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CASE REPORT
Congenital heart disease

Asymptomatic phaeochromocytoma in a patient with Holt-Oram syndrome: a case report

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Background Holt-Oram syndrome (HOS) is a rare congenital disease that affects the heart and upper limbs. Phaeochromocytoma, a catecholamine-secreting tumour, is a rare neuroendocrine disorder. We present an interesting case presentation of these two rare disorders in a patient who was asymptomatic for phaeochromocytoma.

Case summary A 28-year-old woman who was diagnosed at birth with HOS, presented to the hospital with heart failure. She has a past medical history of corrected cyanotic congenital heart disease. She presented with dyspnoea but she did not have headaches, tremors, or diaphoresis. Cardiac magnetic resonance scan was done to investigate the cause of her heart failure and revealed right ventricular systolic dysfunction and a suspicious adrenal lesion. Magnetic resonance imaging adrenal confirmed the presence of the adrenal lesion and concerns were raised for a possible phaeochromocytoma. Biochemical tests showed raised plasma free metanephrine levels. Gallium-68 DOTA positron emission tomography scan showed intense right adrenal gland uptake in keeping with diagnosis of phaeochromocytoma.

Discussion Phaeochromocytoma appears to be more prevalent in patients who are in a chronic hypoxic state. This hypoxic state has been postulated to cause the proliferation of adrenal tissue and therefore the formation of phaeochromocytomas. The hypoxia-inducing factor, which is increased in patients with phaeochromocytoma, has been identified as one of the key factors driving this process as it modulates genes that regulate angiogenesis and proliferation. Congenital heart defects seen in HOS can progress to cyanotic heart disease if left uncorrected and may have been the driver for the development of phaeochromocytoma in our patient.

Keywords Holt-Oram syndrome • Phaeochromocytoma • Asymptomatic • Hypoxia-inducing factor • Case report

Learning points

- Holt-Oram syndrome is a rare congenital disease that affects both the heart and the upper limbs and can result in the development of cyanotic congenital heart disease (CCHD).
- Phaeochromocytoma is a rare neuroendocrine disorder which results in the development of a neuroendocrine tumour which may become malignant.
- Phaeochromocytoma is associated with CCHD due to chronic hypoxia and can have an asymptomatic presentation.

Introduction

Holt-Oram syndrome (HOS) is a rare congenital disease that affects the heart and is associated with upper limb abnormalities.[1] Phaeochromocytoma is a rare endocrine disorder resulting in the development of a neuroendocrine tumour.[2] We present a unique case of two rarities; a 28-year-old woman with HOS and corrected cyanotic congenital heart disease (CCHD), who was incidentally diagnosed with phaeochromocytoma.

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Timeline

Age	Event
3 months old	Right Blalock–Taussig (BT) shunt operation
4 years old	Left BT shunt operation
7 years old	Right pulmonary artery (PA) angioplasty and take-down of right BT shunt as the shunt was stenosed
20 years old	Reconstruction of right and left PA, placement of valved conduit between right ventricle (RV) to main PA in September 2010. Ventricular septal defect was left unrepaired as there was still restricted pulmonary blood flow given the small size of the RV-PA conduit, resulting in concerns that full biventricular repair might not be well tolerated
28 years old	First admission for heart failure

Case presentation

The patient was diagnosed with HOS at birth with complex heart defects including pulmonary atresia, hypoplastic branch pulmonary arteries (PAs), large ventricular septal defect (VSD), secundum atrial septal defect, and a left sided aortic arch. She had an absent right radius with fixed flexion deformities of the right thumb, 2nd and 3rd fingers. She was palliated with bilateral Blalock–Taussig shunts in childhood, but became increasingly cyanotic by 20 years of age. She then underwent surgery; the branch PAs were reconstructed and a small right ventricular-PA (RV-PA) conduit was placed to improve pulmonary blood flow, however, full biventricular repair was not achievable as there were concerns that she may not have adequate cardiac output and the VSD was left unclosed. Post-surgery, she remained cyanosed but her oxygen saturations improved (from 78% to 86%) and she had a reasonable functional status.

At 28 years of age, she had her first admission for heart failure. She was dyspnoeic on examination, heart sounds were dual and there were bibasal crepitations on auscultation of the lungs. Jugular venous pulse was raised and she had no pedal oedema. Telemetry monitoring showed that she had frequent premature ventricular complexes (PVCs). Transthoracic echocardiogram revealed a left ventricular ejection fraction of 55%. There was bidirectional shunting through the large perimembranous VSD, but there was no significant flow in the right ventricle to PA conduit. The RV systolic pressure was elevated at 85 mmHg (normal < 40 mmHg).

