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Pheochromocytoma and paraganglioma in Fontan patients: Common more than expected

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Abstract

Objective: Pheochromocytoma and paraganglioma (extra-adrenal pheochromocytoma) are rare neuroendocrine tumors that arise from the neuroendocrine cells. Chronic hypoxia is known as a possible cause, and a strong link between cyanotic congenital heart disease and these tumors has been reported. However, reports of phechromocytoma/paraganglioma in Fontan patients were scarce. We herein report seven cases of phechromocytoma/paraganglioma after Fontan operation at a single tertiary center.

Methods: We retrospectively reviewed medical records and imaging studies who diagnosed as phechromocytoma/paraganglioma after Fontan operation in Seoul National University Children's Hospital.

Results: Seven patients were identified during follow-up after Fontan operation, and the prevalence was 2.5% among Fontan patients greater than 10 years old on active follow-up. Three patients were diagnosed as phechromocytoma and 4 patients as paraganglioma. Median time interval between Fontan operation and diagnosis of pheochromocytoma/paraganglioma was 21.4 years (range, 10.4–29.7 years). Resting percutaneous oxygen saturation varied from 77% to 94%. All patients underwent complete tumor resection. Phechromocytoma recurred in two patients, of whom one patient died at the age of 18 years due to the tumor progression with multiple metastasis and aggravation of heart failure with profound cyanosis. Pheochromocytoma/paraganglioma developed after hepatocellular carcinoma in two patients.

Conclusion: Phechromocytoma/paraganglioma could occur in Fontan patients more than expected. Because it is curable by tumor resection during its early phase, early diagnosis and treatment of pheochromocytoma are crucial in Fontan patients not to make hemodynamic deterioration and aggravation of heart failure.

KEYWORDS

cyanosis, Fontan procedure, heart diseases, pheochromocytoma

1 | INTRODUCTION

Pheochromocytoma (PHEO) and paragangliomas (PGL) (extra-adrenal pheochromocytoma) are rare neuroendocrine tumors, with known incidence of 0.2%–0.6% in patients with hypertension in the general population and 0.6% in children with hypertension.[1,2] PHEO or PGL is a catecholamine-producing tumor that arises from sympathetic lineage–derived cells of the adrenal medulla or the extra-adrenal paraganglia.[3] Cyanotic congenital heart disease (CHD) was speculated to be associated with PHEO/PGL because of case reports of PHEO/PGL that developed in relatively young patients with cyanotic CHD.[4–7] Opotowsky et al recently reported that patients with cyanotic CHD had

increased odds ratio (6.0; confidence interval, 2.6–13.7; $P < 0.0001$) for PHEO/PGL development compared with those without cyanotic CHD in a multicenter case series.[8]

Fontan circulation is completed by separating the pulmonary circulation from the systemic circulation, and cyanosis is resolved or, at the very least, greatly reduced compared to the pre-Fontan status. However, pulmonary arteriovenous fistula, veno-venous collaterals draining to the systemic atrium or pulmonary vein, and Fontan fenestration cause chronic cyanosis with variable severity. Until now, there were only few reports of PHEO/PGL development in Fontan patients. We investigated the clinical manifestations and treatment of PHEO or PGL occurred after Fontan operation in a single tertiary referral hospital.

2 | SUBJECTS AND METHODS

We retrospectively identified Fontan patients diagnosed with PHEO or PGL who had been followed up at Seoul National University Children's Hospital between 1982 and May 2017, and reviewed their medical records, imaging studies including echocardiography, computed tomography (CT) and pathologic findings. Evaluation of excessive catecholamine production included 24-hour urinary catecholamaines (epinephrine, norepinephrine and dopamine), urinary metanephrines (normetanephrine and metanephrine), urinary vanillylmandelic acid, plasma catecholamines and serum metanephrine and normetanephrine by liquid chromatography-mass spectrometry. The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number H-1701-116-827) and patient's consent was waived because of retrospective study nature.

3 | RESULTS

Currently, 283 Fontan patients older than 10 years have been followed up at the Seoul National University Children's Hospital. Among them, three patients were diagnosed as PHEO and four patients diagnosed as PGL (incidence, 2.5%). Patients' clinical characteristics of these seven patients (four males) were presented in Table 1. Median age at diagnosis was 24.3 years (range, 13.7–38.5 years), and median time interval between Fontan operation and diagnosis of PHEO/PGL was 21.4 years (range, 10.4–29.7 years).

