CASE REPORT

Unsuspected Von Hippel-Lindau syndrome in acute-onset resistant hypertension

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Accepted 2 July 2018

SUMMARY

The discovery of adrenal lesions during routine testing for hypertension requires focused consideration for adrenal overproduction of cortisol, aldosterone or metanephrines. An otherwise healthy 25-year-old woman presented with headaches, diaphoresis and hot flushes with grossly elevated urine catecholamines, normetanephrines and norepinephrine levels, yet normal metanephrines, epinephrine/epinephrine, cortisol and aldosterone levels. Subsequent functional uptake studies and scans identified bilateral adrenal adenomas consistent with pheochromocytomas. There was no family history of pheochromocytomas or familial syndromes; however, a targeted genetic analysis for causes of familial pheochromocytomas identified a heterozygous germline mutation in the *VHL* gene consistent with Von Hippel-Lindau syndrome. In this case, the identification of the *VHL* mutation led to careful screening and detection of clinically occult central nervous system hemangioblastomas and pancreatic neuroendocrine tumours. Verified genetic mutations facilitated best practices for long-term surveillance protocols, preconception counselling and screening of blood relatives. The patient responded well to surgical treatment and has ongoing multidisciplinary long-term surveillance.

BACKGROUND

This case example highlights an approach to hypertension arising from bilateral pheochromocytomas in a patient with no personal or familial history of pheochromocytoma-related syndromes. Von Hippel-Lindau (VHL) syndrome arises from mutations in a single gene (*VHL*) and is an inherited, autosomal dominant syndrome associated with a variety of benign and malignant tumours. It is one of several genetic familial syndromes that are associated with pheochromocytomas and related symptoms, including hypertension. The presence of these familial disorders must be ruled out because of the importance of locating and surgically removing the pheochromocytoma(s) to control blood pressure and symptoms and also because of the potential for associated tumours and malignancies uniquely correlated with each genetic mutation. For example, *VHL* is associated with tumours arising in multiple organs including hemangioblastomas of the brain, spinal cord and eye, plus neuroendocrine tumours and cysts of the pancreas. Every pheochromocytoma-linked syndrome has unique additional phenotypes that may be clinically silent

and unsuspected, yet with high potential for negative health impacts, highlighting the importance of verifying the underlying genetic mutation present.

CASE PRESENTATION

A 25-year-old healthy white woman had a known 2-year history of progressive intermittent headaches, hot flushes, diaphoresis and hypertension noted to be 145/90 mm Hg before medical therapy was initiated. Despite the progressive introduction of an ACE inhibitor (ramipril), calcium channel blocker (amlodipine) and an α_2 -adrenergic agonist (clonidine), her blood pressure unexpectedly continued to rise. She presented to the emergency department at the 2-month mark with a severe headache and a confirmed blood pressure of 165/125 mm Hg. She was fully compliant with the antihypertensive medications in the weeks preceding. She denied current or past symptoms of episodic or sustained tachycardia, palpitations, dyspnoea, abdominal pain, fatigue or weight loss. Her only other medication was an oral contraceptive, which had been taken long term. She is a non-smoker and non-drinker with no comorbidities, no recreational drug use or any family history of endocrinopathies.

INVESTIGATIONS

Sustained hypertension was confirmed in both arms and investigations into secondary causes of hypertension were initiated on her hospital admission. A same-day dedicated renal Doppler ultrasound ruled out renal artery stenosis, but incidentally located a unilateral left adrenal mass of 6.5 cm, supporting the possibility of secondary hypertension from adrenal hormone excess. Investigations into the adrenal incidentaloma ruled out excess cortisol or aldosterone as aetiologies of the hypertension when specifically screened. Other tests for secondary hypertension were similarly normal including calcium, parathyroid hormone (PTH) and thyroid (thyroid stimulating hormone [TSH]) measurements. After a several-day delay for test results, the 24-hour urine collection for catecholamines and metanephrines were ultimately reported to have marked elevations of normetanephrine at 38.76 $\mu\text{mol}/24$ hours (upper limit of normal (ULN) 3.90 $\mu\text{mol}/24$ hours), catecholamines at 13 700 $\mu\text{mol}/24$ hours (ULN 630 $\mu\text{mol}/24$ hours) and norepinephrine 13 652 $\mu\text{mol}/24$ hours (ULN 505 $\mu\text{mol}/24$ hours), without an elevation in urinary epinephrine/epinephrine or metanephrines.

