

A Clinical Insight into Von Hippel-Lindau Syndrome: Diagnostic Challenges

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Abstract: Von Hippel-Lindau (VHL) syndrome is a rare hereditary disorder characterised by the development of multiple benign and malignant tumours across various organs. Caused by mutations in the VHL tumour suppressor gene, it presents a wide range of clinical manifestations, including retinal haemangioblastomas, central nervous system tumours, renal cell carcinoma, pancreatic lesions, and pheochromocytomas. This report describes the case of a 35-year-old woman who presented with visual impairment and abdominal masses. Imaging revealed typical VHL manifestations, including bilateral renal lesions and pancreatic involvement. Genetic testing confirmed the diagnosis. The patient underwent staged partial nephrectomies, with histopathology confirming clear cell renal cell carcinoma in both kidneys. This case highlights the importance of recognising the variable clinical and radiological presentations of VHL syndrome. Early diagnosis and multidisciplinary management are essential to reduce morbidity and mortality. Increased awareness and regular surveillance are critical for timely detection and intervention in patients with VHL syndrome.

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Introduction

Von Hippel-Lindau (VHL) syndrome is a rare condition, with an estimated incidence of 1:36,000 individuals and a penetrance exceeding 90% after the age of 65 (Mourão et al., 2022). It follows an autosomal dominant inheritance pattern, affecting the germline of the VHL tumour suppressor gene, located on chromosome 3. Mutations in this gene increase the risk of developing various benign and malignant tumours across multiple organs. The VHL gene regulates key pathways responsible for angiogenesis and cell growth.

Clinical suspicion typically arises following the detection of retinal haemangioblastomas or central nervous system (CNS) haemangioblastomas, especially when associated with tumours of the kidneys, pancreas, adrenal glands, or endolymphatic sac (Mourão et al., 2022). The average age at onset of VHL-associated tumours is approximately 26 years (Maher et al., 1990). However, the onset, signs, and symptoms vary by tumour type, with initial presentations ranging from childhood to adulthood (VHL Alliance, 2023).

This report presents a case of VHL to enhance clinical awareness of its recognition, pathophysiology, and diagnostic process. The imaging findings illustrate typical VHL-associated lesions. The patient, initially diagnosed with a retinal haemangioblastoma, underwent abdominal computed tomography (CT), which revealed multiple abdominal tumours.

Case report

A 35-year-old woman from Minas Gerais, Brazil, presented with longstanding ocular lesion and progressive visual impairment, along with palpable abdominal masses. She reported a history of tobacco use but denied other comorbidities, prior surgeries, or regular medication use. At physical examination, bilateral retinal capillary haemangioblastomas were identified, along with firm, non-mobile abdominal masses. The remainder of the physical examination was unremarkable.

Abdominal CT revealed a diffusely enlarged pancreas with scattered calcifications, multiple cysts, and hypodense nodules demonstrating contrast enhancement post-intravenous iodinated contrast administration (Figure 1). Both kidneys were enlarged, with multiple cysts, nodules, and enhancing solid and mixed lesions. Brain magnetic resonance imaging (MRI) showed no significant abnormalities. These findings raised strong suspicion for VHL syndrome. Genetic testing confirmed the diagnosis of VHL syndrome.

The patient underwent a right partial nephrectomy for clinically suspected malignant renal lesions. Postoperative recovery was uneventful, and histopathological analysis confirmed clear cell renal cell carcinoma. Two months later, due to the confirmed malignancy, a left partial nephrectomy and marsupialisation of renal cysts were performed. Recovery was again uneventful, and histopathology revealed clear cell renal cell carcinoma in the left kidney lesions. The patient remains under regular outpatient surveillance with the oncology team.

