VIPoma: An Unusual Cause of Chronic Diarrhea

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ABSTRACT

Chronic diarrhea is a significant challenge in clinical practice because of its high prevalence and various causes. Comprehensive clinical assessment and stepwise laboratory approach are crucial for an accurate diagnosis. This report presents a case of an adult woman who experienced chronic watery diarrhea, complicated by renal impairment and multiple electrolyte imbalances, including hypokalemia, hypophosphatemia, and metabolic acidosis. The diagnosis of a vasoactive intestinal polypeptide-secreting tumor (VIPoma) with liver metastases was confirmed by elevated serum levels of a vasoactive intestinal polypeptide (VIP) and imaging findings of a pancreatic mass with multiple hepatic lesions. Preoperative management, including fluid rehydration, electrolyte correction, and somatostatin analog therapy, significantly improved her clinical symptoms. Subsequent surgical tumor removal and radiofrequency ablation of the hepatic lesions resulted in complete resolution of symptoms and normalized VIP levels. This case emphasizes the importance of early recognition of this rare tumor in patients with chronic diarrhea to improve clinical outcomes.

KEYWORDS

VIPoma; vasoactive intestinal polypeptide; WDHA syndrome; functional neuroendocrine tumor; chronic watery diarrhea

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INTRODUCTION

Chronic diarrhea is defined as loose or watery stools (Bristol Stool Chart types 5 to 7) that occur more than three times a day for at least four weeks (1). Its etiologies have a wide spectrum, including infectious diseases, inflammatory bowel diseases, malabsorption disorders, irritable bowel syndrome, food allergies, and adverse drug reactions. Endocrine disorders, such as thyrotoxicosis, hypoparathyroidism, Addison's disease, and diabetes mellitus, as well as functioning endocrine tumors, can also contribute to this clinical entity. This report presents a case of an adult female patient with chronic and severe diarrhea, subsequently diagnosed with a vasoactive intestinal polypeptide-secreting tumor (VIPoma). The diagnostic approach and treatment of this tumor have also been discussed.

CASE REPORT

A 62-year-old Thai woman presented with a one-year history of progressively worsening watery diarrhea. Her medical history included well-controlled type 2 diabetes, hypertension, and dyslipidemia diagnosed six years before. Initially, her diarrhea was treated as gastroenteritis with oral antibiotics at a local hospital. However, she continued to experience recurrent episodes of non-bloody, watery diarrhea exceeding 500–600 mL, with a frequency of more than 10 times daily. These episodes were unrelated to meals or food types and did not respond to loperamide.

The patient reported debilitating fatigue and significant weight loss of 12 kg. She denied fever, recent travel, laxative abuse, or illicit drug use. Physical examination revealed dehydration, cachexia, and proximal muscle weakness. Her vital signs were remarkable for tachycardia (105–110 bpm) and low blood pressure (80–90/50–60 mmHg). Laboratory tests showed renal insufficiency (creatinine 2.12 mg/dL), hyponatremia (134 mEq/L), severe hypokalemia (2.2 mEq/L), hypophosphatemia (1.8 mg/dL), and metabolic acidosis (bicarbonate 8 mEq/L). An electrocardiogram revealed sinus tachycardia with a prolonged QTc interval. Multiple stool examinations were negative for occult blood, parasites, and bacterial infections, including *Clostridium difficile*. Gastrointestinal endoscopy findings were unremarkable. Supportive treatment with intravascular fluids, parenteral nutrition, sodium bicarbonate, and potassium replacement was promptly initiated. The diagnosis of VIPoma was confirmed by significantly elevated serum vasoactive intestinal peptide (VIP) levels of 328 pg/mL (reference range: <75 pg/mL) and plasma chromogranin A (CgA) levels of 161.76 ng/mL (reference range: 27–94 ng/mL). Other laboratory findings included urine 5-HIAA levels of 4.48 mg/24 hours (reference range: 2–8 mg/24 hours) and serum gastrin levels of 32 pg/mL (reference range: 13–115 pg/mL). Computed tomography (CT) revealed a large, well-circumscribed, lobulated, heterogeneously enhancing mass in the body and tail of the pancreas. Additionally, multiple well-defined enhancing lesions were identified in the liver, highly suggestive of hepatic metastasis (Figure 1). A short-acting somatostatin