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To cite: Sivaskandarajah GA, Arnason TG. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-225162

Figure 1 Abdominal MRI post-gadolinium administration, highlighting the 6.5×4.8×3.9 cm left adrenal mass with variable intensity/density and a central area of necrosis. The 0.9×1.2×1.2 cm right adrenal mass is not well defined in this image, but several enhancing masses are clustered in the pancreas.

Given the biochemical evidence for a pheochromocytoma, an abdominal MRI with gadolinium contrast was performed to confirm the location and was intended to better visualise the adrenal glands. This study (figure 1) confirmed the presence of the left adrenal mass (3.9×4.8×6.5 cm) previously found by ultrasound and unexpectedly also detected a smaller (0.9×1.2×1.2 cm) contralateral adrenal mass on the right. A retrospective review of the original renal Doppler ultrasound did not detect the small right-sided adrenal lesion, perhaps being below the level of detection. The same MRI incidentally found multiple lesions in the pancreas that were suspicious for neuroendocrine tumours and pancreatic cysts. Specific testing for chromogranin A, which is a non-specific marker of neuroendocrine tumours, reported a marked elevation at 334 ng/mL (ULN 110) consistent with the presence of pancreatic neuroendocrine tumours (pNETs). The largest pancreatic mass was medial to the uncinate process (3.7×3.0×5.6 cm) and was solid with areas of necrosis. The other pancreatic masses were significantly smaller, cystic, well defined and uniform in character and were in the body and tail of the pancreas.

While in hospital, focused studies were carried out to determine the functionality of the multiple lesions. An ^{111}In octreotide plus SPECT/CT scan confirmed octreotide avidity only in the uncinate process of the pancreas consistent with a pNET and correlating with the largest pancreatic lesion (figure 2). To confirm the activity of the adrenal masses suspected of being pheochromocytomas, a ^{123}I -labelled meta-iodobenzylguanidine (MIBG) whole-body scan was performed (figure 3). As shown, there was activity found within both adrenal glands, confirming bilateral functional pheochromocytomas. The activity was limited to the adrenal glands with no other body sites of increased uptake reported, making paragangliomas or distant metastasis unlikely.

DIFFERENTIAL DIAGNOSIS

The rapid development of resistant hypertension in our young patient led us to look for secondary causes of hypertension, which rapidly ruled out renal artery stenosis, hyperthyroidism or calcium elevations as underlying causes. The unexpected finding

Figure 2 Abnormal octreotide accumulation within the uncinate process of the pancreas correlating with the known mass in this area. Anterior (left) and posterior (right) near whole-body imaging 24 hours after an intravenous dose of ^{111}In -labelled octreotide. SPECT/CT scan not shown but indicated the persistent abnormal octreotide activity within the uncinate process of the pancreas. There is also physiological activity within a loop of large bowel. The adrenal masses seen on MRI do not abnormally accumulate octreotide.

of a large adrenal mass by renal Doppler ultrasound elevated the possibility of adrenal sources of aldosterone, cortisol or catecholamine excess as possible aetiologies. Screening tests were negative for aldosterone excess (a normal aldosterone:renin ratio was reported) or cortisol excess (normal low-dose dexamethasone suppression test). Strikingly, the urinary norepinephrine and normetanephrines were each elevated at least 10× normal, which gave compelling evidence of a pheochromocytoma as the underlying cause of the resistant hypertension. The significance of normal levels of epinephrine and metanephrines in this case is discussed below. Both MRI or CT are acceptable imaging modalities to localise pheochromocytomas prior to surgical excision, with an MRI being more sensitive than CT.¹ In our case, the abdominal MRI with contrast detected asymmetrical bilateral adrenal lesions and multiple pancreatic lesions. These findings are consistent with a previous seminal study finding that almost one-fourth of sporadic pheochromocytomas and more than four-fifths of patients with multifocal tumours have an underlying genetic aetiology that requires genetic analysis.²

