Case Report

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# Connecting the Dots: Multiple Hemangioblastomas and Pheochromocytoma Revealing the Diagnosis of Von Hippel Lindau Disease

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**Citation** Harshitha S, Garg N, Khare J, Suran A. Connecting the Dots: Multiple Hemangioblastomas and Pheochromocytoma Revealing the Diagnosis of Von Hippel Lindau Disease. Case Reports in Clinical Practice. 2026; 11(4): 190-194. DOI: 10.18502/crcp.v11i4.23135

**Running Title** Von Hippel-Lindau with Multiple Hemangioblastomas and Pheochromocytoma

**Article info:**
**Received:** July 19, 2026
**Revised:** July 29, 2026
**Accepted:** August 25, 2026

**Keywords:**
Von Hippel Lindau;
Hemangioblastomas;
Pheochromocytoma

## ABSTRACT

Von Hippel–Lindau (VHL) disease is an autosomal dominant hereditary tumor predisposition syndrome caused by pathogenic variants in the VHL gene located on chromosome 3p25.3. It is characterized by the development of multiple benign and malignant neoplasms and cystic lesions involving various organs, with most manifestations presenting in early to middle adulthood.

We report the case of a young female who initially presented with back pain and was found to have a spinal hemangioblastoma. A concomitant adrenal mass identified incidentally on lumbosacral MRI raised suspicion of an underlying hereditary syndrome. Subsequent brain MRI demonstrated a fourth ventricular hemangioblastoma. The constellation of multisystem lesions prompted germline genetic testing, which confirmed a pathogenic VHL gene variant, establishing the diagnosis of VHL disease.

The coexistence of CNS, spinal, adrenal, renal, or other characteristic tumors should raise suspicion for VHL syndrome. Diagnosis is established through a combination of clinical evaluation, multimodal imaging, and genetic testing, despite considerable phenotypic heterogeneity.

## Introduction

Von Hippel–Lindau disease occurs as the result of germline mutations in the VHL tumor suppressor gene, located on chromosome 3p25–26, inherited in an autosomal dominant pattern, with almost complete penetrance [1]. The estimated incidence of sporadic mutations in VHL disease is 1 in 36,000 live births [2]. It predisposes individuals to a variety of malignant and benign tumors, such as cerebellar and spinal hemangioblastoma, pheochromocytoma, renal cell carcinoma, pancreatic endocrine tumors, or visceral cysts [3].

## Case Presentation

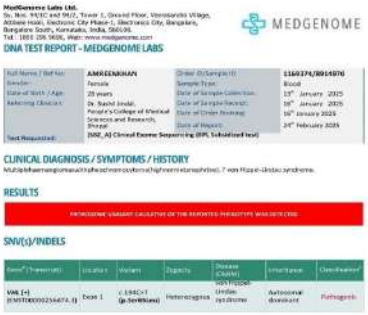
A 28-year-old unmarried female presented with a 2-month history of low back pain. The pain was insidious in onset, dull aching in nature, localized to the lumbosacral region, aggravated by exertion, and partially relieved with rest and analgesics. There was

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1A 1B

**Fig. 1A.** Single café-au-lait macule noted on the lumbosacral region.
**Fig. 1B.** Genetic report confirming mutation of VHL gene.

**Table 1.** Hormonal evaluation

| Investigation | Lab Value | Normal range |
|---|---|---|
| DHEAS | 196 mcg/dl | 35-450 mcg/dl |
| Intact PTH | 30.9 pg/ml | 15- 65 pg/ml |
| Chromogranin A | 136.3 ng/ml | 87.4-100 ng/ml |
| Plasma metanephrines | 40 pg/ml | <90 pg/ml |
| Plasma nor-metanephrines | >760 pg/ml | <190 pg/ml |
| 8 AM serum cortisol | 3.33 mcg/dl | 4.82- 19.5 mcg/dl |
| Plasma aldosterone concentration | 3.5 ng/dl | 3.0-6.0 ng/dl (supine position) |
| Plasma renin activity | 0.17 ng/ml/hr | 0.2-1.6 ng/ml/hr |
| Aldosterone/ renin ratio | 20.59 | ≤20 |

no history of trauma, early morning stiffness, fever, weight loss, lower-limb weakness or paresthesia, or bladder or bowel dysfunction. She had no prior history of similar complaints. Menstrual cycles were regular. There was no history of tobacco or alcohol use.

