Review Article

Vasoactive Intestinal Peptide Tumor

Naveed Natanzi,^{1,2} Mazyar Amini,^{1,2} David Yamini,^{1,2} Shawn Nielsen,^{1,2} and Ramin Ram^{1,2}

¹ Departments of Dermatology and Pathology, Keck School of Medicine of the University of Southern California, Los Angeles, CA 90033, USA

² Department of Internal Medicine, University of Southern California, Los Angeles, CA 90033, USA

Correspondence should be addressed to Ramin Ram, raminram@gmail.com

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Background and aim. Vasoactive intestinal peptide tumor is a rare neuroendocrine neoplasm which causes voluminous watery diarrhea via hypersecretion of electrolytes and water from the intestinal mucosa through a vasoactive intestinal peptide-mediated, cyclic AMP-dependent mechanism. The acid base imbalance generated by the loss of water and electrolytes leads to severe dehydration and potential renal failure, which can ultimately result in death if left untreated. This paper aims to review the clinical, histological, radiological, and diagnostic features of this disease as well as the therapeutic modalities in treating this condition. **Methods.** A review of literature was performed using MEDLINE, Pubmed, and Cochrane databases in collection of data using MeSH terms including vasoactive intestinal peptide, VIPoma, and WDHA. **Results and conclusion.** Vasoactive intestinal peptide tumor is a rare neoplasm associated with significant morbidity and mortality through secretion of water and electrolytes in the gastrointestinal tract. The nonspecific clinical presentation of this neoplasm can pose diagnostic challenges, as these tumors can be easily misdiagnosed as other conditions, ranging from laxative overdose to the presence of a carcinoid secreting tumor. Nevertheless, a number of imaging and laboratory studies can facilitate the correct evaluation and diagnosis of VIPoma. Following proper diagnosis, VIPomas are treated by either medical or surgical modalities depending on the existence and extent of metastasis.

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1. Introduction

WDHA, a syndrome characterized by watery diarrhea, hypokalemia, and achlorhydia was first described by Verner and Morrison in 1958 [1]. These classical clinical findings in WDHA marked the impetus for uncovering the association with vasoactive intestinal peptide tumors (VIPomas). VIPomas are neuroendocrine neoplasms arising from the pancreas in 90% of the cases reported, while the remaining 10% occur in other tissues of neural crest origin [2]. These tumors excessively secrete vasoactive intestinal peptide (VIP), a hormone which stimulates adenosine 3',5'-cyclic phosphate (cAMP) production by the intestinal tract. Hypersecretion of VIP induces a significant increase in cAMP levels, thereby causing massive emission of water and electrolytes, namely, potassium [1, 2]. The acid-base imbalance generated by the loss of water and electrolytes leads to dehydration and potential renal failure, which can ultimately result in death if left untreated [2].

VIPomas can often pose diagnostic challenges because of the nonspecific clinical presentation. It can be easily

misdiagnosed as several other conditions, ranging from laxative overdose to the presence of a carcinoid secreting tumor [3]. Nevertheless, a number of imaging and laboratory studies can facilitate the correct evaluation and diagnosis of VIPoma. Following proper diagnosis, VIPomas are treated by either medical or surgical modalities depending on the existence and extent of metastasis [4]. Remarkably, 50–60% of the cases in the literature have metastasized at the time of diagnosis, regardless of the primary origin of the tumor [2, 3].

2. Vasoactive Intestinal Peptide (VIP)

VIP is a 28-amino acid neuropeptide which stimulates the production of cAMP by the enteric system. The hormone also releases acetylcholine which induces relaxation of vascular and nonvascular smooth muscles [1]. VIP is expressed in neurons of the gastrointestinal tract, respiratory, urogenital tracts, as well as in the central nervous system, primarily the hypothalamus, hippocampus, and cortex [1]. However,

a number of extrapancreatic neoplasms such as neurofibromas, neuroblastomas, ganglioneuromas, ganglioblastomas, mastocytomas, pheochromocytomas, esophageal carcinomas, small cell carcinomas of the lung, and primary VIPoma of the liver have been reported to produce VIP in a paraneoplastic process [2].