More investigations were undertaken to evaluate patency of the RV-PA. A cardiac computed tomography (CT) scan showed that the RV-PA conduit was widely patent (*Figure 1a*). Major aortopulmonary collateral arteries were also seen (*Figure 1b*).

Cardiac magnetic resonance (CMR) scan showed dilated right heart chambers with moderately severe RV systolic dysfunction, a patent RV-PA conduit with mild conduit regurgitation (*Figure 2a*). There was extensive late gadolinium enhancement of the RV myocardium and ventricular septum (*Figure 2b*). However, several faint hyperintense nodular lesions were also seen in the liver.

In view of the liver lesions detected incidentally on the CMR scan, a multiphasic magnetic resonance imaging liver and adrenals was done which showed multiple arterially enhancing hepatic lesions (*Figure 3a*) and a right hyperenhancing adrenal nodule which was 1.3 by 1.6 cm (*Figure 3b*). The suspicion of a malignant phaeochromocytoma was raised.

Further work up revealed elevated normetanephrine level at 4.00 nmol/L (reference range < 0.90) and metanephrine level at 0.89 nmol/L (reference range < 0.50). An overnight dexamethasone suppression test was negative (8 a.m. cortisol < 50 nmol/L).

A follow-up Gallium-68 DOTA positron emission tomography CT scan showed that the known right adrenal mass had intense DOTANOC-avidity in keeping with a diagnosis of phaeochromocytoma (*Figure 4*). The hepatic lesions did not show any significant DOTANOC uptake. There was no other DOTANOC-avid lymphadenopathy or distant metastasis. At this point, the endocrinologist diagnosed the possibility of a right adrenal phaeochromocytoma.

Given the presence of multiple aortopulmonary collaterals, the patient was commenced on sildenafil for segmental pulmonary hypertension. Her symptoms improved and she was eventually discharged well with furosemide, bisoprolol, and sildenafil. With regards to the phaeochromocytoma, as her blood pressure was not elevated and heart rate was well controlled on a β-blocker, it was felt that addition of an α-blocker such as phenoxybenzamine would result in profound hypotension. This would seriously impact her quality of life and hence a decision was made to treat this without any additional antihypertensive agents. Also due to prohibitive surgical risks from the underlying pulmonary hypertension, an informed decision was made with the patient to not proceed with surgery for the adrenal lesion.

Discussion

HOS is inherited in an autosomal dominant fashion, however, most cases of HOS are sporadic and occur via *de novo* mutation and its incidence is 1 in 100 000 people.[1] A heterozygous mutation in the TBX5 gene on chromosome 12q24.1 causes HOS. This gene is responsible for encoding a transcription factor which regulates the expression of other genes in the development of the heart and limbs.[3]

Phaeochromocytomas are catecholamine-secreting tumours with a prevalence of 0.2% in hypertensive patients but with a higher prevalence (~5%) in the setting of adrenal incidentalomas. Most tumours are sporadic but they can also be part of a familial disorder. Phaeochromocytomas associated with familial syndromes can be multifocal and recurrent and have a high risk for malignancy.[4] Phaeochromocytomas are diagnosed through a combination of clinical symptoms, biochemical testing with measurement of metanephrines, imaging studies of the tumour, genetic testing and also with surgical excision of the tumour and confirmation on pathological studies.[4]

It is interesting to note that a phaeochromocytoma was diagnosed incidentally in our patient. The incidence of asymptomatic

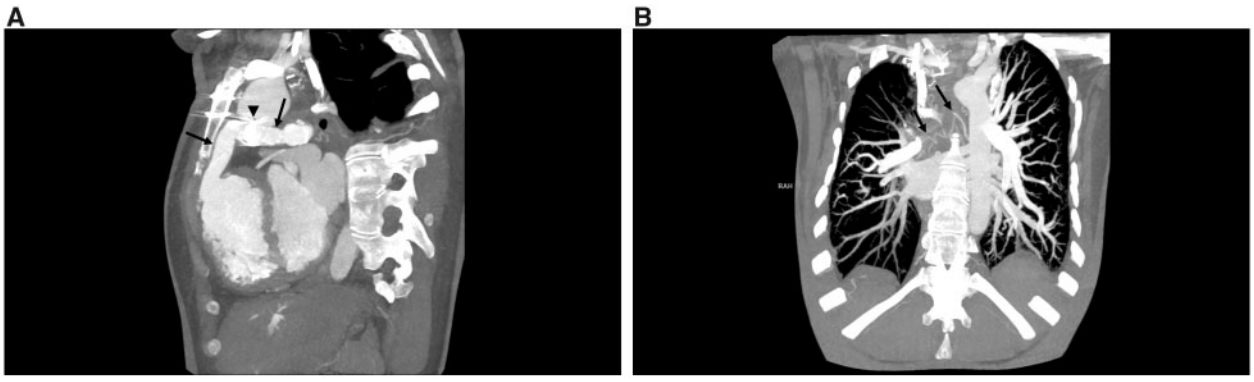

Figure 1 (*A*) Sagittal oblique maximum intensity projection image from a cardiac-gated computed tomography scan demonstrating the valved (arrowhead) right ventricle to pulmonary artery conduit (arrows). (*B*) Coronal oblique maximum intensity projection image from a cardiac-gated computed tomography scan. Small major aortopulmonary collateral artery (arrows) arising from the T6 level of the descending thoracic aorta coursing towards the right hilum.

