COVID-19 Induced Pheochromocytoma Multisystem Crisis

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Abstract

A 43 year old male presented to a community hospital emergency department for evaluation of sudden onset shortness of breath, tachycardia, and hypertension. Initial evaluation showed an adrenal mass on chest computed tomography. There was biochemical evidence of multi organ damage. Patient had elevated plasma metanephrine and normametanephrine levels.

Introduction

Pheochromocytoma is a catecholamine secreting tumor arising from the chromaffin cells. Typically these tumors are located in the adrenal gland, but 15% of the time they arise in other paraganglia in the body. Other locations for pheochromocytomas include the cranial nerves, the parasympathetic ganglion of the vagus nerve, or sympathetic ganglions of the mediastinum, neck and pelvis. The annual incidence of pheochromocytomas is approximately 0.33 cases per 100,000 people [1]. Females were almost twice as likely to be diagnosed. Pheochromocytomas were diagnosed in every decade of life, with a noted increase in frequency with increased age, with incidence peaking the sixth and seventh decades of life [1]. Pheochromocytoma commonly presents with hypertension, tachycardia, and palpitations. A much rarer presentation is termed pheochromocytoma multisystem crisis (PMC). PMC has similar presenting symptoms, but additionally has evidence of end organ damage.

Diagnosis can be performed via measurement of metanephrines. A large study in Alberta noted that metanephrines elevated three times the normal limit were 64% sensitive for detecting pheochromocytoma. Definitive diagnosis can be achieved via tissue biopsy.

Definitive treatment for pheochromocytoma is surgical resection, however special considerations surrounding medical management in the perioperative setting are required. As pheochromocytomas are catecholamine secreting tumors, it is imperative that the care team avoid using exclusively beta blocking agents. Failure to

use an alpha blocking medication can precipitate hypertensive crisis. Phentolamine or phenoxybenzamine are the preferred first line agents, prazosin, doxazosin, terazosin can also be used as alpha blockers. The goal of blood pressure management is to keep blood pressure less than 160/90.

Case Presentation

Our case involves a 43 year old male with a past medical history of hypertension and recently diagnosed type two diabetes mellitus. Patients' home medications were lisinopril 5 mg and metformin. Patient presented to the emergency room via emergency medical services. He reported that at approximately 0600 he took brand name tadalafil for the first time. Approximately 0900 he experienced a violent cough, accompanied with sudden onset right sided flank pain. He became short of breath, his spouse noted that he experienced a vocal change with his voice becoming hoarse. He reported palpitations, stating that for several years he has experienced intermittent palpitations that he believes are triggered by missed meals.

On admission the patient was afebrile, (36.7 degrees Celsius), heart rate was 102 beats per minute, blood pressure was 189/135, 21 respirations per minute, on room air, with an O2 saturation of 93%.

Physical exam was notable for tachycardia, irregular rhythm, no murmurs appreciated. Breath sounds were present bilaterally with no rales, no wheezing, no rhonchi, he was on room air, with no accessory muscle use. There was no swelling of the tongue or lips. Airway was patent, voice normal, he was able to speak in full sentences. Abdomen was soft, non tender on exam, with normoactive bowel sounds. No costovertebral angle tenderness. There was no peripheral edema, no calf tenderness.

Initial labs showed an unremarkable complete blood count. Hemoglobin was 16.0 g/dL, white blood count was 9.1 10ˆ3/uL, with a platelet count of 247 10ˆ3/uL. Complete metabolic panel showed a potassium of 3.3 mmol/L, creatinine of 1.78 mg/dL, glucose of 289 mg/dL, lactic acid of 7.9 mmol/L, high sensitivity troponin was elevated slightly at 95 ng/L.

An electrocardiogram was obtained, which showed tachycardia, frequent premature ventricular complexes, sinus rhythm, no ST segment elevation or depression. Chest x-ray showed no acute cardiopulmonary process, no evidence of pneumothorax. Bedside ultrasound was performed of the heart and showed no gross systolic abnormality, and was without evidence of tamponade or effusion.

Initially he was treated with diphenhydramine 25 mg, methylprednisone 125 mg. Patient reported improvement in shortness of breath. Approximately two hours after presentation he experienced rapid deterioration in condition. He became lethargic, O2 saturation dropped to 83%, he became tachycardic with a rate of 121 beats per minute. Patient was put on a bilevel positive airway pressure system at 45% FiO2. Patient was given 10 mg labetalol. Computed tomography angiography (CTA) chest was performed at this time (Figure 2). Results from this study showed no evidence of pulmonary embolism, however there was noted to be a "large predominantly hypoenhancing mass seen in the visualized right upper abdomen measuring approximately 13 cm in maximal diameter and compressing the right lobe of the liver extrinsically. Although not entirely seen, this is most likely a mass arising from the right kidney". A second troponin resulted, which showed elevation to 2344 ng/L. Heparin drip was ordered at this time for treatment of NSTEMI.

