JBUON 2019; 24(2): 415-423
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

REVIEW ARTICLE

Clinicopathological data and treatment modalities for pancreatic vipomas: a systematic review

Dimitrios Schizas[1], Aikaterini Mastoraki[1], George Bagias[2], Raphael Patras[3], Dimitrios Moris[1], Ioannis I. Lazaridis[4], Nikolaos Arkadopoulos[3], Evangelos Felekouras[1]

[1]1st Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece; [2]Department of General, Visceral and Transplant Surgery, University Hospital Essen, Essen, Germany; [3]4th Department of Surgery, National and Kapodistrian University of Athens, Attikon University Hospital, Chaidari, Athens, Greece; [4]Department of Surgery, University Hospital Basel, Basel, Switzerland.

Summary

Purpose: *Vasoactive intestinal peptide (VIP) secreting tumor (VIPoma) constitutes a rare functional neuroendocrine tumor that most often originates from pancreatic islet cells and presents as a sporadic, solitary neoplasm of the pancreas. The purpose of this study was to systematically review the literature of pancreatic VIPomas and report clinicopathologic data and treatment modalities for this rare entity.*

Methods: *A systematic literature search was performed. The reviewed clinical series and case reports were included if they reported surgical treatment and also analyzed oncological outcomes on individual patients. Data extraction was performed using a standard registry pro-forma.*

Results: *The search resulted in 53 case reports and 2 case series including 65 patients in total. Median age reported was 54 years. The predominant pancreatic location was the pancreatic tail. The most common clinical symptom was watery diarrhea. Serum VIP levels were remarkably elevated in all patients. Distal pancreatectomy with or without splenectomy was the most commonly applied surgical procedure. Overall survival associated with pancreatic VIPoma was 67.7%, recurrence rate 40.4% and relevant median disease-free interval was 16 months.*

Conclusions: *VIPomas are functional tumors that secrete excessive amounts of VIP. Clinically, production of VIP causes refractory watery diarrhea, hypokalemia and achlorydria. As far as diagnosis is concerned, elevated VIP plasma levels are required. Moreover, the majority of VIPomas are malignant or have already metastasized on diagnosis. Despite recent research on the therapeutic strategies against pancreatic VIPoma, surgical resection appears as the only potentially curative approach.*

Key words: *VIPoma, pancreas, Verner-Morison syndrome, neuroendocrine tumors, vasoactive intestinal peptide*

Introduction

Neuroendocrine tumors (NETs) derive from multipotent cells that are located throughout the entire gastrointestinal (GI) tract, belong to the diffuse endocrine system and have the ability to secret peptides [1]. Vasoactive intestinal peptide (VIP) secreting tumor (VIPoma) constitutes a rare functional NET with an estimated incidence of 1/10.000.000 individuals per year in the general population [2]. Women in the 4th decade (65%) are more commonly affected than men (35%) [3,4]. Although their origin remains obscure, VIPomas most often originate from pancreatic islet cells and are presented as sporadic, solitary disorders greater than 3cm in diameter [5]. The majority of

Correspondence to: Dimitrios Moris, MD, MSc, PhD. Department of Surgery, Duke University Medical Center, 2301 Erwin Rd, 27710, Durham, NC, USA.
Tel: +1 2165716614, Fax: +1 2106440590, E-mail: dimitrios.moris@duke.edu
Received: 08/08/2018; Accepted: 01/09/2018

lesions (75%) are detected within the pancreatic body and tail, while 25% are encountered in the head of the pancreas [6,7]. Nevertheless, cases of VIPomas arising from extrapancreatic structures, such as bronchus, colon, liver and neural crest-derived tissues including sympathetic nerve chains, pituitary, thyroid and adrenals have been described [8]. Moreover, 5% of VIPomas occur on the ground of multiple endocrine neoplasia type 1 (MEN-1) syndrome [9]. VIPomas are functional tumors that secrete excessive amounts of VIP. The latter stimulates adenosine 3', 5' - cyclic phosphate (cAMP) production by the intestinal tract, resulting in profuse diarrhea manifesting as water and electrolyte, especially potassium, loss [10,11]. Clinically, production of VIP causes refractory watery diarrhea, hypokalemia and achlorydria, known as WDHA syndrome, which was described by Verner and Morrison in 1958 [12]. It is also known as pancreatic cholera or Verner-Morrison syndrome [3,13]. As far as diagnosis is concerned, elevated VIP plasma levels are required. Unfortunately, it is often delayed and diarrhea may persist even for years before VIPoma is confirmed [14]. In addition, 70-90% of VIPomas are malignant, while 60-80% of the cases have already metastasized on diagnosis. Nevertheless, VIPoma often exhibits slow growth and prognosis depends on its differentiation (Ki-67 and mitotic index), tumor development speed and metastatic extension [3]. Despite recent research on the therapeutic strategies against pancreatic VIPoma, surgical resection appears the only potentially curative approach. Alternative therapies, such as chemotherapy, proved on occasion beneficial [15,16].

