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

Introduction
Holt-Oram syndrome (HOS) is a rare congenital disease that affects the heart and is associated with upper limb abnormalities. Phaeochromocytoma is a rare endocrine disorder resulting in the development of a neuroendocrine tumour. 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.
Timeline

| Age       | Event                                                                 |
|-----------|-----------------------------------------------------------------------|
| 3 months  | Right Blalock–Taussig (BT) shunt operation                            |
| 4 years   | Left BT shunt operation                                              |
| 7 years   | Right pulmonary artery (PA) angioplasty and take-down of right BT shunt as the shunt was stenosed |
| 20 years  | 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  | 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. 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.

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. 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.

It is interesting to note that a phaeochromocytoma was diagnosed incidentally in our patient. The incidence of asymptomatic...
phaeochromocytoma is estimated to be ≈1.6–21% of the total number of phaeochromocytomas diagnosed. 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.

The intriguing combination of CCHD and phaeochromocytoma has been reported in the literature. 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. 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.

One of the main factors that has been identified for this phenomenon is the hypoxia-inducing factor (HIF). HIF is an oxygen-labile 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. Opotowsky et al. reported that hospitalized CCHD patients had an increased likelihood of phaeochromocytoma as compared to non-CCHD. HIF-1 alpha miRNA expression was found to be increased in newborn infants with CCHD.

Treatment of phaeochromocytoma requires surgical resection of the tumour with presurgical medical therapy with an α-adrenergic...
blocking agent. This helps to block the effect of excess catechol-
amines 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 pres-
sure.4 Our patient was started on bisoprolol due to frequent PVCs
that was detected on telemetry before her diagnosis of phaeochro-
mocytoma. It was unusual that she tolerated bisoprolol without com-
plications. 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 phaeo-
chromocytoma in a patient with HOS, with an unusual paucity of
symptoms. There appears to be a strong association between phaeo-
chromocytoma 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 consequen-
ces on the management of such patients, especially if they require
surgical resection of the phaeochromocytoma.

Lead author biography
Perryn Ng is a current Cardiology
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Supplementary material
Supplementary material is available at European Heart Journal - Case
Reports online.

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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.

References
1. Krauser AF, Schury MP. Holt Oram Syndrome StatPearls. Treasure Island, FL: StatPearls Publishing; 2018.
2. Crona J, Taieb D, Pacak K. New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocr Rev* 2017;38:489–515.
3. Jhang WK, Lee BH, Kim GH, Lee JO, Yoo HW. Clinical and molecular characterisation of Holt-Oram syndrome focusing on cardiac manifestations. *Cardiol Young* 2015;25:1093–1098.
4. Lenders JWM, Duh Q-Y, Eisenhofer G, Gimenez-Roqueplo A-P, Grebe SKG, Naruse M, Pacak K, Young WF. Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915.
5. Park JH, Choi SY, Soh EY. Asymptomatic pheochromocytoma. *Korean J Clin Oncol* 2010;6:84–89.
6. Zuber SM, Kantorovich V, Pacak K. Hypertension in pheochromocytoma: characteristics and treatment. *Endocrol Metab Clin North Am* 2011;40:295–311.
7. Zhao B, Zhou Y, Zhao Y, Zhao Y, Wu X, Bi Y. Co-occurrence of pheochromocytoma-paraganglioma and cyanotic congenital heart disease: a case report and literature review. *Front Endocrinol (Lausanne)* 2018;9:165.
8. Yoshiihara A, Tanabe A, Sato H, Hizuka N, Ishizawa A, Honkawa R, Takano K. A case of malignant pheochromocytoma with Holt-Oram syndrome. *Endocr J* 2008;55:153–159.
9. Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectomas. *Hum Pathol* 1973;4:251–263.
10. Kita T, Imamura T, Date H, Kitamura K, Moriguchi S, Sato Y, Asada Y, Eto T. Two cases of pheochromocytoma associated with tetralogy of Fallot. *Hypertens Res* 2003;26:433–437.
11. Jochmanov I, Yang C, Zhuang Z, Pacak K. Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. *J Natl Cancer Inst* 2013;105:1270–1283.
12. Favier J, Gimenez-Roqueplo AP. Pheochromocytomas: the (pseudo)-hypoxia hypothesis. *Best Pract Res Clin Endocrinol Metab* 2010;24:957–968.
13. Jochmanov I, Zelinka T, Widimsky J Jr, Pacak K. HIF signaling pathway in pheochromocytoma and other neuroendocrine tumors. *Physiol Res* 2014;63(Suppl 2):S251–S262.
14. Opotowsky AR, Moko LE, Ginnis J, Rosenbaum M, Greutmann M, Aboulhosn J, Hageman A, Kim Y, Deng LX, Grewal J, Zaidi AN, Almansoori G, Oechslin E, Earing M, Landzberg MJ, Singh MN, Wu F, Vaidya A. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. *J Clin Endocrinol Metab* 2015;100:1325–1334.
15. Lemus-Varela ML, Flores-Soto ME, Cervantes-Munguia R, Torres-Mendoza BMG, Gudino-Cabrera G, Chaparro-Huerta V, Ortuño-Sahagún D, Beas-Zarate C. Expression of HIF-1 α, VEGF, and EPO in peripheral blood from patients with two cardiac abnormalities associated with hypoxia. *Clin Biochem* 2010;43:234–239.