

## Verner-Morrison Syndrome Presenting as Acute Persistent Diarrhea

Eliseo De La Cruz-Escobar<sup>1</sup>, Ignacio García Juárez<sup>2</sup>, Shaddai Urbina<sup>3</sup> and Jonathan Aguirre-Valadez<sup>2\*</sup>

<sup>1</sup>Resident of Oncology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

<sup>2</sup>Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

<sup>3</sup>Department of Pathology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico

### Abstract

Vasoactive intestinal peptide (VIP)-producing tumors account for 10% of all neuroendocrine tumors of the pancreas. The Verner-Morrison syndrome is caused by VIP-producing tumors. It is a rare entity with an incidence of 1/10 million individuals per year. About 800 cases have been reported worldwide. Pancreatic VIPomas are usually solitary. Clinical manifestations are long-standing secretory diarrhea associated to biochemical abnormalities such as hypokalemia, hypochloremia and metabolic acidosis, presentation as acute diarrhea is rare. Up to 60% of tumors are malignant and among these, 60-80% have metastasized at diagnosis. Part of the symptomatic treatment is based on somatostatin analogs; definitive treatment depends on the disease's extent but surgical resection is the treatment of choice of localized tumors.

**Keywords:** Verner-Morrison syndrome; Vasoactive intestinal peptide; Acute diarrhea; Secretory diarrhea

### Introduction

Verner-Morrison (VM) syndrome is characterized by secretory diarrhea and hydroelectrolytic abnormalities such as hypokalemia, hypochloremia and metabolic acidosis; it is due to an increase in vasoactive intestinal peptide (VIP) production [1]. VIP is a polypeptide that binds to intestinal epithelial cells and activates adenylate cyclase and cAMP production. This leads to the secretion of fluids and electrolytes into the intestinal lumen. The diagnosis is suspected in patients with abundant secretory diarrhea (700 to >3000 mL/day, even while fasting) and it is established after detecting elevated VIP serum levels and identifying the neoplasia [2].

We hereby present the clinical case of a patient in whom it manifested as acute persistent diarrhea.

### Case Report

A 44-year old male with no relevant past history, developed epigastric pain and abundant diarrhea (approximately 6 L/day), 3 weeks before admission. Symptoms did not abate with fasting and no other symptoms were present. He was treated with antibiotics and anti-diarrheal agents with no improvement. On admission, the patient was dehydrated, tachycardic, BP was 80/60 and he had no fever. Laboratory results revealed: hemoglobin 17 gr/dL, WBC16,000/mm<sup>3</sup>, glucose 175 mg/dL, creatinine 1.56 mg/dL, Na 130 mEq/L, K 2.4 mEq/L, Cl 107 mEq/L, CO<sub>2</sub> 6 mmol/L, Ca 11.9 mg/L, normal liver function tests; arterial blood gases: pH 7.21, pCO<sub>2</sub> 18.7 mmHg, pO<sub>2</sub> 79.9 mmHg, HCO<sub>3</sub> 7.2 mEq/L, anion gap 15. Complementary tests as part of the diagnostic approach included fresh fecal smear and stool leukocytes, stool culture and microscopy, *C. difficile* toxin, cryptosporidium, isospora and HIV serology; all were negative. Thyroid function tests were normal. Treatment was initiated with IV fluids and bicarbonate. During his hospital stay, he had stools >7,600 mL/day and developed severe hypokalemia with electrocardiographic changes (K=1.8 mEq/L) and hypercalcemia (cCa=12.2 mg/dL). Computed tomography (CT) with contrast showed a tumor of the head of the pancreas and lesions consistent with hepatic metastases as well as portal vein thrombosis (Figures 1A and 1B). Suspecting a neuroendocrine tumor, serum levels of chromogranin A and VIP were requested as well as 5-hydroxy-indolacetic acid in a 24 hour urine sample. Serum levels of PTH and prolactin (requested because of hypercalcemia and to exclude multiple endocrine neoplasia I) were normal. Treatment with octreotide 100 mcg sc q 8 h, was initiated and it decreased the stool volume by over

70% after the first day of therapy. Transendoscopic ultrasound (TEU) corroborated the presence of a lesion measuring 25 × 34 mm in the head of the pancreas, associated to vascular invasion, portal vein thrombosis and liver metastases; the mass was biopsied by fine-needle aspiration. The pathology diagnosis was that of a well-differentiated endocrine carcinoma, positive for chromogranin, synaptophysin and vasoactive intestinal peptide (Figures 2A-2C). The serum chromogranin A level was 84 ng/mL (1.9-15 ng/mL) and VIP was 227 pg/mL (20-40 pg/mL). Octreotide radionuclide imaging revealed increased uptake at the level of the head of the pancreas and the liver lesions; there was no evidence of metastases elsewhere.

