Unilateral Pheochromocytoma in Von Hippel-Lindau Syndrome Revealed by a Hemangioblastoma

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Citation

KC S, Poudyal H, Baral S. Unilateral Pheochromocytoma in Von Hippel-Lindau Syndrome Revealed by a Hemangioblastoma. 2024;87(3):353-5.

ABSTRACT

Von Hippel–Lindau (VHL) syndrome is characterized by the occurrence of both benign and malignant tumors, with typical manifestations such as cerebellar hemangioblastoma, Renal cell carcinoma (RCC) and pheochromocytomas.1 Additional tumors that may be associated include pancreatic cysts; neuroendocrine tumours; epididymal cysts and endolymphatic sac tumors.[1]

This case report details a 29-year-old male who arrived at the Emergency Department (ED) with a one-month history of headaches accompanied by dizziness and vomiting. A Computed Tomography (CT) scan of the head followed by Magnetic Resonance Imaging (MRI) suggested cerebellar hemangioblastoma. Further workup showed multiple tumors, including unilateral pheochromocytoma and pancreatic cysts, which aligned with a diagnosis of von Hippel-Lindau (VHL) syndrome. Notably, the patient's catecholamine and vanillylmandelic acid (VMA) levels were within normal limits. The patient underwent surgical intervention for the cerebellar hemangioblastoma, and the postoperative recovery was uneventful. This case is noteworthy due to its characteristic findings and the rarity of the condition.

KEY WORDS

Hemangioblastoma, Pheochromocytoma, Von Hippel-Lindau syndrome

INTRODUCTION

Von Hippel–Lindau (VHL) syndrome is a rare autosomal dominant disorder, affecting approximately 1 in 36,000 individuals; caused by mutations in the VHL gene located on chromosome 3p25, which significantly increases the likelihood of developing various tumors.[2] The diagnostic criteria for VHL syndrome include the presence of multiple CNS hemangioblastomas, a single CNS hemangioblastoma accompanied by other VHL-related symptoms, or any symptom in conjunction with a family history of VHL disease.[1] The onset of the disease can vary across different ages within families. Given the considerable morbidity and mortality linked to these lesions, early detection, screening, and surveillance are crucial for effective management. This report discusses a patient diagnosed with VHL syndrome who presented with CNS hemangioblastoma, unilateral pheochromocytoma, and pancreatic cysts.

CASE REPORT

A 29-year-old male presented to the emergency department with a one-month history of a sudden, non-radiating headache in the occipital and right temporal areas, along with episodes of dizziness. Associated with vomiting 2-3 times daily, preceded by nausea. Initial examination showed normal vital signs and laboratory tests. CT head revealed a well-defined cystic lesion in the right cerebellar hemisphere. Subsequent contrast-enhanced MRI showed the same cystic lesion with avidly enhancing mural nodule and a mass effect in the form of effacement of 4th ventricle without dilatation of 3rd and lateral ventricle, suggesting hemangioblastoma without obstructive hydrocephalus. Differential diagnoses included pilocytic astrocytoma, ependymoma, glioma and metastasis. A T2 spine screening showed no signficant findings.

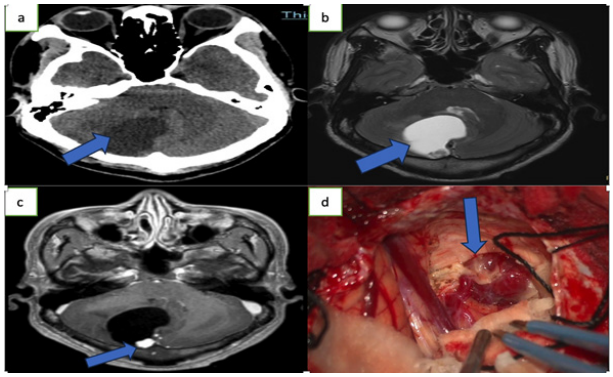

Figure 1. Plain CT head axial section (a) showing cystic lesion (arrow) in right cerebellar hemisphere effacing the 4th ventricle. T2-weighted axial section (b) showing well-defined cystic intra-axial mass lesion in the right cerebellar hemisphere along with eccentric mural nodule showing avid enhancement of nodule (c). Intra operative image (d) showing variegated red and yellow colored mass lesion.

Contrast-enhanced CT scan of the abdomen and pelvis revealed multiple pancreatic cysts, largest suggesting a serous cystadenoma. Avidly enhancing lesion in the left suprarenal area was also noted. Tests for pheochromocytoma, including 24-hour urinary VMA, plasma metanephrine, and 8 AM cortisol levels, were normal. The patient's family history indicated that her sister had previously undergone surgery for a brain tumor.

The patient underwent craniotomy to remove the cerebellar lesion. Intraoperative findings showed 2 X 2 cm pinkish-red, highly vascular nodule with multiple arterial feeders and a dilated draining vein. Clear cystic fluid was aspirated. Histopathology showed blood vessels and mildly pleomorphic tumor cells with enlarged nuclei and minimal mitotic activity, alongside normal glial cells and fibrin deposits, with no necrosis. Immunohistochemical analysis was positive for ERG, CD31, and Inhibin alpha, while GFAP and EMA were negative. The final diagnosis was hemangioblastoma, WHO grade 1.

