006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 32

Endokrinolojide Diyalog 2013; **10**(1): 32-37 **DERLEME | Review Article**

Pancreatic vasoactive intestinal peptide producing tumour (VIPoma): a case report and literature review

Diabetes and melatonin pankreatik vazoaktif intestinal peptid üreten tümör (VIPoma): vaka sunumu ve literatür derlemesi

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Abstract

Vasoactive Intestinal Peptide-producing tumour (VIPoma) is rare. It typically causes the Vernor-Morrison syndrome characterized by watery diarrhoea, hypokalemia and achlorydria/acidosis. We report a case of VIPoma presenting with severe Vernor-Morrison syndrome requiring intensive care and a review of recent English literature from year 2000 till 2010 for this rare disease. Prompt recognition and early diagnosis are crucial to allow early intervention and improve outcome for this rare disease.

Key words: VIPoma, Vernor-Morrison syndrome, pancreatic tumour, chronic diarrhoea, hypokalemia

Özet

Pankreatik vazoaktif intestinal peptid üreten tümör (VIPoma) nadiren görülmektedir. Genellikle Vernor-Morrison sendromuna yol açmaktadır ve bu sendrom sulu dışkılama, hipokalemi ve aklorhidri/asidoz ile karakterizedir. Burada kendini ciddi Vernor-Morrison sendromu ile ortaya koyan VIPoma vakasından ve 2000-2010 yılları arasındaki İngiliz literatürünün derleme sonuçlarından bahsedilmektedir. Erken tanı bu nadir görülen hastalığın tedavisinde ve sağkalımında önemlidir.

Anahtar kelimeler: VIPoma, Vernor-Morrison sendromu, pankreatik tümör, kronik ishal, hipokalemi

Introduction

Vasoactive Intestinal Peptide producing tumour (VIPoma) of the pancreas is a rare neuroendocrine tumour affecting 1 in 10,000,000 individuals[1]. It classically causes the WDHA (watery diarrhoea, hypokalemia, achlorydria/acidosis) syndrome, also known as Vernor-Morrison syndrome after Vernor and Morrison described two patients who presented with refractory watery diarrhoea and severe hypokalemia in 1958 in whom autopsy showed pancreatic islet tumour[2]. It was then later proved in other studies that the hormone VIP was responsible in the above-mentioned syndrome.

We describe a rare case of VIPoma who presented with severe WDHA syndrome to our unit, along with a review of the reported cases found in the recent English literature from 2000 till 2010.

Case presentation

A 27-year old lady, with no known medical history, presented in moribund state after 3 days history of profuse watery diarrhoea associated with faecal incontinence and vomiting. She was afebrile but noted to be drowsy and

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006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 33

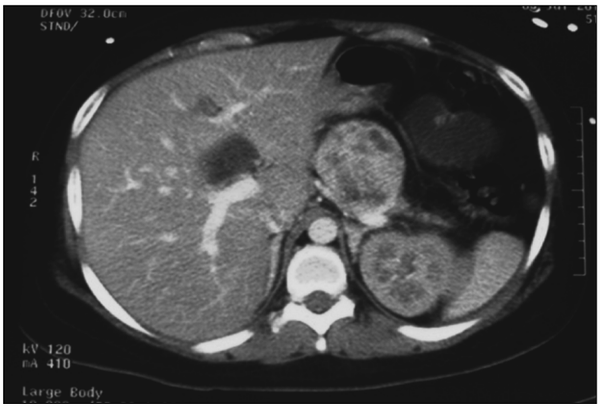

Figure 1a. CT scan of the abdomen showing a well-defined enhancing mass at body of the pancreas

tachypnoiec. Blood pressure was 140/90 mmHg with heart rate of 140 beats/minute. Initial blood investigations showed severe hypokalemia (1.8 mmol/L) and metabolic acidosis (arterial blood gas pH of 7.117, bicarbonate level 7.3 mmol/L, pCO_2 13 mmHg). Serum calcium (3.56 mmol/L), urea (16.8 mmol/L) and creatinine (185 umol/L) were found to be elevated. Full blood count showed hemoglobin of 13 g/dL, elevated total white cell counts at 28 x 103 /uL and platelet of 313 x 103 /uL. Liver function and thyroid function tests were normal.