### Discussion and Review of the Literature

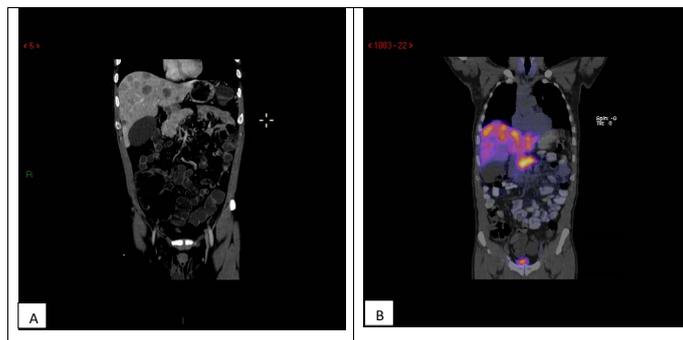
Pancreatic endocrine neoplasias have an annual incidence of 1/10 million individuals and vasoactive intestinal peptide (VIP) producing tumors account for 10%. In 1958, Verner and Morrison described 2 cases of pancreatic tumors associated to secretory diarrhea. The Verner-Morrison syndrome, also known as pancreatic cholera, is characterized by secretory diarrhea (89-100%), hypokalemia (67-100%), hypochloremia and metabolic acidosis [1,2]. Ninety percent of VIP-producing tumors originate in the pancreas, mostly in the pancreatic tail. The most frequent age at presentation is in the fifth decade of life and there is no difference between genders. Clinical manifestations are usually insidious so the diagnosis is usually established in late phases of the disease, on average, after 2-4 months. The diarrhea is characteristically secretory, abundant, >3 lts/day in 70% of cases (stool is usually odorless and has a low fecal osmolar gap); it is associated to hypokalemia, weight loss, non-anion gap metabolic acidosis and dehydration. Hypercalcemia and hyperglycemia may also be a feature [3]. The diagnosis is based on clinical suspicion and is established by elevated serum VIP levels (2-10 fold above normal) with a mean above 75 pg/mL as well as identification of the neoplasia.

**\*Corresponding author:** Jonathan Aguirre-Valadez, Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico City, Mexico, Tel: 55 0445527558049; E-mail: [yanomani@hotmail.com](mailto:yanomani@hotmail.com)

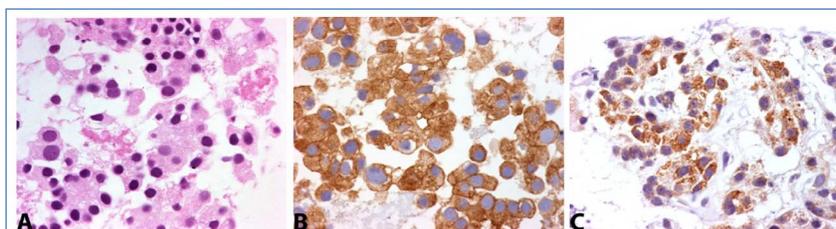
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**Figure 1.** CT coronal image showing enhanced hepatic focal and nodular lesions; some have a hypodense necrotic center; solid heterogeneous tissue is observed in the pancreatic neck (A). Fusion SPECT-CT with octreotide shows increased uptake by the previously described lesions, mediated by expression of somatostatin receptors (B).



**Figure 2:** Fine-needle aspiration biopsy. Epithelial cells with hyperchromatic nuclei, variable in size and with abundant eosinophilic cytoplasm (A). Positive immunohistochemistry for chromogranin in tumor cell cytoplasm (B). Positive immunohistochemistry for vasoactive intestinal peptide in tumor cell cytoplasm (C).

The most useful imaging study is triphasic computed tomography (CT) of the pancreas. Transendoscopic ultrasound (TEU), aside from being diagnostic, is also helpful in determining the extent of the disease and allows for the biopsy of the lesions. The differential diagnosis includes carcinoid tumors, gastrinoma, tropical sprue, villous adenoma, lymphocytic colitis and celiac crisis [4]. The degree of malignancy of these tumors hinges on the presence of metastases. At diagnosis, 60-80% of patients have metastatic disease, particularly in the liver. Treatment in the acute phase is supportive in an effort to correct fluid and electrolyte imbalance. IV somatostatin analogs such as octreotide and lanreotide are the cornerstone of the treatment of diarrhea, with 90% of patients responding favorably (100 mcg q 8 hrs or slow release, 20 mg q 28 days) [5]. Surgery is the only curative method and is limited to localized lesions [6]. In case there is metastatic liver disease, resection is only recommended if the patient is refractory to medical therapy, there is no bilobular compromise nor extrahepatic metastases. Arterial embolization is reserved for a few cases but is contraindicated in patients with liver failure or portal vein thrombosis. Systemic chemotherapy improves these patients' survival; it is beneficial in terms of clinical response, quality of life and survival. It consists of sunitinib, everolimus and bevacizumab [7].

The clinical and temporal presentation of our patient is atypical in terms of the data reported in the literature; although his age is characteristic, the typical clinical presentation is diarrhea of over 2 months duration [2,5]. Our patient presented with a clinical case of acute persistent diarrhea (3 weeks) of very difficult control, with no previous relevant history and with metastatic liver disease. Treatment was based on hydration and octreotide to which the patient responded well almost immediately, after the first 100 mcg dose.

In conclusion, in the presence of a patient with secretory high volume diarrhea associated to hypokalemia and non-anion gap metabolic acidosis and that responds poorly to initial treatment, neuroendocrine tumors should be included in the differential diagnosis,

particularly those producing VIP; this is regardless of whether the disease's presentation is acute, persistent or chronic.

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