3.1 | Patient characteristics

The patients had mild resting cyanosis with mild polycythemia (hematocrit, 40%–54%), except for Patient 1 with severe cyanosis (percutaneous oxygen saturation; 61–77%). Five patients (Patients 3, 4, 5, 6, and 7) had resting percutaneous oxygen saturation (SpO_2) of 85%–90%, and Patient 2 had resting SpO_2 of 94%. However, during exercise, SpO_2 decreased to 83% in Patient 2, to 88% in Patient 3, to 78% in Patient 4, to 70% in Patient 5, and to 83% in Patient 6. The duration of cyanosis with less than 85% of percutaneous saturation was variable from 15 months (Patient 5) to 13 years (Patient 1). Catheterization data was available in three patients. All showed low cardiac index.

The presenting symptoms leading to a diagnosis of PHEO/PGL were variable: hypertension in two patients, palpitation, headache, and sweating in two patients, and incidental detection by CT scan for other reasons in three patients. Patients 3 and 4 had paroxysmal hypertension on 24-hour blood pressure monitoring, and Patient 6 had sustained hypertension without any other symptoms. PHEO/PGL was diagnosed using CT between 6 months and 1 year after symptom presentation. Patient 2 had palpitation, dizziness, and four episodes of syncope in 1 year, mainly while standing for a long time or when standing up from a sitting posture, suggesting vasovagal syncope. Her blood pressure was normal, but her average heart rate was 120 beats per minute and paroxysmal tachycardia was present on 24-hour Holter monitoring; thus, she was admitted for workup of tachyarrhythmia. Abdominal CT scan showed a 3.3-cm diameter of heterogeneously enhancing mass abutted to the left adrenal gland, which was 1.8 cm diameter on CT performed 14 months earlier, when the adrenal mass was not the focus of the examination.

Five of seven patients had ventricular dysfunction and three patients had moderate atrioventricular regurgitation at diagnosis of PHEO or PGL; the ventricular function and valvular regurgitation improved after PHEO/PGL resection in three patients. Patient 4 had cardiogenic shock due to persistent tachycardia and ventricular dysfunction with moderate atrioventricular regurgitation resulting from long-standing junctional tachycardia. After PHEO resection, atrioventricular regurgitation and ventricular dysfunction improved in this patient.

3.2 | Diagnosis and treatment

If PHEO/PGL was suspected, plasma and 24-hour urine catecholamine levels were examined, and abdominal CT scan and ^{123}I MIBG scan or ^{68}Ga-DOPA-TOC PET were performed. An adrenal or abdominal mass in abdominal CT was well correlated with increased ^{123}I MIBG uptake or increased ^{68}Ga-DOPA-TOC uptake by PET. The urine normetanephrine level was markedly elevated in all patients, and the serum norepinephrine level was significantly elevated in six patients (Table 2).

In this study, none of the patients had syndromic face or familial history of PHEO/PGL. Genetic testing was performed in only two patients, but there were no genetic mutations associated with PHEO/PGL-related genes such as RET, *NF1*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *VHL*, and *MAX*.

In all patients, complete tumor resection was performed upon diagnosis based on imaging and biochemical laboratory findings, and PHEO/PGL was confirmed at pathology (Figure 1). All patients had took an α-blocker (phenoxybenzamine, doxazocin, or terazocin) for 2 weeks before tumor resection, and all procedures were uneventful. Five patients were cured after tumor resection without recurrence for median 0.4 years (range, 0.1–6.6 years) of follow-up. Two patients (Patients 1 and 3) had PHEO recurrence. In five of seven patients, inotropes such as dopamine or norepinephrine, which were used during operation and tapered off on the day of operation. Both Patients 1 and 3 needed inotropes for several days. Patient 1

TABLE 1 Clinical characteristics of Fontan patients with PHEO/PGL

No	Underlying disease	Fontan type	Age at Dx	Symptom and sign at Dx	HTN	Resting SpO2 (%)	Cyanosis duration*	CVP (mmHg) /C.I.**	Comorbidity	Diagnosis	Result
1	Left isomerism, uAVSD, RV type fSV	3.3y fenestrated LT	13/M	Incidentally detected by CT	No	61–77	13 y	24/2.0	Massive PAF	Malignant PHEO	Death
2	Tricuspid atresia	13d PA banding 1y BCPC, 8y ECC	16/F	Palpitation, syncope, headache	No	90	8 y	–		PHEO	No recur for 4 months
3	Tricuspid atresia	14m LMBT shunt 2.9y APC, 17y ECC conversion	25/M	Incidentally detected by CT	pHTN	87–91	2.9 y	–	HCC, PLE	PHEO	Recur in 3 years
4	Right isomerism, uAVSD, RV type fSV, TAPVR	10m BCPC 3y fenestrated LT	18/M	Palpitation, sweating, JT	pHTN	90–92	3 y	19/1.3	PAF	Bilateral PGL	No recur for 6.5 years
5	Left isomerism, DORV	15m LT	25/M	Palpitation, AF	No	88	15m	8/2.5		Left PGL	No recur for 15 months
6	Situs inversus, uAVSD, RV type fSV	7.8y APC	35/M	no symptom	HTN	94	7.8 y	–		Left PGL	No recur for 2 months
7	Tricuspid atresia	8.8y APC, 25y ECC conversion	38/F	Palpitation, headache, sweating	pHTN	88–90	8.8 y	–	HCC	Right PGL	Recent Dx

