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CASE REPORT

VIPoma with expression of both VIP and VPAC1 receptors in a patient with WDHA syndrome

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Abstract We report a case of VIPoma in a 72-year-old female patient who presented with excessive diarrhea, severe hypokalemia, and acidemia. She had been referred to our hospital three times because of severe diarrhea. No primary tumor site was found by conventional techniques, including contrast-enhanced CT and MRI, angiography, endoscopy, and positron emission tomography (PET), but a tumor was subsequently found in the head of the pancreas by octreotide scanning. Her diarrhea diminished dramatically after octreotide treatment, while her diarrhea has ceased without the therapy of octreotide at the first admission in the course of 2 years of her disease. Immunohistochemial analysis of the excised tumor tissue revealed the expression of both vasoactive intestinal peptide (VIP) and VIP and pituitary adenylate cyclase-activating peptide 1 (VPAC1) receptors. This is the first case report of a VIPoma that immunostains for VIP and VPAC1 receptors and indicates that abundant VIP produced by VIPoma might inhibit its growth and reduce VIP secretion via the VPAC1 receptor in vivo.

Keywords VIPoma · WDHA syndrome · Diarrhea · Octreotide · VPAC receptor

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Introduction

VIPoma is a rare neuroendocrine tumor with an incidence of less than one case per million per year [1]. Verner and Morrison [2] first described the association of the syndrome of severe, watery diarrhea, and hypokalemia with islet cell tumor. Bloom et al. [3] recognized that patients with this syndrome, Verner–Morrison syndrome, watery diarrhea, hypokalemia, achlorhydria (WDHA) syndrome, and VIPoma syndrome have elevated plasma levels and a high tumor content of vasoactive intestinal peptide (VIP), as well as VIP-containing cells in tumor tissue. We report a case of excessive diarrhea caused by VIPoma in a 72-year-old female patient. Her diarrhea diminished dramatically after treatment with octreotide, while her diarrhea have ceased without the therapy of octreotide at the first admission in the course of 2 years of her disease. This is the first case report of VIPoma that immunostains for both VIP and VIP and pituitary adenylate cyclase-activating peptide 1 (VPAC1) receptors, and it indicates that abundant VIP produced by VIPoma might inhibit its growth and reduce VIP secretion via the VPAC1 receptor in vivo.

Case report

A 72-year-old-woman was admitted to our hospital with a stool output of 3 l/day. On hospitalization, the patient suffered from weakness, tachycardia (150 beats/min), and hypotension (90/52 mmHg). There were no specific gastrointestinal symptoms except diarrhea. The abdominal examination was unremarkable. Biochemical examination revealed metabolic acidosis (pH 7.099, HCO_3^- 5.1 mEq/l), low potassium concentration (1.9 mEq/l), and slightly elevated calcium (11.5 mg/dl) and CRP (5.3 mg/dl) levels. Elevated urea (90.1 mg/dl) and creatinine (6.4 mg/dl) levels were also present. Initial evaluation of stools included bacterial cultures and fecal fat, which indicated normal values. Colonoscopy showed no signs of inflammation. Although ultrasound, contrast-enhanced CT and MRI, endoscopy, angiography, gallium scintigraphy, and positron emission tomography (PET) were performed, no tumor site was located. Despite efforts to relieve symptoms by administration of appropriate fluids, electrolytes, and antidiarrheal drugs, she developed florid diarrhea, producing 3–5 l watery stools per day for 1 month. The findings of secretory diarrhea, lowered potassium level, and acidosis indicated a presumptive diagnosis of WDHA syndrome. The blood level of VIP was significantly elevated at 670 pg/ml (normal range 0–100 pg/ml). Other gastrointestinal hormones showed the following values: somatostatin, 20 pmol/l (normal <100 pmol/l); gastrin, 130 pg/ml (normal range 1.6–12 pg/ml). The clinical findings led to the diagnosis of WDHA syndrome with elevated VIP levels [4, 5]. However, we could not locate any secretary tissue or organ that might constitute the VIPoma. Her diarrhea disappeared suddenly on day 50. Treatment with the somatostatin analog octreotide (100 μg/day subcutaneously once daily) was started, so that VIPoma did not cause diarrhea. She remained in good physical condition and her metabolic abnormalities improved. On day 65, the plasma concentration of VIP decreased to 45 pmol/l, and administration of octreotide was withdrawn and the patient was discharged. She remained healthy, without diarrhea, and was not treated with octreotide for 1 year after the hospital discharge. Thereafter, she was intermittently treated with octreotide when she suffered from WDHA syndrome.

