


# Vasoactive intestinal peptide producing pheochromocytoma and intracardiac thrombosis

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## Abstract

A case of pheochromocytoma producing vasoactive intestinal peptide (VIP) and left ventricular thrombus in the absence of cardiomyopathy or wall motion abnormalities on echocardiogram is presented along with a review of the relevant literature. A 30-year-old female of Afghani descent with past medical history of panic attacks presented with fever, cough, sore throat, vomiting, and was found to have an 11 cm adrenal mass consistent with primary adrenocortical adenoma versus carcinoma. Her tumor elicited catechols and vasoactive intestinal peptide. Her hospitalization was complicated by left ventricular thrombosis leading to an embolic injury to her right kidney, respiratory failure, need for transient dialysis and urinary tract infections. She developed a profuse secretory diarrhea and decision was made to treat with empiric octreotide infusion and imodium with improvement in symptoms. She underwent coil and particle embolization followed by resection. Followup PET gallium scan showed no evidence of residual disease or metastasis. VIP producing pheochromocytoma associated with intracardiac thrombosis is rare. Outcomes depend on prompt diagnosis of the pheochromocytoma and multidisciplinary approach to management.

## Keywords

Thrombus, pheochromocytoma, hypercoagulability, vasoactive intestinal peptide

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## Introduction

Pheochromocytoma is a rare tumor associated with episodic hypertension, palpitations, headaches, and panic disorder due to abnormal catecholamine production.<sup>1,2</sup> Securing the diagnosis poses a significant clinical challenge and is often overlooked for many years even with the most classical presentation. Prevalence estimates for pheochromocytoma vary from 0.01% to 0.1% of the hypertensive population.<sup>3</sup> Germline mutations in five genes have been identified to be responsible for familial pheochromocytoma: the von Hippel-Lindau gene, which causes von Hippel-Lindau syndrome, the RET gene leading to multiple endocrine neoplasia type 2, the neurofibromatosis type 1 gene, which is associated with von Recklinghausen's disease and the genes encoding the B and D subunits of mitochondrial succinate dehydrogenase,

which are associated with familial paragangliomas and pheochromocytomas.<sup>4</sup> Watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome caused by vasoactive intestinal polypeptide (VIP) produced by pheochromocytoma is exceedingly rare.<sup>5–11</sup> Moreover, thrombotic events have been reported rarely in patients with pheochromocytoma.<sup>1,12–18</sup> with intracardiac thrombus even rarer. A case of a patient

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with pheochromocytoma producing VIP and left ventricular thrombus in the absence of cardiomyopathy or wall motion abnormalities on echocardiogram is presented along with a review of the relevant literature.

## Case presentation

A 30-year-old female of Afghani descent with past medical history of intermittent severe headaches, palpitations, anxiety, along with episodes of shaking, tremors, photophobia associated with increase in blood pressure who had previously been diagnosed with panic attacks presented with fever, cough, sore throat, and vomiting. Social history was unremarkable and family history of an aunt with thyroid disease. She was found to be tachycardic and hypertensive with elevated troponin, leukocytosis, elevated procalcitonin, and sinus tachycardia. She was started on empiric antibiotics which were continued throughout her course. Studies included CT abdomen pelvis which revealed an 11 cm heterogeneous adrenal mass consistent with primary adrenocortical adenoma versus carcinoma.

Her 24-h urine metanephrine and normetanephrine levels were significantly elevated at  $>72,500 \mu\text{g/d}$  (normal range:  $36\text{--}229 \mu\text{g/d}$ ), and  $26,610 \mu\text{g/d}$  (normal range:  $95\text{--}650 \mu\text{g/d}$ ) respectively. Her serum epinephrine level was  $>75,000 \text{pg/mL}$  (normal range:  $10\text{--}200 \text{pg/mL}$ ), norepinephrine was  $67,391 \text{pg/mL}$  (normal range:  $80\text{--}520 \text{pg/mL}$ ), and dopamine  $1458 \text{pg/mL}$  (normal range:  $0\text{--}20 \text{pg/mL}$ ). Her 24-h urine vanillylmandelic acid (VMA) to creatinine ratio was also elevated at  $279 \text{mg/gCR}$  (normal range:  $0\text{--}6 \text{mg/gCR}$ ). She was started on aggressive alpha blockade.

