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Pancreatic VIPomas: Subject Review and One Institutional Experience

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Abstract VIPomas are rare pancreatic endocrine tumors associated with a well-defined clinical syndrome characterized by watery diarrhea, hypokalemia, and metabolic acidosis. The objective of this study was to review a single institution's experience with VIPomas, as well as to review the English literature. A retrospective review of the Johns Hopkins pancreatic database revealed four cases of VIPoma, with three patients being male. All patients presented with watery diarrhea, hypokalemia, hypercalcemia, and acidosis. All patients had no family history of multiple endocrine neoplasia. Computed tomography revealed the primary pancreatic tumor in all patients, with three tumors located in the tail of the pancreas. One tumor involved the entire pancreas. Computed tomography and/or octreotide radionuclide scans identified hepatic metastasis in three patients. Mean serum vasoactive intestinal polypeptide levels were 683 pg/ml (range 293 to 1,500 pg/ml). All patients underwent resection of the pancreatic primary tumor. Two patients also had simultaneous liver resections. All patients had evidence of malignancy as defined by the presence of metastatic lymph nodes and/or hepatic metastases. Two patients had complete resolution of symptoms after surgical resection. One patient required radioablation of liver metastases and adjuvant octreotide therapy for control of symptoms. One patient died of progressive metastatic disease 96 months after surgery, whereas the other three remain alive. Extended, meaningful survival can be achieved for VIPoma patients, combining an aggressive surgical approach with additional strategies for treatment of unresected disease.

Keywords VIPomas · Diarrhea · Primary pancreatic tumor

Introduction

Vasoactive intestinal polypeptide (VIP)-secreting tumors of the pancreas are rare islet cell tumors associated with secretory diarrhea. The annual incidence of these tumors is estimated to be about 1 per 10,000,000 individuals in the general population.[1] At the time of presentation, over 70% of patients have metastases identified,[2] and the great majority of these tumors are malignant based on the presence of either hepatic, distant, or lymph node metastases.[3] Ninety percent of VIPomas in adults are primary tumors of the pancreas, although they have been described in the colon, bronchus, adrenals, liver, and sympathetic ganglia.[4] In children, however, these tumors are most commonly found in the adrenal glands and sympathetic ganglia. The clinical syndrome that accompanies this tumor most commonly includes watery diarrhea, hypokalemia, and achloryhdria (or metabolic acidosis); thus, it is commonly referred to as the WDHA syndrome. Other names for the syndrome include watery diarrhea syndrome, pancreatic cholera syndrome, endocrine cholera, and the Verner–Morrison syndrome.

The first description of watery diarrhea and hypokalemia in relation to a pancreatic islet cell tumor was by Priest and Alexander in 1957.[5] They described a 56-year-old woman that had previously undergone resection of an islet-cell tumor from the body and tail of her pancreas. At the time of resection her only symptom was left-sided abdominal pain.

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Six years later, she presented with symptoms of intractable watery diarrhea and hypokalemia. She was medically managed for approximately 1 year before her death. At autopsy, she was found to have a recurrent islet-cell tumor in the pancreatic remnant with no evidence of metastases. In 1958, Verner and Morrison described two male patients, a 67-year-old and a 19-year-old, who had similar presentations with refractory watery diarrhea and hypokalemia. Both patients died secondary to cardiac arrhythmias related to their hypokalemia and each patient had a pancreatic islet cell tumor without metastases at the time of autopsy.[6] In 1973, Bloom et al. found an association between this syndrome, an elevated plasma VIP level, and an increased tumor content of VIP.[7] In 1983, Kane et al.[8] successfully reproduced the clinical syndrome by infusing five healthy human subjects with porcine VIP to achieve VIP levels similar to those of patients with VIPomas. They found that all the subjects developed profuse watery diarrhea within 4 h of infusion, thus solidifying the assertion that VIP is the mediator of the WDHA syndrome.

Vasoactive intestinal polypeptide is a 28-amino acid polypeptide with close structural homology to secretin. Unlike the hormone secretin, VIP normally functions exclusively as a neurotransmitter. In addition to being present in enteric neurons, VIP is also present in neurons of the brain, spinal cord, lung, urogenital system, and other endocrine organs. Vasoactive intestinal polypeptide has a half-life of less than 1 min in the circulation. Plasma levels in normal individuals are quite low and unresponsive to the ingestion of a meal. Among the potential normal actions of VIP are stimulation of enteric smooth muscle,[9] stimulation of pancreatic exocrine and intestinal secretion,[10] inhibition of gastric acid secretion,[11] and modification of immune function and gastrointestinal blood flow.[12] Direct effects on enteric smooth muscle cells and modulatory effects on interneurons have been demonstrated.[13] Two VIP receptors have been cloned: VIP1 (or VPAC1) and VIP2 (or VPAC2) receptors. Both are typical members of the secretin family of G protein-coupled receptors. Vasoactive intestinal polypeptide is also well recognized by the PACAP (or PAC1) receptor. Secretin is recognized weakly by the VIP1 receptor and not at all by the VIP2 receptor.[14] The specific tissue and cellular distribution of these receptors is currently being characterized.

We present our institutional experience with surgically resected pancreatic VIPomas, along with a review of the English language literature describing reports of both surgically resectable and unresectable tumors.

Patients: Clinical History And Management

Patient #1 A 74-year-old male presented to an outside hospital with several months of profuse watery diarrhea. The patient had multiple admissions to the outside hospital for dizziness and dehydration related to his diarrhea. He was repeatedly treated with oral rehydration solutions and electrolyte repletion without resolution of his symptoms. Prior workup had included extensive serologies, esophagogastroduodenoscopy, colonoscopy, fecal leukocytes, clostridium difficile toxin, ova and parasites, quantitative 72-h fecal fat collection, and small bowel series, all of which were negative. Magnetic resonance imaging (MRI) of the abdomen eventually revealed an 11×7×7-cm mass in the tail of the pancreas that abutted the splenic vasculature, stomach, and left adrenal gland, but without clear evidence of local invasion. Octreotide therapy was initiated with good control of his diarrhea and the patient was referred to Johns Hopkins for definitive surgical management.

Abdominal computed tomography (CT) with intravenous contrast was performed to assess surgical resectability of the mass (Fig. 1). The mass compressed and obstructed the splenic vein and displaced the splenic artery. The portal vein, superior mesenteric artery, and celiac artery were patent. His electrolytes, most notably potassium, chloride, and calcium, were all within normal limits. Hormone levels were obtained, which revealed a serum VIP level of 293 pg/ml (normal range 0–50 pg/ml), pancreatic polypeptide (PP) level of 2,087 pg/ml (normal range 51–326 pg/ml), and chromogranin A level of 78 pg/ml (normal range 6–39 pg/ml). His other hormone levels included a normal glucagon, gastrin, and insulin. In addition, the tumor markers CEA and CA19-9 were normal.

The patient underwent a distal pancreatectomy with en bloc splenectomy. The final pathology from this procedure revealed a 14.5-cm well-differentiated pancreatic islet cell tumor, which extended into the peripancreatic soft tissues with involvement of one of eight regional lymph nodes. Immunohistochemical stains of the tumor revealed focally positive staining for VIP (Fig. 2). The patient recovered well, and his serum VIP levels immediately postoperatively and at 1-month follow-up were 40 and 34 pg/ml, respectively. Likewise, his PP and chromogranin levels at 1 month postoperatively normalized to 400 and 31 pg/ml, respectively. The patient is alive, asymptomatic, and disease-free 17 months after his surgical resection.

