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CASE REPORT

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Challenging VIPoma Case Treated with Sunitinib: A Life-Saving Therapeutic Experience

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ABSTRACT VIPoma syndrome, a rare neuroendocrine tumor characterized by watery diarrhea, hypokalemia, and achlorhydria, poses a significant clinical challenge due to its life-threatening symptoms and limited treatment options. We present the case of a 44-year-old female with VIPoma, initially unresponsive to standard therapies such as somatostatin analogs and chemotherapy. Despite a challenging treatment course, including loperamide, glucocorticoids, metoclopramide, carboplatin-etoposide chemotherapy the patient's symptoms persisted. The turning point came with the initiation of sunitinib therapy, leading to a rapid and complete resolution of refractory diarrhea, renal insufficiency, hypotension, and electrolyte imbalances. This case underscores the importance of considering sunitinib as a life-saving treatment in VIPoma patients with resistant symptoms. As VIPoma is a rare entity, collaborative multi-center studies are crucial for enhancing our understanding of its natural course, treatment strategies, and prognosis.

Keywords: VIPoma; neuroendocrine tumors; pancreas; sunitinib

VIPomas are rare, functional neuroendocrine tumors (NET) that are usually located in the pancreas and lead to a clinical syndrome known as Verner-Morrison syndrome. Verner-Morrison syndrome is characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA) due to the excessive release of vasoactive intestinal peptides (VIPs).[1] VIPoma symptoms are difficult to manage and may have life-threatening consequences independent of the oncological status. Surgical resection is crucial in the treatment of primary tumors, and somatostatin analogs are used as the main treatment for symptom control when surgical resection is not possible.[2] VIP is a polypeptide of 28 amino acids that induces adenylate cyclase and cyclic adenosine monophosphate production. Pathophysiologically, VIPomas are characterized by an excessive and irregular release of VIP, which leads to increased fluid and electrolyte secretion into the intestinal lumen, resulting in secretory diarrhea and hypokalemia.[3] Cytotoxic chemotherapy, peptide receptor radionuclide therapy, sunitinib, and everolimus may be considered for treatment in cases that cannot be controlled using somatostatin analogs. In a study that compared the effects of sunitinib, a tyrosine kinase inhibitor, with those of placebo treatment, increased progression-free survival and overall survival rates were noted with the use of sunitinib.[4] VIPoma has a low incidence in the population and, therefore, no treatment standards are reported in the literature comprising both prospective and evidence-based studies. The objective of VIPoma treatment is not limited to tumor growth control and includes the eradication of life-threatening symptoms as well.

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CASE REPORT

A 44-year-old female patient presented to the emergency department with a history of epigastric and left upper quadrant pain, weakness, fatigue, and diarrhea for the past 3 months. The diarrhea was not relieved by fasting and occurred 10-12 times a day, with a watery-clear color and no traces of blood or mucus. The patient had also experienced a loss of 8 kg in weight in the past six months.

The patient had undergone total thyroidectomy 8 years ago for the treatment of compressive symptoms related to goiter. Consequently, the patient was using levothyroxine 75 mcg/day. She had no history of smoking or alcohol consumption.

A physical examination of the patient at the emergency department revealed dry skin, reduced skin turgor, prolonged capillary refill time, normal breath sounds, tenderness in the left upper abdominal quadrant, and no guarding or rebound tenderness. Rectal examination revealed stool staining. Vital signs were also analyzed, and tachycardia (pulse rate 105 bpm) and hypotension (95/65 mmHg) were noted.

Laboratory findings revealed the following: sodium 128 mmol/L (normal range: 135-145 mmol/L), potassium 2.4 mmol/L (normal range: 3.4-5.5 mmol/L), and arterial blood gas with a normal anion gap metabolic acidosis (pH: 7.34, HCO_3: 28 mmol/L, anion gap: 8 meq/L). Complete blood count results and other parameters were within normal limits. The normal anion gap metabolic acidosis revealed in the arterial blood gas analysis was attributed to the loss of bicarbonate due to diarrhea, which was considered the underlying cause of hypokalemia and hyponatremia in the patient. Considering these findings, an etiological investigation was conducted. Several potential diseases, such as viral or bacterial infections and inflammatory bowel disease were ruled out in this investigation.