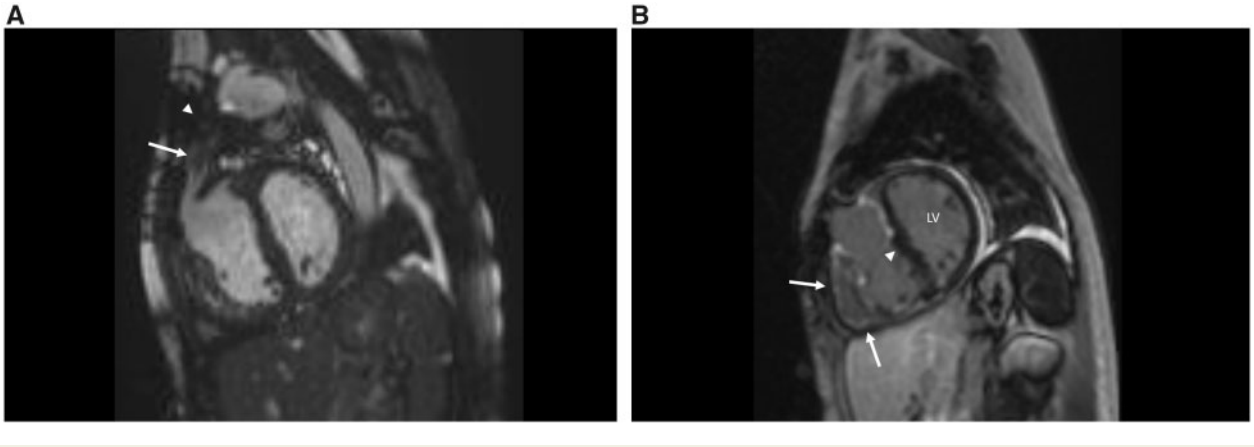

Figure 2 (*A*) Right ventricular outflow tract view from a cardiac magnetic resonance imaging scan showing the valved right ventricle to pulmonary artery conduit (arrow) with significant blooming artefact from the valve (arrowhead). (*B*) Short axis view from a cardiac magnetic resonance imaging scan showing late gadolinium enhancement of the right ventricular anterior (arrow) and inferior (arrow) wall. D-shaped left ventricle (LV) with flattening of the interventricular septum (arrowhead).

phaeochromocytoma is estimated to be ~1.6–21% of the total number of phaeochromocytomas diagnosed.[5] She did not present with typical paroxysmal spells of high blood pressure, diaphoresis, headache, or tremors. Some of the possible reasons for her to be asymptomatic could be due to the relatively low levels of catecholamines being secreted in view of her small tumour size and desensitization of the adrenergic receptors due to chronic exposure to catecholamines resulting in the masking of symptoms.[6]

The intriguing combination of CCHD and phaeochromocytoma has been reported in the literature.[7,8] The basis of this association between CCHD and phaeochromocytoma is tantalizing as it appears that chronic hypoxia is a precursor to the occurrence of phaeochromocytoma. Saldana *et al.*[9] documented a higher prevalence of carotid body paraganglioma in adults living at high altitude than compared with those living at sea level. The hypoxic state stimulates catecholamine secretion from the adrenal medulla and chronic endocrine hyperactivity can potentially lead to hyperplasia and neoplasia.[10]

One of the main factors that has been identified for this phenomenon is the hypoxia-inducing factor (HIF). HIF is an oxygen-liable transcription factor in the pathway of cellular responses to hypoxia, which could modulate a wide variety of target genes in the regulation of angiogenesis, apoptosis, and proliferation.[11–13] Opotowsky *et al.*[14] reported that hospitalized CCHD patients had an increased likelihood of phaeochromocytoma as compared to non-CCHD. HIF-1 alpha mRNA expression was found to be increased in newborn infants with CCHD.[15]

Treatment of phaeochromocytoma requires surgical resection of the tumour with presurgical medical therapy with an α-adrenergic

