

Oroiginal Article - Case Report

A constellation of clear cell tumors: Bilateral clear cell renal cell carcinoma, phaeochromocytoma, pancreatic serous cystadenoma and hemangioblastoma in Von Hippel-Lindau disease

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Submitted: Aug 08, 2026; Revised: Sept. 27, 2026; Accepted: Sept. 28, 2026

Citation: Paramita P. A constellation of clear cell tumors: Bilateral clear cell renal cell carcinoma, phaeochromocytoma, pancreatic serous cystadenoma and hemangioblastoma in Von Hippel-Lindau disease. Discoveries 2026, Jul-Sep, 14(3): e235. DOI: 10.15190/d.2026.14

ABSTRACT

A case of 32-year female with episodic left flank pain, bilateral adrenal and kidney enlargement with multiple cysts, multiple pancreatic cysts, right cerebellar cystic lesion is being described. The constellation of findings pointed towards a diagnosis of Von Hippel-Lindau (VHL) disease. Histopathological examination revealed clear cell renal cell carcinoma, pancreatic micro cystadenoma, all composed of clear cells with intricate capillary vascular network. Adrenals showed bilateral phaeochromocytoma. VHL is an autosomal dominant disorder which involves the inactivation of the VHL tumor suppressor gene present at 3p25-26 responsible for the clinical spectrum. Management aims at continuous surveillance and monitoring with frequent surgical interventions increasing mortality and morbidity. Knowledge about the VHL protein and downstream molecules like HIF α has led to investigate the role of antiangiogenic drugs to reduce or prevent tumorigenesis in VHL disease.

Key words

Von Hippel-Lindau disease, Clear cell renal cell carcinoma, Pheochromocytoma, Hemangioblastoma, Histopathology.

Abbreviations

Central Nervous System (CNS); Clear Cell Renal Cell Carcinoma (CCRCC); computer tomography (CT); Hematoxylin and Eosin (H&E); hemangioblastoma (HB); Hypoxia-Inducible Factor (HIF); intra cranial tension (ICT); magnetic resonance imaging (MRI); Multiple Endocrine Neoplasia type 2 (MEN2); pancreatic neuroendocrine tumors (PanNETs); Platelet-Derived Growth Factor (PDGF); pheochromocytoma (PCC); PET-CT stands for Positron Emission Tomography-Computed Tomography (PET-CT); renal cell carcinoma (RCC); Vascular Endothelial Growth Factor (VEGF); VHL-Elongin B-Elongin C (VBC); Von Hippel-Lindau disease (VHL).

INTRODUCTION

Von Hippel-Lindau disease (VHL, familial cerebello-retinal angiomas) is a rare heritable genetic highly penetrant autosomal dominant disorder diagnosed approximately in 1 in 36,000 people and associated with predisposition to vascular tumors. The VHL (Von Hippel-Lindau) disease was described in von Hippel's literature in 1911 and Lindau's literature in 1926.

Clinical manifestations of the disease are attributed to VHL tumor suppressor gene mutation,

located on chromosome 3p25-26. The clinical spectrum of VHL syndrome includes multiple tumors of various localization (often bilateral) and low histologic grade comprising of hemangioblastoma (HB) of central nervous system (typically posterior fossa or medulla), retinal hemangioblastoma, renal cell carcinoma (RCC) and pheochromocytoma (PCC) pancreatic cystadenoma and pancreatic neuroendocrine tumors (PanNETs) and endolymphatic sac tumors of the middle ear. VHL is clinically classified into two types based on the presence or absence of PCC. Type 1 is without PCC whereas type 2 has PCC. Type 2 is further subclassified into type 2A (no RCC), type 2B (all tumors), type 2C (only PCC). Here we describe the histopathological aspects of a full-blown VHL with multiple tumor manifestations.

CASE PRESENTATION

A 32-year female presented with episodic left flank pain of 5 months duration with occasional episodes of vomiting and headache for one month. Examination revealed a blood pressure of 130/90 mm of mercury. There was no neurological deficit.