*Cyanosis duration was defined as the period with less than 85% of percutaneous saturation.
**Cardiac index (L/min/m^2).
Abbreviations: APC, atriopulmonary connection Fontan; BCPC, bidirectional cavopulmonary connection; BP, blood pressure; C.I., cardiac index; CVP, central venous pressure; DORV, double outlet of right ventricle; Dx, diagnosis; ECC, extracardiac conduit Fontan; fSV, functional single ventricle; HCC, hepatocellular carcinoma; HTN, hypertension; LMBT, left modified Blalock-Taussig shunt; LT, lateral tunnel Fontan; JT, junctional tachycardia; PAF, pulmonary arteriovenous fistula; PGL, paraganglioma; PHEO, pheochromocytoma; pHTN, paroxysmal hypertension; PLE, protein losing enteropathy; RV, right ventricle; TAPVR, total anomalous pulmonary venous return; uAVSD, unbalanced atrioventricular septal defect;.

TABLE 2 Biochemical laboratory findings

	Serum or Plasma					Urine					
Patient	NE	NM	Epi	Meta	DOPA	NE	NM	Epi	Meta	DOPA	VMA/Cr
1	>X2	.	>X2	.	>X1	> X1	>X7	N	N	>X1	>X5
2	>X3	>X2	N	N	N	N	>X4	N	.	N	>X1
3	>X6	.	N	.	N	>X3	>X15	>X1	N	N	>X2
4	>X5	.	N	.	N	>X1	>X9	N	N	N	>X1
5	N	.	N	N	N	N	>X5	N	.	N	N
6	>X2	>X3	N	N	N	N	>X4	N	N	N	N
7	>X1	>X1	N	N	N	>X3	>X1	N	N	N	N

>x number indicate (number-number + 1) X the upper limit of the reference range.
Abbreviations: Epi, epinephrine; DOPA, dopamine; Meta, metanephrine; N, normal; NE, norepinephrine; NM, normetanephrine; VMA/Cr, vanillyl mandelic acid/creatinine ratio.
Reference range; serum or plasma dopamine 0–30pg/ml, epinephrine 0–110 pg/ml, metanephrine 90–930pg/ml, norepinephrine 70–750pg/ml, normetanephrine 100–2300pg/ml, urine (24 hours), dopamine 65–400 ug/d, epinephrine 0–20 ug/d, metanephrine 52–341ug/d, norepinephrine 15–80ug/d, normetanephrine 88–444ug/d.

needed hydrocortisone after PHEO resection because of adrenal insufficiency with elevated serum adrenocorticotrophic hormone and decreased serum cortisol.

3.3 | Cases with complicated disease course

Patient 1 was diagnosed with left isomerism, inferior vena cava interruption with hemiazygous continuation, bilateral superior vena cava,