Patient #2 This 50-year-old woman presented with a 2-month history of diarrhea, vomiting, and anorexia. She was taken to the cardiac care unit emergently following a 10-s episode of asystole. Subsequent evaluation revealed a potassium level of 1.6 mEq/l, a calcium level of 11.7 mg/dl, and a metabolic acidosis (pH 7.25). The patient's watery diarrhea and hypokalemia were believed to be related to a gastrointestinal, endocrine, or renal abnormality, given the broad constellation of signs and symptoms. Thyroid function tests (thyroid-stimulating hormone, T_4, T_3), parathyroid

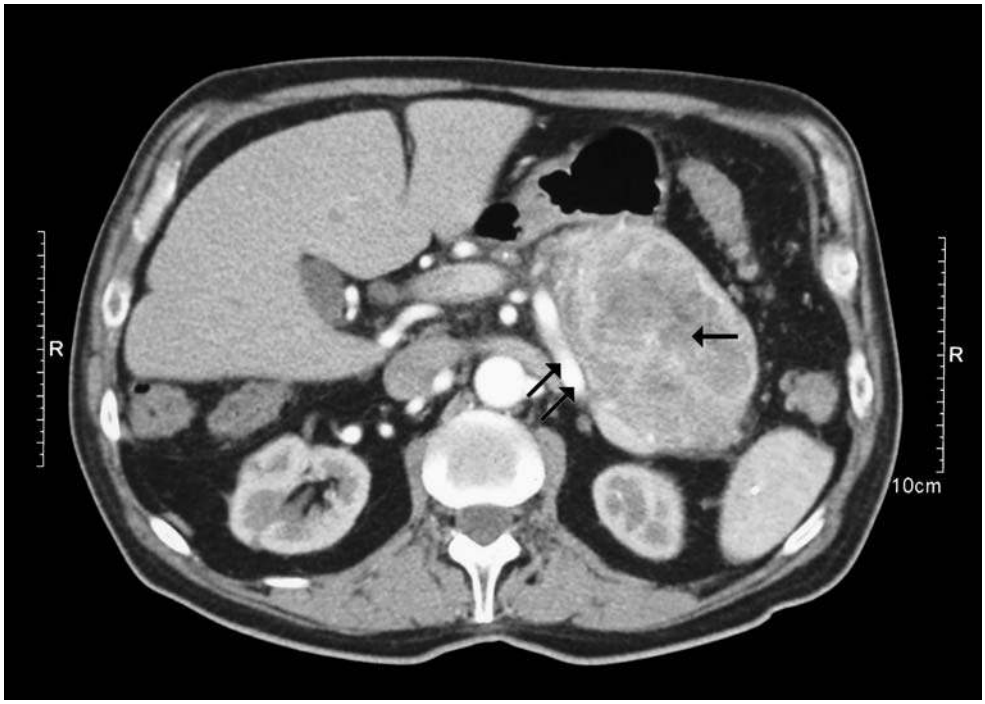

Figure 1 Abdominal CT scan of patient 1 showing large mass of the tail of the pancreas (*arrow*) with displacement of the splenic artery (*double arrow*).

hormone, and serum cortisol were normal. An abdominal CT scan revealed a 3.5-cm mass in the tail of her pancreas and multiple hypodense lesions in the liver, consistent with metastases. Her serum VIP level was 770 pg/ml, with a serum gastrin level of 500 pg/ml. After intravenous hydration and electrolyte repletion, the patient was started on parenteral octreotide in preparation for surgery.

The patient underwent a distal pancreatectomy with en bloc splenectomy, open cholecystectomy, and wedge resection of several hepatic metastases. The final pathology revealed a 4.5-cm islet cell tumor of the body of the pancreas with infiltration into the peripancreatic soft tissues and involvement of one of 14 resected regional lymph nodes. The liver masses measured from 0.5 to 2 cm and were biopsy-confirmed to represent metastatic islet cell tumor. Postoperatively, her serum VIP and gastrin levels declined to less than 35 and 118 pg/ml, respectively. The patient received octreotide therapy for management of her metastatic disease and died 8 years after her pancreatectomy from tumor cachexia related to advanced metastatic disease.

Patient #3 A 66-year-old male presented with a 6-month history of watery diarrhea and a 40-lb weight loss. His laboratory values at the time of presentation were notable for a metabolic acidosis (pH 7.21) and hypokalemia (2.8 mEq/l). His serum VIP level was 169 pg/ml. A CT scan of the abdomen demonstrated an exophytic mass involving the tail of the pancreas measuring 3×5×6 cm without evidence of adenopathy or hepatic involvement (Fig. 3). He also underwent an octreotide radionuclide study, which demonstrated scattered radiotracer uptake in the liver, most consistent with hepatic metastases (Fig. 4).

The patient underwent a distal pancreatectomy with en bloc splenectomy, open cholecystectomy, and resection of segments II and III of his liver. Final pathology of the resected tissue demonstrated a 5-cm malignant endocrine

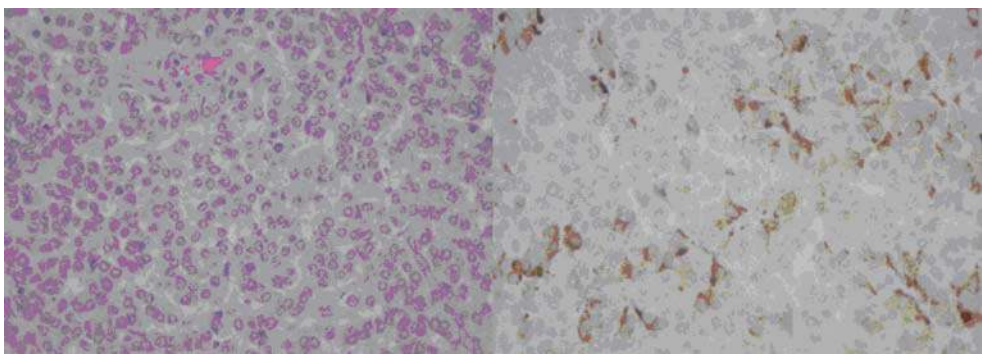

Figure 2 *Left*: Pancreatic VIPoma in patient #1 demonstrating classic features of a neuroendocrine lesion with trabecular architecture and low grade, uniformly round nuclei with finely speckled chromatin (hematoxylin and eosin, ×400). *Right*: Immunohistochemical staining of the tumor demonstrating focal positivity for VIP (VIP immuno stain, ×400).