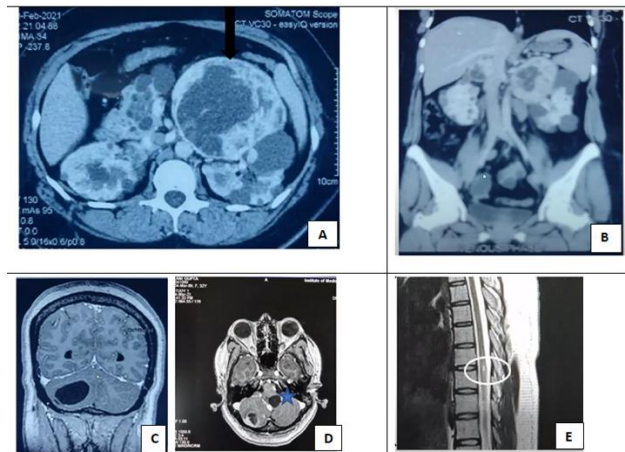


Figure 1. Radiological findings of the case. (A) CECT abdomen: axial view show enlarged bilateral kidneys containing multiple cysts. Left kidney in addition showed a solid component. Multiple cysts were noted in the head of pancreas, some of the cysts are hyperdense which shows internal haemorrhagic and complex contents. The black arrow points towards a large~ 9 t 10 cm mass in the retroperitoneum involving left anterior pararenal space. The lesion is strongly enhancing peripherally. There is central cystic and necrotic component. (B) Coronal section showing bilateral suprarenal masses, adrenals are not visualized separately from renal masses. (C) Coronal and axial images of brain show cystic lesion with septation,

peripherally enhancing with solid mural nodule in right cerebellum, (D) another cystic lesion in the left cerebellar peduncle extending into the foramen of magnum (*). (E) Spinal cord T2 hyperintense lesions noted which were contrast enhancing.

Investigations

Ultrasound revealed bilateral enlarged kidneys with multiple cysts, right kidney measured 143x61mm and left kidney measured 138x60 mm. Pancreas was also enlarged in size with multiple cysts in head, body and tail, largest in the tail measured 93x82mm. A 35x32 mm hemorrhagic cyst was noted in the right ovary. Contrast enhanced CT scan of abdomen ratified the above findings and bilateral adrenal enlargement was also seen. (Figure 1A,B) MRI brain revealed a right cerebellar cystic lesion with septation and peripherally enhancing with solid mural nodule. Another cystic lesion was noted in the left cerebellar peduncle extending into the foramen of magnum. (Figure 1C,D) MRI of spinal cord showed T2 hyperintense lesions contrast enhancing. Indirect ophthalmoscopy was unremarkable.

Plasma metanephrines were within normal limit, 27.10ng (7.9-88ng), however normetanephrines were elevated 695ng (20-135ng). Serum cortisol and 3 methoxy tyramine was within normal limit. 68 gadolinium Dotanoc PET CT scan showed multiple cystic lesions in right cerebellar hemisphere and medulla oblongata, heterogenous dense lesions in bilateral adrenal gland (left>right) (Figure 2A,B). Pancreas appeared bulky with non-tracer avid multiple variable sized cystic lesions. There was no evidence of any metastasis.

With these constellations of findings, a clinical diagnosis of Von Hippel Lindau disease with bilateral pheochromocytoma, bilateral RCC, cerebellar, medullary and spinal hemangioblastoma was being considered.

Treatment and follow up

Bilateral adrenalectomy with bilateral partial nephrectomy, distal pancreatectomy was performed. Patient was doing well till post op day 17 when she developed syncopal attacks and postural hypotension, was managed with hydrocortisone and fludricortisone. However, the patient developed shock on day 22 and succumbed in post operative day 23 due to adrenal insufficiency and septicemia.