The aim of this study was to systematically review the literature of pancreatic VIPomas and report epidemiologic and clinicopathologic data for this rare entity. Biologic behavior of VIPomas as well as available treatment modalities have been also analyzed.

Methods

A systematic literature review was performed using MEDLINE, EMBASE and the Cochrane Library databases, until April, 1st, 2018. Phrase searches, adjacent free text terms and medical subject headings were used. As search terms were pancreatic, pancreas and vasoactive intestinal peptide, VIPoma, WDHA syndrome, pancreatic cholera and Verner-Morrison syndrome. The reviewed clinical series and case reports were included if they reported surgical treatment and also analyzed oncological outcomes on individual patients. Papers not written in English as well as cases of pediatric patients were excluded from our study (Figure 1).

Data extraction was performed using a standard registry pro-forma. Epidemiologic as well as clinicopathologic data, including age, sex, clinical symptoms,

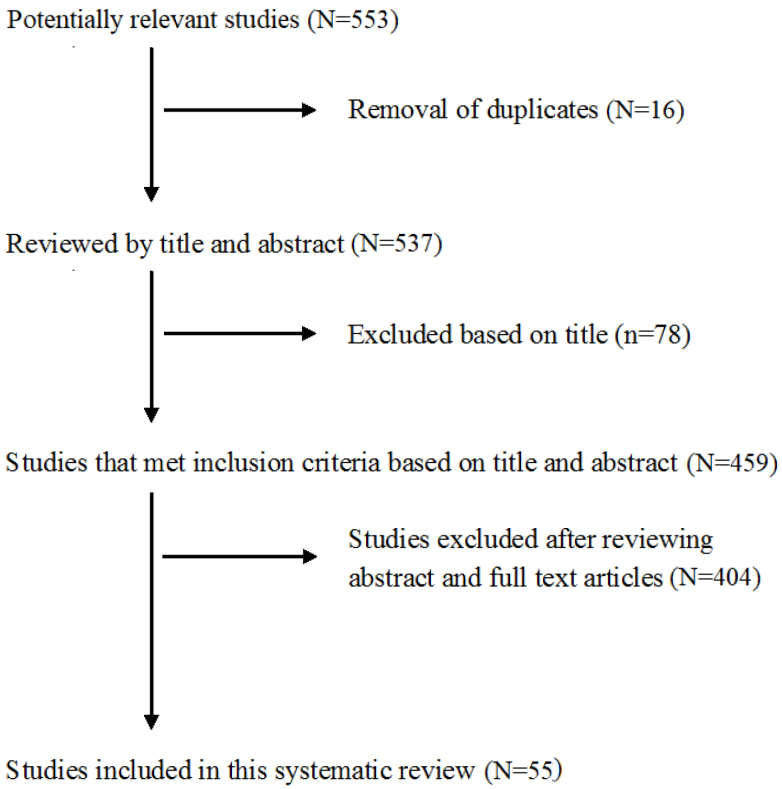

Figure 1. Flow chart of the present study.

