VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOR (VIPoma)

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ABSTRACT

A VIPoma is a neuroendocrine neoplasm secreting vasoactive intestinal peptide (VIP), usually presenting with severe watery secretory diarrhea, which can result in hypokalemia and metabolic acidosis and with flushes. Hypochlorhydria, stimulation of glycogenolysis, and hypercalcemia can be also found in VIPoma patients. Plasma VIP levels are elevated in all patients with the VIPoma syndrome, which is also known as “watery diarrhea, hypokalemia, achlorhydria (WDHA)-syndrome”, or “Verner-Morrison syndrome”. The majority of VIPomas are located in the pancreas (75%) and (usually young) patients can present with VIP-producing neuroblastoma, ganglioneuroblastoma, ganglioneuroma, pheochromocytoma and paraganglioma, or neoplasms of the retroperitoneum and mediastinum. The first treatment aim of a VIPoma patient is to correct the fluid and electrolyte deficits. Administration of a somatostatin analog (SSA) can decrease flushing and diarrhea, further aiding in the restoration of fluid and electrolyte imbalances. Surgical resection should be considered in patients with a locoregionally confined VIPoma. In patients with a metastatic or unresectable VIPoma, SSAs likely prolong progression-free survival. Other treatment options include peptide receptor radionuclide therapy (PRRT) with radiolabeled SSAs, interferon alpha, everolimus, sunitinib, cytotoxic chemotherapy, or liver-directed therapies.

INTRODUCTION

Vasoactive intestinal polypeptide (VIP) is a neurotransmitter found in the central nervous system, in neurons in the intestine, lungs, adrenals, pancreas and liver and in neuroendocrine cells in the pancreas (1). In the gastrointestinal tract, VIP stimulates contraction of enteric smooth muscle cells, secretion from the exocrine pancreas, gastrointestinal blood flow, and inhibits gastric acid secretion (2-4). A VIPoma is a neuroendocrine neoplasm (NEN) secreting VIP. VIP hypersecretion causes severe watery secretory diarrhea, which can result in hypokalemia and metabolic acidosis (VIPoma syndrome) (5).

HISTORY

In 1958 the US physician John V. Verner Jr. (1927-2022) and the Irish-US pathologist Ashton B. Morrison (1922-2008) reported on two patients with a VIPoma syndrome (6). Both patients presented with watery diarrhea and severe refractory hypokalemia and

subsequently died of cardiac arrhythmias. Autopsy revealed pancreatic “islet cell” tumors in both patients (6). One of their patients was a 19-year-old male who also developed hypercalcemia and at autopsy hyperplasia of one of the parathyroid glands was found. The pituitary was not examined (6, 7). The publication by Verner and Morrison further cites 7 similar cases already published in the literature at that time (6) Thereafter, the VIPoma syndrome was also named “watery diarrhea, hypokalemia, achlorhydria (WDHA)-syndrome”, or “Verner-Morrison syndrome”. In the late 1960s and early 1970s, VIP was first isolated from the lungs and small intestine of experimental animals by the group of the Estonian scientist Viktor Mutt (1923-1998) in Sweden (8-10). In 1973, a radioimmunoassay for VIP became available and subsequently the British physician Stephen R. Bloom and colleagues could for the first time measure elevated VIP levels in the blood of a patient with the VIPoma syndrome (11). In 1983, the US gastroenterologist Mary G. Kane and colleagues injected five healthy subjects with porcine VIP, which resulted within 4 hours in high plasma VIP levels and was followed by secretory diarrhea in all patients (12).

CLINICAL PRESENTATION

Secretory diarrhea is the most characteristic symptom of a VIPoma. In severe cases, patients can produce up to 6-8L of watery stools per day. The stool is rich in electrolytes like potassium and bicarbonate, resulting in hypokalemia and metabolic acidosis in the VIPoma patient (13, 14). Another VIPoma symptom is facial flushing (occurring in 15-30% of patients). Hypochlorhydria, stimulation of glycogenolysis, and hypercalcemia can be diagnosed in patients with a VIPoma (5, 14-19). VIP has a structural homology with secretin, glucagon, and GIP which may account for the enhanced secretion of pancreatic enzymes, inhibition of gastric acid secretion, and glycogenolysis (9). The cause of the patchy erythematous flushing is not clear, but the flushing has been attributed to VIP, or to prostaglandins co-secreted by the tumor. Approximately 50% of patients have hypercalcemia, but again the mechanism of action is unknown. Hypercalcemia might be related to the co-secretion of parathyroid hormone related peptide (PTHrp) by the tumor (20, 21), or in specific cases coexisting primary hyperparathyroidism in the spectrum of the multiple endocrine neoplasia 1 (MEN1) syndrome (7).

