A Case of Paraganglioma with Cyanotic Congenital Heart Disease

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ABSTRAK

Kejadian penyakit jantung bawaan sianotik (CCHD) dengan phaeochromocytoma-paraganglioma (PCC-PGL) secara bersamaan jarang terjadi walaupun beberapa kasus telah dilaporkan. Kami melaporkan kasus paraganglioma kiri pada seorang wanita berusia 20 tahun dengan CCHD yang mendasarinya dan menjalani rawatan paliatif Glenn, yang kemudian ditemukan memiliki polisitemia dan thrombosis sinus kavernosus disertai dengan palpitasi, berkeringat, nyeri kepala dan hipertensi berdurasi 3 bulan pada usia 17. CT scan abdomen menunjukkan peningkatan massa paraaortik kiri berukuran 5,2 cm x 4,4 cm x 3,4 cm. Ketokolamin urin 24 jam menunjukkan peningkatan kadar noradrenalin hingga enam kali batas normal, dan oleh karena itu diagnosis PGL kiri ditegakkan. Mengingat diagnosis yang tertunda dan morbiditas yang signifikan terkait dengan kondisi pasien tersebut, perawatan bedah tidak lagi menjadi pilihan. Oleh karena itu, skrining waspada dan pengobatan dini PCC-PGL pada pasien dengan CCHD sangat penting untuk menghindari morbiditas yang signifikan dan memastikan kualitas hidup yang baik

***Kata kunci**: penyakit jantung bawaan sianotik, paraganglioma, phaeochromocytoma, hipoksia.*

ABSTRACT

Co-occurrence of cyanotic congenital heart disease (CCHD) and phaeochromocytoma (PCC) and paraganglioma (PGL) are rare, although some cases have been reported. We report a case of left paraganglioma in a 20-year-old lady with an underlying CCHD who underwent palliative Glenn shunt, subsequently developed polycythaemia and cavernous sinus thrombosis presented with palpitation, sweating, headache and hypertension of 3-months duration at the age of 17. The abdominal CT scan revealed an enhancing left paraaortic mass measuring 5.2 cm x 4.4 cm x 3.8 cm. A 24-hour urine catecholamine demonstrated raised noradrenaline level to six times upper limit of normal and hence diagnosis of left sympathetic (sPGL) was made. In view of the delayed diagnosis and significant morbidity associated with her condition, surgical treatment is no longer an option. Therefore, vigilant screening and early treatment of PCC-PGL in patients with CCHD are crucial in order to avoid significant morbidity and ensure a good quality of life.

***Keywords**: cyanotic congenital heart disease, paraganglioma, phaeochromocytoma, hypoxia.*

INTRODUCTION

Phaeochromocytoma (PCC) and paraganglioma (PGL) are rare tumours derived from either chromaffin cells in the adrenal medulla or non-chromaffin cells of sympathetic or parasympathetic tissue, usually at the paravertebra or head and neck region. PCC accounts for about 80 to 85% while PGL accounts for 15 to 20% of PCC/PGL.[1] PCC and sympathetic paraganglioma (sPGL) usually secrete catecholamine whereas parasympathetic paraganglioma (pPGL) is usually non-functioning.

Most of PCC and sPGL are benign. Only 10-15% are malignant as defined by the presence of metastatic chromaffin cells in sites without chromaffin cells such as lymph nodes, liver, bones and lungs.[2] These tumours can be sporadic or hereditary. Hypoxia, along with genetic mutation, may be a risk factor for the development of PCC or PGL. There are reported cases of PCC and sPGL associated with cyanotic congenital heart disease, although the exact mechanism is still unclear. *Opotowsky et al*.[3] reported that patients with cyanotic congenital heart disease have a higher risk of developing PCC or sPGL compared to non-cyanotic congenital heart disease patients with an odds ratio (OR) of 6.0 and 0.9, respectively.We report a unique case of cyanotic congenital heart disease associated with malignant PGL.

CASE ILLUSTRATION

A 20-year-old woman was diagnosed at the age of 3 months with right isomerism, inclusive of dextrocardia, univentricular heart, complete atrioventricular septal defect, valvular and infundibular pulmonary stenosis. She underwent bidirectional cavo-pulmonary shunt (Glenn shunt) at six years of age. Her echocardiography at that time showed infundibular-valvular pulmonary stenosis with a pressure gradient of 62 mmHg. Given the high pulmonary artery pressure with underlying atrioventricular regurgitation, corrective Fontan procedure was not able to be performed, and she was managed conservatively. Subsequently, at the age of 17, she developed symptomatic polycythemia complicated with cavernous sinus thrombosis and treated with rivaroxaban 20 mg daily.