Table 1. Presentation of studies including our analysis

Study	*#*	*Age*	*Sex*	*Loc*	*Symptoms*	*VIP*	*Meta*	*Size*	*NaTx*	*OP*	*ATx*	*Rec*	*DFS*	*FU*	*DOD*
Sofka 1997	1	32	M	Tail	WD	365	Liver	2	No	DP	NR	NR	NR	NR	NR
Bellows 1998	1	75	F	Tail	Other	NR	No	3	No	DP	No	No	7	7	No
Song 2009	1	41	M	Head	WD, Hk	NR	No	NR	Yes	1	No	No	6	6	No
Song 2009	2	50	F	Body	WD, Hk	NR	No	2,5	Yes	2	No	Yes	20	21	Yes
Song 2009	3	53	M	Head	WD, Hk	2019	Liver	NR	Yes	2	Yes	No	20	20	No
Song 2009	4	62	F	Body	WD, Hk	529	Liver	NR	Yes	4	Yes	No	6	6	No
Venkatesh 1989	1	54	M	Tail	WD, Hk, Ach	255	Liver	NR	No	DP	No	Yes	92	120	No
Shorter 2002	1	20	F	Tail	WD	NR	No	NR	No	DP	No	NR	NR	NR	NR
Crowley 1996	1	68	F	Tail	WD	802	No	5,5	No	DP	NR	NR	NR	NR	NR
Lam 2013	1	37	M	Tail	Hk	175	Liver	5,9	Yes	DP	No	Yes	2	15	No
Abu-Zaid 2014	1	47	M	Tail	WD, Hk, Ach	989	Liver	4,6	Yes	DP	No	Yes	6	18	No
Koberstein 1989	1	57	M	Tail	Hk	250	No	NR	Yes	DP	No	No	6	6	No
Brunani 1991	1	53	F	Tail	WD, Hk	522	No	5	Yes	0	Yes	Yes	48	56	No
Cavali 2016	1	58	M	Head	WD, Hk	183	Liver	2,8	Yes	1	No	No	19	19	No
Ghaferi 2007	1	74	M	Tail	WD, Hk, Ach	293	No	14,5	Yes	DP	No	No	17	17	No
Ghaferi 2007	2	50	F	Tail	WD, Hk, Ach	770	Liver	4,5	No	DP	Yes	Yes	NR	96	Yes
Ghaferi 2007	3	66	M	Tail	WD, Hk	169	Liver	5	No	DP	Yes	Yes	NR	68	No
Ghaferi 2007	4	68	M	Body	WD, Hk	1500	Liver	14	Yes	1	NR	Yes	NR	22	No
Jonston 2010	1	46	M	Body	WD, Hk, Ach	1550	No	5	No	DP	Yes	Yes	12	300	Yes
Nakayama 2009	1	72	F	Head	WD, Hk, Ach	670	No	NR	Yes	5	No	No	24	24	No
Mortele 2001	1	75	F	Tail	WD, Hk, Ach	3486	No	7	No	DP	No	NR	NR	NR	NR
Nguyen 1999	1	53	F	Body	WD, Hk	1287	Liver	NR	No	0	Yes	Yes	120	134	No
Nguyen 1999	2	45	M	Tail	WD, Hk	867	Liver	3	Yes	0	Yes	NR	NR	44	Yes
Dreanic 2016	1	60	M	Tail	WD, Hk	2600	Liver	2,3	Yes	DP	No	No	44	44	No
Dreanic 2016	2	64	M	Tail	WD, Hk, Ach	2570	No	6	No	DP	No	Yes	12	24	No
Ichimura 2003	1	50	F	Tail	WD, Hk, Ach	7200	No	6	No	DP	No	No	240	240	No
Chandra 2000	1	18	F	Body	WD, Hk, Ach	NR	No	5	Yes	DP	No	No	18	18	No
Müller 2012	1	69	M	Tail	WD, Hk, Ach	650	Liver	9	Yes	DP	No	No	50	50	No
Thomason et al 2000	1	63	F	Body	WD, Hk, Ach	295	No	4	No	DP	No	No	6	6	No
Drivas 2004	1	34	M	Head	WD	326	No	6	No	Wh	No	No	6	6	No
Tham 1989	1	44	F	Head	WD, Hk, Ach	124	Liver	5	Yes	Wh	No	Yes	6	8	No
Adam 2010	1	58	F	Head	WD, Hk	NR	Liver	2	Yes	Wh	No	Yes	NR	36	No
You Peng 2004	1	56	M	Head	WD	NR	Liver	5	No	Wh	No	No	6	6	No