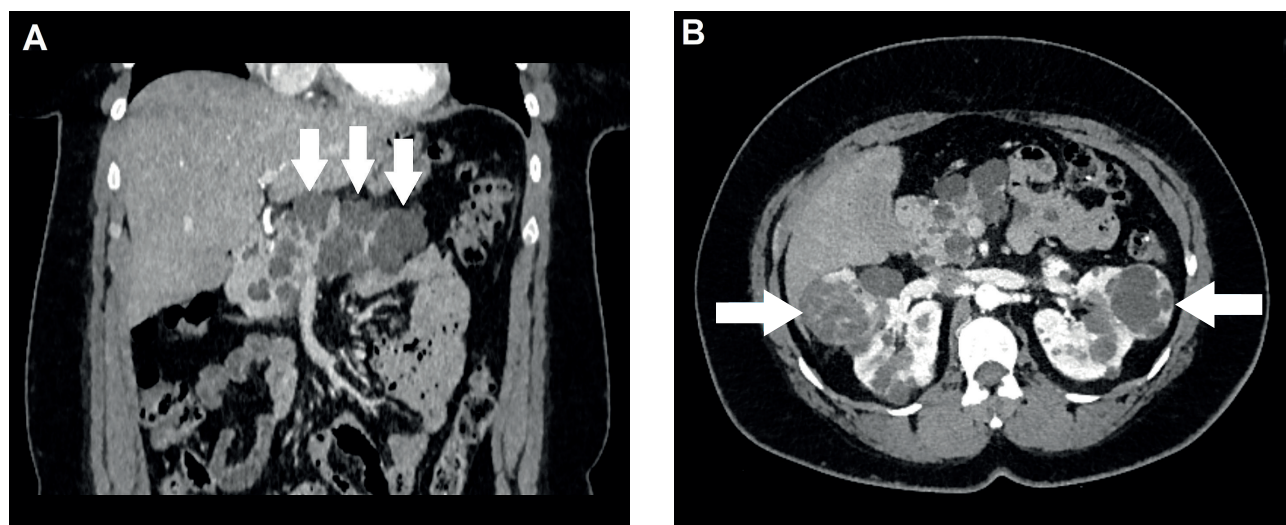


Figure 1: Coronal (A) and axial (B) computed tomography scans in the arterial phase demonstrating enlarged pancreas (A – white arrows) and kidneys (B – white arrows) with multiple cysts, nodules, and solid masses with enhancement after intravenous infusion of contrast, highlighting the characteristic findings of Von Hippel-Lindau syndrome.

Discussion

The VHL gene encodes pVHL, a tumour suppressor involved in cellular signalling pathways located at chromosome 3p25.3, regulating vascular endothelial growth factor (Costa et al., 2023). Mutation predisposes individuals to hypervascular neoplasms such as CNS and retinal haemangioblastomas, renal cell carcinoma, pheochromocytoma, and pancreatic tumours (Leung et al., 2008; Mikhail and Singh, 2022). Clear cell renal cell carcinoma and haemangioblastomas are the leading causes of mortality (Leung et al., 2008).

pVHL dysfunction results in upregulation of hypoxia-inducible genes, increasing erythropoietin, VEGF, platelet-derived growth factor B, and other growth factors (Costa et al., 2023). Most cases are inherited, though *de novo* mutations exist (Costa et al., 2023).

Clinical manifestations depend on lesion location. CNS haemangioblastomas may cause headaches, vomiting, sensory or motor deficits, and ataxia. Retinal haemangioblastomas can result in vision loss. Pheochromocytomas may present asymptotically or with adrenergic symptoms such as headaches, panic attacks, diaphoresis, and hypertension. Endolymphatic sac tumours may produce tinnitus, vertigo, or hearing loss (Mikhail and Singh, 2022). VHL syndrome is classified into two main groups: Type 1 (without pheochromocytoma) and Type 2 (with pheochromocytoma). Five subtypes have been described based on genotype and clinical phenotype (Nielsen et al., 2016).

Diagnosis is clinical or genetic. In patients without a family history, two or more characteristic lesions confirm the diagnosis (Pantigozo-Rimachi et al., 2022). Genetic testing is definitive but underutilised in regions with limited access to molecular diagnostics (VHL Alliance, 2020). Imaging with MRI and CT is essential for identifying phenotypic manifestations and guiding surveillance (VHL Alliance, 2020). Regular screening is recommended, starting in infancy for retinal evaluation and progressing to whole neuraxis MRI and abdominal imaging in adolescence and adulthood, following guidelines from the VHL Alliance (VHL Alliance, 2020). Differential diagnoses include sporadic retinal or CNS haemangioblastomas, renal cell carcinoma, pheochromocytoma, and pancreatic or endolymphatic sac tumours (Mikhail and Singh, 2022).

Management depends on lesion size, location, and the number of organs involved. Surgical resection is common, with radiosurgery used for inoperable CNS lesions (Laks et al., 2022).

Belzutifan, a hypoxia-inducible factor-2 α (HIF-2 α) inhibitor, has shown promise for treating advanced disease (Victorio, 2023). CNS haemangioblastomas may require surgery, embolisation, or radiosurgery (Laks et al., 2022). Retinal lesions are treated with laser photocoagulation or cryotherapy. Renal lesions often require partial or total nephrectomy (Laks et al., 2022). Pheochromocytomas demand surgical resection with preoperative adrenergic blockade. Pancreatic neuroendocrine tumours are surgically treated when high-risk features are present (Laks et al., 2022). Asymptomatic pancreatic cysts may be managed conservatively (Laks et al., 2022).

Conclusion

The clinical impact of VHL syndrome depends on tumour location and burden, with treatment sequelae potentially exceeding disease-related morbidity. Lifelong multidisciplinary follow-up is essential to manage both disease manifestations and treatment complications.

Raising awareness among healthcare providers is crucial to reduce underdiagnosis and improve patient outcomes, especially in cases involving high-mortality tumours like clear cell renal cell carcinoma and CNS haemangioblastomas.

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