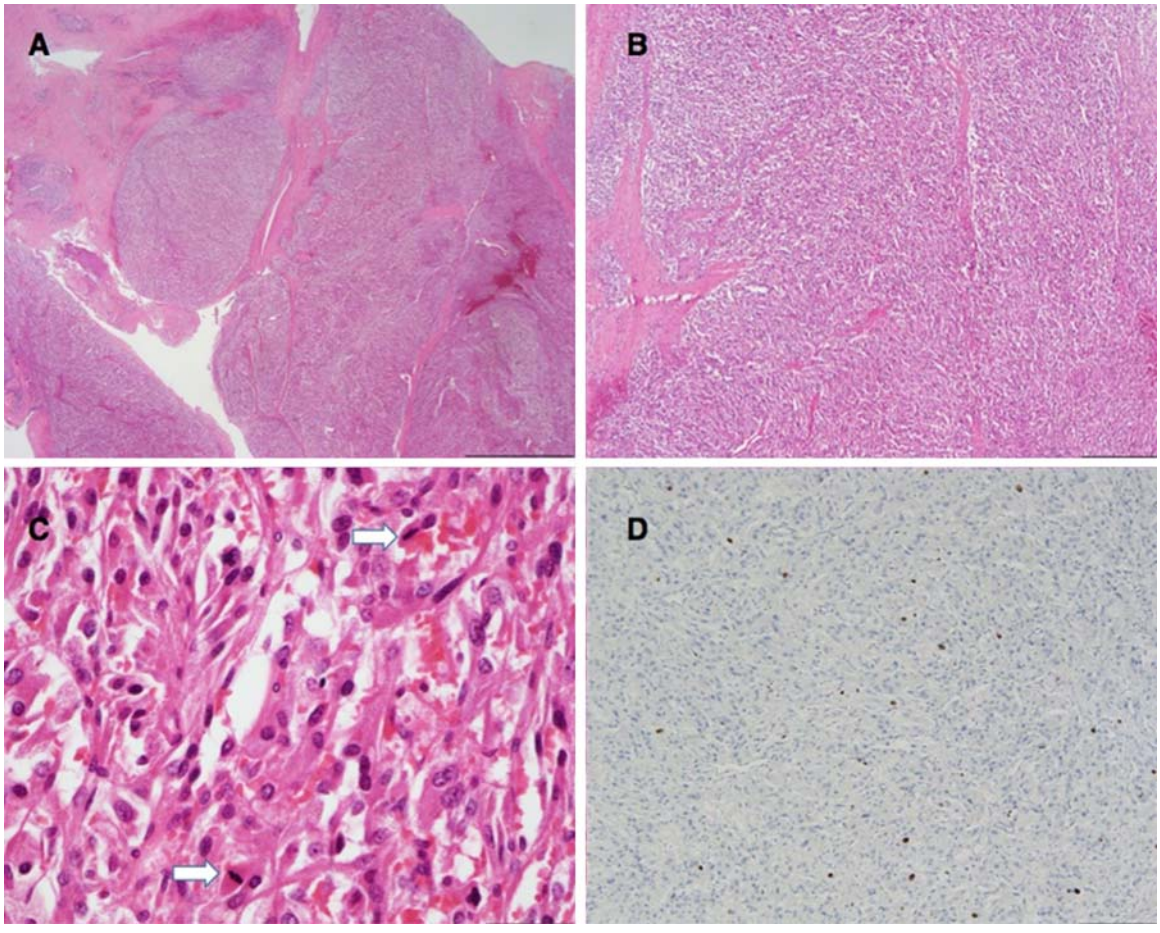

FIGURE 1 Pathologic findings of recurred pheochromocytoma in Patient 3. (A) Recurred pheochromocytoma with invasive features to adjacent soft tissues. HE staining, X10. (B) Diffuse growth pattern and tumor cell spindling. HE staining, X40. (C) Two mitotic figures (arrows) in one high power field: increased mitotic activity. HE staining, X400. (D) 4% of Ki-67 positive rate in Ki-67 immunohistochemistry

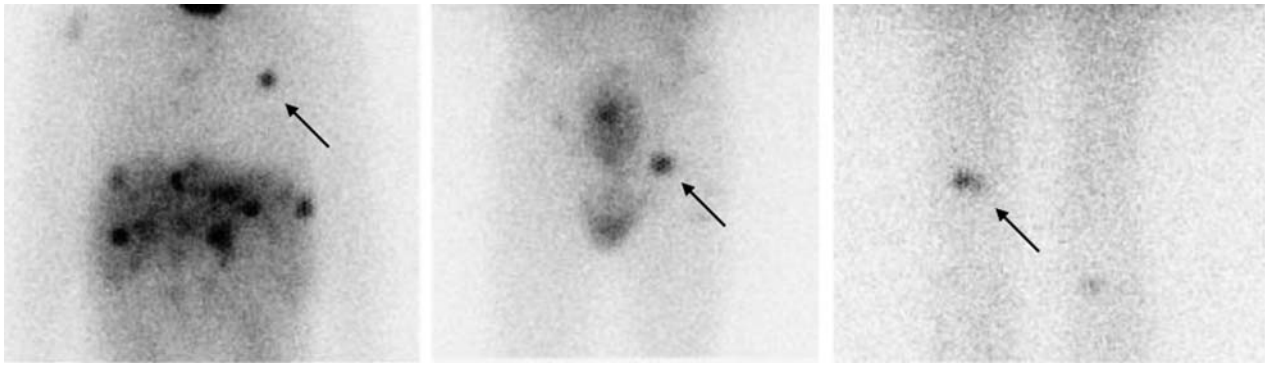

FIGURE 2 MIBG scintigraphy of Patient 1 revealed multiple metastasis of pheochromocytoma; liver and bone (arrows; rib, acetabulum, and right distal femur)