Continued on the next page

Study	*#*	*Age*	*Sex*	*Loc*	*Symptoms*	*VIP*	*Meta*	*Size*	*NaTx*	*OP*	*ATx*	*Rec*	*DFS*	*FU*	*DOD*
Xiang 2012	1	69	F	Head	WD, Hk	989	No	11	Yes	Wh	No	No	11	11	No
Niu 2017	1	34	M	Body	WD, Hk, Ach	498	No	6	Yes	No	No	No	3	3	No
Sjöqvist 1998	1	30	F	Tail	WD, Hk, Ach	NR	No	5	Yes	DP	No	No	36	36	No
Kirkpatrik 1996	1	63	M	Head	WD, Hk	228	No	2	Yes	Wh	No	No	12	12	No
Torrez 2014	1	54	M	Tail	WD, Hk	242	Liver	1,5	Yes	DP	Yes	Yes	12	36	No
Fujiya 2015	1	47	M	Body	WD, Hk	748	No	3,2	No	Wh	No	No	24	24	No
Sclembri 2013	1	51	F	Tail	WD, Hk	500	No	7,6	Yes	No	No	No	1	1	Yes
Zhang 2015	1	65	M	Head	WD, Hk, Ach	600	Liver	6	Yes	Deb	No	Yes	15	18	No
Virgolini 1998	1	38	M	Tail	WD, Hk, Ach	640	No	NR	Yes	DP	No	No	24	24	No
Maltese 1990	1	56	F	Head	WD, Hk, Ach	190	No	10	No	Wh	No	Yes	32	36	Yes
Canosa 2011	1	33	F	Head	WD, Hk, Ach	119,4	No	3,2	No	Wh	No	No	18	18	No
Mark 2015	1	54	F	Tail	WD	1299	Liver	NR	No	DP	No	Yes	38	46	No
Nilubol 2016	1	67	F	Tail	WD, Hk	3750	No	5,4	Yes	DP	No	No	48	48	No
Masel 2000	1	43	F	Tail	WD, Hk	132	No	5,5	Yes	DP	No	No	2	2	No
Chen 2015	1	50	F	Head	WD, Hk	+++	Liver	2,2	No	Wh	NR	No	27	27	No
Camera 2014	1	70	F	Tail	WD	NR	No	3,7	Yes	DP	No	No	60	60	No
Rood 1988	1	35	F	Head	WD, Hk, Ach	2400	Liver	NR	Yes	Wh	No	Yes	NR	48	Yes
Christensen 1989	1	60	F	Body	WD, Hk, Ach	632	No	NR	Yes	No	No	Yes	NR	12	No
Bramley 1990	1	41	F	Tail	WD, Hk	1330	Liver	NR	Yes	DP	No	No	12	12	No
Yanagi 1991	1	20	F	Head	WD, Hk, Ach	130	No	3	Yes	Wh	No	No	2	2	No
Sacchi 1992	1	41	M	Tail	WD, Hk, Ach	1480	Liver	NR	Yes	DP	No	NR	NR	NR	NR
Sacchi 1992	2	55	F	Tail	WD, Hk, Ach	881	Liver	8	Yes	DP	No	NR	NR	NR	NR
Sacchi 1992	3	61	F	Head	WD, Hk, Ach	1448	Liver	9	Yes	Wh	No	NR	NR	NR	NR
Udelsman 1993	1	50	M	Head	Hk	NR	Liver	3	Yes	Wh	No	Yes	NR	NR	Yes
Antonelli 1993	1	72	F	Tail	WD, Hk	100	Liver	NR	Yes	Wh	No	NR	NR	NR	NR
Brunt 1994	1	26	M	Head	WD, Hk	697	No	5	Yes	Wh	No	NR	NR	NR	NR
Cesani 1994	1	67	F	Tail	WD, Hk	540	No	6	Yes	DP	No	NR	NR	NR	NR
Crowly 1996	1	68	F	Tail	WD, Hk	2667	No	3	Yes	DP	No	NR	NR	NR	NR
Hengst 1998	1	54	M	Tail	WD, Hk, Ach	452	Liver	NR	Yes	DP	No	No	108	108	No
Huang 1998	1	51	M	Head	WD, Hk, Ach	NR	Liver	4	Yes	DP	No	Yes	NR	52	Yes
Yek 2001	1	68	F	Tail	WD, Hk	NR	No	7	Yes	DP	No	No	5	5	No
Smith 2001	1	32	M	Tail	WD, Hk	365	Liver	2	Yes	No	No	NR	NR	NR	NR

Loc:Location, VIP: Vasoactive Intestine Peptide serum levels (pg/ml), Meta: Metastases at presentation, NaTx: Neoadjuvant Therapy, OP: Operation, ATx: Adjuvant Therapy, Rec: Recurrence, DFS: Disease-free survival, FU: Follow-up, DOD: Died-of-disease, WD: Watery Diarrhea, Hk: Hypokaliaimia, Ach: Achlorydria, DP: Distal Pancreatectomy, Wh: Whipple's procedure, NR: Not Reported

location, tumor size, stage, diagnostic approach, surgical intervention, potential administration of adjuvant treatment, tumor recurrence or metastasis and survival were extracted in each case. Statistical analysis was performed using the R environment for Statistical Computing. Study variables were assessed for normality using the Shapiro-Wilks test.

Results

The search resulted in 53 case reports consisting of 60 patients and 2 case series including 5 patients. A total number of 65 patients with pancreatic VIPomas were identified (Table 1). The median age reported was 54 years (range 18-75). A slight female predominance (35 females, 53.8% vs 30 males, 46.2%) was also found. The predominant pancreatic location was the pancreatic tail (35 cases, 53.8%) followed by pancreatic head (20 cases, 30.8%) and pancreatic body (10 cases, 15.4%). The most common clinical symptom was watery diarrhea (54.5%), nonetheless, the classical triad of symptoms was present in 27 patients (42.2%). Serum VIP levels were remarkably elevated in all patients (median value 636 pg/ml). The clinical presentation as well as the elevated serum VIP levels established in almost all cases the diagnosis. Further diagnostic strategy included computed tomography (CT) and magnetic resonance imaging (MRI) in order to rule out metastatic lesions; an octreoscan was performed in 24.1% of the cases. At the time of presentation, 31 patients had already hepatic metastatic foci (47.7%), whereas the rest presented without distant metastases.

