Case Report

Von Hippel–Lindau disease with renal cell carcinoma and multiple cerebellar and spinal hemangioblastomas without retinal manifestations: A case report

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Abstract

A 35-year-old gentleman presented with headache in the occipital region, neck pain, slurring of speech, and vomiting. There was reported history of Von Hippel–Lindau disease (VHL) in his mother, who was operated for a cerebellar hemangioblastoma. On investigations, magnetic resonance imaging brain showed bilateral cerebellar hemangioblastomas and a tiny spinal hemangioblastoma. Contrast-enhanced computed tomography abdomen showed multiple small well-defined, non-enhancing hypodense lesions with fluid attenuation in the left kidney and pancreas, suggestive of simple cysts. There was history of right partial nephrectomy in the past for renal cell carcinoma. Complete excision of bilateral cerebellar hemangioblastomas was performed. Histopathological examination and immunohistochemical workup confirmed the clinical diagnosis of hemangioblastoma.

Keywords: Cerebellum, hemangioblastoma, renal cell carcinoma, Von Hippel–Lindau without retinal manifestation

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INTRODUCTION

Von Hippel–Lindau disease (VHL) is an autosomal dominant neoplasm with a spectrum of tumors. The term VHL was first used in 1936 which was named after two ophthalmologists—Von Hippel and Lindau.[1] Diagnosis of VHL can be made with a single criterion of VHL tumor in a relative if there is a confirmed family history of VHL. Clinical diagnosis of VHL disease in a patient without family history requires the criteria of two tumors. VHL disease is suggested to account for one-third of central nervous system (CNS) hemangioblastomas, 50% of retinal hemangioblastoma, 50% of isolated familial pheochromocytoma, 1% of renal cell carcinoma, and 11% of sporadic pheochromocytoma. CNS hemangioblastoma occurs in 60–80% of VHL patients. Retinal hemangioblastomas are one of the most common presenting features of VHL disease.[2] Here we present a case of multiple hemangioblastomas and renal cell carcinoma in a young gentleman in the absence of retinal hemangioblastoma.

CASE REPORT

A 35-year-old gentleman with family history of VHL presented with headache, neck pain, slurring of speech,

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and vomiting. Three years ago, he underwent right partial nephrectomy for renal cell carcinoma. Left kidney lesions were very small and were considered for conservative management. At the time of the surgery, he was evaluated by the ophthalmic surgeon and was not found to have any retinal hemangioblastomas. His neuraxis was screened, which revealed multiple cerebellar and spinal hemangioblastomas. These were very small and were managed conservatively; however, he was informed to come for regular follow-up.

