Pheochromocytoma-Induced Acute Myocarditis

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Pheochromocytoma is a neuroendocrine tumor, characterized by an excess of catecholamine production, which results in paroxysmal or sustained hypertension, even hypertensive crisis. The classic triad of pheochromocytoma is paroxysmal headache, sweating and palpitation. Myocarditis is a rare manifestation of pheochromocytoma. We report 2 middle-aged women with a long history of hypertension and headache, presenting initial symptoms mimicking acute coronary syndrome and finally developing heart failure and unstable hemodynamics. The characteristic fluctuation of blood pressure and hypertensive crisis prompted us to further survey and diagnose this rare pheochromocytoma-related myocarditis.

Key Words: Catecholamine • Myocarditis • Pheochromocytoma

INTRODUCTION

Pheochromocytoma is a rare catecholamine-producing tumor that arises from chromaffin cells of the adrenal medulla or the sympathetic ganglia, accounting for less than 0.2% of overall hypertension.1 Although the spells of the typical triad of pheochromocytoma are headache, sweating and palpitation, paroxysmal hypertension or hypertensive crisis is also suggestive of the disease. Acute myocarditis is a rare complication of pheochromocytoma. We report 2 cases with pheochromocytoma-induced myocarditis. Both patients manifested blood pressure fluctuation, and one of them presented cardiogenic shock requiring mechanical circulatory support.

CASE REPORTS

Case 1

A 41-year-old woman, who had 7 years of regularly treated hypertension and chronic headache, presented hemoptysis, short of breath, dyspnea on exertion, and vomiting one day prior to admission. She visited our outpatient clinic on the day of admission, and her chest roentgenogram showed acute pulmonary edema. She denied any flu-like symptoms prior to admission. Enlarged jugular vein, breathing sound with diffuse crackles, and a heart sound with S3 gallop were found on physical examination. Acute respiratory failure together with profound shock developed a few hours after admission. The patient’s blood pressure was 62/50 mmHg, with a body temperature of 37.5 °C, a heart rate of 130 beats per minute and a respiratory rate approaching 40 per minute. The electrocardiogram demonstrated sinus tachycardia and ST segment depression in precordial leads V4-V6 (Figure 1A). The cardiac markers were elevated (troponin I > 100 ng/ml, creatine phosphokinase-MB 60.3 U/L and creatine phosphokinase 2006 IU/L), with the other hemodynamic data obtained from pulmonary arterial catheter consistent with a cardiogenic shock. To exclude the possibility of acute coronary syndrome, the patient underwent emergency coronary angiography,
which demonstrated a substantially normal study. We placed an intra-aorta balloon pump because of her profound cardiogenic shock. Echocardiography showed a generalized left ventricular (LV) hypokinesia with an ejection fraction of 34%. We weaned her off the intra-aorta balloon pumping 3 days after admission because of improved hemodynamics. Nevertheless, paroxysmal elevation of blood pressure (220/130 mmHg) occurred on day 5. Angiotensin-converting enzyme inhibitor, nitrate, diuretic, β-blocker and calcium channel blocker were given, and her hypertension and pulmonary edema were ameliorated after treatment. She was weaned off ventilator and extubated successfully after 2 weeks of admission. However, the hypertensive crisis recurred.