She deteriorated despite fluid resuscitation and subsequently received ventilator support in the intensive care unit. While on total parenteral nutrition, she had persistent voluminous diarrhoea with large amount of nasogastric aspirate (200-300 ml/hour). Despite fluid and continual potassium and bicarbonate infusion, her metabolic acidosis persisted and her renal function deteriorated with reduced urine output and rising creatinine (469 umol/L). Haemodialysis was initiated. Further history from family revealed that she had been having intermittent diarrhoea for 6 months associated with palpitation and flushing episodes.

A suspicion of VIPoma with a differential diagnosis of carcinoid syndrome was raised. She was initiated on subcutaneous octreotide injection. She responded dramatically where her diarrhoea and nasogastric aspirate reduced tremendously. Her electrolytes, metabolic derangement and renal function normalized.

Further investigation showed elevated VIP level at 269 pg/mL (0-165pg/mL). Intact PTH level was suppressed at 0.881 pmol/L (1.6-6.9) and 24-hour urine 5-hydroxyindolacetic acid level was normal. CT scan of abdomen showed a well-defined enhancing mass at the body of the pancreas measuring 4.9x6.1 cm ***(figures 1a and 1b)*** and a smaller mass at the tail of the pancreas measuring 2.4x2.8 cm ***(figure 2)***, with no evidence of liver metastasis.

She underwent distal pancreactectomy with splenectomy. Histopathology examination showed well-differentiated pancreatic neuroendocrine tumour cells, with centrally located round to oval nucleus, salt-and-pepper chromatin pattern and finely granular eosinophilic cytoplasm ***(figures 3a and 3b)***. The tumour cells were immunoreactive to Neuron Specific Enolase (NSE), Chromogranin A and Synaptophysin stains but negative to Carcinoembryonic Antigen (CEA) stain (figure 3c). There was no local invasion. She recovered well after surgery but developed diabetes mellitus requiring insulin therapy four months later. In addition, eight months post surgery, she experienced abdominal pain associated with loose bulky stools. Abdominal CT and later Gallium-68 PET scan showed no recurrent lesion or evidence of metastasis. Her diarrhoea resolved with pancreatic enzyme replacement and abdominal pain was alleviated by coeliac block. She remained well and disease-free 14 months post surgery.

Discussion

VIPoma is rare with only isolated case reports and case series being described previously. The largest literature review was reported by Soga et al in 1998 describing 179 cases of intrapancreatic VIPoma[3]. Subsequently, Ghaferi et al did a review of the English literature in 2004 and found 35 isolated cases reported since 1988[4]. In addition, there were 3 case series: Smith et al reported their experience with 18 cases from the Mayo Clinic[5], Nikou et al described 11 cases from Athens[6] while Peng et al described 31 cases from China7.

We did a literature search from 2000 to 2010 and found 22 cases of VIPoma reported in the English literature. 12 of the cases had been included in Ghaferi's review previously[4]. These cases together with ours are studied in more detail here and the findings are summa-

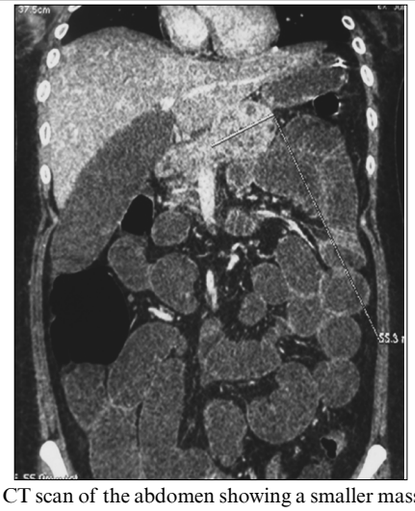

Figure 1b: CT scan of the abdomen showing a smaller mass at the tail of the pancreas

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006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 34

