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CASE REPORT

Bilateral Pheochromocytoma with a Novel Pathogenic Variant in the MAX gene: A Case Report

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Abstract

Pheochromocytomas and paragangliomas syndrome are grouped into three specific disease clusters based on their underlying genetic alterations. Pathogenic variants affecting the myelocytomatosis-associated factor X (MAX) gene predispose pheochromocytomas and paragangliomas syndrome to occur at younger ages, with more than half having bilateral pheochromocytomas. We report a case of bilateral pheochromocytomas with a novel pathogenic variant identified in the MAX gene (c.234_235dup). This young male was found to have a huge left suprarenal mass after he presented with severe hypertension and myocardial infarction. His endocrine workup confirmed a diagnosis of pheochromocytoma as evidenced by elevated levels of normetanephrine, metanephrine, and 3-methoxytyramine in the urine. CT of the adrenal glands revealed bilateral adrenal masses; the widest diameter for the left adrenal mass was almost 8 cm whereas for the right one was 2 cm. ^{68}Gallium-DOTATATE functional imaging showed significant uptake in the left adrenal mass, but indeterminate on the right, and no significant uptake was seen elsewhere to suggest metastatic lesions. He did not have syndromic features associated with multiple endocrine neoplasia, neurofibromatosis or von Hippel Lindau disease. The collective findings raised the clinical dilemma of whether unilateral or bilateral adrenalectomy should be pursued. The detection of pathogenic MAX gene was therefore crucial in guiding personalized treatment strategy. Following the bilateral adrenalectomy, his hypertension was cured. Annual biochemical screening and 2-yearly MRI imaging to look for recurrence of pheochromocytomas were planned according to international consensus.

Key words: hypertension, pheochromocytoma, genetic predisposition to disease, adrenalectomy

INTRODUCTION

The understanding of the genetic pathophysiology of pheochromocytomas and paragangliomas (PPGLs) syndromes has advanced significantly over the last two decades. More than 20 driver genes have been discovered in either the disease's hereditary or sporadic form.[1] The eponym "ten percent tumour" derived from the belief that 10 % of PPGLs are familial has since become obsolete. In fact, forty percent of PPGLs cases are hereditary in origin and they are typically present at a young age. The Cancer Genome Atlas (TCGA) has classified PPGLs into three distinct molecular clusters namely pseudohypoxic PPGLs (cluster 1), kinase-signaling PPGLs (cluster 2), and Wnt-signaling PPGLs (cluster 3).[2,3] Hereditary proportions of Cluster 2 PPGLs are approximately 20% and the driver genes classified under this group include RET, NF1, MAX, and TMEM127.[3] Each cluster has a unique molecular-clinical-biochemical-imaging phenotype, which can be used to facilitate personalized treatment strategy for individuals with PPGLs.[2,3]

CASE

A 28-year-old Malay male was found to have severe hypertension during dental scaling. Unfortunately, he did not continue treatment for hypertension. Four months later, he was hospitalized for non-ST elevation myocardial infarction with supraventricular tachycardia. The echocardiogram showed a good left ventricular ejection fraction with some septal wall hypokinesis, otherwise, there were no features of cardiomyopathy. Coronary angiography findings were normal. Renal Doppler scan was negative for renal artery stenosis; however, a large left suprarenal mass was discovered. He was then referred to the endocrine team for further management.

This patient did not recall significant hyperadrenergic spells to suggest PPGLs. He reported no family history of multiple endocrine neoplasia (MEN) or von Hippel Lindau (VHL) syndrome among his parents and siblings. Endocrine workup revealed significantly elevated urine fractionated metanephrines with the presence of dysglycemia (Table 1). His thyroid ultrasonography and retinal examination were normal. Contrast-enhanced computed tomography (CT) of the adrenal glands reported a huge left suprarenal mass

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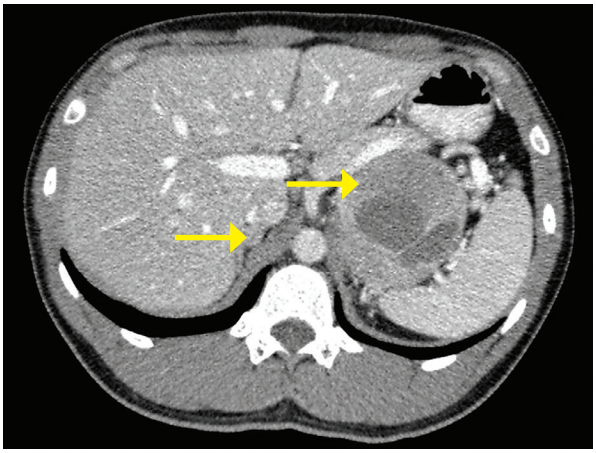