The patient made uneventful recovery without intraoperative and postoperative complications. Thorough counseling was done with the patient as well as his family members, and currently, they are in regular follow-up with periodic radiologic evaluation. Since pheochromocytoma was asymptomatic, the patient has been kept on close follow-up with plan for surgery if any symptoms develop.

DISCUSSION

VHL syndrome is an autosomal familial cancer syndrome that affects multiple organ systems. Von Hippel and Lindau independently identified this syndrome in 1911 and 1926, respectively.[3] The estimated prevalence of the disease is 1 in every 36,000 live births, with 80% of cases having a positive family history and the remaining 20% due to de novo mutation.[1] It is classified into VHL type 1 (without pheochromocytoma) and VHL type 2 (with pheochromocytoma). VHL type 2 is further

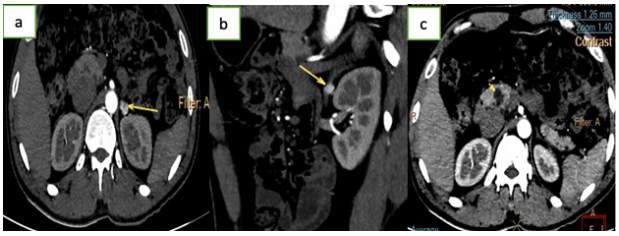

Figure 2. Post contrast axial and sagittal CT scan of abdomen (a,b) showing hypervascular lesion(yellow arrow) in left suprahilar region in left para-aortic region of abdomen. Axial CT abdomen (b) showing multiple cysts in pancreas; one of the cysts in pancreatic head showing multiple septations.

divided into type 2A (low risk of RCC or cerebellar hemangioblastoma), type 2B (high risk for developing RCC or cerebellar hemangioblastoma), and type 2C (familial pheochromocytoma without RCC or hemangioblastoma).[1]

Hemangioblastomas are rare, slow-growing tumors of spinal cord and posterior fossa. Spinal hemangioblastomas typically occur in the cervical or thoracic extradural regions but can affect the entire spinal cord.[4] They are often associated with cysts or syringomyelia and are linked to VHL syndrome, usually appearing in childhood and growing until around age 30. Symptoms vary by location and may include dizziness, ataxia, nerve dysfunction, weakness, and pain, with potential neurological complications from compression, hemorrhage, or paraneoplastic syndrome.[5]

Hemangioblastomas can appear as cystic lesions with enhancing nodules or solid tumors with dilated blood vessels on MRI. Gadolinium-enhanced MRI is the preferred diagnostic method, with CT/MRI angiography as alternatives. Differentiating hemangioblastomas from conditions like pilocytic astrocytoma, metastasis, ependymoma, glioma, and Schwannoma is essential for accurate diagnosis.[6]

Most pheochromocytomas are sporadic (80-90%), with 10-20% being hereditary. In VHL syndrome type 2, about 10% of cases involve bilateral or multiple pheochromocytomas.7 Diagnosing pheochromocytoma involves biochemical test, with lower epinephrine compared to norepinephrine being a key indicator. Catecholamine and VMA levels may remain normal during the "pre-biochemical phase," explaining the lack of classical symptom such as headaches, palpitations, and excessive sweating, as seen in our case.[8] Pheochromocytoma are identified via CT or MRI, while extra-adrenal pheochromocytoma requires 131I-Meta-Iodo-Benzyl-Guanidine (MIBG) scintigraphy.[9] Current contrast media guidelines do not place phaeochromocytomas as a contraindication to iodinated contrast administration. Urine catecholamine monitoring and ophthalmic evaluations should start at age 5 years, with annual abdominal ultrasounds from age 16. Preoperative α-adrenergic blockade with careful hemodynamic management are essential for surgery which is recommended for functional tumors, MIBG-positive

lesions, and tumors over 35 mm, ensuring at least one-third of the adrenal gland is preserved for adequate function.

In VHL disease, renal complications are common, with at least 75% of cases showing multicentric and bilateral involvement.[4] Renal cysts occur in 59-63% of patients, and RCC is found in 24-45%, primarily as clear cell carcinoma (75-80%). However, most cases are sporadic, with only 5% linked to VHL.[10] Our study found no renal involvement.

Pancreatic cystadenomas or cysts are often asymptomatic and detected as multiple cysts via imaging, as seen in our patient. Solid lesions are typically neuroendocrine tumors, while cystic lesions are mostly simple cysts or serous cystadenomas.[1,4] Given the association between renal cell carcinoma and VHL, it's essential to consider RCC metastasis when evaluating pancreatic lesions. While VHL-related cystic lesions are generally benign, distinguishing them from potentially malignant tumors like mucinous cystic tumors and intraductal papillary mucinous tumors is crucial.[11]

VHL diagnosis can be made through clinical observations. VHL gene mutation analysis is recommended for newly diagnosed cases. In individuals with a family history, a single hemangioblastoma in the retina or cerebellum, pheochromocytoma, or RCC suffices for diagnosis.[12] Isolated renal or epididymal cysts are not diagnostic due to their common prevalance.

