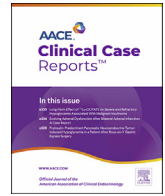


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## Case Report

# Vasoactive Intestinal Peptide-Secreting Pheochromocytoma: A Case Report and Review of Literature

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## ABSTRACT

**Objective:** To describe a case of composite vasoactive intestinal peptide (VIP)-secreting pheochromocytoma and review literature to provide insight into the various presentations and potential management of these rare tumors.

**Case Report:** A 64-year-old male patient presented with hypertensive emergency and coronary demand ischemia with development of watery diarrhea, hypokalemia, and achlorhydria syndrome. Serum and urine studies demonstrated elevated metanephrine and VIP levels. Definitive surgical resection resolved symptoms and normalized laboratory values. Pathologic examination of the specimen revealed pheochromocytoma with a Pheochromocytoma of the Adrenal gland Scaled Score of 4 and patchy expression of VIP.

**Discussion:** Given the different actions of hormones that can be secreted by these composite tumors, we suggest that pheochromocytomas with diversified secretory capabilities may be an underrecognized clinical entity. Localized disease is often amenable to surgical resection, although management of metastatic disease is not well established due to the rarity of these tumors and lack of randomized trials.

**Conclusion:** In patients presenting with diarrhea of unclear etiology or the suggestion of secondary hypertension, assessment for a possible neuroendocrine tumor may be prudent. If an adrenal mass is discovered but the patient exhibits atypical symptoms of catecholamine excess, a diagnosis of composite pheochromocytoma with multisecretory properties should be considered.

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## Introduction

Vasoactive intestinal peptide (VIP) is a polypeptide neurohormone that induces the intestinal excretion of electrolytes and water.<sup>1</sup> In the setting of excessive VIP levels, patients may develop a profound secretory diarrhea and a set of features known as watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome. Hypersecretion of VIP is typically associated with pancreatic tumors, although cases describing VIP secretion associated with extrapancreatic tumors (ganglioneuroblastomas, ganglioneuromas, neurofibromas, and pheochromocytomas) have been reported.<sup>2,3</sup>

The rare case of a VIP-secreting pheochromocytoma was first reported in 1975 by Loehry et al<sup>4</sup>, and since this time, only

approximately 25 cases have been described.<sup>5–17</sup> We describe a case of a man found to have a pheochromocytoma who presented with hypertensive emergency and WDHA syndrome, resolved with adrenalectomy.

## Case Report

A 64-year-old Caucasian male patient with a history of essential hypertension, hyperlipidemia, and diabetes mellitus initially presented with chest pain, dyspnea, nausea, and diaphoresis. The patient did not report a prior history of headaches, palpitations, diaphoresis, or diarrhea. Family history was negative for endocrinologic or oncologic disease. On admission, his heart rate and blood pressure were 122 beats per minute and 200/110 mm Hg, respectively. Admission laboratory testing demonstrated a leukocytosis ( $20.7 \times 10^9/L$ ) and elevated troponin level ( $>260$  ng/mL). He was administered IV clevidipine and nitroglycerin to control his blood pressures and then later transitioned to oral lisinopril, carvedilol, and nifedipine. Electrocardiography revealed a non-ST-elevated

**Abbreviations:** VIP, vasoactive intestinal peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria.

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myocardial infarction; however, emergent cardiac catheterization demonstrated nonobstructive coronary artery disease. His acute symptoms resolved, but he then developed severe diarrhea and syncope. The computed tomography scan of the brain was unremarkable. He was placed on empirical metronidazole, but all stool test results were eventually negative for infectious causes. Over the following days, he developed acute kidney injury with the creatinine level increasing from 0.89 to 1.91 mg/dL and progressive hypercalcemia to 15.7 mg/dL with a parathyroid hormone level of 31 pg/mL. Despite calcitonin administration, he became obtunded and required endotracheal intubation. Zoledronate was added. The surveillance computed tomography scan of the chest, abdomen, and pelvis showed a 12.0 × 9.5 × 11.2-cm soft tissue mass at the upper pole of the right kidney with 5 cm of central necrosis and hemorrhage. Hounsfield units were variable; measured at 37 to 60 Hounsfield units within the mass. He was transferred to a tertiary referral center where magnetic resonance imaging of the abdomen confirmed a heterogeneously enhancing adrenal mass compressing the right renal vein and abutting the liver and inferior vena cava (Fig. 1).

