Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Urology

Von Hippel-Lindau Disease: Case Report of a Rare Condition

Md. Paúl Aldaz Apolo[1*], Md. Jimena Molina Fernández[2], Md. Liliana Uvillus[2], Md. Dania Cisneros Mejía[2], Md. Jenniffer Núñez López[3], Md. Carina Contreras Yanez[1], Md. Gabriela Ortiz Verdezoto[4], Md. Lorena Chiluisa Cobo[1], Md. Michelle Dávila Torres[1]

[1]Resident Doctor, Military Hospital N°1, Gran Colombia y Queseras del medio, Quito 170112, Ecuador
[2]Medical, Central University of Ecuador, Iquique 132, Quito 170136, Ecuador
[3]Medical, Catholic University of Ecuador, Ave 12 de Octubre 1076, Quito 170143
[4]Postgraduate Doctor of Urology, Central University of Ecuador, Iquique 132, Quito 170136, Ecuador

DOI: 10.36347/sjmcr.2023.v11i02.019 | **Received:** 07.01.2023 | **Accepted:** 13.02.2023 | **Published:** 16.02.2023

***Corresponding author:** Paul Alejandro Aldaz Apolo
Resident Doctor, Military Hospital N°1, Gran Colombia y Queseras del medio, Quito 170112, Ecuador

Abstract **Case Report**

Introduction*:** Von Hippel-Lindau disease (VHL) also known as familial cerebello-retinal angiomatosis is an inherited disease caused by mutation of a gene, characterized by a variety of benign and malignant tumors in different parts of the body [1]. VHL disease is classified as: type 1 which is presented as hemangioblastoma at the level of the central nervous system (CNS), renal cancer and type 2, which is subdivided into A characterized by (retinal angioma, CNS hemangioma, renal cancer), B characterized by (hemangioblastoma, renal cancer, pheochromocytoma) and C characterized by isolated pheochromocytoma [2]. ***Clinical Case*:** A 32-year-old female patient of Jehovah's Witness religion with a clear family history of Von Hippel-Lindau disease, who at 28 years of age was admitted to the Neurosurgery Department with a severe headache; therefore, a basic cranial CT was performed with evidence of an infratentorial lesion in the left cerebellar hemisphere causing obstructive hydrocephalus due to compression of the fourth ventricle. It is complemented with brain MRI when there is evidence of an image compatible with hemangioblastoma that exerts mass effect. Through the Nephrology Service, renal ultrasound shows a non-vascularized mass; therefore, simple and contrast CT urogram is requested to rule out malignancy, nephroprotective scheme is placed to prevent CIN, Merhan Score of 2, low risk of 7.5%. In simple and contrast CT urogram, the findings described suggest left renal neoplasm, to be correlated with histopathological study, BOSNIAK type I renal cysts, right ovarian cyst. ***Conclusions: The treatment of Von Hippel-Lindau disease, due to all its clinical manifestations, is a challenge that should be approached in a multidisciplinary manner. Early detection of tumors means a more effective early management, also alerts family trees with high risk of suffering it.

Keywords: Von Hippel Lindau disease, Cerebellar hemangioblastoma, Clear cell renal carcinoma.

INTRODUCTION

Von Hippel-Lindau disease (VHL) also known as familial cerebello-retinal angiomatosis is an inherited disease caused by mutation of a gene, characterized by a variety of benign and malignant tumors in different parts of the body [1].

The disease is caused by a mutation of the VHL onco-suppressor gene, which is located on chromosome 3 p25- 26; it has an autosomal dominant genetic pattern with complete penetrance, this gene has the function of promoting vascular endothelial growth factor, but a de novo mutation can occur. It occurs in one in every 36,000 people and with a 2:1 male to female ratio [2].

The mean age of occurrence is approximately 26 years, but manifestations may occur in children, adolescents or adults and vary according to the size and location of the tumors. Among the neoplasms that occur are hemangioblastomas in the cerebellum and spine, retinal capillary hemangioblastomas, clear-cell renal-cell carcinomas (CCRCC), pheochromocytomas, middle ear endolymphatic sac tumors, serous cystadenomas and neuroendocrine tumors in the pancreas, papillary cystadenomas in the epididymis and broad ligament [1].

VHL disease is classified as: type 1 which is presented as hemangioblastoma at the level of the central nervous system (CNS), renal cancer and type 2,

which is subdivided into A characterized by (retinal angioma, CNS hemangioma, renal cancer), B characterized by (hemangioblastoma, renal cancer, pheochromocytoma) and C characterized by isolated pheochromocytoma [2].

Once the disease is diagnosed, it should be followed up over time and family members should be screened to rule out new cases. Genetic counseling should also be provided in the event of a possible pregnancy [3]. Due to the diverse ways in which VHL disease manifests itself, treatment includes the coordination of several medical specialties [4].

