Fatal Catecholamine-Induced Cardiotoxicity Associated with Pheochromocytoma: Report of a Postpartum Case and Review of the Literature

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ABSTRACT

Pheochromocytomas and paragangliomas are catecholamine-secreting tumors characterized by excessive adrenergic stimulation. Common manifestations include hypertension, headache, sweating, and palpitations; however, rare life-threatening conditions have also been reported and include cardiovascular shock, myocardial infarction, arrhythmias, and cardiomyopathy. We report a case of a previously healthy 31-year-old postpartum female presenting with headache who died suddenly in an emergency room. Autopsy revealed a pheochromocytoma of the right adrenal with significantly elevated metanephrine concentrations and acute "myocarditis." Sudden excessive catecholamine release can cause cardiovascular complications and be rapidly fatal without significant elevation of blood pressure. Awareness of this association by the medical examiner/coroner is vital in order to properly classify the death and apprise relatives of the potential utility of genetic screening. *Acad Forensic Pathol.* 2016 6(2): 315-324

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INTRODUCTION

Pheochromocytomas are chromaffin cell-derived neuroendocrine tumors of the adrenal medulla with the ability to synthesize and secrete excessive catecholamines. Pheochromocytomas are relatively rare, accounting for approximately 4% of primary adrenal tumors and in 0.2-0.4% of hypertensive patients (1). However, autopsy studies have indicated a much higher prevalence. Paragangliomas are also neuroendocrine tumors, but arise in the extra-adrenal sympathetic and parasympathetic nervous systems and have a lower incidence (less than one per 300 000 people per year) (2). The majority of these tumors arise sporadically, but several genes are now known to play an important role in the pathogenesis.

Common manifestations are associated with catecholamine excess and adrenergic stimulation, typically resulting in paroxysmal or sustained hypertension, headache, sweating, and palpitations. Other less common manifestations have been described and can be life-threatening, including cardiovascular shock, myocardial infarction, dysrhythmias, cardiomyopathy, acute pulmonary edema, stroke, acute abdomen, renal failure, and multiorgan failure. The clinical presentation is highly variable. Patients may remain asymptomatic but may also present with multiple and nonspecific symptoms. A distinct group of patients (approximately 30%) remain normotensive despite active metabolic secretion (3). It is these asymptomatic and normotensive patients that are more likely to die suddenly and unexpectedly and come under the purview of the medical examiner/coroner (ME/C). Cardiovascular complications are often the predominant causes of death in patients with pheochromocytomas, and descriptions detailing the morphology of the myocardium and histologic lesions in such patients have been reported.

Herein we report a case of a postpartum female with an unsuspected pheochromocytoma who died suddenly and unexpectedly as a result of an overwhelming catecholamine release-associated myocardial toxicity. Catecholamine-induced cardiotoxicity can be fatal and therefore a diagnosis of pheochromocytomas/

paraganglioma should be entertained and explored at autopsy in patients who present with acute decompensated heart failure or sudden death without a clear etiology. A review of catecholamine-induced cardiotoxicity will follow.

CASE REPORT

A 31-year-old female with a past medical history of mild hypercholesterolemia had an unremarkable pregnancy with spontaneous vaginal delivery of a healthy infant three weeks prior to term without complications. Two weeks postpartum, the patient presented to the emergency room with new onset of headache, nausea, and vomiting that improved with symptomatic treatment. Her vital signs were normal, routine blood work showed no abnormalities, and she was discharged home. She returned several hours later with the same symptoms in addition to dizziness upon standing. She denied a prior history of headaches. Her blood pressure upon presentation was 116/66 mmHg and a physical exam was unrevealing. Routine blood work, a computed tomography scan of the head, and a lumbar puncture were performed and were all unremarkable. The patient was given intravenous fluids and medication for pain, and her symptoms slowly improved over the course of a few hours. However, she suddenly experienced shortness of breath, had an episode of emesis, and appeared cyanotic. Her blood pressure was noted to be 141/98 mmHg and an electrocardiogram demonstrated sinus tachycardia up to 172 beats per minute without any acute ST changes. She was intubated and resuscitated with occasional return of pulses, but eventually entered a state of complete cardiopulmonary arrest and she was pronounced dead. The local medical examiner took jurisdiction of the case, and a complete autopsy was performed nine hours after death.