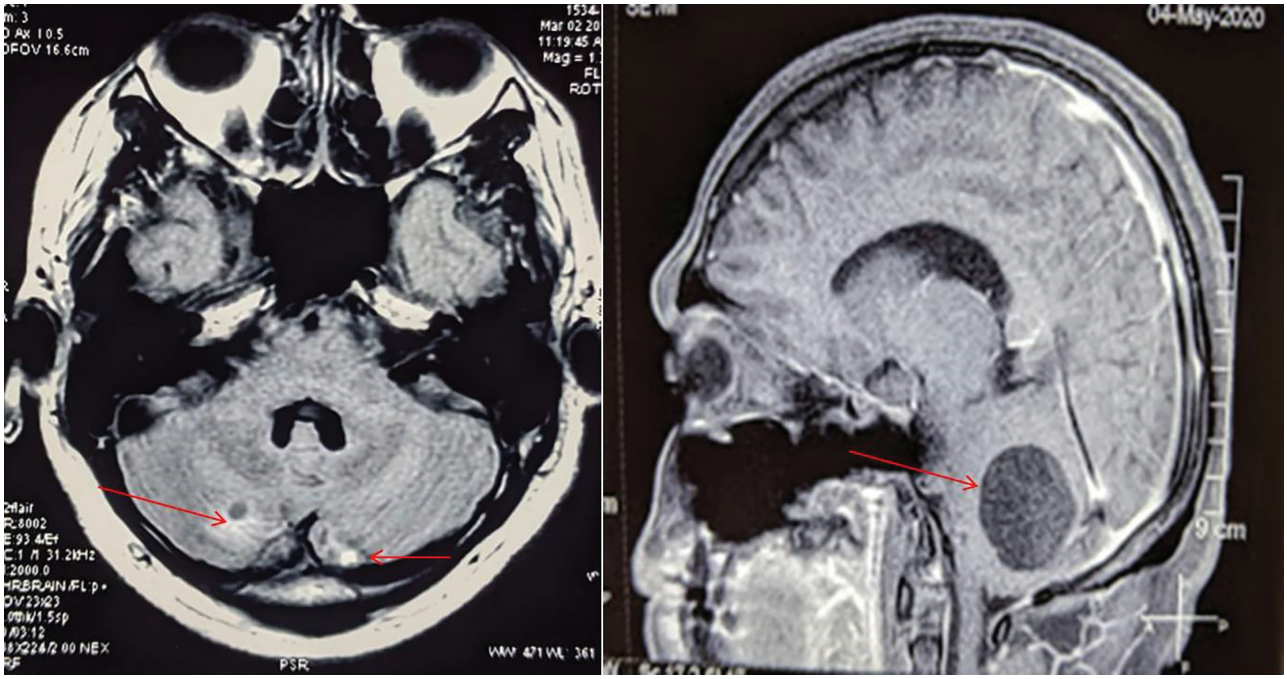

Figure 1: MRI brain showing bilateral hemangioblastomas

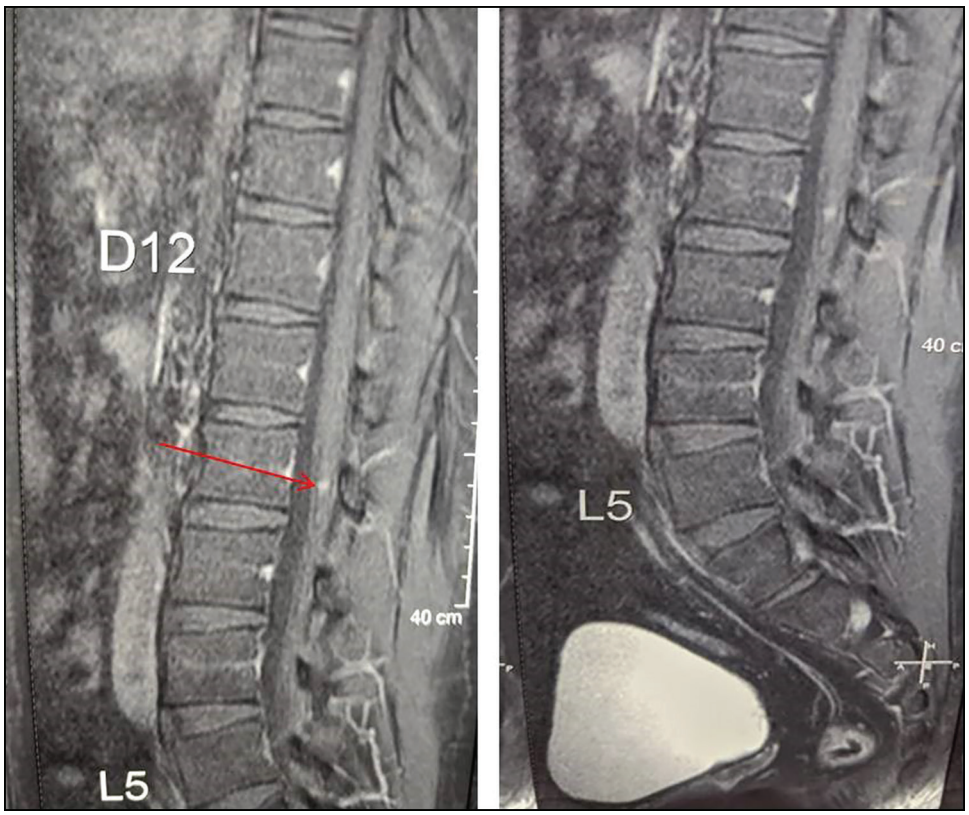

Figure 2: Contract MRI spine depicting a spinal hemangioblastoma at L2 level

Unfortunately, he was lost to follow-up for 3 years. Now the patient presented with the above symptoms. There were no retinal lesions on indirect fundoscopy. There were no neurocutaneous markers. Magnetic resonance imaging (MRI) scan showed bilateral cerebellar hemangioblastomas—4.4 × 3.4 cm-sized cystic lesion in the right cerebellar hemisphere with two eccentric enhancing solid nodules in the posterior and right posterolateral aspects of the lesion causing mass effect on the fourth ventricle. There was a 0.8 × 0.5 cm-sized enhancing nodule in the left cerebellar hemisphere [Figure 1]. His post-contrast neuraxis screening picked up a small enhancing nodule in conus at the L2 level of spine suggestive of spinal hemangioblastoma [Figure 2].