CLINICAL CASE

A 32-year-old female patient of Jehovah's Witness religion with a clear family history of Von Hippel-Lindau disease, who at 28 years of age was admitted to the Neurosurgery Department with a severe headache; therefore, a basic cranial CT was performed with evidence of an infratentorial lesion in the left cerebellar hemisphere causing obstructive hydrocephalus due to compression of the fourth ventricle. It is complemented with brain MRI when there is evidence of an image compatible with hemangioblastoma that exerts mass effect. Also, there are lesions in the spinal cord at intradural extramedullary level of C7-T1. An investigation on lesions through the body is performed with evidence of neoplasm at the left renal level.

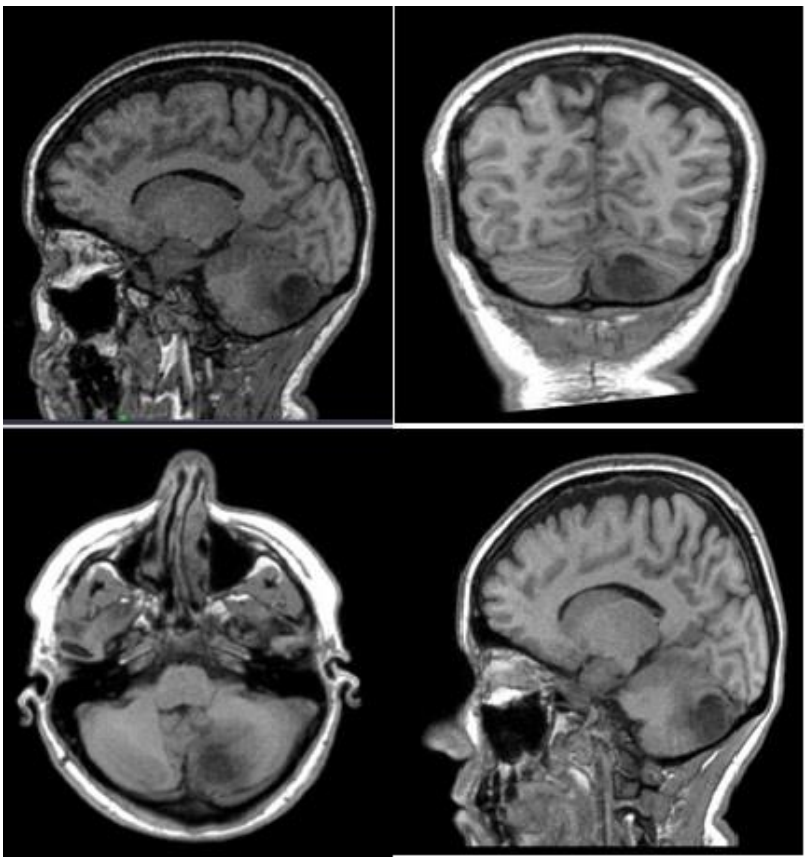

Figure 1: Tumor in the left cerebellum suggestive of hemangioblastoma with peripheral gliosis. T1 weighted image

With surgical indication by the Neurosurgery Department to approach the infratentorial lesion, but due to the patient's religious beliefs (Jehovah's Witness) and the possibility of requiring transfusion of blood products, the patient does not accept excision of the lesion and it is decided to place a high-flow VPS (ventriculoperitoneal shunt) to solve the hydrocephalus condition. Due to the above, treatment possibilities were evaluated and stereotactic radiosurgery (Gamma knife) was indicated, which was performed in 2018.

Genetic studies have been carried out which indicate the existence of maternal inheritance, with several individuals affected by brain and spinal column tumors, ocular and renal lesions. Genetic testing of this condition with autosomal dominant and recessive inheritance is not available at the moment. In post-radiosurgery brain MRI studies, there is evidence of reduction of the left infratentorial lesion without signs of hemorrhage. Currently, she is neurologically stable, with preserved higher mental functions, uninjured cranial nerves, no ophthalmoparesis, clear, fluent language, she controls and can repeat words, without

motor or sensory deficits, in subsequent quarterly control since she has no signs of intracranial hypertension and VPS is operating.

