

Octreotide reverses shock due to vasoactive intestinal peptide-secreting adrenal pheochromocytoma: A case report and review of literature

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Abstract

Vasoactive intestinal peptide-producing tumors (VIP-oma) usually originate in the pancreas and are characterized by diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). In adults, nonpancreatic VIPoma is very rare. Herein, we report an unusual case of VIP-producing pheochromocytoma marked by persistent shock, flushing, and watery diarrhea and high sensitivity to octreotide. A 53-year-old woman was hospitalized for sudden-onset hypertension with convulsions, which then rapidly evolved to persistent shock, flushing, and watery diarrhea. Abdominal computed tomography indicated a left adrenal mass, accompanied by bleeding; and marked elevations of both plasma catecholamine and VIP concentrations were documented *via* laboratory testing. Surprisingly, all clinical symptoms responded swiftly to octreotide treatment. Once surgically treated, hormonal levels normalized in this patient, and the clinical symptoms dissipated. Postoperative pathological and immunohistopathological studies confirmed a VIP-secreting pheochromocytoma with strong, diffuse positivity for somatostatin receptor type 2. During a 6-mo follow-up period, she seemed in good health and

was symptom-free.

Key words: Pheochromocytoma; Vasoactive intestinal peptide; Octreotide; Shock; Flushing; Diarrhea; Case report

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Core tip: Vasoactive intestinal peptide-producing tumors (VIPoma) usually originate in the pancreas. VIP-secreting pheochromocytoma is very rare and most of the related cases reported are characterized by diarrhea, hypokalemia, and gastric acid deficiency (WDHA syndrome). To our knowledge, this is the first reported instance of VIP-secreting pheochromocytoma marked by persistent shock flushing and diarrhea and high sensitivity to octreotide. This case helps to improve the understanding of the pathogenesis, biology, and behavior of VIPoma and pheochromocytoma.

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INTRODUCTION

Vasoactive intestinal peptide-producing tumor (VIPoma) is an unusual neuroendocrine tumor that autonomously secretes VIP. In adult, almost all VIPomas (90%) originate from pancreatic tissues whereas the remaining 10% originate from extra-pancreatic tissues, such as the bronchus, colon, liver, and pheochromocytoma^[1]. VIP-secreting pheochromocytoma is extremely rare and most of the related cases reported are characterized by diarrhea, hypokalemia, and gastric acid deficiency (WDHA syndrome)^[2-4]. In this case, the patient harbored an exceedingly rare adrenal pheochromocytoma, which ultimately ruptured and bled. Its principal manifestations included persistent shock, flushing, and watery diarrhea in the aftermath of sudden-onset hypertension with convulsions. Laboratory diagnostics and immunohistochemical attributes indicated that this pheochromocytoma secreted both catecholamines (CATs) and VIP.

CASE REPORT

A 53-year-old woman was admitted to the local hospital after 1 d of convulsions leading to loss of consciousness. After the attack (approximately 20 min), the patient eventually became conscious. Six months prior, she reported having paroxysmal palpitation attacks (5-20 min each), which spontaneously subsided, and had



Figure 1 Flushing in the face and neck of the patient.

suffered occasional headaches, without sweating or chest pain. Consequently, medical attention was never sought.

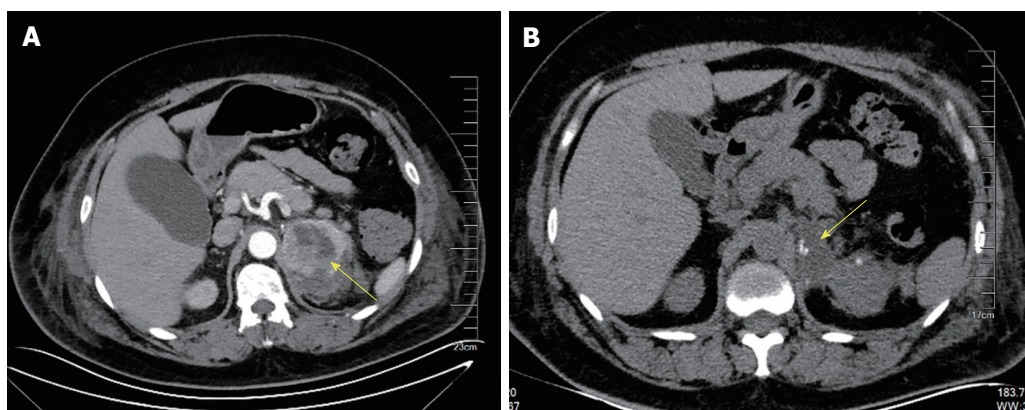
Computed tomography (CT) of the head showed no abnormalities; but this historically normotensive patient produced a blood pressure (BP) reading of 230/100 mmHg. Nicardipine hydrochloride (3 µg/kg per min; Astellas Pharma Tech Co, Ltd, Tokyo, Japan) was administered for BP control, which was achieved approximately 8 h later (160/90 mmHg), and the convulsions disappeared. However, treatment was withdrawn without rebound effect following a sudden drop in BP (nadir: 53/35 mmHg). She was then transferred to our facility.