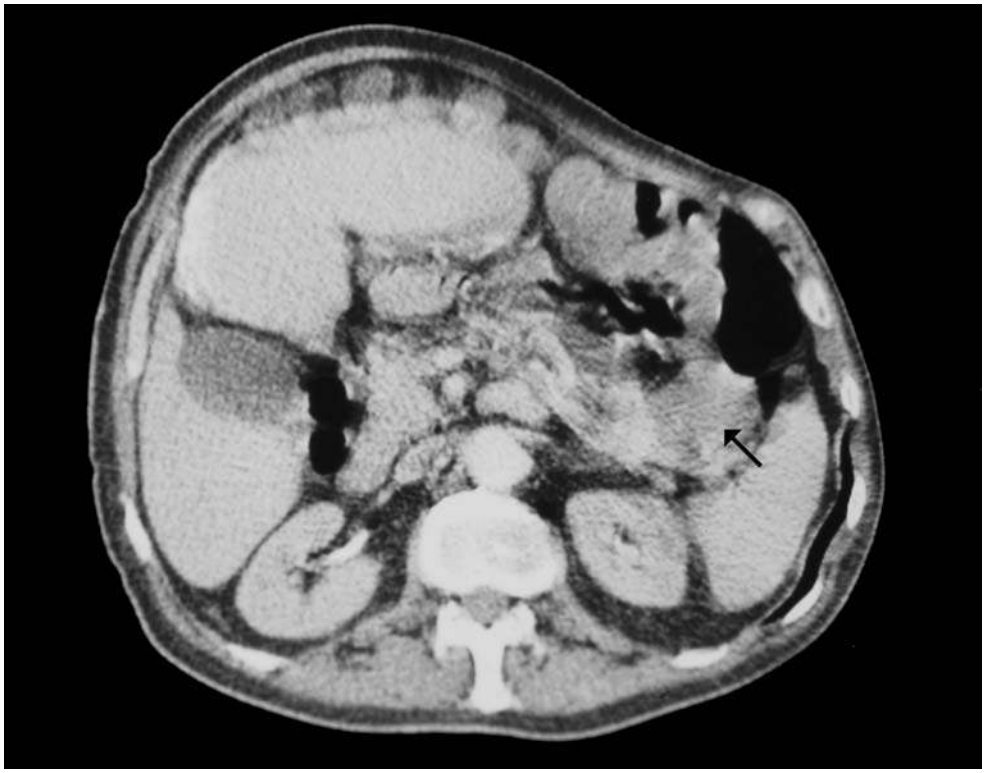

Figure 3 Abdominal CT scan of patient 3 demonstrating a hypodense pancreatic tail mass (*arrow*).

neoplasm of the pancreas with large vessel vascular invasion, invasion of peripancreatic soft tissues, and lymph node involvement. The resected segments of the liver also revealed two foci, measuring 1.7 and 0.3 cm, of metastatic neuroendocrine neoplasm. Immunohistochemical staining was positive for chromogranin, synaptophysin, and neuron-specific enolase, whereas stains for somatostatin, insulin, serotonin, glucagon, and gastrin were negative. An immunohistochemical stain for VIP was unavailable at the time of tissue processing. His postoperative serum VIP level declined to 58 pg/ml and his 1-month follow up VIP level was 32 pg/ml. The patient is still living 68 months after resection of the primary tumor, and had rising VIP levels and recurrent diarrhea. He has since undergone a partial hepatectomy and radiofrequency ablation of persistent metastases with some decline in VIP levels. He is currently receiving long-acting (depot) octreotide treatment, with excellent control of his diarrhea.

Patient #4 A 68-year-old gentleman presented to an outside hospital with increased weakness, weight loss, and an 8- to 9-year history of diarrhea requiring multiple hospitalizations for dehydration. His laboratory values at the time of presentation were significant for an elevated calcium level at 10.7 mg/dl and hypokalemia (3.1 mEq/l). After an abdominal CT scan was suggestive of a pancreatic malignancy, a serum VIP level returned at 1,500 pg/ml. The CT scan showed a large heterogeneous tumor involving the entire pancreas measuring approximately 8 cm in the anteroposterior dimension and 14 cm in width, with multiple hepatic and lymph node metastases (Fig. 5). There was evidence of encasement of the splenic and hepatic arteries by the tumor, with external compression of the portal/splenic vein confluence. The patient was started on octreotide with relatively good control of his diarrhea and was then referred for definitive surgical management.

The patient underwent a pylorus preserving total pancreaticoduodenectomy with en bloc splenectomy. Final pathology demonstrated a malignant neuroendocrine neoplasm measuring 14 cm in maximal dimension, centered in the head of the pancreas and extensively infiltrating the remainder of the pancreas. The lesion extended into the peripancreatic fat, but all resection margins were negative. Sixteen of 29 sampled lymph nodes were positive for metastatic disease. The patient is alive and remains asymptomatic 22 months postoperatively, with stable hepatic metastases.

Literature Review

In our review of the last 25 years of the English language literature, we found 35 individual case reports of patients with pancreatic VIPomas and four case series/reviews. This is the first paper to examine the English language literature so extensively.

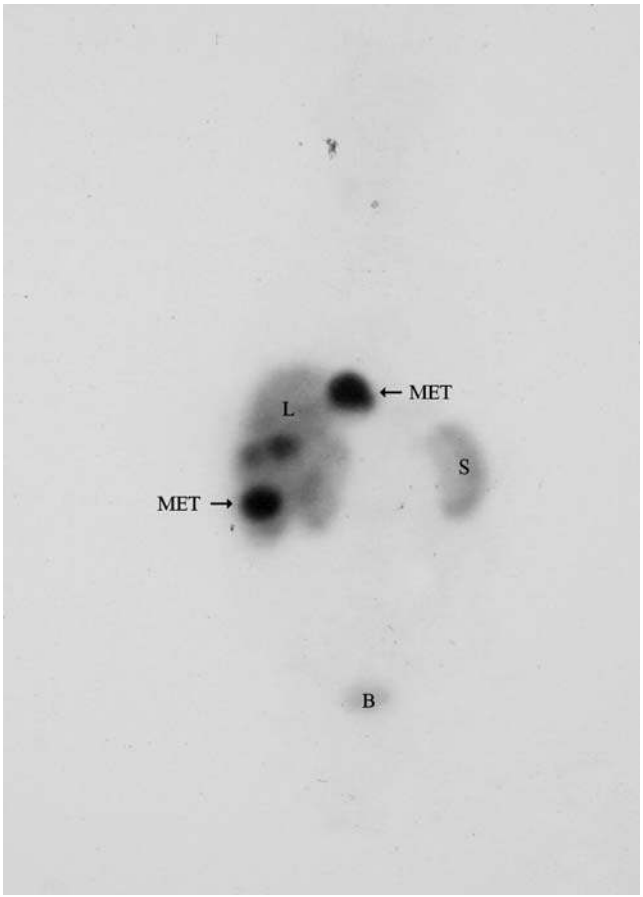

Figure 4 Octreotide radionuclide scan of patient 3. The liver (*L*), spleen (*S*), and bladder (*B*) are seen. Scattered hepatic metastases are evident (*MET*).

Individual Case Reports

The 35 case reports are summarized in Table 1.

Age and sex Thirty five patients were identified with 20 females and 15 males, ranging in age from 11 to 75 years old (mean 48, median 51).

Presenting signs and symptoms The most common clinical and laboratory findings in the 35 patients are outlined in Table 1. As expected, nearly 100% of patients presented with watery diarrhea. Only one patient, presented by Koberstein et al.,[15] did not present with watery diarrhea. This 57-year-old male presented with a paralytic ileus of unknown origin. The patient had a transient episode of loose, melanotic stools several days prior to admission following an episode of prolonged epistaxis. The patient had not mentioned this episode during the initial interview. This unusual presentation, in conjunction with the laboratory findings of hypokalemia, hypercalcemia, and acidosis, which were refractory to intravenous repletion, led the physicians to consider a neuroendocrine etiology such as VIPoma. Indeed, the patient was found to have a mass in the tail of the pancreas, confirmed to be a VIPoma, with serum VIP levels ranging from 173 to 266 pg/ml.

VIP radioimmunoassay Values were reported in 29 of the 35 cases reviewed. The values ranged from 100 to 7,200 pg/ml (mean 1,209 pg/ml, median 632 pg/ml).

