A Patient with Pheochromocytoma Showing Periodic Fluctuations of Blood Pressure and Electrocardiographic Abnormalities Mimicking Acute Coronary Syndrome

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A forty-eight-year-old woman was admitted because of substernal chest pain, profuse diaphoresis, vomiting and palpitation. Electrocardiography suggested acute coronary syndrome. However, the emergency coronary angiographic findings were normal. Periodic fluctuations in her blood pressure raised a clinical suspicion of pheochromocytoma. A subsequent computed tomography scan revealed a single left adrenal mass (8.5×8×6cm). Elevated 24-hour urine levels of vanillylmandelic acid and catecholamines supported the diagnosis of pheochromocytoma. After therapy with adrenergic blockade, a repeat ECG revealed near complete resolution of the ischemic changes. Her symptoms, diabetes and hypertension resolved after a left adrenalectomy. This case illustrates that pheochromocytoma should be included in the differential diagnosis of acute coronary syndrome.

Key words: blood pressure, chest pain, diabetes mellitus, electrocardiography, pheochromocytoma

Case Report

A 48-year-old woman presented at our emergency department because of multiple episodes of substernal chest pain, profuse diaphoresis, vomiting and palpitations for one day. Three years earlier, the patient had been evaluated for mild episodic palpitations, diaphoresis and high blood pressure. The ECG showed a normal sinus rhythm, clockwise rotation and left atrial enlargement (Fig. 1, A). The levels of thyrotropin and thyroxine were normal. Transthoracic echocardiography showed left ventricular hypertrophy with preserved left ventricular function and mild aortic regurgitation. The patient had a history of hypertension, diabetes mellitus, anemia and hypercholesterolemia (total cholesterol 304mg/
dl, triglycerides 212mg/dl) over 3 years. Her medications for hypertension and diabetes consisted of doxazosin, indapamide, glimepiride and metformin.

On physical examination, the patient appeared anxious and diaphoretic. Her blood pressure was 128/66mmHg, the pulse was 120 beats per minutes, the respiratory rate was 20 breaths per minute and the temperature was 37.3°C. There was a grade 2/6 systolic murmur over upper sternal border and apex. The rest of the examination was normal. She was treated with plasma expander for one episode of hypotension (79/56mmHg) and this resulted in a rapid improvement in her blood pressure. The cardiac markers of myocardial damage were

Fig. 1 ECG (A) Three years ago, showing a normal sinus rhythm, clockwise rotation and left atrial enlargement. (B) On arrival at the emergency department, showing a normal sinus rhythm, clockwise rotation, left atrial enlargement and a deep T wave inversion in V2-V6 with a markedly prolonged QT interval
creatinine kinase 317U/l (normal <174U/l); creatine kinase isoenzymes 39ng/ml (normal <6.3ng/ml); and troponin I 0.269ng/ml (normal <0.5ng/ml). Blood creatinine was 1.9 mg/dl, blood urea nitrogen 33.7mg/dl and blood glucose 173mg/dl. The level of electrolytes and her liver function were normal. The white blood cell count was 186200/mm$^3$ and the hemoglobin level was 15.6g/dl. An ECG demonstrated normal sinus rhythm, clockwise rotation, left atrial enlargement and deep T-wave inversion in V2-V6 with a markedly prolonged QT interval (Fig. 1, B). A radiograph of the chest showed mild cardiomegaly and a tortuous thoracic aorta. Bedside transthoracic echocardiography revealed left ventricular hypertrophy, preserved left ventricular function without regional wall motion abnormality and mild aortic, mitral and tricuspid valve insufficiency. The patient was treated with aspirin, clopidogrel and a single dose of heparin 4000U for presumed acute coronary syndrome.

