VIPOMA: Uma Causa Rara de Diarreia

Vipoma: A Rare Cause of Diarrhea

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Resumo:

O VIPoma é um tumor neuroendócrino raro (incidência 1:10 000 000), geralmente localizado no pâncreas. Este tumor está associado a elevado risco de malignidade e secreta o peptídeo intestinal vasoativo (VIP) resultando na síndrome de diarreia aquosa, hipocaliémia, acidose, hipocloridria e hipercalcemia. O único tratamento curativo é a cirurgia.

Apresentamos o caso de um homem, com 60 anos, internado com um quadro de vómitos e diarreia aquosos, com uma evolução de 6 meses, que após extensa investigação se concluiu tratar de um VIPoma duodenal. Os autores destacam a raridade do diagnóstico, a localização atípica (extrapancreática) e expõem a dificuldade diagnóstica quer pela evolução clínica flutuante, quer pela dificuldade de localização anatómica e obtenção de um diagnóstico definitivo.

Palavras-chave: Diarreia; Neoplasias Duodenais; Tumores Neuroendócrinos; Vipoma.

Abstract:

VIPoma is a rare neuroendocrine tumor (incidence 1:10 000 000), generally located in pancreas. This tumor is associated to increased risk of malignancy and secretes vasoactive intestinal peptide (VIP) resulting in the syndrome of watery diarrhea, hypokalemia, acidosis, hypochloridria and hypercalcemia. The only curative treatment is surgery.

We present the case of a 60-year-old male, admitted to the ward with vomiting and watery diarrhea, with 6-month duration. After detailed investigation, this case revealed to be due to a VIPoma located in duodenum. The authors underline the rarity of the diagnosis, its atypical location (extrapancreatic) and state the diagnostic difficulties due to fluctuating symptoms, locating the tumor and obtaining a definitive diagnosis.

Keywords: *Diarrhea; Duodenal Neoplasms; Neuroendocrine Tumors; Vipoma.*

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Introduction

Neuroendocrine tumors (NETs) are rare neoplasms (5.86: 100 000 individuals per year), in which harbors two components: neuro and endocrine.[1]

Given the neuroendocrine cells distribution through the human body, NETs can arise almost everywhere, although the most common sites affected are the gastrointestinal tube and lungs.[2]

Examples of these tumors include insulinomas, gastrinomas and VIPomas. Amongst these, VIPomas are the rarest.[3]

VIPomas are rare neuroendocrine tumors (1:10 000 000), located in the pancreas in 95% of the cases.[2] In adults, it occurs mainly between the fourth and fifth decades.[2] These tumors are associated with elevated malignant risk as they are metastasized in 60% to 80% of the cases at the time of the diagnosis.[4,5] Despite being a solitary tumor, in 5% of the cases is associated to the endocrinologic syndrome MEN-1 (multiple endocrine neoplasia type 1).[6]

Here we present a case of a VIPoma with extrapancreatic location and the challenging pathway towards its definitive diagnosis.

Caso Clínico

A 60-year-old Caucasian male, living in Lisbon for the last 4 years, was admitted due to vomiting and diarrhea complicated with acute kidney injury. His past medical history revealed an adenocarcinoma of the colon treated with curative intent in 2016, an iron deficient anemia due to gastrointestinal angiectasis, essential hypertension, chronic kidney disease (KDIGO III), patent *foramen ovale*, non-stratified chronic obstructive pulmonary disease and depression. He was a heavy drinker (71 g/day) and smoker (>40 pack year units). He was regularly on olmesartan+hydrochlorothiazide, 40 + 12.5 mg, *id*, furosemide, 40 mg, *id*, clopidogrel, 75 mg, *id*, atorvastatin, 40 mg, *id*, thiamine, 100 mg, *id*, tiapride, 100 mg, *bid*, oxazepam, 15 mg, *bid*, folic acid, 5 mg, *id*, ferrous sulfate, 247 mg, *id*, tiotropium bromide, 10 µg, *id*, pantoprazol, *id*.

Referring to his complaints, the vomiting and diarrhea were watery, had one week duration, with more than 10 episodes a day, occurring during day and night. He denied blood or mucous presence, any temporal relation with food ingestion, fever or other associated symptoms. In his social history he had lived one year in Angola (from 1999 to 2000) and 12 years in Timor-Leste (from 2004 to 2016). He denied