At the time of admission, the patient was somnolent but could be aroused and appeared dispirited, evoking a Glasgow coma score of 9 (E, 2; M, 4; V, 3). She presented with watery diarrhea > 10 times/d (total volume, 800-1200 mL/24 h). At a height of 162 cm and a body weight of 82 kg, her baseline vital signs were as follows: BP, 68/44 mmHg; heart rate, 92 bpm; respiratory rate, 18 bpm; and temperature, 36.8 °C. There was flushing of the face and neck (Figure 1) and sensitivity to percussion in the region of the left kidney. Thyromegaly, rales (neither lung by auscultation), cardiac murmurs, abdominal tenderness, and palpable lumps were not observed.

Laboratory tests showed that hematocrit and hemoglobin were within standard reference ranges and did not deviate significantly in several repeat attempts. Other results were as follows: glucose, 17.2 mmol/L (3.9-6.1); creatinine, 289.9 µmol/L (45-84); troponin I (TnI), 0.14 ng/mL (0.010-0.023); creatine kinase (CK), 230 ng/L (45-145); and CK-MB, 15 ng/L (2.0-7.2). A battery of biochemical tests, including liver function studies, blood gas analysis, blood coagulation indices, and electrolyte (K, Na, Cl, Ca, P, and Mg) levels, returned essentially normal results. The electrocardiogram showed T-wave inversion and slight ST-segment depression (0.1-0.2 mv) in leads V1-V6, II, III, and AVF. Coronary arteriography confirmed no coronary artery obstruction. By ultrasonic

Table 1 Catecholamines and vasoactive intestinal peptide levels in plasma and urine

	Day 2	Day 5	Post-operation	Reference range
Plasma				
Epinephrine (pg/mL)	547	624	35	< 130
Norepinephrine (pg/mL)	1683	1662	376	150–520
Dopamine (pg/mL)	214982	345	14	< 30
Vasoactive intestinal peptide (pg/mL)	377	126	< 10	< 100
Urine				
Metanephrine (mg/24 h)	2.4	2.3	0.12	0.04–0.19
Normetanephrine (mg/24 h)	3.2	3.4	0.21	0.09–0.37
Vanillylmandelic acid (mg/24 h)	53.8	47.5	2.80	1.4–6.5

**Figure 2** Abdominal computed tomography. A: The arrow indicates a heterogeneous left adrenal mass; B: After operation, the left adrenal mass was removed (arrow) and a small amount of encapsulated effusion remained.

cardiography (UCG), the following parameters were determined: interventricular septal thickness, 10–12 mm; width of posterior left ventricular wall, 10 mm; left ventricular end-diastolic (156 mL) and end-systolic (69 mL) volumes; stroke volume, 87 mL; and ejection fraction, 56%. CT studies of the patient's head and chest were not abnormal, but on the enhanced abdominal CT, a solitary mass of the left adrenal gland was identified, with signs of bleeding (Figure 2). In addition, blood and urinary CAT concentrations and urinary vanillylmandelic acid were significantly elevated (Table 1).

Treatment included copious intravenous fluid replacement (0.9% NaCl, 4000 mL/24 h), with potassium supplementation (KCl, 3–6 g/24 h), and an intravenous dopamine drip (12 µg/kg per min; Shanghai Fenge Pharmaceutical Co, Ltd, Shanghai, China) was initiated. The patient's BP increased slightly in response, with systolic pressures still fluctuating from 80–100 mmHg. There was no mental improvement or resolution of facial and neck flushing, and despite complete solid/liquid fasting, the diarrhea persisted. Besides, we administered the patient with continuous intravenous insulin to keep the blood glucose around 10 mmol/L. We rechecked CK, CK-MB, TnI, and electrocardiogram every 6 h. The patient's myocardial enzymes and TnI levels gradually returned to normal, and the ischemic manifestations on electrocardiogram were

also significantly improved. This symptomology was not typical of pheochromocytoma. Given the array of hormones implicated in neuroendocrine tumors, significant elevation of plasma VIP (Table 1) was subsequently verified through additional diagnostics, whereas other substances [plasma pancreatic polypeptide, adrenocorticotrophic hormone, somatostatin (SST), thyroid hormones, parathyroid hormone, calcitonin, adrenomedullin, and urine 5-hydroxy indoleacetic acid] remained normal.

