WHOLE SPECTRUM OF NATURAL PROGRESSION OF HAEMANGIOBLASTOMA SEEN WITHIN A SINGLE PATIENT: A VERY RARE CASE REPORT AND LITERATURE REVIEW

*Sunil Munakomi, Binod Bhattarai

Department of Neurosurgery, College of Medical Sciences, Chitwan, Nepal
*Correspondence to sunilmunakomi@gmail.com

ABSTRACT

This paper reports a rare case of sporadic variation of haemangioblastoma (HB) presenting as multiple lesions within the posterior fossa. A whole spectrum of radiological variants of HB were seen during its natural progression in one patient. A discussion of the management algorithm taken while managing this case is provided, and there is also a literature review to outline current insights on such a rare epiphenomenon.

Keywords: Haemangioblastoma (HB), progression, management.

INTRODUCTION

Sporadic variants of haemangioblastoma (HB) presenting as multifocal central nervous system (CNS) lesions within the posterior fossa are a rare phenomenon.[1] Herein, there is a case report of such an extreme rarity. There is a paradigm shift in the approaches used to manage such multiple lesions compared with focal variants. Multiple surgeries and radiation therapy are required to manage as well as halt the proliferation, relapse, and dissemination of multifocal CNS HB.[1]

In this report there is a discussion of the management algorithm taken for the case and a review that adds to knowledge regarding the behaviour and progression of such a rare entity.

CASE REPORT

A 38-year-old female presented to our neurosurgical clinic with a history of persistent dizziness. The patient reported no history of trauma, falls, weakness of limbs, changes in bladder and bowel habits, or similar episodes in the past; nor did she have a history of ear discharge, hearing impairment, nasal regurgitations, choking episodes, or change in the pitch of her voice.

The patient stated that she had no significant past medical or surgical illnesses and there was no significant family history of such conditions. Her vital parameters were within normal range, and upon neurological examination the patient was found to be well-oriented to time, place, and person. Examination also revealed normal function of the cranial nerves. The patient demonstrated unusual cerebellar signs more on the left compared to the right, exhibiting nystagmus, and the presence of an abnormal finger to nose test. Power and tone of the muscles were normal.

Radioimaging identified the presence of multiple lesions within the posterior fossa, showing high enhancement (Figure 1). It revealed a whole spectra of imaging variants of the lesion, ranging between solid, solid with microcysts, and cystic lesions with an enhancing nodule. Cystic lesions with a mural nodule were present within the cerebellomedullary junction on the left, whereas a solid lesion with microcysts was present in the cerebellopontine angle (CPA) on the right (Figure 2). There were additional small solid lesions scattered predominantly in the tentorium along with multiple flow voids highly suggestive of vascular lesions. Magnetic resonance (MR) spectroscopy showed characteristic lipid peaks,

which were highly suggestive of HB. A screening ultrasound and computed tomography of the abdomen and pelvis, as well as a fundoscopy examination (to rule out retinal angiomas), presented normal results, ruling out von Hippel–Lindau (VHL) syndrome. Blood metanephrines and urinary vanillylmandelic acid levels were also within normal range (screening for phaeochromocytoma [PCC]). A systemic work-up was performed to rule out the differentials of the lesions being metastatic, due to the multiple lesions in the posterior fossa.