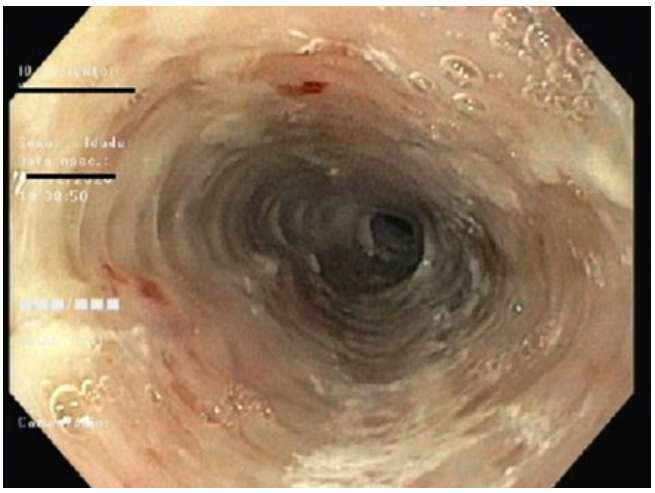

Figure 1: Esophageal mucosa with white plaques and small hemorrhagic points.

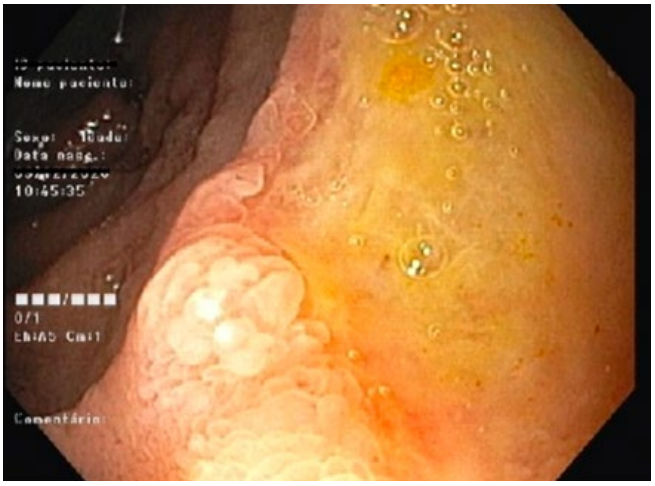

Figure 2: Wide ulcers in duodenum.

recent travels, contact with animals, recent change in his diet or consumption of raw meat and fish as well as herb and dietary supplements. His physical examination revealed: vital signs 113/74 mmHg, 100 bpm, room air SpO2 95%, dehydration, malar telangiectasis, increased bowel sounds, but with normal pitch and timbre, diffuse painful abdomen, but without rebound tenderness, masses or organomegaly and digital clubbing. Relevant blood results showed Hb 8.9 g/dL, normocytic normochromic with increased red cell distribution width (RDW), ferritin 157 ng/mL, transferrin saturation 24%, no leukocytosis or eosinophilia, creatinine 13.62 mg/dL, anion gap metabolic acidosis, K+ 5.1 mmol/L, without other ionic imbalances, negative C reactive protein and an unremarkable urinalysis except for the presence of protein 150 mg/dL.

Despite recovering from kidney injury, ionic imbalances and improving clinically, after rehydration and implementation of a low residue and lactose free diet, on the third day of stay his complaints relapsed. After detailed anamnesis, we verified that, although fluctuating, these symptoms were present for the last 6 months.

An additional work-up was performed, excluding endocrine causes, revealing negative autoimmunity (ANCAs, anti-Tg IgA, antigliadin IgA, IgG and slightly increased faecal calprotectin 250 mg/kg (< 50 mg/kg)), excluding colon carcinoma relapse (negative carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19.9)) and ruling out infectious causes (serology for HIV, HCV, HBV and DNA load for *Cytomegalovirus* (CMV), coproculture, ova and parasite stool test). Considering his past countries of residence and microorganisms associated with chronic diarrhea, it was not identified neither *Giardia*, nor *Entamoeba histolytica*. Fecal elastase analysis was not possible due to extreme watery stools. It also showed normal urinary 5- hydroindoloacetic acid, but an increase in chromogranin A 4779 ng/mL (< 102 ng/mL), gastrin 437 (<100 pg/mL), VIP 119 (<30 pg/mL). Esophagealgastroduodenoscopy revealed white plaques in the esophagus (Fig. 1), wide ulcers in duodenum (Fig. 2) and gastroduodenal angiectasis and colonoscopy without lesions. Gastric and duodenal biopsies did not reveal evidence of CMV or *Strongyloids stercoralis* infection. Body computed tomography (CT) scan was remarkable for wall thickening of the third duodenal portion (D3) and local lymphadenopathies and magnetic resonance imaging (MRI) for an area with restricted diffusion in D3 (Fig. 3). Somatostatin receptor scintigraphy marked in the ileal area.

