Metastatic pheochromocytoma/paraganglioma in a child with von Hippel-Lindau disease: An uncommon cause of paediatric hypertension

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Catecholamine-secreting chromaffin tumours are common among individuals with germline predisposition. Von Hippel-Lindau (VHL) disease is the most common genetic cause of pediatric pheochromocytoma/paraganglioma (PPGLs). While tumours may be multifocal (either synchronous or metachronous), metastatic PGGL are rare outside of carriers of germline SDHB variants, with an estimated rate of 5-8% in VHL disease. We present the case of a previously healthy male with multiple incidental secreting tumours, including a suspected metastasic lesion. We describe his diagnostic evaluation and treatment course.

A 6-year-old boy was referred for evaluation of bilateral undescended testicles. Abdominal-pelvic ultrasound demonstrated an incidental retroperitoneal mass in the right supra-renal fossa. More detailed evaluation demonstrated three retroperitoneal masses.

During his evaluation, asymptomatic hypertension with peak systolic blood pressure of 149 mmHg was noted. He had no other symptoms of catecholamine excess or family history of PPGLs or endocrine neoplasms. Biochemistry was notable for elevated serum normetanephrine (>7.5 nmol/L; ref. range <0.9 nmol/L) and urine VMA (12.8 mmol/mol Cr; ref range <=5.0 mmol/mol Cr) with normal levels of remaining serum metanephrines. He was diagnosed with PPGL. MRI abdomen confirmed three discrete heterogeneously enhancing lesions, ranging from 1.1-2.6 cm in the right adrenal gland, midline retroperitoneum and adjacent to the right liver. ^{68}Ga--DOTATATE scan showed similar somatostatin-avid lesions and an additional mid-retroperitoneal focus.

Pre-operative alpha-blockade was initiated with doxazosin, as was salt-loading and hyperhydration. He underwent an uncomplicated complete right adrenalectomy and excision of multiple paragangliomas. Multiple intra-adrenal pheochromocytomas, one extra-adrenal paraganglioma with negative excision margins and one subdiaphragmatic lesion with positive resection margins were identified. Given the rarity of metastatic disease in VHL, particularly at this young age, careful histological examination of the subdiaphragmatic lesion was performed. This was felt to be consistent with metastatic, as opposed to synchronous, tumour due to its atypical site, extensive infiltration of connective tissue and vascular space and a solitary lymph node containing tumour cells. Germline analysis demonstrated a *de novo* c482G>A variant in the *VHL* gene and a variant of uncertain significance in the *FH* gene. As germline FH variants have been associated with PPGL predisposition, it is unclear whether the *FH* variant in this child is disease-modifying or an incidental finding.

Post-operatively, he remains normotensive with normal metanephrines and no residual disease on repeat imaging.

This patient highlights the importance of histologic scrutiny with PPGLs located in atypical locations and of germline analysis for any child presenting with PPGL, to allow for pre-symptomatic surveillance to minimize morbidity attributable to associated lesions.