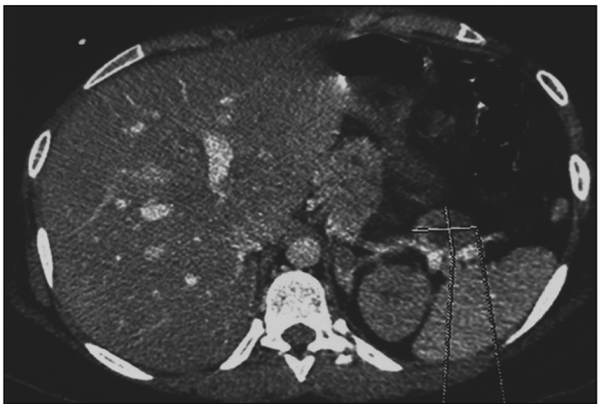

Figure 2. CT scan of the abdomen showing a well-defined enhancing mass at body of the pancreas (coronal view)

rized in ***table 1***. There were 15 females and 8 males with a mean age of 53.9 (range: 19 to 86 years old).

Clinical presentation

Patients with VIPoma most commonly present with chronic diarrhoea. While there is a long list of causes for chronic diarrhoea, VIPoma-associated diarrhoea usually persists despite fasting for 48 to 72 hours, and faecal volumes often exceed 6-8L a day[4]. Not surprisingly, almost all patients in the case reports presented with diarrhoea, except for a 19 years old lady with family history of MEN I reported by Longo et al.[8] She presented rather acutely with one week history of abdominal pain, lethargy, nausea, loss of appetite and loss of weight. She did not have any diarrhoea throughout her illness, nor was any observed during her hospitalization. She was found to have a mass in the tail of pancreas with an elevated VIP level. After undergoing surgery, her calcium level remained high, hence raising the diagnosis of primary hyperparathyroidism associated with Multiple Endocrine Neoplasia I.

Other presentations documented in the reports included abdominal pain (26%), rash (13%) and flushing (8.7%). VIP is not associated with intestinal hypermotility, hence the abdominal pain is likely due to potassium deficit[9]. The flushing could be associated with high VIP levels, which are known to cause vasodilatation[10].

Duration of symptoms

Most patients with VIPoma have long duration of symptoms before seeking medical attention or coming to the final diagnosis. In the initial phase of the disease, the diarrhoea tends to be episodic or intermittent. It is only when the disease progresses and when the tumour achieves certain size that patients experience debilitating large volume diarrhoea[9]. As a result, there is usually a delay in establishing the diagnosis of VIPoma. For the patients with documented duration of symptoms in our review, the median time to arrive at the diagnosis was 52 weeks, with the longest delay of 9 years as reported by Ghaferi et al[4].

Laboratory data

As suggested by the WDHA syndrome, hypokalemia is a consistent finding in VIPoma. All of the reports which documented potassium level showed hypokalemia in the

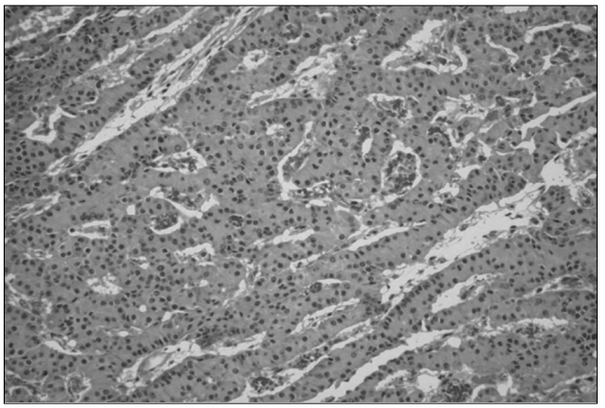

Figure 3a. Tumour cells arranged in anastomosing trabeculae separated by scant fibrovascular stroma (H&E, x100)

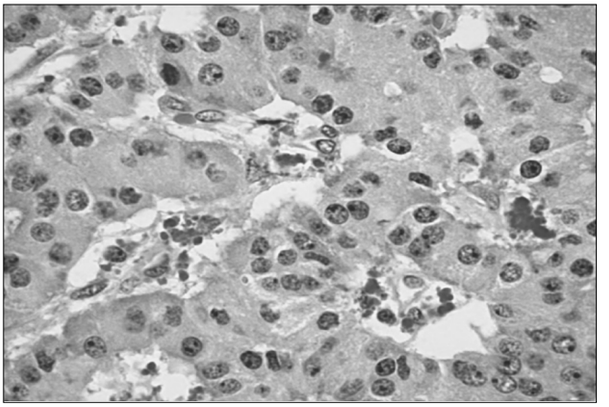

Figure 3b. Tumour cells have typical salt-and-pepper chromatin pattern (H&E, x 400)