Endogenously produced at a physiological rate and concentration, VIP is responsible for a number of functions, including regulation of gastrointestinal secretions. The hormone functions as a potent stimulator of adenylate cyclase, which induces the secretion of water and electrolytes by intestinal mucosa [5]. Furthermore, VIP stimulates alkaline pancreatic juice and acid secretion, lipolysis, glycogenolysis, pentagastrin secretion, and inhibits histamine release [1], and is therefore widely considered to be a major regulator of human intestinal motility [6].

Normal VIP levels for a healthy adult range from 0–30 pmol/L or 0–190 pg/mL [2, 7]. Patients with VIPoma generally have elevated serum VIP levels ranging from 60 to as high as 2100 pg/mL [7]. Serum levels greater than 200 pg/mL is considered by several authors as a likely indication of VIPoma. Elevated serum VIP can be used to make a preliminary diagnosis of VIPoma when correlated clinically. Tissue sampling confirms the diagnosis.

3. Vasoactive Intestinal Peptide Tumor (VIPoma)

Originating in amine precursor uptake and decarboxylation (APUD) cells of the gastroenteropancreatic endocrine system and in adrenal or extra-adrenal neurogenic sites [1], VIPoma is a rare tumor that stimulates excessive production of the VIP hormone. By elevating VIP production, VIPoma causes symptomatic watery diarrhea through dysregulation of electrolyte shift in the gastrointestinal tract.

Although VIPoma has also been referred to as pancreatic cholera, it should be clarified that not all tumors arise from the pancreas. While 90% of known cases of this tumor arise from pancreatic endocrine cells, the remaining 10% arise from neural crest-derived tissues such as the pituitary, thyroid, adrenal medulla, and sympathetic nerve chains [2]. When VIPoma is found in the pancreas, 75% of the tumors occur in the corpus and cauda, while 25% occur in the pancreatic head, which may be of radiologic importance for diagnosis and follow-up for treatment [2]. Adult VIPomas are primarily neuroendocrine islet cell tumors of the pancreas [1]. The liver is another known source for VIPoma [4]. Interestingly, childhood VIPomas are more likely to form outside of the pancreas, in ganglioneuromas or ganglioneuroblastomas, arising from the neural crest tissue of sympathetic ganglia or the adrenal medulla [2, 5].

4. Incidence and Prevalence

The annual incidence of VIPoma in the United States has been reported as 0.05–0.2 per million adults [7]. Of the affected adult population, 65% are women and 35% are men,

whereas the pediatric population does not appear to have a gender predilection [8].

5. Clinical Presentation

VIPoma patients characteristically present with high volume, chronic, and intractable watery diarrhea causing significant pH and electrolyte imbalances [7]. Furthermore, there may also be an excessive loss of electrolytes resulting in hypo- or achlorhydria, hypokalemia, hypercalcemia, and interestingly, hyperglycemia and suffer clinically from a spectrum of related conditions [9]. The mechanisms of this diabetogenic effect and the calcium derangements seen with this condition are poorly understood. These electrolyte imbalances often result in many of the observed clinical symptoms: massive diarrhea, ECG abnormalities, muscle weakness, and renal failure [1].

Other symptoms associated with these neoplasms include abdominal pain, bloating, nausea, vomiting, skin rash, backache, facial flushing, and lethargy [7]. Furthermore, one author describes an association of this condition to increased colonic polyps [7].

6. Diagnosis

Diagnosis of VIPoma begins with a thorough history and clinical examination, followed by a comprehensive metabolic and chemistry panel as well as a VIP level with close attention to electrolytes such as potassium, sodium, chloride, as well acid-base disturbances, and glucose levels.

Computed tomography (CT), visceral angiography, magnetic resonance imaging (MRI), traditional and endoscopic ultrasound (EUS), and nuclear medicine scintigraphy have all been used to image pancreatic neuroendocrine tumors. Currently, either CT or MRI is the imaging modalities of choice in the primary evaluation of VIPomas. During the mid 1990s, two-phase dynamic incremental CT was considered standard, with a reported sensitivity ranging from 64–82% [10, 11]. The role of MRI, however, has quickly gained recognition as an equivalent, if not superior, modality for diagnosing pancreatic tumors, with a reported sensitivity of 75–100% [11, 12]. There is also a suggestion that MRI may be superior in imaging tumors less than 2.5 cm in diameter [12] with one retrospective study finding tumors as small as 1 cm in diameter [12].