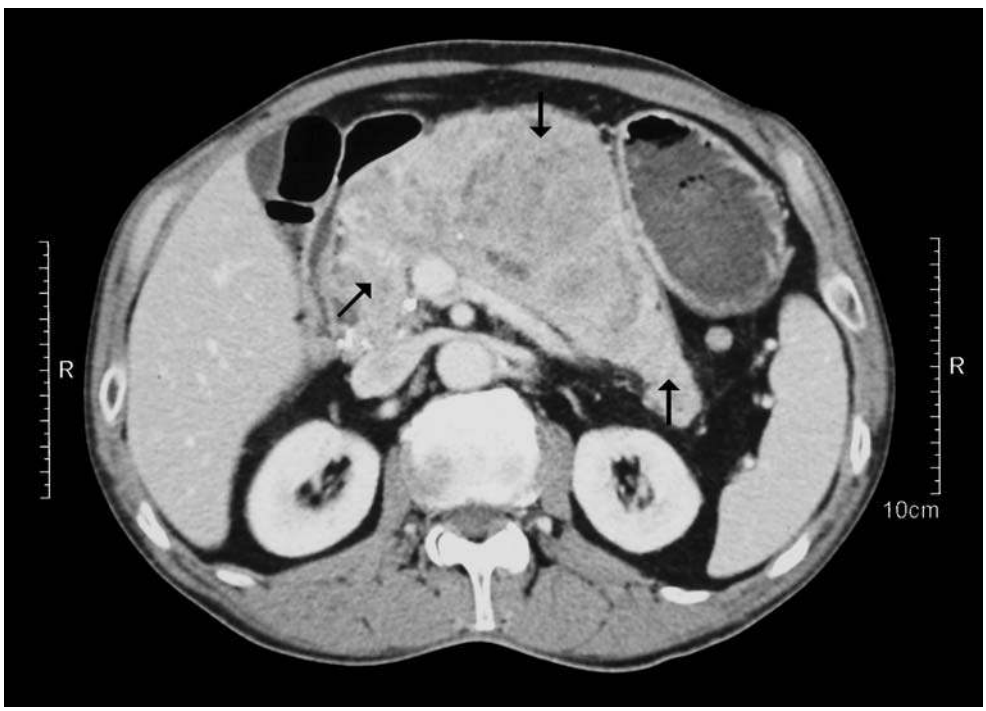

Figure 5 Abdominal CT scan of patient 4. The pancreatic parenchyma is largely replaced by tumor (*arrows*).

Table 1 Individual Case Reports in the Literature and our Four Institutional Cases

References	Year	Age	Gender	Size (cm)	Site	Metatases	Surgery	Symptoms	Imaging	VIP (pg/ml)	Outcome	TSD (Months)
Rood et al.[21]	1988	35	F		Head	Yes	PDD,HG,LR	wd,hk,a	CT	2,400	DOD	48
Cavallo-Perin et al.[34]	1988	55	M		Tail	Yes	None	wd,hk,f	CT	755		
Koberstein et al.[15]	1989	57	M		Tail	No	DP	hk,a,hc,paralytic ileus	CT	266	AWD	
Christensen et al.[35]	1989	60	F		Body		None	wd,hk,a,wtls	CT	632	AWD	12
Tjon et al.[36]	1989	44	F	7	Head	Yes	PDD	wd,hk,ahc,d	CT	412	AWD	6
Venkatesh et al.[37]	1989	54	M		Tail	Yes	DP	wd,hk,a,hc,wtls,d		255	NED	120
Maltese et al.[38]	1990	56	F	10	Head	Yes	PDD	wd,hk,a,wtls,d,hch	Arterio	118	DOD	36
Bramley et al.[39]	1990	41	F		Tail	Yes	DP	wd,hk,f,wtls		1,330	NED	12
Yanagi et al.[40]	1991	20	F	3	Head	No	PDD,S	wd,hk,a,hc	CT	130	NED	2
Brunani et al.[41]	1991	53	F	5	Tail	Yes	DP	wd,hk,wtls		520		
Bani Sacchi et al.[42]	1992	41	M	6	Tail	Yes	DP,S	wdhk,a,ac		1,480		
Bani Sacchi et al.[42]	1992	55	F	8	Tail	Yes	DP,S	wd,hk,a,ac		881		
Bani Sacchi et al.[42]	1992	61	F	9	Head	Yes	PDD,S	wd,hk,a,ac		1,448		
Udelsman et al.[43]	1993	50	M	3	Head	Yes	PDD,HG	wd				DOD
Antonelli et al.[44]	1993	72	F		Tail	Yes	PDD	wd,hk,bp,wtls		100		
Brunt et al.[45]	1994	26	M	5	Head	No	PDD	wd,hk	CT	697		
Cesani et al.[46]	1994	67	F	6	Tail	No	DP,S	wd,hk,hc,d	CT	540		
Crowly et al.[47]	1996	68	F	3	Tail	No	DP,S	wd,hk	MRI	2,667		
Kirkpatrick et al.[48]	1996	63	M	5	Head	No	PDD	wd,hk,hc	CT	228	NED	12
Sofka et al.[49]	1997	32	M	2	Tail	Yes	DP,S,LR	wd,wtls	MRI	365		
Virgolini et al.[50]	1998	38	M	3.5	Tail	No	DP,S	wd,hk,f,d	CT	529	NED	24
Hengst et al.[51]	1998	54	M		Tail	Yes	DP,S	wd,hk,a,hc,hch	CT	452	NED	108
Huang et al.[52]	1998	51	M	4	Head	Yes	Enuc,DP,S	wd,hk,a,f,d,hch	CT		DOD	52
Sjoqvist et al.[53]	1998	30	F		Tail	No	DP,S	wd,hk,a,wtls			NED	36
Nguyen et al.[54]	1999	53	M		Body	Yes	None	wd,hk	CT	3,159	AWD	12
Nguyen et al.[54]	1999	45	M	3	Tail	Yes	None	wd	CT	2,128	DOD	12
Samal et al.[55]	2000	11	F	5	Body	No	DP,S	wd,hk,a,wtls,d	CT		NED	18
Masel et.[56]	2000	43	F	5	Tail	No	DP	wd,hk,a,n,abd	CT	439	NED	3.5
Thomason et al.[57]	2000	63	F	4	Tail	Yes	DP,S	wd,hk,a,wtls,d	CT	981	NED	6
Yek et al.[58]	2001	68	F	7	Tail		DP,S	wd,hk	CT		NED	5
Mortele et al.[59]	2001	75	F	7	Tail	No	DP	wd,hk,a,hc,d	MRI	3,486	NED	
Smith et al.[60]	2001	32	M	2	Tail	Yes	None	wd,hk	MRI	365		
Shorter et al.[61]	2002	20	F		Tail	No	DP	wd				
Ichimura et al.[62]	2003	50	F		Tail		DP,S	wd,hk,a,hc		7,200	NED	240
Drivas et al.[63]	2004	34	M	6	Head	No	PDD	wd,wtls,v		1,084		
Ghaferi et al. #1		74	M	14.5	Tail	Yes	DP,S	wd,hk,a,hc,d	CT	293	AWD	17
Ghaferi et al. #2		50	F	4.5	Tail	Yes	DP,S,LR,CB	wd,hk,v,a,hc	CT	770	DOD	96
Ghaferi et al. #3		66	M	5	Tail	Yes	DP,S,LR	wd,hk	CT	169	AWD	68
Ghaferi et al. #4		68	M	14	Head/body/tail	Yes	PDD,S	wd,hk,hc,wtls	CT	1,500	AWD	22

TSD = time since diagnosis, HG = hemigastrectomy, LR = liver resection, DP = distal pancreatectomy, S = splenectomy, PDD = pancreaticoduodenectomy, Enuc = enucleation, CB = celiac block, wd = watery diarrhea, hk = hypokalemia, a = achlorhydric, f = flushing, hc = hypercalcemic, d = dehydration, hch = hypochlorhydria, v = vomiting, ac = acidosis, DOD = dead of disease, AWD = alive with disease, NED = no evidence on disease

Radiologic features/modalities The imaging modality used to diagnose a pancreatic mass was reported in 23 of the 35 cases. The most common diagnostic study was CT (18/23, 78%). Magnetic resonance imaging and selective angiography were utilized in four cases and in one case, respectively. The primary tumor was always identified using one of the aforementioned modalities. Furthermore, metastatic disease to regional lymph nodes or liver was often diagnosed via imaging. Of the 35 case reports, 32 reported on the presence or absence of metastases, with 19 of the 32 (59%) reporting the presence of metastases, most commonly to the liver.

