At the beginning of 2013, pancreatic tail resection and splenectomy were performed, and a pancreatic lesion 5 cm in diameter was detected on the tail of the pancreas without adherence to the surrounding tissues, as well as no lymph node metastasis. The final pathological diagnosis showed well-differentiated endocrine pancreatic tumors approximately 2 cm in size. Immunohistochemistry (IHC) staining indicated that CK8, CD56, Syn, CgA and VIP were positive, and Ki67(+) < 1% (Fig. 4). This patient was followed up for 8 years, and she had no diarrhea or other special discomfort and no recurrence, even without any somatostatin analog treatment. The VIP value decreased from 260.6 pg/ml before treatment to 131.7 pg/mL after the operation and was kept at stable and normal levels (36.625 pg/mL) for 8 years. The serum potassium level was increased from 2.34 mmol/L before the operation to 3.67 mmol/L after treatment and remained stable at normal levels for 8 years. Upper abdominal CT showed that the tail of the pancreas was absent, but no obvious abnormality and no metastasis were observed 8 years after the operation.

Table 1
Summary of Laboratory Data.

<Hematology>			<Blood chemistry>		<Coagulation profile>	
WBC	10.27*10 ⁹ /L	↑	TP	58.20 g/L	↓	PT% 110.00%
NEUTRO	79.00%		Alb	35.90 g/L		<Hormone profile>
EOSINO	1.21%		AST	28.00 U/L		Insulin 7.00 µIU/mL
RBC	4.34*10 ¹² /L		ALT	29.00 U/L		(2.60–24.90 µIU/mL)
Hb	137.00 g/L		AST/ALT	0.97		Gastrin 27.00 ng/L
Ht	26.00%		T-Bil	5.40 µmol/L		(15.00-105.00 ng/L)
Plt	344*10 ⁹ /L	↑	Cre	52.00 µmol/L		VIP 260.60 pg/mL ↑
<Tumor maker>			BUN	4.77 mmol/L		(2.00-36.80 pg/mL)
CEA	0.57 ng/mL		Na ⁺	136.40 mmol/L		
CA19-9	4.45 U/mL		K ⁺	2.34 mmol/L	↓	
AFP	0.35 ng/mL		Cl ⁻	107.40 mmol/L		
NSE	10.80 ng/mL		Ca ²⁺	2.34 mmol/L		

Alb: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CEA: Carcinoembryonic antigen; Cre: Creatinine; EOSINO: Eosinophils; Hb: Hemoglobin; Ht: Hematocrit; NEUTRO: Neutrophils; NSE: Neuron specific enolase; Plt: Platelets; PT: Prothrombin time; T-Bil: Total bilirubin; TP: Total protein; VIP: Vasoactive intestinal peptide.

Discussion And Conclusions

Pancreatic neuroendocrine tumors (PNETs) have long fascinated clinicians and investigators despite their relative rarity. Their clinical presentation varies depending on whether the tumor is functional or not³ and according to the specific hormonal syndrome produced. VIPoma constitutes a rare functional neuroendocrine neoplasm that most often originates from pancreatic islet cells and presents as a sporadic, solitary neoplasm of the pancreas, as well as ectopically expresses VIP, leading to large-volume diarrhea (90–100%; 100% > 700 mL/day, 70–80% > 3 L/day), electrolyte disturbances (notably hypokalemia, 70–100%), dehydration (45–95%), hyperglycemia (20–50%), hypercalcemia (25–50%), hypochlorhydria (35–76%), and flushing (15–30%)^{1,3,4}. Large-volume diarrhea often results in dehydration without an osmolar gap because it is secretory in nature^{1,3,4}. The diagnosis is confirmed by the presence of large volume secretory diarrhea with an increased serum VIP level together with imaging evidence. However, even in the absence of a tumor that can be imaged, an increased serum VIP level in