functional single ventricle (right ventricle type) with atrioventricular septal defect and underwent fenestrated lateral tunnel Fontan operation at 3.3 years old. Moderate cyanosis (SpO_2 70%–80%) was persistent due to large venous collaterals from the left hepatic vein to the systemic atrium and pulmonary arteriovenous fistula after Fontan operation. Atrioventricular valvuloplasty, ascending aorta reduction plasty, and ligation of the collateral were performed at 9 years old. However, cyanosis persisted due to a significant left pulmonary arteriovenous fistula because hepatic vein flow preferentially directed to the right pulmonary artery via Fontan pathway and azygous vein flow mainly directed to the left superior vena cava and left pulmonary arteries. His arterial oxygen saturation was 71%. At 13 years old, direct connection between inferior vena cava and Fontan pathway with Gore-Tex graft was established. Nine months later, a juxta-adrenal mass was detected on CT scan when he presented to the emergency room because of abdominal pain. He had neither palpitation nor hypertension. On echocardiography, moderate ventricular dysfunction and atrioventricular valvular regurgitation were noted. For the evaluation of the juxta-adrenal mass, blood and urine catecholamine level test and MIBG scan were performed. Urinary normetanephrine level was markedly elevated (Table 2), and MIBG scan demonstrated increased MIBG uptake around right adrenal gland. Right adrenalectomy was performed uneventfully and PHEO was confirmed pathologically. However, 2 years after surgery, ^{131}I MIBG scan revealed multiple bone and liver metastases (Figure 2). He underwent MIBG therapy for malignant PHEO, but the metastasis and tumor growth progressed with aggravation of heart failure and profound cyanosis. He died at the age of 18 years old.

Patient 3 was born with tricuspid atresia and underwent atriopulmonary connection Fontan operation at 2.9 years old. He was diagnosed as hepatocellular carcinoma (HCC) at the age of 19 years (16 years after Fontan operation). He has undergone several times of transarterial chemoembolizations because of recurrence of HCC. Follow-up abdominal CT for HCC at 25 years showed a right adrenal mass. A review of the previous CT scan showed that right adrenal mass was present one year ago and had increased from 3.5 to 5 cm diameter with newly noted internal low attenuation, suggesting necrosis (Figure 3). When questioned about symptoms, the patient mentioned that he had experienced paroxysmal palpitation, facial flush, and diaphoresis for 6 months. Catecholamine level of blood and urine was elevated (Table 2) and PHEO was strongly suspected. Right adrenalectomy was performed and PHEO was confirmed on pathology. When the patient was 28 years old, PHEO recurred in the previous operation site, and

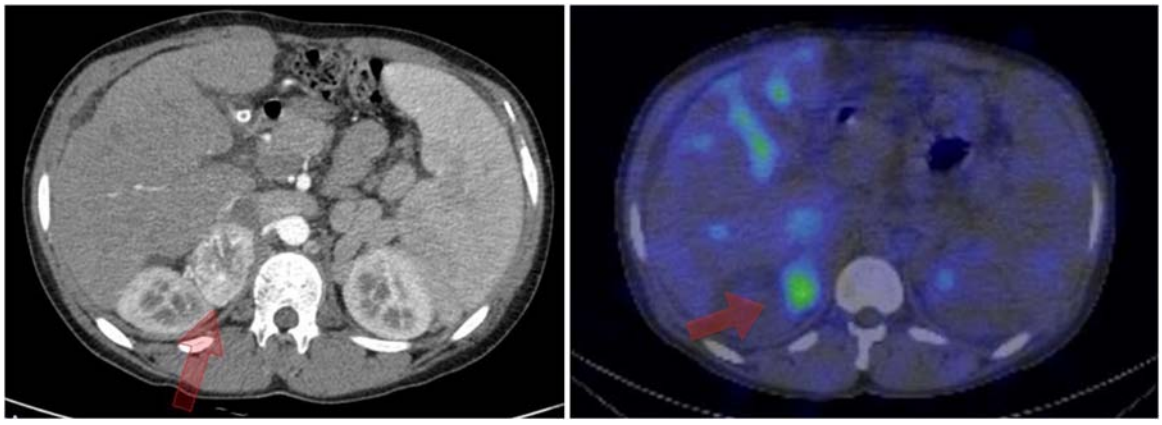

FIGURE 3 Abdominal CT scan (A) and ^{123}I MIBG scan (B) of Patient 3. (A) Right adrenal mass (arrow) with arterial enhancement and delayed washout and internal low attenuation suggesting necrosis in CT scan of Patient 1. (B) Mild I-123MIBG uptake in right adrenal mass (arrow) is shown

TABLE 3 Clinical characteristic differences between Fontan patients and patients with normal heart in literature

Clinical characteristic	Fontan (n = 17) [6,8,24,25]	Non-CHD patients [3]
Onset age (average)	25.5 years (median 23)	40–50 years (sporadic form)
Family history	0	10%
Extra-adrenal (paraganglioma)	8/17 (47%)	15–20%
Malignant PHEO	2/17 (11%)	10%
Hypertension	10/17 (59%)	51–90%
Tumor recurrence	18%	13% (sporadic form)
Race	Asian 9/white 5/Hispanic 1/black 1	No ethnic difference

Abbreviations: CHD = congenital heart disease; PHEO = pheochromocytoma.

total mass excision was performed again. HCC also recurred repeatedly, and six transarterial chemoembolization and three percutaneous ethanol injection therapies were performed until now.