Site The site of primary disease in the pancreas was identified in all of the reported cases. The distribution of the primary tumors was as follows: 25 in the body and tail of the pancreas (72%) and 10 in the head of the pancreas (28%).

Size The primary tumors ranged in size from 2 to 10 cm in their greatest dimension, reported in 23 cases. The mean and median sizes were both 5 cm. Histologic confirmation of the tumor was reported in 18 cases with either routine hematoxylin and eosin staining or VIP immunohistochemical staining.

Treatment (surgery/none) Surgical intervention was reported in 30 of 35 cases (86%). The procedures included distal pancreatectomy (54%), pancreaticoduodenectomy (29%), splenectomy (43%), hemigastrectomy (6%), liver resection (6%), and tumor enucleation (3%).

Outcome The outcomes were reported with varying follow up periods. The mean follow up time was 40 months, with a median of 15 months. Outcome data were reported in 22 of the cases. Fifty nine percent of the patients were reported as alive with no evidence of disease, 23% had died of disease, and 18% were alive with disease.

Case Series

Summaries of the case series are tabulated in Table 2. Soga et al.[16] published the largest review of reported VIPoma cases including 241 patients found in an international literature search. The authors identified 179 patients with *pancreatic* VIPomas and compared the clinically reported data for this group of patients to the group diagnosed with *extrapancreatic* neurogenic tumors (n=48). They found statistically significant differences (p<0.05) between the two groups (pancreatic vs. extrapancreatic) in the rate of associated syndrome (84 vs. 96%), tumor size larger than 20 mm (79 vs. 100%), rate of metastases (56 vs. 29%), rate

Table 2 Summary of Case Series Reporting on VIPomas and our Institution's Cases

Case Series	Number of Cases	M:F	Mean Age (Range)	Mean Tumor Size (cm)	Mean VIP (pg/ml)	Presenting Symptoms (%)					Location of Tumor (%)			
						Diarrhea	Weight Loss	Dehydration	Hypokalemia	Flushing	Head	Body	Tail	Other
Soga et al.[16]	179	84:95	51 (15-82)	5.4		98	36		89	14	29	8	60	3
Smith et al.[17]	18fs	9:9	51 (23-74)	4.4	698	89	72	44	67	28	11	22	50	17
Peng et al.[18]	31	16:15	48 (26-73)	5.4	963	100	100	100		33	52	13	29	6
Nikou et al.[19]	11	7:4	53 (2-83)			100	45	45	81		18	9	55	18
Ghaferi et al.	4	3:1	65 (50-74)	9.5	683	100	50	25	100	0	0	25	75	0

of malignancy (64 vs. 33%), and rate of resection of the primary lesion (69 vs. 88%). The 5-year actuarial survival rate for patients with pancreatic VIPoma was found to be 69%. A significant difference existed between those with metastases at diagnosis vs. those without: 60% 5-year survival in patients with metastases vs. 94% 5-year survival in those without evidence of metastatic disease.

Smith et al.[17] presented the Mayo Clinic's 15-year experience with VIP-secreting islet cell tumors (Table 2). They reported on 18 patients with a mean age of 51 years (range 23–74) at presentation. There were equal numbers of male and female patients. As expected, secretory diarrhea was the most common presenting symptom in 89% of patients, and the most common location of the tumor was the tail of the pancreas (50%). The mean survival was 3.6 years, with the longest survival reaching 15 years.

Peng et al.[18] in 2004 presented a case report and clinical review of 31 cases of VIPoma in China (Table 2). They reported typical clinical manifestations, imaging features, surgical procedures, and pathologic findings. They found that the mean age of presentation was 48 years, with the mean size of the primary being 5.4 cm. The mean preoperative VIP level was 963 pg/ml (range 68–2,100), and the mean postoperative VIP value was 132 pg/ml (range 20–450).

In 2005, Nikou et al.[19] presented 11 patients with VIPoma (Table 2). Seven of the 11 patients were male, with an age range of 2 to 83 years (mean age 53.1 years). All patients presented with chronic secretory diarrhea that persisted despite fasting. Nine (81%) patients also presented with hypokalemia. Weight loss was observed in 45% of patients. Vasoactive intestinal polypeptide levels were three

