

CLINICAL PROBLEM-SOLVING

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Hypertensive Heartbreak

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Amy L. Miller, M.D., Ph.D., and Joseph Loscalzo, M.D., Ph.D.*In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 61-year-old man with chronic knee pain was scheduled to undergo elective total knee arthroplasty. He was a construction foreman with an active lifestyle and had not received medical care for 20 years. His only medication was ibuprofen. He drank 4 to 5 alcoholic beverages per week but had never used tobacco, illicit substances, or dietary supplements. His family history was notable for coronary artery disease in his brother. During a preoperative visit, the patient's blood pressure was 178/92 mm Hg, and his body-mass index (the weight in kilograms divided by the square of the height in meters) was 27.3. Physical examination was limited to the examination of both hips. The patient reported that he did not have headaches, chest pain, shortness of breath, or palpitations. Routine laboratory values were unremarkable, and an electrocardiogram showed a mild intraventricular conduction delay. Essential hypertension was diagnosed, and the patient began receiving hydrochlorothiazide. His blood pressure was 140/82 mm Hg at a subsequent outpatient visit.

Although we do not know the chronicity of hypertension, this patient does not otherwise meet the indications for screening for secondary causes of hypertension. Anesthesia guidelines recommend that patients be referred for elective surgery only if the blood pressure averages less than 160/100 mm Hg over the preceding 12 months; however, in patients without documentation of longitudinal blood pressures, elective surgery need not be delayed as long as the blood pressure is less than 180/100 mm Hg. Given that this patient has not received routine care, preventive health screening for chronic conditions should be recommended.

The patient underwent an uncomplicated left total knee arthroplasty while he was receiving spinal anesthesia with bupivacaine and conscious sedation with midazolam and propofol. The preoperative blood pressure was 168/92 mm Hg; intraoperative systolic blood pressures ranged from 120 to 170 mm Hg and diastolic blood pressures from 60 to 90 mm Hg, with a heart rate ranging from 60 to 80 beats per minute and an oxygen saturation of more than 95% while he was breathing ambient air. On day 1 after surgery, while the patient was working with a physical therapist, his blood pressure was noted to be 216/99 mm Hg with a heart rate of 141 beats per minute, a respiratory rate of 20 breaths per minute, and an oxygen saturation of 90% while he was breathing ambient air. He reported that he did not have chest discomfort, shortness of breath, headache, or severe pain. An electrocardiogram showed sinus tachycardia with a premature ventricular com-