Transthoracic echocardiogram revealed a large left ventricular thrombus, ejection fraction 50%. She was started on heparin drip given concern for myocardial infarction. The patient experienced bilateral lower extremity paresthesias, numbness, and discomfort concerning for acute limb ischemia and there was difficulty obtaining a pulse in her lower extremities with doppler. A stat arterial duplex revealed severe bilateral lower extremity arterial insufficiency. Imaging and examination revealed extensive thrombotic occlusion of the distal aorta, bilateral common iliac arteries, and the left distal superficial femoral artery. She underwent bilateral groin cutdowns with thrombectomies and was continued on heparin infusion. Repeat echocardiography revealed significant reduction in the amount of left ventricular clot burden, likely due to cardioembolic disease but with residual clot present. Hypercoagulability workup was unremarkable including negative heparin induced thrombocytopenia (HIT) antibody, lupus anticoagulant, antiphospholipid antibody panel, and no MTHFR mutation. Her novel coronavirus (COVID19) Immunoglobulin G (IgG) was negative. Her disseminated intravascular coagulation (DIC) panel was positive with the pheochromocytoma suspected as the culprit. The patient developed an ileus prompting consideration of bowel ischemia related to

embolic phenomenon, however an attempted colonoscopy was aborted due to hemodynamic instability. She did not develop evidence of gastrointestinal hemorrhage despite heparin and lactate remaining normal, which was felt to make ischemic colitis less likely. Her GI distension and concern for possible intestinal embolic events severely limited the ability for standard alpha blockade. Despite persistent colonic dilation, she developed the new onset of a profuse secretory diarrhea up to 6L per day, which partially responded to empiric octreotide infusion and imodium. Her vasoactive intestinal peptide levels were found to be markedly elevated at  $3230 \text{pg/mL}$  (normal range  $<75 \text{pg/mL}$ ).

Course further complicated by shock liver and acute oliguric kidney injury requiring dialysis secondary to multiple factors including bilateral renal artery thromboembolism, multiple contrast exposures, dehydration, and pheochromocytoma. The patient developed acute pulmonary edema due to fluid overload from renal failure necessitating intubation. She underwent thrombectomy of the right main and inferior renal artery branches and thrombolysis with restored blood flow to the right kidney. She developed significant anemia necessitating transfusion without evidence of bleeding. She was persistently tachycardic with heart rates up to the 130s and was treated with esmolol infusion for beta blockade. Patient was successfully extubated however required reintubation for recurrent respiratory failure in the setting of significant tachycardia, hypertension likely resulting in acute pulmonary edema, metabolic acidosis with significant work of breathing for respiratory compensation, as well as a new left lower lobe pneumonia. Blood cultures and bronchoscopy with bronchoalveolar lavage was performed but all cultures remained negative. She was started on ivabradine for persistent sinus tachycardia. She had very labile hemodynamics related to infection, pain, agitation, and underlying pheochromocytoma.

Given her prolonged course and difficult to optimize clinical status, the decision was made to begin metyrosine prior to surgery as well as to pursue embolization of her mass prior to surgery. She underwent successful coil and particle embolization and the following day underwent successful laparoscopic converted to open (given size and challenging accessibility) right adrenal tumor resection (see Figures 1 and 2). Surgical pathology was consistent with adrenal pheochromocytoma with thrombi present within the tumor, accompanied by regions of necrosis. Post operatively she was initially hypotensive requiring vasopressin, neosynephrine at maximum dosing, and norepinephrine most likely due to iatrogenic catecholamine deficiency and blockade. Doxazosin, esmolol, ivabradine, and metyrosine were discontinued. Her diarrhea resolved and octreotide infusion and imodium were discontinued. Given gross hematuria thought to be from renal ischemia reperfusion injury, her anticoagulation was limited to 40 mg of lovenox nightly.