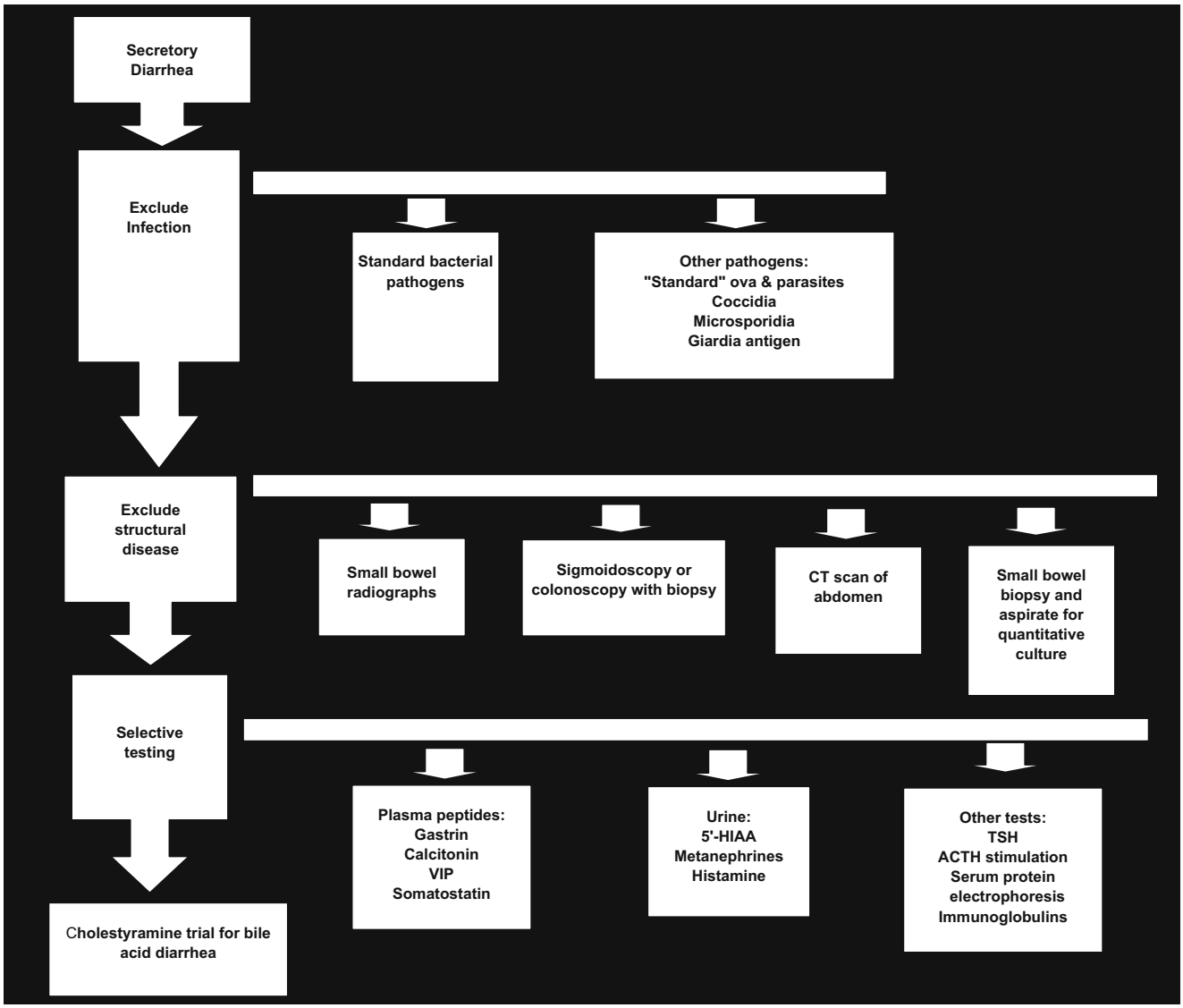

Figure 6 Algorithm for the identification of an etiology for secretory diarrhea. *5-HIAA*, 5-hydroxyindoleacetic acid; *TSH*, thyroid-stimulating hormone; *ACTH*, adrenocorticotropic hormone (adapted from Schiller[64]).

times normal in seven of the 11 patients and 10 times normal in the remaining four patients. Serum chromogranin A levels were elevated in all patients. Fifty four percent of lesions were detected by CT or MRI, whereas EUS or angiography detected 4/11 lesions (36%). Octreoscan detected the primary lesion in 10/11 (91%) and the metastases in 3/4 (75%). The primary lesion was located in the pancreatic tail in 6/11 (55%), the pancreatic body in 1/11 (9%), and the second portion of the duodenum in 2/11 (18%). A 2-year-old child included in the review had the primary tumor located in the retroperitoneum. Four patients had metastatic disease at the time of diagnosis. Sixty three percent of the patients underwent resection. At the time of the report, six patients were alive with no evidence of disease, two were alive with disease, and three had died of disease.

Discussion

VIPomas are rare tumors that often elude prompt diagnosis. As demonstrated by our review of the literature, nearly 100% of patients present with a primary complaint of watery diarrhea refractory to traditional medical management. Chronic diarrhea is defined as that which lasts at least 4 to 6 weeks; the prevalence of chronic diarrhea is estimated to approximate 3–5% of the US population.[20] Figure 6 depicts an algorithm for the workup of a patient with secretory diarrhea. Table 3 lists the causes of chronic watery diarrhea. The diarrhea associated with a neuroendocrine etiology, such as VIPoma, is typified by its persistence for 48 to 72 h after fasting, and by fecal volumes in excess of 6 to 8 l per day. The elevated serum levels of VIP result in all segments of the intestine secreting Na^+, K^+, Cl^-, and HCO_3^-, as well as water, thus accounting for the dehydration, hypokalemia, and acidosis associated with this syndrome. Other effects of excessive circulating VIP include inhibition of gastric acid secretion, bone resorption, glycogenolysis, and vasodilation. These effects lead, respectively, to the hypochlorhydria, hypercalcemia, hyperglycemia, and flushing often seen with these tumors.[21]

The VIPoma syndrome can be difficult to diagnose, as many other conditions can mimic its presentation. Laxative abuse and the Zollinger–Ellison syndrome have presentations similar to VIPoma. These entities can be differentiated by a careful medication history and by measuring serum gastrin and serum VIP and quantifying gastric acid production. Pancreatic islet cell tumors can secrete more than one hormone, as they may be comprised of more than one cell type. VIPomas have been noted to produce additional peptides including PP, calcitonin, gastrin, neurotensin, gastric inhibitory peptide, serotonin, glucagon, insulin, somatostatin, growth hormone-releasing hormone, and peptide histidine–methionine.[22] Two of the four patients at our institution had serum elevations of other peptides, and nearly 30% of the patients presented in the literature had multiple elevations.

Table 3 Differential Diagnoses of Chronic Watery Diarrhea

Diagnosis
Osmotic diarrhea
Mg^{2+}, PO_4^{3-}, SO_4^{2-} ingestion
Carbohydrate malabsorption
Secretory diarrhea
Laxative abuse (nonosmotic laxatives)
Congenital syndromes
Bacterial toxins
Ileal bile acid malabsorption
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Microscopic (lymphocytic and collagenous) colitis
Diverticulitis
Vasculitis
Drugs and poisons
Disordered motility
Postvagotomy diarrhea
Postsympathectomy diarrhea
Diabetic autonomic neuropathy
Hyperthyroidism
Irritable bowel syndrome
Neuroendocrine tumors
Gastrinoma
VIPoma
Somatostatinoma
Mastocytosis
Carcinoid syndrome
Medullary carcinoma of the thyroid
Neoplasia
Colon carcinoma
Intestinal lymphoma
Villous adenoma
Addison's disease
Epidemic secretory diarrhea
Idiopathic secretory diarrhea

Radiologic examination of patients serves as an important adjunct to clinical presentation and laboratory studies. Most pancreatic neuroendocrine tumors are highly vascular, making contrast-enhanced imaging very sensitive, with some groups reporting sensitivities as high as 92%.[23] Size of the lesion is an important factor in the ability of CT to detect a discrete mass. For tumors less than 1 cm, CT sensitivity is less than 10%. Because VIPomas are usually diagnosed at >3 cm, the sensitivity can approach 100%.[24] Our institutional experience with four cases yielded a mean tumor size of 9.5 cm, whereas the literature reports a mean of 5.2 cm. The role of MRI has gradually evolved, such that it is now an excellent technique for differentiating small

pancreatic tumors from surrounding normal pancreatic tissue. Thoeni and associates found the overall sensitivity of MR in detecting a pancreatic neoplasm in 20 patients suspected of having a malignancy to be 85% and the specificity to be 100%.[25] Somatostatin receptor scintigraphy relies on the relatively abundant expression of somatostatin receptors on these VIPomas. Eighty to 90% of VIPomas are somatostatin receptor-positive, making this scintigraphic study useful in most patients.

Histologically, the cellular patterns of VIPomas can be either solid, acinar, or trabecular with scant mitoses.[26] The pathologic evaluation of resected lesions serves as an important indicator of malignancy and prognosis. The only method of confirming malignancy is examination of local lymph nodes and suspicious distant sites of metastases, such as the liver. As reported in the literature, 60–80% of VIPomas are metastatic at the time of presentation.[22,27] Our institutional experience revealed that all four patients presented with local and/or distant metastases, with three patients having liver lesions in conjunction with local lymph node involvement and two patients having isolated local lymph node involvement.

Therapeutic intervention in VIPoma patients involves two interconnected pathways. Prior to the initiation of any curative or palliative therapy, the patient's potentially life-threatening electrolyte and volume status abnormalities must be corrected. Patients may require massive intravenous potassium replacement because the chronic gastrointestinal losses create a substantial potassium deficit. Once stabilized, the patient can be considered for surgical management. Over one-half of VIPomas have been reported as resectable, with a 10% "resectable for cure" rate.[28] Our institutional experience following surgical resection has yielded a 100% 1-year survival, with inadequate sample sizes to determine further survival rates. Two of our patients had complete resolution of their symptoms with surgical resection alone and are doing well at 17 and 22 months postoperatively. Another patient is alive and well 68 months postoperatively, following adjuvant octreotide therapy and radioablation of his liver lesions. Only one patient died 96 months after her resection, secondary to complications from diffuse metastatic disease. Our review of the literature found an 86% rate of resection. The range of follow up in that group was from 2 to 240 months, with a median of 15 months. Approximately 23% of the patients died of their disease from 12 to 52 months after the time of diagnosis or surgery.