Autopsy revealed a well-nourished female weighing 73 kg with lactating breasts and no evidence of trauma. The uterus was intact and of appropriate size and appearance for a two week postpartum interval, and was lined by an involuting postpartum endometrium producing appropriate lochia. The 390 g heart was of normal size, shape, structure, and symmetry, with

no focal lesions detected. No significant lesions were found in the coronary arteries. The lungs were heavy, congested, and edematous. A round tumor weighing 350 g and measuring 10 cm in greatest dimension was found between the right adrenal gland and kidney, and on closer inspection, appeared to be arising from the adrenal medulla (**Image 1**). Cut section demonstrated a pale, tan, well-circumscribed mass with few small hemorrhagic foci (**Image 2**). No other significant trauma or pathology was noted.

Histological examination of the heart revealed diffuse acute myocardial injury characterized by predominantly neutrophilic and chronic interstitial inflammatory infiltrates with associated myocyte necrosis (**Im-**

age 3), but without evidence of myocyte hypertrophy or interstitial fibrosis. Sections of the right adrenal tumor exhibited typical features of a pheochromocytoma, including nests of medullary cells divided by fine vascular trabeculae (**Image 4**), with focal areas containing a thin rim of normal appearing medulla separating the tumor from the cortex of the uninvolved adrenal gland.

Samples available for laboratory testing included approximately 15 mL of postmortem urine and 1-2 mL of antemortem serum. Although the fractionated urine metanephrine test is not validated for postmortem specimens and the fractionated free plasma metanephrine test is neither validated for serum nor for

Image 1: *In situ* image demonstrating the right adrenal gland, tumor, and kidney.

Image 2: Pheochromocytoma with pale-tan cut surface and scattered small hemorrhagic foci.

Image 3: Myocardium with predominantly neutrophilic inflammatory infiltrate and myocardial destruction (H&E, x200).

postmortem specimens, these tests were performed under an exception protocol. The laboratory had performed testing on serum samples before and had found that metanephrine concentrations in serum did not differ substantially from those in plasma. Plasma is the preferred sample type primarily because it can be processed quicker than serum, allowing expeditious freezing of the sample, thus preventing degradation of metanephrines. The only potential problem with the analysis of serum was therefore a false low result. Similar considerations apply to the testing of the postmortem urine sample. The actual testing was performed on extracted serum and urine, respectively, by liquid chromatography/tandem mass spectrometry, a methodology considered highly specific and largely free from interferences by drugs or endogenous compounds. The testing showed urine concentrations per gram of creatinine of $>58,000 \mu\text{g/g}$ for metanephrine, $>17,000 \mu\text{g/g}$ for normetanephrine, and of $>75,000 \mu\text{g/g}$ for the sum of the two, the total metanephrines. Although there are no established reference ranges for

postmortem samples when compared to the reference ranges for random urine metanephrine and normetanephrine in living patients, these concentrations are 150-fold and 30-fold higher, respectively, than what would be expected for a female in the deceased patient's age group. Concentrations as high as these are rarely seen in urine samples from living patients with pheochromocytoma or paragangliomas. Serum fractionated free metanephrine were similarly elevated substantially, again, to concentrations that are rarely seen in living pheochromocytoma or paraganglioma patients; metanephrine measured 69.9 nmol/L and normetanephrine measured 71.1 nmol/L . In a healthy population, the reference ranges for plasma fractionated free metanephrines are: metanephrine $<0.50 \text{ nmol/L}$ and normetanephrine $<0.90 \text{ nmol/L}$.

Therefore, the cause of death was issued as catecholamine-induced myocardial toxicity due to pheochromocytoma of the right adrenal gland, and the manner of death was natural.

Image 4: Pheochromocytoma demonstrating nests of medullary cells divided by fine vascular trabeculae and focal acute hemorrhage (H&E, x60).