One year later, she complained of intermittent palpitation, profuse sweating and headache with a blood pressure of 150/120 mmHg. She was started on Amlodipine 2.5 mg daily and was referred to our centre for further workup of young hypertension. Initial full blood count showed haemoglobin of 18.9 g/dL (normal range (NR): 11.0-16.5) with a haematocrit of 61.5% (NR: 35-50), renal and liver functions were within a normal range. Her fasting blood glucose was 8.0 mmol/L, HbA1c of 6.9%. A 24-hour urine noradrenaline was significantly elevated with 548.2 microgram/day (NR: 12.1-85.5); normal adrenaline at 11.6 microgram/day (NR: 1.7-22.4) and normal dopamine 233 microgram/day (NR: <498.1). Contrast-enhanced computed tomography (CECT) neck, thorax, abdomen and pelvis showed dextrocardia with complex aortic, pulmonary and inferior vena cava branches. There is also a large heterogeneous enhancing oval solid mass at the left paraaorta below the pancreatic body with a size of 5.2 cm x 4.4 cm x 3.8 cm with 2 small internal calcified focuses. Both kidneys and adrenals appear normal. There was no evidence of metastasis (**Figure 1**). A diagnosis of left paraganglioma was made. Her anti-hypertensive was changed to oral prazosin 0.5mg twice daily (bd) to block the excess catecholamines, and her blood glucose was controlled with oral metformin 500 mg bd.

Clinically, there was central and peripheral cyanosis with finger clubbing. Her lying blood pressure was 166/120 mmHg, standing blood pressure 158/118 mmHg, pulse rate 107 bpm, and oxygenation saturation (room air) 86%. Cardiac examination showed median sternotomy scar with an apical beat at the right fifth inter-costal space, mid-clavicular line, presence of pan-systolic murmur at the right lower sternal edge and a loud, harsh ejection systolic murmur at the right second intercostal space. Abdominal examination revealed hepatomegaly with a liver span of 16 cm.

Her prazosin dose was increased to 1 mg thrice a day (tds) and metoprolol 75 mg bd was added with up-titration of the dose. As a result of persistent tachycardia with a heart rate of 100-110 bpm, labetalol 100 mg tds was added. Unfortunately, because of the underlying

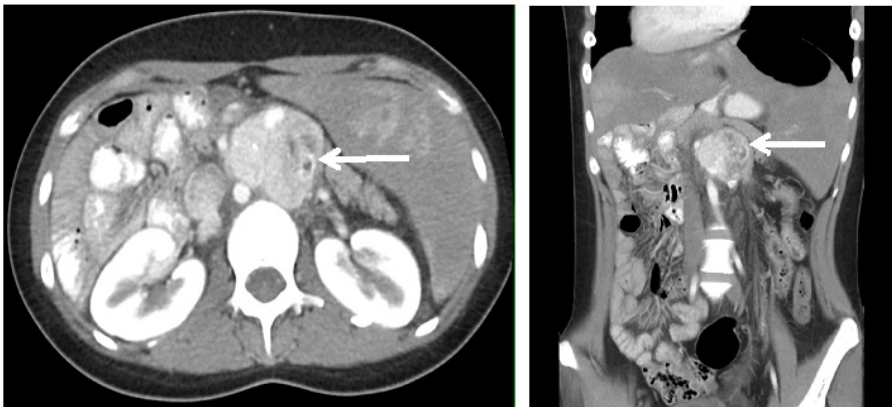

Figure 1. CECT addominal region (axial left and coronal right) showed a large heterogenous enhancing oval solid mass at left paraaortic region below the pancreatic body measuring 5.2 cm x 3.8 cm with 2 small internal calcified focus.

comorbidities and significant high risk of surgical treatment, the family members opted for medical therapy. During her subsequent follow-ups, she was asymptomatic, and her blood pressure was controlled with prazosin of 1mg tds, metoprolol 200 mg bd and labetalol 100 mg tds.

DISCUSSION

Cyanotic heart disease accounts for approximately 25% of all congenital heart disease.[4] The co-occurrence of cyanotic congenital heart disease (CCHD) and PCC/PGL was well described in case reports and supported by a study by Opotowsky et al.[3] These authors postulated that chronic hypoxia exposure seen in CCHD predisposes these individuals to develop PCC/PGL.[3] There are a few case series that reported the incidences of PCC/PGL in patients with CCHD. Opotowsky AR et al. reported 18 cases with PCC/PGL, 8 cases the tumour located in adrenal glands suggestive of PCC and 8 cases extra-adrenal (PGL) and 2 from adrenal and extra-adrenal (PCC+PGL).[3] In a recent study by Zhao Bingbin et al, out of 47 cases, 46.8% (22) were PCC, 51.1%(24) were PGL and 2.1%(1) was PCC+PGL.[4] Ponz de Antonio I et al reported that among 3311 follow up patients with congenital heart disease over the span of 25 years, the incidence of PCC-PGL was 7 cases in cyanotic patients (206) while no incidence in 3105 patients who are acyanotic. Amongst the 7 cases, 4 cases were PGL, and 3 cases were PCC.[5]

The clinical presentations of PGL are variable. The signs and symptoms depend on the amount, type and pattern of catecholamine secretion. PGL usually secrete noradrenaline while malignant PCC and sPGL produce predominantly dopamine due to less well-differentiated catecholamine biosynthesis pathway. The typical symptoms of PGL are the paroxysmal triad of severe headache, palpitation and diaphoresis. These symptoms are similar to hypercoagulable state; thus, diagnosis can be delayed. About 5 % of the patients are asymptomatic and noted to have adrenal incidentaloma.[5] This can be in the parasympathetic type of PGL or when the secretion of catecholamines relatively low.