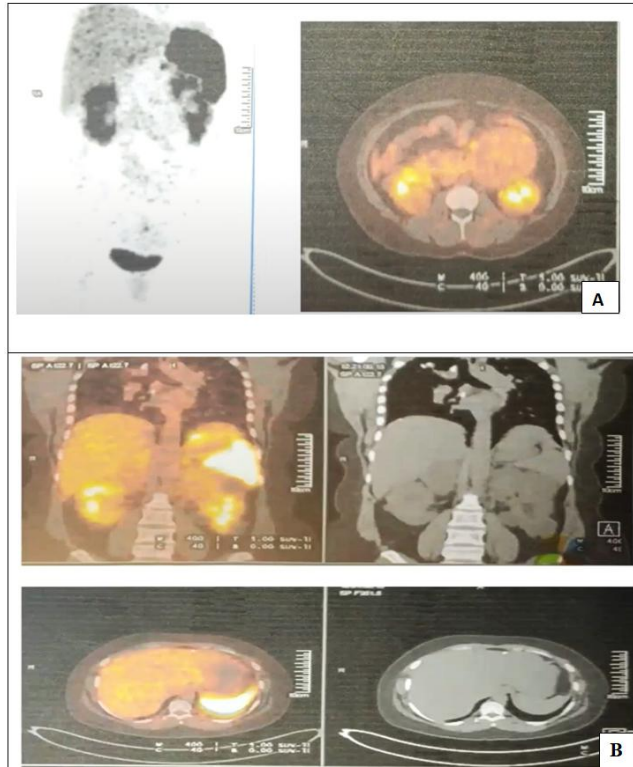


Figure 2. 68 gadolinium Dotanoc PET CT scan showed (A) heterogenous dense lesions in bilateral kidney and adrenal glands (left more than right). (B) Pancreas appeared bulky with non-tracer avid multiple variable sized cystic lesions.

Pathology

Grossly the bilateral kidney tumors were solid cystic (left more cystic in appearance), pancreatic tumor was entirely cystic and the adrenal gland showed mahogany brown cut surface (**Figure 3A-F**).

Histopathological examination of the bilateral partial nephrectomies showed a tumor disposed in alveolar pattern surrounded by thin capillary network. The tumor cells showed abundant clear cytoplasm with prominent cytoplasmic membrane. One of the kidneys was largely cystic. (**Figure 4C-D**). Pancreas was largely cystic lined by cells with clear cytoplasm supported by thin vascular network. Few areas show papillary infoldings, however no complex branching was seen. (**Figure 4E-G**). Sections from adrenal gland show tumor cells arranged in Zellballen pattern surrounded by intricate vascular network (**Figure 4H,I**).

A diagnosis of bilateral renal CCRCC, pheochromocytoma and pancreatic microcystadenoma was confirmed and the patient fitted into type 2B VHL.

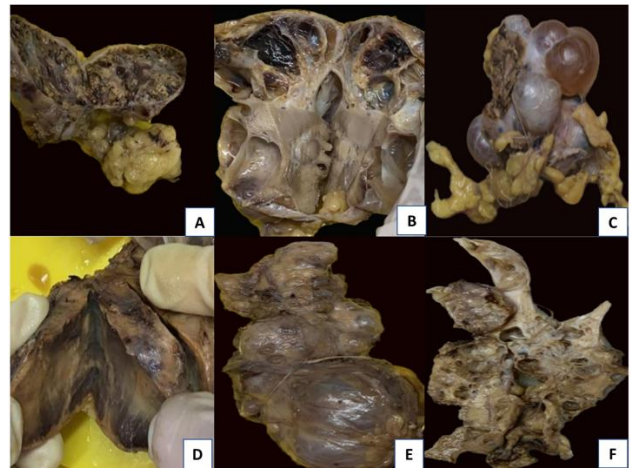


Figure 3. Gross images of specimens. (A) Cut surface of right kidney showed variegated appearance (B) External surface and (C) cut surface of left kidney shows multiple cysts. (D) Cut surface of adrenal gland shows a solid mahogany tumor in the medulla (E) External surface and (F) cut surface of pancreas shows variable sized cystic spaces.

