Case Report

A case of von Hippel-Lindau disease with multi-organ involvement: a rare case report

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ABSTRACT

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant syndrome manifested by a spectrum of tumours in the central nervous system (CNS) and other visceral organs. We herein report a case of 35 years aged newly diagnosed diabetic female patient presented with headache, gait instability, loss of vision in both eyes, left sided hearing impairment and subsequently diagnosed to have VHL disease. The pathophysiology involves the inactivation of the VHL tumour suppressor gene. Early recognition and treatment remains the mainstay of management. Even many years after the complete tumour excision, newer neoplasms may develop. Increasing knowledge about the molecular enabled us to investigate the role of anti-angiogenic drugs. Continuous surveillance at regular interval must be conducted in patients with VHL disease.

Keywords: Anti-angiogenic drugs, Autosomal dominant, Tumour suppressor gene, VHL disease

INTRODUCTION

The VHL disease was described in von Hippel's literature in 1911 and Lindau's literature in 1926.^{1,2} It is caused by mutation in the VHL tumour suppression gene located on chromosome 3.³ The prevalence of VHL has been estimated to be between 1:35,000 to 40,000.⁴ The mean ages (and ranges) of diagnosis of retinal hemangioblastoma (RHb), cerebellar hemangioblastoma (CHb), and renal cell carcinoma are 25 years (1-67), 30 years (11-78), and 37 years (16-67), respectively.⁵ It has been well documented that VHL patients may develop further de novo lesions, occasionally many years after the initial diagnosis, despite the complete excision of initial neoplasm.² Thus, long-term follow-ups for patients with VHL disease are necessary.⁶

The current study reports a case of VHL disease complicated with multi-organ involvement.

CASE REPORT

The patient was a married 35-year-aged female who presented to our hospital in 2019 complaining of headache, left sided hearing loss and gait instability for 1 year. She had intermittent vomiting, vertigo and non-specific abdominal pain on and off. She had gradual onset of loss of vision on both the eyes and subsequently diagnosed to have bilateral retinal hemangioblastoma, for which she underwent Laser photocoagulation on both the eyes 7 years ago. She found to be diabetic 6 months back, in the absence of any gynecologic symptoms or familial involvement.

On examination, there was no perception of light on either side and sensory neural hearing loss was present on left side. Signs of cerebellar involvement was present on right side.

Figure 1: MRI brain showing a left sided endolymphatic sac tumour (arrow head) and a right cerebellar hemangioblastoma (arrow).

Auditory tests revealed profound left sided hearing loss. Magnetic Resonance Imaging (MRI) brain revealed a left sided endolymphatic sac tumour and a right cerebellar hemangioblastoma (Figure 1). Whole spine MRI showed cervical spine hemangioblastoma (Figure 2).

Figure 2: MRI spine showing cervical spine hemangioblastoma (arrow).

Computer tomography (CT) abdomen detected bilateral multiple renal cysts, diffuse pancreatic cystic lesions with calcific foci causing architectural distortion and bulky left adrenal gland (Figure 3). A diagnosis of von Hippel-Lindau disease was made. She underwent surgical resection of the cerebellar hemangioblastoma (Figure 4) and histopathological examination (HPE) confirmed our pre-operative diagnosis. Further course of management was decided by multi-disciplinary approach. We advised regular follow-up and appropriate genetic testing to identify the VHL gene mutation.

Figure 3: CT abdomen showing bilateral multiple renal cysts (arrow).

Figure 4: Intra-operative finding of cerebellar hemangioblastoma (arrow).

DISCUSSION

Von Hippel-Lindau is a rare disease which is inherited in autosomal dominant manner and causes multi-system involvement in the form of development of hemangioblastoma of central nervous system (CNS), retinal hemangioblastoma, renal cell carcinoma or renal cyst, endolymphatic sac tumour, neuroendocrine tumours and cyst of pancreatic gland, pheochromocytoma, epididymal cyst adenoma.⁵ Our case showed several VHL-associated tumours. The CNS lesions in our patient had intense homogeneous enhancement. Flow voids were seen due to the high vascularity. Renal lesions were further evaluated by MRI using HASTE sequences which helps us to delineate the cystic lesions as well as its internal contents

VHL disease has been recognized for almost 70 years and recent developments in the genetics and imaging of VHL have significantly improved our understanding of the disease and its natural history.⁷ VHL disease has an

estimated prevalence of 2-3 per 100,000 persons with geographical variations. It is seen in all ethnic groups with equal numbers in both sexes. The age at diagnosis varies from infancy to the seventh decade of life or later.⁸

Hemangioblastoma of the CNS usually develop from childhood at an age of <10 years or early teen until the age of 30 years. These are benign tumours. Some hemangioblastomas remain unchanged in size over several years and if they do not cause symptoms, their surgical removal may not be necessary.⁴ The symptoms of hemangioblastoma are usually caused by expansion of tumour in intracranial space and spinal cord. Asymptomatic small tumour are carefully watched until the onset of symptoms. The best treatment modality for this tumour is surgical resection, in cases of large tumour burden where surgical resection is not possible gamma knife surgery can substitute the treatment modality.⁵ The most common sites for hemangioblastoma development are cerebellum and spinal cord as evident in our patient.