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006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 35

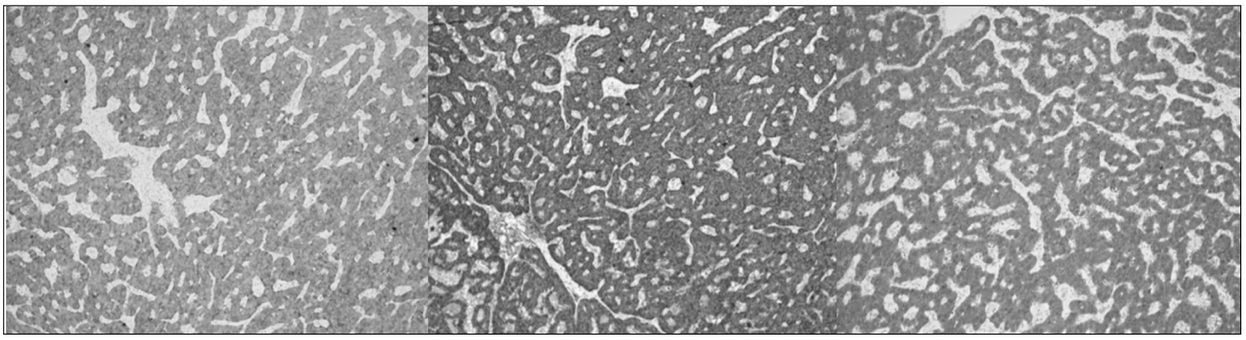

Figure 3c. Tumour cells are strongly positive for synaptophysin (Synaptophysin Immunohistochemical stain x40), Chromogranin A (Chromogranin A Immunohistochemical stain x40) and Neuron-Specific Enolase (NSE Immunohistochemical stain x40)

patients. This includes the 19-year old lady who did not have diarrhoea, hence raising the question of mechanism of hypokalemia in her. Although hypokalemia can be caused by the chronic voluminous diarrhoea, the true pathophysiology of low potassium in these patients is unknown, especially for patients who do not present with diarrhoea. It is postulated that the hypokalemia can be caused by aldosterone secretion by VIPoma, intestinal exchange for sodium in attempt to preserve the ion, or stimulation of potassium secretion by enterocytes due to VIP[9].

Apart from hypokalemia, acidosis and achlorhydria or hypochlorhydria are common findings in VIPoma. Due to the profuse secretory diarrhoea, apart from electrolytes losses, there is bicarbonate wasting leading to metabolic acidosis. Hypo- or achlorhydria is believed to be due to inhibitory effect of VIP on the parietal cells of the gastric mucosa leading to a reduction in gastric acid secretion[11].

Another common laboratory finding in VIPoma is hypercalcaemia. Out of the 11 patients with documented calcium level in our review, 9 had hypercalcaemia. The reason of hypercalcaemia in patients with VIPoma is poorly understood. iPTH is often suppressed except for patients with associated MEN I. Calcium level normalizes with octreotide therapy or removal of the tumour.

17 of the 23 patients had recorded VIP levels, of which all were raised, ranging between 169 pg/mL to 7200 pg/mL.

Tumour characteristics

The primary tumour was identified in the pancreas in 21 out of the 23 cases reported. The two cases without identification of pancreatic tumour included a case of metastatic non small cell carcinoma with ectopic VIP hormone secretion13 and an elderly lady with secretory diarrhoea associated with elevated VIP level with only a metastatic lesion identified in the liver on abdominal CT scan and Indium-111-octreotide scintigraphy[12].

Pancreatic VIPomas are usually discrete tumours located at the body or tail of the pancreas. In our case review, 91.3% were discrete tumour, the commonest site being at the tail (66.7%), followed by body (33.3%) and head (19%) of pancreas. Other case series also reported the tail of pancreas to be the commonest site (50-75%) 3-6, except Peng et al[7] who reported a higher percentage of tumour at the head of the pancreas (52%) in the Chinese population.