The subsequent abdominal ultrasound revealed a suspicious solid mass in the liver, which prompted further evaluation through contrast-enhanced abdominal computed tomography (CT). A 40x30 mm malignant mass in the pancreatic head, along with multiple metastatic lesions in the liver's right lobe (largest 25 mm) and a 15x13 mm lesion close to the portal hilus, were detected (Figure 1). The patient received hydration and potassium replacement in the emergency department followed by discharge. The patient was followed up in the gastroenterology outpatient clinic after the normalization of vital signs.

Contrast-enhanced abdominal magnetic resonance imaging performed at the gastroenterology clinic revealed a 30x26 mm mass in the pancreatic head, nodular lesions in the pancreatic tail (largest 20 mm), and liver metastases (Figure 2). The subsequent liver biopsy revealed neuroendocrine neoplasia consistent with well-differentiated Grade 3, although the differential diagnosis between neuroendocrine carcinoma and well-differentiated Grade 3 NET remained non-definitive. The Ga-68 tetra-azacyclo-dodecane-

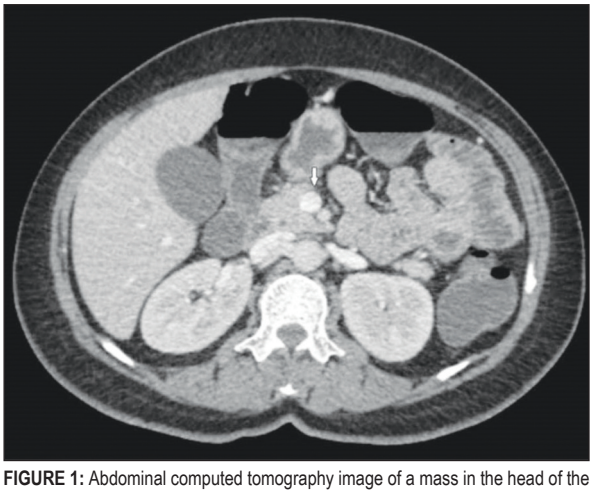

FIGURE 1: Abdominal computed tomography image of a mass in the head of the pancreas; axial section.

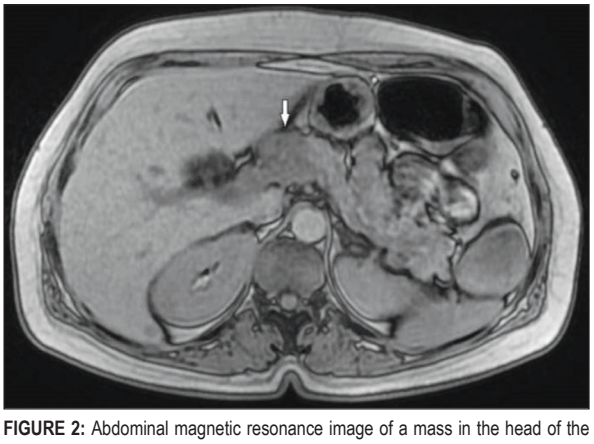

FIGURE 2: Abdominal magnetic resonance image of a mass in the head of the pancreas; axial section.

tetra-acetic acid-DPhe1-Tyr3-octreotate positron emission tomography (PET)/CT scan confirmed a primary tumor in the pancreatic tail and the presence of metastatic lesions in the left para-aortic region and the left sacral bone (Figure 3). The patient was, therefore, referred to the medical oncology clinic, although the patient did not visit the clinic for follow-up.

A month later, the patient presented to the emergency department again with increased diarrhea (10-12 times/day) and decreased oral intake. The patient's blood pressure at admission to the department was 70/40 mmHg. The laboratory findings revealed the following: creatinine 5.1 mg/dL, sodium 120 mmol/L, potassium 2.45 mmol/L, calcium 13.6 mg/dL, pH 7.34, and HCO_3 10 mmol/L. The patient was admitted to the nephrology ward due to acute kidney injury, where she received hydration, IV potassium, and bicarbonate replacement. After the resolution of acute kidney injury and electrolyte abnormalities, the patient was transferred to the medical oncology department.