**Figure 1.** Intraoperative photograph of pheochromocytoma.

Her post-operative course was complicated by urinary tract infection secondary to *Pseudomonas*. Renal function improved and dialysis was able to be discontinued. She developed a pseudoaneurysm of the right femoral artery necessitating surgical repair. At her last office follow-up her symptoms had significantly improved. She was ambulating without difficulty, recovering well from being significantly deconditioned. Her kidney function was approaching baseline. She is to remain on anticoagulation for 6 months given her thromboembolic disease. Followup PET gallium scan showed no evidence of residual disease or metastasis.

## Discussion

Here we have presented a case of pheochromocytoma producing vasoactive intestinal peptide and associated with intracardiac thrombosis in the absence of left ventricular dysfunction or wall motion abnormalities. Pheochromocytoma producing vasoactive intestinal peptide (VIP) is exceedingly rare.<sup>5-11</sup> Similarly, thrombosis occurring in patients with pheochromocytoma has been reported previously in only a few cases.<sup>1,12-18</sup> We have reviewed the existing literature on these rare presentations and include two tables with recent notable cases here for reference (see Tables 1 and 2).

Typically VIP is produced in association with a neuroendocrine tumor, most commonly pancreatic in origin. This amino acid peptide causes secretory diarrhea by stimulating adenylate cyclase production which in turn causes intestinal secretion of water and electrolytes and leads to the syndrome of watery diarrhea associated with hypokalemia and achlorhydria (WDHA).<sup>5</sup> In 1975 the first pheochromocytoma associated with WDHA syndrome was reported and only a handful of nonpancreatic tumors associated with the WDHA syndrome have been reported since<sup>5-11</sup> (see Table 1). For instance, ganglioneuroma-pheochromocytoma producing VIP in Neurofibromatosis type I has been reported.<sup>6</sup>



**Figure 2.** Intraoperative photograph of pheochromocytoma.

Additionally, there has been report of malignant pheochromocytoma producing VIP.<sup>11</sup> No pancreatic mass was seen on our patient's CT and her diarrhea improved with the use of intravenous octreotide and Imodium. Octreotide is a somatostatin synthetic analogue which acts as an inhibitory hormone throughout the body and specifically in the case of VIP producing tumors improves diarrhea by inhibiting VIP hormone production.<sup>19,20</sup> Our patient's diarrhea resolved after resection of her pheochromocytoma was resected, so her VIP elevation was thought to be primarily from her pheochromocytoma.

The other unusual association our patient's case was her cardiac thrombus. Intracardiac thrombus is typically identified in the setting of reduced ventricular contraction with a history of myocardial infarction or in the setting of a hypercoagulable state such as in the late presentation of carcinomas.<sup>21</sup> Cardiac thrombosis associated with pheochromocytoma has only been reported in a handful of cases.<sup>1,12-18</sup> (see Table 2). In one case, a patient with medullary thyroid cancer and adrenal pheochromocytoma developed an intracardiac thrombus and, similar to our patient, there was no evidence of ventricular wall contraction abnormalities.<sup>13</sup> One case described a patient with a large left ventricular thrombus and a 7 cm pheochromocytoma in which the patient developed systemic embolization leading to kidney infarction and lower extremity infarction requiring bilateral below-the-knee amputation.<sup>17</sup> While pro-coagulant factors secreted by the pheochromocytoma are postulated to be contributing factors, definite underlying coagulation defects have rarely been identified.<sup>1</sup> It is likely that catecholamines and other hormones, cytokine or factors secreted by the pheochromocytoma may play an important role in the pathogenesis of thrombosis in the absence of a predisposing coagulation disorder.<sup>1</sup> The thrombosis in our patient is likely related to her pheochromocytoma especially given her unrevealing hypercoagulability workup.

