Cardiology in the Young

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Two rare cases of paraganglioma in patients with Fontan physiology

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Brief Report

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Abstract

Pheochromocytoma/paraganglioma is an exceedingly rare tumour, thought to share an association with cyanotic CHD. This association is thought to be a result of chronic hypoxaemia (Antonio et al, Revista Española de Cardiología (English Edition) 2017; 70: 673–675; Folger et al, Circulation 1964; 29: 750–757; Opotowsky et al, J Clin Endocrinol Metab 2015; 100: 1325–1334) We report two cases of paraganglioma over a 4-year period in patients with hypoplastic left heart syndrome who had undergone Fontan completion by ages 2 and 4. Based on a very small number of reported cases of CHD, the mechanism of tumourigenesis is unclear. It is imperative that cases associated with CHD continue to be reported so that we may learn more about the pathogenesis and epidemiology of this entity.

Pheochromocytoma/paraganglioma is a rare neuroendocrine tumour arising in the chromaffin cells. The incidence rate in the paediatric population is around 0.3 per million per year, making it very uncommon.[1] Although the majority of these tumours are sporadic, recent literature suggests an increased risk of pheochromocytoma/paraganglioma in patients with cyanotic CHD.[2–4] This association was first noted in 1964, when Folger et al[2] published a report of five cases of pheochromocytoma in a 13-year period at the Johns Hopkins Hospital in patients who also had cyanotic congenital heart lesions.[5] This association has continued to be trended. In a more recent multi-centre study, Opotowsky et al[3] suggest that the combination of chronic hypoxaemia and genetic susceptibility may contribute to the development of this tumour. We report two cases of paraganglioma in patients who were born with a cyanotic CHD that was surgically corrected at an early age.

Case 1

A 13-year-old male with history of hypoplastic left heart syndrome and complete Fontan palliation at 4 years of age presented with hypertension during a routine clinic visit. On examination, blood pressure was 192/100 mmHg, pulse rate was 101 beats/minute, and oxygen saturations were 91% on room air. Oxygen saturations remained in the low 90s from the time of Fontan palliation through the time of presentation of hypertension. He was admitted to the hospital for further workup and was found to have highly elevated levels of urinary catecholamines and their metabolites. Abdominal CT revealed a 3.8 cm × 2.9 cm soft tissue mass in between the inferior pole of the left kidney and the abdominal aorta (Fig 1a), which showed abnormal accumulation of ^{131}I-metaiodobenzyl guanidine on scintigraphy (Fig 1b and c). An area of focal increased uptake was noted below the left kidney, corresponding to the left extra adrenal mass that had been previously identified on CT scan. Physiologic uptake of the radioisotope was also seen in the salivary glands, liver, and bladder. Patient underwent surgical resection of the mass after pre-operative treatment with phenoxybenzamine and propranolol. Pathology reports confirmed the diagnosis of paraganglioma. Regrettably, specific information about the biochemical profile of the tumour was never made available. Patient's post-operative course was uncomplicated and his blood pressure subsequently normalised after surgery. He has been free from recurrence for 4 years now, and his oxygen saturations remain in the mid 80s to low 90s. Unfortunately, genetic testing assessing germline mutations was not performed in this patient. The only genetic testing available for this case was a normal chromosomal microarray, which only excludes duplications and deletions of the genetic material.

Case 2

A 23-year-old male with history of hypoplastic left heart syndrome and complete Fontan palliation at 2 years of age, aortic aneurysm, central adrenal insufficiency, and type II diabetes

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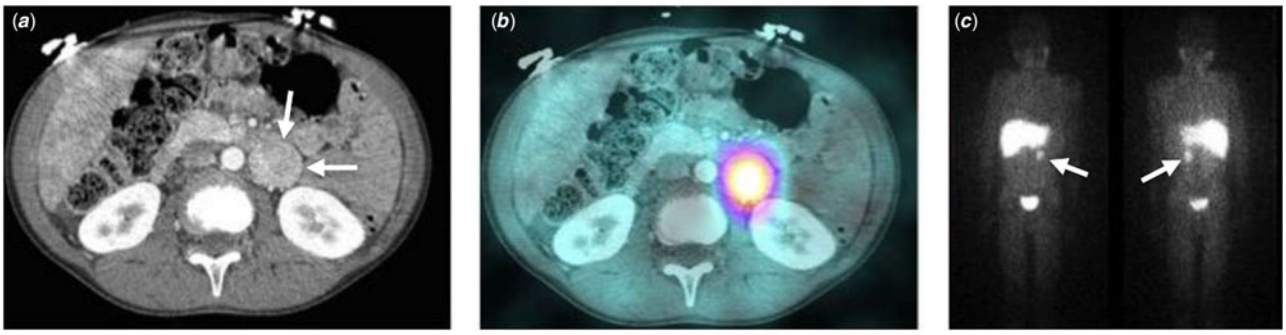

Figure 1. Case 1. (***a***) Abdominal CT showing a left extra adrenal mass. (***b*** and ***c***) ^{131}I-MIBG scintigraphy. Abnormal accumulation of ^{131}I-MIBG in the tumour is seen.