Ultrasound whole abdomen showed a scar in the right kidney, suggestive of post-operative change. Contrast-enhanced computed tomography showed multiple small well-defined, rounded, non-enhancing hypodense lesions with fluid attenuation in the left kidney, pancreas, and segment 8 of liver, suggestive of simple cysts. The patient was taken up for surgery. Microsurgical excision of bilateral cerebellar hemangioblastoma and drainage of the cyst were performed through midline suboccipital craniotomy. It was decided that the spinal cord lesion was to be followed up and to be operated at a later date if indicated.

Histopathological examination of both the lesions showed cerebellar tissue with a neoplasm composed of proliferating thick-walled blood vessels closely admixed with clusters of polygonal stromal cells having abundant pale cytoplasm and eccentrically located nuclei. Few pigmented hemosiderophages were noted. Immunostains were positive for Inhibin alpha, EMA (focal) and negative for CD10, Pan cytokeratin, PAX8, and RCC1, excluding a metastatic renal cell carcinoma as there was significant past history [Figure 3]. CT scan brain was repeated on day 1 of surgery which revealed no residual lesion [Figure 4]. Post-operative period was uneventful.

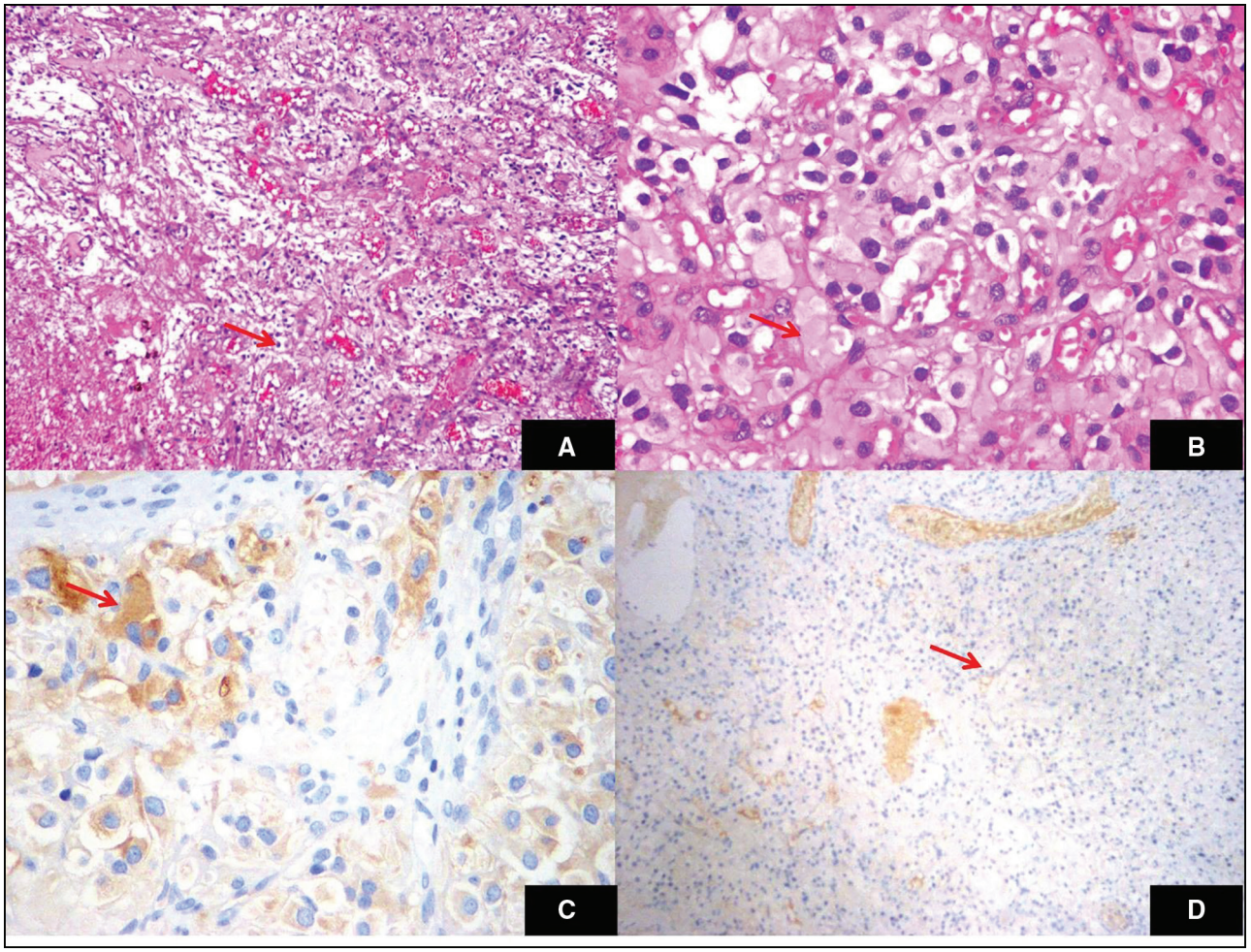

Figure 3: (a and b): Proliferating blood vessels of varying shapes and sizes lined by a single layer of endothelium and the intervening spaces between blood vessels show stromal cells (H & E 100×, 400×). (c): Positive immunostain with Inhibin alpha (400×). (d): Negative immunostain with PAX8 (100×)