Transabdominal ultrasonography (US) has played a limited role in primary detection of pancreatic tumors with a sensitivity of approximately 60%. There is, however, a clear role for US, and in particular EUS, in patients undergoing both diagnostic and preoperative evaluations as it provides high-resolution images of the pancreas and surrounding structures [13]. In a relatively large prospective trial evaluating the use of EUS, Anderson et al. found a sensitivity of 93% in detecting pancreatic tumors with a mean tumor diameter of 1.51 cm [13]. Furthermore, EUS has showed the added utility of allowing fine needle aspiration to distinguish visualized masses further aiding in diagnosis, staging, and in determining a management strategy [14, 15].

Visceral angiography is generally less sensitive than both MRI and CT in localizing neuroendocrine tumors. With reported sensitivity of approximately 66% [10], the clinician must weigh the risks of invasive angiography with the benefits of information gained. In patients with hepatic dominant disease and substantial symptoms caused by tumor bulk or release of VIP, procedures such as hepatic artery embolization or chemoembolization may be of benefit [16, 17]. For these patients, visceral angiography may provide important information preoperatively, especially in preembolization vascular mapping [10].

7. Imaging

Following VIP level analysis, magnetic resonance imaging (MRI) and computed tomography (CT) are employed for localization of disease, and aid in biopsy and determining resectability (see Figure 1). Naturally, the sensitivity of these two imaging techniques improves with increasing tumor size [12, 18]. If the tumor is larger than 3 cm, there is a 50–80% sensitivity in its identification via imaging, while one which is smaller than 3 cm can be detected with a 30–40% sensitivity [12, 18]. These imaging techniques also yield useful information regarding the local anatomy of the tumor, presence of metastases, staging, and may ultimately affect the decision of medical versus surgical management.

8. Scintigraphy

Additionally, a more advanced method of detecting islet-cell tumors, including VIPomas, has been reported by Virgolini et al. [19]. Somatostatin receptor scintigraphy employs the use of somatostatin analogs in binding with the high affinity receptors overexpressed in a number of such tumors [19]. One such procedure is known as the octreotide scan. In this procedure, the patient is given a small amount of a radioactive agent, usually Indium111-labeled octreotide that is absorbed by the VIPoma [19]. Other markers, beside Indium111-labeled octreotide, include radiolabelled DOTA-Tyr(3)-octreotide and DOTA-Tyr(3)-octreotate derivatives which have shown considerable improvement of imaging results with increased tumor uptake [19]. Of note, the (68)Ga-labelled DOTA-Tyr(3)-octreotide scan has been demonstrated with promising success for pancreatic islet-cell tumors, as it has been attributed to its high-affinity binding to the somatostatin receptor subtype 2 in combination with positron emission tomography (PET) technology [19]. Finally, there have been reports of the successful use of iodine-123-VIP scintigraphy, further adding an important assay to the diagnostic armamentarium [20]. The combination of diagnostic techniques allows more comprehensive staging and guide in the management of such tumors.

9. Other Diagnostic Modalities

Other diagnostic procedures such as arteriography, endosonography, and venous sampling can aid in the diagnosis of

VIPomas [21, 22]. These processes have been demonstrated to be effective, and are considered when a diagnosis is unclear or further anatomical or metastatic information is required.

10. Histology

After imaging studies localize the tumor, sampling of the tissue in the form of a biopsy or aspirate yields the final and official diagnosis. Histologically, a VIPoma demonstrates a composition of uniform, small to intermediate-sized cells in clusters, nests, and trabecular growth patterns with hyperchromatic nuclei and scant cytoplasm [23]. A few nests may also exhibit pseudorosettes [23]. Immunohistochemistry of this entity typically reveals positive immunoreactivity for vasoactive intestinal peptide, cytokeratin, neuron specific enolase, chromogranin, synaptophysin and somatostatin, and negative reactivity for S100, calcitonin, PSA, CEA, insulin, glucagon, and growth hormone [23]. (See Figure 2).