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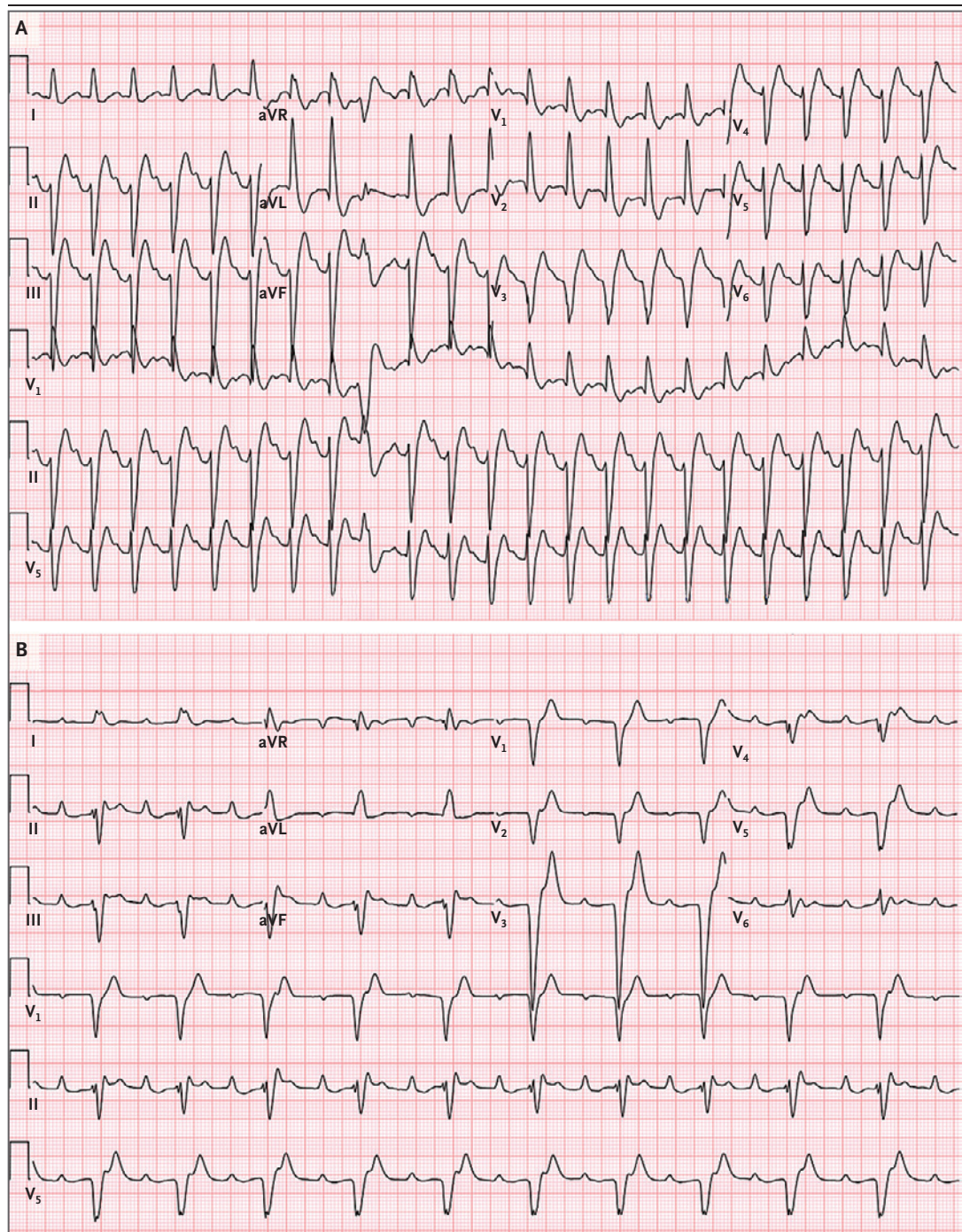


Figure 1. Electrocardiograms.

An electrocardiogram from day 1 after surgery shows sinus tachycardia, left anterior fascicular block, and right bundle-branch block (Panel A). An electrocardiogram that was obtained after the cardiac arrest shows sinus rhythm with first-degree atrioventricular block, left axis deviation, and left bundle-branch block (Panel B).

plex, a left anterior fascicular block, and a new right bundle-branch block (Fig. 1A). A radiograph of the chest showed a hazy opacity in the right-upper-lobe airspace with diffuse vascular prominence, findings suggestive of asymmetric pulmonary edema.

Spinal anesthesia with bupivacaine can precipitate hypotension, not hypertension. Although intraoperative hypertension is more common in patients with existing hypertension than in normotensive patients, acute increases in blood pressure intraoperatively should always prompt evaluation of reversible causes such as pain, hypoxemia, and hypercarbia. Volume overload, laryngoscopy, endotracheal intubation, and withdrawal of any antihypertensive medications can contribute to intraoperative hypertension.

The patient's severe hypertension (systolic blood pressure, >180 mm Hg) and findings on chest radiography that are consistent with pulmonary edema constitute a hypertensive emergency and raise the question of secondary hypertension. In general, for hypertensive emergencies, blood-pressure targets are below 180/120 mm Hg within the first hour and then below 160/110 mm Hg over the subsequent 23 hours, unless there is an acute process necessitating more rapid blood-pressure control. Pulmonary edema in this context suggests acutely elevated left-sided filling pressures that are due to either systolic or diastolic heart failure, a situation that supports more rapid reduction of blood pressure in this case.

Excess catecholamine is a potential cause of hypertensive emergency, particularly in the postoperative state. There was no history of withdrawal of antihypertensive therapy, ingestion of sympathomimetic agents, or severe pain. Pheochromocytoma is rare but warrants consideration.

I would carefully review with the patient his preoperative history, with attention to any suggestive symptoms or signs, including headaches, palpitations, or sweating. In patients with pheochromocytoma, catecholaminergic crises may be precipitated by medications such as dopamine-receptor blockers (metoclopramide), anticholinergic drugs (atropine), catecholamine-sensitizing anesthetic agents (halothane and desflurane), and beta-blockers. I would avoid these medications and would request laboratory evaluation of plasma metanephrine levels or 24-hour urinary fractionated metanephrine levels. I would also consider cross-sectional imaging, because metanephrine levels may take days to be reported.