The surgical procedure applied in each case depended on the tumor primary site. Therefore, distal pancreatectomy with or without splenectomy (36 cases, 62.1%) was the most common surgical operation. In 19 patients the tumor was located in the pancreatic head, thus Whipple's procedure

Table 2. Study demographics and data presentation

Parameter	*Total*	*N*	*Percentage*	*Median*	*Range*
Age, years	Σ= 65			54	18 - 75
Gender	Σ= 65				
Male		30	46.2		
Female		35	53.8		
Symptoms	Σ=64				
Watery diarrhea		7	10.9		
Watery diarrhea + hypokalaemia		27	42.2		
Watery diarrhea + hypokalaemia + achlorydria		27	42.2		
Hypokalaemia		3	4.7		
Serum VIP Level (pg/ml)	Σ=52			636	100-7,200
Liver Metastases	Σ=65	31	47.7		
Octreoscan needed	Σ=58	14	24.1		
Tumor size (cm)	Σ=49			5	1.5 - 14.5
Tumor site	Σ=65				
Head		20	30.8		
Body		10	15.4		
Tail		35	53.8		
Neoadjuvant	Σ=65	45	69.2		
Operation	Σ=58				
Distal pancreatectomy		36	62.1		
Whipple		19	32.8		
Management of metastases	Σ=17				
No treatment		4	23.5		
Surgery		8	47.1		
Ablation		5	29.4		
Adjuvant	Σ=61	9	6.8		
Follow-up (months)	Σ=52			21.5	1 - 300
Recurrence	Σ=52	21	40.4		
Disease-free survival (months)	Σ=44			16	1 - 240
Died of disease	Σ=53	9	17		

was implemented (32.8%), while in 3 patients the tumor proved inoperable (5.2%). In patients with liver metastases, a simultaneous surgical resection was performed in 47.1% of the cases, whereas radiofrequency ablation of liver metastases was performed in 5 patients. Tumor size varied from 1.5 to 14.5cm (median 5). Immunohistological analysis of the specimens was positive to chromogranin A and synaptophysin in all cases. Finally, median follow-up period was 21.5 months. At the end of follow up, 44 patients were alive (67.7%), 9 died of disease progression (17%) and 12 were lost to follow-up (18.5%). Among the alive patients at the end of the studies, 21 experienced disease recurrence (40.4%). The median disease-free interval was 16 months (range 1-240) (Table 2).

Discussion

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) constitute a biologically heterogeneous entity that cause a great variety of clinical outcomes and pose severe challenges when it comes to establishing guidelines for therapeutic management [17,18]. GEP-NETs are considered to be rare with an estimated incidence of 3-5/100.000 inhabitants [19]. Pancreatic NETs (PNETs) arise from multipotent stem cells in the pancreatic ductal epithelium and are classified into two major categories including functional and non-functional lesions. Therefore, PNETs are considered a wide subgroup of GEP-NETs and their incidence is reported 1-5/1.000.000 per year. Manifestation occurs at the fourth to sixth decade and is equal between men and women. Adults are more commonly affected while children are more prone to PNETs when hereditary predisposition exists [9]. Non-functional PNETs (NF-PNETs) do not secrete any hormones; therefore, they do not cause specific symptoms. Functional PNETs (F-PNETs) are presented with specific clinical syndromes according to the hormone that is synthesized and secreted. Insulinoma is the most common and benign F-PNET followed by gastrinoma. Glucagonoma, somatostatinoma, VIPoma and carcinoid tumor are rare among PNETs, while ACTHoma, PTHrp-oma and GRFoma are even less common.

VIPoma was first reported by Priest and Alexander back in 1957 and a year later WDHA syndrome was described by John Verner and Ashton Morrison [12]. In the United States, the annual incidence has been estimated as 0.05-0.2/1.000.000 adults per year. In our survey the mean age reported was 52.2 years, with a slight female predominance. The most common pancreatic location was the pancreatic tail (53.8%) followed by pancreatic head (30.8%). VIPomas most commonly arise from pancreatic cells while extrapancreatic origin has been also reported. Adrenal glands are involved in 35% of extrapancreatic locations, paraspinal retroperitoneal ganglia in 30-35%, posterior mediastinum in 20%, head and neck in 1-5% and pelvis in 2-3%; rare locations include the thymus, lung, kidney or anterior mediastinum [10,20].

