Case Report

Pheochromocytoma Crisis Presenting With ARDS Successfully Treated With ECMO-Assisted Adrenalectomy

Manita Choudhary, MD 1, Yufei Chen, MD 2, Oren Friedman, MD 3, Natasha Cuk, MD 4, Anat Ben-Shlomo, MD 1, *

1 Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California
2 Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California
3 Women's Guild Lung Institute, Cedars-Sinai Medical Center, Los Angeles, California
4 Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California

Article history:
Received 30 December 2020
Received in revised form 15 March 2021
Accepted 16 March 2021
Available online 26 March 2021

Key words:
pheochromocytoma
pheochromocytoma crisis
acute respiratory distress syndrome
extracorporeal membrane oxygenation
adrenalectomy

Abstract

Objective: Pheochromocytoma (PCC) crisis caused by acute catecholamine release from an adrenal PCC or extra-adrenal paraganglioma can be difficult to diagnose and may require an unconventional management strategy to achieve good outcomes. We describe a case of PCC crisis presenting with acute respiratory distress syndrome (ARDS) that resolved with stabilization on veno-venous (VV) extracorporeal membrane oxygenation (ECMO) during adrenalectomy.

Case Description: A 30-year-old man with a history of severe alcohol use disorder and a prior hospital admission for alcohol withdrawal syndrome presented with sudden-onset hemoptysis, altered mental status, and severe dyspnea that rapidly deteriorated to ARDS requiring ECMO support. He demonstrated hemodynamic collapse after cannulation for VV-ECMO and stabilized after conversion to veno-arterial-ECMO, but ARDS persisted and he developed acute renal failure. Computed tomography without contrast done as part of work-up for a presumed infection revealed a 6.9 x 6.4 cm right adrenal mass suspicious for pheochromocytoma. Plasma and random urine metanephrine levels were markedly elevated. ARDS persisted despite α- and β-adrenoreceptor blockade, and he underwent laparoscopic right adrenalectomy with VV-ECMO support. Pathology confirmed PCC with intermediate risk for malignancy. Post-operatively, he was weaned off respiratory and renal support within 10 days, showed rapid clinical improvement, and was discharged 1 month later.

Conclusion: This case highlights diagnostic and management challenges associated with patients with PCC crisis presenting with ARDS. A multidisciplinary team approach is critical to identifying appropriate treatment strategies.

Introduction

Pheochromocytoma (PCC) crisis is caused by rapid release of catecholamines from a PCC or paraganglioma, neuroendocrine tumors arising from the adrenal medulla or paraganglionic chromaffin cells of the neural crest, respectively. 1 PCC crisis often presents acutely with hemodynamic instability, severe hyper- or hypotension, and cardiac failure, leading to multiorgan dysfunction and death in 6% to 18% of patients. 1 Surgical resection of the whole tumor can provide cure; however, medical therapy with α-adrenoreceptor blockers is recommended for patients with PCC, followed by β-adrenoreceptor blockers as needed to stabilize the patient before surgical resection is attempted. 1,2 Such hemodynamic stabilization is critical to avoid associated perioperative surgical complications and mortality in the setting of PCC crisis and can be achieved in most patients. 1 However, patients who exhibit uncommon signs and symptoms of PCC crisis may have delayed diagnosis and deteriorate rapidly without appropriate management.

PCC crisis commonly manifests with cardiogenic shock, necessitating hemodynamic support. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO), which pressurizes and...
oxygenates venous blood and returns oxygenated blood to the arterial system, has proven beneficial as a bridge to surgery, allowing time for patient hemodynamic stabilization and initiation of p-adrenoreceptor blockade prior to surgical removal of the PCC. In cases of persistent hypoxic respiratory failure and acute respiratory distress syndrome (ARDS), veno-venous (VV) ECMO can be used as respiratory support for gas exchange alone, in which venous blood is oxygenated and returned to the venous system. We report a case of PCC crisis with an uncommon presentation of sudden-onset hemoptysis and dyspnea that progressed to treatment-resistant and persistent ARDS. To our knowledge, this is the first report of a patient with PCC crisis requiring VV-ECMO stabilization for ARDS that allowed for successful adrenalectomy to remove the tumor.