Surgical outcomes are usually favorable for sporadic and cystic hemangioblastomas, but managing solid, familial, and multiple hemangioblastomas, especially in the brainstem and spinal cord, can be challenging.[13] Other treatment option includes radiation therapy, belzutifan, and anti-angiogenic therapies. Patients with complete tumor resection typically have a good prognosis, with recurrence rates of 12% to 14%, often manageable through further surgery.[13]

Screening, surveillance, and genetic counseling are crucial for patient management. For organs without lesions, a baseline contrast MRI of the brain and spine should be done every two years to detect CNS lesions, along with a biennial abdominal MRI, using CT and ultrasonography as needed.[1] Follow-up frequency for patients with cystic lesions of pancreas and kidney should be tailored, as these may progress to malignancies. Awareness of potential lung complications from VHL disease is important, especially regarding the risk of metastasis from RCC.

Early detection and monitoring of VHL syndrome symptoms are vital for timely intervention. This case underscores the importance of genetic testing for VHL patients and their family members. Diagnosing VHL can be complex, necessitating a thorough medical history and clinical assessment. A multidisciplinary management approach is crucial for enhancing life expectancy and quality of life.

ACKNOWLEDGEMENTS

We thank the patient and their family for their participation in this study. We want to acknowledge Department of Neuro surgery, Patan Hospital for their help.

REFERENCES

1. Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A Review of Von Hippel-Lindau Syndrome. *J Kidney Cancer VHL*. 2017 Aug 2;4(3):20-29. doi: 10.15586/jkcvhl.2017.88. PMID: 28785532; PMCID: PMC5541202.
2. Signoretti S, Choueiri TK, Kaelin WG. Molecular Abnormalities in Kidney Cancer. In: The Molecular Basis of Cancer [Internet]. Elsevier; 2015 [cited 2024 Sep 6]. p. 561-572.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9781455740666000391
3. Charlesworth M, Verbeke CS, Falk GA, Walsh M, Smith AM, Morris-Stiff G. Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. *J Gastrointest Surg*. 2012 Jul;16(7):1422-8. doi: 10.1007/s11605-012-1847-0. Epub 2012 Feb 28. PMID: 22370733.
4. Leung RS, Biswas SV, Duncan M, Rankin S. Imaging features of von Hippel-Lindau disease. *Radiographics*. 2008 Jan-Feb;28(1):65-79; quiz 323. doi: 10.1148/rg.281075052. PMID: 18203931.
5. Lonser RR, Butman JA, Huntoon K, Asthagiri AR, Wu T, Bakhtian KD, et al. Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. *J Neurosurg.* 2014 May;120(5):1055-62. doi: 10.3171/2014.1.JNS131431. Epub 2014 Feb 28. PMID: 24579662; PMCID: PMC4762041.
6. Khan MM BS. Hemangioblastoma. In: StatPearls [Internet]. StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK606126/
7. Neumann HPH, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, et al. Germ-Line Mutations in Nonsyndromic Pheochromocytoma. *N Engl J Med*. 2002 May 9;346(19):1459-66.
8. Eisenhofer G, Huynh TT, Hiroi M, Pacak K. Understanding catecholamine metabolism as a guide to the biochemical diagnosis of pheochromocytoma. *Rev Endocr Metab Disord.* 2001 Aug;2(3):297-311. doi: 10.1023/a:1011572617314. PMID: 11708294.
9. Ilias I, Divgi C, Pacak K. Current role of metaiodobenzylguanidine in the diagnosis of pheochromocytoma and medullary thyroid cancer. *Semin Nucl Med.* 2011 Sep;41(5):364-8. doi: 10.1053/j.semnuclmed.2011.03.003. PMID: 21803186; PMCID: PMC3415306.
10. Northrup BE, Jokerst CE, Grubb RL, Menias CO, Khanna G, Siegel CL. Hereditary renal tumor syndromes: imaging findings and management strategies. *AJR Am J Roentgenol.* 2012 Dec;199(6):1294-304. doi: 10.2214/AJR.12.9079. PMID: 23169721.
11. Ayloo S, Molinari M. Pancreatic manifestations in von Hippel-Lindau disease: A case report. *Int J Surg Case Rep.* 2016;21:70-2. doi: 10.1016/j.ijscr.2016.02.031. Epub 2016 Mar 2. PMID: 26945487; PMCID: PMC4802197.
12. van Leeuwaarde RS, Ahmad S, van Nesselrooij B, Zandee W, Giles RH. Von Hippel-Lindau Syndrome. 2000 May 17 [updated 2024 Feb 29]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. PMID: 20301636.
13. Liao CC, Huang YH. Clinical features and surgical outcomes of sporadic cerebellar hemangioblastomas. *Clin Neurol Neurosurg*. 2014 Oct;125:160-5. doi: 10.1016/j.clineuro.2014.08.001. Epub 2014 Aug 11. PMID: 25156409.