The F18-FDG PET-CT scan of the patient revealed irregular lesions in the pancreatic neck (SUVmax: 9.3) and tail (SUVmax: 5.8), along with multiple liver metastases (Figure 4). A diagnosis of neuroendocrine carcinoma was established based on the high Ki67 index (42.5%) and tumor size. The patient was administered carboplatin-etoposide chemotherapy and octreotide treatment. Another liver biopsy was performed due to the non-definitive distinction in the previous biopsy. The patient's symptoms improved, and she was discharged with the

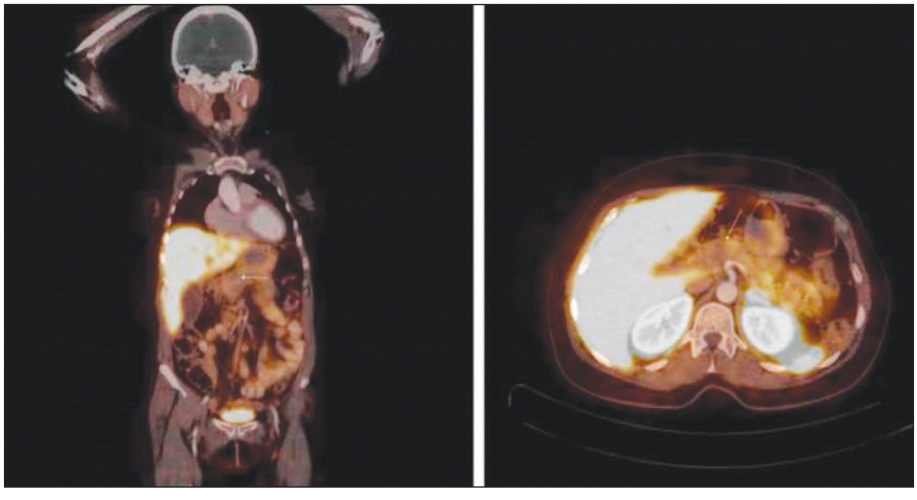

FIGURE 3: The GA-68 DOTATATE positron emission tomography-computed tomography scan results revealing a mass in the pancreas; coronal and transverse sections.
DOTATATE: Tetra-azacyclo-dodecane-tetra-acetic acid-DPhe1-Tyr3-octreotate.

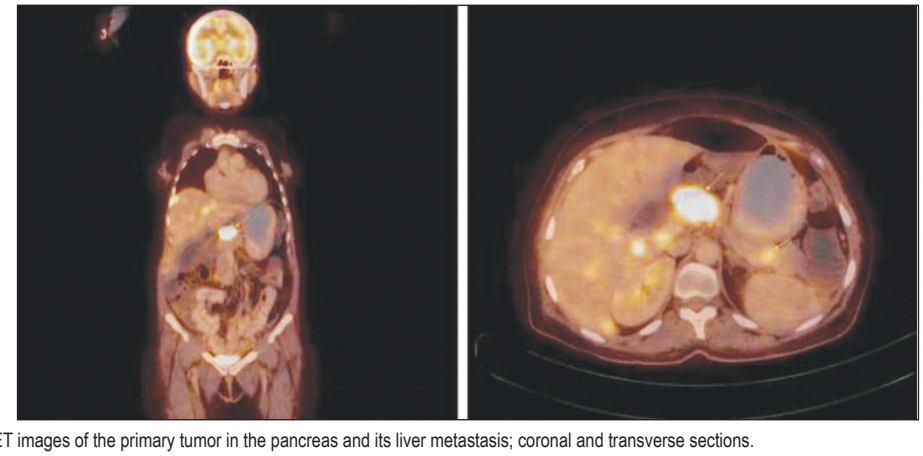

FIGURE 4: FDG-PET images of the primary tumor in the pancreas and its liver metastasis; coronal and transverse sections.
FDG-PET: [^{18}F] fludeoxyglucose-positron emission tomography.

prescription of loperamide until the 2nd cycle of chemotherapy.