**Table 1.** Cases of pheochromocytoma associated with VIP hormone production.

Author/year	Case presentation	outcome
Smith et al. <sup>5</sup> /2002	Pheochromocytoma producing VIP	Treated initially with cholestyramine and Octreotide and then surgery with relief of symptoms
Onozawa et al. <sup>6</sup> /2005	Ganglioneuroma-pheochromocytoma producing VIP in neurofibromatosis type I	Surgery with resolution of clinical and biochemical abnormalities
Ikuta <sup>7</sup> /2007	Pheochromocytoma producing VIP	Surgery with resolution of clinical and biochemical abnormalities
Øzbay <sup>8</sup> /2008	Pheochromocytoma producing VIP and masking hypertension	Surgery with resolution of clinical and biochemical abnormalities
Hu et al. <sup>9</sup> /2018	Pheochromocytoma produced VIP and persistent shock	Octreotide reversed shock and resolved all symptoms, surgery completed thereafter
Jiang et al. <sup>10</sup> /2014	Pheochromocytoma produced VIP	Surgery with resolution of clinical and biochemical abnormalities
Lebowitz-Amit et al. <sup>11</sup> /2014	Malignant Pheochromocytoma producing VIP	Surgery with resolution of symptoms. Three years later metastatic disease with exquisite clinical response to sunitinib

**Table 2.** Cases of pheochromocytoma associated with intracardiac thrombus in the absence of cardiomyopathy.

Author/year	Case presentation	Outcome
Yebra Yebra <sup>18</sup> /2005	Acute myocardial ischemia and ventricular thrombus associated with pheochromocytoma	Complicated by embolic stroke. Treated with surgery and anticoagulation.
Pishdad <sup>13</sup> /2000	Multiple endocrine neoplasia type 2 medullary, thyroid cancer, and adrenal pheochromocytoma developed a left ventricular thrombus	Treated surgically
Hou <sup>1</sup> /2011	Pheochromocytoma presenting with arterial and intracardiac thrombus	Surgery with resolution of symptoms, anticoagulation with resolution of thrombus

## Conclusion

Devastating consequences can occur if pheochromocytomas are not recognized and treated appropriately. VIP producing pheochromocytoma is a rare entity. Moreover, concomitant thrombosis with pheochromocytoma is rare and the exact mechanism of thrombosis is not well understood. We report a case of VIP producing pheochromocytoma associated with left ventricular thrombus. This case highlights the association of pheochromocytoma with VIP hormone production and treatment with octreotide infusion in addition to pheochromocytoma associated with LV thrombus and embolic complications. As with other case reports, we aim to remind clinicians of the possibility for VIP hormone production by pheochromocytomas<sup>5-11</sup> and the pro-thrombotic state in patients with pheochromocytoma.<sup>1,12-18</sup> As with our case, octreotide infusion may be helpful in managing the secretory diarrhea associated with VIP hormone production, and anticoagulation should be initiated early on to avoid cardioembolic events. With prompt vigilant management, morbidity and mortality may be significantly reduced.

## Patient perspective

Before being diagnosed with a pheochromocytoma, I spent almost ten years with doctors who brushed off my symptoms as stress-induced. I went to therapy and was diagnosed

as having panic disorder, but with only the physical symptoms. The episodes became worse overtime to where I was experiencing them almost every day at varying degrees of severity, sometimes leaving me bedridden. Since the surgery I have not experienced any episodes and can live without the fear of another crippling “panic attack”. Although there were many complications and there is still numbness from the surgery, I am extremely happy with how everything turned out.

## Author Contributions

Dr. Hermel wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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## Ethical approval

Scrpps Clinic does not require ethical approval for reporting individual cases.