Although the patient was examined repeatedly for the presence of a tumor, no tumor site was located. No further attempts to detect the tumor by octreotide scanning could be made, because this was not permitted by the Ministry of Health of Japan and the patient refused further scanning. However, because of the considerable risk of tumor growth and metastasis, and repeated diarrhea, which might result in life-threatening dehydration, she finally agreed to another octreotide scan. The scan was performed after administration of 244 MBq of indium 111-labeled octreotide on day 675. Planar imaging performed 24 h after injection demonstrated intense uptake in the region of the head of the pancreas. There were no other areas of increased uptake to confirm the presence of metastasis (Fig. 1). The pancreatic mass was surgically debulked. Laparotomy confirmed the presence of a tumor nodule (2 cm in diameter) in the head of the pancreas, which was excised by wedge resection (Fig. 2).

Histological examination confirmed the diagnosis of VIPoma. Light microscopy of the tumor parenchyma

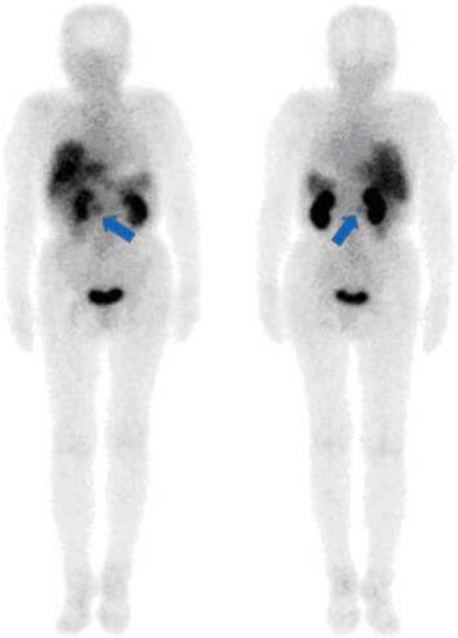

Fig. 1 Octreoscan showing intense activity 24 h after injection at the location of the pancreatic tumor, with no signs of metastatic activity

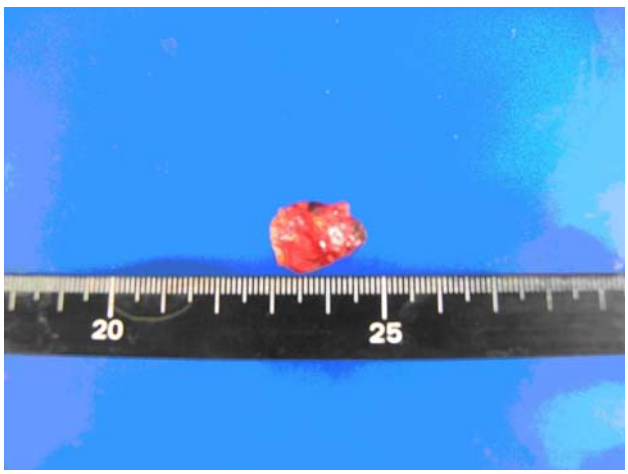

Fig. 2 Gross pathologic specimen shows the resected VIPoma that was present within the pancreatic head

revealed pseudoglandular structures intermingled or continuous with sparse solid nests. These duct-like structures were formed from columnar cells. Several tumor cells with round nuclei in mitosis were observed (Fig. 3a). Immunocytochemistry on formalin-fixed postmortem tissue using an unlabeled antibody enzyme method was positive for antibody to VIP (Biomol, Hamburg, Germany) (Fig. 3b) and chromogranin A (Dakopatts, Glostrup, Denmark).