Medical management with the synthetic octapeptide analog of somatostatin (octreotide) has proven useful in VIPoma patients with unresectable disease and/or metastases.[18,29] Octreotide inhibits hormone secretion by various neuroendocrine tumors (such as VIPomas and glucagonomas) and may very occasionally induce a reduction in the metastatic tumor burden.[30] Varying data exist about the quantitative reduction of tumor size and symptomatic relief. Oberg[31] reports a significant tumor response observed in less than 5% of patients but symptomatic response in 60% of patients. Similarly, Maton et al. reported that 83% of their patients with VIPomas had a good sustained symptomatic response to treatment, with fewer than 20% showing a reduction in tumor size.[32] Cho and Vinik evaluated tumor blood flow using angiography in eight patients with neuroendocrine tumors who were receiving octreotide. They found a marked decrease in blood flow to the tumor in two patients with gastrinomas and two patients with VIPomas, hypothesizing that there was either a direct vasoactive effect of the octreotide on the tumor blood supply or that this was a secondary effect from the decreased tumor hormonal secretion.[33]

Other forms of intervention exist for metastatic disease, including hepatic artery embolization, radiofrequency ablation, hepatic transplantation, radioactive octreotide, intravenous chemotherapy, alpha interferons, and cryotherapy. Each has been used in select cases. Despite the difficulty in diagnosing such a rare tumor, there are multiple treatment modalities available for VIPomas that provide meaningful, extended survival with excellent control of the watery diarrhea.

References

1. Friesen SR. Update on the diagnosis and treatment of rare neuroendocrine tumors. Surg Clin North Am 1987;67:379.
2. Mekhijian HS, O'Dorisio TM. VIPoma syndrome. Semin Oncol 1987;14:282–291.
3. Capella C, Polak JM, Buffa R, Tapia FJ, Heitz P, Usellini L, Bloom SR, Solcia E. Morphologic patterns and diagnostic criteria of VIP-producing endocrine tumors. A histologic, histochemical, ultrastructural, and biochemical study of 32 cases. Cancer 1983;52 (10):1860–1874.
4. Ectors N. Pancreatic endocrine tumors: diagnostic pitfalls. Hepatogastroenterology 1999;46:679.
5. Priest WM, Alexander MK. Islet cell tumor of the pancreas with peptic ulceration, diarrhea and hypokalemia. Lancet 1957;273: 1145–1147.
6. Verner JV, Morrison AB. Islet cell tumour and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 1958;25:374.
7. Bloom SR, Polak JM, Pearse AGE. Vasoactive intestinal peptide and watery-diarrhea syndrome. Lancet 1973;2:14–16.
8. Kane MG, O'Dorisio TM, Krejs GJ. Production of secretory diarrhea by intravenous infusion of vasoactive intestinal polypeptide. N Engl J Med 1983;309:1482–1485.
9. Holst JJ, Fahrenkrug J, Knuhtsen S, Jensen SL, Poulsen SS, Nielsen OV. Vasoactive intestinal peptide (VIP) in the pig pancreas: role of VIPergic nerves in the control of fluid and bicarbonate secretion. Regul Pept 1984;8:245.
10. Robberecht P, Conlon TP, Gardner JD. Interaction of porcine vasoactive intestinal peptide with dispersed pancreatic acinar cells from the guinea pig. Structural requirements for effects of vasoactive intestinal peptide and secretin on cellular adenosine 3′,5′-monophosphate. J Biol Chem 1976;251:4635.