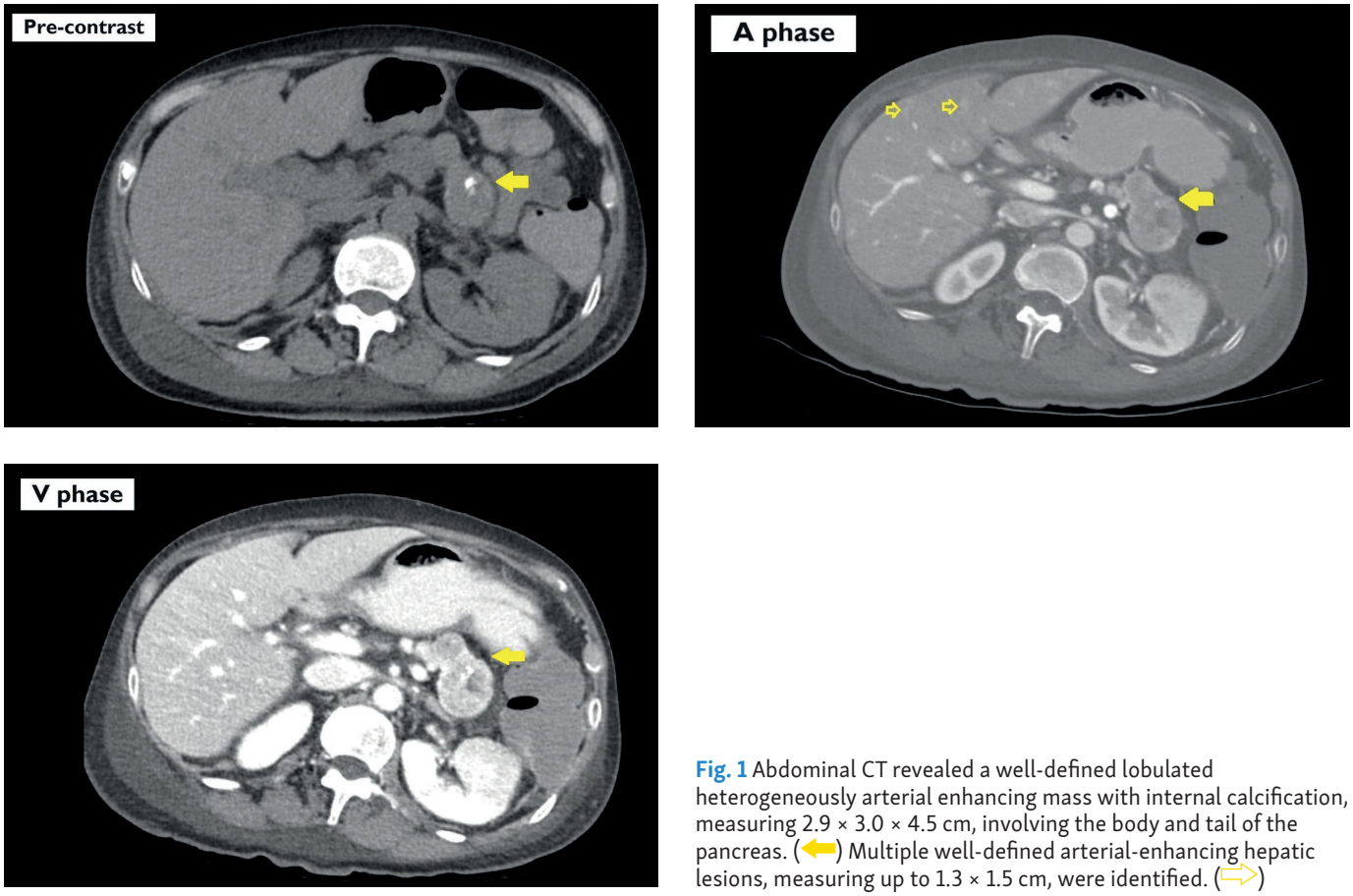

Fig. 1 Abdominal CT revealed a well-defined lobulated heterogeneously arterial enhancing mass with internal calcification, measuring 2.9 × 3.0 × 4.5 cm, involving the body and tail of the pancreas. (⬅) Multiple well-defined arterial-enhancing hepatic lesions, measuring up to 1.3 × 1.5 cm, were identified. (⇨)