Patient 7 had tricuspid atresia and atriopulmonary connection Fontan operation was performed at 8 years old. A 1-cm diameter hepatic nodule was noted during liver MRI and CT scan with elevated α-fetoprotein at the age of 37 years. Transarterial chemoembolization was performed. After 6 months, paroxysmal palpitation, headache, and dyspnea started, which persisted for 3 months. On 24-hour blood pressure monitoring, paroxysmal high blood pressure (140/76 mm Hg) was shown. Serum and urine catecholamine level elevated significantly and ^{68}Ga-DOPA-TOC positron emission tomography (PET) showed increased DOPA-TOC uptake in the retrocaval area. She underwent excision of the right aortocaval mass, which was confirmed as PGL by pathology.

4 | DISCUSSION

The incidence of moderate and severe forms of congenital heart disease is about 6 in 1000 live births,[9] and the incidence of PHEO is about 0.2%–0.6% in the general population with hypertension.[1] Thus, concomitant PHEO in Fontan patients is extremely rare. The incidence of PHEO/PGL in Fontan patients older than 10 years in our hospital (2.5%) is very high compared with general population. We summarized clinical characteristics of PHEO/PGL of Fontan patients including our patients (n = 7) and patients in the literature (n = 10) and compared with PHEO/PGL patients without congenital heart disease (Table 3). The onset age of PHEO/PGL was earlier than that of non-CHD patients. Incidence of malignant PHEO was similar, but tumor recurrence rate in Fontan patients was higher than in non-CHD patients.

Lack of recognition might have underestimated the true incidence of PHEO/PGL in Fontan patients in other centers. To the best of our knowledge, this is the first report raising an issue of PHEO/PGL as late Fontan complication and also first report on PHEO/PHL and HCC dual neoplasms in Fontan patients.

4.1 | Cyanosis in Fontan patients

Patients 2 and 6 had good resting SpO_2 (90% and 94%, respectively), but they underwent Fontan operation at 8 years and at 7 years, respectively, which was relatively late, as Fontan operation is usually completed at around 3 years of age in our center, nowadays. However, cyanosis duration and severity was variable between patients and different during resting and exercise. Three patients (Patients 3, 4, and 6) did not have prolonged duration of cyanosis, with only mild cyanosis (87%–92%), after Fontan completion. The exact duration and severity of cyanosis could not be calculated, but all patients had been exposed to chronic cyanosis for many years. Opotowsky et al also mentioned this group of patients, who had a history of cyanosis but no active cyanosis at time of diagnosis of PHEO/PGL.[8] They speculated that Fontan patients with mild hypoxia at diagnosis also have a risk for PHEO/PGL presumably due to early severe cyanosis, chronic low level hypoxemia, or both. Unique conditions in Fontan patients such as low cardiac output, elevated central venous pressure, and chronic cyanosis may aggravate tissue hypoxia and render these patients prone to neoplasm such as PHEO/PGL and HCC, but the precise mechanisms need further studies. In one patient with moderate hypoxemia, PHEO was advanced with metastasis to multiple sites, including bone and liver. Malignant PHEO is rare, but which was also reported in the cyanotic CHD previously.[10] Since PHEO/PGL has the potential of malignant transformation, early detection is crucial.

4.2 | Hemodynamic effects of PHEO/PGL in Fontan patients

In Fontan circulation, systolic and diastolic ventricular dysfunction due to various insult during surgery or by volume overload during neonate or infancy, non–left ventricular morphology, dyssynchronous contraction of a single ventricle, impaired atrioventricular function, and chronic hypoxia are present in various ways. High central venous pressure and low cardiac output due to decreased cardiac preload also could lead to chronic heart failure.[11] These various hemodynamic problems can promote chronic neurohumoral activation and increased level of circulating neuro-hormones, which leads to vasoconstriction, sodium and water retention, and progressive ventricular remodeling.[12] In Fontan patients, elevated plasma level of norepinephrine is associated with cardiac event such as arrhythmia, heart failure, thromboembolism, and mortality.[13,14]

Therefore, prolonged exposure to excessive catecholamine in PHEO/PGL can lead to further elevation of central venous pressure,

systemic congestion, edema, ascites, lymphatic failure, and progressive veno-venous collaterals with aggravated cyanosis. Excessively increased sympathetic activity can also cause or trigger tachyarrhythmia, which can result in acute decrease of cardiac output following ventricular dysfunction, chamber enlargement, and aggravation of valvular regurgitation. Furthermore, hypertension from elevated catecholamine can worsen ventricular dysfunction and valvular regurgitation.