Preoperative laboratory results, including metabolic panel and complete blood count, were largely unremarkable with only mild electrolyte derangements. Urine studies (24 hours) revealed marked elevations in the levels of vanillylmandelic acid, metanephrines, normetanephrine, total metanephrines, and free catecholamines (Table 1). The free cortisol level was also noted to be mildly elevated (Table 1), but this was attributed to physiologic stress. Serum studies demonstrated elevated free metanephrine and normetanephrine levels (Table 1). The aldosterone, testosterone, dehydroepiandrosterone sulfate levels and aldosterone/renin activity ratio were within normal limits. He continued to have up to 3.3 L/day of watery diarrhea. Stool studies revealed high osmolarity (328 mOsm/kg; normal, 280–303 mOsm/kg) and elevated fecal sodium level (114 mmol/L; normal, approximately 30 mmol/L), confirming a secretory diarrhea. The serum VIP level was extremely elevated (Table 1).

Metastatic workup was unremarkable except for magnetic resonance imaging of the brain, which showed several 3-mm lesions that were thought to be small subacute infarcts. The patient was prepared for surgery with 2 weeks of  $\alpha$ -adrenergic followed by  $\beta$ -adrenergic blockade and octreotide to control the diarrhea. The diarrhea persisted despite octreotide administration but was

### Highlights

- Composite pheochromocytomas with diversified secretory capabilities may be an underrecognized clinical entity.
- In localized disease, surgical resection is generally definitive with good prognosis.
- The approach to metastatic disease is not clear due to the rarity and lack of larger studies; however, medical therapies targeting common growth or metabolic pathways may show promise.

### Clinical Relevance

Given the high morbidity and potential for mortality in advanced disease, early diagnosis and treatment of composite tumors are essential, but can be difficult given the opposing actions of catecholamines and VIP. This underscores the importance of conducting a thorough workup in patients that present with or develop additional symptoms that are uncharacteristic of the primary tumor, with recognition of the possibility of multiseptary properties.

attenuated to approximately 1 L/day. He underwent open right adrenalectomy for presumed VIP-secreting pheochromocytoma. Intraoperatively, his blood pressure was labile with systolic pressures ranging from 60 to 300 mm Hg during manipulation of the tumor.

In the postoperative period, he regained hemodynamic stability. His postoperative course was uneventful. His blood pressure and electrolyte levels stabilized, and diarrhea resolved over the course of a few days. The metanephrine, normetanephrine, and VIP levels normalized, and he was discharged home on postoperative day 7 (Table 1). The patient has remained asymptomatic at 2 and 4.5 months after operation.

Pathology revealed a 14.5 × 13.0 × 9.5-cm tumor replacing the entire right adrenal gland. On sectioning, the tumor had a focal region of necrosis comprising approximately 30% of the tumor. Diffuse growth was noted as evidenced by the absence of sustentacular cells on S100 immunostaining. VIP immunostaining showed focal/patchy expression in neoplastic cells (Fig. 2). The tumor was