11. Staging

Proper diagnosis and staging of VIPoma are the most principal determinants of treatment modalities. Due to the relative rarity of VIPoma, even among other neuroendocrine tumors, this entity is usually discussed together with somatostatinoma and pancreatic polypeptide cancers in the “miscellaneous” islet cell carcinoma category, separate from their more common and somewhat better studied counterparts: gastrinoma, insulinoma, and glucagonoma [16].

12. General Treatment Principles

According to the most recent recommendations of the National Cancer Institute (NCI), surgery constitutes the mainstay of therapy, and should be considered standard of care when tumors are localized and lend themselves to resection. Without metastases, a single lesion in the head of the pancreas or a small lesion (less than 1.0 cm) in the body or tail of the pancreas can be treated with enucleation if surgically feasible [16]. For larger lesions in the body or tail or for multiple pancreatic tumors, distal pancreatectomy [16] or Whipple procedure may be performed depending upon the intraoperative findings [10]. Metastatic disease to lymph nodes or distant sites and VIPomas originating in locations other than the pancreas should also be resected when possible [16]. There is limited data on the utility of radiofrequency [16, 24] and cryosurgical ablation [16] when disease sites are not resectable by conventional techniques.

In the majority of patients with pancreatic neuroendocrine cancers, an aggressive surgical approach is indicated with the intent of cure via complete resection of the primary lesion and metastases [10]. Surgical cure is less feasible in those patients with advanced metastatic disease and, therefore, determining the extent of disease as well as the size and anatomic locations of any metastases plays a pivotal role in defining a management strategy. For this purpose,

FIGURE 1: *MRI*: MRI scans obtained with permission from a 32 year-old male with a mass in the region of the tail of the pancreas. (a) Coronal HASTE image through the plane of the gall bladder fossa demonstrates multiple liver lesions which are heterogeneous and fully to moderately hyperintense (arrows). (b) Fat suppressed axial image through the tail of the pancreas demonstrates a low-attenuation lesion in the region of the tail of the pancreas which is conspicuous against a background of high signal intensity pancreas (short arrow). Liver metastasis in the medial segment of the left lobe of the liver is also observed (long arrow). (c) Precontrast T_1 -weighted axial image at the level of the portal vein demonstrates multiple low-attenuation lesions throughout the liver (arrows), predominantly located in the left lobe. (d) Early postgadolinium axial T_1 -weighted image demonstrates radial enhancement of the multiple liver lesions, suggestive of metastases from a neuroendocrine tumor. These images are courtesy of Dr. Richard Semelka of University of North Carolina, Chapel Hill.

surgical exploration including intraoperative ultrasonography remains essential for the localization of occult tumors not seen with conventional imaging [10].

13. Systemic Therapy

13.1. Medical (Nonsurgical)

13.1.1. Chemotherapy. Cytotoxic chemotherapy for VIPoma attempts to destroy the cancer cells, and is administered either orally or by injection. Success rates have been relatively low, however, they improve with combination chemotherapy or in addition to surgical resection. In patients with unresectable disease, combination chemotherapy with doxorubicin and streptozocin should be used [25]. Combination of fluorouracil and streptozocin can be given to patients in whom doxorubicin is contraindicated [16, 25]. Chlorozotocin, a drug structurally similar to streptozocin, is currently under investigation in its role in combination with fluorouracil to provide a regimen which may be more tolerable [25].

Though the treatment effectively terminates cancerous cells, these chemotherapy agents are not without side effects, such as bone marrow suppression, leukopenia, anemia, and/or thrombocytopenia leading to an elevated risk of

infections, bruising, and bleeding. Other side effects include poor appetite, vomiting, nausea, diarrhea, oral sores, hair loss, and fatigue.