Case Report

A 30-year-old man with a 14-year history of alcohol use disorder and prior hospitalization for alcohol withdrawal syndrome (AWS) was brought to the emergency department with sudden-onset severe dyspnea, significant hemoptysis, and altered mental status. He reportedly was drinking heavily (5-6 bottles of wine daily) until his last drink the day before and was exercising at the gym a few hours prior to presentation. A 10-year history of untreated hypertension and anxiety were also reported later during hospitalization.

Upon exam, he was febrile (38.4°C), hypoxicemic (SaO2 86% on room air), and tachycardic (148 beats/min), with mild systolic hypertension (140/80 mm Hg) and mottled skin. Key laboratory test results upon initial presentation are shown in Table 1.

Computed tomography (CT) of the chest showed bilateral lung reticular and airspace opacities, suspicious for ARDS (Fig. 1 A). The patient was intubated and sedated with propofol and midazolam for suspected AWS. Despite 100% inspired oxygen, high (20 mm Hg) positive end expiratory pressure, deep sedation, and paralysis, he continued to be profoundly hypoxicemic and was cannulated for VV-ECMO to provide respiratory support. However, soon after, he developed hemodynamic collapse and cardiac arrest. Despite resuscitation and rapid up-titration in pressor and inotropic support, return of spontaneous circulation could not be achieved, and he was converted to VA-ECMO for hemodynamic support. Trans-thoracic echocardiography revealed severe biventricular dysfunction, with left ventricular ejection fraction 5% to 10% and minimal pulsatility on arterial waveform, suggesting profound cardiogenic shock. Within 24 hours of VA-ECMO support, cardiac function improved; 4 days later, VA-ECMO was removed and he showed recovery of left ventricular ejection fraction to 60% by hospital day 10. He was weaned from inotropic support but continued to experience severe ARDS, requiring 100% oxygen, high positive end expiratory pressure, prone positioning, and paralysis, and developed acute renal failure requiring continuous renal replacement therapy.

Treatment for AWS was continued with propofol, fentanyl, and lorazepam; broad-spectrum antibiotics were added for a presumed infection, and stress-dose glucocorticoids were given. High fevers (>40°C), sinus tachycardia, mild-moderate systolic hypertension, and leukocytosis persisted, but blood and bronchial cultures were consistently negative.

Once he demonstrated relatively stable oxygenation upon repoisioning, CT of the chest, abdomen, and pelvis without contrast was...
done as part of the work-up for presumed infection. A 6.9 × 6.4 cm unilateral right adrenal mass was detected, with hyperdense central components, possibly representing hemorrhage and suspicious for PCC (Fig. 1 B,C). Plasma and random urine metanephrine levels were elevated more than 10-fold (Table 2), confirming a diagnosis of PCC.

α-Adrenergoreceptor blockade with oral phenoxycbenzamine was initiated, with dose escalation over 10 days up to 160 mg daily. Dihydropyridine calcium-channel blockers were added for mostly mild systolic hypertension, and β1-adrenergoreceptor blockers were used to control tachycardia. The central s2 adrenergoreceptor agonist clonidine was given both for hypertension and presumed AWS. Despite treatment, the patient showed persistent ARDS, requiring continuous use of deep sedation and neuromuscular blockade, with FlO2 requirements between 40% and 100%. He had persistent tachycardia, large fluctuations in blood pressure, and worsening lung infiltrates. Hemodynamic status through hospitalization and significant interventions with emphasis on the first 2 days are shown in Figure 2.

After multidisciplinary discussions with critical care, endocrinology, cardiology, and surgery, the patient was again placed on VV-ECMO. He underwent VV-ECMO—supported laparoscopic right adrenalectomy 1 week later, on hospital day 37. The patient tolerated the procedure and was transferred back to the intensive care unit. Within the first 24 hours, he displayed evidence of postoperative intra-abdominal bleeding, and a reoperation with abdominal packing was performed. However, this was only a temporary measure, as the abdominal packing also compressed his inferior vena cava, restricting flow from his venous cannula. The patient was transfused and resuscitated and laparotomy the following day was able to successfully achieve hemostasis.