Genetic testing targets those genes most likely associated with pheochromocytomas (European–American Pheochromocytoma Registry defined frequency): MEN2 affecting the *RET* oncogene (23.1%), von Hippel-Lindau (VHL) syndrome affecting the *VHL* gene (34.7%), neurofibromatosis type 1 (NF-1) affecting the *NF1* gene (12.4%) and hereditary paraganglioma–pheochromocytoma affecting the succinate dehydrogenase genes (*SDHB*, *SDHD* and *SDHC*) (21.1%, 8.1%, 29.2% and 0.002%).³ The combined finding of pheochromocytomas and pancreatic neuroendocrine tumours in a young healthy patient made VHL the single most likely aetiology, as these two findings have been associated with VHL syndrome. Our patient had no additional physical examination findings, which is also consistent with VHL syndrome. This contrasts with the café au lait macules found frequently in individuals with neurofibromatosis type 1, for example. VHL has an autosomal dominant inheritance, but can also arise spontaneously in younger people, such as in our case. Notably, these pheochromocytomas are non-epinephrine secreting and have normal urinary concentrations of epinephrine

Figure 3 ^{123}I -labelled meta-iodobenzylguanidine (MIBG) scan at 24 hours (right side). There is an intense MIBG-avid lesion involving the left adrenal gland corresponding to the large adrenal mass in this location identified on the correlative MR study (left side). Moderately intense uptake is also identified involved in a second lesion involving the right adrenal gland, which is significantly smaller and less intense than the left. No other abnormal foci of increased MIBG uptake are identified.

and normetanephrine, a pattern that we found in our analysis of this case.⁴ The only other genetic syndrome with this characteristic pattern of catecholamines and metanephrines are the succinate dehydrogenase mutations (SDHB/D) that also have normal urinary concentrations of epinephrine/epinephrine and normetanephrine. Unlike VHL, however, SDHB/D syndromes present with octreotide-avid extra-adrenal paragangliomas, which we did not detect in our patient using whole-body MIBG.⁵

While awaiting our genetic confirmation of VHL, which took several weeks to be completed, we carried out several investigations broadly related to other possible genetic syndromes associated with pheochromocytomas. We did not find elevated urinary concentrations of epinephrine, which would be expected in both MEN2 and NF-1 syndromes. MEN2A was also felt to be less likely as these individuals classically present early with hyperparathyroidism and medullary thyroid cancer. We found no evidence of primary hyperparathyroidism or thyroid carcinoma as no thyroid nodules or biomarkers were detected (normal calcium, PTH, calcitonin and benign thyroid ultrasound). MEN2B and NF-1 are also associated with distinct physical examination findings that were not present in our patient, making these underlying genetic defects less likely. It would be expected in MEN2B that a marfanoid habitus or mucosal neuromas would be present. In contrast, in NF-1, it is common to be able to find multiple cutaneous neurofibromas, café au lait or Lisch nodules on examination, none of which were present.⁵

Genetic sequencing reported from the Hereditary Endocrine Cancer Panel at the Children's Hospital of Philadelphia confirmed a *VHL* gene mutation localised to R167W that had been previously reported in a kindred from Newfoundland (Canada); none of the other genes in the panel were found to be pathogenic variants (*CDC73*, *CDKN1B*, *MAX*, *MEN1*, *PRKAR1A*, *PTEN*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127* and *TP53*). Interestingly, she has no known family history of ancestors living in that region of Canada.

VHL is a syndrome associated with multiple comorbidities, but the most common are bilateral pheochromocytomas,

hemangioblastomas of the brain, cord and eyes, and pancreatic neuroendocrine tumours/cysts.⁵ Many of these tumours are occult in younger patients and are only found on dedicated imaging and specific biochemical testing. As we clinically suspected, VHL was genetically confirmed in our patient, and imaging dedicated to detecting these additional tumours was done, which ultimately detected multiple lumbar and thoracic hemangioblastomas.

