Sustained Hypotension Complicating an Extra-adrenal Pheochromocytoma

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CASE REPORT
A 52-year-old woman with a 7-year history of hypertension presented to the emergency department of a regional 2nd-grade community hospital complaining of dyspnea, chest pain, headache, and palpitations for the past 6 h. She also reported blood pressure (BP) levels measured at home of 220/110 mm Hg for 2 h before admission, which were not reduced after receiving her usual antihypertensive medication (amlodipine 10 mg, quinapril 20 mg, and hydrochlorothiazide 12.5 mg), with the addition of furosemide 40 mg. The patient also reported being under treatment with ursodeoxycholic acid 500 mg/24 h for Crohn’s disease. There were no other contributory findings from her personal and family history. She reported poor control of her BP during the past week (BP levels were 140/90 mm Hg, with a heart rate of 110 bpm). During resection, mean BP fell below 60 mm Hg requiring fluid resuscitation and epinephrine administration. A 6-cm hard circumscribed mass, with central areas of hemorrhage, was resected. Histological analysis confirmed the diagnosis of pheochromocytoma, showing polygonal tumor cells into a clustered pattern, separated by an abundant vascular network. Postoperatively, the patient remained under norepinephrine and epinephrine administration, which was gradually reduced during the following 48 h. The patient was released from the intensive care unit on the 12th day after her admission. She was transferred to the First Department of Medicine, where she received carvedilol 6.25 mg b.i.d. Her BP ranged from 100/70 to 120/80 mm Hg, requiring intubation.

Antihypertensive treatment was withdrawn and treatment with normal saline and dopamine was accompanied by a BP of 80/50 mm Hg. Computed tomography scan revealed an extra-adrenal mass 7 cm in diameter that lay anteromedial to the left kidney. Plasma noradrenaline in resting position was 0.74 ng/ml (normal levels: 0.12–0.70 ng/ml), plasma adrenaline was 0.17 ng/ml (normal levels: 0.03–0.19 ng/ml), and urinary vanillyl mandelic acid was 16.75 mg/24 h (normal levels: 1–7 mg/24 h). Plasma metanephrine levels were not obtained, because their measurement was not feasible in the regional hospital. The remaining routine blood tests, including urea, creatinine, and electrolytes, were within normal limits.

At this stage (with BP levels at 90/70 mm Hg during dopamine administration), the patient was transported to the 3rd-grade AHEPA University Hospital Intensive Care Unit with the diagnosis of possible pheochromocytoma. During the admission, atrial fibrillation occurred, which was treated with amiodarone. Administration of dopamine hydrochloride (12 μg/kg/min) maintained BP levels between 70/40 mm Hg and 90/50 mm Hg. Addition of epinephrine (10 μg/kg/min) in combination with norepinephrine (0.3 μg/kg/min) increased her BP to 120/80 mm Hg with a pulse rate of 100 bpm. On the 4th day, the computed tomography scan of the abdomen was repeated (Figure 1) and magnetic resonance imaging was also performed (Figure 2); both showed a retroperitoneal 7 cm tumor situated anterolaterally to the left kidney, immediately adjacent to the aorta. Chromogranin blood levels were 20.3 nmol/l (normal levels: <4 nmol/l).

On the 7th day, surgical transperitoneal resection of the tumor was performed (Figure 3). During resection, mean BP fell below 60 mm Hg requiring fluid resuscitation and epinephrine administration. A 6-cm hard circumscribed mass, with central areas of hemorrhage, was resected. Histological analysis confirmed the diagnosis of pheochromocytoma, showing polygonal tumor cells into a clustered pattern, separated by an abundant vascular network. Postoperatively, the patient remained under norepinephrine and epinephrine administration, which was gradually reduced during the following 48 h. The patient was released from the intensive care unit on the 12th day after her admission. She was transferred to the First Department of Medicine, where she received carvedilol 6.25 mg b.i.d. Her BP ranged from 100/70 to 120/80 mm Hg,

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with normal sinus rhythm and her pulse ranged from 70 to 95 bpm between the 12th and the 22nd day of treatment. Vanillylmandelic acid levels were found to be elevated both before (16.75 mg/24 h) and on the 3rd day (16.10 mg/24 h), and 7th day (14.27 mg/24 h) after tumor resection, while a normal value (5.08 mg/24 h) was first observed 12 days after resection of the tumor. At that time, a meta-iodobenzylguanidine ($^{123}$I-MIBG) scintigram showed no areas of increased uptake.

Postoperative period was uneventful. Three months after surgical resection, the patient was in good health, normotensive, with normal cardiac rhythm, and was not receiving antihypertensive treatment.

