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Pheochromocytoma associated with cyanotic congenital heart disease

Seung Joon Chung, M.D., Young Ah Lee, M.D., Choong Ho Shin, M.D., Sei Won Yang, M.D., Eun Jung Bae, M.D. and Jung Il Noh, M.D.

Department of Pediatrics, College of Medicine, Seoul National University, Seoul, Korea

Pheochromocytoma is a rare tumor of childhood, arising from adrenal medullary and chromaffin tissue. Because chronic hypoxia may induce pheochromocytoma, there have been several reports of pheochromocytoma development in cyanotic patients after corrective or palliative cardiac surgery. The variable clinical presentation of pheochromocytoma is obscured by both underlying heart disease and medications. If sudden hypertension, aggravation of a heart condition, or unusual symptoms such as diabetes mellitus develops in a cyanotic patient with congenital heart disease, pheochromocytoma must be ruled out. We report two patients presenting with cyanotic single-ventricle heart disease with pheochromocytoma. (Korean J Pediatr 2008;51:93-97)

Key Words : Pheochromocytoma, Cyanotic, Hypoxia, Congenital heart defect, Diabetes mellitus

Introduction

Pheochromocytoma is a rare tumor of childhood, arising from adrenal medullary and chromaffin tissue[1]. It occurs sporadically, but in 10% of cases, it is associated with certain familial disorders like von Hippel-Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1. Because chronic hypoxia may induce pheochromocytoma, there have been several reports of pheochromocytoma development in cyanotic patients after corrective or palliative cardiac surgery[2-4].

The clinical presentation of pheochromocytoma is highly variable. Symptoms may be absent or unrecognized. The classic triad of symptoms consists of headache, palpitations, and sweating[1]. Hypertension is observed in 60-70% of adult and pediatric patients[1, 5, 6]. Because the symptoms and signs can be masked by underlying heart disease and medications, pheochromocytoma may be belatedly or incidentally detected.

We report two patients presenting with cyanotic single-ventricle heart disease with pheochromocytoma, one with diabetes mellitus (DM).

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책임저자 : 신충호, 서울대학교 의과대학 소아과학교실
Correspondence : Choong Ho Shin, M.D.
Tel : 02)2072-3357 Fax : 02)743-3455
E-mail : chshinpd@snu.ac.kr

Case Report

Case 1

A 20-year-old woman presented with polydipsia and polyuria of one month's duration. She had a history of palliative surgery at five months and 18 years of age for visceral situs inversus with isolated levocardia, absence of the inferior vena cava, a single ventricle, a single atrium, pulmonary atresia, and aortopulmonary collaterals. She was taking digoxin, carvedilol, and enalapril. Her blood pressure was about 115/75 mmHg and her baseline heart rate was 75 beats per minute. She was diagnosed with type 2 DM: fasting and 2 hour postprandial glucose, 81 and 213 mg/dL, respectively; HbA1c, 16.4%; serum C-peptide, 1.7 ng/mL; insulin antibody, 8%; and glutamic acid decarboxylase antibody, <0.05%. She was treated with insulin injections.

After two months, she presented with chest discomfort, palpitations, facial flushing, hypertension, and frequent epistaxis. Her blood pressure increased to 155/96 mmHg. Her peripheral blood oxygenation level (SpO_2) was 80% by pulse oximetry. Secondary polycythemia was observed (hemoglobin level of 21.8 g/dL). Echocardiography showed mild aortic valvular regurgitation, which was not aggravated relative to previous data. Abdominal computerized tomo-