TREATMENT

The patient was discharged home prior to the surgical removal of the pheochromocytomas and prior to genetic confirmation of the diagnosis by genetics, as she was clinically stable with medically normalised blood pressure and without end-organ damage. Pending her adrenalectomy, her blood pressure was controlled as an outpatient by ramipril, amlodipine and prazosin. She was referred out-of-province to a surgical team with national expertise in neuroendocrine tumours. The patient was sent to the Neuroendocrine Surgery Centre in Calgary, Alberta. There, a discussion of surgical options was discussed by the surgical team and ultimately decided on a laparoscopic bilateral total adrenalectomy, the usual surgical practice for bilateral pheochromocytomas at that centre. This was followed by her return to Calgary several weeks later for a modified Whipple procedure, which included a partial pancreatectomy to remove the octreotide-positive uncinate pancreatic lesion plus enucleation of the two additional solid pancreatic masses. On receiving the confirmation of the VHL gene mutations, she was counselled and supported regarding her VHL diagnosis from our local medical genetics team.

OUTCOME AND FOLLOW-UP

The surgery normalised the biochemical excess of catecholamines and metanephrines from the pheochromocytomas and all associated symptoms improved, along with normalisation of her blood pressure off all antihypertensive medications.

As anticipated, the bilateral adrenalectomy resulted in adrenal insufficiency. Thus, she was immediately initiated on both glucocorticoid and mineralocorticoid replacement therapy and counselled regarding sick days and stress management to avoid adrenal crises. In addition, she also started dehydroepiandrosterone (DHEA) supplementation for the loss of adrenal androgens. The modified Whipple was successful and resulted in no loss of pancreatic exocrine or endocrine function. Her endogenous insulin production was maintained, with preserved postprandial C-peptide and normal blood glucose levels, without the need for medical therapy or pancreatic support.

In the month after the modified-Whipple procedure, the patient had vomiting due to mucosal thickening at the anastomosis site between the stomach and the small bowel that resolved with conservative treatment. A repeat MRI 3 months after the modified-Whipple procedure found postsurgical changes with no concerning findings, acknowledging that normal postoperative findings may resemble pathological changes, such as fluid collection or ischaemia.⁶ Clinical follow-up confirmed there was no need for insulin or pancreatic enzymes and that she had recovered well physically with a return to normal activities. To continue monitoring for pNET, a postoperative baseline linear endoscopic oesophagogastroduodenal ultrasound was performed that visualised the three small cysts remaining within the pancreas, all without malignant features. These will also be subject to ongoing surveillance.

The R167W variant of the VHL gene, as was found in our case, results in the amino acid substitution of arginine (R) for tryptophan (W) at position 167. This VHL mutation is associated with pheochromocytomas and pancreatic cysts and tumours, but also haemangiomas, endolymphatic sac tumours, renal clear cell cysts and renal carcinomas, which may be clinically silent. This led us to initiate a multimodal surveillance plan and we detected small hemangioblastomas along the cervical and thoracic spine using dedicated spinal MRI imaging. Fortunately, auditory testing looking for early signs of endolymphatic sac tumours, ophthalmic evaluation for retinal angiomas and renal CT screening for renal cell carcinoma were all negative.

