Pheochromocytoma Crisis due to Glucocorticoid Administration: A Case Report and Review of the Literature

Farin Rashid-Farokhi MD*, Ali Cheraghvandi MD**, Mohammad-Reza Masjedi MD**

We report a patient who presented with two episodes of severe hypertension after intramuscular injection of betamethasone. The first attack was associated with pulmonary edema, while the second attack was associated with high anion gap metabolic acidosis, renal failure, hyperglycemia, and hypokalemia. The attacks led to the diagnosis of pheochromocytoma, which was confirmed by appropriate diagnostic tests. The tumor was excised successfully and the patient is presently asymptomatic.

We believe that these episodes were initiated by glucocorticoid injection, an event reported in a few cases. We briefly review potential mechanisms resulted in hypertensive crisis in such patients.

Keywords: Betamethasone • glucocorticoids • hypertension • pheochromocytoma • pulmonary edema

Introduction

Pheochromocytoma is a rare neuroendocrine tumor derived from chromaffin cells of the sympathetic nervous system. Typically affected patients present with hypertension and the triad of headache, palpitation, and sweating. However, there are many reports of other unusual presentations. Severe paroxysms of pheochromocytoma have been induced by several drugs.

Presentation of pheochromocytoma after administration of steroid is rarely reported. We report an unusual presentation of pheochromocytoma after steroid administration.

Case Report

A 36-year-old man was admitted to the hospital with hypertension and respiratory failure. The patient was visited one day before admission in an outpatient clinic because of persistent dry cough after an upper respiratory tract infection. He had received 4 mg betamethasone intramuscularly as well as an oral antihistamine.

The following day he developed palpitation, headache, tremor, anxiety, abdominal pain, and nausea and vomiting. He was severely hypertensive with blood pressure 200/110 mmHg for which he was referred to our hospital for admission.

On admission, he was diaphoretic, tachypnic, tachycardic with blood pressure of 200/100 mmHg, and had bilateral diffuse crackles over both lung fields. The patient’s extremities were cyanotic. Laboratory findings included the following: leukocyte count: 23300 cells/mm³ with 88% polymorphonuclear cells, urea: 38 mg/dL, creatinine: 1.2 mg/dL, erythrocyte sedimentation rate (ESR): 12 mm/hr, hemoglobin (Hb): 15.5 mg/dL, sodium: 140 meq/L, and potassium: 4.2 meq/L.

Initial arterial blood gas values were: pH: 7.40, PCO₂: 38.2 mmHg, PaO₂: 68 mmHg, and O₂ saturation: 83%. Chest radiography revealed severe bilateral infiltration. Echocardiography was normal and electrocardiography showed sinus tachycardia.

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The patient became more dyspneic requiring intubation and mechanical ventilation.

A brain computed tomography (CT) yielded normal findings. The patient was treated with intravenous antibiotics with the presumed diagnosis of pneumonia and adult respiratory distress syndrome (ARDS). Five hours after initiation of mechanical ventilation, he became agitated and three hours later he was completely conscious. He was therefore extubated and oral nutrition was begun. By the next day, he felt much better with a blood pressure of 137/66 mmHg and O₂ saturation of 96% on room air. High resolution CT showed diffuse ill-defined opacities filling the air spaces. Multiple blood cultures were negative.

By the third day, chest radiograph had significantly improved and the patient was discharged on oral antibiotics.

During the next nine months, his blood pressure was no more than 130/85 mmHg and he was in a good condition until he developed an upper respiratory tract infection. He was again treated with intramuscular betamethasone for persistent dry cough. Twelve hours later he developed palpitation, diaphoresis, tremor, nausea, vomiting, headache, chest wall pain, and severe anxiety. The patient was again admitted to the hospital. On this admission the blood pressure was 200/100 mmHg. Laboratory findings showed blood sugar: 359 mg/dL, urea: 41 mg/dL, creatinine: 2 mg/dL, sodium: 142 meq/L, potassium: 3.2 meq/L, and chloride: 106 meq/L. Arterial blood gas analysis on room air revealed: pH: 7.21, PCO₂: 31.9 mmHg, HCO₃⁻: 12 meq/L, PO₂: 98 mmHg, O₂ saturation: 98.7%, and base excess: -14.

Chest radiograph was normal. On the second hospital day, all of the clinical and laboratory abnormalities improved and antihypertensive drugs were discontinued. Kidney ultrasonography and renal Diethylene Triamine Penta-Acetic Acid (DTPA) scan with and without captopril were normal.

Further studies showed vanilmandelic acid (VMA): 6 mg/24 hr, (normal range: less than 13.6), and metanephrine: 876 μg/24 hr, (normal range: between 20 and 345). These laboratory evaluations were repeated with the following results: urine VMA: 16.5 mg/24 hr and urine metanephrine: 652 Micg/24 hr.

Abdominal magnetic resonance imaging (MRI) showed a round image 20×20 mm attached to the inferior border of the left adrenal gland (Figure 1).

Figure 1. Magnetic resonance imaging shows an abnormal 20×20 mm round image under the left adrenal gland.

Adrenal scintigraphy showed focal intense radiotracer collection at the left adrenal region in favor of pheochromocytoma (Figure 2).

The patient underwent left adrenalectomy and the diagnosis of pheochromocytoma was confirmed by pathologic evaluation (Figure 3). Following the surgery the patient has remained symptom free, although he has not been challenged with high-dose glucocorticoids.