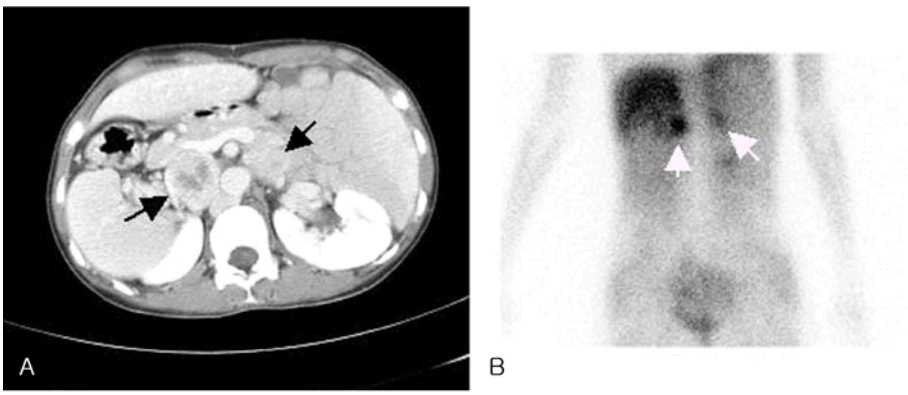

Fig. 1. A) Abdominal CT of patient 1. There was a 3 cm sized necrotic enhanced mass lesion anterior to the right kidney and a about 2.7×2.4 cm sized necrotic enhanced mass lesion anterior to the left renal vessel (filled arrow). B) An MIBG scan of patient 1 showed I-123MIBG accumulated in both adrenal glands at the level of the liver (open arrow).

Table 1. Hemodynamics and Hormones in Case 1

	At diagnosis	Pre-operation	Post-operation
Blood pressure (mmHg)	140/100	120/75	100/60
Baseline heart rate (bpm)	95	85	75
SpO_2 (%)	80	83	83
Urine, metanephrine (mg/day)	3	-	-
Urine, VMA (mg/day)	14.8	7.7	1.2
Urine, epinephrine (μg/day)	17.8	-	-
Urine, norepinephrine (μg/day)	231.9	-	-
Plasma, epinephrine (pg/mL)	-	-	62
Plasma, norepinephrine (pg/mL)	-	-	654
Fasting blood glucose (mg/dL)	285	-	81
HbA1c (%)	16.4	-	7.8

Abbreviations : SpO_2, O_2 saturation; VMA, vanillylmandelic acid Normal references: urine, metanephrine 0.3-0.9 mg/day; urine, VMA 2-7 mg/day; urine, epinephrine 3-38 μg/day; urine, norepinephrine 16-125 μg/day; plasma, epinephrine 0-375 pg/mL; plasma norepinephrine 0-1,050 pg/mL

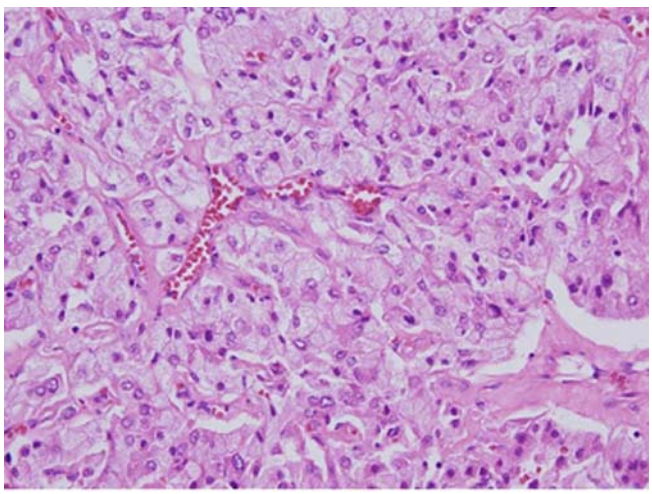

Fig. 2. In patient 1, the tumor cells had prominent nucleoli and basophilic cytoplasm (adrenal gland, hematoxylineosin stain, × 400).

graphy (CT) demonstrated left (2.7×2.4 cm^2) and right (3 cm) adrenal masses, which showed abnormal accumulation of ^{131}I-meta-iodobenzylguanidine (MIBG) on scintigraphy (Fig. 1). The patient's daily urinary vanillylmandelic acid (VMA), norepinephrine, and metanephrine levels were elevated (Table 1). Carvedilol was stopped and phenoxybenzamine therapy was commenced. After two weeks, the patient underwent bilateral adrenalectomy and pheochromocytoma was confirmed by histopathology (Fig. 2). After surgery, her blood pressure normalized without antihypertensive medication. HbA1c was maintained at a moderately elevated level (7.5-7.9%) without insulin or oral antidiabetic medications. After two years of follow-up, her fasting/2 hour postprandial glucose and HbA1c were elevated to 145/413 mg/dL and 12.1% respectively, despite no evidence of tumor recurrence. She was commenced on metformin and insulin.