After admission to our intensive care unit, the patient still experienced episodes of chest pain, profuse diaphoresis, palpitation and hypotension. A repeat electrocardiogram revealed an occasional accelerated junctional rhythm with a symmetric giant T wave inversion, markedly prolonged QT interval and ST segment elevation in V2-V3 (Fig. 2, A). Emergency cardiac catheterization was performed because of a suspicion of acute anterior myocardial infarction. The coronary angiographic findings were normal and left ventriculography revealed normal left ventricular function. At the beginning of the procedure, a high blood pressure (237/110mmHg) was recorded and she was treated with one intracoronary injection of 100μg nitroglycerin. Her blood pressure level declined rapidly to as low as 55/40mmHg within few minutes. We then started infusion of dopamine at a dose of 9μg/kg/minute, which was discontinued few minutes later due to high blood pressure that reached 274/137mmHg. During these procedures, the patient’s central blood pressure was found to markedly fluctuate at 8-minute intervals (Fig. 3). The periodic fluctuations in blood pressure raised our clinical suspicion of pheochromocytoma. In view of the history of diuretics therapy, profuse sweating and recent vomiting, the patient was treated with an infusion of normal saline (2 liters a day) based on a clinical suspicion of dehydration.

By the second hospital day, the blood pressure fluctuations had been corrected by fluid repletion. When the test for cardiac markers of myocardial damage were repeated they were: creatine kinase 208U/l, creatine kinase isoenzymes 22.7ng/ml and troponin I 0.162ng/ml. Blood creatinine was 1.2mg/dl and blood urea was nitrogen 26.9mg/dl. The white blood cell count was 10700/mm$^3$ and the hemoglobin (12.7g/dl) had returned to her usual level. The 24-hour urine collection revealed marked elevations in vanillylmandelic acid (81.06mg/day; normal range 1-7.5mg/day), epinephrine (369.9μg/day; normal range 0-22.4μg/day) and norepinephrine (1446.5μg/day; normal range 11.1-85.5μg/day). Subsequently, a computed tomography scan disclosed a single left adrenal mass (8.5×8×6cm), which was enhanced on 18F-flurodeoxyglucose positron emission tomography (18F-FDG PET) without evidence of metastasis.

After one-week of treatment with phenoxybenzamine (20mg twice a day) and bisoprolol (5mg once a day), the patient was asymptomatic. Her blood pressure was 130/80mmHg and her pulse rate 77 beats per minute. In addition, the ECG abnormalities were almost normalized (Fig. 2, B). On her 12th hospital day, the patient underwent an uneventful left adrenalectomy with the histological examination confirming the diagnosis of pheochromocytoma.

One month after the tumor resection, she remained asymptomatic. Her 24-hour urine
Fig. 2 ECG (A) One hour after admission to our intensive care unit, showing an occasional accelerated junctional rhythm with symmetric giant T wave inversion in V2-V6, a markedly prolonged QT interval and a ST segment elevation in V2-V3 suggesting an acute anterior myocardial infarction. (B) After one-week of treatment with phenoxybenzamine and bisoprolol, the ECG abnormalities were almost normalized.

vanillylmandelic acid and catecholamines levels had returned to within the reference ranges. She was normotensive and normoglycemic without medication with a fasting blood glucose level of 90mg/dl and a blood pressure of 115/75mmHg.

Discussion

The diverse ECG abnormalities observed in patients with pheochromocytoma result from excessive adrenergic stimulation of the myocardium by the high plasma catecholamine levels. Although
Fig. 3  The periodic fluctuations in blood pressure during cardiac catheterization

Fig. 4  A computed tomography scan disclosed a single left adrenal mass (8.5×8×6cm) with focal tumor necrosis
several catecholamine-related ECG abnormalities have been described, T wave inversion, lengthening of the QT interval and even ST elevation can be mistaken for those found during acute coronary syndrome\(^{(2-4)}\). Catecholamines, particular norepinephrine, are known to have a toxic effect on the myocardium and this may account for many of the ECG changes commonly reported. In our patient, her symptoms, which consisted of ischemic ECG abnormalities and multiple coronary risk factors suggested acute coronary syndrome, but her coronary angiography demonstrated normal coronary vessels. Excess catecholamines cause functional coronary insufficiency that results in a mismatch of supply and demand for oxygen due to increased afterload (vasoconstriction), catecholamine-driven tachycardia and catecholamine-driven coronary vasospasms. The direct toxic effect and the demand ischemia that are induced by the catecholamines can precipitate myocardial ischemia with concomitant ECG abnormalities even in normal coronary vessels.

In the absence of underlying cardiac disease, the ischemic ECG abnormalities in patients with pheochromocytoma often revert to normal after pharmacological blockade or tumor removal\(^{(2,5)}\). Our finding, together with earlier reports, demonstrated that when there is rapid normalization of the ECG changes after adrenergic blockade this might suggest an early stage of catecholamine toxicity. However, prolonged elevation of serum catecholamines and long-standing arterial hypertension may produce ventricular hypertrophy and chronic ST segment and T wave changes.