the presence of documented secretory diarrhea is highly suggestive of VIPoma^{1,4}. VIP, a 28-amino-acid polypeptide whose function is similar to that of pituitary adenylate cyclase activating peptide (PACAP)⁵, which is mostly found in neurons of the gastrointestinal tract, is secreted by pancreatic D1 cells and acts as a neurotransmitter or neuromodulator⁶, it can influence surrounding cells or neurons in a paracrine manner⁷, thereby inhibiting gastric acid secretion. After VIP receptor overexpression, vascular smooth muscle relaxes, including some nonvascular muscle vessels, which can also relax peripheral blood vessels, result in lower blood pressure, flush the face, and manifest as hypercalcemia in some patients. Furthermore, the high expression of VIP receptors can promote the continuous proliferation of tumor cells and provide an impetus for the progression of VIPoma⁸. VIP binds to intestinal epithelial receptors, which belong to the family of G protein-coupled receptors that activate cellular adenylate cyclase (CAMP) through the G protein-coupled pathway and increase the expression of CAMP. At the same time, VIP can cause a large amount of water and electrolyte secretion in the intestine (mostly potassium ions), which can explain the clinical symptoms of watery diarrhea and hypokalemia. Additionally, VIP may induce hypokalemia by inducing increased aldosterone⁹. Notably, because the secretion of VIP is intermittent, the level of VIP during the intermittent period of diarrhea is usually normal, and false negative results are prone to occur. Therefore, serological determination should be repeated during diagnosis to improve the overall diagnosis rate of the disease. CT and B-ultrasound are the most common imaging examinations. Because VIPoma is a neuroendocrine tumor of the pancreas, it is highly vascular; therefore, plain CT scans and enhanced imaging are extremely sensitive in its diagnosis. For pancreatic tumors with a diameter > 3 cm, its sensitivity can be as high as 92%, but for tumors < 1 cm in size, the sensitivity of CT is less than 10%¹⁰. B-Ultrasound is not sensitive to pancreatic tumors with a diameter of < 2 cm. EUS can detect 91% of CT-negative PNETs, so the sequential detection of CT and EUS can detect most PNETs¹¹. Furthermore, somatostatin receptor imaging has obvious advantages in the diagnosis of microscopic, occult and metastatic lesions. A total of 80%-90% of vasoactive intestinal peptide tumors express somatostatin receptors, so it is effective for most patients. The detection of poorly differentiated tumors is more likely with the use of 18F-FDG-PET-CT and 68Ga-SSA-PET-CT. The latter two methods are recommended more for the clinical staging of PNET¹². In summary, the diagnostic inclusion criteria of VIPoma are mainly based on the typical symptoms of the disease, high levels of VIP in plasma, imaging examinations and the final pathological diagnosis. In terms of treatment, radical surgical resection is currently the most suitable treatment and the only modality that offers the possibility of cure¹³, which was well presented in this case. Additionally, the use of somatostatin and its analogs (SSAs) can significantly improve the clinical symptoms of 80–90% of patients¹⁴, so SSAs have become the first choice for the treatment of VIPoma¹⁵. In addition, the use of new drugs, such as sunitinib and the mTOR inhibitor everolimus, can increase patient progression-free survival and overall survival rates to obviously higher levels than those of the placebo group¹⁶. In the United States, sunitinib has been approved for the treatment of advanced, well-differentiated pancreatic neuroendocrine tumors, including VIPoma¹⁷. Such tyrosine kinase inhibitors can not only control the secretion of VIP but also curb the growth of tumors and provide a new direction for clinical VIPoma treatment¹⁸. Because most VIPoma patients have watery diarrhea and the diarrhea is not improved after fasting, it is accompanied by hypokalemia and low gastric