Intravenous hydralazine and a 20-mg bolus of labetalol were administered over a period of 30 minutes, and the patient's blood pressure decreased to 187/95 mm Hg. The patient was admit-

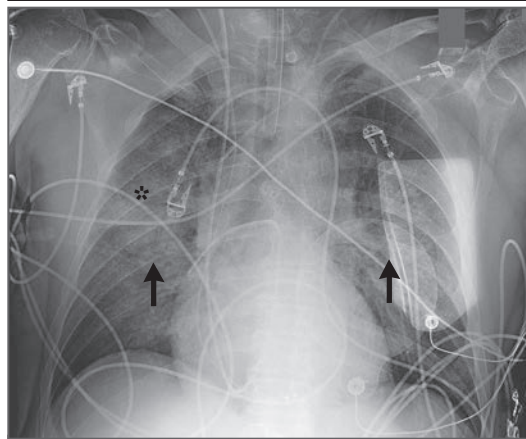


Figure 2. Radiograph of the Chest.

A radiograph of the chest after intubation shows a hazy opacity in the right-upper-lobe airspace (asterisk) with diffuse vascular prominence (arrows), findings suggestive of asymmetric pulmonary edema. An endotracheal tube, pulmonary-artery catheter, and external monitoring and external pacing pads are in place.

ted to the intensive care unit (ICU). On examination, he appeared to be uncomfortable and diaphoretic. Heart sounds were regular and tachycardic, without murmurs. Diffuse rhonchi were present. The surgical site was clean, dry, and intact. His hands and feet were cool. The bicarbonate level was 17 mmol per liter with an anion gap of 26 mmol per liter. The blood urea nitrogen level was 24 mg per deciliter (8.5 mmol per liter), and the creatinine level was 2.16 mg per deciliter (190 μ mol per liter; from a preoperative baseline level of 0.85 mg per deciliter [75 μ mol per liter]). The lactate level was 6.8 mmol per liter, and the fourth-generation troponin T concentration was 3.96 ng per milliliter.

The patient was transitioned to an esmolol drip for continued management of hypertension. Multiple doses of intravenous furosemide were administered, but little urine was produced. Progressive tachypnea and hypoxemia developed quickly, which prompted intubation and paralysis with cisatracurium. A frontal chest radiograph showed findings consistent with pulmonary edema (Fig. 2). After intubation, his blood pressure was 130/88 mm Hg, and his heart rate was 126 beats per minute. On day 2 after surgery, approximately 12 hours after admission to the ICU, the patient had an asystolic arrest. Cardiopulmonary resuscitation was initiated; he received epinephrine, sodium bicarbonate, and calcium chloride and had

a return of spontaneous circulation (blood pressure, 127/73 mm Hg). Infusions of vancomycin, cefepime, metronidazole, and epinephrine were initiated.

Before the asystolic arrest, the patient's cool hands and feet, oliguria, and lactic acidosis were worrisome since these conditions can indicate acute left ventricular dysfunction and cardiogenic shock. Progressive hypoxemia and acidosis may have been inciting causes of his asystolic arrest, although his electrocardiogram suggests cardiac conduction disease as an alternative culprit.

After resuscitation, the patient's temperature was 39.9°C, blood pressure 127/73 mm Hg, heart rate 123 beats per minute, and respiratory rate 30 breaths per minute. The oxygen saturation was 94% while he was receiving 100% oxygen from a volume-control ventilator with a tidal volume of 450 ml and a positive end-expiratory pressure of 14 cm of water. The white-cell count was 16,900 per cubic millimeter, the hemoglobin level 12.0 g per deciliter, and the platelet count 165,000 per cubic millimeter. The serum sodium level was 152 mmol per liter, the potassium level 5.1 mmol per liter, the bicarbonate level 23 mmol per liter, the blood urea nitrogen 40 mg per deciliter (14.5 mmol per liter), and the creatinine level 4.62 mg per deciliter (410 μ mol per liter).

