

CLINICAL VIGNETTE

A Curious Case of Carcinoid Crisis

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Introduction

Endocrine causes of shock are rare. Carcinoid crisis is an exaggerated manifestation of the carcinoid syndrome and is characterized by the catecholamine-mediated release of serotonin, bradykinin, kallikrein, and histamine. While the release of these hormones usually results in benign symptoms such as flushing or diarrhea, in rare cases, the potent vasodilatory properties of these hormones precipitate distributive shock. When endocrine causes of shock are appropriately diagnosed, a dramatic change in management usually follows.

Case Report

A 51-year-old woman with mesenteric carcinoid tumor complicated by liver metastases was admitted to the medical intensive care unit (ICU) with two days of worsening encephalopathy and septic shock. She was initially resuscitated with intravenous crystalloids and treated for infection from a urinary source. Her mental status improved, but she remained profoundly hypotensive, requiring continuous vasopressor therapy over the subsequent five days despite broad spectrum antibiotics, empiric adrenal replacement, and extensive evaluation for cardiogenic, obstructive, and neurogenic causes of shock. She also developed diarrhea during her hospitalization, but no other signs of infection. Of note, she had two extended hospitalizations in the prior three months for management of volume overload and carcinoid syndrome symptoms.

Vital signs at the time of admission were temperature 36.8° C, heart rate 87/min, blood pressure 82/33 mmHg, respiratory rate of 13 and oxygen saturation of 98% on room air. Her physical exam was notable for jugular venous pulsation to mid-neck and anasarca. A comprehensive neurologic exam revealed an awake and alert patient orientated only to self. Strength, sensation and reflexes were intact. There were no meningeal signs or asterixis.

Initial labs revealed an elevated lactate at 3.4 mmol/L, leukocytosis of 12 x1000 cells/ μ L with 90% neutrophils and creatinine of 1.2 mg/dL, increased from her baseline of 0.6 mg/dL. Urinalysis contained trace white blood cells and both blood and urine cultures were positive for pan-sensitive *Enterococcus coli*. Stool culture and Clostridium difficile toxin polymerase chain reaction was negative. Liver function tests

were unremarkable. Chest radiography was unremarkable and abdominal ultrasound was negative for acute biliary pathology. Her echocardiogram remained unchanged from prior with a normal ejection fraction of 60-65%, severe tricuspid stenosis, and severe tricuspid regurgitation with moderate pulmonary hypertension. Thyroid stimulating hormone and cosyntropin stimulation testing were normal. Serum chromogranin A was elevated at 17,192 ng/mL (normal range 25-140 ng/mL) and urine 5-hydroxyindoleacetic acid (5-HIAA) was elevated at 732.7 mg/g Cr (normal <10 mg/g Cr).

Based on this patient's clinical and laboratory findings, the diagnosis of carcinoid crisis with persistent distributive shock was made. She received 40 mg of subcutaneous octreotide and was successfully titrated off vasopressors three days later. She spent a total of 10 days in the intensive care unit (ICU) and 30 days in the hospital before being discharged to hospice care.

Discussion

Shock is a commonly encountered entity in the ICU and is defined as acute circulatory failure resulting in end organ hypoperfusion and tissue ischemia. Shock is broadly divided into hypovolemic, distributive, cardiogenic, and obstructive subtypes. Distributive shock, otherwise known as vasodilatory shock, is characterized by low systemic vascular resistance with a relatively normal cardiac output. While septic shock accounts for most distributive shock presentations, there are several less common etiologies that fall under the distributive shock umbrella. Endocrine causes of distributive shock (Table 1) are rarely encountered in the ICU and, therefore, often go unrecognized.¹ However, when they do occur and are diagnosed in a timely manner, they have the potential to dramatically change management.

Endocrinology studies the secretion of hormones. In health, the balance of these hormones is responsible for maintaining a wide variety of essential functions including mood, metabolism, and fertility. In critical illness, the disruption of these systems can require targeted intervention to prevent significant negative impact. Although disruptions in the hormonal system are often secondary to illness, they can also be primary pathologies.

Our patient remained in persistent distributive shock after initial resuscitation and appropriate treatment of a urinary tract infection with *E. coli* bacteremia. Evaluation for nosocomial infections, including colitis in the setting of diarrhea, did not reveal any convincing new source. Endocrine workup revealed normal thyroid and adrenal function, but very high urine 5-HIAA levels indicating high circulating levels of serum serotonin in the setting of known carcinoid tumor. This raised the possibility of acute carcinoid crisis precipitated by tumor lysis following both her infection and general physiological stress.

