ACUTE CARDIOMYOPATHY WITH CARDIOGENIC SHOCK IN AN ADOLESCENT WITH PHEOCHROMOCYTOMA: A CASE REPORT

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Abstract. Acute cardiomyopathy with cardiogenic shock is a rare complication of pheochromocytoma among adults and even rarer among children. The morbidity and mortality are high among affected patients. We hereby report a 14-year-old boy with pheochromocytoma who developed acute cardiomyopathy with cardiogenic shock despite being on α-adrenergic blockade with adequate blood pressure control. He recovered within 72 hours of an extra-corporeal membrane oxygenation (ECMO) and multiple inotropic drugs. We discussed the possible pathogenesis and highlighted the seriousness of this complication.

Keywords: pheochromocytoma, cardiomyopathy, cardiogenic shock, adolescent

INTRODUCTION

Pheochromocytoma is a rare cause of hypertension in children. The most common symptoms consist of sweating, palpitation and headache due to excess catecholamines (Manger and Eisenhofer, 2004; Pham *et al*, 2006). Once the biochemical diagnosis of pheochromocytoma is demonstrated, computerized tomography (CT) or magnetic resonance imaging (MRI) of the adrenal glands must be performed to localize the tumor (Darr *et al*, 2012). The treatment of choice of pheochromocytoma is surgery. Preoperative administration with an α-adrenergic receptor blocker followed by a β-adrenergic receptor blocker to control blood pressure is mandatory (Pacak, 2007).

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Potential serious complications of pheochromocytoma include hypertensive crisis, shock and arrhythmia. Acute myocarditis with cardiogenic shock has been reported as a rare complication of adult pheochromocytoma (Haas *et al*, 1988; Wu *et al*, 2007; Wu *et al*, 2008; Leite *et al*, 2010). This serious complication is even more unusual among children. This report details the case of a 14-year- old boy with pheochromocytoma who developed acute cardiomyopathy with cardiogenic shock despite preoperative well-controlled blood pressure by prazosin, an α-adrenergic receptor blocker. We discussed the possible pathogenesis and highlighted the seriousness of this complication.

CASE REPORT

A 14-year-old Thai boy presented with repeated episodes of headache without palpitation for two months. On physical examination, severe hypertension (blood pressure > 250/150 mmHg) and tachycardia (heart rate 130 beats/min) were detected. The 24-hour urine fractionated metanephrines revealed markedly elevated

urine normetanephrine of 1,621 µg/day (normal 88-444) and normal urine metanephrine which indicated the presence of pheochromocytoma. Computerized tomography with contrast of the adrenal glands showed a hypervascular tumor, measuring 3.8x4.4 cm, at the right adrenal gland (Fig 1). The diagnosis of pheochromocytoma was made. Because of the high prevalence of genetic mutations associated with multifocal disease among children with pheochromocytoma, some experts recommend that 123I-labeled meta-iodobenzylguanidine (MIBG) scintigraphy should be performed unless otherwise contraindicated (Havekes *et al*, 2009). We therefore scheduled MIBG scintigraphy for the patient. His blood pressure was controlled with a α-adrenergic receptor blocker, prazosin which was gradually titrated up to 20 mg per day. A β-adrenergic receptor blocker should be added to oppose the reflex tachycardia often associated with α-blockade (Darr *et al*, 2012). However, while awaiting for the MIBG to be performed, a β-adrenergic receptor blocker was not started for the patient since it could possibly interfere with the result of the MIBG (Solanki *et al*, 1992). The patient's blood pressure was adequately controlled (BP 95-114/60-83 mmHg). Meanwhile, he had tachycardia with a heart rate of 102-126 / min.

Four weeks later the patient presented with a 6-hour history of acute severe dyspnea and a one-day history of low grade fever and sore throat without chest pain or palpitation. Physical examination revealed a blood pressure of 140/100 mmHg, heart rate of 180/min, bilateral fine crepitation without cardiac murmur and hepatomegaly. A chest X-ray showed acute pulmonary edema and normal heart size. Due to severe respiratory distress, the patient was intubated and transferred to the pediatric intensive care unit. Laboratory evaluation