Diarrhea is responsible for various metabolic abnormalities including dehydration (45-95%), hypokalemia (70-100%), achlorhydria (35-76%), hypophosphatemia, hypomagnesaemia and metabolic acidosis [18]. Hypokalemia may be ascribed to several factors such as VIPoma-induced chronic diarrhea, secondary hyperaldosteronism and direct potassium excretion by enterocytes. Consequently, VIPoma causes a hyperchloraemic, hypokalemic, non-anion gap metabolic acidosis. In accordance with previous research, the most common clinical sign in our study was watery diarrhea (54.5%). The latter is also related to various dietary deficiencies due to malabsorption of electrolytes including magnesium, zinc and vitamins [8].

VIPoma may also be associated with other symptoms such as facial flushing, skin rash, bloating, indigestion, nausea, vomiting, backache, lethargy and documented unintentional weight loss. Intense dehydration due to diarrhea can also lead to severe renal failure [8]. It is interesting that facial flushing is presented in nearly 8% of patients during episodes of diarrhea, resembles that of carcinoid syndrome and has been imputed to VIP or prostaglandins [14]. Hypercalcemia (25-50%) may also be noted. However its cause remains unclear. It may be linked to dehydration, electrolyte disturbances, paraneoplastic syndrome or coincidental MEN-1 syndrome with hyperparathyroidism [10]. Hypomagnesaemia with tetany secondary to diarrhea has also been reported. In addition, VIP exhibits glucogenolytic effect on the liver causing hyperglycemia (20-50%). In our investigation, watery diarrhea (54.5%) was the most common clinical finding, followed by hypokalemia (45.6%) and achlorhydria (42.4%); nonetheless, the classical triad of symptoms was present only in 27 patients (42.2%). Finally, ischemic stroke attributed to high hematocrit due to diarrhea has been mentioned in an extremely rare case report [21].

By definition, VIP plasma levels are increased in almost all VIPoma cases [9]. Diagnosis is based on two pillars with regard to secretory diarrhea (>700mL/day) and plasma VIP levels above 200pg/mL [1]. Evidence of tumor mass on imaging is apparent in the majority of the cases. In all our patients, remarkably elevated serum VIP levels (median value 636 pg/ml) along with clinical im-

ages established the diagnosis. Additional blood laboratory findings indicate the presence of hypokalemia, hypochlorhydria or achlorhydria, non-anion gap metabolic acidosis, hyperglycemia and hypercalcemia as well. Moreover, elevated serum blood urea nitrogen (BUN) and creatinine levels are related to renal insufficiency. Differential diagnosis of elevated plasma VIP levels includes small bowel ischemia and diarrhea of other etiology [10]. On the other hand, a physician should also take into account that between the episodes of diarrhea, plasma VIP levels remain normal [12]. It is common knowledge that liver remains the most common site of metastasis, whereas distant metastases to lymph nodes, lungs, kidneys and bones have been cited [10]. In our analysis, at the time of presentation, 31 (47.7%) patients appeared already with liver metastases.

Imaging studies constitute a crucial aid in localizing tumor and determining size and thus in providing optional treatment [17,22]. CT is vital in deciding size, location and organ of tumor origin, as well as participation of adjacent structures, vessels, lymph nodes and presence of calcification [10]. On the other hand, MRI is useful for assessment of spinal tumors. As most pancreatic VIPomas are greater than 3cm in diameter, they can be easily identified by CT scans [8]. In our study tumor size varied from 1.5 to 14.5cm. Although only a few CT findings of VIPomas have been described, the pattern of this pancreatic tumor exhibits a hyperattenuating lesion on arterial phase followed by an obscure mass on venous depiction. Calcifications may also be evident. VIPomas are hypervascularized tumors rich in cells and fibrous tissue. The latter is poorly supplied and thus contrast agent is retained within the lesion [6]. Furthermore, over 90% of PNETs, including non-syndromic tumors, contain elevated concentrations of specific subtypes of somatostatin receptors related to the type, origin and grade of the tumor, and this characteristic allows imaging using radio-labeled octreotide (a somatostatin analog) [8]. Several different radiotracers can be bound to octreotide, and applied in conjunction with single photon emission CT (SPECT) or positron emission tomography (PET) imaging to localize areas of enhanced uptake. Relevant tests are colloquially referred to as 'octreotide scans'. Finally, according to a recent publication, the high sensitivity of Ga-PET/CT in the identification of PNETs suggests its potential role in VIPomas prognostication and risk stratification [23]. In our survey, diagnostic strategy included CTs and MRIs in order to rule out metastatic lesions; an octreoscan was performed in 24.1% of the cases.