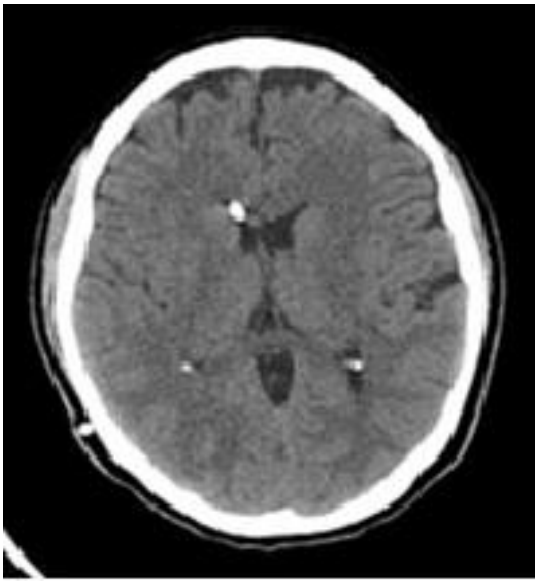

Figure 2: External ventricular drain with its distal end in the right frontal horn of the lateral ventricle. No hydrocephalus is observed

Through the Nephrology Service, renal ultrasound shows a non-vascularized mass; therefore, simple and contrast CT urogram is requested to rule out malignancy, nephroprotective scheme is placed to prevent CIN, Merhan Score of 2, low risk of 7.5%. In simple and contrast CT urogram, the findings described suggest left renal neoplasm, to be correlated with histopathological study, BOSNIAK type I renal cysts, right ovarian cyst.

Due to the findings, the Urology Service proposes a possible left endoscopic radical nephrectomy, with pre- surgical authorizations detailing: MOTZER criteria: intermediate risk, average overall survival of 14 months; TNM: T1b NX MX; ROBSON classification: I confined to the renal parenchyma; PADUA: 10 points, so a patient with a case of left renal tumor stage 1, high surgical complexity in RENAL SCORE, PADUA and NEPHRO SCORE. Laparoscopic nephrectomy was performed with the following findings: left kidney of approximately 12 cm x 10 cm x 6 cm of normal macroscopic characteristics, left renal hilum with multiple vessels of neoformation, a renal artery that bifurcates close to the aorta and 1 renal vein, ureter and left gonadal vein of normal macroscopic characteristics.

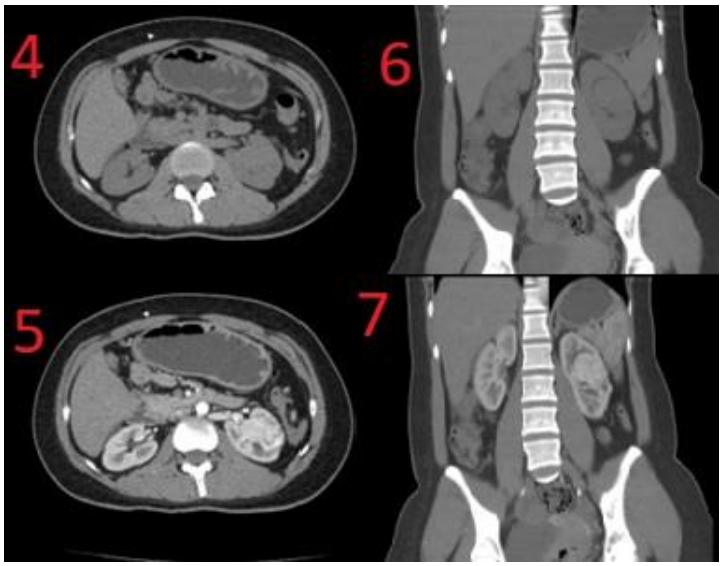

Figure 3: 4-5: Isodense image to the upper renal pole endophytic parenchyma measuring approximately 2.9 cm in anteroposterior diameter and 3.9 cm in cranial-caudal diameter, with densities between 32 and 53 HU. 6-7: Increase in nephrographic phase contrast uptake to 148 HU

Procedure performed without complications with a trans-surgical bleeding of 100cc that progress without complications post-surgery. The histopathological report was clear-cell carcinoma, uncompromised borders. The patient is being monitored up to date.

In the Ophthalmology Service examination, images suggestive of capillary hemangioma in the optic nerve were found to rule out Von Hippel-Lindau disease, for which reason fluorescein angiography was requested in the left eye, which reported that no retinal angiomas were detected in both eyes.

DISCUSSION

Von Hippel-Lindau disease (VHL) is an inherited disease in which multiple neoplasms appear such as hemangioblastomas of the central nervous system (CNS) mainly of the cerebellum and spinal cord, retina hemangioblastomas, clear-cell renal carcinoma, pheochromocytoma, cysts in the pancreas, kidney, liver and epididymis and tumors in the endolymphatic sac [5].

It occurs in 1 out of 35,000 people and is transmitted in an autosomal dominant pattern. Symptoms often appear in the second to fourth decades of life [6]. Retinal or cerebellar hemangioblastomas are the most common form of the disease. Clear-cell renal cell carcinoma is the third most common form and cystic disease involving the kidneys, pancreas and epididymis is also common [2].

Other manifestations that may accompany neoplasms such as subarachnoid hemorrhages may be the result of the combined action of hemangiomas and hypertension. In some cases, polyglobulia is present due to increased erythropoietin production. Hypercalcemia may manifest due to renal failure, since it disappears with tumor removal [6].