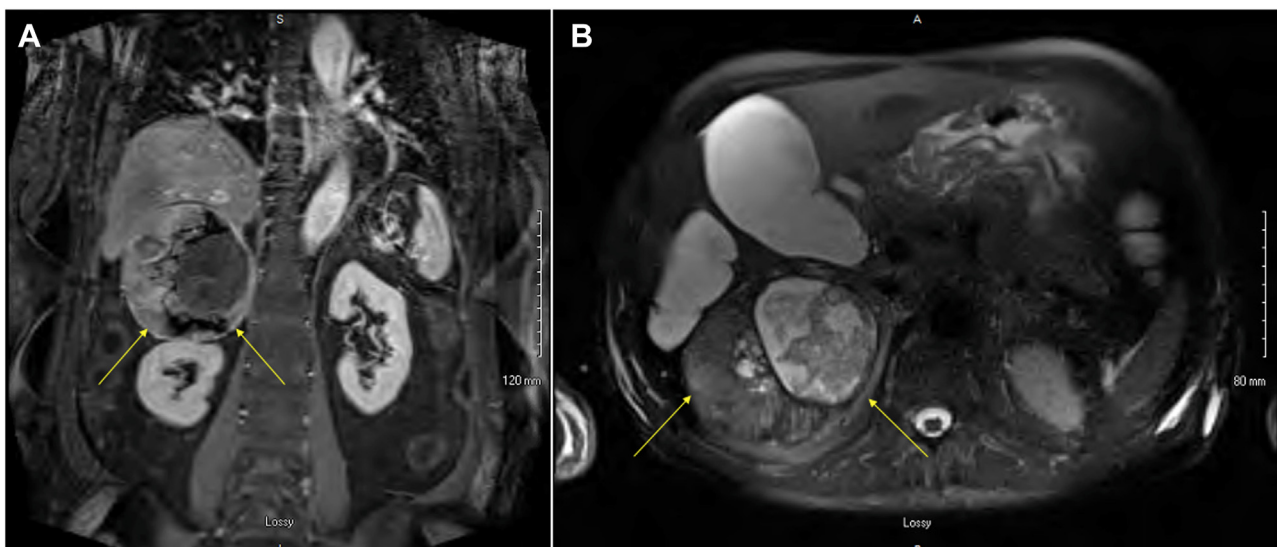


Fig. 1. Abdominal magnetic resonance imaging showing a heterogeneously enhancing right adrenal mass in, A, coronal view and, B, axial view (yellow arrows).

**Table 1**  
Laboratory Values

Serum studies			
	Preoperative	Postoperative	Reference values
Free metanephrines	>20 000 pg/mL <sup>a</sup>	88 pg/mL	≤57 pg/mL
Normetanephrine	>20 000 pg/mL <sup>a</sup>	197 pg/mL	≤148 pg/mL
Total free metanephrines and normetanephrine	>40 000 pg/mL <sup>a</sup>	285 pg/mL	≤205 pg/mL
Vasoactive intestinal peptide	799 pg/mL	<50 pg/mL	<75 pg/mL
24-hour urine studies			
	Patient values		Reference values
Creatinine	1.48 g		0.50–2.15 g
Free cortisol	94.5 µg		4–50.0 µg
Metanephrines	70 126 µg		90–315 µg
Vanillylmandelic acid	138.3 mg		≤6 mg
Normetanephrine	27 635 µg		122–676 µg
Total metanephrines	97 761 µg		224–832 µg
Free catecholamines			
Dopamine	2001 µg		52–480 µg
Epinephrine	>2138 µg <sup>a</sup>		2–24 µg

<sup>a</sup> Above clinical reportable range for an analyte.

determined to have a Pheochromocytoma of the Adrenal gland Scaled Score of 4, indicating potential for biologically aggressive behavior. Genetic testing was not performed but was recommended as part of outpatient follow-up.