Due to the relatively young age of this patient, the possibility of a genetic predisposition to pheochromocytoma/paraganglioma was considered. Although the clinicians and family members were made aware of the final cause of death and potential utility of genetic testing, first-degree relatives were all living outside the country and unavailable for follow up.

DISCUSSION

Excessive concentrations of catecholamines have numerous profound effects on a variety of organ systems. Pheochromocytomas present clinically with paroxysmal episodes of hypertension, palpitations, sweating, headache, anxiety, and tremors. Other symptoms such as cerebrovascular accidents, ischemic ileus, acute renal failure, and multiorgan failure occur less frequently (4). Cardiovascular manifestations of pheochromocytoma have occasionally been documented and include cardiogenic shock, myocardial infarction, arrhythmias, and cardiomyopathy. Apart from pheochromocytoma/paraganglioma, other causes of catecholamine excess exist and are listed in **Table 1**. Stress, solvent abuse, chronic overuse of an adrenaline inhaler in asthma patients, prolonged amphetamine use, and cocaine must all be considered in the differential of catecholamine excess and have the potential to cause cardiomyopathy and toxicity (5-14).

For an in depth review of these alternative causes, the reader can refer to Kassim et al. (11).

There are few proposed mechanisms by which catecholamines induce cardiac injury, and the pathogenesis is likely multifactorial. Overstimulation of β -adrenergic receptors increases heart rate and enhances cardiac contractility, which may lead to an imbalance in oxygen supply and demand and result in “functional” hypoxia. This can further be exacerbated by α -adrenergic receptor stimulation causing vasoconstriction and vasospasm of the coronary arteries, resulting in myocardial ischemia and cell death (15, 16). Investigators have also postulated that excess catecholamine levels lead to a downregulation in cardiac β 1-adrenergic receptors, thereby inducing suboptimal functioning and a net reduction in viable myofibrils (17). In addition to the aforementioned processes, there is now evidence implicating calcium overload, oxidative stress, and mitochondrial dysfunction as the main players in catecholamine-induced cardiotoxicity (14). Free radicals and oxidized products of catecholamines alter sarcolemmal and mitochondrial permeability, leading to an influx of calcium, which has a direct toxic effect ultimately leading to irreversible myocardial damage and cellular necrosis (18-21). Metabolic changes and electrolyte imbalances may also disturb homeostatic processes and foster additional myocyte dysfunction and death.

Table 1: Causes of Catecholamine-Induced Cardiotoxicity*

Pheochromocytoma and/or paraganglioma
Stress-induced/Takotsubo syndrome
Long-term solvent abuse
Long-term use of adrenaline inhaler
Long-term methamphetamine use
Scorpion envenoming
Funnel-web spider envenoming
Septic cardiomyopathy
Baclofen withdrawal
Cocaine

*Table adapted from Kassim et al. (11); data from references 5-14.

Furthermore, polymorphisms in adrenergic receptors have been described as potential risk factors for causing heart failure (11). The mechanism is presumed to be through modulation of the sympathetic nervous system by increasing synaptic norepinephrine concentrations through loss of negative feedback and increased responsiveness to norepinephrine. Although a thorough investigation into these polymorphisms in patients with pheochromocytomas has not been performed, it can be postulated that the patients would have an increased risk for the development of catecholamine-induced cardiotoxicity (22).

Thirty percent of pheochromocytomas are found incidentally in asymptomatic patients (23). Cardiac lesions, such as in the form of acute myocardial in-

farction, myocardial stunning, and cardiomyopathy, ultimately lead to cardiac failure. In hypertensive patients, elevated blood pressures may return to normal due to myocardial damage (3, 24), thus masking the underlying pheochromocytoma in the later stages. In pregnancy, the classical symptoms of catecholamine excess are less frequent. Although supine hypertension may be present due to compression from the gravid uterus on the tumor, a standing or sitting position may result in normalization of the blood pressure (25). If hypertension is identified, it may be mistakenly attributed to pre-eclampsia. The tumor may only be discovered when there are unusual responses to drugs that affect catecholamines or as reactions to anesthesia, labor, or delivery (25, 26). Manipulation of the tumor during surgery or when intra-abdominal pressure increases, such as during uterine contractions or even vigorous fetal movement, may trigger catecholamine release resulting in severe clinical consequences and even death (26, 27).

