Case Report

Pheochromocytoma complicated by cyanotic congenital heart disease: a case report

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Abstract. Coincidental cyanotic congenital heart disease and pheochromocytoma is uncommon, although some cases have been reported. We describe a girl aged 15 yr and 11 mo with pheochromocytoma and tricuspid atresia treated by performing the Fontan surgery. The patient did not have any specific symptoms of syndrome related to pheochromocytoma or a family history of pheochromocytoma. During cardiac catheterization, her blood pressure increased markedly, and an α-blocker was administered. Catecholamine hypersecretion was observed in the blood and urine, and abdominal computed tomography revealed a tumor in the right adrenal gland. Scintigraphy showed marked accumulation of 123I-metaiodobenzylguanidine in the tumor, which led to a diagnosis of pheochromocytoma. We did not detect any germline mutations in the RET, VHL, SDHB, SDHD, TMEM127, or MAX genes. This patient had experienced mild systemic hypoxia since birth, which may have contributed to the development of pheochromocytoma.

Key words: pheochromocytoma, cyanotic congenital heart disease, hypoxia-inducible factor, hypoxia

Introduction

In the pediatric population, the reported incidence of pheochromocytoma (PHEO) is as high as 0.3 per million per year (1). Most cases are sporadic, and according to Waguespack et al., 56% of patients with sporadic PHEO who are less than 18 yr of age have germline DNA mutations (1). Genes thought to be associated with PHEOs include the RET proto-oncogene, VHL (von Hippel-Lindau), NF1 (neurofibromin 1), SDHB (succinate dehydrogenase complex subunit B), SDHD (succinate dehydrogenase complex subunit D), SDHAF2 (succinate dehydrogenase complex assembly factor 2), TMEM127 (transmembrane protein 127), Max (Myc-associated factor X), PHD2 (prolyl
hydroxylase 2), *H-RAS* (Harvey rat sarcoma viral oncogene), and *HIF2A* (hypoxia-inducible factor 2α) (2, 3).

Hypoxia may be a risk factor for PHEO along with genetic abnormalities. Because the protein products of *VHL* and *SDH* mediate the cellular response to hypoxia by activating the hypoxia-inducible factor (HIF) signaling pathway, a pseudohypoxic mechanism may underlie PHEO (the pseudohypoxia hypothesis) (2, 4). The MAPK (mitogen-activated protein kinase) and mTOR (mammalian target of rapamycin) signaling pathways have also been implicated in the development of PHEO (2, 4).

Although the direct relationship between systemic hypoxia and PHEO development is unclear, several cases of PHEO in patients with cyanotic congenital heart disease (CCHD) have been reported (5–16). According to a recent estimate, patients with CCHD have a greater risk of developing PHEO or paraganglioma (odds ratio: 6.0) than do those with non-cyanotic congenital heart disease (odds ratio: 0.9) (17). In addition, an epidemiologic study reported a relatively high incidence of PHEO in people living at high altitudes (18). These findings link CCHD and hypoxia with PHEO. Here, we present a case of PHEO and tricuspid atresia (TA) that was treated by performing the Fontan surgery and that supports a relationship between PHEO and systemic hypoxia.

**Case Report**

The patient was a girl 15 yr and 11 mo of age. Cyanosis was noted 8 h after her birth, at which point her percutaneous oxygen saturation (SpO₂) level was 80%. Type Ic TA was diagnosed via echocardiography. Palliative surgery (the hemi-Fontan surgery and pulmonary artery banding) was performed at Osaka University Hospital when she was 9 mo of age, but the SpO₂ level remained around 80%. Functional repair (a modified Fontan surgery) was performed at 2 yr of age, and the SpO₂ level improved to 90–94%. At 3 yr of age, sick sinus syndrome was additionally diagnosed, and a pacemaker was implanted. Thereafter, venovenous shunts gradually developed from the hepatic and innominate veins to the pulmonary vein, and the SpO₂ level was 80–90% at 10 yr and 7 mo of age. Coil embolization of the venovenous shunts was performed twice, at 10 yr and 10 mo of age and 12 yr and 10 mo of age, and the SpO₂ level subsequently improved to 90–94%.

At 15 yr of age, paroxysmal sweating, dizziness, and transient hypertension (systolic blood pressure: 180 mmHg) were noted. Examinations showed normal thyroid function, normal plasma renin activity, a normal plasma aldosterone level, and a slightly elevated level of total plasma catecholamines (2.1 ng/mL, normal range: 0.15–0.74 ng/mL). We initiated β-blocker therapy (carvedilol) to control hypertension at that time.

The patient was admitted to Osaka University Hospital for further evaluation at the age of 15 yr and 11 mo. There was no family history of PHEO. On examination, her height was 161 cm, weight was 56 kg, blood pressure was 122/62 mmHg, pulse rate was 84 beats/min, and SpO₂ level was 90% (room air). Secondary polycythemia was not detected (hemoglobin level: 13.2 g/dL). During cardiac catheterization and contrast angiography, her blood pressure transiently increased to 180/106 mmHg. Therefore, these procedures were discontinued, and she received continuous infusion of the α-blocker phentolamine mesylate (Regitine®). Laboratory tests performed after cardiac catheterization revealed a highly elevated level of total plasma catecholamines (8.0 ng/mL). Seven days after cardiac catheterization, the catecholamine levels were as follows: fasting total plasma catecholamines, 2.6 ng/mL (normal range: 0.15–0.74 ng/mL), noradrenaline (NA), 2.6 ng/mL (normal range: 0.15–0.74 ng/mL), urinary noradrenaline, 1092 µg/day (normal range: 29–120 µg/day), and urinary normetanephrine (NM), 3.57 mg/day (normal range: 0.07–0.26 mg/
Pheochromocytoma with heart disease