The disease was explained to the patient and she was advised to have surgery. The predominant presence of a large cystic lesion on her left side resulted in the patient undergoing a left lateral suboccipital approach with aspiration of the cystic content, followed by *en bloc* excision of the nodule (Figure 3).
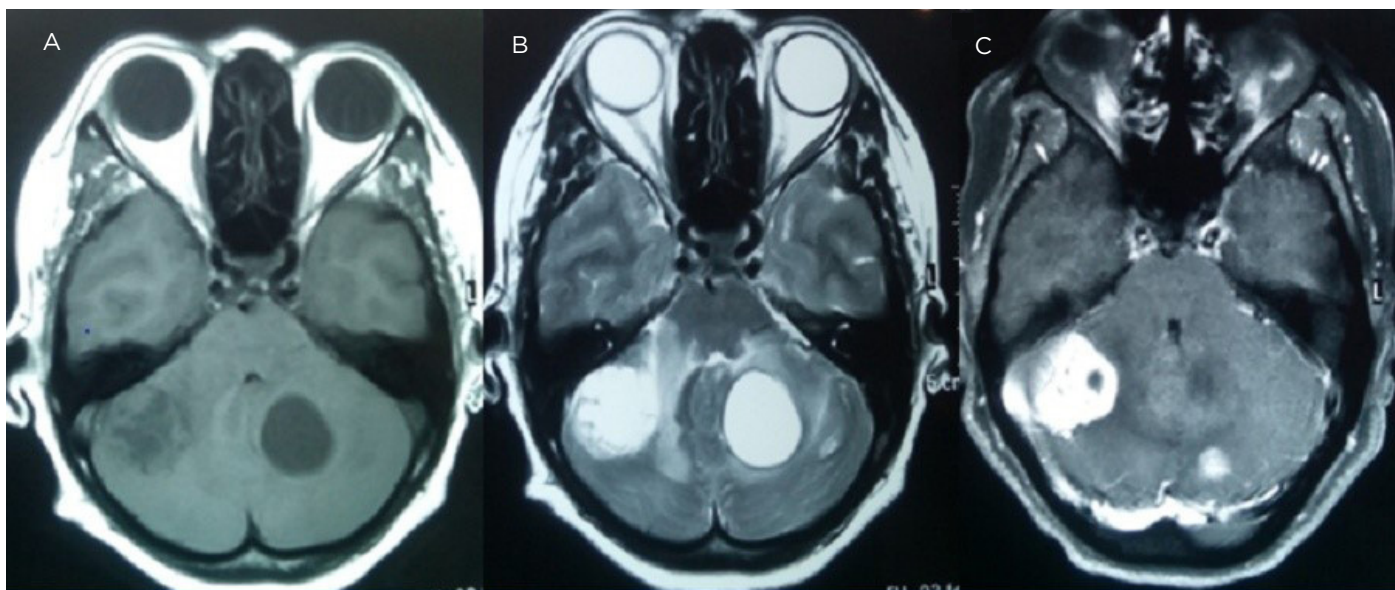

Figure 1: Characteristic magnetic resonance imaging findings of the lesions with enhancement.
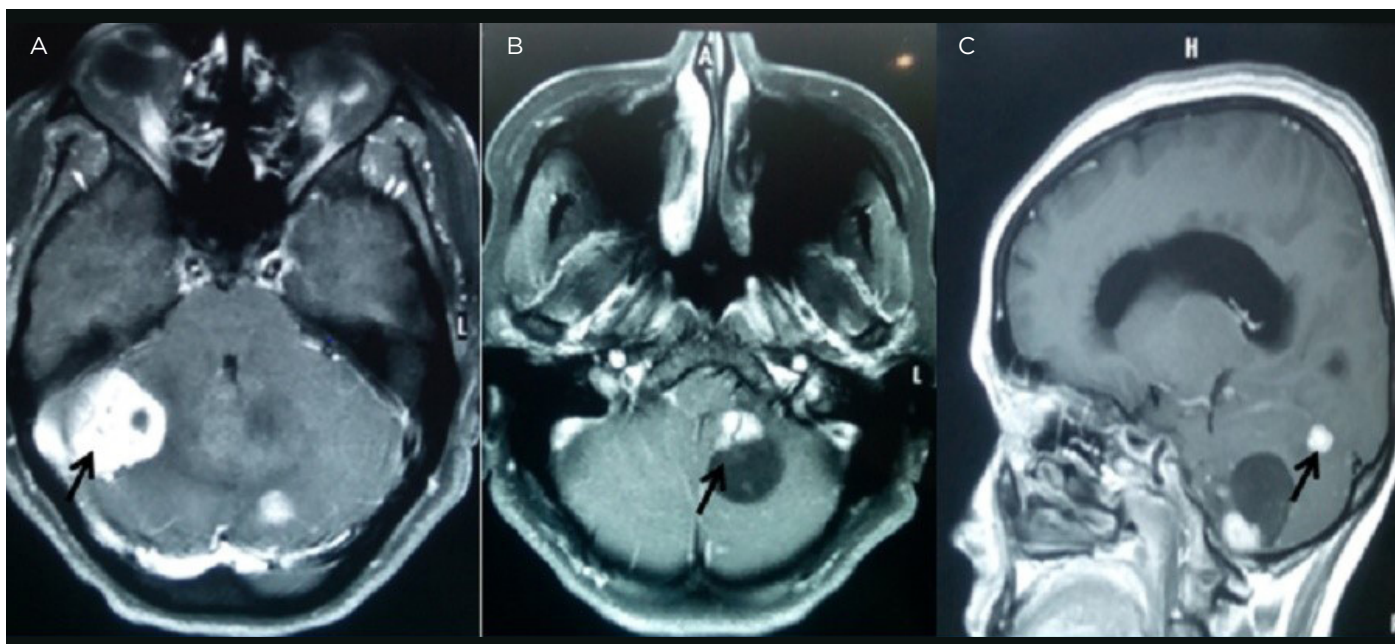A) T1; B) T2; C) T2 contrast.