Discussion

We present a patient with pheochromocytoma who developed two episodes of hypertensive crisis 12 hours after steroid administration. This is a rare event and review of the English-language literature has revealed only six cases of steroid-induced pheochromocytoma (Table 1). The hypertensive crisis occurred either during ACTH stimulation test or several hours after administration of glucocorticoids. In one case pheochromocytoma presented after intra-articular administration of glucocorticoid. Acute heart failure was reported in three patients. One patient developed cardiogenic shock and another developed myocardial infarction.

Steroids can stimulate enzymes involved in synthesis of catecholamines including tyrosine hydroxylase, dopamine β-hydroxylase, and phenylethanolamine N-methyltransferase (PNMT). Steroid administration also augments the release of catecholamines from isolated perfused dog adrenal glands. Additionally, steroids appear to play a permissive role in the action of catecholamines on...
peripheral tissues. Administration of ACTH and steroids increases the vasopressor response to infused norepinephrine.\textsuperscript{13}

An alternative explanation for clinical presentation of pheochromocytoma after glucocorticoid administration has also been suggested. In adrenal medulla norepinephrine combines with PNMT to produce epinephrine. A high level of adrenal glucocorticoid is required for PNMT activation, a condition provided by intimate relationship of adrenal cortex to adrenal medulla. So, medullary chromaffin cells are bathed in a sufficiently high level of glucocorticoids to produce epinephrine, provided the adrenal cortex is producing cortisol. Exogenous glucocorticoid administration decreases adrenal steroids production by direct ACTH suppression resulted in decreased PNMT activity and, secondarily, decreased epinephrine production. In patients with pheochromocytoma the vasoconstrictor effect of norepinephrine can be antagonized by epinephrine. By the above-mentioned mechanism, in these patients exogenous glucocorticoid administration would result in increased norepinephrine: epinephrine ratio resulted in unprotected norepinephrine-induced vasopressor effects.\textsuperscript{14}

Our patient presented with pulmonary edema, an uncommon and usually fatal manifestation of pheochromocytoma. In such patients pulmonary edema is cardiogenic in origin partially due to severe hypertension. In some patients non-cardiogenic pulmonary edema has also been reported. This is thought to be due to catecholamine-induced increase in pulmonary capillary pressure and increase in pulmonary capillary permeability.\textsuperscript{15–21} It is difficult to be certain whether pulmonary edema in our patient was cardiogenic or noncardiogenic in origin as

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Scintigraphy with (MIBG) iodine-131-meta-iodobenzylguanidine shows focal intense radiotracer collection at the left adrenal region compatible with the diagnosis of pheochromocytoma.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Pathology of the adrenal mass compatible with the diagnosis of pheochromocytoma (x400).}
\end{figure}
pulmonary capillary wedge pressure was not measured.

In our patient two presenting features are worth noting. In the first admission, fever and leukocytosis led to a diagnosis of pneumonia and sepsis. These findings have been reported as presenting feature of pheochromocytoma.\(^{22,23}\)

During the second admission, our patient developed hyperglycemia, acidosis, hypokalemia, and renal failure. Both diabetic ketoacidosis and lactic acidosis have been reported in patients with pheochromocytoma. The pathophysiology of lactic acidosis in pheochromocytoma is related to increased production of lactate in peripheral tissues or by reduced rate of removal by the liver.\(^{24,25}\)

In summary, we report a patient with pheochromocytoma who presented with two episodes of hypertensive crisis induced by exogenous steroid administration. This presentation, while rare, should alert physicians to the possible presence of pheochromocytoma.

Acknowledgment

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Table 1. The summary of reported cases of pheochromocytoma crisis after glucocorticoid administration.

<table>
<thead>
<tr>
<th>Authors, journal ,and publishing year</th>
<th>Age, sex</th>
<th>The causes of steroid administration</th>
<th>Main presenting feature of pheochromocytoma</th>
<th>Administration route, preparation ,and dosage of glucocorticoids</th>
<th>Interval between glucocorticoid administration and presenting feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paget et al. <em>Am J Med</em>; 1969(^2)</td>
<td>57-year-old man</td>
<td>ACTH stimulation test</td>
<td>Heart failure</td>
<td>ACTH, prednisolone</td>
<td>During the test</td>
</tr>
<tr>
<td>Cowley, et al. <em>Br J Surg</em>; 1970(^3)</td>
<td>71-year-old woman</td>
<td>Treatment of giant cell arteritis, preparation for angiography</td>
<td>Hypertension (240/140), palpitation, tremor</td>
<td>Oral prednisolone, 45 mg/day Intravenous, hydrocortisone, 100mg single dose</td>
<td>For prednisolone: within third day, for hydrocortisone : after one hour</td>
</tr>
<tr>
<td>Daggett and Franks, <em>Br Med J</em>; 1977(^4)</td>
<td>34-year-old woman</td>
<td>Atypical migraine headache</td>
<td>Heart failure, hypotension</td>
<td>Dexamethasone, 16 mg</td>
<td>After 12 hours</td>
</tr>
<tr>
<td>Takagi, et al. <em>Jpn Circ J</em>; 2000(^6)</td>
<td>52-year-old man</td>
<td>Shoulder pain</td>
<td>Heart failure, cardiogenic shock</td>
<td>Intrajoint dexamethasone</td>
<td>After 12 hours</td>
</tr>
<tr>
<td>Brown, et al. <em>J Clin Endocrinol Metab</em>; 2005(^7)</td>
<td>44-year-old woman</td>
<td>Migraine headache resistant to other treatments, Severe headache, myocardial infarction, severe hypertension after beta-blocker administration</td>
<td>Oral dexamethasone, 2 mg three times a day</td>
<td>Within 24 hours, myocardial infarction on the third day</td>
<td></td>
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References