Case 2

A 13-year-old boy presented with abdominal pain, nausea, and vomiting for five days. He had cyanotic heart disease, with a single ventricle, a single atrium, and bilateral superior venae cavae. The inferior vena cava drained to the hemiazygous vein, and the patient had pulmonary stenosis and a patent ductus arteriosus. He had undergone a fenestrated Fontan operation and bilateral bidirectional cavopulmonary shunts at three years of age, aortic root reconstruction and atrioventricular valve repair when aged nine,

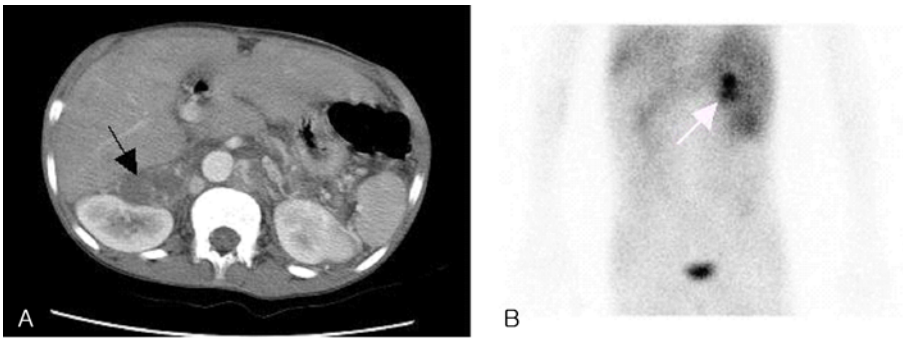

Fig. 3. A) Abdominal CT of patient 2. There was a multiseptate cystic lesion with peripheral-wall enhancement in the anterior aspect of the right kidney (filled arrow). B) An MIBG scan of patient 2 (posterior view) showed abnormal MIBG accumulation adjacent to the right kidney (open arrow).

Table 2. Hemodynamics and Hormones in Case 2

	At diagnosis	Pre-operation	Post-operation	Recur
Blood pressure (mmHg)	90/50	100/50	95/55	
Baseline heart rate (bpm)	65	80	75	
SpO_2 (%)	78	82	80	
Urine, metanephrine (mg/day)	1.3	-	0.032	
Urine, normetanephrine (mg/day)	-	-	0.726	
Urine, VMA (mg/day)	12.9	7.7	4.9	11.6
Plasma, epinephrine (pg/mL)	216	164	<30	<30
Plasma, norepinephrine (pg/mL)	1518	566	673	5939

Abbreviations : SpO_2, O_2 saturation; VMA, vanillylmandelic acid

and a repeated Fontan operation at age 13. He was taking losartan, carvedilol for his atrial fibrillation and premature ventricular complex, and digoxin. His blood pressure was 90/50 mmHg. Pulse oximetry showed an SpO_2 of 78%. Echocardiography showed moderately decreased ventricular function and moderate aortic valvular regurgitation. Abdominal CT scans to investigate his abdominal pain showed multiple gallbladder stones and a multiseptate cystic mass near the right adrenal gland (Fig. 3). He was scheduled for a cholecystectomy and excision of the mass. After the cholecystectomy, manipulation of the adrenal mass caused a sudden increase in his systolic blood pressure to 200 mmHg. The operation was halted and an MIBG scan was performed. This showed an abnormal accumulation of MIBG in the right adrenal gland. The patient's daily urinary VMA and metanephrine levels were elevated (Table 2). He underwent a right adrenalectomy after phenoxybenzamine therapy for two weeks. On postoperative day 1, inotropic-resistant hypotension developed suddenly and his plasma adrenocorticotropic hormone (ACTH) level was increased to 2,990 pg/mL (normal range, 0-60 pg/mL). He was treated with stress-dose hydrocortisone. He was discharged and treated with hydrocortisone and fluorocortisone. After one year, multiple abnormal accumulations of MIBG were observed on a follow-up MIBG scan. A bone scan showed multiple active bone lesions. He underwent a bone biopsy and was eventually diagnosed with malignant pheochromocytoma (Fig. 4). He is scheduled to undergo ^{131}I-MIBG therapy.