To control diarrhea and facial flushing, the patient received intramuscular injections of octreotide (0.1 mg/8 h; Novartis International AG, Basel, Switzerland) on day 3 after admission, followed by a surprisingly rapid rise in BP. After 24 h, the dopamine drip was discontinued, and her BP had reached 123/75 mmHg. The patient's mental state also cleared significantly, and she was more alert; the facial and neck flushing was relieved; and diarrhea was less frequent. On day 5 after admission, she was completely conscious, her facial and neck skin had returned to normal, and the diarrhea had stopped. At this point, she developed paroxysmal hypertension (peak BP: 190/100 mmHg), for which oral terazosin hydrochloride (2 mg/d; Abbott Laboratories, Chicago, IL, United States) was given.

After 20 d, left laparoscopic adrenalectomy was performed. The mass of the left upper kidney and an encapsulated, posteriorly placed hematoma (due to

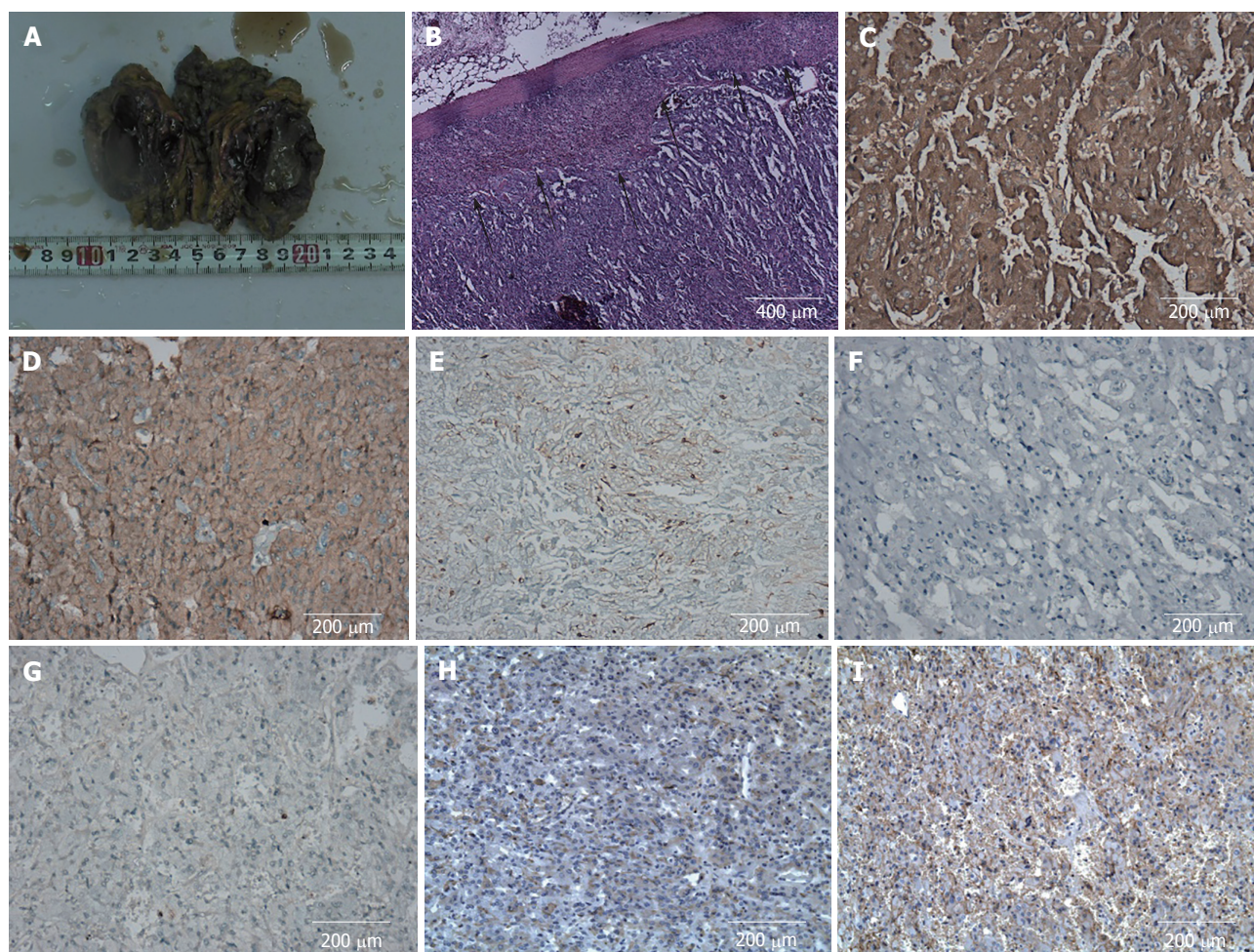


Figure 3 Histopathological and immunohistochemical staining. A: A gross pathological finding of the resected adrenal tumor; B: Hematoxylin-eosin staining of tumor tissue, black arrows indicate the juncture of normal adrenal cortex and tumor tissue; C-I: Immunohistochemical staining for synaptophysin (C), chromogranin A (D), S-100 (E), creatine kinase (F), KI67 (G), vasoactive intestinal peptide (H), and somatostatin receptor 2 (I).

rupture) were located. When dissecting this mass, the patient's BP again climbed to 240/130 mmHg. No other abdominal tumors were discovered, and the right adrenal gland was morphologically normal. The resected mass measured 7 cm × 4.5 cm. On cut section, it was soft and yellow-brown, demonstrating two subcapsular clefts of 2-4 cm (Figure 3A). In histological sections, the tumor cells were nested or arranged in trabecular pattern, with variably sized, pleomorphic nuclei. Their cytoplasm was abundant, showing basophilic or amphophilic stippling. A compressed rim of normal adrenal cortex was retained at the tumor's edge, and there was no obvious intervening septum (Figure 3B).

Immunohistochemical staining properties were as follows: Syn (+), CgA (+), S-100 (+), CK (-), and KI67 (< 5%+) (Figure 3C-G). On this basis, the histopathological diagnosis was adrenal pheochromocytoma. We then pursued immunohistochemical staining for VIP and SST receptor 2 (SSTR2), confirming 60%-70% cytoplasmic VIP positivity of pheochromocytoma cells. No positively stained ganglioneuroma component was evident (Figure 3H). Nearly all tumor cell membranes