Surgery remains the gold standard for the management of primary as well as metastatic VIPoma inducing curative results in 40% of patients with benign and non-metastatic disease [3,15]. Concurrent treatment with octreotide, a somatostatin analog, improves preoperative electrolyte management [6,24]. Somatostatin analogs (SSAs) -octreotide, lanreotide and pasireotide- imitate the effect of somatostatin on G-coupled receptors of cell membrane and have been proved to reduce VIP secretion, thus leading to control of secretory diarrhea and inhibition of tumor growth [8, 22]. In severe cases with Verner-Morison syndrome, rapid intravenous fluid supplementation is required in order to restore relevant losses, electrolyte abnormalities and acid-base disorders [19]. Therefore, SSAs control diarrhea in more than half of the patients while in 25% significant improvement is achieved. Additional administration of glucocorticoids, loperamide and opiates might be implemented [25]. In non-resectable liver metastatic disease, debulking operation has been proposed [17]. This cytoreductive approach can lead to symptom control in 95% of the cases, as far as metastatic NETs to the liver are concerned [9]. Consequently, in our study, distal pancreatectomy with or without splenectomy (62.1%) was the most frequent surgical operation followed by Whipple's procedure (32.8%), while in 3 patients the tumor proved to be inoperable (5.2%). In patients with liver metastases, a simultaneous surgical resection was performed in 47.1% of the cases, whereas radiofrequency ablation of liver metastases was implemented in 5 patients. Neoadjuvant therapy with octreotide was applied in 69.2% of patients in our study.

Second-line therapy for VIP-producing PNETs includes IFN-a, everolimus and sunitinib [14]. Everolimus is a selective mTOR pathway inhibitor, which decreases VEGF exhibiting antiangiogenic properties. Sunitinib inhibits various receptor tyrosine kinases (RTKs) that are essential to tumor growth, neoangiogenesis and metastatic expansion [19]. In addition, ENETS 2016 guidelines approve everolimus and sunitinib as antiproliferative therapies in progressive pancreatic NETs, recommended after failure of SSA or chemotherapy. Finally, as far as chemotherapy is concerned, doxorubicin/streptozotocin combination is the gold standard with 5-fluorouracil replacing doxorubicin when the latter is contraindicated [8]. In our study 6.8% of patients received systemic adjuvant therapy. A promising treatment for VIPomas expressing SSTRs is peptide receptor radionuclide therapy (PRRT) that leads radionuclides directly to cancer cells taking advantage of SSTR expression on the cell surface [18]. Last but not least, liver transarte-

rial chemoembolization (TACE) has emerged as a new therapeutic option for liver metastases [3].

Finally, according to our results 5-year overall survival of patients with pancreatic VIPoma was 67.7%, recurrence rate was 40.4% and relevant median disease-free interval was 16 months. These data confirm a malignant behavior for pancreatic VIPomas, which is comparable to the similar 5-year survival (66%) reported for glucagonomas, as well as the 77% tumor-related deaths described for malignant insulinomas [26,27].

In conclusion, VIPomas are functional tumors that secrete excessive amounts of VIP. Clinically, production of VIP causes refractory watery diarrhea, hypokalemia and achlorydria. As far as diagnosis is concerned, elevated VIP plasma levels are required. Moreover, the majority of VIPomas is malignant or have already metastasized on diagnosis. Despite recent research on the therapeutic strategies against pancreatic VIPoma, surgical resection appears the only potentially curative approach.

Conflict of interests

The authors declare no conflict of interests.