There are few reports in the literature describing pheochromocytoma-induced cardiotoxicity during the postpartum period (22, 27-29). Kim et al. described a case of a 34-year-old female without a history of hypertension who developed catecholamine-induced cardiomyopathy one day following delivery and made a dramatic recovery through proper medical management (27). Similarly, Berger reported on a 37-year-old female who presented within 48 hours after delivery with headache and back pain. She progressed rapidly into fulminant heart failure, but was stabilized with a noninvasive left ventricular assist device and subsequent removal of the pheochromocytoma (22). Santani et al. reported a case of a 35-year-old female with a history of migraines, but without documented hypertension, who experienced acute heart failure with ST-segment changes one day postpartum, which rapidly improved after the initiation of an α - and β -blocker. Her catecholamine concentrations were noted to be significantly elevated and further workup revealed an adrenal mass, suggesting that the presentation may have been due to catecholamine-induced coronary artery vasospasm (28). Takotsubo-like (stress-induced) cardiomyopathy has also been described in patients with pheochromocytoma. Jozwik-Plebanek described

a case of a 32-year-old female with no history of hypertension who presented with transient left ventricular apical ballooning shortly after undergoing a cesarean section, and was later found to have a pheochromocytoma with elevated metanephrines (29). In all of these cases, the crisis occurred within 48 hours of delivery and may have been precipitated by an increase in intra-abdominal pressure, uterine contractions, anesthesia induction, drug administration, or therapeutic manipulations. However, in our patient, the catecholamine surge occurred two weeks following delivery, and cannot easily be attributed to these peripartum causes. A more likely explanation may be tumor hemorrhage. Agarwal et al. showed that 22% of patients with Takotsubo-like cardiomyopathy in pheochromocytoma had hemorrhagic necrosis of the tumor, which might trigger the sequence of events leading to the development of the cardiac symptoms and hemodynamic collapse (30). Pinpoint and microscopic hemorrhages were identified in our patient's pheochromocytoma. Perhaps this, or spontaneous occurrence without an identifiable trigger, led to the rapid cardiac collapse.

Descriptions detailing the morphology of the myocardium and histologic lesions in human subjects with pheochromocytomas date back to the 1920s. Hausmann and Getzowa (1922) and Biebl and Wichels (1925) described myocardial fibrosis and degenerative lesions associated with adrenal medulla derived tumors (31). These findings were confirmed by Raab in 1950 in patients with pheochromocytomas (32). Lesions termed "myocarditis" began to be reported by the mid 20th century. Kline studied the myocardium of seven patients with pheochromocytoma at autopsy, and in four of them, he found acute necrotic and inflammatory lesions, as well as chronic fibrosing lesions, and stressed that these lesions were the cause of death (33). Van Vliet reported similar findings after studying the hearts of 26 patients with an autopsy diagnosis of pheochromocytoma between 1928 and 1964 and reported a 58% incidence of cardiomyopathy, with degenerative, inflammatory, and reparative processes present (31). More recent reports describe left ventricular hypertrophy, cardiomyocyte necrosis and apoptosis, focal lymphocytic and polymorphonu-

clear leukocyte infiltration, contraction bands, interstitial edema, the progressive development of interstitial fibrosis over time (3, 14).