Pancreatic VIPomas account for only 0.6–1.5% of all pancreatic neuroendocrine neoplasms (panNENs) (17) and approximately 2–6% of all functioning panNENs (17). The incidence is 0.05–0.2 cases per 1 million person-years with no gender predilection (15, 17, 18, 22). The mean age of these patients is 50.5 years (17). Pancreatic VIPomas can be associated with the MEN1 syndrome, but they are present in less than 1% of MEN1 patients (7, 23, 24). Around 75-90% of WDHA syndrome originates from a VIP-secreting panNEN. Approximately 70% of these pancreatic VIPomas are located in the body or tail and 30% in the head (18, 19, 25, 26). 10-25% of the WDHA syndrome derives from extra-pancreatic sources and can be found in patients with neuroblastoma, ganglioneuroblastoma, ganglioneuroma, pheochromocytoma and paraganglioma, and neoplasms of the retroperitoneum and mediastinum (5, 19, 27-30). The neurogenic tumors are more commonly found in the pediatric population (mean age 7.3 years). VIP-production from medullary thyroid carcinoma and lung neoplasms can also occur but this generally does not lead to the VIPoma / WDHA syndrome (31-33).

DIAGNOSIS

In the circulation, VIP has a very short half-life of less than 1 minute and, normally, plasma levels of VIP are

low (below 20 pmol/L = 70 pg/mL) (34, 35). In the absence of a VIPoma, plasma VIP levels reflect the overflow of VIP from VIP-containing vascular nerves. By definition, plasma VIP levels should be elevated in all patients with the VIPoma syndrome. Bloom and colleagues measured plasma VIP levels in nearly 1000 patients with diarrhea and the diagnosis of VIPoma could be confirmed in all patients with plasma VIP levels greater than 60 pmol/L (= 203 pg/mL) (13, 34). In another series of 52 pancreatic VIPoma patients, elevated VIP levels were also measured with a median of 188 pmol/L (= 630 pg/mL - range 30-2131 pmol/L) (14). Moderately elevated plasma VIP levels can also be caused by gastrointestinal ischemia, renal insufficiency, or congestive heart failure (36-38).

The diameter of the primary pancreatic VIPoma is on average larger than 2 cm in 80% of patients (19). Therefore, these tumors can be easily detected with abdominal MRI, 3 phase CT, or endoscopic ultrasound (EUS). Additionally, a positron emission tomography (PET)-CT/MRI with ^{68}Ga-labelled somatostatin analogs (DOTATATE, DOTANOC, DOTATOC) should be performed to determine, or exclude metastatic spread. In most centers, somatostatin receptor scintigraphy and SPECT using ^{111}In-pentetreotide (OctreoScan) has become obsolete. In a small case series, ^{111}In-pentetreotide scintigraphy proved to be superior to conventional radiological imaging for localizing the VIPoma and its metastases (39).

Similar to work-up for all NENs, a biopsy of the primary tumor or its metastases is recommended to confirm the diagnosis and for grading (Ki67 index), since the tumor grade can influence treatment decisions (17). An overview of the current panNEN staging and grading systems is provided in the chapter “Insulinoma” (40). Pancreatic VIPoma tumor cells usually express neuroendocrine differentiation markers (chromogranin-A, synaptophysin, INSM1), keratins, transcription factors, and somatostatin receptor subtype 2 (17). The extent of VIP expression can be variable given the rapid turnover of the protein synthesis. Secondary, or metachronous insulin secretion and/or positive insulin immunohistochemistry on the tumor specimen is generally associated with poor survival (41-43).

In patients with metastatic VIPoma, the 5-years survival is 60% (14, 16). Patients with high circulating VIP levels (plasma VIP ≥ 5xULN) have a poorer prognosis than those with moderately elevated levels (plasma VIP <5xULN) (16).

