Pheochromocytoma crisis precipitated by dexamethasone with profound lactic acidosis, but without severe hypertension

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Summary
We describe a case of a 47-year-old patient who presented with severe lactic acidosis, troponinemia, and acute kidney injury after receiving 8 mg of intramuscular dexamethasone for seasonal allergies in the setting of an undiagnosed epinephrine-secreting pheochromocytoma. This case was atypical, however, in that the patient exhibited only mildly elevated noninvasive measured blood pressures. Following a period of alpha-adrenergic blockade, the tumor was resected successfully. Steroid administration can precipitate pheochromocytoma crisis that may present unusually as in our patient with mild hypertension but profound lactic acidosis.

Learning points
- Steroids administered via any route can precipitate pheochromocytoma crisis, manifested by excessive catecholamine secretion and associated sequelae from vasoconstriction.
- Lack of moderate/severe hypertension on presentation detracts from consideration of pheochromocytoma as a diagnosis.
- Lactatemia after steroid administration should prompt work-up for pheochromocytoma, as it can be seen in epinephrine-secreting tumors.
- Noninvasive blood pressure measurements may be unreliable during pheochromocytoma crisis due to excessive peripheral vasoconstriction.

Background
Pheochromocytomas and paragangliomas are often discovered as incidental findings on imaging or when patients undergo physiologic stress, such as trauma, surgical procedures, or anesthesia. Additionally, certain drugs and foods can exacerbate catecholamine secretion, leading to pheochromocytoma crises, commonly associated with severe hypertension and end-organ ischemia from intense vasoconstriction. Triggering agents include but are not limited to tyramine-containing foods, caffeine, nicotine products, over-the-counter decongestants containing phenylephrine, beta-blockers, tricyclic antidepressants, cyclobenzaprine, monoamine oxidase inhibitors, amphetamines, prochlorperazine, levodopa, reserpine, cocaine, metoclopramide, and as in our case, steroids. Crisis precipitation by steroids may occur via any administration route as it has been described with oral, intravenous, intramuscular, and even intra-articular sites. We review an unusual case that highlights the mechanism and clinical implications of steroid-induced pheochromocytoma crisis.
Case presentation

A 47-year-old male with no prior medical history was admitted to the hospital with evidence of apparent myocardial ischemia, acute kidney injury, and a significant anion gap metabolic acidosis. He had received 8 mg intramuscular dexamethasone to treat seasonal allergies the evening prior to admission. The following morning, he developed non-exertional pleuritic chest pain, shortness of breath, intermittent fevers, polyuria, polydipsia, and two episodes of non-bloody non-bilious emesis. The patient also endorsed mild episodic dizziness occurring 3 to 4 times a day lasting up to several minutes, fleeting mild daily headaches, and an unexplained 8 kg weight gain over the prior 2 months.

In the emergency department, the patient was mildly hypertensive with a blood pressure of 144/88 mmHg, tachycardic to 116 beats per minute, and tachypneic with a respiratory rate of 22 breaths per minute. He remained afebrile and was oxygenating normally on room air. The remainder of his physical exam was unremarkable.

Investigation

Initial laboratory findings were notable for total leukocyte count: 31.4 K/μL with 89.3% polymorphonuclear cells, hemoglobin: 14.4 mg/dL, platelet count: 469 K/μL, sodium: 135 mmol/L, potassium: 4.0 mmol/L, bicarbonate: 10 mmol/L, anion gap 32, blood urea nitrogen: 16 mg/dL, creatinine: 1.33 mg/dL, glucose: 515 mg/dL, and lactate 15.1 mmol/L. Venous blood gas revealed profound metabolic acidosis with incomplete respiratory compensation; pH 7.15, PCO₂ 25 mmHg, bicarbonate 10 mmol/L, and a base deficit of 17 mmol/L. Hemoglobin A1C was 6.2%; urinary and serum ketones were undetectable. Initial troponin was mildly elevated at 0.08 ng/mL. ECG demonstrated sinus tachycardia with diffuse ST segment depressions in leads I, II, III, aVF, V₃–V₆. Chest radiography was unremarkable.