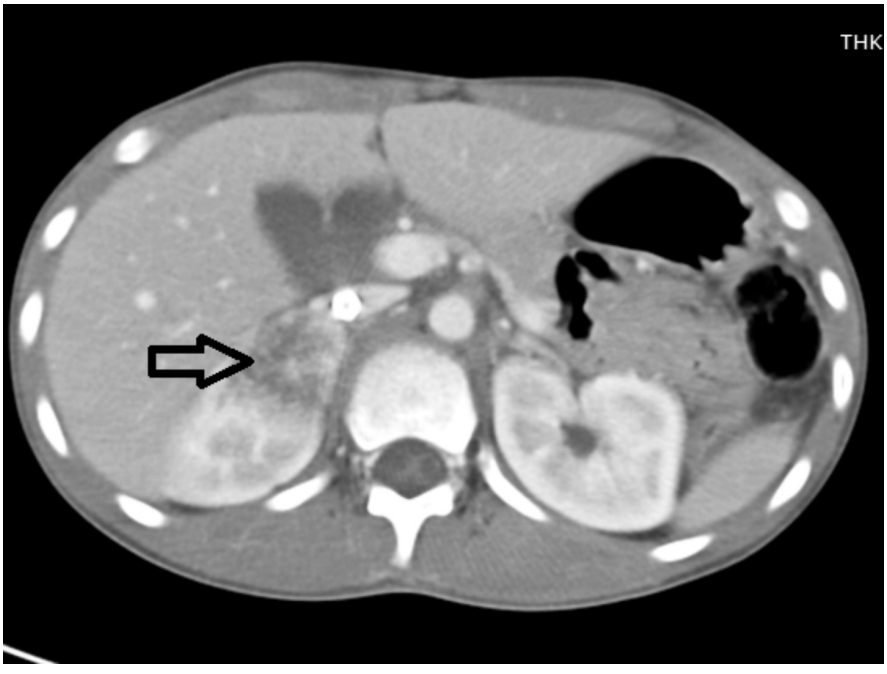

Fig 1- Computerized tomography of the abdomen demonstrated a large well-defined heterogenous enhancing mass (arrow) in the right suprarenal region, measuring 3.8 cm x4.4 cm in size with faint calcification.

showed elevated serum cardiac biomarkers: creatinine kinase-MB 10.73 ng/ml (normal 0-5 ng/ml), cardiac troponin-T 3.05 µmol/l (normal <0.1µmol/l) and N-terminal-pro-B-type natriuretic peptide (NT-proBNP) 16,093 pg/ml (normal 0-160 pg/ml). The electrocardiogram (ECG) showed sinus tachycardia and ST-T elevation in V2-4 (Fig 2) leads. The echocardiogram revealed a global left ventricular (LV) systolic dysfunction, ejection fraction (EF) of 25% with normal coronary artery origins.

Subsequently, the patient developed cardiogenic shock (systolic BP < 70 mmHg) and later cardiac arrest. Aggressive inotropic drugs including dopamine, dobutamine and adrenaline were administered. Thoraco-abdominal CT did not show aortic dissection or acute coronary artery disease. Due to persistent hypotension, an extra-corporeal membrane oxygenation (ECMO), veno-arterial type, was initiated in order to maintain his hemodynamic status.

After 72 hours of ECMO, all inotropic drugs were discontinued since the patient's hemodynamic status was stable. Repeated echocardiogram revealed an improvement of LV systolic function (ejection fraction of 50%). Serum NT-proBNP level decreased to 3,131 pg/ml. ECMO and inotropic drugs were successfully discontinued. Antigens for respiratory syncytial virus, influenza, parainfluenza, enterovirus and adenovirus from nasopharyngeal wash were all negative. Antibodies for mycoplasma, cytomegalovirus and Ebstein-Barr virus in blood were all negative. The final diagnosis of this patient was catecholamine-induced cardiomyopathy associated with pheochromocytoma. Three days after the discontinuation of ECMO and inotropic drugs, right adrenalectomy was performed without any complication. The histology of the tumor was consistent with pheochromocytoma. Ten days after surgery, the patient was discharged from the hospital without any medication.

Up to 59% of children ≤ 18 years old with apparent sporadic pheochromocytoma had identifiable germline mutations (Neumann *et al*, 2002). The hereditary pheochromocytoma syndromes include von Hippel-Lindau (VHL) disease, multiple