A deep symmetric T-wave inversion with prolongation of QT interval is not specific for coronary artery disease. For example, reversible ST-T changes have been observed in patients with subarachnoidal hemorrhage and Takotsubo cardiomyopathy\(^{(6)}\). In these patients, cardiac ischemia appeared to be related to increased and possibly toxic levels of catecholamines, which cause transient wall-motion abnormality (apical ballooning) on echocardiography. However, such abnormalities in wall motion were not observed in our patient.

The patient described in this report exhibited an unusual pattern of periodic alternating hypertension and hypotension. Most patients with pheochromocytoma have paroxysmal or sustained hypertension. Although paroxysmal hypertensive pheochromocytoma is observed in about 50% of patients, such episodes occur at irregular intervals. Patients with pheochromocytoma may also present with hypotension, which may be caused by contracted blood volume, arrhythmias, cardiac damage or loss of vascular tone. In addition, patients with tumors that secrete only epinephrine can present with episodic hypotension. In our patient, the tumor secreted both norepinephrine and epinephrine. The periodic blood pressure changes seen in the present case were distinct and unusual. Oishi et al collected and reviewed 14 cases with similar blood pressure changes\(^{(7)}\). Although the exact mechanism that causes this pattern is not clear, treatment with an alpha-adrenergic antagonist and fluid repletion would seem to be beneficial\(^{(7-10)}\). In view of the history of alpha-adrenergic antagonist therapy and a clinical suspicion of dehydration in our patient, we prescribed an infusion of saline. By the next day, the periodic fluctuations of blood pressure had disappeared following the fluid repletion. Ganguly et al reported a similar response in a 67 year-old man with a pheochromocytoma. In their case, alpha-adrenergic blockade alone did not control the blood pressure fluctuations, which were abolished only after fluid repletion. They described a possible reflex neurogenic mechanism for the cyclic fluctuations in blood pressure, which may be attributable to intravascular volume contraction\(^{(8)}\).

The patient described in this report also
had diabetes mellitus, which resolved after the left adrenalectomy for pheochromocytoma. The development of diabetes associated with pheochromocytoma is assumed to be as a result of increased hepatic gluconeogenesis, insulin resistance and inhibition of peripheral glucose uptake secondary to the high level of catecholamines\textsuperscript{11,12}. Our patient was likely to have harbored the pheochromocytoma for a number of years because her long history of diabetes and hypertension was resolved after tumor removal.

In conclusion, this unusual case demonstrates several catecholamine-mediated cardiovascular manifestations. Although uncommon, we should maintain a high index of suspicion for pheochromocytoma in patients presenting with chest pain, ischemic ECG changes and fluctuating blood pressure despite multiple coronary risk factors. Our report illustrates the importance of including pheochromocytoma in the differential diagnosis of acute coronary syndrome, because high catecholamine levels may cause chest pain and ECG changes that mimic an ischemic episode. Patients with pheochromocytoma must be recognized as soon as possible to allow early and appropriate treatment that will lead to a good prognosis.

References

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一名心電圖異常類似急性冠心症的嗜鉻細胞瘤患者
及其血壓週期性波動

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一名四十八歲的婦女由於胸痛、盜汗、嘔吐和心悸而住院。心電圖顯示有急性冠心症。但是，緊急
冠狀動脈攝影檢查結果正常。血壓週期性波動讓我們臨床懷疑為嗜鉻細胞瘤。隨後電腦斷層掃瞄發現一
顆左腎上腺腫瘤(8.5×8×6公分)。24小時尿液檢查發現vanillylmandelic acid (VMA)和兒茶酚胺過高，進
一步支持了嗜鉻細胞瘤的診斷。經歷交感神經阻斷劑的治療後，再追蹤心電圖，顯示心肌缺氧的異常幾
乎恢復正常。經由左腎上腺切除術以後，患者主訴的症狀，糖尿病和高血壓完全消失。這個病例說明嗜
鉻細胞瘤應該被包含在急性冠心症的鑑別診斷中。

關鍵詞：血壓，胸痛，糖尿病，心電圖，嗜鉻細胞瘤

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