Given the severe laboratory derangements, the patient was admitted to the hospital for treatment of presumed severe sepsis and non-ST-elevation myocardial infarction (NSTEMI). He was fluid resuscitated with 30 mL/kg of balanced crystalloids and received broad-spectrum antibiotics, aspirin, atorvastatin, and insulin. He was also given ticagrelor, metoprolol, and started on a heparin infusion for treatment of NSTEMI. Given no clear source of sepsis on physical examination and initial laboratory studies, abdominal imaging was obtained for possible source of sepsis.

Abdominal and pelvic CT 6 h after presentation showed no evidence of bowel ischemia but did reveal a 2 cm right adrenal mass (Fig. 1). The patient remained asymptomatic and hemodynamically stable with serial ECGs demonstrating normalization of ST depressions and troponin peaking at 0.119 ng/mL. Lactate levels normalized by the next morning. A transthoracic echocardiogram demonstrated no pathology. Serum metanephrine levels showed elevated plasma-free metanephrine 13 nmol/L (normal < 0.5) and normetanephrine 4.4 nmol/L (normal < 0.9). Additionally, urinary metanephrines were elevated at 1457 μg/24 h (normal < 400) and urinary normetanephrines were normal at 661 μg/24 h (normal < 900).

Treatment

On hospital day 3, the patient was discharged on phenoxybenzamine 10 mg by mouth 3 times a day. He met with his primary care provider and multiple consultants over the next 3 weeks. During this time, he denied any additional chest discomfort; however, he continued to have mild intermittent headaches and dizziness despite normal daily blood pressures monitored at home.

Uneventful right laparoscopic adrenalectomy was performed 6 weeks following his initial presentation. The patient’s intra-operative course was notable for significant blood-pressure lability with femoral arterial blood pressure as high as 180/105 mmHg during tumor manipulation, effectively managed with clevidipine and sodium nitroprusside infusions. Sinus tachycardia was treated with esmolol. Severe hypotension occurred after adrenal vein ligation, lasting 4 min with blood pressure as low as

Figure 1
CT of the abdomen and pelvis noting right adrenal mass measuring 2 cm confirmed to be a pheochromocytoma with positive plasma-free and 24-h urine metanephrines.
Our patient’s lactic acidosis was dramatic and likely multifactorial from combined tissue hypoperfusion and hypoxia (type A lactic acidosis) and metabolic or non-hypoperfusion derangements (type B lactic acidosis), which has been observed in pheochromocytomas, particularly epinephrine-predominant tumors (3). Case reviews of steroid-induced pheochromocytoma crises all revealed epinephrine-secreting tumors (Table 1). Epinephrine causes β2 adrenergic receptor stimulation that upregulates glycogenolysis and gluconeogenesis while simultaneously stimulating lipolysis and glycolysis. This combined effect leads to hyperglycemia and increased pyruvate production and metabolism, increasing lactate production, which is ordinarily converted back to glucose in the liver through the Cori cycle. However, adrenergic excess leads to lactate accumulation and subsequent lactic acidosis. Though type B lactic acidosis explains some of the elevated lactate seen in our patient, epinephrine-stimulated lactate production alone appears insufficient to explain such a high level. This is evident in other pheochromocytoma cases that report severe lactic acidosis, as many show evidence of concomitant end-organ hypoperfusion (4). We suspect that there was an element of type A lactic acidosis generated by intense vasoconstriction and hypovolemia, causing regional hypoperfusion in the gastrointestinal tract, kidneys, and myocardium.