Taking into account these results, it was assumed the neuroendocrine tumor diagnosis (probably a VIPoma due to clinical presentation) and the patient was started on octreotide, 30 mg, intramuscular, per month, with clinical improvement. Thereafter, the patient was submitted to surgery, namely, to duodenotomy with lymphadenectomy. D3 histopathology revealed a well differentiated neuroendocrine tumor. Patient is currently asymptomatic and without evidence of relapse.

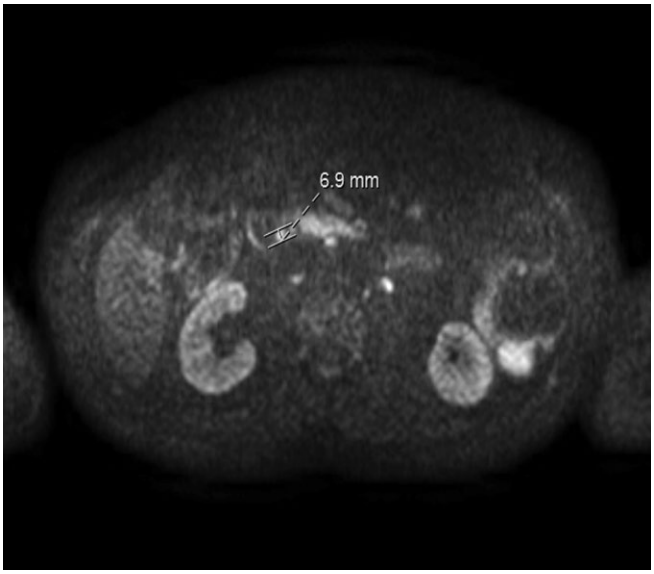

Figure 3: Restricted diffusion in duodenum (D3).

Discussion

The great majority of VIPomas presents with the WDHA syndrome (watery diarrhea, hypokalemia and achloridria).6 The watery diarrhea is characterized by persistence even during fasting and by its volume (can totalize up to 3000 mL per day).[7] Besides WDHA syndrome, this tumor can also be associated with hypercalcemia (25% - 50%), hyperglycemia (20% – 50%) and/or "flushing" (15% - 30%).[6]

The pathophysiology is related to VIP secretion (vasoactive intestinal peptide) in great quantity by the tumor.8 VIP is a neurohormone which connects to the enterocyte receptor, inhibiting potassium, chloride and water reabsorption, resulting in watery diarrhea and hypokalemia.[6,9]

This neurohormone stimulates hepatic glycogenolysis and osteolytic activity resulting, respectively, in hyperglycemia and hypercalcemia.[4] VIP is the hormone secreted in more quantity, although others hormones are secreted as well (calcitonine, glucagin, insulin, gastrin and others).[10] Treatment is implemented on 3 grounds: the first is supportive care with fluids and ions for electrolyte imbalances; the second is octreotide administration for symptom control and consequently avoiding further electrolyte imbalances; and the third is surgery, which is considered gold standard and the only with curative intent.[3] Furthermore, some authors consider that octreotide may prevent tumor growth due to its cytostatic activity.[11]

Evidence of the use of cytotoxic chemotherapy is limited due to the reduced number of patients included in clinical series.[2] This article presents a 60-year-old male, with an extrapancreatic VIPoma. The diagnosis was challenging due to the fluctuating and self-limiting symptoms and tumor small size. Diagnosis is often delayed and diarrhea may persist for years before VIPoma is confirmed.[3] Besides being a rare tumor, the extrapancreatic location makes the diagnosis even rarer. After VIPoma diagnosis, it is necessary to establish its location. In this case, although somatostatin receptor scintigraphy pointed towards ileum, the real location was in the third portion of duodenum. This divergence might be explained by the fact that scintigraphy is a functional exam, and thus lacks anatomical acuity. Furthermore, although expected hypokalemia as part of WDHA syndrome, in the case it was attenuated by acute kidney injury. Finally, despite the increase in fecal calprotectin, it was considered to be indicative of low grade inflammatory disease and not suggestive of inflammatory bowel disease.[12]

The authors underline the rarity of the diagnosis and its challenging pathway towards its diagnosis. ■

Declaração de Contribuição

JSF – Redação do manuscrito, colheita de informação, aprovação da versão final

MA – Redação do manuscrito, aprovação da versão final

MRR– Correção do manuscrito, aprovação da versão final

PA– Redação e Correção do manuscrito, aprovação da versão final

Todos os autores aprovaram a versão final a ser submetida.

Contributorship Statement

JSF – Writing of the manuscript, gathering of information, approval of the final version

MA – Writing of the manuscript, approval of the final version

MRR – Correction of the manuscript, approval of the final version

PA– Writing and Correction of the manuscript, approval of the final version

All authors approved the final draft.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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Recebido / Received: 2022/02/14

Aceite / Accepted: 2022/06/30

Publicado online / Published online: 2023/03/31

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