Figure 1. Axial view of the contrasted adrenal-directed CT during the venous phase showed bilateral adrenal masses of lipid-poor content, measuring in size [left: 7.1 x 7.5 x 7.4 cm; right: 2.0 x 1.1 x 1.8 cm] *(yellow arrows)*.

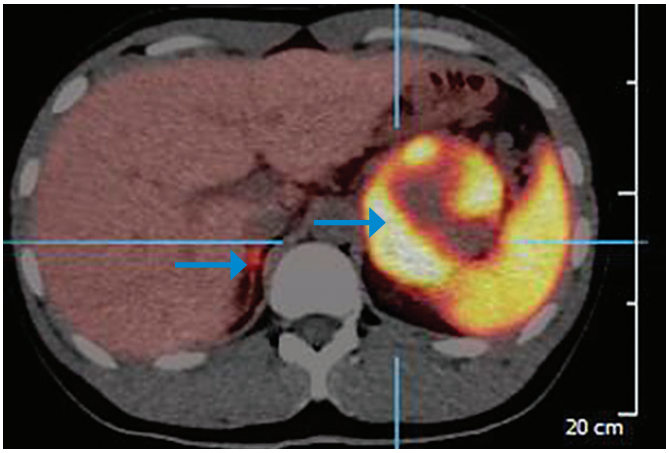

Figure 2. Axial view of the ^{68}Gallium-DOTATATE PET-CT showed an avid left adrenal mass (SUVmax 45.0) with necrotic centre whereas the right adrenal nodule was still within the physiological uptake (SUVmax 19.6) *(blue arrows)*.

Table 1. Biochemical results

Investigations	Initial diagnosis	6 months after surgery	Reference range
24-hour urine metanephrine			
Normetanephrine (µmol/day)	30.8	1.8	0 – 2.13
Metanephrine (µmol/day)	38.8	0.1	0 – 1.62
3-methoxytyramine (µmol/day)	6.5	0.9	0.1 – 1.79
Serum cortisol after overnight dexamethasone suppression test (nmol/L)	21.0	Not Relevant	<50
Fasting plasma glucose (mmol/L)	7.6	4.6	3.9 – 6.0
Glycated hemoglobin (%)	6.4	4.7	≤5.6

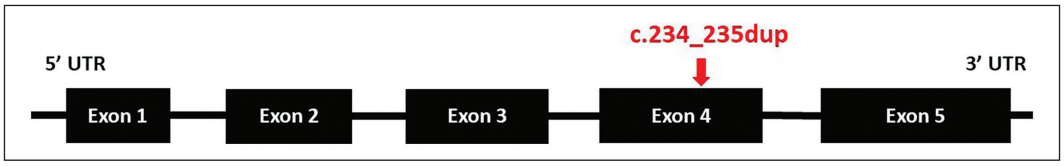

Figure 3. Schematic diagram of MAX gene mutation in the patient. UTR, untranslated region.

with mixed areas of central haemorrhage, necrosis, and cystic components measuring 7.1 x 7.5 x 7.4 cm (anterior-posterior x width x cranio-caudal)]. There was another smaller lipid-poor adenoma found in the right adrenal gland (Figure 1). Next, ^{68}Gallium-DOTATATE positron emission with computed tomography (PET-CT) showed significant uptake in the left adrenal mass, but indeterminate on the right (Figure 2). There was no evidence of nodal involvement or distant metastasis.