Her family history was notable for the death of a maternal cousin at 25 years of age due to an undiagnosed neurological disorder; however, medical records were unavailable. There was no history of parental consanguinity.

On examination, she was hemodynamically stable with a pulse rate of 80 beats/min, blood pressure of 110/70 mmHg (supine) and 120/70 mmHg (3 minutes after standing), and was afebrile. Anthropometric measurements revealed a weight of 49.6 kg, height of 161 cm, and a body mass index of 19.1 kg/m². General physical examination showed no pallor, icterus, cyanosis, clubbing, lymphadenopathy, or peripheral edema.

Cutaneous examination demonstrated a single café-au-lait macule over the back (Figure 1A). Local examination revealed a soft, non-tender lumbosacral bulge that became apparent in the sitting position and disappeared on standing. Systemic examination, including detailed neurological evaluation, was otherwise unremarkable.

Routine laboratory investigations were largely within normal limits, and hormonal evaluation is summarized in Table 1.

Contrast-enhanced magnetic resonance imaging (MRI) of the dorsolumbar spine revealed a cystic lesion measuring 15 × 14 × 90 mm involving the conus medullaris and extending from D9, possibly an arachnoid cyst.

Dedicated MRI of the lumbosacral spine further characterized the lesion as a large intramedullary lobulated cystic neoplasm extending from D9 to L1, favoring hemangioblastoma (Figure 2A & 2B). In addition, a well-defined cystic lesion was identified in the right suprarenal region, raising suspicion for pheochromocytoma.

Contrast-enhanced computed tomography (CECT) of fothe abdomen (Figure 2C) confirmed the presence a predominantly necrotic right adrenal mass, .suggestive of an adrenal adenoma




**Fig. 2A & 2B.** MRI DORSOLUMBAR SPINE AXIAL VIEW– Intramedullary lobulated cystic lesion extending from D9 to L1 vertebra measuring 11.5mm * 15 mm-intramedullary cystic spinal neoplasm? Hemangioblastoma

**Fig. 2C.** CEMRI ABDOMEN CORONAL SECTION – Large well defined heterogenous enhancing necrotic soft tissue density lesion in right suprarenal region - 44*43 MM- necrotic adrenal mass? ADENOMA

**Fig. 2D.** MRI-BRAIN AXIAL SECTION- T2 weighed Figure -hyperintense lesion occupying the inferior half of the fourth ventricle with superior extension into the upper cervical spinal canal most consistent with hemangioblastoma.

In view of the coexistence of spinal and adrenal lesions along with a positive family history of neurological disease, MRI of the brain (Figure 2D) was performed, which revealed a hemangioblastoma occupying the inferior half of the fourth ventricle with superior extension into the upper cervical spinal canal.

Given the constellation of central nervous system hemangioblastomas and an adrenal mass suspicious for pheochromocytoma, an inherited tumor predisposition syndrome was suspected. Targeted genetic testing (Figure 1B) identified a pathogenic variant in the VHL gene, confirming the diagnosis of Von Hippel–Lindau (VHL) syndrome, an autosomal dominant multisystem tumor predisposition disorder.

The patient was started on antihypertensive management for pheochromocytoma and was well controlled. All other routine systemic evaluations were normal and did not require any intervention.

## Discussion

Von Hippel–Lindau (VHL) disease is an autosomal dominant hereditary tumor syndrome with near-complete penetrance, characterized by the development of cysts and benign and malignant neoplasms in multiple organs.

VHL disease is caused by germline mutation or deletion of the VHL gene, a tumor suppressor gene. The VHL gene targets the HIF-1α (hypoxia-inducible factor) isoform and is a regulator of key cellular processes and angiogenesis. Defective VHL leads to accumulation of HIF-1α, which, along with HIF-1β, induces the production of several growth factors, such as VEGF, PDGF-β, and TGF-α, promoting both tumor cell growth and neoangiogenesis [4].

Currently, clinical diagnostic criteria include the following manifestations: CNS hemangioblastoma (including retinal hemangioblastoma), endolymphatic sac tumor (ELST), renal cell carcinoma (RCC), pheochromocytoma, paraganglioma, and neuroendocrine neoplasm. VHL is diagnosed when an individual exhibits the following set of symptoms or genetic/family factors:

- at least two CNS hemangioblastomas,
- at least one CNS hemangioblastoma and one other manifestation described above,
- at least one of the manifestations described above, and a pathogenic mutation in the VHL gene or a first-degree relative with VHL [5].