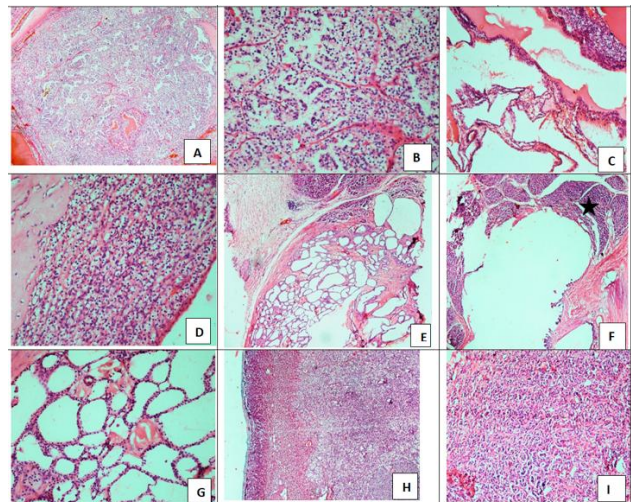


Figure 4. Microscopic images of clear cell renal cell carcinoma (A-D) show tumor cells disposed in alveolar pattern separated by thin vascular septae (A, H&E, $\times 40$), (B, H&E, $\times 100$), cystically dilated spaces lined by clear cells (C, H&E, $\times 40$); (D, H&E, $\times 100$). (E) Multiloculated cystic spaces in the pancreas (H&E, $\times 40$), (F) some of which contain thin papillary excrescences, pancreas marked with * (H&E, $\times 100$), (G) dilated spaces are lined by clear cells resting on thin vascular septae (H&E, $\times 200$), (H) Adrenal gland shows expanded medulla (H&E, $\times 40$) with (I) tumor cell disposed in Zellballen pattern (H&E, $\times 100$)

DISCUSSION

VHL, an autosomal dominant multiorgan inherited neoplastic disorder characterized by a constellation of highly vascular benign and malignant tumors and cysts. The inactivation and loss of function of the tumor suppressor VHL protein and the elongin B, C complex (VBC complex) causes inability to degrade and ubiquitinate HIF leading to development of pseudohypoxic conditions; accumulation of HIF and other proteins lead to increased transcription of pro-tumorigenic molecules like VEGF, PDGF, and TGF- α that results in development of highly vascular tumors characteristic of VHL. In 80% cases it is inherited as a germ-line mutation whereas in 20% it is due to de novo mutation. In a background of confirmed family history of VHL, finding a single major VHL tumor (CNS hemangioblastoma, retinal hemangioblastoma, clear cell RCC, PCC, pancreatic endocrine tumors or endolymphatic sac tumor) suffices for a VHL diagnosis in an at-risk relative. In cases of sporadic (or a nonfamilial) event, a clinical diagnosis of VHL disease requires presence of two tumors. This case did not have any family history, and genetic assessment was not performed.

PCC occurs usually due to missense mutations rather than deletions; the mutation is usually at nucleotide 238 in exon 3. The cause of development of PCC is threefold. One, increased production of tyrosine hydroxylase by HIF and subsequent overproduction of catecholamines, two, dysfunction of VBC complex leading to accumulation of atypical protein kinase gamma with overproduction of B-jun (anti-apoptotic) which prevents apoptosis of neural crest cells in the adrenal medulla and third, binding of pVHL with fibronectin resulting in loss or change of fibronectin matrix assembly¹. The risk of malignancy is about 5% in VHL PCCs.

VHL-related paragangliomas/PCCs show increased levels of dopamine and norepinephrine. This might be due to a reduced expression of tyrosine hydroxylase and phenylethanolamine N-methyltransferase (norepinephrine to epinephrine converting enzyme) in VHL-related PCCs. It has also been postulated to be one of the reasons why patients with VHL are less likely to present with hypertension (especially of the paroxysmal type) than patients with MEN2 as was the scenario in this case too. Measurement of plasma normetanephrine levels is reported to be the most sensitive test for detecting pheochromocytoma

The identification of mutation in proband allows identification of mutation carriers among asymptomatic family members. A 62% risk for PCC was associated with the arg238trp and arg238In mutations².

The lifetime risk of developing clear cell RCC (ccRCC) is 69%.^[3] Mean age at diagnosis is 40 years but routine screening may detect asymptomatic tumors.