Central nervous system hemangioblastomas commonly involve cerebellum, spine and medulla. CHb associated with VHL occurs at a younger age, is often multiple and has a worse prognosis than sporadic CHb, which occurs in 44-72% of VHL patients, making it one of the most common manifestations of the disease. Medullary hemangioblastomas (MHb) occur in about 5% of VHL patients.⁵ They had found in postrema of the medulla and may lead to syringobulbia. Unusual sites of hemangioblastomas in VHL include the anterior lobe of the pituitary, pituitary stalk, hypothalamus, optic nerve, corpus callosum, wall of the third ventricle, temporal horn of the lateral ventricles, frontal and temporal lobe and meninges.^{5,6}

Renal cyst are present in 59-63% of individual in VHL and Renal cell carcinoma develops in 24-45% of VHL patients.^{5,7} Renal involvement in VHL is multicentric and bilateral in at least 75% of the patients.⁹ Bilateral renal involvement is also a common finding in VHL disease. RCC has been reported to occur in 25% to 50% of VHL patients and almost always are of clear cell type.¹⁰ In contrast to pancreatic cysts and hemangioblastomas, which usually show a benign course, RCC is a major cause of mortality in VHL.¹¹ A nephron-sparing approach is the recommended management for multiple renal cysts instead of radical nephrectomy.¹¹ In our patient, the multiple bilateral renal cysts frequently remains asymptomatic, in contrast to the RCC, which compromises the renal function and thus remains a significant cause of mortality.

Pancreatic cystadenomas or cysts are generally asymptomatic, characteristically seen as multiple cyst in the pancreas on imaging.¹⁰

Retinal hemangioblastomas (RHb) is seen in 45-59% of patients with VHL.⁴ They have been called "retinal angiomas" and "retinal haemangiomas" but

hemangioblastoma is the preferred term since they are histologically identical to lesions found in the CNS.⁵

Our patient had several solid and cystic lesions which are associated with VHL disease in variable proportions. This case shows that in a patient with cranio-spinal hemangioblastoma, high index of suspicion should be raised regarding the possibility of VHL disease and it has to be ruled out with appropriate diagnostic modalities, often in association with multi-disciplinary approach. Hence, in any patient, where multiple CNS hemangioblastomas are present, diagnosis of Von Hippel-Lindau disease should be considered and a search for cysts and tumours in other organs must be made.

CONCLUSION

The current study reinforces the importance of regular follow-ups with thorough evaluation of cranio-spinal hemangioblastoma by appropriate diagnostic modalities. Although these tumours often have multiple periods of tumours growth separated by periods of arrested growth, and many untreated tumours may remain static for several years, yet follow-up of VHL patients must not be discontinued after their initial diagnosis and treatment. If chromosomal analysis of the affected patient results in an identifiable mutation, at-risk relatives can be offered the option of pre-symptomatic gene testing.

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REFERENCES

1. Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260:1317-20.
2. Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. *Nat Rev Cancer*. 2002;2:673-82.
3. Keutgen XM, Hammel P, Choyke PL, Libutti SK, Jonasch E, Kebebew E. Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. *Nature Rev Clin Oncol*. 2016;13(9):537.
4. Neumann HPH, Wiestler OD. Clustering of features of von Hippel Lindau syndrome: evidence for a complex genetic locus. *Lancet*. 1991;337:1052-4.
5. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, et al. Temporal sequence. *QJ Med*. 1990;77(1):51-63.
6. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. *Nat Rev Cancer*. 2014;15:55-64.
7. Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, et al. Von Hippel-Lindau disease: a genetic study. *J Med Genetics*. 1991;28(7):443-7.

8. Hes FJ. Pheochromocytoma in Von Hippel-Lindau Disease. *J Clin Endocrinol Metab.* 2003;88:969-74.
9. Quadery FA, Okamoto K. Diffusion-weighted MRI of haemangioblastomas and other cerebellar tumours. *Neuroradiology.* 2003;45:212-9.
10. Junaid M, Rashid MU, Tahir A, Ahmad M, Kalsoom A. Von Hippel Lindau syndrome and surveillance: A five year follow up case report. *J Ayub Med Coll Abbottabad.* 2015;27(4):930-2.
11. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: A clinical and scientific review. *Eur J Hum Genetics.* 2011;19(6):617-23.
12. Motzer RJ, Rini BI, Michaelson MD, Redman BG, Hudes GR, Wilding G, et al. Phase 2 trials of SU11248 show antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma (RCC). *J Clin Oncol.* 2005;23(16):4508.

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