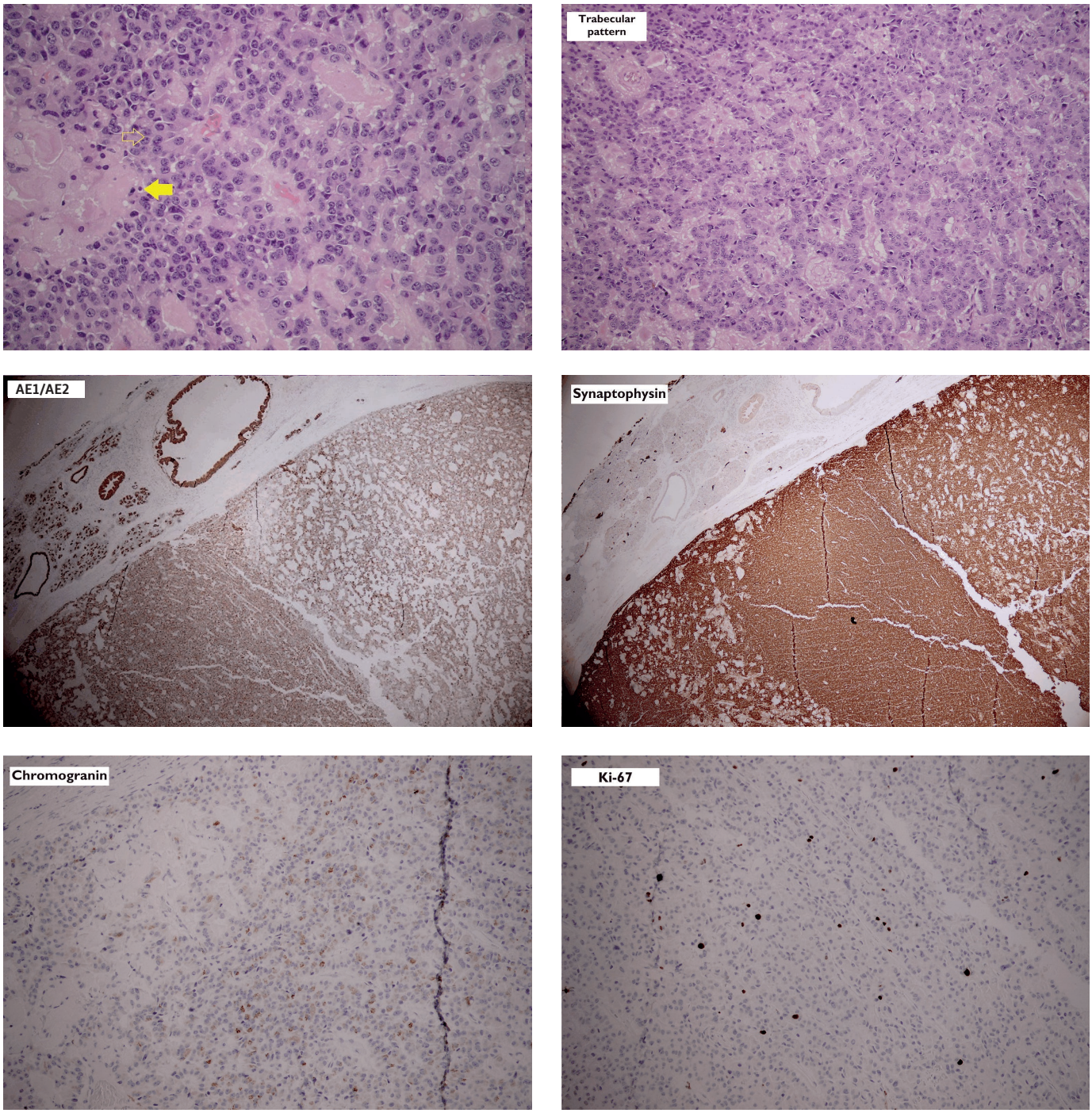

Fig. 2 Histopathology revealed epithelioid-shaped cells with uniform nuclei (⇨), arranged in a trabecular pattern in a hyalinized background. (⬅) Immunohistochemically, the tumor cells showed diffuse reactivity with synaptophysin and AE1/AE3 (cytoplasmic staining), while only a small portion of tumor cells exhibited reactivity with chromogranin A. The Ki-67 index was 5%.

analog (SSA), octreotide, was initiated at a dose of 50 mg subcutaneously every 12 hours and increased to 250 mg every 6 hours as symptoms improved. Distal pancreatectomy, splenectomy, cholecystectomy, and wedge liver resection with intraoperative radiofrequency ablation were performed with successful outcomes. Pathological examination revealed a well-differentiated grade 2 neuroendocrine tumor according to the European Neuroendocrine Tumor Society (ENETS) criteria. Immunohistochemical staining demonstrated diffuse positivity for synaptophysin and AE1/AE3 and focal positivity for CgA (Figure 2). Lymphovascular and perineural invasions were identified. The mitotic rate was low (1 per 2 mm²) and the Ki-67 proliferation index was 5%. Based on the American Joint Committee on Cancer (AJCC) Eighth Edition criteria, the tumor was classified as stage IV (T4, N1, M1). Postoperatively, the patient achieved clinical recovery and did not require further SSA therapy. Throughout the 12-month follow-up period, functional imaging and serological studies showed no evidence of disease recurrence. Genetic testing for multiple endocrine neoplasia type 1 (MEN1) syndrome was negative.

DISCUSSION

This report describes a case of VIPoma, a rare etiology of chronic diarrhea. Despite our patient having distinct symptoms of this tumor, there was a delay in diagnosis, resulting in an advanced stage at presentation and an increased risk of life-threatening complications.