The patient’s episodes of nausea and vomiting were initially concerning for intra-abdominal pathology, especially considering the fever, leukocytosis, and lactic acidosis. However, his abdominal exam was benign, and the abdominal CT was unremarkable aside from the adrenal tumor. We theorized that perhaps the patient experienced transient intestinal vasoconstriction, which has been reported in a patient with a pheochromocytoma who developed an acute abdomen and was found to have bowel ischemia (5). Given that our patient’s symptoms resolved quickly by the time the CT was performed, intestinal vasoconstriction was likely not severe or prolonged but may have contributed to a type A lactic acidosis on presentation.

While the patient’s presentation of diffuse ST depressions and troponinemia could be attributed to a type 2 NSTEMI, the patient was previously healthy with a normal functional capacity. It would also seem unlikely that a heart rate of 120 beats per minute combined with mildly elevated blood pressures were enough to produce demand myocardial ischemia without prior cardiac disease. Given the transient nature of the ECG changes and quick clearance of troponin, we suspect a mild case of acute catecholamine-induced myocarditis which has

Outcome and follow-up

Postoperatively, the patient was observed in the ICU for 24 h, during which he remained euglycemic and hemodynamically stable, requiring no vasoactive drugs. He was discharged on postoperative day 2. Since then, he has remained symptom-free.

Discussion

We describe a case of catecholaminergic crisis precipitated by intramuscular dexamethasone in the presence of an undiagnosed pheochromocytoma. The patient presented with a constellation of concerning, but not readily explained, laboratory derangements including profound lactic acidosis, severe hyperglycemia (in the setting of normal hemoglobin A1C and lack of ketonemia/-uria), and elevated troponin levels. While sepsis was suspected as the reason for the lactic acedia, no source was identified on physical exam and his blood pressure remained incongruously normotensive to mildly hypertensive. This prompted an abdominal CT that eventually led to the diagnosis of pheochromocytoma.

Typical symptoms of pheochromocytoma or catecholamine crisis include episodic hypertension, headaches, palpitations, and diaphoresis. Prior reports of steroid-induced pheochromocytoma crisis in the literature observed variable blood pressures (Table 1). The majority of patients were noted to have moderate-to-severe hypertension and others were in shock with multiorgan dysfunction secondary to severe vasospasm. While our patient did not present with a documented hypertensive emergency (>180/120 mmHg), the potential error of noninvasive blood pressure devices should not be overlooked and is known to underestimate elevated blood pressure in some patients (1). In pheochromocytoma patients, noninvasive blood pressure error can be dramatic and associated with unobtainable measurements. One case reported difficulty palpating peripheral pulses or obtaining noninvasive blood pressure readings in a setting of apparent hypotension, pulmonary edema, and evidence of myocardial injury. However, a central aortic pressure as high as 320/200 mmHg was documented, demonstrating that the patient’s ‘shock’ was in fact a hypertensive crisis due to severe arterial vasoconstriction (2).
been described in pheochromocytoma patients and can be aggravated by the administration of corticosteroids (6). This complication is often referred to as a 'tako-tsubo-like phenomenon'. In that situation, some abnormalities of the left ventricle kinetics are often observed. In our case, this was not detected, but the formal echo was not obtained until the day after admission, by which time he had rapidly improved. The mechanism of catecholamine-induced myocarditis is likely multifactorial. First, the elevation in circulating catecholamines leads to a downregulation of β-adrenergic receptors and a reduction of myofibrils. Second, there is a direct toxic effect of catecholamines and their oxidation byproducts, leading to increased sarcolemma membrane permeability, increased release of calcium into the cytosol, and subsequent myocardial damage and necrosis. Lastly, the catecholamine excess may cause coronary artery vasospasm, another factor leading to myocardial ischemia.