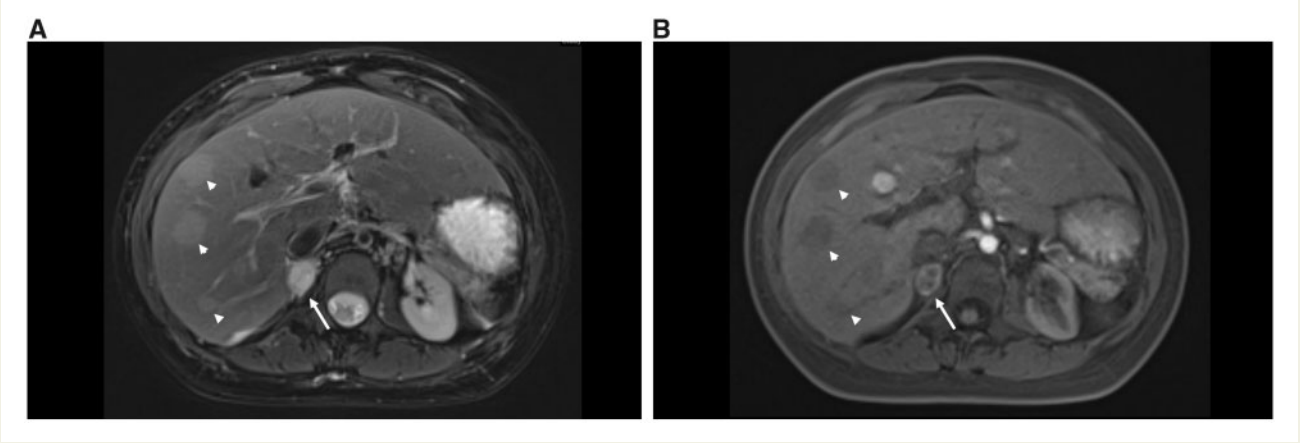

Figure 3 (*A*) T2 weighted fat saturated axial image from a magnetic resonance imaging abdomen scan which shows a hyperintense right adrenal nodule (arrow). The ovoid right hepatic lobe lesions are faintly hyperintense (arrowheads). (*B*) T1 weighted fat saturated post-contrast axial image from a magnetic resonance imaging abdomen which shows an arterially enhancing hyperintense right adrenal nodule (arrow). The ovoid right hepatic lobe lesions do not show arterial enhancement (arrowheads).

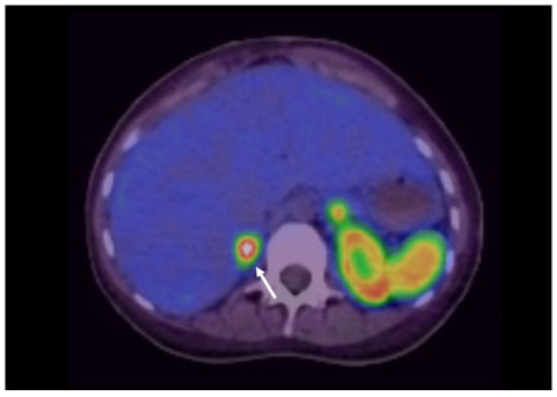

Figure 4 Axial image from a Gallium-68 DOTANOC scan which shows intense DOTANOC uptake by the right adrenal nodule consistent with a phaeochromocytoma. The hepatic lesions do not show DOTANOC uptake and are unlikely to be metastases.

blocking agent. This helps to block the effect of excess catecholamines on the α-adrenergic receptor. Beta-adrenergic blocking agents should not be initiated first because blockade of vasodilatory peripheral beta 2-adrenergic receptors with unopposed α-adrenergic receptor stimulation can lead to a further elevation in blood pressure.[4] Our patient was started on bisoprolol due to frequent PVCs that was detected on telemetry before her diagnosis of phaeochromocytoma. It was unusual that she tolerated bisoprolol without complications. Given that her blood pressure and heart rate were well controlled after commencing bisoprolol, no further changes were made to her medication regime. She is currently on regular clinic follow-up with the endocrinologist who monitors her plasma free metanephrines levels yearly.

Conclusion

In conclusion, we present a unique and doubly rare case of phaeochromocytoma in a patient with HOS, with an unusual paucity of symptoms. There appears to be a strong association between phaeochromocytoma and CCHD. It is prudent to consider the diagnosis of phaeochromocytoma in patients with CCHD and this can occur in patients who are asymptomatic too. There are important consequences on the management of such patients, especially if they require surgical resection of the phaeochromocytoma.

Lead author biography

Perryn Ng is a current Cardiology Senior Resident training at the National University Heart Centre, Singapore. He graduated from Monash University in 2011 with an MBBS qualification. He subsequently obtained his MRCP qualification in 2015. His research interests include Adult Congenital Heart Disease and Structural Heart Intervention.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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