Chronic diarrhea can be categorized into four main types: watery, malabsorptive, inflammatory, and functional (1). Watery diarrhea can be further classified into osmotic or secretory types through fasting trials. The diagnostic process involves a detailed history, a thorough physical examination, and appropriate investigations. It is also important to review medication history and screen for irritable bowel syndrome. Based on the stool characteristics and persistent symptoms during fasting in our patient, a secretory diarrhea subtype was suspected despite the unavailability of stool osmotic gap testing at our facility. Following a comprehensive workup to exclude common etiologies, including stool examinations, gastrointestinal endoscopy, and evaluation for prevalent endocrine disorders, we investigated less frequent hormone-secreting neuroendocrine tumors, such as carcinoid, gastrinoma, and VIPoma.

VIPoma is an extremely rare functional neuroendocrine neoplasm, accounting for less than 5% of all pancreatic neuroendocrine tumors, with an estimated annual incidence of 1 per 10 million individuals (2). The tumor is described in various terms, including pancreatic cholera, WDHA (watery diarrhea, hypokalemia, achlorhydria), and Verner-Morrison syndrome. Most affected individuals are adults between the ages of 30 and 50, with a slight female predominance (3). About 90% of these tumors are in the body and tail of the pancreas, while the remaining originate in extra-pancreatic tissues such as the adrenal medulla or sympathetic ganglia, particularly in pediatric patients (4). These tumors usually present as solitary lesions, often larger than 3 cm in size, and approximately 80% have metastasized at the time of diagnosis, primarily to the liver (5). Most cases of VIPoma occur sporadically, with about 5% of cases associated with MEN1 syndrome (6).