The international normalized ratio was 4.8, the aspartate aminotransferase level 26,240 U per liter (normal range, 10 to 50), the alanine aminotransferase level 12,080 U per liter (normal range, 10 to 50), the alkaline phosphatase level 96 U per liter (normal range, 40 to 130), the total bilirubin level 2.6 mg per deciliter (44.5 μ mol per liter; normal range, 0.0 to 1.0 mg per deciliter [0.0 to 17.1 μ mol per liter]), and the direct bilirubin level 1.1 mg per deciliter (18.8 μ mol per liter; normal range, 0.0 to 0.3 mg per deciliter [0.0 to 5.1 μ mol per liter]). The lactate level was 12.9 mmol per liter (normal range, 0.5 to 2.2), and the troponin T concentration was 12.42 ng per milliliter (normal value, <0.01). The thyrotropin level was normal. Urine and plasma samples were sent to determine the levels of fractionated metanephrines.

The patient is now in shock with associated multisystem organ failure, including ischemic hepatitis ("shock liver"), anuric renal failure, myocardial injury, and refractory hypoxemic respiratory

failure. Further cardiac evaluation is needed, including transthoracic echocardiography and coronary angiography to rule out obstructive coronary disease. Finally, therapeutic hypothermia should be initiated. This therapy is called for in order to minimize neurologic injury in patients after an arrest who are unable to follow commands or make purposeful movements or in whom the neurologic status cannot be reliably assessed, as is the case in this patient.

Therapeutic hypothermia and continuous venovenous hemodialysis were initiated. An electrocardiogram showed sinus rhythm with first-degree atrioventricular block, left axis deviation, and left bundle-branch block (Fig. 1B). Transthoracic echocardiography revealed a left ventricular ejection fraction of 25%, with diffuse hypokinesis with regional variation, most prominently affecting the septum. Right ventricular size and function were normal. The left atrium was mildly enlarged. There was no pericardial effusion. Emergency coronary angiography revealed no clinically significant coronary artery disease. Left ventriculography with the use of contrast material revealed global hypokinesis with preserved apical contractility (Video 1, available at NEJM.org).

The right atrial pressure was 12 mm Hg (normal range, 0 to 5), the right ventricular pressure was 29/12 mm Hg (normal value, <25/5), the pulmonary-artery pressure was 32/23 mm Hg (normal value, <25/10) with a mean pressure of 27 mm Hg (normal value, $\leq$ 20), and the pulmonary capillary wedge pressure was 17 mm Hg (normal value, <12). The pulmonary-artery saturation was 59% while the patient was receiving mechanical ventilation with 100% oxygen. The cardiac output and index, calculated with the Fick method, were 6.52 liters per minute (normal range, 4.0 to 8.0) and 3.02 liters per minute per square meter of body-surface area (normal range, 2.5 to 4.2), respectively. The systemic vascular resistance was 700 dyn $\cdot$ sec $\cdot$ cm⁻⁵ (normal range, 800 to 1200), and the pulmonary vascular resistance was 123 dyn $\cdot$ sec $\cdot$ cm⁻⁵ (normal value, <250).

The absence of acute plaque rupture or obstructive coronary artery disease and the pattern of left ventricular dysfunction (preserved apical contractility and basilar hypokinesis) arouse suspicion for stress (Takotsubo) cardiomyopathy. Although apical ballooning is the most common pattern



A left ventriculogram is available at NEJM.org

of stress cardiomyopathy, apical hyperkinesis and basilar hypokinesis have been described in other cases (so-called inverted Takotsubo cardiomyopathy). Stress cardiomyopathy commonly manifests as chest pain, dyspnea, or syncope, although patients may also have heart failure, tachyarrhythmias and bradyarrhythmias, sudden cardiac arrest, or cardiogenic shock, as was seen in this patient. His elevated right-sided and left-sided filling pressures are consistent with acute biventricular dysfunction and can be explained by stress cardiomyopathy, postarrest stunned myocardium, or both. However, the low systemic vascular resistance with preserved cardiac output is consistent with mixed distributive and cardiogenic shock rather than with isolated cardiogenic shock.

The pathophysiology of stress cardiomyopathy is not well understood, but catecholamine excess, coronary-artery spasm, and microvascular dysfunction have all been postulated. In this context, I am most concerned about catecholamine excess, specifically from a pheochromocytoma. Although biochemical testing is generally recommended before imaging in the evaluation of suspected pheochromocytoma, urgent imaging is indicated in the context of critical illness, given the slow turnaround time for metanephrine levels and the likelihood that levels will be elevated owing to vasopressor therapy and elevated adrenergic activity. Computed tomographic (CT) imaging is the most sensitive test for the diagnosis of an adrenal mass but may not be possible in this severely ill patient. In that case, ultrasonography of the abdomen may be helpful, although it is much less sensitive.