Figure 1. (A) The 12-lead electrocardiogram on admission shows sinus tachycardia, and ST segment depression over inferior and precordial leads. (B) The abdominal computed tomography reveals one well-defined, ovoid, right adrenal mass, estimated at 2.5 × 3 × 2.5 cm, with inhomogenous strong enhancement (arrow). (C) Microscopically, the sections of adrenal medullar tumor show the feature of pheochromocytoma. The tumor cells have copious cytoplasm with dense eosinophilic staining in alveolar and trabecular patterns. Hyaline globules are occasionally seen (haematoxylin and eosin stain, 200X). (D) The tumor cells are immunoreactive to chromogranin-A staining (200X). (E) The tumor cells are immunoreactive to synaptophysin staining (200X).
which prompted us to consider the possibility of second-
ary hypertension. The laboratory data, including adreno-
corticotropic hormone, aldosterone, plasma renin activ-
ity, cortisol and thyroid profile, were all within normal
limit. Urine catecholamines and metabolites revealed ab-
normally high levels (vanillylmandelic acid [VMA]:
14.5 mg/day [reference 1~7.5]; epinephrine: 311 µg/day
[reference < 22.4]; norepinephrine: 314.4 µg/day [refer-
ence 11~85], dopamine: 215.6 µg/day [reference 50~
450]). Abdominal computed tomography disclosed a 2.5
× 3 × 2.5-cm, well-defined, right adrenal tumor with
inhomogenous strong enhancement (Figure 1B). She un-
derwent right adrenalectomy after a short period of treat-
ment with α-blocker. The histopathology showed the tu-
mor cells were immunoreactive with chromogranin-A,
synaptophysin, neuron-specific enolase, vimentin, and
negative for cytokeratin, supporting the diagnosis of
pheochromocytoma (Figures 1C, D, E). The follow-up
echocardiography showed fair contractility with an EF
of 66% one month after surgery, and the levels of urine
catecholamine had returned to normal (VMA: 3.4
mg/day; epinephrine: 4.6 µg/day; norepinephrine: 45.2
µg/day; dopamine: 248 µg/day).

**Case 2**

A 56-year-old woman, who had had paroxysmal hy-
pertension with palpitation and headache for 2 years,
was incidentally found to have an adrenal tumor by ab-
dominal sonography. All checkups for the secondary hy-
pertension appeared normal except for abnormal 24-hour
urine catecholamines and metabolites (VMA: 11 mg/
day; epinephrine: 36 µg/day; norepinephrine: 36.5 µg/
day; dopamine: 127 µg/day). The abdominal computed
tomography demonstrated a big left adrenal tumor 3 ×
3.5 × 5 cm in size with eccentric necrosis (Figure 2A).
I-131 MIBG adrenal scan was scheduled to further con-
firm the diagnosis and elucidate if there was extra-adre-
nal tumor. However, the patient came to our emergency
department before the time of the scheduled scan with a chief complaint of chest tightness, palpitation, dizziness and nausea. She denied any flu-like symptoms before the admission. The vital signs on admission were blood pressure 162/107 mmHg, heart rate 111 beats/minute, and respiratory rate 18/minute. The chest film exhibited pulmonary congestion, and her electrocardiogram revealed sinus tachycardia and ST depression in precordial leads V4-V6 (Figure 2B). Cardiac markers were elevated (troponin I: > 100 ng/ml; creatine phosphokinase-MB: 78 U/L; creatine phosphokinase: 2205 IU/L). The physical examination was unremarkable except for tachycardia. The bedside echocardiography showed mild but generalized LV hypokinesia, with an ejection fraction of ~45-50%. Emergency coronary angiography was done to exclude the possibility of acute myocardial infarction, but coronary arteries were found normal. The patient’s blood pressure levels fluctuated between 150/70 and 70/40 after admission. We followed up urine catecholamines, and the readings were even higher than before (VMA: 16.4 mg/day; epinephrine 83 μg/day; norepinephrine: 108.8 μg/day; dopamine: 102.8 μg/day). The patient’s blood pressure was maintained by α-blocker. Although surgery was highly recommended, she hesitated and was discharged one week after admission.

**DISCUSSION**

Pheochromocytoma is a rare catecholamine-producing tumor. The vast majority of patients manifest the classical triad: headache (~90%), sweating (60~70%), and palpitation in symptomatic individuals.2,3 Other less common associated symptoms include chest pain, pallor, nausea, vomiting, dyspnea, weight loss, general weakness and visual blurring. The most common sign in clinical practice is sustained or paroxysmal hypertension with occasional orthostatic hypotension, which results from episodic excess catecholamine release (mostly norepinephrine though some are epinephrine).4 Physicians usually suspect the disease because of clinical symptoms and histories, such as refractory hypertension, recurrent hypertensive crisis, family history of multiple endocrine tumor syndrome or onset at young age.