Discussion

The incidence of congenital heart disease is 6-10 per 1,000 live births[7, 8]. Single-ventricle syndrome accounts for about 0.4% of instances of congenital heart disease in South Korea[8]. Pheochromocytoma is seen in about 1 per 1,000 people with hypertension[9]. Single-ventricle heart disease and pheochromocytoma are both rare diseases, so any combination of these two diseases is unlikely to be coincidental. There have been several case reports of the combination of congenital heart disease and pheochromocytoma in the United States[3, 10] and Japan[2]. In most of these, clinical manifestations of the tumor appeared at ages above 10 years, which indicates that this tumor is unlikely to be congenital.

An association between hypoxia and peripheral neuro-

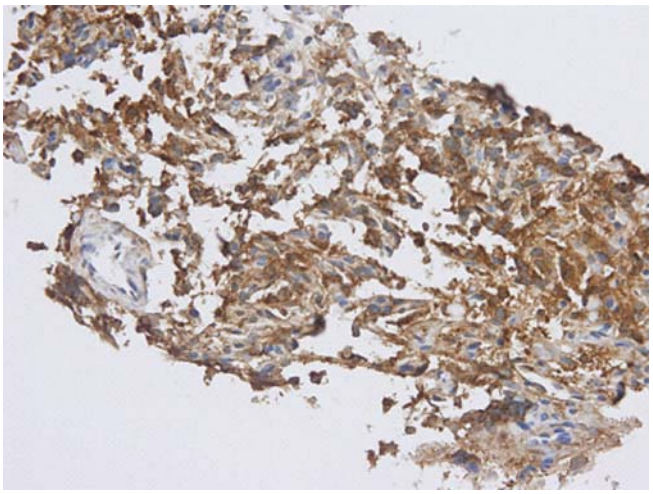

Fig. 4. Tumor cells were positive for chromogranin, with a cytoplasmic granular pattern, the most reliable neuroendocrine marker for pheochromocytoma (bone biopsy, chromogranin stain, ×400).

blastic tumors, including pheochromocytoma, has been reported, suggesting a possible role for hypoxia in tumor induction[4]. And there were some experimental reports of hypoxic state on the rat pheochromocytoma cells (PC12 cells). Glutamate induces neuronal cell damage under hypoxic conditions[11, 12]. In the hypoxic state, expression of the *BCL2* gene is also increased[12-14]. Bcl-2 protein protects rat PC12 cells from the toxic effects of glutamate and apoptosis[12, 14]. In the rat PC12 cell line, hypoxia alters signaling pathways that participate in cell growth and survival[13]. These include the stress- and mitogen-activated pathways, the phosphatidylinositol-3-kinase-Akt pathway, and the expression of the genes for Bcl-2 and protein kinase C[13]. Thus, hypoxia may induce the growth and proliferation of adrenal cells, leading to a tumorous condition. But these reports are only experimental and PC12 cells are not human origin. And cases of this report are not confirmed for changes of signal pathway molecules by laboratory. So the relationship of pheochromocytoma and chronic hypoxic state are currently not obvious.