**DISCUSSION**

Pheochromocytoma arises from chromaffin cells of the adrenal gland or associated with sympathetic nerves and ganglia. The estimated prevalence of pheochromocytoma in the hypertensive population is 0.1%. In the vast majority (80%) of the cases, tumors are unilateral, located in an adrenal gland, whereas up to 18% of tumors in adults are found in extra-adrenal locations.1,2 About 25–30% of all pheochromocytomas are part of hereditary familial syndromes, namely Multiple Endocrine Neoplasia 2a, Multiple Endocrine Neoplasia 2b, von Hippel-Lindau disease (retinal angioma and cerebellar hemangioblastoma), von Recklinghausen’s disease (neurofibromatosis 1),1,2 and succinate dehydrogenase mutations, (SDHD) and (SDHB); such patients usually present with extra-adrenal pheochromocytoma for which the prevalence of malignancy is relatively high.

Hypertension is the most frequent finding in pheochromocytoma. More than half of the patients present sustained hypertension, whereas about 45% have paroxysmal BP elevations during a crisis. A crisis is almost invariably accompanied by several symptoms, typically palpitations, headache, excessive perspiration, and sometimes by pain in the chest or the abdomen, associated with nausea and vomiting.3,4 About 5% of tumors do not cause hypertension—particularly familial tumors and those that secrete large amounts of vasodilating substances, including precursors of dopa and dopamine.3,5

Our patient experienced a hypertensive crisis which was followed by a sustained drop in BP. This deterioration of the patient’s condition required admission to the intensive care unit, where she was intubated and received normal saline and inotropic medication. Inotropic support was required for 2 days after surgical resection of the paraganglioma.

The presence of pulmonary edema in this patient implies an excess of extravascular fluid which is extravasated due to increased hydrostatic pressure or increased capillary permeability. Pheochromocytoma can lead to pulmonary edema through different pathways, i.e., via cardiogenic decompensation due to cardiomyopathy and increased vascular resistance,6,7 via noncardiogenic edema due to increased hydrostatic pressure through overfilling or constriction of the efferent pulmonary veins,8 or via increased permeability of the pulmonary capillaries due to high catecholamine concentrations.8,9

Hypotension (especially orthostatic) may be seen in patients with pheochromocytoma; it is considered a result of fluctuation in vascular tone and subsequent suppression of baroceptor signaling,10–13 and/or hypovolemia and/or downregulation of adrenergic receptors.3 However, sustained hypotension is a rare finding. Since 1954,14 fewer than 20 cases have been
reported. Severe hypotension in patients with pheochromocytoma has been associated with anesthesia or operation.\textsuperscript{15}

Hypertension caused by pheochromocytoma is initially treated with phenoxybenzamine, which is usually administered for a period varying from a few days to a month prior to surgical excision.\textsuperscript{1,16,17} Treatment with an α-adrenergic receptor blocker should precede β-blockade for the treatment of tachycardia to prevent a paradoxical increase in BP that can occur when α-adrenergic receptors are stimulated and vasodilating β-adrenergic receptors are blocked. In addition, when there is evidence of cardiomyopathy, or markedly elevated catecholamine levels, methylparatyrosine can be added.

However, in patients presenting with shock, volume expansion and administration of vasoactive substances, such as dopamine and norepinephrine are needed to maintain BP at normal levels. This treatment algorithm should be followed by immediate surgical excision since tumor removal constitutes the only definitive treatment. In our patient, a typical hypertensive crisis was followed by a sustained hypotensive phase. The latter required large doses of fluids and catecholamines to reverse the hypotension, which was not related to anesthesia or operation. Hypotension seen in patients with pheochromocytoma can be attributed to myocardial damage (cardiomyopathy) caused by circulating catecholamines,\textsuperscript{5} but in our case, there was no evidence of cardiac dysfunction. Alternatively, large amounts of secreted dopa and dopamine may have contributed to the pathogenesis of the hypotensive episodes;\textsuperscript{5} however, this would be an extremely unlikely cause of hypotension, because these substances are only very rarely secreted by pheochromocytomas. Tumor necrosis, leading to sudden withdrawal of large amounts of catecholamines can subsequently result in prolonged hypotension.\textsuperscript{18} This is the most probable explanation in our patient, also supported by the nondiagnostic catecholamine levels found and by the histopathologic findings.

In conclusion, in the rare case of pheochromocytoma complicated by sustained hypotension refractory to treatment, prompt surgical resection of the tumor may be lifesaving. After excluding the common causes of shock, the possibility that sustained hypotension following hypertensive episodes may result from necrosis in a pheochromocytoma should be considered.

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