Figure 2: Spectra of radioimaging variants of one lesion.
A) Solid with microcyst; B) cyst with nodule; C) solid.

Figure 3: Gross specimen of the solid haemagioblastoma excised *en bloc*.

The histological examination confirmed the diagnosis of HB. Two weeks later, the patient underwent a right retrosigmoid approach with complete excision of the lesion adhered to the pia of the cerebellar hemisphere and projecting into the CPA. The postoperative imaging revealed bilateral cerebellar oedema with narrowing of the forth ventricle. Since the patient was asymptomatic with regards to signs and symptoms of raised intracranial pressure, she was started on oral acetazolamide therapy 250 mg every 8 hours (as an anti-oedema measure) and was strictly monitored for features of acute hydrocephalus. The protocol of starting with oral acetazolamide before commencing diuretic therapy (intravenous furosemide, 20 mg every 8 hours) was followed. This strategy was chosen as diuretics may abruptly decrease the mean arterial pressure thereby reducing the cerebral perfusion pressure and increasing the risk of vasospasm in the posterior circulation during the postoperative period. If a patient is still symptomatic with evidence of progressive hydrocephalus in the repeat imaging, despite these measures, then we opt for external ventricular drainage placement for cerebrospinal fluid diversion. Steroids are not routinely used in such scenarios as it increases the risk of infection and adversely affects wound healing. The patient, however, showed gradual clinical improvement with repeat imaging, revealing no progression of the hydrocephalus; she made an uneventful recovery.

Follow-up was recommended every 6 months with routine imaging to assess the progression of other small solid lesions, and the patient was also counselled for periodic screening to rule out dissemination or other systemic involvement as a result of the HB.

DISCUSSION

Posterior fossa HB is a rare entity.[2] These tumours have been broadly divided into sporadic form and those associated with VHL syndrome.[3] Classically, patients with VHL syndrome present with multiple craniospinal as well as systemic vascular lesions with a high propensity for recurrence in the future.[4]

The *VHL* gene checks transcriptional elongation along with its interplay with other transcriptional factors like elongin B and C. Mutation in the tumour suppressor gene *VHL* leads to upregulation of vascular endothelial growth factor (VEGF) proteins, thereby leading to unopposed angiogenesis in targeted organs following its action on VEGF1 and VEGF2 receptors in stromal cells.[5] This leads to systemic tumours such as craniospinal HB, retinal angiomas, renal cell carcinoma, PCC, endolymphatic sac tumour, and others. Radiologically and with regard to its natural progression, HB has been classified into: purely cystic, cystic lesions with mural nodules, solid lesions, and solid lesions with microcysts.[6]

Judicious surgery for symptomatic lesions along with stringent follow-up for non-progressive variants is the cornerstone of management.[7] Typically, lesions within the posterior fossa present with cerebellar or brain stem compression. However, they have the propensity for spontaneous rupture as well.[8] These lesions are pial vascular lesions showing characteristic homogenous enhancement. They show characteristic vascular blush on angiography, however systemic screening needs to be performed to rule out metastasis in patients harbouring such multiple lesions. Advancements in radioimaging with newer modalities like positron emission tomography, dynamic contrast enhanced MR imaging, and MR spectroscopies have added new dimensions in diagnosis of these lesions.[9-11]

The correct therapeutic approach needs to be undertaken while managing HB. Cystic lesions classically tend to grow and cause compressive symptoms. Surgical excision is

therefore justified with *en bloc* removal of the nodule. Aspiration of the cystic content is not justified due to the fact that the mural nodules are foci for secretion into the cyst, and therefore, there remains a high chance of recurrence.[12] Compared with the cystic lesions, solid lesions should be managed similarly to those with cerebral arteriovenous malformations.[13] Selective preoperative embolisation of major feeders[14] and wide exposure with a tailored skull base approach with circumferential dissection for *en bloc* resection[15] are the key aspects to be followed during their management. The excision can be aided by the use of intraoperative fluorescence and indocyanine green.[16,17] There is also risk of dissemination of the lesions following tumour cell spillage during improper tumour handling.[18]