These data suggested hypersecretion of catecholamines. Abdominal computed tomography revealed a tumor 3.8 cm in diameter in the right adrenal gland (Fig. 1). Because scintigraphy showed marked accumulation of $^{123}$I-metaiodobenzylguanidine in the mass (Fig. 1), we diagnosed PHEO. To reduce systemic vascular resistance and maintain an appropriate circulating blood volume in preparation for surgery, we gradually terminated $\beta$-blocker therapy (carvedilol) and began $\alpha$-blocker (doxazosin) therapy. Total right adrenalectomy was performed after $\alpha$-blocker pretreatment on the 56th day after admission. Her pulse rate before surgery was 60–65 beats/min. After resection of the tumor, her blood pressure decreased to 60 mmHg, and the pulse rate increased transiently to 70 beats/min before returning to 63–64 beats/min. We discontinued $\alpha$-blocker administration on the second postoperative day. After the surgery, catecholamine hypersecretion had ceased, and the blood NA and urinary NM levels were 0.13 ng/mL and 0.12 mg/day, respectively. Her pulse rate was 60 beats/min on the 80th day after admission, and she was discharged from the hospital on the 81st day (Fig. 2).

Histological examination of the resected mass showed numerous clear white tumor cells with alveolar structures and abundant blood vessels. The Pheochromocytoma of the Adrenal Gland Scaled Score is used to distinguish benign versus malignant neoplasms, and the maximum score is 20 (Appendix). The tumor may be benign if the score is below 4 (19). The score of our patient’s tumor was 0, suggesting that it was benign (Fig. 3). After informed consent was obtained, genetic testing was performed to detect germline mutations in the $RET$, $VHL$, $SDHB$, $SDHD$, $TMEM127$, and $MAX$ genes via polymerase chain reaction and direct sequencing. No mutations were found. Unfortunately, we did not examine mutations in the DNA of the tumor cells.

Discussion

We presented a case of PHEO and TA treated by performing the Fontan surgery. In patients who undergo this procedure, venovenous shunts develop in response to the elevated systemic venous pressure and carry blood from the systemic veins to the pulmonary veins via remnant fetal vessels. The $SpO_2$ level is normally above 90% (20), and the subnormal level in our patient indicated hypoxia due to CCHD and the
Fig. 2. Clinical course, blood pressure, and administration of carvedilol and doxazosin. After diagnosis of pheochromocytoma, β-blocker (carvedilol) therapy was discontinued, and an α-blocker (doxazosin) therapy was initiated, with gradual increases in the dose until surgery. Blood pressure was well controlled. uNM: urinary normetanephrine (mg/day), sNA: serum noradrenaline (ng/mL).

Fig. 3. Histology of the resected pheochromocytoma. (a) Hematoxylin-eosin (HE) staining (low power view). (b) HE staining (high power view): There are numerous clear white tumor cells and alveolar structures with abundant blood vessels. The Pheochromocytoma of the Adrenal Gland Scaled Score was 0. (c) Immunohistochemistry for chromogranin A: The brown staining indicates expression of chromogranin A in the tumor cells.
presence of venovenous shunts. Systemic hypoxia has been linked to PHEO by data showing a higher frequency of PHEO in patients living at high compared with low altitudes (18). Although our patient did not live in a high-altitude area, she had experienced systemic hypoxia since birth owing to CCHD. We searched for previous reports of patients with both CCHD and PHEO and identified 17 such patients (Table 1) (5–16). The mean age of these patients at the time of diagnosis of PHEO was 24.1 yr, which was younger than the mean age (40 yr) of patients with PHEO without other diseases (21). This difference suggests that systemic hypoxia promotes the development of PHEO in younger patients. Although the relationship between CCHD and PHEO remains controversial, our findings suggest a positive association.

Various genes, including RET, VHL, NF1, SDHB, SDHD, TMEM127, MAX and HIF2A, are thought to be associated with PHEO, and most of these genes can be divided into two clusters. The genes in cluster 1 (VHL, SDHB, SDHD, and HIF2A) encode proteins that mediate oxygen-independent stabilization of HIF, while the genes in cluster 2 (RET, NF1, TMEM127, and MAX) encode proteins associated with receptor tyrosine kinase signaling (22). The HIF pathway is a downstream target of proteins encoded by genes in both clusters (22), and the blood level of HIF1α is high in patients with CCHD (23). Although we did not measure HIF1α levels in our patient, it is possible that hypoxia promoted the development of PHEO via the HIF1α pathway.

Our case may have clinical significance for pediatricians. Diagnosing PHEO was difficult for two reasons: 1) PHEO was not immediately considered when our patient developed...
paroxysmal sweating and dizziness because she also had CCHD, and 2) paroxysmal hypertension occurs in only 7% of young patients with PHEO, and thus, is uncommon (24). Although PHEO is rare in children, we need to carefully consider its possible occurrence in patients with CCHD. When hypertension is observed in children with CCHD, catecholamine levels should be examined before cardiac catheterization.

Appendix

Pheochromocytoma of the Adrenal Gland

Scaled Scores are based on 12 criteria as follows: large nests or diffuse growth, 2 points; central (middle of the large nests) or confluent tumor necrosis, 2 points; high cellularity, 2 points; cellular monotony, 2 points; tumor cell spindling, 2 points; > 3 mitotic figures/10 high power fields, 2 points; atypical mitotic figure(s), 2 points; extension into adipose tissue, 2 points; vascular invasion, 1 point; capsular invasion, 1 point; profound nuclear pleomorphism, 1 point; and nuclear hyperchromasia, 1 point. The maximum score is 20.

References