The patient's wife reported that he had been fully active without symptoms before his surgery but that he had a tendency to minimize health concerns. On day 3 after surgery, complete heart block developed, with intermittent ventricular asystole, which prompted the temporary placement of a right ventricular pacing wire. Over the subsequent 2 days, progressive shock and multi-organ system failure developed in the patient despite vasopressor support with norepinephrine, vasopressin, epinephrine, phenylephrine, and dopamine. He was evaluated by a multidisciplinary shock team for consideration of venoarterial extracorporeal membrane oxygenation, but this treatment was not thought to be indicated owing

to extensive multisystem organ failure and adequate cardiac output. His hemodynamic and respiratory status was too unstable for him to be transported to the radiology suite for cross-sectional imaging.

On day 5 after surgery, he was transitioned to comfort care and died shortly thereafter. At autopsy, hypertensive cardiomegaly (600 g; normal range, 270 to 360) with concentric hypertrophy was noted. There was multifocal myocyte necrosis with a pattern suggestive of vasospasm or catecholamine toxicity (Fig. 3A and 3B). The coronary arteries were patent without clinically significant atherosclerosis. The left adrenal gland had been replaced by a 280-g solid mass that measured up to 11.0 cm in the greatest dimension arising from the adrenal medulla and compressing the adrenal cortex. Gross examination showed a variegated tan-to-pink cut surface and central areas of hemorrhage and degeneration (Fig. 3C). Histologically, the tumor was composed of large, polygonal cells with moderate-to-large amounts of granular, eosinophilic–amphophilic cytoplasm and irregularly shaped nuclei with frequent hyperchromasia, polymorphism, and pseudoinclusions (Fig. 3D). There was evidence of acute kidney injury, liver necrosis, small intestinal ischemia, and diffuse upper gastrointestinal bleeding, all of which are consistent with cardiogenic shock.

Results regarding plasma free and urinary fractionated metanephrine levels were returned post mortem. The plasma metanephrine level was 194 nmol per liter (normal value, <0.5), and the plasma normetanephrine level was 316 nmol per liter (normal value, <0.9). The urinary metanephrine excretion was 68,000 μ g per gram of creatinine (normal range, 29 to 158), and the urinary normetanephrine excretion was 52,000 μ g per gram of creatinine (normal range, 89 to 332).

The pathological findings of the adrenal gland and the markedly elevated urine and plasma metanephrine levels are diagnostic of pheochromocytoma.

COMMENTARY

Pheochromocytoma is a frequently discussed, yet exceedingly rare, neoplasm of the adrenal gland that occurs mostly in middle-aged adults, affecting women and men equally, with an incidence of 0.6 cases per 100,000 person-years.¹ Its rarity