Approximately 60 % of sPGL is sporadic while 40 % is associated with a hereditary syndrome such as von-Hippel Lindau, Carney-Stratakis syndrome, multiple endocrine neoplasias 2 (MEN-2), and neurofibromatosis type 1 (NF1).[6] Various genes have been associated with sPGL. The genes are divided into two clusters. Cluster 1 (*VHL*, *SDHB*, *SDHD*, and *HIF2A*) encode proteins that mediate independent oxygen stabilization of hypoxia-inducible factors (HIF), while the genes in cluster 2 (*RET*, *NF1*, *TMEM127*, and *MAX*) encode proteins associated with receptor tyrosine kinase signalling. Eventually, these 2 clusters of genes will form HIF and promote the development of sPGL via HIF1α pathway.[3,7] HIF1α level has been found to be high in patients with congenital cyanotic heart disease. The previous report by Opotowsky AR et al. suggested that cyanotic congenital heart disease is strongly associated with the incidence of sPGL, probably due to

chronic hypoxia, but the direct relationship is still under investigations.[3] The oxygen saturation of this patient was persistently less than 90% which suggest that chronic hypoxia might be the contributing factor for the development of sPGL. This chronic hypoxia postulation can be supported by the higher incidence of in sPGL cyanotic CHD as compared to non-cyanotic. However, there is no genetic studies and measurement of HIF done to support this postulation. Besides that, there are also several confounding factors including older age which indicates longer hypoxic duration (OR 1.013), female gender (OR 1.5), association with hereditary syndromes such as MEN (OR 59.8), VHL (OR 15.9), neurofibromatosis (OR10.8) and renal cell carcinoma (OR 8.2).[3] Presence of comorbidities such as hypertension (OR 2.2), hypothyroidism (OR 1.04) and diabetes (OR 1.12) also increase the risk of PCC-PGL.[3].

A delayed diagnosis of PGL might lead to cardiovascular complications such as hypertensive encephalopathy, cardiomyopathy, stroke and neurogenic pulmonary oedema from excess circulating catecholamine. Thus, early detection of PGL is crucial in order to avoid complications related to PGL. Screening of sPGL has been recommended in symptomatic and asymptomatic patients with adrenal incidentaloma or patient predisposed to hereditary PGL.[10] This recommendation should also be made to CCHD patients who developed hypertension and sympathetic symptoms. The diagnosis of PGL should be confirmed biochemically before any imaging modality performed. Plasma or urinary free metanephrines have been shown to be more reliable due to the continuous secretion of metanephrines into the circulatory compartment The sensitivity and specificity of plasma metanephrines are 97 to 99% and 82 to 100%, respectively.[11] Furthermore, to localize the tumour, the use of CECT and MRI are justified. CECT has high sensitivity (77 to 98%) but poor specificity (29 to 92%), while MRI sensitivity and specificity has been reported between 90 to 100% and 50 to 96%, respectively.[12,13] Hence, functional imaging tests are recommended to localize the tumour, and these include ^{131}I or ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy.[14] In the present case, urine catecholamine and functional imaging test were not carried out due to limited resources.

The mainstay of treatment for PGL is still surgical resection. A preferred approach is laparoscopic. Conventional laparotomy should be considered in a large tumour of more than 6 cm due to the higher risk of malignancy and seedlings.[15] In order to minimize surgical complications (hypertensive crisis and arrhythmia), adequate preoperative treatment is essential. The main aim of preoperative management is to normalize the blood pressure and heart rate, to restore volume depletion and prevent hypertensive crisis intra-operatively.[14,15] The recommendation is to start adrenergic blockade at least seven days prior to surgery in order to allow enough time for blood pressure and heart rate to normalize as well as to expand the contracted blood volume.[16]

In present case, a long term medical treatment was opted due to poor heart status and its complication. From various works of literature, we did not find any reference for long-term medical therapy for PGL. During her subsequent follow-up, she remains asymptomatic, and her blood pressure was within optimal control.

Castilho et al.[17] demonstrated that 90% of their patients had normal blood pressure immediately after surgery. Patients with sPGL will require life-long follow-up as the condition might recur. At present, there is still no definite medical therapy for patients with inoperable sPGL. In light of the current evidence where hypoxia pathway has been implicated in sPGL, there are suggestions that pharmacological inhibition of HIF might be the future therapeutic option for this group of patients.[8]

CONCLUSION

This case demonstrated that in CCHD patient who developed hypertension during follow-up, clinicians should have a high index suspicion of sPGL. Early treatment and follow-up of PGL in CCHD is essential to avoid tumour recurrence if hypoxia is not corrected.

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