DISCUSSION

VHL is an autosomal dominant multisystem syndrome associated with germline mutation of tumor suppressor gene located at chromosome 3p25. Offspring of a parent who carries VHL gene will have more than 50% chance of having the VHL gene. Some have less than 50% chance, and some parents of affected offspring may not manifest VHL gene, even though they are "obligate carriers." This is due to incomplete penetrance in which the gene is not expressed even though it is inherited.

The incidence of VHL occurs in approximately 1 in 36,000 live births.[3] The criteria for diagnosis of VHL disease have been represented in Table 1.

National Cancer Institute (NCI) proposed three phenotypes of VHL:

Type I: VHL without pheochromocytoma;

Type II: VHL with pheochromocytoma;

A: Pheochromocytoma and retinal/CNS hemangioblastoma;

B: Pheochromocytoma and retinal/CNS hemangioblastoma, renal cancer, and pancreatic involvement.

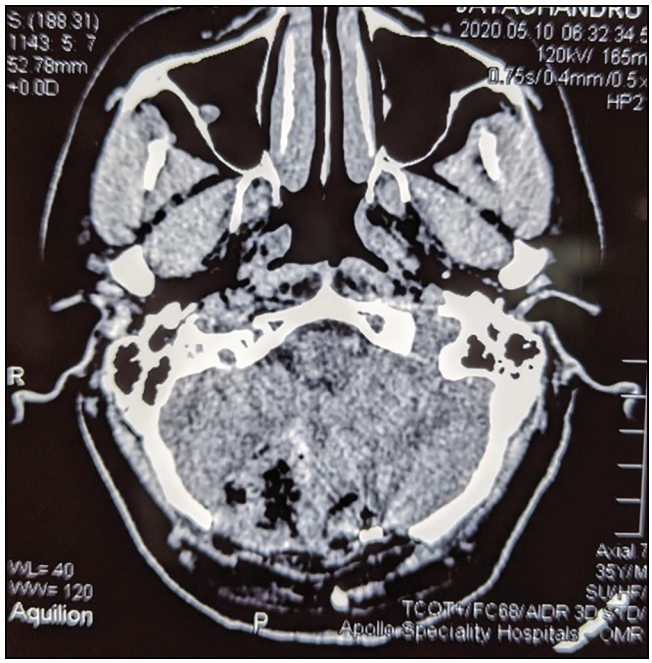

Figure 4: CT scan brain with no residual lesion

Table 1: Criteria for diagnosis of Von Hippel–Lindau disease

Ocular	Retinal hemangioblastoma
Visceral	Multicystic renal disease, renal cell carcinoma, pheochromocytoma, pancreatic cysts, epidermal cysts
Central nervous system	Cerebellar hemangioblastoma, hemangioblastoma of other CNS locations (cortex, spinal cord, brainstem)