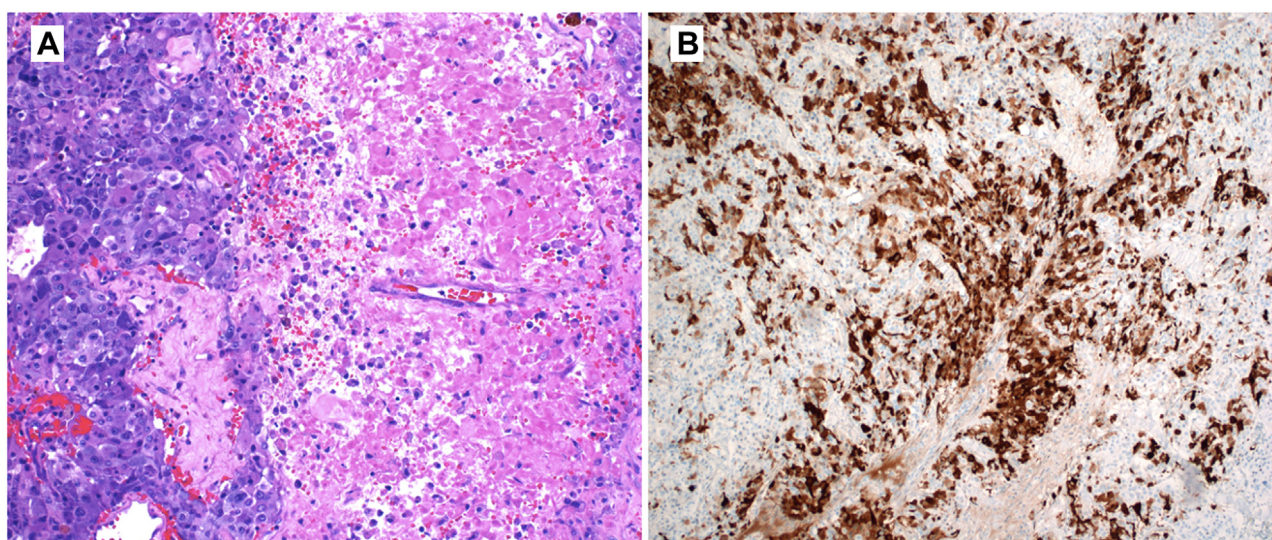
## Discussion

Pheochromocytomas are rare catecholamine-producing neuroendocrine tumors of chromaffin cells of the adrenal medulla or extra-adrenal sympathetic ganglia (termed “paragangliomas”). These tumors are notoriously difficult to diagnose due to the wide array of sometimes vague clinical presentations. A recent study by Gruber et al<sup>18</sup> demonstrated that only 25% of tumors were diagnosed from workup following recognition of symptomatology despite most patients being symptomatic, suggesting that pheochromocytomas often go undiagnosed and contribute to significant morbidity and even early mortality. Common signs and symptoms include paroxysmal hypertension (39.5%), tachycardia/palpitations (55.7%), sweating (41.6%), headache (43.2%), and spells (37.3%).<sup>18</sup> Less commonly, psychological states such as panic and anxiety

occur<sup>18</sup>. The clinical picture can become more convoluted because pheochromocytomas can secrete hormones other than catecholamines, including erythropoietin, calcitonin, parathyroid hormone-related peptide, atrial natriuretic protein, renin, angiotensin-converting enzyme, serotonin, gastrin, somatostatin, and VIP.<sup>13,19</sup>

Hypersecretion of VIP leads to a set of symptoms known as WDHA syndrome.<sup>1</sup> Patients commonly present with a profound secretory diarrhea (often ≥3 L/day) that persists with fasting (54.5%), electrolyte abnormalities such as hypomagnesemia or hypokalemia (45.6%), and hypochlorhydria/achlorhydria (42.4%).<sup>1</sup> Other possible features include hypotension from vasodilation, a hypokalemic nonanion gap metabolic acidosis from bicarbonate wasting, hyperglycemia (20%–50%) secondary to increased glycogenolysis, and hypercalcemia (25%–50%) likely due to dysregulation of bone metabolism.<sup>1,8</sup>

VIP-secreting pheochromocytomas have only been reported in case reports, and studies with larger series are not available (Table 2). These tumors were generally large on diagnosis and presented with classical symptoms of excess catecholamine release



**Fig. 2.** Histopathologic images and immunohistochemical staining for vasoactive intestinal peptide. A, Hematoxylin and eosin staining showing a “nested” architecture of tumor cells characteristic of pheochromocytoma and necrosis (200×). B, Immunohistochemical staining for vasoactive intestinal peptide (100×).

**Table 2**  
Review of Literature Describing Pheochromocytoma With Associated VIP Secretion

Author, y	Age/ sex	Baseline hypertension	Case presentation	Tumor size, characteristics	Metastatic disease	Intervention	Outcome
Hermel et al <sup>5</sup> , 2021	30F	N	Hypertension, tachycardia, headache, anxiety	11 cm	N	Octreotide, metyrosine, embolization, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Negro et al <sup>6</sup> , 2021	71M	N	WDHA syndrome	10 cm, PASS of 20	Y, metastatic at presentation	Surgical resection of primary tumor, octreotide, sunitinib for recurrence	Recurrence, death 3 mo after resection
Hu et al <sup>7</sup> , 2018	53F	N	Hypertension, seizure, followed by shock, flushing, WDHA syndrome	7 cm	N	Octreotide, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Jiang et al <sup>8</sup> , 2014	45M	N	WDHA syndrome	9 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Leibowitz- Amit et al <sup>9</sup> , 2014	51M	N	WDHA syndrome with progression	Not reported	Y	Octreotide, radiation, surgical resection of primary tumor, sunitinib	Metastatic disease 3 y after resection with elevated VIP levels and WDHA syndrome responsive to sunitinib
Kikuchi et al <sup>10</sup> , 2012	12F	N	, WDHA syndrome	8.0 cm	Y	Surgical resection of primary tumor	Lung/liver metastases, 3 y after resection WDHA syndrome, 13 y after resection Death, 14 y after resection
Ozbay et al <sup>11</sup> , 2008	77F	N	WDHA syndrome, sweating, palpitations	12 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Ikuta et al <sup>12</sup> , 2007	49F	N	WDHA syndrome	7 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Smith et al <sup>13</sup> , 2002	78F	Y	WDHA syndrome	6 cm	N	Octreotide, surgical resection	Complete resolution of symptoms, normalization of laboratory values
Nigawara et al <sup>14</sup> , 1987	43M	Unknown	WDHA syndrome	11 cm	Y	Surgical resection	Surgical resection of primary tumor, embolization of metastases
Sackel et al. <sup>15</sup> , 1985	55F	N	WDHA syndrome	8.5 cm	N	Surgical resection	
Viale et al <sup>16</sup> , 1985	30M	N	WDHA syndrome	5 cm	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values
Matta et al <sup>17</sup> , 1978	43F	Unknown	WDHA syndrome	15 cm	N	Surgical Resection	
Loehry et al <sup>4</sup> , 1975	28F	Unknown	WDHA syndrome, headaches, palpitations, hypertension	Not reported	N	Surgical resection	Complete resolution of symptoms, normalization of laboratory values