Strongly immunoreactive cytoplasmic areas were observed on the side facing the interstitium. The tumor cells were also positive for somatostatin receptor 2 (SSR2) (Novus Biologicals, Littleton, CO, USA) (Fig. 3c).

Interestingly, they were positive for the VPAC1 receptor (AS58; GeneTex, Inc., San Antonio, TX, USA) (Fig. 3d) but not for the VPAC2 receptor (AS69, GeneTex, Inc., Texas).

These results suggest that there might be an autocrine negative feedback loop for VIP via the VPAC1 receptor in vivo. Postoperatively, the patient remained diarrhea-free and in good physical condition without the need for octreotide medication.

Discussion

The diagnosis of VIPoma with associated WDHA syndrome can be confirmed by repeated elevated serum levels of VIP in excess of 200 pg/ml [4, 5]. In most cases (90%), VIPoma originates from endocrine pancreatic cells [6]. When the tumor is located outside of the pancreas (10%), it arises from other organs containing neural crest-derived cells, such as cells of the pituitary and thyroid glands, adrenal medulla, and sympathetic nerve chains [7].

Vasoactive intestinal peptide is a 28-amino acid peptide that was first isolated from the porcine duodenum and found to be similar to pituitary adenylate cyclase-activating polypeptide [8, 9]. VIP is expressed in the central nervous system and neurons of the gastrointestinal, respiratory, and urogenital tracts. In the gastrointestinal tract, VIP is a potent stimulator of adenylate cyclase and adenosine 3′,5′-cyclic phosphate, leading to massive secretion of water and electrolytes, mainly chloride and potassium [10]. Pharmacological evidence suggesting that VIP acts via multiple receptors has been confirmed by the cloning of two VIP receptors, VPAC1 and VPAC2 receptors, which have very