Pancreatic manifestations in VHL disease include benign multiple cysts (70%), serous microcystadenomas (10%), and panNET (20%)³. VHL-related NET tends to be multiple, asymptomatic, with overall indolent behavior in contrast to sporadic NETs. Therefore, noninterventional options might be desirable to reduce mortality and morbidity, such as potential loss of pancreatic function.

The lifetime risk of developing CNS hemangioblastomas in VHL is 84% and it is the presenting feature in 40% cases. Patients present with symptoms of raised intra cranial tension (ICT) and with limb or truncal ataxia.

Management of VHL disease involves lifelong radiological and biochemical surveillance, with repeated surgical intervention causing significant morbidity and mortality. CNS-HB are usually monitored until development neurological symptoms which warrants a surgical intervention although stereotactic radiosurgery may also provide disease control. The other dilemma is which lesion to operate on first in patients with concurrent PCC. If HB is operated first, there is a substantial risk of hemodynamic instability due to excessive catecholamine release. If PCC is operated first there is a risk of significant rise of ICT during surgery. As CCRCC are frequently bilateral and multifocal nephron sparing surgery is most commonly performed when the dominant lesion reaches 3 cm diameter as the risk of metastasis is minimal below this threshold. For tumors less than 3 cm careful observation/surveillance is preferable although consideration may be given to removal of a rapidly growing lesion measuring >3cm⁴. PanNETs are treated by either excision, or Whipple's or distal pancreatectomy depending upon the size and location of the lesion.

Systemic therapies are being investigated that would prevent or reduce the need for surgical intervention could improve clinical outcomes and quality of life for affected individuals. VEGF

- Von Hippel–Lindau (VHL) disease is a hereditary tumour syndrome defined by characteristic lesions, although sporadic cases also occur
- Concurrent pheochromocytoma and haemangioblastoma present a surgical dilemma regarding which lesion to operate on first
- Postoperative adrenal insufficiency remains a management challenge

inhibitors like sunitinib and pazopanib have been tried in patients with localized VHL diseases, however, was associated with significant toxicity leading to early therapy discontinuation. Belzutifan, a second-generation small molecule hypoxia-inducible factor 2a (HIF-2 α) inhibitor has recently been approved by US and UK regulators for the treatment of VHL (disease)-associated ccRCC, CNS-HB and panNET, however more research is required to decide on type of patient selection (localized/advanced disease), adverse events etc⁵.

CONCLUSION

VHL is associated with worse prognosis because of multisystem involvement which requires frequent follow up and interventions, leading to increased morbidity and mortality. Management of VHL-associated tumors requires multidisciplinary approach. Advances in genetic testing have allowed early diagnosis of this syndrome and may lead to early intervention and improved outcome. Besides surgical approach, with advances in understanding the molecular biology of VHL disease, several anti-angiogenic therapies are currently available in treating patients with common manifestations such as RCC.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Acknowledgements

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given consent for her images and other clinical information to be reported in the journal. The patient understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be

guaranteed. **Source of Funding:** This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Generative AI and AI-assisted technologies

No datasets were generated or analyzed during the current study Competing interests

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References

1. Hoffman MA, Ohh M, Yang H, Klcio JM, Ivan M, Kaelin WG Jr. von Hippel Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. *Hum Mol Genet* 2001;10:1019-27
2. Crossey PA, Richards FM, Foster K, Green JS, Prowse A, Latif F, et al. Identification of intragenic mutations in the von Hippel Lindau disease tumour suppressor gene and correlation with disease phenotype. *Hum Mol Genet* 1994;3:1303-8.
3. Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel-Lindau disease. *Q J Med* 1990; 77(283):1151-63
4. Steinbach F, Novick AC, Zinke H, Miller DP, Williams RD, Lund G, et al. Treatment of Renal Cell Carcinoma in von Hippel Lindau Disease a Multicenter Study. *JUrol* 1995;153:1812-6
5. Shepherd STC, Drake WM, Turajlic S. The road to systemic therapy in von Hippel-Lindau (VHL) disease: Are we there yet? *Eur J Cancer*. 2023 Mar;182:15-22. doi: 10.1016/j.ejca.2022.12.011. Epub 2022 Dec 20. PMID: 36708612.

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