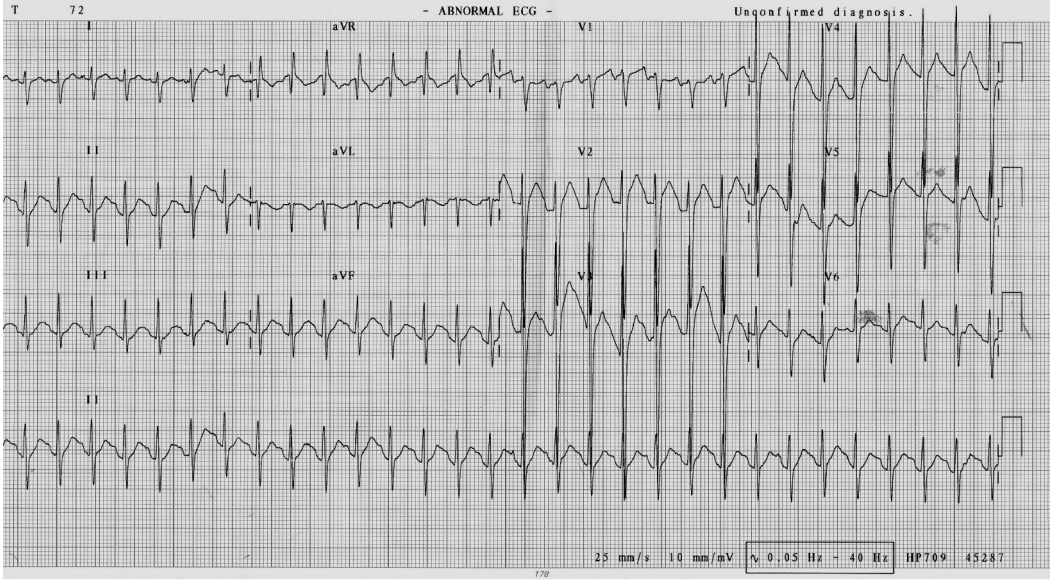

Fig 2- Electrocardiogram demonstrates sinus tachycardia and ST elevation in V2-V4.

endocrine neoplasia (MEN), paraganglioma (PGL) syndrome and neurofibromatosis I (Jimenez *et al*, 2006). The Endocrine Society recommends that all patients with pheochromocytoma should be tested for genetic mutations according to the proposed algorithm (Lenders *et al*, 2014). Since our patient had an adrenal pheochromocytoma with noradrenergic phenotype (elevated urine normetanephrine), we performed the mutation analysis of *VHL* gene and the result was negative. We plan to perform further genetic testings of the subunits D and B of succinate dehydrogenase (*SDHD* and *SDHB*) gene for familial paraganglioma syndrome (PGL1 and PGL4) which could possibly be the cause of noradrenergic adrenal pheochromocytoma in this patient. Patients with pheochromocytoma-associated with MEN usually have predominant elevated urine metanephrine (Jimenez *et al*, 2006). However, we also performed the *RET* proto-oncogene mutation analysis and the result was negative.

DISCUSSION

Acute cardiomyopathy with cardiogenic shock is a rare complication of pheochromocytoma among adults and even rarer among children. The morbidity and mortality are high among affected patients. We demonstrate an adolescent with acute cardiomyopathy and cardiogenic shock associated with pheochromocytoma.

To our knowledge, there have been only two previous reports of cardiomyopathy associated with pheochromocytoma in adolescents. The first patient was an 18- year-old girl with silent pheochromocytoma who presented with severe hypertension and acute heart failure (Nanda *et al*, 1995). The second patient was a 17-year-old boy with silent pheochromocytoma who developed cardiomyopathy while receiving β-adrenergic receptor blockade to control his blood pressure (Von Bergen *et al*, 2009). Different from the previously described patients, our patient developed acute cardiomyopathy with cardiogenic shock while being treated with an α-adrenergic blocker, prazosin with adequate blood pressure control.

Poor myocardial contractility among patients with pheochromocytoma is hypothesized to be associated with catecholamine-induced myocardial injury. However, the mechanisms of this injury have not been well understood. Direct toxicity of norepinephrine, increased oxygen demand and coronary vasoconstriction secondary to increased cathecholamines, increased free radicals and long-standing tachycardia are possible mechanisms of cardiotoxic effects of cathecholamine. (Wu *et al*, 2007). Devaux *et al* (2004) previously described abnormal preoperative transthoracic echocardiography including LV dilatation or dysfunction, LV wall motion abnormalities, LV hypertrophy or valvular abnormalities in 24/63 (38%) patients with pheochromocytoma. Since catecholamine is postulated to be the major cause of cardiomyopathy in patients with pheochromocytoma, surgical removal of pheochromocytoma is the treatment of choice (Manger and Eisenhofer, 2004). Meanwhile, the actual risk factors of developing cardiomyopathy are still unknown.

Cardiomyopathy among adults with pheochromocytoma mostly occurred in those who did not receive any α- or β- adrenergic receptor blockers and those patients present with cardiomyopathy as the initial manifestation of pheochromocytoma. To our knowledge, our patient was the only patient with pheochromocytoma who developed severe cardiomyopathy while being treated with an α- adrenergic receptor blocker.