On pathology, the resected pheochromocytoma scored 5 of 20 on the Pheochromocytoma of the Adrenal Gland Scoring Scale (PASS) and 3 of 10 on the Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) scale, consistent with a pheochromocytoma with intermediate risk for malignancy. Succinate dehydrogenase B was present on tumor immunostaining.

Within 10 days of tumor resection, the patient showed resolution of ARDS and normalization of vital signs and plasma and urine metanephrine levels, and he was weaned off both VV-ECMO and continuous renal replacement therapy. Tracheostomy was placed for gradual ventilator weaning and removed prior to discharge to an acute rehabilitation unit just over 1 month after surgery.

On outpatient follow-up 6 months after discharge, the patient was asymptomatic, sober, and normotensive without tachycardia after discontinuing all medications and had returned to work. Plasma and urine metanephrine levels were normal. CT of the chest, abdomen, and pelvis did not reveal additional lesions.

**Discussion**

PCC crisis is potentially fatal if left untreated. Patients typically present with hemodynamic instability and cardiac failure from excessive acute catecholamine release. Treatment with α- and β-adrenergic blockade, and, occasionally VA-ECMO, is successful in these cases to provide hemodynamic stabilization prior to surgical resection of the PCC. Our patient presented with persistent ARDS. His long history of alcohol use disorder and a toxicology screen positive for cannabinoids led to a suspected diagnosis of aspiration pneumonitis and/or bacterial or viral pneumonia with contribution of septic shock in the setting of AWS and illicit drug use, rather than an uncommon presentation of PCC crisis.

A number of other underlying causes were considered in the differential diagnosis. Pulmonary embolism might have explained the tachycardia and severe hypoxemia, but not the severe left ventricular dysfunction seen on echocardiography; as a precaution, he was empirically treated with anticoagulation while on VA-ECMO. Acute coronary syndrome was thought to be unlikely given the lack of significant troponin elevation or specific risk factors. Diabetic ketoacidosis can trigger ARDS,11 but although he showed elevated blood glucose levels at presentation, he had no prior history of diabetes mellitus, and urine was negative for ketones.

New-onset hemoptysis and acute respiratory failure as initial signs and symptoms of PCC crisis have been reported, with a suggestion that pulmonary venous congestion secondary to high blood pressure leads to pulmonary edema and hemorrhage.12-14 Our patient, however, developed treatment-resistant ARDS that only resolved after adrenalectomy, indicating that factors other than pulmonary edema contributed to the ARDS. Possible causes for this presentation could include catecholamine surge-induced vascular lung injury and constriction, increased alveolar fluid reabsorption via Na,K-adenosine triphosphate activity, and activation of the lung immune system.

To our knowledge, this is the first report of VV-ECMO—assisted adrenalectomy in a patient with PCC crisis and resistant ARDS. VA-ECMO has been used in PCC crisis with severe cardiogenic shock to allow cardiopulmonary support and hemodynamic stabilization prior to adrenalectomy. However, only rarely is surgery performed while on VA-ECMO, as most patients receiving medical therapy experience clinical improvement prior to surgery. In a recent report, adrenalectomy was performed immediately after VA-ECMO cannulation without preoperative α-adrenergoreceptor blockade in 4 patients with presumed PCC crisis, but feasibility of such an approach is unclear, as metanephrine levels were not reported and only 2 of 4 patients had pathology confirmation of PCC.

Importantly, although ECMO can stabilize patients with PCC during surgery in critically ill patients such as ours, its use should be considered very judiciously. Excess bleeding or clotting as well as vascular injury and ischemia have all been reported and can exacerbate the course of disease.