demonstrated SSTR2 positivity (Figure 3I).

After surgery, the patient discontinued octreotide and terazosin hydrochloride and recovered uneventfully from surgery. Her BP and heart rate returned to normal levels, as did various hormonal concentrations; and symptoms such as headache, palpitation, chest pain, facial flushing, and diarrhea were no longer problematic. During a 6-mo follow-up period, she seemed in good health and was symptom-free.

DISCUSSION

VIPoma syndrome of watery diarrhea, hypokalemia and achlorhydria was first described by Verner *et al*^[5] in 1958, and has been considered to be due to excessive secretion of VIP. In adults, this syndrome is most commonly associated with pancreatic islet cell tumors, but is rarely caused by non-pancreatic tumors, such as bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and adrenal pheochromocytoma^[6]. In an investigation of 62 VIPoma patients, 52 (84%) had pancreatic tumors and 10

(16%) had ganglioneuroblastomas. Of the 10 patients with ganglioneuroblastomas, seven were children^[7]. The first description of a nonpancreatic tumor producing VIP was a retroperitoneal ganglioneuroma reported by Fausa *et al*^[8] in 1973. Loehry *et al*^[9] first reported an WDHA syndrome caused by a pheochromocytoma in 1975. VIP is a 28-amino acid peptide that may stimulate the production of intestinal cyclic adenosine monophosphate, leading to massive intestinal secretion of water and electrolytes^[6,7]. VIP also inhibits gastric acid secretion, promotes hepatic glycogenolysis and dilates peripheral systemic blood vessels. Clinical presentations of VIPoma commonly include secretory diarrhea, hypokalemia, hypochlorhydria, flushing, hyperglycemia, and metabolic acidosis^[8]. Although this patient had obvious diarrhea, there was no apparent hypokalemia, which may be related to the relatively short onset time and electrolyte supplementation. Most patients with WDHA syndrome have suffered several months or years before seeking medical treatment, so their conditions are dire. Accordingly, we suspected that VIP was produced but only a small amount was secreted, as reported in the literature^[9]. Rupture and bleeding may in fact have initiated a massive release of VIP into the circulation, igniting the patient's progression of symptoms.