Preoperative embolisation helps reduce intraoperative bleeding, thereby facilitating excision. N-butyl cyanoacrylate (NBCA) and onynx have been used for preoperative embolisation.[19] NBCA, however, has the risk of gluing the microcatheter following its polymerisation after its contact with blood. Onynx, due to its diffusive properties, allows rapid embolisation of the feeders.[20] The major limitation of its use is the associated lengthy procedure: it can approach 1 hour in duration. A severe complication to be aware of during the embolisation of cerebellar HB is the risk of intratumoural bleeding and death, due to venous congestion in small capillaries and subsequent rupture.[21]

Studies have proven the efficacy of stereotactic radio surgery (SRS) for the management of small, recurrent, deep seated, and disseminated lesions.[22-24] Radiotherapy provides good tumour control. The 1, 2, and 6-year local control rates were 98%, 88%, and 73%, respectively, in one study.[24] Another study validated VHL disease-associated HB, solid tumour, lower tumour volume, and greater marginal dose with improved progression-free survival.[25] There are advantages of SRS and therapy compared with external beam radiation therapy, such as accurate and conformal dose to the target, minimal radiation effects to surrounding neurovascular structures, and provision for providing fractionated doses.[24] Complications related to radiotherapy include perilesional oedema, hydrocephalus, malignant transformation, *de novo* malignancy, and radiation necrosis.[26,27] Some authors therefore do not advocate SRS for prophylactic treatment of asymptomatic tumours.[26]

Our case was unique in that it was a sporadic form of HB presenting with multiple lesions within the posterior fossa. Furthermore, it presented with a whole spectrum of radiological variants seen during its natural progression. We opted for surgical management as both the cystic and solid lesions were large, symptomatic, and were leading to effacement of the forth ventricle.

Patients are advised for a lifelong follow-up with periodic screening for early diagnosis of recurrence, progression, and dissemination of the lesion. Patients with sporadic HB are to be followed up at 6, 12, and 24 months, respectively. For VHL-associated HB, yearly craniospinal MR imaging (for HB), annual ophthalmoscopy (for retinal angiomas), abdominal computed tomography (for renal cell carcinoma, pancreatic cysts, PCC), audiometry (for endolymphatic sac tumour), and blood and urinary screening for PCC is advocated.[28] Gene-targeted therapy in familial CNS HB, though still not proven, may provide new insights in the future.[1] Anti-angiogenic treatments have been tried, but results have shown them to be futile.[29] Timely gene testing and genetic counselling is prudent in early diagnosis and management of HB associated with VHL syndrome.[30,31]

CONCLUSION

A case of a sporadic variant of HB presenting with multifocal lesions in the posterior fossa was diagnosed. In addition to this, there were multiple radiological variants seen. Sites of involvement were also variable, concerning the cerebellomedullary junction, tentorium, as well as the CPA. Therefore, such presentation should be kept in mind during the differential diagnosis of posterior fossa lesions, as it may create uncertainty regarding the correct therapeutic approach to managing the condition. Due to the paucity of such cases, it is prudent to advise the patients to undertake regular screening for timely diagnosis of any systemic involvement, as well as for early management of recurrence of such lesions.

REFERENCES

1. Chu LZ et al. Multifocal central nervous system hemangioblastoma: A case report and review of the literature. Genet Mol Res. 2014;13(3):7904-11.

2. Friedmann DR et al. Nonschwannoma tumors of the cerebellopontine angle. Otolaryngol Clin North Am. 2015;48(3):461-75.

3. Conway JE et al. Hemangioblastomas of the central nervous system in von Hippel-Lindau syndrome and sporadic disease. Neurosurgery. 2001;48(1):55-63.

4. Abd Hamid D et al. Cerebellar hemangioblastoma in a patient with von Hippel-Lindau disease: A case report. Malays J Med Sci. 2000;7(2):43-8.

5. Wizigmann-Voos S, Plate KH. Pathology, genetics and cell biology of hemangioblastomas. Histol Histopathol. 1996;11(4):1049-61.