The clinical presentation of pheochromocytoma is highly variable. Symptoms may be absent or unrecognized. For those patients with symptoms, headache, palpitations, sweating, and hypertension are the classic symptoms[1]. Nausea and vomiting are observed in 30% of pediatric patients[6]. Hypertension is observed in 60-70% of adult and pediatric patients[1, 5, 6]. Approximately 50% of adult patients have sustained hypertension and the other 50% have paroxysmal hypertension[1]. Because some symptoms and signs of pheochromocytoma can be masked by underlying heart disease and medications, pheochromocytoma may be belatedly or incidentally detected. In our second patient, hypertension was not the first symptom of pheochromocytoma and pheochromocytoma was incidentally detected by an abdominal CT performed to investigate abdominal pain. If unexpected or unusual symptoms develop in a patient with congenital heart disease, especially cyanotic disease, pheochromocytoma must be ruled out[2].

Reports of the perioperative management of patients with a single ventricle and pheochromocytoma are rare[15]. There is a risk of uncontrolled vasodilation, with decreased venous return and decreased systemic vascular resistance from a preoperative β-blockade[15]. In these two patients, phenoxybenzamine, a noncompetitive and nonselective long-acting α-blocker, was introduced two weeks before the removal of the pheochromocytoma. The dose was titrated based on blood pressure and oxygen saturation. Carvedilol was discontinued or reduced after the initiation of phenoxybenzamine. Losartan was reduced because case 2 developed hypotension. In this patient, hypertension did not develop with normal activity, but manipulation of the adrenal mass caused a sudden increase in systolic blood pressure. Of patients with pheochromocytomas, 25-30% show no hypertension[1, 6]. There are no clear guidelines for the preoperative preparation of patients with normotensive pheochromocytoma. However, most patients with normotensive pheochromocytoma also develop sudden hypertension during the operation, so preoperative preparation is likely to be needed[16].

Hyperglycemia and impaired glucose tolerance (IGT) are observed in 25-75% of patients with pheochromocytoma[17, 18]. Hyperglycemia and IGT are associated with decreased insulin secretion mediated by α-adrenergic receptors[18, 19] and increased insulin resistance mediated by the activation of β-adrenergic receptors[20]. Diabetes mellitus, especially type 2, is observed in 25% of adult patients with pheochromocytoma[17]. Type 2 DM may be induced by high plasma catecholamine concentrations, and antidiabetic treatments could be stopped after tumor removal[20]. However, in some cases, type 2 DM is not induced but is aggravated by high catecholamine levels, and antidiabetic treatments may be required after tumor removal[20]. We do not know whether high catecholamine levels induced type 2 DM in patient 1. However, the persistence of DM, despite her tumor removal, suggests that type 2 DM may have de-

veloped independently of the pheochromocytoma and was aggravated by the pheochromocytoma in this patient.

In conclusion, the chronic hypoxic state associated with cyanotic heart disease may contribute to the development of pheochromocytoma. The variable clinical presentation of pheochromocytoma is often obscured by underlying heart disease and medications. If sudden hypertension, aggravation of a heart condition, or unusual symptoms such as DM develops in a patient with cyanotic congenital heart disease, pheochromocytoma must be ruled out.

한 글 요 약

청색증형 선천성 심질환에 동반된 갈색세포종

서울대학교 의과대학 소아과학교실

정승준 · 이영아 · 신충호 · 양세원 · 배은정 · 노정일

갈색세포종은 부신 수질과 크롬친화성 조직에서 발생하는 소아기에는 드문 종양이다. 갈색세포종은 저산소증 상태와 연관이 있어, 단심실성 심장질환 수술 후에도 청색증이 지속되는 환자에서 병발하는 경우가 드물게 보고되고 있다. 갈색세포종의 증상이 애매할 뿐만 아니라 심장 질환 또는 치료 약제에 의하여 전형적인 증상들이 나타나지 않을 수 있다. 청색증형 선천성 심질환 환자에서 갑작스런 고혈압, 심장 상태의 악화, 또는 당뇨병 등을 포함한 애매한 증상들이 나타나는 경우에는 갈색세포종을 감별진단하여야 한다. 저자들은 선천성 단심실성 심장질환과 갈색세포종이 동반된 2례를 보고한다.

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