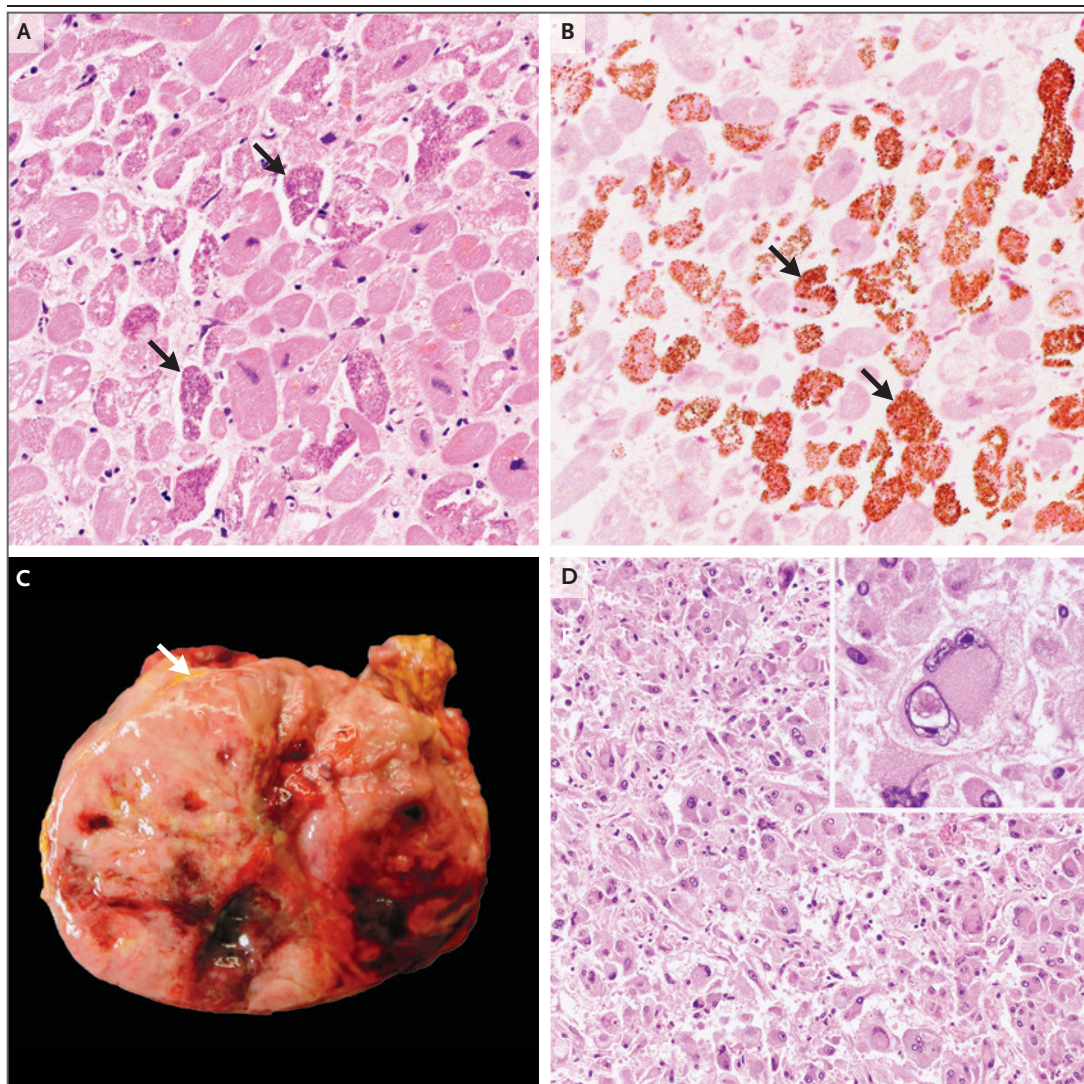


Figure 3. Autopsy Specimens of the Heart and Adrenal Tumor.

Histologic examination of the myocardium revealed multifocal myocyte necrosis and calcification (Panel A, arrows; hematoxylin and eosin stain), findings consistent with recent myocardial infarction caused by vasospasm. A von Kossa stain to detect mineralization highlights multifocal mitochondrial calcification (Panel B, arrows). Gross examination revealed an 11.0-cm mass arising from the adrenal medulla and compressing the surrounding adrenal cortex (Panel C, arrow), with a variegated tan-to-pink cut surface and central areas of hemorrhage and degeneration. Histologically, the tumor was composed of large, polygonal cells with moderate-to-large amounts of granular, eosinophilic–amphophilic cytoplasm and irregularly shaped nuclei with frequent hyperchromasia, polymorphism, and pseudo-inclusions (Panel D, inset; hematoxylin and eosin stain).

and its protean manifestations make its clinical recognition challenging, and yet, early recognition is imperative given the potential for lethal consequences, as was seen in this case.

Pheochromocytoma has been dubbed the “great masquerader,” given that its various clinical manifestations can mimic numerous other

conditions. Most patients do not have the classic triad of headaches, palpitations, and episodic sweating, and 10 to 15% of patients may be asymptomatic.² Hypertension, either sustained or paroxysmal, is common, although 5 to 15% of patients are normotensive. In more than half the cases, the tumor is discovered incidentally on

abdominal imaging. Pheochromocytoma manifests in rare cases as a catecholamine crisis that leads to heart failure, pulmonary edema, arrhythmias, renal failure, intracranial hemorrhage, or multisystem failure. Cardiovascular complications, including myocardial ischemia, myocarditis, cardiomyopathy, and tachyarrhythmias and bradyarrhythmias, occur in a small minority of cases but can be fatal.^{3,4}