On the 12th day of the 1st chemotherapy cycle, the patient returned to the hospital with worsening diarrhea and weakness. The patient was hypotensive and hypokalemic, and presented with acute kidney failure and metabolic acidosis. She was, therefore, admitted to the nephrology intensive care unit. After stabilization, she was again transferred to the medical oncology ward, where the 2nd cycle of carboplatin-etoposide chemotherapy was begun. The follow-up PET-CT revealed stabilized disease, although the diarrhea persisted. Despite several days of administering fluids and electrolytes along with bicarbonate replacements and symptomatic and palliative treatments such as octreotide, loperamide, steroids, and cytotoxic chemotherapy, the patient continued to present with resistant diarrhea, renal insufficiency, and hypotension symptoms. Even after switching from octreotide to lanreotide, no improvement was noted in the symptoms. Therefore, another liver biopsy was performed, based on which the patient was diagnosed with a well-differentiated Grade 2 NET with metastasis (Figure 5). The diagnosis of VIPoma was confirmed based on the serum VIP level of 1,258 pg/mL in the investigated sample (normal range <75 pg/mL). VIPoma had been initially suspected due to the clinical symptoms of the patient. The treatment plan was revised accordingly, and sunitinib administration was begun at a daily dose of 37.5 mg. A rapid improvement in clinical symptoms was noted, in contrast to the unsuccessful outcomes noted with previously applied treatment options. Lanreotide administration subcutaneously at a dose of 120 mg per month was continued.

In the 26th month, the patient continues to visit the outpatient clinic for follow-ups, with stable disease. The patient provided informed consent for using their data in the present case report.

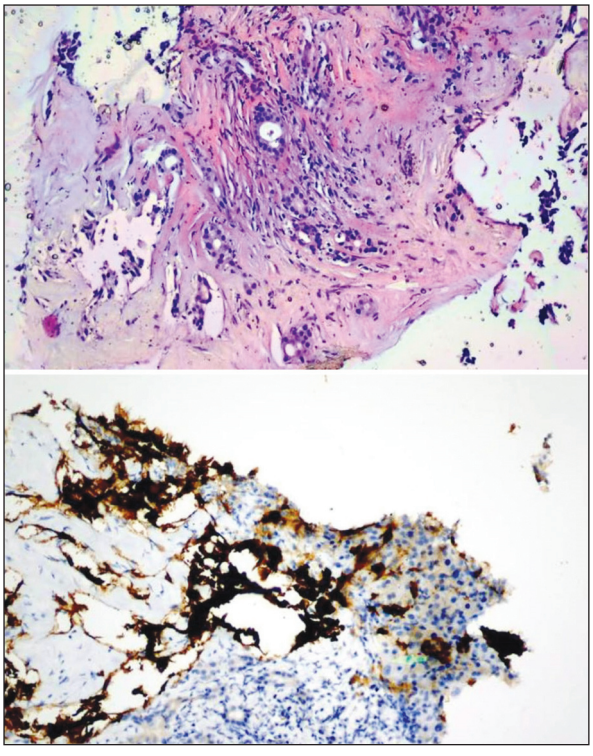

FIGURE 5: A) H&E staining revealing the neuroendocrine tumor metastasis to the liver; 20x magnification; **B)** Synaptophysin staining revealing the neuroendocrine tumor metastasis to the liver; 20x magnification.

DISCUSSION

Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors that originate from neuroendocrine cells that express both neural and endocrine markers. PNETs are rare and gradually-growing tumors, although aggressive PNETs with local invasion and rapid metastasis have also been reported. PNETs constitute 1%-2% of all pancreatic tumors, with an annual incidence of ≤1 per 100,000 cases.[5] Recently, an increase has been noted in the diagnosis of asymptomatic PNETs, which is attributed to cross-sectional imaging and endoscopy for other reasons.[6] These tumors may occur at any age, although occurring most commonly in the fourth to sixth decades of life.

The classification of PNETs established by the World Health Organization was revised in 2017. According to this classification, well-differentiated tumors with low proliferative activity are termed NETs, while those with poor differentiation and high proliferative activity are termed neuroendocrine carcinomas.[7]

VIPomas are among the rare functional PNETs and are detected in over 95% of cases of tumors developed within the pancreas. However, other tumors, including lung cancer, colorectal cancer, ganglioneu-

roblastoma, and medullary thyroid carcinoma, are also reported to secrete VIP. A VIP is a peptide hormone composed of 28 amino acids. It is released from parasympathetic nerve fibers and ganglion cells. VIPomas were first described by Verner and Morrison in 1958.[8] VIP secretion leads to WDHA, and the resulting syndrome is known as Verner-Morrison syndrome or WDHA syndrome.