acid symptoms. Therefore, in addition to combining the above symptoms in the diagnosis of the disease, it is still necessary to consider there are other causes of the severe diarrhea symptoms, such as carcinoid syndrome, colitis, short bowel syndrome, bacterial diarrhea (*Vibrio cholerae*, enterotoxigenic *Escherichia coli*), etc.⁸. Currently, polypeptide receptor radionuclide therapy (PRRT) has become the most effective second-line treatment to control refractory WHDA syndrome, and combined with SSAs, it can prevent symptoms such as diarrhea, flushing, and hormonal crisis after PRRT¹³. In addition, because this neuroendocrine tumor tends to be insidious and slow-growing, the prognosis of patients can be predicted by evaluating tumor metastasis, size, depth, and histological grade¹⁹. In this case, the immunohistochemical Ki-67 proliferation index was less than 1%, and the surrounding tissues had no infiltration or metastasis, so the patient was completely cured after surgery with long-term follow-up.

VIPoma is an uncommon neuroendocrine tumor of the pancreas, the clinical symptoms are dominated by WHDA syndrome, and most patients seek medical treatment for recurrent watery diarrhea. Although its concept is clearly defined, it is clinically similar to chronic gastroenteritis, and misdiagnosis is still a phenomenon that cannot be ignored. We reviewed the characteristics of VIPoma disease through a brief analysis of the medical records. On the one hand, this review aims to improve people's awareness of early diagnosis and treatment, which can significantly improve the prognosis of the disease. On the other hand, it will consolidate doctors' understanding of the disease, and then doctors will be able to diagnose PNETS early and accurately so that patients have a greater probability of fully recovering.

Abbreviations

CAMP: Cellular adenylate cyclase

CDFI: Color Doppler Flow Imaging

CT: Computerized tomography

EUS: Endoscopic ultrasonography

IHC: Immunohistochemistry

PACAP: Pituitary adenylate cyclase activating peptide

PNETs: Pancreatic neuroendocrine tumors

PRRT: Polypeptide receptor radionuclide therapy

SSAs: Somatostatin and its analogues

VIPoma: Vasoactive intestinal polypeptide-secreting tumor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written consent and publicly issued consent have been obtained from the patient in this case.

Availability of data and materials

All information about the patient come from Department of Gastroenterology, Affiliated Hospital of Zunyi Medical University. The data generated or analyzed during this study are included in this published article.

Competing interests

The authors have no conflicts of interest to declare.

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Author contributions

X.M.L & Y.Y.Z wrote the manuscript; H.C.W & X.M.L diagnosed and performed the treatment. H.C.W & B.G.T revised the article; Q.Z.Z, K.W & X.L.W contributed to the imaging and histopathology; all other authors approved the final manuscript to be published.

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Figures

Figure 1

Blood examination of this case. Serum VIP (A) and potassium (B) before and after operation, as well as 8 years followed up.

Figure 2

Images of upper abdominal CT. An uneven density mass of about 27 mm × 31 mm is seen in the back of the pancreas tail, which is unevenly enhanced on enhanced scanning in 2013 before operation (A-C). The tail of the pancreas was absent, the pancreatic duct was not dilated and no other metastasis was observed in the year of 2020. Hemangiomas in the lateral segment of the left liver with multiple small cysts were still observed after 8 years later (D-F).

Figure 3

Images of EUS. EUS showed that a 2.6 cm × 3.3 cm circular hypoechoic area was detected in the tail of the pancreas, with clear boundaries and uniform internal echo. There was no abnormality in the head and body of the pancreas, and the pancreatic duct was not dilated. The distribution of blood vessels was clear, and there were spots of blood in the CDFI (Color Doppler Flow Imaging) hypoechoic area stream signal.

Figure 4

H&E and IHC analysis. A pancreatic well-differentiated endocrine tumor was detected. Tumor cells are clustered into clusters. The tumor cells are uniform in size, with large and deeply stained nuclei, and mitotic images can be seen in few places under different magnifications (A-C). IHC experiment showed that the tumor lesions were positive in CgA (D), Syn (E), CD56 (F), Ki67 (+) < 1% and VIP (+).

Supplementary Files

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- [7.30CAREchecklistEnglish2013.pdf](#)