She will be followed long term by a variety of specialists to perform ongoing dilated ophthalmologic assessment, neurological examinations and formal audiological evaluations. In addition to these clinical assessments, the patient will also be annually assessed by MRI of the brain and spinal cord and abdominal imaging. Annual laboratory testing of the patient's urine for metanephrine, normetanephrine and chromogranin A were also scheduled. This schedule of surveillance is per the methodology put forward by the Danish national guidelines for the diagnosis and surveillance of VHL syndrome.⁷

DISCUSSION

This young patient presented with resistant hypertension with two of the three classic symptoms of pheochromocytoma: headache and diaphoresis, but without palpitations. The subsequent finding of a large adrenal mass by ultrasound further strengthened the suspicion of a pheochromocytoma causing the progressive rise in blood pressure. This presentation is consistent with the literature reporting that less than 25% of patients with pheochromocytomas present with all three cardinal symptoms. Moreover, many often present with symptoms or signs that are not typically associated with pheochromocytomas, including abdominal pain, nausea, vomiting, visual disturbances, papilloedema, orthostatic hypotension and anxiety, or are completely asymptomatic.^{8–10} The combination of a young patient with

a pheochromocytoma, multiple pancreatic lesions, isolated elevations of normetanephrine and norepinephrine (but not metanephrine or epinephrine) all strongly supported the diagnosis of VHL syndrome, even without the genetic confirmation. Literature suggests that pheochromocytomas in VHL are most frequently unilateral,¹¹ yet there are many reports of bilateral tumours such as in our patient.^{12–15}

A guiding principle in the approach to pheochromocytomas is to confirm the presence of biochemical elevations of catecholamines and metanephrines before radiographic imaging due to the likelihood of finding non-functioning adrenal incidentalomas on imaging. In our case, the clinical presentation was consistent with a pheochromocytoma, but our first hard indication that an adrenal source and/or pheochromocytoma was involved was the incidental finding of an adrenal mass during the renal Doppler ultrasound. Adrenal incidentalomas should be evaluated for the possibility of elevated catecholamines, based on best practice guidelines, particularly in the presence of hypertension.

There are also well-described steps once a pheochromocytoma is suspected to minimise false positives. Antihypertensive and other medications that could interfere with catecholamine and metanephrine testing should be held (eg, tricyclic antidepressants, alpha-blockers, beta-blockers, acetaminophen and levodopa, among others).¹⁶ Personal habits that could elevate catecholamines and metanephrines also need to be curbed during testing, such as smoking, caffeine intake and recreational stimulants, to name a few. Serum metanephrines, versus the 24-hour urine collections, are becoming more widely available and popular for use for diagnosis. The serum levels come with the caveat that the sample reflects a single point in time, and not a 24-hour average, and have a sensitivity and specificity of 97% and 85%, respectively, as compared with 24-hour urinary metanephrine and catecholamine assays with a sensitivity and specificity of 90% and 98%, respectively, making false negatives more likely with serum testing.¹⁷ At our centre, a 24-hour urine panel was used to measure fractionated metanephrines and catecholamines, as per the Endocrine Society (USA) recommendations.¹⁶

VHL syndrome is a rare disease due to an autosomal dominant genetic mutation that frequently arises from spontaneous mutations, as appears to be true for our case. The VHL gene product, the VHL protein, regulates angiogenesis through the hypoxia-inducible factor-1 α (HIF-1 α) signalling pathway. Under normal oxygenation conditions, HIF-1 α levels are low as it is ubiquitinated and degraded by the pVHL-containing E3 ubiquitin ligase complex. On tissue hypoxia, HIF-1 α is stabilised and forms a protein complex that localises to the endothelial cell nucleus and increases nuclear transcription of vascular endothelial growth factor (VEGF), promoting local angiogenesis.¹⁸ In VHL syndrome, HIF-1 α putatively upregulates VEGF-induced angiogenesis and tumour growth contributing to increased risk for multiple tumour types clinically found in these individuals.¹⁹

Historically, VHL syndrome has been subdivided into type 1 and type 2, depending on the absence or presence of pheochromocytomas, respectively.²⁰ In those with pheochromocytomas, the European–American Pheochromocytoma-Paraganglioma Registry found 39% presented bilaterally in childhood and increased to 63% during adolescence, a very strong penetrance.²¹ Type 2 can be further classified as 2A and 2B indicating the risk (low or high, respectively) of renal cell carcinoma and pancreatic tumours. Furthermore, there is a 2C subtype for VHL syndrome with isolated pheochromocytomas.¹² The R167W variant found in our case presented as VHL type 2B due to a missense mutation at the amino acid position 167 resulting in the combined findings of pheochromocytomas and the additional finding of

pancreatic neuroendocrine tumours.²² Furthermore, the European–American–Asian VHL PanNET Registry assessed the morbidity and mortality of pancreatic neuroendocrine tumours in VHL and determined that all tumours greater than 2.8 cm in diameter should be excised to improve 10-year survival.²³