Most common sites of CNS hemangioblastoma include cerebellum, spinal cord, and brainstem. Patients present with symptoms of increased intracranial tension and ataxia and symptoms relating to mass effect depending on the location of the tumor. The mean age of presentation is third decade when associated with VHL, and sporadic cases are seen a decade later. Microscopic examination reveals proliferating blood vessels of varying shapes and sizes lined by a single layer of endothelium. The intervening spaces show stromal cells which are regarded as neoplastic cells. Hemangioblastoma is classified as "tumor of uncertain origin," as the origin of stromal cells is not known. The stromal cells are diffusely positive for Vimentin, Neuroendocrine markers (synaptophysin, NSE), and Inhibin alpha. The differential diagnoses to be considered on histologic examination are metastatic renal cell carcinoma, which may be associated with VHL. Rarely, metastasis may lodge within a hemangioblastoma.[4]

Hemangioblastomas exhibit a stuttering growth pattern and may remain asymptomatic for long intervals.[4,5] Primary line of treatment is surgical removal in symptomatic patients. The mural nodule is the actual lesion. Drainage of the cyst without excising the entire tumor is found to be ineffective. Mortality is due to wide spectrum of the syndrome and complications of the disease. After complete surgical removal, recurrence is rare but other small lesions may grow in size and cause symptoms.

Upon discharge, our patient was advised regular follow-up visits, ophthalmic examination, blood pressure monitoring, ultrasound abdomen, audiometry, and urine examination for catecholamine metabolites.

CONCLUSION

VHL is an autosomal multisystem disorder involving CNS, retina, and viscera. Young patient with a diagnosis of multiple hemangioblastomas should be investigated for VHL disease, and genetic counseling should be given. The retinal lesions are the initial manifestation but may not be always seen, and various combinations and permutations of lesions are possible.[6-8] Multispecialty evaluation and management by ophthalmologist, endocrinologist, neurosurgeon, surgical oncologist, and pathologist for appropriate triage of management is necessary.[9]

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Woodward ER, Buchberger A, Clifford SC, Hurst LD, Affara NA, Maher ER. Comparative sequence analysis of the VHL tumor suppressor gene. Genomics 2000;65:253-65.
2. Dollfus H, Massin P, Taupin P, Nemeth C, Amara S, Giraud S, *et al*. Retinal hemangioblastoma in von Hippel-Lindau disease: A clinical and molecular study. Invest Ophthalmol Vis Sci 2002;43:3067-74.
3. Maher ER, Iselius L, Yates JR, Littler M, Benjamin C, Harris R, *et al*. Von Hippel–Lindau disease: A genetic study. J Med Genet 1991;28:443-7.
4. Jarrell ST, Vortmeyer AO, Linehan WM, Oldfield EH, Lonser RR. Metastases to hemangioblastomas in von Hippel–Lindau disease. J Neurosurg 2006;105:256-63.
5. Ammerman JM, Lonser RR, Dambrosia J, Butman JA, Oldfield EH. Long-term natural history of hemangioblastomas in patients with von Hippel–Lindau disease: Implications for treatment. J Neurosurg 2006;105:248-55.
6. Newman S, Wasserberg J. A case report of the management of multiple metachronous haemangioblastomas in a patient with von Hippel–Lindau disease. Br J Neurosurg 2008;22:104-6.
7. Rahman A, Hoque SU, Bhandari PB, Alam S. Contiguous hemangioblastomas of the brain and spine in a patient of Von Hippel–Lindau disease. BMJ Case Rep 2013;2013:bcr2012007989. Published January 22, 2013. doi:10.1136/bcr-2012–007989.
8. Sun Y, Sun Q, Shen J, Wu H, Guan Y, Gong K, *et al*. Cauda equina hemangioblastoma at L5 vertebral level related to von Hippel–Lindau disease. Br J Neurosurg 2012;26:576-7.
9. Crespigio J, Berbel LCL, Dias MA, Berbel RF, Pereira SS, Pignatelli D, *et al*. Von Hippel–Lindau disease: A single gene, several hereditary tumors. J Endocrinol Invest 2018;41:21-31.