A computed tomography of the abdomen and pelvis was performed which revealed a 13 cm retroperitoneal suprarenal mass, exhibiting compression on the liver, right kidney, and inferior vena cava (Figure 1). Differential diagnosis per radiology for these findings is adrenal cancer vs pheochromocytoma. Patient was given 5 mg phentolamine, which resulted in dramatic improvement in heart rate and blood pressure. Plasma metanephrine and normetanephrine were sent at this time, they would result several days later at $>$ 10,000 pg/ml (reference range 0 - 88.0 pg/ml), and $>$ 10,000 pg/ml (reference range 0 - 218.9 mg/ml). Both samples underwent repeat analysis to confirm the values.

The patient was transferred to the Intensive Care Unit (ICU), where he was treated with doxazosin 4 mg. He was treated with carvedilol 6.25 mg once, and a onetime dose of metoprolol tartrate 12.5 mg. Additional doses of phentolamine were unavailable due to pharmacy supply shortages. Patient again became hypertensive and tachycardic, despite the aforementioned medical therapy. His heartrate remained consistently elevated

in the range of 141-162, with his systolic blood pressure ranging from 140 - 182 mmHg. He was started on nicardipine drip for blood pressure control. His labs after one day in the ICU were notable for an increase in creatinine to 3.07 mg/dL, lactic acid had trended upwards and peaked at 9.0 mmol/L. His troponins peaked at 7272 ng/L, renin level was collected and resulted at 11.153 ng/ml/hr (reference range 0.167 - 5.380 ng/ml/hr). Aldosterone level was 58.7 ng/dl (reference range 0 - 30 ng/dL). DHEA was within normal reference range at 265 mcg/dL.

Discussion

Mortality was high in prior case reports of Pheochromocytoma Multisystem Crisis (PMC) without emergency surgery [3]. However, our case is unique in that we did not have surgeons with expertise in this particular condition readily available. In addition, COVID-19 pandemic has made it difficult for hospital transfers as our patient was positive for COVID-19. COVID-19 infection has been associated with an overwhelming inflammatory response. Early studies noted significant elevation in IL-6 as well as other cytokines [2]. Our suspicion is that COVID-19 gave rise to this catecholaminergic crisis secondary to acute infection as COVID-19 has been implicated causing a cytokine storm [4]. He had an elevated d-dimer at 13,492 ng/mlFEU. Computed tomography with pulmonary angiography was obtained to evaluate for possible pulmonary embolism (PE) given its association with COVID-19, PE was ruled out but ground glass infiltrates were observed in the right lower lobe. Pheochromocytoma is also known to produce cytokines. Review of the literature details a case report discussing an IL-6 secreting pheochromocytoma [4], which can possibly act synergistically with COVID-19 infection, triggering massive cytokine release, with subsequent catecholamine release in response, precipitating pheochromocytoma multisystem crisis. One article reports that PMC is not a surgical emergency, citing high surgical morbidity and mortality even without COVID-19 pneumonitis and hyperinflammatory syndrome complicating its course [5]. Indeed, our patient did have initial stabilization with a one time dose of phentolamine which is a nonselective but reversible alpha blocker [5]. However, this was transient as within the next several hours our patient went back into hypertensive crisis, with worsening lactic acidosis, worsening acute kidney injury, and sinus tachycardia averaging 150 beats per minute. Beta blockers were preferentially avoided. He was given high dose doxazosin and started on a continuous infusion of nicardipine but this was to no avail as our hospital did not have any more doses of phentolamine nor phenoxybenzamine. Once our patient was transferred to the nearest tertiary care center with the required surgical expertise and was able to receive phenoxybenzamine, his condition stabilized. This allowed him to be discharged safely with follow up surgery two weeks after his presentation. Even though our patient's condition was critical, this case highlights a conservative surgical management approach compared to other case reports that have used emergency surgery to acutely manage the patient in PMC. This case illustrates the absolute importance of therapeutic alpha blockade with phenoxybenzamine which is an irreversible alpha blocker in PMC [6]. It also gives us insight into how COVID-19 can impact rare diseases. A prior case report has documented PMC after receiving the COVID-19 vaccine, JNJ-78436735 [7]. While another case documented intratumoral hemorrhage from COVID-19 coagulopathy inducing catecholaminergic crisis [8].

Conclusion

Our case touches on several important aspects of management in patients presenting with PMC. Phentolamine was demonstrated to better control the patient's hypertensive crisis compared to doxazosin. Surgical colleagues at our institution remarked on the complexity of the surgery due to size of tumor and general hemodynamic instability, being able to transfer the patient to a tertiary center with surgical teams experienced in this complex surgery was crucial for ensuring the best chance for a positive outcome. Our case shows a viable management strategy that avoids emergent surgery, which has been associated with worse patient outcomes.

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Figure 1. Computed Tomography Abdomen Pelvis, demonstrating right suprarenal mass Figure 2. Computed Tomography Angiography Chest, capturing suprarenal mass displacing the liver.

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