Our clinical dilemma was whether both adrenal lesions were pheochromocytomas (PCCs). We explained to the patient the role of genetic screening for hereditary PPGLs syndrome in facilitating the decision-making process during the multidisciplinary team meeting. He agreed and consented to genetic testing in an overseas genetic laboratory. Saliva sample was collected and exported to Invitae Laboratory, an accredited genetic laboratory based in the United States. Next-generation sequencing-based technique was used, targeting 14 genes susceptible to hereditary PPGLs. In this panel genes, EGLN1, FH, KIF1B, MAX, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, and VHL were covered. His genetic study identified a variant c.234_235dup (p.His79Profs*92), a sequence change that resulted in a frameshift mutation in the MAX gene (Figure 3). The genetic report explained that the variant would disrupt the last 82 amino acids of the MAX protein and extend the protein by 9 additional amino acid residues. Furthermore, this variant interrupts a region of the MAX protein in which other variants (p.Gln97*) have been determined to be pathogenic, further supporting this is a clinically significant region of the protein, for which the disruption caused by the variant would generate a pathogenic process. This is also a variant that was not previously registered in the population databases. Invitae Laboratory submitted this novel finding to the ClinVar registry, the public archive of the reports of the relationships among human variations and phenotypes curated by the National Center for Biotechnology Information (NCBI).

Following the multidisciplinary team discussion, bilateral adrenalectomy was proposed to the patient. Before the

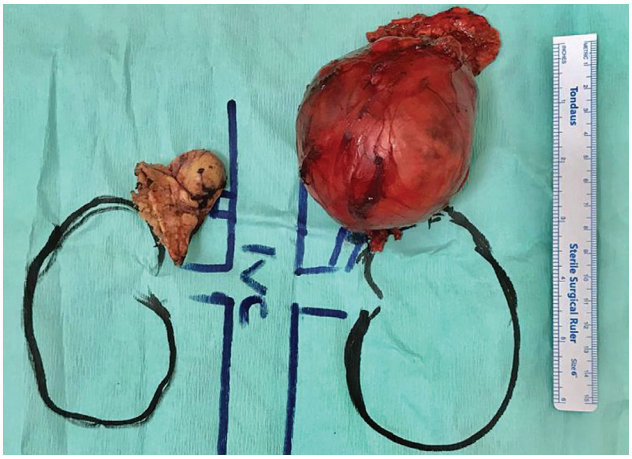

Figure 4. The gross specimen showed a huge, well-encapsulated left adrenal mass and a smaller right adrenal nodule.

surgery, he received combined alpha- and beta-adrenergic blockade using phenoxybenzamine and metoprolol. The right adrenal gland with the smaller nodule was first removed laparoscopically via a retroperitoneal approach. Then, the left adrenal gland and tumour were resected by open laparotomy (Figure 4). Pathology examination confirmed both adrenal masses were PCCs with benign histological characteristics. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) for the left PCC was 2/20, and for the right PCC was 0/20.

He was discharged home a week after the surgery, with hydrocortisone and fludrocortisone replacement. Six months later, repeated CT scan did not show any evidence of recurrence, and 24-hour urine for catecholamines was within normal limits (Table 1). He was advised for lifelong follow-up and an MRI from the base of the skull to the pelvis was scheduled in two years. Among the immediate family members, only his elder brother consented to do genetic testing, and he tested negative for MAX gene mutation.

DISCUSSION

PPGLs are a rare secondary cause of hypertension, accounting for only about 0.3 % of cases.[4] Untreated disease often leads to cardiovascular morbidity, as seen in our case. According to the 2014 Endocrine Society guideline, clinical scenarios that prompt evaluation for PPGLs include patients presenting with hyperadrenergic symptoms, symptoms provoked after using medications associated with adverse effects, incidental lipid-poor adrenal adenomas, hereditary predisposition or syndromic features suggesting hereditary PPGLs.[5]

Bilateral PCCs are uncommon, comprising 7–10 % of PPGLs.[6] Between 60 – 90% of bilateral PCCs harbor a germline mutation.[6] They are particularly associated with MEN type 2A and type 2B, in families with neurofibromatosis type 1 and VHL disease or in patients with MAX and TMEM127 gene mutation.[6] Additionally, bilateral PCCs can manifest either as synchronous or metachronous lesions, creating further clinical challenges for surgical technique planning and future tumour surveillance.

There is scarce data depicting the genetic landscape of PPGLs in our country due to limited access to genetic screening. As one of the major referral centers for PPGLs, findings from our research conducted in the year 2013 revealed two of twenty-four patients with non-syndromic features of PPGLs had bilateral PCCs and both carried a pathogenic mutation in the VHL gene.[7] Other gene mutations identified in this cohort were RET, SDHB, SDHA, and KIF1B. More recently, Burciulescu et al., reported that 14 out of 112 PPGLs patients in their series were bilateral PCCs, and most carried RET and VHL mutations.[6] It is therefore noteworthy to highlight the rarity of bilateral PCCs associated with MAX gene variants in the current literature.