VIP, a neuropeptide, has significant effects on various physiological processes, including the regulation of pancreatic enzyme and gastric acid secretion, vasodilation, and intestinal motility. These effects are mediated through the activation of cyclic adenosine monophosphate (cAMP) and adenylate cyclase. Patients with VIPoma typically experience chronic and profuse secretory diarrhea, with stool volume exceeding 3 liters per day. Notably, the stool is odorless, tea-colored, and free of blood or mucus. VIP-mediated potassium secretion from intestinal cells leads to hypokalemia, while concurrent bicarbonate wasting contributes to metabolic acidosis. Its inhibitory effect on gastric parietal cells resulting in hypo- or achlorhydria leads to malabsorption. Co-secretion with other islet cell peptides, such as gastrin and pancreatic polypeptide, is observed in approximately 30–50% of cases (7). Severe dehydration can lead to renal failure and hypercalcemia. In patients with MEN1 syndrome, hypercalcemia may be attributed to concurrent hyperparathyroidism. Additionally, VIP has a glycogenolytic effect on the liver, contributing to hyperglycemia in up to 50% of cases. Other less common symptoms, including flushing, bloating, nausea, vomiting, and weight loss, have been described (8).

The diagnosis of VIPoma is based on elevated serum VIP levels, with levels above 75 pg/mL considered indicative and values exceeding 200 pg/mL strongly suggestive (9). However, these levels can fluctuate between episodes of diarrhea. Due to the rarity of the tumor, nonspecific symptoms, and limited availability of diagnostic tools, the definitive diagnosis often takes over a year from symptom onset, as observed in our patient. Both CT and magnetic resonance imaging (MRI) have sensitivities of 75–100% in identifying tumors. While transabdominal ultrasonography (USG) has a lower sensitivity of 60%, it can serve as an initial imaging modality to guide further diagnostic investigations (10). Additionally, endoscopic ultrasound (EUS) provides higher-resolution images and enables fine-needle aspiration of tumors. Functional imaging techniques, such as somatostatin receptor scintigraphy or Ga-68 DOTATATE Positron Emission Tomography-Computed Tomography (PET-CT), have emerged as valuable methods for detecting metastatic lesions because of their high expression of somatostatin receptors.

Surgical resection is the main treatment for both primary and metastatic lesions, effectively improving symptoms and extending disease-free intervals. Preoperative care is crucial to ensure adequate hydration, appropriate blood glucose control, phosphate replacement, and correction of electrolyte abnormalities. SSA is the cornerstone of medical therapy, effectively controlling diarrhea up to 65% (10). This medication can decrease VIP levels and potentially stabilize tumor growth. In cases of resistance or tachyphylaxis to SSA, glucocorticoids, loperamide, and opiates may be added (11). Other interventions, such as systemic chemotherapy, interferon, radiofrequency ablation, and embolization, have yielded varying successes in treating unresectable or metastatic lesions. Molecular targeted drugs, such as sunitinib and everolimus, as well as peptide receptor radionuclide therapy (PRRT) using 177Lu-DOTATATE, have emerged as promising options (12). The prognosis is excellent for patients who undergo successful surgical removal of benign tumors without distant metastases, with 5-year survival rates reported exceeding 90%. Conversely, patients with distant metastases have a significantly lower estimated 5-year survival rate of around 60% (13).

CONCLUSION

This case report describes a rare tumor, VIPoma, which presents a significant clinical challenge in terms of diagnosis and management. Clinicians should consider this tumor in patients with chronic diarrhea that remains undiagnosed. Preoperative treatment with SSA administration followed by definitive surgical removal plays a crucial role in achieving successful outcomes. Furthermore, multidisciplinary management may improve the prognosis, even in advanced-stage patients.

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