In our case patient had hemangioblastoma in the spinal region and was also found to have in the fourth ventricle.

Hemangioblastomas (HBs) are benign vascular neoplasms. Patients with VHL disease are at increased risk of developing HBs, often in the cerebellum or the retina, with less common occurrence in the spinal cord or brainstem [6]. In VHL patients, HBs often present in the third decade, with a mean age of diagnosis of 29 years, although they have been reported in the pediatric population as well [7].

Spinal hemangioblastomas are generally intradural and most commonly occur in the cervical or thoracic

regions, unlike in our case, where the lesion involved the dorsolumbar region. Most symptom-producing spinal hemangioblastomas are associated with cysts/syringomyelia/syrinx, as in our patient. Spinal hemangioblastomas usually present with pain; sensory and motor loss may develop with cord compression [8]. Our patient was also found to have a spinal and a brainstem hemangioblastoma. The gold standard for identifying and monitoring CNS hemangioblastomas is contrast-enhanced magnetic resonance imaging [9]. Microsurgical resection is the preferred therapy for CNS hemangioblastomas. If the patient is asymptomatic, as in our case, frequent neurological monitoring and imaging should be performed [10]. Despite their benign nature, hemangioblastomas are a substantial cause of morbidity and death in VHL patients because of their mass effect on CNS structures [11].

Renal lesions occur in approximately one-third of patients, with an increased likelihood of multiple bilateral tumors, mostly with clear cell features. The remaining lesions were either simple cysts (31%) or atypical cysts (7%). Simple renal cysts are usually asymptomatic; however, complicated cysts can develop into solid RCC tumors [11]. Our patient did not have any renal lesion and had preserved renal function. However, RCC is the most common cause of death in patients with VHL disease, accounting for 50% of deaths [12].

Pheochromocytomas and paragangliomas are neoplasms of the autonomic nervous system and develop in approximately one-fifth of patients with VHL disease. The phenotypic presentation of VHL disease (i.e., type 1 vs. type 2) is based on the presence or absence of pheochromocytomas [3]. Pheochromocytomas tend to present at a younger age, mostly secreting normetanephrine in VHL patients as compared with non-syndromic patients, with a mean age of diagnosis of 28 years, as in our case [3]. Conservative surgical resection of adrenal lesions has been advocated [13]. Although our patient was found to be normotensive at presentation and did not require any medication, regular monitoring and multidisciplinary follow-up were advised. However, our patient was lost to follow-up.

Other clinical manifestations include simple h VHLtpancreatic cysts, seen in 75% of patients wi opingldisease; 20% of patients have a risk of deve pancreatic neuroendocrine tumors; and 10–15% may . [develop endolymphatic sac tumors [14

A VHL mutation may now be discovered in about NAD100% of cases using genetic testing, such as sequencing and semiquantitative Southern blotting Clinical exome sequencing performed in our .[15] evealed a mutation on exon 1 occurring atr easc codon 194, with a high risk of pheochromocytoma, . [correlating with a VHL type 2A phenotype [16

Patients with Von Hippel–Lindau (VHL) disease should undergo annual clinical evaluation for neurological, visual, and hearing symptoms beginning in the first decade of life; brain and total spine MRI every 2 years from age 11 years (with particular attention to the inner/petrous temporal bone for endolymphatic sac tumors and the posterior fossa); annual ophthalmologic examination with indirect ophthalmoscopy from age 1 year (no later than 5 years) for retinal angiomas; abdominal MRI every 2 years from age 15 years for visceral lesions; and annual blood pressure monitoring from the first decade of life with annual plasma free or 24-hour urinary fractionated metanephrines from age 5 years for pheochromocytoma surveillance [14].

Insights into VHL gene mutations affecting the VEGF signaling pathway have spurred progress in targeted drug therapies, such as belzutifan (HIF-2 inhibitor), tivozanib (VEGF receptor tyrosine kinase inhibitor), and bevacizumab (anti-VEGF monoclonal antibody) [17].

Pazopanib is an FDA-approved treatment for advanced renal cell carcinoma [18].

## Conclusion

VHL disease should be considered in patients with hypertension and multisystem tumors. Genetic testing, cascade family screening, and lifelong risk-adapted surveillance are fundamental to early diagnosis and organ-preserving management.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

### Funding

No funding was received to assist with the preparation of this manuscript.

### Conflict of Interests

The authors have no conflict of interest to declare.

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