Germline mutation affecting the MAX gene (five exons, located on chromosome 14q23) was first identified in 2011 as one of the causes of hereditary PPGLs.[4] MAX encodes a component of the MYC/MAX/MXD protein signaling pathway which are essential for regulating cell proliferation, differentiation, and apoptosis.[4] It exhibits an autosomal dominant inheritance with preferential paternal transmission of the disease.[4] Thus far, 58 cases have been described with 29 different germline mutations.[8] Mutations include missense in 38 %, nonsense mutations in 46 %, and splice site or frameshift mutations in 16 % of patients.[8]

Although the mean age at diagnosis is 32 years, 21 % of patients are diagnosed at pediatric age.[1] Considering the enormous size of the left PCC, our patient most likely developed the tumour at a much younger age as well. Mutations in MAX gene are associated with a distinctive biochemical profile with elevated levels of normetanephrines and normal or slightly increased levels of metanephrines.[9] This is, however, different from what was observed in our patient, which demonstrated hypersecretion of normetanephrines, metanephrines and 3-methoxytyramines. Interestingly, Daly et al., also reported a young male without apparent family history had markedly elevation for plasma epinephrine and norepinephrine; and urinary norepinephrine, normetanephrine and vanillyl mandelic acid levels.[10] Suffice it to say, further research would be needed to clarify the secretory phenotypes of PCCs associated with MAX gene mutations.

Fifty percent of PCCs related to germline MAX mutation manifest as bilateral disease.[4] The rate of metastatic disease is difficult to define given the low incidence of MAX mutation (<2 % of PPGLs).[1] Nonetheless, the case series reported by Burnichon et al., found two of twenty-three cases (8.7 %) having metastases.[10] Apart from bilateral PCCs, pituitary neuroendocrine tumours (NETs), pancreatic NET, erythrocytosis, and renal oncocytomas have also been described.[1,8]

A recent meta-analysis involving 1444 patients with bilateral PCCs concluded that partial adrenalectomy offers a chance of preserving adrenal hormone function but is associated

with a higher risk of local tumour recurrence.[11] There was no difference in the risk of metastasis and overall mortality among the group with bilateral PCCs undergoing total or partial adrenalectomy.[11] These findings will facilitate the shared decision-making process between the patient and the multidisciplinary team. Our patient underwent bilateral total adrenalectomy after considering the tumor size, the risk of recurrence, and metastasis.

Expert consensus suggested patients with any of the following criteria should undergo lifelong follow-up: germline mutation, age less than 20 years at initial diagnosis, tumour size of at least five centimeters, multiple or recurrent PPGLs, history of PGL, or noradrenergic/dopaminergic phenotype.[12] Screening with annual biochemical testing and full-body MRI imaging from the skull base to the pelvis every two years are therefore recommended for our patient. MRI is superior to CT imaging for identifying extra-adrenal tumours and minimizing radiation exposure for patients who require lifelong follow-up.[12]

The main limitation of this case report would be the lack of genetic screening for all immediate family members, which will further establish the germline status of his MAX gene variant. On the contrary, Burnichon et al., analysed 245 PCCs tumours in their case series and found 4 cases (1.65 %) carrying a mutation that was confirmed as somatic, which was supported by an absence of mutation in the germline DNA.[10] Greater public awareness is needed to promote the inferred benefit of genetic screening for this intriguingly rare, yet highly heritable endocrine tumour.

CONCLUSION

In the era of precision medicine, genetic screening of PPGLs is fundamental to ensure optimal outcomes for the patient and their immediate family members. Our case has also highlighted the importance of managing PPGLs in a specialized center dedicated to the diagnosis, treatment, and surveillance of this rare syndrome. Lastly, all patients with a history of PPGLs require a lifetime, individualized follow-up schedule according to their mutation status and disease characteristics.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
CKL: Conceptualization, Writing – original draft preparation, Visualization; **KK:** Writing – original draft preparation, Visualization; **ABN:** Conceptualization, Writing – review and editing; **ZH:** Conceptualization, Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

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