## Informed Consent

Written informed consent was obtained from the patient for publication of this anonymised case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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## References

- Hou R, Leathersich AM and Ruud BT. Pheochromocytoma presenting with arterial and intracardiac thrombus in a 47-year-old woman: a case report. *J Med Case Rep* 2011; 5: 310.
- Pacak K, Linehan WM, Eisenhofer G, et al. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. In: *Annals of internal medicine*. vol. 134. American College of Physicians, 2001, pp.315–329.
- Štrauch B, Zelinka T, Hampf M, et al. Prevalence of primary hyperaldosteronism in moderate to severe hypertension in the Central Europe region. *J Hum Hypertens* 2003; 17(5): 349–352.
- Widimský J. Recent advances in the diagnosis and treatment of pheochromocytoma. *Kidney Blood Press Res* 2006; 29(5): 321–326.
- Smith SL, Slappy ALJ, Fox TP, et al. Pheochromocytoma producing vasoactive intestinal peptide. *Mayo Clin Proc* 2002; 77(1): 97–100.
- Onozawa M, Fukuhara T, Minoguchi M, et al. Hypokalemic rhabdomyolysis due to WDHA syndrome caused by VIP-producing composite pheochromocytoma: a case in neurofibromatosis type 1. *Jpn J Clin Oncol* 2005; 35(9): 559–563.
- Ikuta S. Watery diarrhea, hypokalemia and achlorhydria syndrome due to an adrenal pheochromocytoma. *World J Gastroenterol* 2007; 13(34): 4649.
- Øzbay L, Obukhau A, Buhl L, et al. Adrenal pheochromocytoma producing vasoactive intestinal peptide and masking hypertension. *Horm Res* 2008; 70: 188–192.
- Hu X, Cao W and Zhao M. Octreotide reverses shock due to vasoactive intestinal peptide-secreting adrenal pheochromocytoma: a case report and review of literature. *World J Clin Cases* 2018; 6(14): 862–868.
- Jiang J, Zhang L, Wu Z, et al. A rare case of watery diarrhea, hypokalemia and achlorhydria syndrome caused by pheochromocytoma. *BMC Cancer* 2014; 14: 553.
- Leibowitz-Amit R, Leibowitz-Amit R, Mete O, et al. Malignant pheochromocytoma secreting vasoactive intestinal peptide and response to sunitinib: a case report and literature review. *Endocr Pract* 2014; 20(8): e145–e150.
- Heindel SW, Maslow AD, Steriti J, et al. A patient with intracardiac masses and an undiagnosed pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002; 16(3): 338–343.
- Pishdad GR. Ventricular thrombosis in Sipple's syndrome. *South Med J* 2009; 93(11): 1093–1095.
- Shulkin BL, Shapiro B and Sisson JC. Pheochromocytoma, polycythemia and venous thrombosis. *Am J Med* 1987; 83(4): 773–776.
- Paola Stella, Giancarlo Bignotti, Simona Zerbi, et al. Concurrent pheochromocytoma, diabetes insipidus and cerebral venous thrombosis—a possible unique pathophysiological mechanism. *Nephrol Dial Transplant* 2000; 15(5): 717–718.
- Stevenson S, Ramani V and Nasim A. Extra-adrenal pheochromocytoma: an unusual cause of deep vein thrombosis. *J Vasc Surg* 2005; 42(3): 570–572.
- Zhou W and Ding SF. Concurrent pheochromocytoma, ventricular tachycardia, left ventricular thrombus, and systemic embolization. *Intern Med* 2009; 48(12): 1015–1019.
- Yebra Yebra M, Martín Asenjo R, Arrue I, et al. Isquemia miocárdica aguda y trombosis ventricular asociadas a feocromocitoma [Acute myocardial ischemia and ventricular thrombus associated with pheochromocytoma]. *Rev Esp Cardiol* 2005; 58(5): 598–600.
- Murphy E, Prommer EE, Mihalyo M, et al. Octreotide. *J Pain Symptom Manage* 2010; 40(1): 142–148.
- Katz MD and Erstad BL. Octreotide, a new somatostatin analogue. *Clin Pharm* 1989; 8(4): 255–273.
- Zwicker JI, Furie BC and Furie B. Cancer-associated thrombosis. *Crit Rev Oncol Hematol* 2007; 62(2): 126–136.