We hypothesize that an α- adrenergic receptor blocker alone could not totally prevent the effect of catecholamine on myocardial injury. Whether, the reflex tachycardia due to an α- adrenergic receptor blocker without a β- adrenergic receptor blocker partially contributed to acute cardiomyopathy in this particular patient is not known. However, we recommend that a β- adrenergic receptor blocker such as propranolol should be started after α- adrenergic receptor

blockade as soon as the reflex tachycardia occurs in patients with pheochromocytoma.

Patients with acute cardiomyopathy associated with pheochromocytoma can present with a wide spectrum of clinical severity. They often required inotropic drugs with or without mechanical ventilatory support. The recovery period varies from one to ten days (Pham *et al*, 2006; Brukamp *et al*, 2007). Our patient developed very severe acute cardiomyopathy leading to cardiogenic shock. He required mechanical ventilatory support, ECMO and multiple inotropic drugs for three days.

In summary, we demonstrate an adolescent with catecholamine-induced cardiomyopathy associated with pheochromocytoma which required ventilatory support, ECMO and multiple inotropic drugs. This serious complication can occur in children with pheochromocytoma as in adults regardless of blood pressure control and the presence of an α- adrenergic receptor blocker. Therefore, we recommend that the surgical removal of pheochromocytoma should be performed as early as possible once the diagnosis of pheochromocytoma is confirmed and blood pressure control is achieved with both α- and β- adrenergic blockades.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

REFERENCES

Brukamp K, Goral S, Townsend RR, Silvestry FE, Torigian DA. Rapidly reversible cardiogenic shock as a pheochromocytoma presentation. *Am J Med* 2007; 120: e1-2.

Darr R, Lenders JW, Hofbauer LC, Naumann B, Bornstein SR, Eisenhofer G. Pheochromocytoma - update on disease management. *Ther Adv Endocrinol Metab* 2012; 3: 11-26.

Devaux B, Lentschener C, Jude N, *et al*. Predictive value of preoperative transthoracic echocardiography in patients undergoing adrenalectomy for pheochromocytoma. *Acta Anaesthesiol Scand* 2004; 48: 711-5.

Haas GJ, Tzagournis M, Boudoulas H. Pheochromocytoma: catecholamine-mediated electrocardiographic changes mimicking ischemia. *Am Heart J* 1988; 116: 1363-5.

Havekes B, Romijn JA, Eisenhofer G, Adams K, Pacak K. Update on pediatric pheochromocytoma. *Pediatr Nephrol* 2009; 24: 943-50.

Jimenez C, Cote G, Arnold A, Gagel RF. Review: should patients with apparently sporadic pheochromocytomas or paragangliomas be screened for hereditary syndromes? *J Clin Endocrinol Metab* 2006; 91: 2851-8.

Leite LR, Macedo PG, Santos SN, Quaglia L, Mesas CE, De Paola A. Life-threatening cardiac manifestations of pheochromocytoma. *Case Report Med* 2010; 2010: 976120.

Lenders JW, Duh QY, Eisenhofer G, *et al*. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99: 1915-42.

Manger WM, Eisenhofer G. Pheochromocytoma: diagnosis and management update. *Curr Hypertens Rep* 2004; 6: 477-84.

Nanda AS, Feldman A, Liang CS. Acute reversal of pheochromocytoma-induced catecholamine cardiomyopathy. *Clin Cardiol* 1995; 18: 421-3.

Neumann HP, Bausch B, McWhinney SR, *et al*. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002; 346: 1459-66.

Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab* 2007; 92: 4069-79.

Pham TH, Moir C, Thompson GB, *et al*. Pheochromocytoma and paraganglioma in children: a review of medical and surgical management at a tertiary care center. *Pediatrics* 2006; 118: 1109-17.

Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). *Nucl Med Commun* 1992; 13: 513-21.

Von Bergen NH, Lyon JK, Edens RE. Takotsubo-like cardiomyopathy in a 17-year-old male with a pheochromocytoma. *Pediatr Cardiol* 2009; 30: 184-7.

Wu GY, Doshi AA, Haas GJ. Pheochromocytoma induced cardiogenic shock with rapid recovery of ventricular function. *Eur J Heart Fail* 2007; 9: 212-4.

Wu XM, Chen JJ, Wu CK, Lin LY, Tseng CD. Pheochromocytoma presenting as acute myocarditis with cardiogenic shock in two cases. *Intern Med* 2008; 47: 2151-5.