Most VIPomas are more than 3 cm in size at the time of diagnosis. Our mean tumour size was 6.6 cm (range 2 - 18 cm) at presentation. Ghaferi et al pointed out that for tumours less than 1 cm, sensitivity of CT to detect a discrete mass is <10%. Other imaging modalities included magnetic resonance imaging, endoscopic ultrasound and abdominal angiography. As 80-90% of VIPomas are somatostatin receptor-positive, octreoscan is also a useful imaging modality[4]. In the case series of 11 patients with VIPoma reported by Nikou et al, CT or MRI managed to detect 54% of the lesions, EUS or angiography picked up 36% of the lesions, whereas octreoscan detected 91% of the primary lesion and 75% of metastatic lesion[6].

Half of these tumours are benign. It is deemed as malignant when there is presence of metastasis[9], usually to the liver or regional lymph nodes. This rough estimation is seen in the cases reported here, as 11 of them had metastasis at presentation, of which 7 were to the liver and 6 had regional lymph nodes involvement. 8 patients were reported to have no local invasion or metastasis.

Treatment and Outcome

Surgery remains the mainstay of treatment[9]. Out of the 23 reported cases, 19 patients (82.6%) underwent sur-

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006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 36

No	Year	Country	Age	Gender	Presentation	Duration of Sx	Potassium level	Calcium level	VIP level (pg/mL)	Site of tumor (pancreas)	Metastasis	Size of primary tumor (cm)	Associations	Surgery	Other treatment	Outcome	Time since diagnosis (months)
1	2000	USA	63	Female	D	3 years	Low	Unknown	973	Tail	Nil	4		DP, Sp		AND	6
2	2000	Australia	43	Female	D, AP, N, L, R	4 years	Low	Normal	439	Tail	Nil	5.5		DP		AND	2
3	2001	Taiwan	68	Female	D	5 years	Low	Unknown	Unknown	Tail	Unknown	7		DP, Sp		AND	5
4	2001	Belgium	75	Female	D	1 year	Low	High	3486	Tail	Unknown	Unknown		Debulking		AND	Unknown
5	2001	Switzerland	86	Female	D, LOW	Few weeks	Low	High	620	Unknown	Liver	Unknown		Nil	Sandostatin LAR	Died	18
6	2001	USA	32	Male	D, LOW, R	11 months	Low	Low	365	Tail	Liver	2		DP		Unknown	
7	2002	USA	20	Female	D	Unknown	Unknown	Unknown	Unknown	Tail	Nil	Unknown		DP		Unknown	
8	2003	Japan	50	Female	D	Unknown	Low	High	7200	Tail	Unknown	Unknown	Calcitonon secretion	DP, Sp		AND	240
9	2004	Australia	34	Male	D, V, L	7 years	Unknown	Unknown	1076	Head	Nil	6		Whipple		AND	Unknown
10	2004	China	56	Male	D, BA, R, Fl	6 years	Unknown	Unknown	Unknown	Head	Liver, nodes	5		PD, LR		AQS	6
11	2005	USA	38	Male	D	2 weeks	Low	High	2200	Unknown	Unknown	Unknown	Lung cancer	Nil	Chemo	Died	Unknown
12	2005	USA	61	Female	D	2 years	Low	Unknown	565	Tail	Nil	3	Calcitonin secretion	DP		Unknown	
13	2005	USA	19	Female	AP, L, N, V, LOA, LOW	1 week	Low	High	249	Tail	Nil	5.4	MEN I	DP, Sp		AND	5
14	2005	Netherlands	83	Female	D, W, AP	1 year	Low	High	505	Body	Nil	6		Nil	Sandostatin LAR	AWD	12
15	2006	UK	61	Female	D, LOA, LOW	5 weeks	Low	Unknown	181	Neck, body	Liver, nodes	4		DP, Sp	Octreotide, RFA	AND	10
16	2006	USA	61	Male	D, LOW	3 weeks	Unknown	Unknown	Unknown	Body	Liver	Unknown	Skin metastasis	Nil	RT, chemo	Unknown	
17	2008	USA	46	Female	D, AP	Unknown	Unknown	Unknown	Unknown	Body, tail	Stomach, spleen, bowe	18		MVR	Pre-op splenic artery embolization	AND	6
18	2008	USA	74	Male	D	Few months	Unknown	Unknown	293	Tail	Soft tissues nodes	14.5		DP, Sp		AND	17
19	2008	USA	50	Female	D, V, LOA	2 months	Low	High	770	Body	Liver, soft tissues, nodes	4.5		DP, Sp, OC, LR	Octreotide	Died	96
20	2008	USA	66	Male	D, LOW	6 months	Low	Unknown	169	Tail	Liver, soft tissues, nodes, vessels	5		DP, Sp, OC, LR	RFA, octreotide	AWD	68
21	2008	USA	68	Male	D, LOW, W	9 years	Low	High	1500	Head, body, tail	Soft tissues, nodes	14		PD, Sp	Octreotide	AWD	22
22	2010	Malaysia	58	Female	D, AP	2 years	Low	Unknown	Unknown	Head	Liver, bowel	2		Whipple	RFA, octreotide	AWD	Unknown
23	2011	Malaysia	27	Female	D, AP, Fl	6 months	Low	High	269	Body, tail	Nil	6.1		DP, Sp	Octreotide	AND	15