The disease is caused by high penetrance alterations in a tumor suppressor gene, the VHL gene (3p25.3). It is usually diagnosed by a germline mutation [4, 5].

Affected individuals have a germline mutation of the VHL tumor suppressor gene. The VHL protein (pVHL) interacts with elongins B, C and Cullin-2 to form the VBC complex, an E3 ubiquitin ligase. This complex mediates ubiquitin-mediated degradation. Bi-allelic inactivation of VHL is believed to underlie tumor genesis in VHL disease [7].

To diagnose VHL disease, one of the following clinical criteria should be considered: 1) more than one hemangioblastoma in the CNS or retina; 2) a single hemangioblastoma in the CNS or retina plus a visceral complication (such as multiple renal, pancreatic or hepatic cysts, pheochromocytoma or renal cancer) with the exception of epididymal and renal cysts; 3) any of the above manifestations with a family history [8].

VHL disease classified into type 1 is associated with the development of retinal and CNS hemangioblastomas and clear-cell renal carcinoma, but rarely pheochromocytoma/paraganglioma. VHL type 2 disease is associated with pheochromocytomas/ paragangliomas. VHL type 2 disease is subdivided into type 2A (pheochromocytoma/paraganglioma, hemangioblastomas but not clear-cell renal carcinoma), type 2B (pheochromocytoma/paraganglioma, hemangioblastomas, and clear-cell renal carcinoma), and type 2C (pheochromocytoma/paraganglioma only) [9].

Treatment for VHL disease varies by tumor type and when presenting with various clinical manifestations poses an interdisciplinary coordination challenge. Treatment of most tumors involves surgery to remove them; some can be treated with radiation therapy. Annual surveillance programs for patients with VHL disease are needed to achieve adequate control [2, 9].

Intravitreal injections of bevacizumab can currently be considered for refractory and exudative retinal hemangioblastomas. Although prospective randomized trials are needed, regarding to monoclonal antibodies, larger randomized trials including control groups is needed to differentiate therapeutic stabilization from natural tumor behavior. Agents such as sorafenib, thalidomide, HIF2α, octreotide and immunotherapy may appear promising, but further preclinical and larger patient studies are needed to assess their efficacy and safety profile [7].

CONCLUSIONS

The treatment of Von Hippel-Lindau disease, due to all its clinical manifestations, is a challenge that should be approached in a multidisciplinary manner. Early detection of tumors means a more effective early management, also alerts family trees with high risk of suffering it. According to his presentation, there are currently medical and surgical treatments that can improve the quality of life of these patients.

CONFLICT OF INTEREST

We, the authors, declare that we have no personal, financial, intellectual, economic, and corporate conflicts of interest.

Financing: Self-funded

ACKNOWLEDGMENTS

We thank the Urology Surgery Service of the Military Hospital No. 1 Quito, for allowing us access to the information to carry out this case report.

REFERENCES

1. Plon, S., & Jonasch, E. (2020). Clinical features, diagnosis, and management of von Hippel-Lindau disease. *Uptodate*, 2020.
2. Woodward, E., & Maher, E. (2006). Von Hippel Lindau disease and endocrine tumour susceptibility. *Endrocrine-Related Cancer*, 13(2), 415-425.
3. Solís, L., & Alemañy, E. (2017). Carcinomas renales múltiples como manifestación inicial del Síndrome de Von Hippel Lindau. Presentación de caso. *Rev haban cienc méd.*, 16(5), 751-760.
4. Rojas, E. (2013). Enfermedad de Von Hippel Lindau. *Revista Médica de Costa Rica y Centroamerica*, LXX, 181-184.
5. Salinas, I., & Oriola, J. (1999). La Enfermedad de Von Hippel-Lindau. *Endocrinología y Nutrición*, 46(2).
6. Hernández, R. (2010). Fundamentos moleculares de la enfermedad de von Hippel Lindau. *Rev Cubana Invest Bioméd*, 29(2), 262-273.
7. Gläsker, S., Vergauwen, E., Koch, C. A., Kutikov, A., & Vortmeyer, A. O. (2020). Von Hippel-Lindau Disease: Current Challenges and Future Prospects. *Onco Targets Ther.*, 13, 5669-5690.
8. Wu, P., Zhang, N., Wang, X., Ning, X., Li, T., Bu, D., & Gong, K. (2012). Family history of von Hippel–Lindau disease was uncommon in Chinese patients: suggesting the higher frequency of de novo mutations in VHL gene in these patients. *Journal of Human Genetics*, 57, 238-243.
9. Maher, E., & Sandford, R. (2019). Von Hippel-Lindau Disease: an Update. *Curr Genet Med Rep.*, 7, 227-235.