Abbreviations: F = female; M = male; N = No; VIP = vasoactive intestinal peptide; WDHA = watery diarrhea, hypokalemia, achlorhydria; Y = yes.

(hypertension, paroxysmal headaches, and palpitations) or symptoms of WDHA syndrome. It is possible that the vasodilatory effects of VIP “masked” the hypertensive effects of catecholamines, potentially delaying diagnosis. There were no reports of associations with other endocrinopathies, and only 1 case (in the study by Hermel et al<sup>5</sup>) reported a family history positive for an aunt with thyroid disease. Genetic testing was reported in 4 cases (in the studies by Negro et al<sup>6</sup>, Jiang et al<sup>8</sup>, Leibowitz-Amit et al<sup>9</sup>, and Ozbay et al<sup>11</sup>), of which only 1 (in the study by Negro et al<sup>6</sup>) reported a “synonymous single nucleotide variant of the SDHA gene” associated with “probably benign pheochromocytoma.” In localized disease, surgical resection is generally definitive with good prognosis. The approach to metastatic disease remains unclear due to the rarity of this tumor. Emerging therapies, such as everolimus, sunitinib, peptide receptor radionuclide therapy with radiolabeled somatostatin analogs in metastatic VIPoma, and meta-iodobenzylguanidine therapy in metastatic pheochromocytoma, show promise; however, their efficacy in composite tumors is largely unproven.<sup>9,20</sup> Leibowitz-Amit et al<sup>9</sup> described successful treatment of metastatic VIP-secreting pheochromocytoma with

sunitinib, which resulted in complete symptomatic resolution and stabilization of all metastases. Systemic therapies targeting common growth or metabolic pathways may be potentially effective in the treatment of composite neuroendocrine tumors; however, larger studies will be needed to determine the true efficacy.

In this case, our patient had a pheochromocytoma with hypersecretion of catecholamines and patchy expression of VIP, which may explain the unusual clinical manifestations. He initially presented in a catecholamine-induced hypertensive crisis causing a non-ST-elevated myocardial infarction due to demand ischemia. Aggressive management of his blood pressure may have resulted in underperfusion, ischemia, and necrosis within the undiscovered adrenal mass. Cell lysis within the tumor may have led to the sudden release of large amounts of VIP, resulting in massive watery diarrhea and hypersecretion of electrolytes. The severe hypercalcemia observed may be attributable to a direct effect of VIP on osteoclasts as suggested in Jiang et al<sup>8</sup>, in combination with decreased calcium excretion due to the concomitant acute kidney injury. Resolution of his symptoms occurred rapidly following surgical resection of the tumor.

## Conclusion

This case is an unusual presentation because the VIP-secreting properties of the tumor were not clinically apparent until the patient received treatment for symptoms secondary to catecholamine secretion from the tumor. This suggests that composite pheochromocytomas with diversified secretory capabilities are an under-recognized clinical entity. Given the high morbidity and potential for mortality in advanced disease, early diagnosis and treatment are essential. However, diagnosis of these rare tumors can be difficult due to the “masking” effect of VIP that can significantly delay the manifestation of symptoms. Patients can present with a complex clinical picture with features of WDHA syndrome, catecholamine excess, or both. This underscores the importance of conducting a thorough workup in patients who present with or develop additional symptoms that are uncharacteristic of the primary tumor, with recognition of the possibility of multisecretory properties.

## Disclosure

The authors have no multiplicity of interest to disclose.

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