Although many historical descriptions refer to catecholamine-induced myocardial injury as “myocarditis,” this term is likely better reserved for those cases in which inflammatory cells are the primary mediators of myofiber damage, such as those with an infectious etiology. In cases of catecholamine-induced cardiac injury, the inflammatory response is secondary to tissue destruction. These mechanistic differences are reflected in the histologic findings as well. The pathological diagnosis of lymphocytic (viral) myocarditis, for example, requires the presence of a lymphocyte-rich inflammatory infiltrate associated with myocyte degeneration or necrosis. The inflammatory component is often extensive and out of proportion to the paucity of necrosis. When significant necrosis does occur, it is often confluent. In contrast, catecholamine-induced toxicity tends to reproduce many aspects of myocardial infarction, with various degrees of cardiomyocyte

necrosis and apoptosis intimately associated with the infiltration of polymorphonuclear and mononuclear leukocytes. Despite these differences, overlap does exist among categories, and histological features of myocardial injury from any etiology change over time. In our case, which was almost certainly very acute, the infiltrate consisted predominantly of neutrophils and chronic inflammatory cells. Lymphocytic myocarditis, including viral and autoimmune forms, is rich in T cells and macrophages, but in the early phases, a neutrophilic infiltrate can occur (**Image 5**). The lack of eosinophils and giant cells argues against a hypersensitivity myocarditis and giant cell myocarditis, respectively. Pathological classification can be difficult, and the clinical history, laboratory results, and other postmortem findings need to be taken into consideration before reaching a conclusion as to etiology.

Pheochromocytomas and paragangliomas may be familial or sporadic. The familial cases, along with 10-20% of the presumed sporadic cases, carry germline

Image 5: Lymphocytic myocarditis attributed to Coxsackie viral infection, showing diffuse infiltrates composed mostly of lymphocytes and macrophages, but with some neutrophils, and myocyte necrosis (H&E, x120).

mutations in one of ten known genes (34). At present, these include mutations in the *RET* proto-oncogene, von Hippel-Lindau disease tumor suppressor gene (*VHL*), neurofibromatosis type 1 tumor suppressor gene (*NF1*), genes encoding the succinate dehydrogenase (*SDH*) complex subunits *SDHB*, *SDHC*, and *SDHD*, but also *SDHA*, the gene encoding the enzyme responsible for the flavination of *SDHA* (*SDHAF2* or *hSDH5*), and the *TMEM127* and *MAX* tumor suppressor genes. Somatic mutations in *RET* and *VHL* are found in an additional 10-15% of tumors, thus increasing the number of patients with a disruption in one of these genes to approximately one-half (35). Two main transcription signatures underlie these mutations: a pseudohypoxic cluster (*VHL* and *SDH* mutations) and a cluster rich in kinase receptor signaling and its downstream pathways (*RET*, *NF1*, *TMEM127*, and *MAX* mutations) (4, 35). An in-depth review of the molecular pathogenesis of these tumors is beyond the scope of this article. However, an understanding of specific characteristics may be helpful in determining the potential utility of genetic testing in first-degree relatives. Younger age at the onset of symptoms, bilateral localization of tumors, and a positive family history could indicate the presence of a familial syndrome. Although patients do tend to be younger in inherited forms of the disease, especially for *VHL* syndrome, the age range at presentation is still quite wide, being 5-69 years in mutation carriers versus 4-81 years in sporadic tumor patients (36). Careful evaluation of the biochemical profile of catecholamine secretion may also aid in determining the most likely underlying genetic syndrome and guide molecular testing. For example, an epinephrine-secreting tumor suggests the presence of MEN 2 syndrome or *NF1*, while norepinephrine-secreting tumors are more consistent with *VHL* (4). In the current patient, the absence of a documented family history, unilateral location, absence of other associated tumors and lesions, and significant elevation of both metanephrine and normetanephrine (metabolites of epinephrine and norepinephrine, respectively) are not suggestive of a familial syndrome or specific to an underlying germline mutation; however, this cannot be entirely ruled out without formal testing, especially in a patient presenting at such a young age.

In decedents who have died suddenly and unexpectedly without an apparent cause, or in those who presented with unexplained rapid and acute heart failure, catecholamine-induced myocardial toxicity should be considered. A thorough examination of the heart, both grossly and histologically, as well as a search for an underlying pheochromocytoma and/or paraganglioma, should be performed. Awareness of this entity by the forensic pathologist is crucial and may have implications in both death certification and public health.

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