In this study, two patients had tachyarrhythmia at the time of diagnosis of PHEO/PGL. PHEO/PGL can induce lethal complications in Fontan patients. However, delayed diagnosis was not uncommon since the presenting symptoms are vague or indistinguishable from symptoms of tachyarrhythmia or heart failure. The CT scan, which did not focus on the PHEO, missed adrenal mass in two patients. Most Fontan patients have impaired sinus node function and sinus bradycardia is common during resting state. High blood pressure in Fontan patients is unusual; therefore, a patient with elevated sinus rate and blood pressure during resting state, even if patient is in prehypertensive status, needs prompt evaluation for PHEO/PGL, such as biochemistry tests.

4.3 | PHEO/PGL-associated genes

PHEO/PGL diagnosed before the age of 40 years has been known to be associated with hereditary forms such as multiple endocrine neoplasia type 2, von Hippel-Lindau (VHL) syndrome, neurofibromatosis type 1, and familial PGLs,[3] and only about 10% of PHEO/PGL was traditionally considered hereditary. However, with recent advancement in genetic testing, more than 50% of PHEO/PGL was identified to have a genetic driver mutation including somatic mutation in sporadic disease, and to date, more than 15 genes have been reported.[15,16]

PHEO/PGL with gene mutation can be classified into two main clusters. Cluster 1 includes tumor with mutation of the *VHL* and *SDH* complex (*SDHA*, *SDHB*, *SDHC SDHD*, and *SDHAF2*), which is associated with the hypoxic response, and cluster 2 contains *RET* and *NF1*.[15,17,18] We performed genetic testing in only two patients, but there was no genetic mutation related with PHEO/PGL. To date, four patients from two studies have been reported to had performed genetic testing including *SDHx*, *TMEM127*, and *MAX*, and only one patient had pathogenic missense SDHB mutation.[6,8] The patient had a strong family history (three affected siblings and one affected child).

Cluster 1 mutation has a common feature of hypoxia-inducible factor (HIF) activation, which is a physiological response to low cellular oxygen levels. Hypoxia or pseudohypoxia-related HIF upregulate genes stimulating erythropoiesis, angiogenesis, energy metabolism (glycolysis), innovation, and metastasis or cell proliferation/survival, which eventually protect hypoxic tissues.[16]

In patients with cyanotic CHD, the HIF pathway can be chronically stimulated, which induces a wide variety of target genes involved in cellular and tissue adaptation to chronic hypoxia. There have been sporadic cases of patients with cyanotic CHD who developed PHEO or PGL and Opotowsky et al. reported that cyanotic CHD was associated with an increased risk for PHEO/PGL development in multivariate analysis (odds ratio, 6.0; confidence interval, 2.6–13.7).[8] This study also included Fontan patients with only mild hypoxemia. They speculated early severe cyanosis, chronic low level hypoxemia, or both might be the risk for PHEO/PGL in this group. PHEO/PGL in Fontan patients seems to be a good model to represent gene-environment interactions. Hypoxic environment may be the second hit for early development of PHEO/PGL in Fontan patients who has a genetic predisposition under investigation. Therefore, it needs to be elucidated whether genetic pathway-hypoxia interactions is related to development of PHEO/PGL in Fontan patients.

4.4 | Biochemistry pattern in Fontan patients with PHEO/PGL

The tumors in our patients can be subclassified as having a noradrenergic-based catecholamine release pattern. The urine normetanephrine (metabolite of norepinephrine) level was significantly elevated in all patients by more than fourfold above the reference range, and the serum norepinephrine level was elevated in six of seven patients. Measurements of plasma-free metanephrines (normetanephrine and metanephrine) or urinary-fractionated metanephrines are the diagnostic tests of choice because of their high sensitivity (approaching to 100% sensitivity).[3] Noradrenergic PHEO/PGL secretes norepinephrine and normetanephrine, as seen in VHL disease, which is classified as cluster 1 and associated with the hypoxic response.[19] This coincides with other reports of Fontan patients with PHEO/PGL (Table 4).