In the case described in the present report, the patient was experiencing chronic WDHA due to VIP secretion from the PNET. VIP inhibits gastric acid secretion, which may lead to achlorhydria. In addition, VIP stimulates the secretion of potassium and bicarbonate in the intestines, leading to hypokalemia and metabolic acidosis. VIP also promotes intestinal fluid secretion, leading to watery diarrhea.[9] These findings are consistent with the clinical symptoms and laboratory results noted for the patient discussed in the present case report. Elevated levels exceeding 75 pg/mL are indicative of a VIPoma, although typically, concentrations reach 160-250 pmol/L or even higher.[3] The VIP concentration in our patient was 1,258 pg/mL, consistent with the levels in VIPoma syndrome. It is essential to differentiate VIPomas from other causes of watery diarrhea, such as infectious causes, inflammatory bowel disease, and other NETs that may secrete, although rarely, VIP. In the present case, other potential causes of diarrhea were excluded based on the results of stool examination and laboratory tests.

VIPomas are typically diagnosed at an advanced stage due to the non-specific nature of symptoms, and at the time of diagnosis, approximately 60%-80% of VIPomas have metastasized.[4] In the present case, a primary tumor was detected in the pancreatic tail, with multiple metastases to the liver and other regions.

In patients with VIPoma syndrome, control of diarrhea and dehydration is the primary objective of treatment. In cases with mild symptoms, fluid and electrolyte replacement may be sufficient. However, in cases with severe symptoms, somatostatin analogs, including octreotide and lanreotide, are the mainstream treatment option. Chemotherapy and targeted therapies may be considered in cases with resistant or metastatic disease. Somatostatin analogs inhibit the secretion of multiple hormones, including VIP, and exert anti-proliferative effects on NETs. The use of somatostatin analogs may provide symptom relief and lead to reduced tumor size in 67% of patients.[4] In the present case, despite the initial use of octreotide followed by administration of the somatostatin analog lanreotide, symptom control could not be achieved. Dehydration, acute renal failure, hypotension, and electrolyte imbalance continued, threatening the life of the patient. The patient was, therefore, subjected to carboplatin-etoposide chemotherapy, although without success. The desired treatment objectives were not achieved. The alteration in the pathological diagnosis during the treatment process prompted the reconfiguration of the patient's treatment, and sunitinib therapy was initiated. Sunitinib is preferred particularly for cases of well-differentiated pancreatic NETs that are unresectable, locally advanced, or metastatic. According to a Phase III study reported by Raymond et al. in 2011, which involved 171 patients, sunitinib administration resulted in better progression-free survival compared to placebo (11.4 versus 5.5 months).[10] Sunitinib exhibits both antitumor and antisecretory effects in patients with VIPomas. It is an orally administered multiple tyrosine kinase inhibitor targeting platelet-derived growth factor receptor, vascular endothelial growth factor, stem cell factor receptor, and rearranged during transfection, resulting in the inhibition of tumor proliferation and angiogenesis.[11] In the study by de Mestier et al., two patients with pancreatic NET exhibited rapid resolution of refractory diarrhea under sunitinib treatment during follow-up, and recurrence was observed after the discontinuation of this treatment.[12] The patient discussed in the present report also experienced rapid improvement in symptoms, including refractory diarrhea, renal insufficiency, hypotension, and electrolyte disturbances, under sunitinib treatment. Sunitinib is, therefore, recommended as a life-saving treatment for patients presenting with life-threatening symptoms due to VIPoma. Considering the rarity of this disease, multicenter studies are warranted to obtain further comprehensive information on the natural course of VIPoma syndrome, the potentially effective treatment options, and the prognosis.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melikşah Yüksel, Erkan Kayıkçıoğlu;* ***Design:*** *Melikşah Yüksel, Erkan Kayıkçıoğlu;* ***Control/Supervision:*** *Erkan Kayıkçıoğlu;* ***Data Collection and/or Processing:*** *Melikşah Yüksel;* ***Analysis and/or Interpretation:*** *Melikşah Yüksel, Erkan Kayıkçıoğlu;* ***Literature Review:*** *Erkan Kayıkçıoğlu, Melikşah Yüksel;* ***Writing the Article:*** *Melikşah Yüksel;* ***Critical Review:*** *Erkan Kayıkçıoğlu, Melikşah Yüksel;* ***References and Fundings:*** *Erkan Kayıkçıoğlu;* ***Materials:*** *Sevim Süreyya Şengül.*

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