Left ventricular dysfunction with apical hyperkinesis and basilar and midventricular akinesis in the absence of coronary artery disease, as were observed in our patient, are highly suggestive of a variant of stress cardiomyopathy (inverted Takotsubo cardiomyopathy). The most common form of stress cardiomyopathy (classic Takotsubo cardiomyopathy) is characterized by left ventricular dysfunction with apical ballooning. Pathological testing that shows multifocal myocyte necrosis suggestive of vasospasm and microvascular ischemia, as described in the patient's autopsy report, provides further evidence for this diagnosis. The pathophysiology of stress cardiomyopathy is poorly understood but is thought to involve catecholamine excess and associated microvascular dysfunction and myocardial stunning. Emotional stress, physical stress, adrenergic hyperactivity, and catecholamine-producing tumors are documented triggers. Case reports have described the occurrence of both classic Takotsubo cardiomyopathy and variants such as inverted Takotsubo cardiomyopathy in patients with pheochromocytoma.⁵⁻⁷ The diagnosis of stress cardiomyopathy should prompt consideration of pheochromocytoma in the absence of other recognized precipitants.⁸

Plasma free metanephrine and 24-hour urinary fractionated metanephrine levels are the recommended screening tests for the catecholamine excess that is characteristic of pheochromocytoma.⁹ Plasma free metanephrine levels have the greatest sensitivity (95 to 100%) and specificity (85 to 90%).¹⁰ Reported sensitivity and specificity of traditional assays of urine fractionated metanephrines have been reported to be slightly lower than those of plasma free metanephrines, but mass spectrometry of urine fractionated metanephrines has excellent sensitivity (97%) and specificity (91%). Although metanephrine and normetanephrine levels that are measured in a spot urine sample are not recom-

mended for screening, a recent article showed high correlations between these measurements and 24-hour urinary measurements.¹¹ Elevations in any measure must be interpreted with caution because false positive results are common.¹² Medications, including levodopa, sympathomimetic agents, tricyclic antidepressants, diuretics, and alpha- and beta-blockers; physiologic and psychological stress; and acute illness can all elevate metanephrine and catecholamine levels. In our patient, samples were obtained while the patient was receiving multiple sympathomimetic agents, including norepinephrine and epinephrine; although the infusion of vasopressors may increase catecholamine levels, the extremely elevated levels in this patient were unlikely to be explained by sympathomimetic agents alone. In contrast to the usual recommendation that imaging to identify pheochromocytoma be performed only after biochemical results suggest the diagnosis,¹ in critically ill patients in whom suspicion is high, imaging is recommended early, given delays in biochemical test results and the high likelihood that the elevated levels are due to physiologic stress and vasopressor use. Imaging with contrast-enhanced CT is typically preferred over magnetic resonance imaging, owing to superior spatial resolution for adrenal tumors. CT can also help to distinguish pheochromocytomas from other adrenal neoplasms, because CT attenuation of less than 10 Hounsfield units indicates that a neoplasm is lipid-rich, which essentially rules out pheochromocytoma.

The devastating outcome in this patient offers many lessons. Although the patient reported no symptoms other than knee pain before surgery, the findings at autopsy raise questions as to whether he was truly asymptomatic; if a history of headache, sweating, or palpitations had been elicited, this information might have influenced the original evaluation of hypertension. In addition, although the decision to proceed promptly to surgery despite his newly diagnosed hypertension was concordant with anesthesia guidelines,¹³ further preoperative monitoring or evaluation might have been helpful. The administration of intravenous beta-blockers without adequate alpha-adrenergic blockade is strictly contraindicated in patients with pheochromocytoma because unopposed alpha-adrenergic-receptor stimulation can precipitate or exacerbate hyper-

tensive crises. Finally, the use of cross-sectional imaging when pheochromocytoma was first considered would have enabled antemortem diagnosis.

Cardiomyopathy and multisystem crisis are rare and potentially fatal manifestations of pheochromocytoma. In this patient, because of a lack of historical clues, the diagnosis of pheochromo-

cytoma was not suspected until after the development of cardiogenic shock. The present case highlights the importance of considering pheochromocytoma, because early recognition and appropriate treatment may prevent catastrophic outcomes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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