TREATMENT

Correction of Fluid and Electrolyte Deficits

The first treatment aim in a patient with a VIPoma is to correct the fluid and electrolyte deficits. In the majority of severe cases, intravenous resuscitation with saline, potassium and bicarbonate is required. Administration of a somatostatin analog (SSA) can decrease the secretory diarrhea, further aiding in the restoration of fluid and electrolyte imbalances (13, 44, 45). In the acute setting, the SSA octreotide can be administered subcutaneously, or via continuous intravenous infusion (46).

Surgery

After initial stabilization, a surgical resection should be performed in patients with a locoregionally confined VIPoma. The 5-year overall survival after surgery of patients with a localized VIPoma is >90% (14, 16, 19). In these patients the symptomatology of the VIPoma syndrome also completely resolved after surgery (16). Extended surgical resection, also involving the liver,

can be considered in selected patients with limited liver metastases (47).

In case of an unresectable VIPoma, treatment is focused on tumor stabilization and control of VIP hypersecretion and symptoms (16). In general, anti-tumor therapy is similar to that used for other non-functioning and functioning panNENs and described in the guidelines by ENETS, NANETS and ESMO (48-50).

Somatostatin Analogs

Somatostatin analogs (SSAs) represent the first-line palliative treatment for metastatic or unresectable VIPomas. SSAs can have an antiproliferative effect, based on randomized trials with low grade (G1-G2) panNEN. In the CLARINET trial, including grade 1-2 panNENs, treatment with lanreotide autogel (120 mg every 4 weeks) prolonged median progression-free survival (PFS) from 18 to 38 months as compared to placebo by slowing tumor growth (51, 52). Treatment with SSAs results in a reduction of diarrhea episodes and volume in approximately 65-85% of VIPoma patients (15, 16, 45, 53, 54). It is, therefore, recommended to continue SSAs for symptom control when further lines of treatment are instituted for the control of tumor progression.

Everolimus

Everolimus is registered for the second-line treatment of G1-2 panNENs based on the result of the RADIANT-3 trial. In this study, 24% of patients had a functioning (= hormone-secreting) panNEN and treatment with everolimus (10 mg / day) improved median progression-free survival by 6.4 months compared with placebo. Everolimus treatment was associated with a (statistically not significant) overall survival benefit of 6.3 months (55, 56). Only a few VIPoma patients treated with Everolimus have been reported. In these patients, a symptomatic response was found in less than 10% of patients (15).

Sunitinib

In a randomized controlled trial in patients with G1-2 panNENs, second-line sunitinib treatment (37.5 mg/day) resulted in an increased progression-free survival by 5.9 months compared to placebo (57, 58). Two patients with a VIPoma were included in this trial, but they were both treated with placebo (57). In case series, a symptomatic response rate of 30-100% has been described for VIPoma patients treated with sunitinib (15, 16, 59, 60).

Other Medical Options

Next to SSAs, interferon-alpha is an established first-line antiproliferative and anti-secretory therapy for NENs of the gastrointestinal tract and pancreas either as monotherapy, or in combination with an SSA. However, the many side-effects mainly preclude its widespread use. Variable symptomatic responses with this therapy in VIPoma patients have been reported (61, 62). Prednisone has also been occasionally used to control the diarrhea frequency and stool volume in selected cases (45, 63).

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE results in a response rate of 55% for panNENs, with a median PFS of 30 months and median overall survival (OS) of 71 months (64). PRRT with ^{177}Lu-DOTATATE has only been reported in a limited number of patients with a VIPoma. In case

series, the symptomatic response rate of VIPomas to this therapy was approximately 80% and disease control rate was 67% (15, 65, 66). Withdrawal from non-radioactive SSAs can lead to swift recurrence of severe watery diarrhea, providing rationale to limit the time for SSA withdrawal before PRRT cycles with ^{177}Lu-DOTATATE to a very minimum e.g., by continued use of short-acting octreotide until shortly before the administration of this therapy (64).

Liver Directed Therapy

In patients with liver-dominant disease, liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability (47). Reduction of liver tumor burden was associated with a symptomatic response of VIPomas in small series (15, 16, 67). Orthotopic liver transplantation with removal of the diseased liver in VIPoma patients preoperatively diagnosed with “liver-only” disease can result in an improved disease course, or even complete cure (68-70).

Chemotherapy

Chemotherapy is also effective for the treatment of panNEN with symptomatic and tumor growth control achieved in a significant proportion of VIPoma patients (42, 55, 56)(15, 16, 43).

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