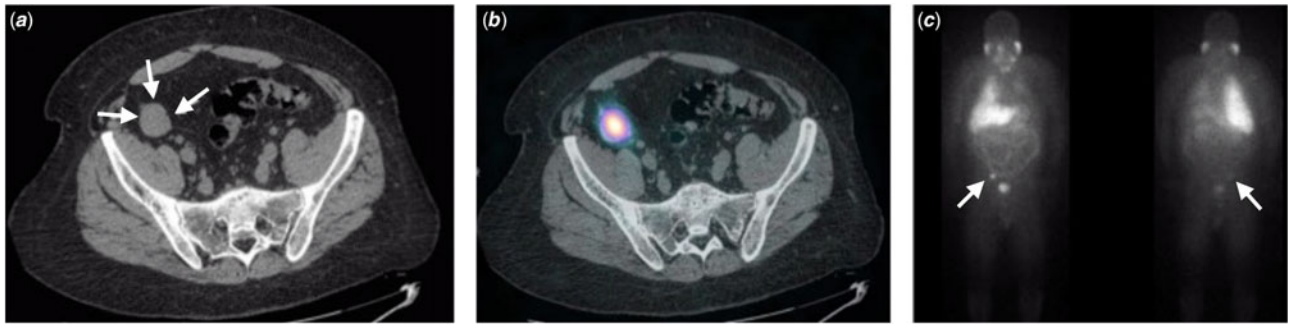

Figure 2. Case 2. (***a***) Abdominal CT shows a right pelvic mass. (***b*** and ***c***) ^{131}I-MIBG scintigraphy. Abnormal accumulation of ^{131}I-MIBG in the tumour is seen.

mellitus presented to the hospital with fever, shortness of breath, and abdominal pain. Abdominal CT scan was obtained and revealed a 3 cm × 2.5 cm right pelvic mass (Fig 2a). Subsequent outpatient workup revealed elevated urinary metanephrines and abnormal enhancement on metaiodobenzylguanidine scan (Fig 2b and c). The scan showed an abnormal focal area of increased radioisotope uptake in the right lower quadrant of the pelvis, corresponding to the pelvic mass that was previously identified on CT scan. Physiologic uptake in the salivary glands, lungs, liver, and bladder was also noted. Prior to presentation, oxygen saturations had remained in the low 90s from the time of palliation at 2 years of age. Patient eventually underwent surgical resection of the mass after initiation of autonomic blockade with phenoxybenzamine and propranolol. Surgical pathology confirmed the diagnosis of sympathetic paraganglioma. Details regarding the biochemical profile of the tumour are not known. Patient's symptoms resolved shortly after tumour removal; however, he developed adrenal insufficiency requiring treatment with hydrocortisone. He has been free from tumour recurrence for almost a year now and his oxygen saturations remain in the low 90s. He later underwent total genome sequencing which revealed several gene mutations involving the DYNC2H1 gene. This specific gene encodes the protein cytoplasmic dynein 2 heavy chain, which is involved in ciliary intraflagellar transport.[6] Although classified as a variant of uncertain significance, further investigation into the pathophysiologic interplay between this gene and pheochromocytoma/paraganglioma may be warranted.

Discussion

The co-occurrence of pheochromocytoma/paraganglioma and cyanotic CHD is an extremely rare phenomenon thought to be the result of chronic hypoxaemia. Although the mechanism of tumourigenesis remains unclear, recent studies hypothesise that the hypoxemic state stimulates catecholamine secretion from the chromaffin cells, leading to endocrine hyperactivity and subsequent hyperplasia and neoplasia.[7,8] Both patients we present had Fontan completion early in life and presented with paragangliomas following years of relatively normal oxygen saturation; thus, assertions that chronic hypoxaemia provides the link between cyanotic heart lesions and pheochromocytoma/paraganglioma need further scrutinising. Based on prior reports, it is clear that long-standing cyanotic heart disease increases the incidence of pheochromocytoma/paraganglioma.[3] However, the pathophysiologic mechanisms of this phenomenon are not yet clearly elucidated. With the prevalence of adult CHD on the rise, better understanding of related pathologies will help us better care for this increasing population of patients. Practitioners caring for adult congenital heart patients with a history of a cyanotic heart lesion should consider earlier workup for pheochromocytoma/paraganglioma in the presence of new onset hypertension.

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Conflicts of Interest. None.

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