As we mentioned above, VIP is also a superactive vasodilatory substance capable of producing a generalized peripheral vascular effect^[10,11]. Although published reports have yet to link hypotension or shock with VIP-producing pheochromocytomas, most of the affected patients show no hypertensive manifestations^[12-14], implying that VIP may effectively antagonize vasoconstrictive CAT activity due to strong action of vasodilation. In this case, octreotide treatment not only significantly improved diarrhea and flushing symptoms, but also corrected situation of shock synchronously. However, octreotide had little impact on plasma CAT concentration, corroborating previous reports^[15,16], which indicate that excessive VIP release may be the most important reason causing shock. On the other hand, the cardiotoxic effects of CATs are chronicled in a number of publications, having linked CAT excess with acute myocarditis and cardiogenic shock^[17,18]. This is the most common cause of shock due to pheochromocytoma. In this case, however, UCG showed that left ventricular contractility was within normal range, which is different from most of patients with pheochromocytoma-induced shock. Although single echocardiography cannot completely exclude the possibility of cardiogenic shock, this result still indicates that cardiotoxic effects of CATs may not be the main cause of shock. Unfortunately, the patient refused invasive hemodynamic so that we cannot prove our presuming.

Octreotide is a synthetic long-acting SST analogue that effectively inhibits release of VIP from tumors and is approved by the FDA for treatment of WDHA^[19]. Its

biologic effects are exerted largely through binding with SSTRs on target cell membranes. SSTRs are G protein-coupled receptors of five subtypes (SSTR1-5). SSTR2 is expressed in > 80% of neuroendocrine tumors and is the subtype with the strongest affinity for octreotide^[20]. Although some VIP-secreting pheochromocytomas are poorly responsive to octreotide due to lack of SSTR expression^[4,12], this patient was promptly restored to near-normal VIP levels through such treatment, with substantial abatement of diarrhea and flushing. Immunohistochemistry later confirmed strong, diffuse SSTR2 positivity (Figure 3I) of tumor cells and this may be the reason why octreotide plays a magical role in the present case. Despite the significant efficacy of octreotide, the definitive treatment for VIPoma is surgery^[21-25]. In the cases in which complete surgical resection is either unsuccessful or not feasible, octreotide is an important pharmacotherapeutic approach to controlling symptoms in VIPoma patients^[26,27]. However, the long-term administration of octreotide may result in the development of resistance, sometimes extremely high doses of octreotide is necessary for continuous effects^[28,29]. In patients with poor efficacy of somatostatin, interferon- α can be combined with octreotide to improve clinical symptoms and promote tumor regression^[30,31].

In summary, we report an extremely rare case of VIP-secreting pheochromocytoma marked by persistent shock, flushing, and diarrhea and high sensitivity to octreotide. This case reminds us that the diversity of hormones secreted by neuroendocrine tumor gives rise to clinically complex patient scenarios and a sudden overdose of hormonal substances, when the tumor ruptures, may be fatal to the patient. Therefore, comprehensive hormone testing may be useful for early diagnosis and effective treatment, especially when the patient is in crisis due to unknown reasons.

ARTICLE HIGHLIGHTS

Case characteristics

In adults, vasoactive intestinal peptide-producing tumors (VIPoma) is most commonly originates from pancreatic islet cell tumors, but is rarely caused by pheochromocytoma. We report a VIP-secreting pheochromocytoma case marked by persistent shock, flushing, and diarrhea and high sensitivity to octreotide.

Clinical diagnosis

VIP-secreting pheochromocytoma.

Differential diagnosis

Acute myocardial infarction and cardiogenic shock induced by pheochromocytoma.

Laboratory diagnosis

Pheochromocytoma and VIPoma.

Imaging diagnosis

Left adrenal pheochromocytoma.

Pathological diagnosis

VIP-secreting pheochromocytoma.

Treatment

Surgery after octreotide improved clinical symptoms.

Related reports

It is the first reported instance of VIP-secreting pheochromocytoma marked by persistent shock flushing and diarrhea and high sensitivity to octreotide.

Experiences and lessons

This case reminds us that the diversity of hormones secreted by neuroendocrine tumor gives rise to clinically complex patient scenarios, and a sudden overdose of hormonal substances, when the tumor ruptures, may be fatal to the patient. Comprehensive hormone testing may be useful for early diagnosis and effective treatment, especially when the patient is in crisis due to unknown reasons.

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