### Table 1 Case reports of pheochromocytoma crisis precipitated by steroids

<table>
<thead>
<tr>
<th>Case (age/sex)</th>
<th>Reason</th>
<th>Steroids administered</th>
<th>Symptoms of pheochromocytoma crisis</th>
<th>Catecholamine profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 male (12)</td>
<td>Shoulder bursitis</td>
<td>Hydrocortisone i.v., ACTH i.v., prednisone p.o., Prednisone 45 mg PO x 3 d hydrocortisone 100 mg i.v., Prednisone p.o.</td>
<td>Severe Htn (220/110) N/V, NSTEMI, acute heart failure Severe Htn (280/140)</td>
<td>E</td>
</tr>
<tr>
<td>69 female (13)</td>
<td>Giant cell arteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47 male (14)</td>
<td>Histiocytic lymphoma</td>
<td>Prednisone 100 mg p.o. x 3 d</td>
<td>Labile BP (70/40–200/130) myocardial ischemia arrhythmias Severe Htn (240/120) tachycardia, syncope Orthostasis (95/67–62/55, HR 150) Labile BP, HFrEF (25%), CA Htn (150/90) HFrEF (9%), AKI, hypoxemic respiratory failure</td>
<td>E, NE</td>
</tr>
<tr>
<td>58 male (15)</td>
<td>Lymphocytoma</td>
<td>Dexamethasone 16 mg p.o., Prednisone 60 mg p.o. Dexamethasone intra-articular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 female (16)</td>
<td>Headaches</td>
<td>Dexamethasone 2 mg PO x 3 d</td>
<td>Severe Htn (260/165) s/p metoprolol NSTEMI, retroperitoneal hemorrhage Severe Htn (160/110) cardiogenic shock, acute pulmonary edema severe metabolic acidosis</td>
<td>E, NE</td>
</tr>
<tr>
<td>43 female (16)</td>
<td>Asthma</td>
<td>Dexamethasone 2 mg PO x 3 d</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>52 male (17)</td>
<td>Shoulder bursitis</td>
<td>Dexamethasone 2 mg PO x 3 d</td>
<td>Severe Htn (240/140) CA, cardiogenic shock, aspiration encephalopathy, AKI, hepatic insufficiency</td>
<td>E, NE</td>
</tr>
<tr>
<td>44 female (18)</td>
<td>Headaches</td>
<td>Dexamethasone 2 mg PO x 3 d</td>
<td>Severe Htn (260/165) s/p metoprolol NSTEMI, retroperitoneal hemorrhage Severe Htn (160/110) cardiogenic shock, acute pulmonary edema severe metabolic acidosis</td>
<td>E, NE</td>
</tr>
<tr>
<td>26 female (19)</td>
<td>Dexamethasone suppression test</td>
<td>Dexamethasone 2 mg POq 6 h x 2 d</td>
<td></td>
<td>E</td>
</tr>
<tr>
<td>39 male (19)</td>
<td>Airway congestion</td>
<td>Betamethasone 6 mg i.m.</td>
<td>Severe Htn (240/140) CA, cardiogenic shock, aspiration encephalopathy, AKI, hepatic insufficiency</td>
<td>E, NE</td>
</tr>
<tr>
<td>27 male (19)</td>
<td>MIBG treatment protocol</td>
<td>Methylprednisolone 1.5 g i.v.</td>
<td>Severe Htn (189/119) tachycardia, N/V</td>
<td>N/A</td>
</tr>
<tr>
<td>39 female (19)</td>
<td>Dexamethasone suppression test</td>
<td>Dexamethasone 2 mg p.o.</td>
<td>Severe Htn 220/120 NSTEMI</td>
<td>E</td>
</tr>
<tr>
<td>36 male (20)</td>
<td>URI symptoms</td>
<td>Betamethasone 4 mg i.m.</td>
<td>Severe Htn (200/110) NSTEMI, retropertitoneal hemorrhage Severe Htn (240/140)</td>
<td>E, NE</td>
</tr>
<tr>
<td>61 female (21)</td>
<td>Dexamethasone suppression test</td>
<td>Dexamethasone 2 mg p.o. q 6 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66 female (22)</td>
<td>PMR</td>
<td>Prednisolone 15 mg p.o. daily</td>
<td>Htn (165/102) Tachycardia, MSOF, Rhabdomyolysis Severe Htn (218/108) tachycardia, nausea/dizziness/fatigue CA s/p metoclopramide for nausea</td>
<td>E, NE</td>
</tr>
<tr>
<td>63 male (23)</td>
<td>Hearing loss</td>
<td>Prednisolone 100 mg i.v.</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>73 male (24)</td>
<td>Dental implant infection</td>
<td>Dexamethasone 4 mg PO x 3 d</td>
<td>Labile BP (BPsys 60–250) elevated lactate, troponin</td>
<td>E, NE</td>
</tr>
<tr>
<td>70 male (25)</td>
<td>Contrast pre-treatment</td>
<td>Hydrocortisone 100 mg i.v.</td>
<td>Severe Htn palpitations, NSTEMI Severe Htn (240/160) DKA, elevated lactate, severe metabolic acidosis</td>
<td>E</td>
</tr>
<tr>
<td>45 male (26)</td>
<td>Arthritis</td>
<td>Betamethasone 2 mg intra-articular</td>
<td></td>
<td>E, NE</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; AKI, acute kidney injury; BPsys, systolic blood pressure; CA, cardiac arrest; DKA, diabetic ketoacidosis; E, epinephrine; F, female; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; Htn, hypertension; M, male; MIBG, metiodobenzylguanidine; MSOF, multi-system organ dysfunction; NE, norepinephrine; NSTEMI, non-ST-elevation myocardial infarction; N/V, nausea and vomiting; PC, pheochromocytoma crisis; Pheo, pheochromocytoma; PMR, polymyalgia rheumatica; URI, upper respiratory tract infection.
and potentially irreversible damage with necrosis (7). Our patient experienced rapid resolution of his crisis following the initiation of alpha-adrenergic blockade, which is known to reverse myocardial injury. Relatively normotensive patients that have early ischemic changes on ECG and preserved left ventricular systolic function on echocardiogram have been found to have cardiac MRI findings of myocarditis that was reversed with adequate alpha-adrenergic blockade and successful resection of the tumor (8).