The specific R167W mutation confirmed and discussed in this case has been identified elsewhere and is associated with a relatively high risk for bilateral pheochromocytomas and severe cardiac sequelae if untreated. Familial follow-up of primary cases identified relatives with clinically silent pheochromocytomas, either unilateral or bilateral, and a strong association with retinal angiomas that otherwise would not have been identified.^{13 14} A family in northwestern China with nine affected members consistently presented with bilateral adrenal pheochromocytomas and pancreatic neuroendocrine tumours, yet no member developed renal cell carcinoma.¹² This is consistent with our newly identified case, where we have confirmed bilateral pheochromocytomas, a pNET and multiple haemangiomas, yet no evidence of additional tumours.

The surgical treatment of bilateral syndromic pheochromocytomas need to be individualised to the patient and surgical practices, and treatments may include total bilateral adrenalectomy either by open or laparoscopic approach. However, in a young person with a genetic cause for bilateral pheochromocytomas, a subtotal adrenalectomy may be performed to preserve cortical function.²⁴ Subtotal bilateral adrenalectomies obviate the need for glucocorticoid therapy and the risks associated with chronic adrenal replacement therapy; however, the risk for recurrence has been difficult to quantify due of short follow-up times.^{24 25}

In summary, young patients with resistant hypertension require rigorous algorithmic work-up assessing biochemical, radiographic and potentially genetic testing to identify the underlying aetiology, especially if there is a clinical suspicion of pheochromocytoma. Genetic studies have found that approximately 24%–32% of pheochromocytomas are familial and one institution found 41% of all individuals seen for pheochromocytoma had familial syndromes.²⁶ Genetic confirmation can expedite the initiation of treatment, surveillance of associated

conditions, and identify family members with occult pheochromocytomas or associated tumours.

Learning points

- ▶ A pheochromocytoma is a rare but serious cause of refractory hypertension that needs a systematic and methodical approach to identify and treat.
- ▶ Bilateral pheochromocytomas in young adults may be due to familial syndromes that need to be appropriately identified to localise all pathological lesions.
- ▶ Von Hippel-Lindau (VHL) syndrome is the second most common of the familial syndromes causing bilateral pheochromocytoma. Following appropriate identification of VHL syndrome, the patient needs to have a multimodal whole-body assessment to identify neoplasia and hemangioblastomas, followed by life-long surveillance.

Acknowledgements We extend our thanks to Dr Nijjar of Radiology/Nuclear Medicine for his assistance with images.

Contributors GAS performed the literature review and wrote the first draft of the manuscript. TA is the patient's current physician who obtained patient consent, supervised all aspects of this report and edited the final manuscript. TA is the corresponding author and guarantor of this manuscript and takes responsibility for the integrity of the data and the accuracy of the reporting.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

The process of being diagnosed with VHL was a long and terrifying one. After seeing many specialists, having multiple types of imaging and still no concrete answer, each day felt like it dragged on forever.

We were so desperate for answers that we travelled to Alberta on two different occasions to have an MIBG and PET scan done because the wait time was quicker there. It felt like there was no single doctor looking after my whole case, and that I was being tossed around because no one knew the answer. If it wasn't for my husband being my biggest advocate, the entire process would have taken even longer. The possibility of having VHL was only mentioned to me after my bilateral adrenalectomy and genetic testing to confirm VHL wasn't started until then.

I was very lucky to have amazing surgeons and I am happy to report that I have no lasting side effects from my Whipple procedure and I am back to living a life of normalcy. After connecting to many people with VHL and Whipple patients through social media, I feel thankful that my surgeries thus far have been very successful, and I consider myself very lucky after hearing about other's complications.

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