13.1.2. Biologic Therapy (Immunotherapy). Biologic therapy includes administration of alpha interferon. Treatment by biological therapy is used to relieve symptoms rather than effectively terminate cancerous cells of VIPoma [26, 27]. Alpha interferon inhibits both tumor growth and the biochemical response of the tumor cell by limiting hormone release; the biological treatment agent simulates natural killer cell function by these mechanisms. Though more than 500 patients have been treated with alpha interferon, only 11% experienced actual tumor regression, and when compared to long-acting somatostatin analogs, the two treatments appear to differ primarily in the area of side effects [26, 27]. In treating these symptoms, alpha interferon has been noted to have severe potential side effects including fatigue, depression, and flu-like symptoms [26, 27].

13.1.3. Hepatic Artery Embolization. Hepatic artery embolization (HAE) is a procedure designed to block the blood supply to the tumor by sealing off the blood vessels flowing to the affected area [28, 29]. It is used in patients

FIGURE 2: *Histology*: (a) this image reveals uniform, small- to intermediate-sized cells in clusters, nests, and trabecular growth pattern. The cells demonstrate enlarged hyperchromatic nuclei and scant cytoplasm. A few nests may exhibit psuedorosettes. (b) Immunohistochemistry of this entity typically reveals positive immunoreactivity for vasoactive intestinal peptide (VIP). VIPoma also stains positive cytokeratin, neuron-specific enolase, chromogranin, synaptophysin and somatostatin, and negative reactivity for S100, calcitonin, PSA, CEA, insulin, glucagon, and growth hormone (not shown).

with a hepatic primary or metastatic involvement. HAE targets specific sites within the hepatic parenchyma [28, 29].

13.1.4. Somatostatin/Octreotide. Somatostatin administration has been shown to stop diarrhea and normalize electrolyte and acid-base imbalances induced by VIP. Octreotide, the most common hormonal therapy, is administered to relieve symptoms induced by the tumor [30–32]. The hormone, in the form of sandostatin, can be administered daily via subcutaneous injections or monthly by intramuscular injections [30–32].

Somatostatin and octreotide, though effective initially in controlling diarrhea, have one major drawback. They are known to become gradually ineffective as resistance toward this medication develops. Therefore, these agents are only short-lasting solutions to combat the symptomatic component of VIPomas [30–32].

13.1.5. Supportive Therapy. Volume loss is a key concern in VIPoma, and rigorous volume replenishment, and meticulous electrolyte correction is the mainstay of supportive management of this condition. Antidiarrheal medications such as loperamide, often in combination with octreotide,

are used in preventing large outputs of diarrhea, especially in cases where frequent breakthroughs are affecting the patient.

13.2. Surgical Approach. Of the treatments options for VIPoma, surgery is the most common and successful method. Although excision of VIPoma is undoubtedly the most effective treatment method, this is not always possible due to the presence of extensive metastasis and/or significant morbidity associated with collateral surgical impairment during the procedure.

The type of surgery performed is highly dependent on the location and the size of the neoplasm. The Whipple procedure is one surgical option. This procedure, which involves the surgical removal of the pancreas head and part of the small intestine, bile duct, and stomach, may be required in order to effectively treat the patient. Following these procedures, the digestive tract and biliary system are anastomosed [33, 34]. Nevertheless, if the VIPoma is localized to a single organ, such as the pancreas, localized resections have also produced satisfactory results [33, 34].

Partial or complete pancreatectomy may result in insulin-dependent diabetes mellitus on account of insulin depletion from pancreatic damage or resection. These patients should be treated similar to an insulin-dependent diabetic. Additionally, other endocrine and exocrine hormones replacement must be considered whenever a pancreatectomy is performed. The stomach and spleen are not commonly resected organs as they may be affected by the spread of tumor or related pathology. Nevertheless, the general side effects of surgery, such as post-op pain, infection, bleeding, fatigue, and others, should be considered for the elderly and other patients with limited tolerability for such invasive procedures [33, 34].

13.3. Emerging Therapy. Though currently considered an investigative treatment technique, researchers have found that somatostatin-receptor antibodies attached to radioactive isotopes, such as indium 111, have the potential to treat VIPomas and other neuroendocrine neoplasms, in a similar fashion used to diagnose this condition (see above Diagnosis section). The antitumor antibodies are thought to be effective because they utilize the overexpression of somatostatin receptors in such tumors.

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