11. Barbezat GO, Grossman MI. Intestinal secretion: stimulation by peptides. Science 1971;174:422.
12. Fahrenkrug J. Transmitter role of vasoactive intestinal peptide. Pharmacol Toxicol 1993;72:354.
13. Biancani P, Walsh JH, Behar J. Vasoactive intestinal polypeptide. A neurotransmitter for lower esophageal sphincter relaxation. J Clin Invest 1984;73:963.
14. Usdin TB, Bonner TI, Mezey É. Two receptors for vasoactive intestinal polypeptide with similar specificity and complementary distributions. Endocrinology 1994;135:2662.
15. Koberstein B, Layer P, Balzer K, Muller MK, Singer MV, Goebell H. Paralytic ileus responding to somatostatin therapy: First manifestation of a VIPoma. Dig Dis Sci 1989;34(11):1803–1804.
16. Soga J, Yakuwa Y. Vipoma/diarrheogenic syndrome: a statistical evaluation of 241 reported cases. J Exp Clin Cancer Res 1998;17 (4):389–400.
17. Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, Grant CS, van Heerden JA. Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. Surgery 1998;124(6):1050–1055.
18. Peng SY, Li JT, Liu YB, Fang HQ, Wu YL, Peng CH, Wang XB, Qian HR. Diagnosis and treatment of VIPoma in China: (case report and 31 cases review) diagnosis and treatment of VIPoma. Pancreas 2004;28(1):93–97.
19. Nikou GC, Toubanakis C, Niklolaou P, Giannatou E, Safioleas M, Mallas E, Polyzos A. VIPomas: An update in diagnosis and management in a series of 11 patients. Hepatogastroenterology 2005;52:1259–1265.
20. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology 1999;116: 1464–1486.
21. Rood RP, DeLellis RA, Dayal Y, Donowitz M. Pancreatic cholera syndrome due to vasoactive intestinal polypeptide-producing tumor: further insights into the pathophysiology. Gastroenterology 1988;94:813.
22. Perry RR, Vinik AI. Clinical review 72: Diagnosis and management of functioning islet cell tumors. J Clin Endocrinol Metab 1995;80(8):2273–2278.
23. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, Coste J, Louvel A, Rouseu G, Couturier D, Bonnin A. Pancreatic tumors: Comparison of dual-phase helical CT and endoscopic sonography. Am J Roentgenol 1998;170(5): 1315–1322.
24. King CM, Reznek RH, Dacie JE, Wass JA. Imaging islet cell tumours. Clin Radiol 1994;49(5):295–303.
25. Thoeni RF, Mueller-Lisse UG, Chan R, Do NK, Shyn PB. Detection of small functional islet cell tumors in the pancreas: Selection of MR imaging sequences for optimal sensitivity. Radiology 2000;214(2):483–490.
26. Capella C, Polak JM. Morphologic patterns and diagnostic criteria of VIP-producing endocrine tumors. A histologic, histochemical, ultrastructural and biochemical study of 32 cases. Cancer 1983;52:1860–1874.
27. Jensen RT. Pancreatic endocrine tumors: Recent advances. Ann Oncol 1999;10:6 (Suppl).
28. Thompson GB, van Heerden JA, Grant CS, Carney JA, Ilstrup DM. Islet cell carcinomas of the pancreas: a twenty year experience. Surgery 1988;104:1011–1017.
29. O'Dorisio T, Mekhjian HA, Gaginella TS. Medical therapy of VIPomas. Endocrinol Metab Clin North Am 1989;18:545–556.
30. Kraenzlin ME, Ch'ng JL, Wood SM, Carr DH, Bloom SR. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. Gastroenterology 1985;88(1 Pt 1):185–187.
31. Oberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumours. Ann Oncol 2001;12(Suppl 2):S111–S114.
32. Maton PN, Gardner JD, Jensen RT. Use of long-acting somatostatin analog SMS 201-995 in patients with pancreatic islet cell tumors. Dig Dis Sci 1989;34:28S–39S.
33. Cho KJ, Vinik AI. Effect of somatostatin analogue (octreotide) on blood flow to endocrine tumors metastatic to the liver: angiographic evaluation. Radiology 1990;177(2):549–553.
34. Cavallo-Perin P, De Paoli M, Guiso G, Sapino A, Papotti M, Coda R, Pagano G. A combined glucagonoma and VIPoma syndrome. First pathologic and clinical report. Cancer 1988;62(12):2576–2579.
35. Christensen C. The somatostatin analogue SMS 201-995 in long-term treatment of vipoma. Case report. Acta Chir Scand 1989;155 (10):541–543.
36. Tjon A Tham RT, Jansen JB, Falke TH, Roelfsema F, Griffioen G, van den Sluys Veer A, Lamers CB. MR, CT, and ultrasound findings of metastatic vipoma in pancreas. J Comput Assist Tomogr 1989;13(1):142–144.
37. Venkatesh S, Vassilopoulou-Sellin R, Samaan NA. Somatostatin analogue: use in the treatment of vipoma with hypercalcemia Am J Med 1989;87(3):356–357.
38. Maltese JY, Monge G, Giraud P, Salers P, Ouafik LH, Pelen F, Oliver C. Characterization of an alpha-amidating activity in a human pancreatic tumour secreting vasoactive intestinal peptide (VIP). Clin Endocrinol (Oxf) 1990;33(4):467–480.
39. Bramley PN, Lodge JP, Losowsky MS, Giles GR. Treatment of metastatic vipoma by liver transplantation. Clin Transplant 1990;4 (5 part 1):276–278; discussion 279.
40. Yanagi H, Kusunoki M, Sakanoue Y, Shoji Y, Yamamura T, Murai M, Kikkawa N, Utsunomiya J. Vipoma of the pancreas complicating ulcerative colitis. Am J Gastroenterol 1991;86(8):1066–1069.
41. Brunani A, Crespi C, De Martin M, Dubini A, Piolini M, Cavagnini F. Four year treatment with a long acting somatostatin analogue in a patient with Verner–Morrison syndrome. J Endocrinol Invest 1991;14(8):685–689.
42. Bani Sacchi T, Bani D, Biliotti G. Immunocytochemical and ultrastructural abnormalities of islet tissue in patients with VIP-producing tumors of the pancreas. Pancreas 1992;7(5):601–610.
43. Udelsman R, Yeo CJ, Hruban RH, Pitt HA, Niederhuber JE, Coleman J, Cameron JL. Pancreaticoduodenectomy for selected pancreatic endocrine tumors. Surg Gynecol Obstet 1993;177 (3):269–278.
44. Antonelli A, Gambuzza C, Bertoni F, Baschieri L. Calcitonin, as SMS 201-995, ameliorates the VIPoma syndrome. J Endocrinol Invest 1993;16(1):57–59.
45. Brunt LM, Mazoujian G, O'Dorisio TM, Wells SA Jr. Stimulation of vasoactive intestinal peptide and neurotensin secretion by pentagastrin in a patient with VIPoma syndrome. Surgery 1994;115(3):362–369.
46. Cesani F, Ernst R, Walser E, Villanueva-Meyer J. Tc-99m sestamibi imaging of a pancreatic VIPoma and parathyroid adenoma in a patient with multiple type I endocrine neoplasia. Clin Nucl Med 1994;19(6):532–534.
47. Crowley PF, Slavin JL, Rode J. Massive amyloid deposition in pancreatic vipoma: a case report. Pathology 1996;28(4):377–379.
48. Kirkpatrick AW, Hanna SS, Skinner BA. Surgical treatment of pancreatic cholera: a case report. Can J Surg 1996;39(2):155–158.
49. Sofka CM, Semelka RC, Marcos HB, Woosley JT. MR imaging of metastatic pancreatic VIPoma. Magn Reson Imaging 1997;15 (10):1205–1208.
50. Virgolini I, Kurtaran A, Leimer M, Kaserer K, Peck-Radosavljevic M, Angelberger P, Hubsch P, Dvorak M, Valent P, Niederle B. Location of a VIPoma by iodine-123-vasoactive intestinal peptide scintigraphy. J Nucl Med 1998;39(9):1575–1579.
51. Hengst K, Nashan B, Avenhaus W, Ullerich H, Schlitt HJ, Flemming P, Pichlmayr R, Domschke W. Metastatic pancreatic VIPoma: deteriorating clinical course and successful treatment by liver transplantation. Z Gastroenterol 1998;36(3):239–245.

52. Huang YH, Lee CH, Wu JC, Wang YJ, Chang FY, Lee SD. Functional pancreatic islet cell tumors with liver metastasis: the role of cytoreductive surgery and transcatheter arterial chemoembolization: a report of five cases. Zhonghua Yi Xue Za Zhi (Taipei) 1998;61(12):748–754.
53. Sjoqvist U, Permert J, Lofberg R, Larsson J, Gadaleanu V, Adrian TE. Life threatening diarrhoea ultimately cured by surgery. Eur J Gastroenterol Hepatol 1998;10(11):963–967.
54. Nguyen HN, Backes B, Lammert F, Wildberger J, Winograd R, Busch N, Rieband H, Matern S. Long-term survival after diagnosis of hepatic metastatic VIPoma: report of two cases with disparate courses and review of therapeutic options. Dig Dis Sci 1999;44(6):1148–1155.
55. Samal SC, Paul AC, Venkateswari S, Nair S, Venkatramani S, Perakath B, Simon A, Chandy G, Kurian G. VIPoma of pancreas in a child. Indian J Gastroenterol 2000;19(4):194–195.
56. Masel SL, Brennan BA, Turner JH, Cullingford GL, Cullen DJ. Pancreatic vasoactive intestinal polypeptide-oma as a cause of secretory diarrhoea. J Gastroenterol Hepatol 2000;15(4):457–460.
57. Thomason JW, Martin RS, Fincher ME. Somatostatin receptor scintigraphy: the definitive technique for characterizing vasoactive intestinal peptide-secreting tumors. Clin Nucl Med 2000;25 (9):661–664.
58. Yeh CN, Chen MF, Chen TC. Surgical treatment of pancreatic vasoactive intestinal polypeptide-secreting tumor: a case report. Hepatogastroenterology 2001;48(38):421–423.
59. Mortele KJ, Oei A, Bauters W, Timmermans F, Cuvelier C, Kunnen M, Ros PR. Dynamic gadolinium-enhanced MR imaging of pancreatic VIPoma in a patient with Verner–Morrison syndrome. Eur Radiol 2001;11(10):1952–1955.
60. Smith CS, Houston M, Jensen B, Mlinar K, Toulson C, Tillotson LG. A 32-year-old man with copious, watery diarrhea. N C Med J 2001;62(3):134–139.
61. Shorter NA, Glick RD, Klimstra DS, Brennan MF, Laquaglia MP. Malignant pancreatic tumors in childhood and adolescence: The memorial Sloan–Kettering experience, 1967 to present. J Pediatr Surg 2002;37(6):887–892.
62. Ichimura T, Kondo S, Okushiba S, Morikawa T, Katoh H. A calcitonin and vasoactive intestinal peptide-producing pancreatic endocrine tumor associated with the WDHA syndrome. Int J Gastrointest Cancer 2003;33(2–3):99–102.
63. Drivas I, Mansberg R, Roberts JM. VIPoma: a rare cause of a pancreatic mass. Clin Nucl Med 2004;29(3):201–203.
64. Schiller LR. Chronic diarrhea. Gastroenterology 2004;127(1): 287–293.