Index

D=Diarrhea, AP=Abdominal pain, N=Nausea, L=Lethargy, R=Rash, LOW=Loss of weight, V=Vomiting, BA=backache, Fl=Facial flushing, LOA=Loss of appetite, W=weakness, DP=Distal pancreatectomy, Sp=Splenectomy, STP=Subtotal pancreatectomy, PD=Pancreaticoduodenectomy, LR= Liver resection, MVR=Multi-visceral resection, OC=Open cholecystectomy, RFA=Radiofrequency ablation, Chemo=Chemotherapy, RT=Irradiation, AND=Alive without disease, AQS=Alive query status, AWD=Alive with disease

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006_Loh Huai Heng_Layout 1 20.03.2013 21:31 Page 37

gery, similar to surgical intervention rate of >80% reported by Ghaferi and Peng et al, but in contrast to the lower surgical rate reported in earlier literature by Smith et al (28%) and Soga et al (68%). Peng et al[7] reported that patients in their group who had palliative or radical excision were alive at 6 months of follow up whereas two patients with metastatic VIPoma who did not undergo radical excision but underwent hepatic artery embolization died after 6 months.

Octreotide is a useful adjunct therapy and had been used pre-operatively to ameliorate diarrhoea or as palliative treatment for symptom relief in patients who are unable to undergo surgery or patients with metastatic disease. Some believe that long-acting octreotide such as sandostatin has antiproliferative properties and can stabilize tumour growth[14]. The drawback of prolonged use of octreotide is resistance to this drug[15]. Among the 23 cases, 6 patients received octreotide as pre operative treatment, 2 as long term treatment due to non-suitability for operation. Other treatment modalities were also employed and included radiofrequency ablation (3 patients), chemotherapy (3 patients) and pre-operative splenic artery embolization (1 patient).

Prognosis for VIPoma depends on presence of metastasis at presentation as well as the use of surgical resection as mode of treatment. Soga et al.[3] analysed 179 patients with pancreatic VIPomas, and found a significant difference in 5-year survival rate of patients with metastasis at presentation (60%) compared with those without metastasis (94%). Peng et al and Ghaferi et al in their institutional experience, found a good prognosis in their patients with surgical resection[4,7]. Song et al pointed out that surgery should be performed to achieve radical cure once the disease is diagnosed[16] whereas Remme et al stated that even in patients with metastatic disease, surgical resection is effective in reducing symptoms and may increase the survival rate[11]. Despite advanced disease, patients with VIPoma can have extended survival[5]. The mean follow up time for these patients is 35 months. Outcome of the patients were reported in 19 cases, of which 11 were alive without disease, 4 were alive with disease, 1 alive but unknown disease status and 3 had died.

Conclusion

We reported a rare case of pancreatic VIPoma presented with classical WDHA syndrome. Although very rare, the constellation of symptoms and laboratory findings should alert physician towards possibility of this disease. Prompt diagnosis allows early surgical intervention with the potential for cure. While still around 50% of patients present with metastatic disease at diagnosis, aggressive surgery coupled with various adjunctive treatment modalities allow good palliation of symptoms and prolonged survival.

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