**Conclusion**

This case highlights diagnostic and management challenges associated with PCC crisis in a patient with persistent ARDS. Medical therapy with α- and β-adrenergoreceptor blockade was unsuccessful in resolving ARDS, ultimately necessitating VV-ECMO support while undergoing adrenalectomy and PCC resection, with full and rapid recovery. Given the complexity of such cases, a multidisciplinary team approach comprising critical care pulmonology specialists, cardiologists, endocrinologists, and surgeons can help identify appropriate treatment strategies that yield good outcomes.
The authors have no multiplicity of interest to disclose.

Acknowledgment

We would like to thank Shira Berman for assistance with manuscript preparation. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This case was previously presented in abstract form at the 49th Critical Care Congress held February 16-19, 2020, in Orlando, Florida (https://doi.org/10.1097/01.ccm.0000643252.88160.a2).

Fig. 2. Vital signs and critical events from initial presentation (Day 1) until discharge (Day 75). A, Summary of Days 1 through 75. B, Days 1 and 2 shown in detail.

References

1. Whitelaw BC, Prague JK, Mustafa OG, et al. Phaeochromocytoma crisis. Clin Endocrinol (Oxf). 2014;80(1):13–22.
2. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–1942.
3. Scholten A, Cisco RM, Vriens MR, et al. Pheochromocytoma crisis is not a surgical emergency. J Clin Endocrinol Metab. 2013;98(2):581–591.
4. Grinda JM, Bricourt MO, Salvi S, et al. Unusual cardiogenic shock due to pheochromocytoma: recovery after bridge-to-bridge (extracorporeal life support and DeBakey ventricular assist device) and right surrenalectomy. J Thorac Cardiovasc Surg. 2006;131(14):913–914.
5. Hekiman G, Kharcha F, Bréchot N, et al. Extracorporeal membrane oxygenation for pheochromocytoma-induced cardiogenic shock. Ann Intensive Care. 2016;6(1):117.
6. Dang Van S, Hany A, Hubert N, Fouquet O. Cardiogenic shock induced by a voluminous phaeochromocytoma rescued by concomitant extracorporeal life support and open left adrenalectomy. *Eur J Cardiothorac Surg*. 2016;50(4):782–783.

7. Sauneuf B, Chudeau N, Champigneulle B, et al. Pheochromocytoma crisis in the ICU: a French multicenter cohort study with emphasis on rescue extracorporeal membrane oxygenation. *Crit Care Med*. 2017;45(7):e657–e665.

8. Ohshima S. Oxygen administration for patients with ARDS. *J Intensive Care*. 2021;9(1):17.

9. Jesse S, Brathen G, Ferrara M, et al. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. *Acta Neurol Scand*. 2017;135(1):4–16.

10. Wood E, Albarqouni L, Tkachuk S, et al. Will this hospitalized patient develop severe alcohol withdrawal syndrome?: the rational clinical examination systematic review. *JAMA*. 2018;320(8):825–833.

11. Konstantinov NK, Rohrscheib M, Agaba EI, Dorin RI, Murata GH, Tzamaloukas AH. Respiratory failure in diabetic ketoacidosis. *World J Diabetes*. 2015;6(8):1009–1023.

12. Flayhan NA, Hales MA, Aleskowitch TD, Gaine SP, Vanhoutte PM. Alpha1L-adrenoceptors in canine pulmonary artery. *J Cardiovasc Pharmacol*. 1998;32(2):308–316.

13. Zazzam S, Adir Y, Crespo A, et al. Norepinephrine increases alveolar fluid reabsorption and Na,K-ATPase activity. *Am J Respir Crit Care Med*. 2004;170(7):730–736.

14. Johnson JD, Campisi J, Sharkey CM, et al. Catecholamines mediate stress-induced increases in peripheral and central inflammatory cytokines. *Neuroscience*. 2005;135(4):1295–1307.

15. Schmid C, Philipp A, Hilker M, et al. Venovenous extracorporeal membrane oxygenation for acute lung failure in adults. *J Heart Lung Transplant*. 2012;31(1):9–15.

16. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965–1975.