References

1. Anderson CW, Bennett JJ. Clinical Presentation and Diagnosis of Pancreatic Neuroendocrine Tumors. Surg Oncol Clin N Am 2016;25:363-74. PMID: 27013370
2. Yao JC, Eisner MP, Leary C et al. Population based study of islet cell carcinoma. Ann Surg Oncol 2007;14:3492 3500. PMID:17896148
3. Dréanic J, Lepère C, El Hajjam M, Gouya H, Rougier P, Coriat R. Emergency therapy for liver metastases from advanced VIPoma: surgery or transarterial chemoembolization? Ther Adv Med Oncol 2016;8:383-7. PMID: 27583030
4. Ghaferi AA, Chojnacki KA, Long WD, Cameron JL, Yeo CJ. Pancreatic VIPomas: subject review and one institutional experience. J Gastrointest Surg 2008;12:382-93. PMID: 17510774
5. Bani Sacchi T, Bani D, Biliotti G. Are pancreatic VIPomas paraneuron neoplasms? A clue to neuroectodermal origin of these tumors. Pancreas 1992;7:87-97. PMID: 1313559
6. Chen Y, Shi D, Dong F et al. Multiple-phase spiral CT findings of pancreatic vasoactive intestinal peptide-secreting tumor: A case report. Oncol Lett 2015;10:2351-4. PMID: 26622850
7. Cynthia Ro, Wanxing Chai, Victoria E. Yu, Run Yu. Pancreatic neuroendocrine tumors: biology, diagnosis, and treatment. Chin J Cancer 2013;32:312-24. PMID: 23237225
8. Abu-Zaid A, Azzam A, Abudan Z, Algouhi A, Almana H, Amin T. Sporadic pancreatic vasoactive intestinal peptide-producing tumor (VIPoma) in a 47-year-old male. Hematol Oncol Stem Cell Ther 2014;7:109-15. PMID: 24785507
9. Parbhu SK, Adler DG. Pancreatic neuroendocrine tumors: contemporary diagnosis and management. Hosp Pract 1995 2016;44:109-19. PMID: 24404266
10. Belei OA, Heredea ER, Boeriu E et al. Verner-Morrison syndrome. Literature review. Rom J Morphol Embryol 2017;58:371-6 PMID: 28730220
11. de Herder WW, Rehfeld JF, Kidd M, Modlin IM. A short history of neuroendocrine tumours and their peptide hormones. Best Pract Res Clin Endocrinol Metab 2016;30:3-17. PMID: 26971840
12. Grozinsky-Glasberg S, Mazeh H, Gross DJ. Clinical features of pancreatic neuroendocrine tumors. J Hepatobiliary Pancreat Sci 2015;22:578-85. PMID: 25689919
13. Brelian D, Tenner S. Diarrhea due to pancreatic diseases. Best Pract Res Clin Gastroenterol 2012;26:623-31. PMID: 23384807
14. Adam N, Lim SS, Ananda V, Chan SP. VIPoma syndrome: challenges in management. Singapore Med J 2010;51:e129132. PMID: 20730389
15. Kos-Kudła B, Ćwikła J, Ruchała M et al. Current treatment options for gastroenteropancreatic neuroendocrine tumors with a focus on the role of lanreotide. Contemp Oncol Poznan Pol 2017;21:115-22. PMID: 28947880
16. Song S, Shi R, Li B, Liu Y. Diagnosis and treatment of pancreatic vasoactive intestinal peptide endocrine tumors. Pancreas 2009;38:811-4. PMID: 19657309
17. Pasricha G, Padhi P, Daboul N, Monga DK. Management of Well-differentiated Gastroenteropancreatic Neuroendocrine Tumors (GEPNETs): A Review. Clin Ther 2017;39:2146-57. PMID: 29173655
18. Crabtree JS. Clinical and Preclinical Advances in Gastroenteropancreatic Neuroendocrine Tumor Therapy. Front Endocrinol 2017;8:341. PMID: 29255447
19. Dimitriadis GK, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2016;23:R423-36. PMID: 27461388
20. Remme CA, de Groot GH, Schrijver G. Diagnosis and treatment of VIPoma in a female patient. Eur J Gastroenterol Hepatol 2006;18:93-9. PMID: 16357627
21. Maheshwari RR, Desai M, Rao VP et al. Ischemic stroke as a presenting feature of VIPoma due to MEN 1 syndrome. Indian J Endocrinol Metab 2013;17:S215-8. PMID: 24251163

22. Debray MP, Geoffroy O, Laissy JP et al. Imaging appearances of metastases from neuroendocrine tumours of the pancreas. Br J Radiol 2001;74:1065-70. PMID: 11709476
23. Cingarlini S, Ortolani S, Salgarello M et al. Role of Combined 68Ga-DOTATOC and 18F-FDG Positron Emission Tomography/ComputedTomography in the Diagnostic Workup of Pancreas Neuroendocrine Tumors: Implications for Managing Surgical Decisions. Pancreas 2017;46:42-7. PMID: 27906872
24. Zhang X, Zhou L, Liu Y et al. Surgical resection of vasoactive intestinal peptideoma with hepatic metastasis aids symptom palliation: A case report. Exp Ther Med 2016;11:783-7. PMID: 26997993
25. Gut P, Waligórska-Stachura J, Czarnywojtek A et al. Management of the hormonal syndrome of neuroendocrine tumors. Arch Med Sci AMS 2017;13:515-24. PMID: 28507564
26. Câmara-de-Souza AB, Toyoshima MTK, Giannella ML et al. Insulinoma: A retrospective study analyzing the differences between benign and malignant tumors. Pancreatology 2018;18:298-303. PMID: 29452754
27. Eldor R, Glaser B, Fraenkel M, Doviner V, Salmon A, Gross DJ. Glucagonoma and the glucagonoma syndrome - cumulative experience with an elusive endocrine tumour. Clin Endocrinol (Oxf) 2011;74:593-8. PMID: 21470282