Carcinoid tumors are relatively rare neoplasms that typically arise from the midgut. The aptly named “carcinoid syndrome” is a paraneoplastic process that occurs in <5% of carcinoid tumors and is the result of catecholamine-mediated release of vasoactive hormones including serotonin, bradykinin, kallikrein, and histamine. The classic manifestation of carcinoid syndrome is the duo of cutaneous flushing and intractable diarrhea. The precise pathologic mechanism behind carcinoid syndrome is not fully understood, but “carcinoid crisis” is thought to be an extension of these potent vasodilatory effects to the broader cardiovascular system.² Intra-operative pulmonary artery catheterization of a patient who developed carcinoid crises showed a decrease in pulmonary and systemic vascular resistance, consistent with distributive shock physiology.³ Emerging data suggests that the implicated hormones in carcinoid syndrome are not necessarily the same causative agents that precipitate a carcinoid crisis. Only high serum serotonin levels, which our patient had, have been identified as markers of elevated risk for developing carcinoid crisis.

Unlike carcinoid syndrome, carcinoid crisis is characterized by acute hypotension with or without preceding carcinoid syndrome symptoms. Other manifestations of carcinoid crisis include acute bronchospasm, arrhythmia and hypertension. Our patient’s diarrhea, which developed after treatment of her infection, was likely a manifestation of carcinoid crisis. Carcinoid crisis is well recognized in the surgical literature with a reported peri-operative incidence of 24-30% during carcinoid tumor resection.⁴ There are very few reports describing carcinoid crisis in the inpatient setting, possibly due to under-recognition, given how rarely endocrine disorders are implicated as the primary causes of distributive shock. As is the case with carcinoid syndrome, patients with carcinoid crisis will have elevated urine 5-HIAA and elevated serum serotonin, tryptophan, and chromogranin levels.

The optimal management of carcinoid crisis, even in the peri-operative setting, is not well defined. There are little to no high-quality data regarding management of carcinoid crisis in the critical care setting.⁵ However, early fluid support and vasopressors should be administered for distributive shock, regardless of cause. Somatostatin analogues have clear benefit in mitigating serotonin-mediated carcinoid syndrome. In carcinoid syndrome, 10-30 mg, and sometimes up to 60 mg, of long acting subcutaneous octreotide may be administered every 4 weeks. Alternatively, 100-500 mcg of the short acting form

of octreotide may also be given 3 times daily. However, the data examining the role of somatostatin analogues in carcinoid crisis come mainly from nonrandomized prospective studies and case reports of peri-operative patients.⁶⁻⁹ These studies suggest that prophylactic octreotide can reduce carcinoid crisis duration but does not reduce the overall incidence of episodes.^{10,11} The reported dosage and efficacy of octreotide are variable, with the general intraoperative practice being administration of an intravenous dose of at least 100 mcg, but as high as 1000 mcg, to aid in resolution of shock.¹² In some reported cases of persistent carcinoid shock, patients remained on continuous octreotide infusions for several days.

The five-year survival for patients with metastatic carcinoid tumors is approximately 20%, but may depend on tumor burden, site of primary lesion, 5-HIAA levels and histologic growth pattern. However, while these factors do have some prognostic value, they are generally considered unreliable. Mortality associated with carcinoid crisis, both peri-operatively and in critically ill patients, has not been well described. More generally, mortality in patients with both cancer and septic shock is exceptionally high, approaching 50-60%. It is reasonable to expect that the addition of further hemodynamic stability of endocrine origin raises mortality even higher.

Conclusion

Carcinoid crisis is a form of vasodilatory shock most commonly precipitated by the manipulation of carcinoid tumors in surgery, but may also be seen after exposure to other stressors including infection. It should be suspected in critically ill patients with elevated urinary or serum 5-HIAA levels, especially those with liver and cardiac metastases. Administration of a somatostatin analogue such as octreotide should be considered in critically ill patients with carcinoid crisis. However, evidence is limited to small, nonrandomized prospective studies in patients undergoing surgery.

Table 1 - Endocrinologic causes of shock	
-	Adrenal crisis
-	Carcinoid crisis
-	Hypoadosteronism
-	Myxedema coma
-	Hypopituitarism
-	Pheochromocytoma
-	Diabetic dysautonomia

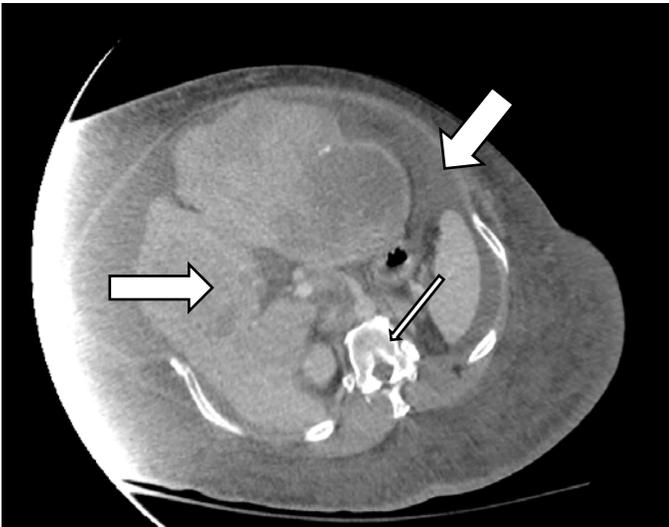


Figure 1 – Computed tomography scan of the abdomen demonstrating widespread hepatic metastases (thick arrows) and left adrenal gland enlargement (thin arrow).

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