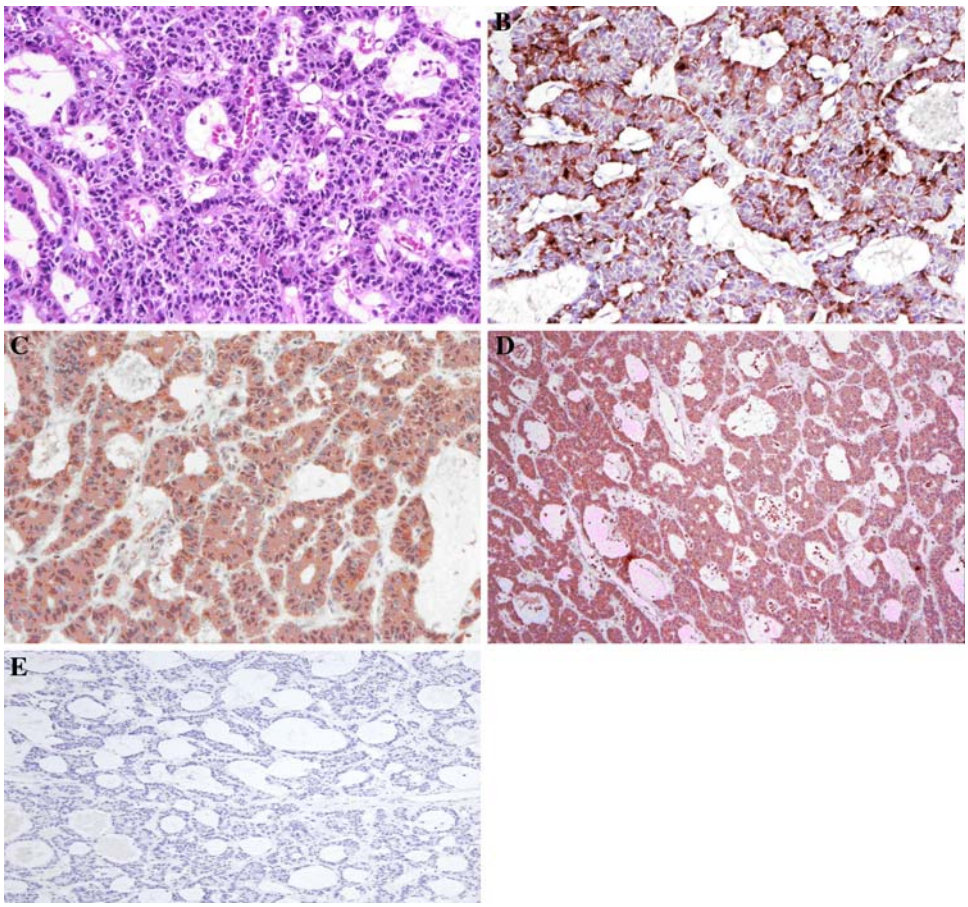

Fig. 3 **a** VIPoma cells are columnar and arranged to form pseudoglandular structures, intermingled or continuous with sparse solid nests. Hematoxylin and eosin stain; original magnification, ×60. **b** Immunohistochemical analysis showed strong immunopositivity for VIP in VIPoma tissue. Original magnification, ×60. **c** Immunohistochemical analysis showed strong immunopositivity for SSR2 in VIPoma issue. Original magnification, ×60. **d** Immunohistochemical analysis showed strong immunopositivity for the VPAC1 receptor in VIPoma issue. Original magnification, ×30. **e** Negative control, which was a preincubation of the antibodies with the immunogen. Original magnification, ×30

different amino acid sequences [11]. The mRNAs for the two receptors have completely different distributions, as mapped by in situ hybridization histochemistry. VPAC1 receptor mRNA is predominantly found in the lung, small intestine, thymus, walls of pancreatic blood vessels, and cerebral cortex and hippocampus of the brain. VPAC2 receptor mRNA is present in a number of areas where VIP acts but the VPAC1 receptor mRNA is not present, including the stomach, pancreatic islet, and testes [12]. However, there are no studies that delineate well-defined differences between the VPAC1 and VPAC2 receptors. Both these receptors stimulate cyclic adenosine-3,5-monophosphate (cAMP) accumulation. Higher concentrations of peptides were required to stimulate cAMP production via the VPAC2 receptor compared with the VPAC1 receptor in vitro [13].

More recent studies suggest that VIP regulates the growth and function of tumor cells [14]. Although little is known about the role of VIP as a mediator of normal and neoplastic pancreatic duct cell growth, VIP clearly regulates the growth of other normal and neoplastic cells. VIP inhibits the growth of small cell lung cancer [15], neuroblastoma cells [16], gastric carcinoma cells [12], and colonic adenocarcinoma cells in vitro [17]. The ability of VIP to inhibit cell growth appears to be linked to adenylyl cyclase activation. Indeed, the VPAC1 receptor coupling to both adenylyl cyclase and phospholipase C has been demonstrated in certain cell types [18], and cAMP analogs, such as 8-Cl- or N^6-benzyl-cAMP, were found to inhibit the growth of several human colon cancer cell lines, including HT29 [19]. This inhibition was due to delayed G1/S transition and a reduced rate of DNA synthesis rather than a cytotoxic effect [17]. Dose-related inhibition of cell proliferation by VIP and concentration-dependent increases in cAMP induced by VIP were reported [13, 15]. These effects are only slight in the presence of very low concentrations of VIP. However, the regulation of cell growth by VIP is quite unclear, and the observed effects are usually very weak in very specific experimental conditions.

VIPoma expresses the receptor for VIP, but which subtype is expressed (VPAC1 or VPAC2) is unknown; and the VIPoma cells in this case were immunostained for VIP and VPAC1. Moreover, this patient's diarrhea symptom ceased in the early phase of the disease without octreotide therapy. This clinical course suggests that abundant VIP produced by VIPoma might inhibit the growth of VIPoma and reduce the secretion of VIP via the VPAC1 receptor in vivo. This can be demonstrated at high concentrations of VIP but not at low concentrations.

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