In our cases, both patients presented clinical symptoms and signs mimicking acute coronary syndrome. Acute coronary syndrome is a common but serious disease, and thus should be considered first and excluded immediately. Normal coronary angiography, together with elevation of cardiac makers and abnormal LV wall motion in our patients, suggested acute myocarditis rather than myocardial infarction. Both of our patients denied flu-like symptoms prior to the occurrence of myocarditis, and no known etiology of myocarditis could be identified, suggesting pheochromocytoma was the most likely underlying cause of the myocarditis.

The first case demonstrated a fulminant cardiac presentation (pulmonary edema, cardiogenic shock, hypertensive crisis) as a serious complication of pheochromocytoma. The pathophysiology for catecholamines in the occurrence of acute myocarditis is complex and not well understood. Several mechanisms have been proposed.4,5 For example, increased left ventricular work and hypertrophy contribute to vasoconstriction and hypertension; excess catecholamines could induce direct toxic effect and free radical production, which in turn impair cardiomyocyte structure and contractility. Catecholamine could also cause coronary thickening and spasm, tachycardia or arrhythmia. Finally, chronic myocardial ischemia could result in left ventricular dysfunction and cardiomyopathy. Our two patients didn’t show coronary spasm in angiography, but both of them demonstrated poor LV contractility. Singal et al. reported that catecholamine may inhibit viability of myocytes via cyclic AMP-mediated calcium overload.6 Van Vliet et al. documented 16 instances of catecholamine-induced myocarditis in 26 necropsy cases with pheochromocytoma,7 suggesting that pheochromocytoma-induced myocarditis could be a more common phenomenon than we actually encounter in the clinical setting.

Chromogranin-A is a protein that is stored and secreted along with the catecholamines from the adrenal medulla and the sympathetic nervous system. It may be detected in more than 80 percent of patients with pheochromocytoma but is not a pheochromocytoma-specific protein.8 Synaptophysin, a synaptic vesicle glycoprotein, presents in the membrane of neuronal presynaptic vesicles in the brain, spinal cord, retina, vesicles of the adrenal medulla, neuromuscular junctions, and endocrine cells. It usually acts as a marker for neuroendocrine tumors. Neuron-specific enolase (NSE) is the isoform of enolase, a glycolytic enzyme found in the neural tissue
and neuroendocrine system. Cytokeratins and vimentin are intermediate filaments. The former is found in the intracytoplasmic cytoskeleton of epithelial tissue and the latter attaches to the nucleus, endoplasmic reticulum, and mitochondria. Both were detectable in 29% and 24% of studied pheochromocytomas, respectively. In our case 1, the immunostains were positive for chromogranin-A, synaptophysin, neuron-specific enolase and vimentin, but negative for cytokeratin, a picture compatible with the diagnosis of pheochromocytoma.

Surgical resection is still the treatment of choice to eliminate the malignant myocardial effects from catecholamines secreted by pheochromocytoma. α-blockade is given preoperatively to control the norepinephrine-mediated hypertension. β-blockade combination therapy can be prescribed but never initiated before α-blockade because an unopposed α stimulation may trigger another hypertensive storm. Plouin et al. conducted a study of the largest series of 147 patients with pheochromocytoma undergoing surgery and showed overall mortality and morbidity of 2.4% and 24%, respectively.

In summary, we have presented here two rare cases with pheochromocytoma-induced myocarditis. These case reports remind us that pheochromocytoma is one of the causes of acute myocarditis, especially for those who have a simultaneous blood pressure fluctuation or hypertensive crisis.

REFERENCES