The sensitivity of biochemical study is very high and biochemical study can be easily performed by blood and urine sampling. If Fontan patient had mild sinus tachycardia or high blood pressure, even if it happens only one time and the patient has not severe cyanosis, prompt biochemical study is required and CT image or I-123 MIBG scans needs to be considered. The Fontan patients with palpitation with diaphoresis and headache also need investigation for PHEO/PGL.

4.5 | Dual neoplasms, HCC, and PHEO/PGL in Fontan patients

HIF can play a critical role in liver cancer as well as in PHEO/PGL pathogenesis, and thus, its pathway has been targeted in cancer therapy.[16,20] High HIF-1α expression has been correlated with worse clinical outcome in patients with HCC and lower treatment response.[21,22] In our report, two patients had dual neoplasms, HCC and PHEO/PGL. Patient 3 developed HCC at 19 years and PHEO at 24 years. The adrenal mass was resected, but PHEO recurred at the previous operation site 3 years later. HCC also recurred many times and he underwent multiple chemoembolizations and ethanol injections. Patient 7 was diagnosed with HCC at 37 years and diagnosed with PGL 6 months later. Hypoxia can have a significant role in the development of HCC via the HIF pathway.[21] Furthermore, in Fontan patients, chronic liver injury, fibrogenesis, and cirrhosis can increase tissue hypoxia, which might be linked to liver cancer. In these two patients, PHEO/PGL and HCC may share an HIF pathway pathologically activated by chronic hypoxia in tumorigenesis. This is the first report of Fontan patients with dual neoplasms, HCC and PHEO/PGL.

TABLE 4 Published reports of pheochromocytoma/paraganglioma in patient with Fontan

	year	n	Age (years) at diagnosis	Presentation	Congenital Heart Disease	SpO_2	diagnosis	Elevated biochemistry
Chung et al.[23]	2008	2	13, 20	Chest discomfort, HTN, palpitation, facial flushing, nausea, vomiting	1 SV 1 Fontan	80% 78%	PHEO	Urine NE Plasma NE, Epi
Cheung et al.[24]	2008	1	14	Palpitation, sweating, headache, dyspnea, fatigue, hypertension	Fontan	NA	PHEO	Plasma NE, urine NM
Yuki et al.[25]	2008	1	20	Severe paroxysmal HTN with diaphoresis and flushing	Fontan without fenestration	NA	PHEO	Plasma NM, NE Meta, DOPA
Opotowsky et al.[8] Multicenter study	2015	20	Median 31.5 (range 15–57)		7 Fontan, 3 TOF, 3 ES, 2 SV	72–96%	9 PHEO, 17 PGL	Plasma NE, NM, urine NE, NM, Meta
Yamamoto et al.[6]	2016	1	15	Paroxysmal sweating, dizziness and transient hypertension	Fontan	90–94%	PHEO	Plasma NE, urine NE, urinary NM

Abbreviations: Epi, epinephrine; DOPA, dopamine; ES, Eisenmenger syndrome; HA, headache; HTN, hypertension; MAPCA, major aortopulmonary collateral arteries; Meta, metanephrine; NA, not available; NE, norepinephrine; NM, normetanephrine; PGL, paraganglioma; PHEO, pheochromocytoma; SV, single ventricle; SpO_2 percutaneous oxygen saturation; TGA, transposition of great arteries; TOF, tetralogy of Fallot.

5 | LIMITATIONS

This study has limitation by its retrospective nature and small sample size. The exact duration of cyanosis in each patient was not determined because oxygen saturation changes with position or exercise in Fontan patients. Because only two patients had a genetic testing, we also have a limitation to analyze an association between genetic background and development of PHEO/PGL in patients with cyanotic CHD.

6 | CONCLUSION

PHEO/PGL is a rare neuroendocrine tumor, but could induce lethal complications in Fontan circulation, and Fontan patients had higher risk for PHEO/PGL compared with general population. Although PHEO/PGL is curable by resection during the early phase, its presenting symptoms are vague, which can lead to a delay in the diagnosis or being missed completely. Clinical suspicion and early biochemical screening with imaging study to determine PHEO/PGL are very crucial in Fontan patients.

CONFLICT OF INTEREST

The authors report no relationships that could be construed as a conflict of interest

AUTHOR CONTRIBUTIONS

Concept/Design: Song MK, Kim GB, Bae EJ; Data analysis/interpretation: Song MK, Kim GB, Lee YA, Kim HY, Kim JH; Drafting article: Song MK; Critical revision of article: Song MK, Kim GB, Bae EJ, Lee YA, Kim HY, Approval of article: Song MK, Kim GB, Bae EJ, Lee YA, Kim HY, Min SK, Kim JH, Won JK: Statistics: Song MK; Data collection: Song MK

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