6. Choyke PL et al. von Hippel-Lindau disease: Genetic, clinical and imaging features. Radiology. 1995;194(3):629-42.

7. Lonser RR et al. Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J Neurosurg. 2014;120(5):1055-62.

8. Ene CI et al. Spontaneous hemorrhage from central nervous system hemangioblastomas. World Neurosurg. 2015;83(6):1180.

9. Sharma P et al. Von Hippel-Lindau syndrome: Demonstration of entire disease spectrum with 68Ga-DOTANOC PET-CT. Korean J Radiol. 2014;15(1):169-72.

10. Cha J et al. Differentiation of hemangioblastoma from metastatic brain tumor using dynamic contrast-enhanced MR imaging. Clin Neuroradiol. 2016. [Epub ahead of print].

11. Isobe T et al. Proton magnetic resonance spectroscopy findings of hemangioblastoma. Jpn J Radiol. 2010;28(4):318-21.

12. Miyagami M et al. Long-term prognosis of hemangioblastomas of the central nervous system: Clinical and immunohistochemical study in relation to recurrence. Brain Tumor Pathol. 2004;21(2):75-82.

13. Igari Y et al. Sudden death due to a cystic lesion in the cerebellum. Forensic Sci Int. 2014;245C:e25-8.

14. Sakamoto N et al. Preoperative endovascular embolization for hemangioblastoma in the posterior fossa. Neurol Med Chir (Tokyo). 2012;52(12):878-84.

15. Moon BH et al. Large solid hemangioblastoma in the cerebellopontine angle: Complete resection using the transcondylar fossa approach. Brain Tumor Res Treat. 2014;2(2):128-31.

16. Rey-Dios R et al. Intraoperative fluorescence for resection of hemangioblastomas. Acta Neurochir (Wien). 2013;155(7):1287-92.

17. Hojo M et al. Usefulness of tumor blood flow imaging by intraoperative indocyanine green videoangiography in hemangioblastoma surgery. World Neurosurg. 2014;82(3-4):e495-501.

18. Akimoto J et al. Disseminated cerebellar hemangioblastoma in two patients without von Hippel–Lindau disease. Surg Neurol Int. 2014;5:145.

19. Shin GW et al. Preoperative embolization of cerebellar hemangioblastoma with onyx: Report of three cases. Neurointervention. 2014;9(1):45-9.

20. Seong Eom K et al. Preoperative embolization of a cerebellar haemangioblastoma using onyx: A case report and literature review. Neurol Neurochir Pol. 2011;45(3):292-6.

21. Cornelius JF et al. Hemorrhage after particle embolization of hemangioblastomas: Comparison of outcomes in spinal and cerebellar lesions. J Neurosurg. 2007;106(6):994-8.

22. Hanakita S et al. The long-term outcomes of radiosurgery for intracranial hemangioblastomas. Neuro Oncol. 2014;16(3):429-33.

23. Lee GJ et al. The clinical experience of recurrent central nervous system hemangioblastomas. Clin Neurol Neurosurg. 2014;123:90-5.

24. Puataweepong P et al. The clinical outcome of intracranial hemangioblastomas treated with linac-based stereotactic radiosurgery and radiotherapy. J Radiat Res. 2014;55(4):761-8.

25. Kano H et al. The role of stereotactic radiosurgery for intracranial hemangioblastomas. Neurosurgery. 2008;63(3):443-50; discussion 450-1.

26. Asthagiri AR et al. Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel–Lindau disease. Neuro Oncol. 2010;12(1):80-6.

27. Moss JM et al. Stereotactic radiosurgical treatment of cranial and spinal hemangioblastomas. Neurosurgery. 2009;65(1):79-85; discussion 85.

28. Bamps S et al. What the neurosurgeon should know about hemangioblastoma, both sporadic and in Von Hippel-Lindau disease: A literature review. Surg Neurol Int. 2013;4:145.

29. Seystahl K et al. Neuropathological characteristics of progression after prolonged response to bevacizumab in multifocal hemangioblastoma. Oncol Res Treat. 2014;37(4):209-12.

30. Frantzen C et al, "Von Hippel-Lindau Syndrome," Pagon RA et al. (eds.), GeneReviews® (2000), Seattle (WA): University of Washington, Seattle; 1993–2016.

31. Nielsen SM et al. Von Hippel-Lindau disease: Genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 2016. [Epub ahead of print].