Since 1968, there have been 20 reported cases of steroid-induced catecholamine crisis in patients with pheochromocytoma. There are many mechanisms as to why this may occur. First, glucocorticoids will upregulate many enzymes in the catecholamine synthesis pathway, including tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine N-methyltransferase (9), which leads to the augmentation of catecholamine release. Second, glucocorticoids potentiate the action of peripheral catecholamines, which has led to clinical use in shock patients where relative adrenal insufficiency is suspected (10). Finally, there may also be certain subsets of pheochromocytoma patients who have increased glucocorticoid receptor expression in the adrenal medulla, which may predispose them to a massive catecholamine response (11). In reviewing reports of steroid-induced pheochromocytoma crises (Table 1), it should be noted that any form of glucocorticoid may precipitate a crisis, with a predictably faster onset with parenteral administration. Lack of general recognition of steroids precipitating pheochromocytoma crisis persists despite previous reports on this subject. This is important because steroids are ubiquitous in medicine. They have broad indications across multiple specialties: anti-inflammation, postoperative nausea and vomiting, extension of regional anesthesia nerve blockade, management of cerebral edema, as part of chemotherapy regimens, dexamethasone suppression test, and septic shock, among others. Either by innocence (undiagnosed pheochromocytoma) or ignorance (known pheochromocytoma), these events are likely to recur.

In summary, we recommend listing glucocorticoid administration as a contraindication in patients with suspected or confirmed pheochromocytomas. Acute care clinicians should consider the diagnosis of pheochromocytoma when patients present with acute lactic acidosis and end-organ injury after recent steroid administration, with or without documented severe hypertension, as pheochromocytoma continues to be a ‘great masquerader’.


13 Daggett P & Franks S. Steroid responsiveness in pheochromocytoma. *BMJ* 1977 **1** 84. (https://doi.org/10.1136/bmj.1.6053.84)


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