Clinical Case Report

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Von Hippel-Lindau with early onset of hemangioblastoma and multiple drop-metastases like spinal lesions

A case report

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Abstract

Rationale: Hemangioblastoma is a rare tumor of the central nervous system (CNS). It is usually observed in patients with von-Hippel Lindau (VHL). The peak age for hemangioblastoma is between 20 and 50 years of age with very few cases over 65 or below 18 years of age.

Patient concerns: We report a female with a rare VHL mutation (c.337C>T) who was diagnosed with multifocal CNS hemangioblastoma at a very young age.

Diagnosis: At 17-years of age, she presented with obstructive hydrocephalus due to large cystic cerebellar mass. Imaging showed multiple lesions resembling drop metastases throughout her spinal cord. Immunohistochemistry of the resected tumor confirmed the pathological diagnosis of hemangioblastoma (World Health Organization Grade 1).

Interventions and outcome: She was treated with multi-stage resection of her primary and drop- metastasis like disease. She presented six months later with retinal hemangioblastoma while her other lesions were stable. She presented with multiple CNS and eye hemangioblastomas after failing to follow up for 2 years. Subsequently, Everolimus was started to treat her systemic disease.

Lessons: The unique feature of our case is the presence of multiple drop-metastases like spinal lesions, which has not been reported in the literature to be associated with hemangioblastoma.

Abbreviations: CNS = central nervous system, CT = computed tomography, HIF = hypoxia-inducible factor, MRI = magnetic resonance imaging, NF1 = neurofibromin 1, VHL = Von Hippel-Lindau.

Keywords: drop metastases, hemangioblastoma, von Hippel-Lindau

1. Introduction

Hemangioblastoma is a vascular tumor that usually affects the brain, brainstem, spinal cord, and the retina.[1] Most cases of hemangioblastoma develop in the middle age with 25% of central nervous system (CNS) cases associated with Von Hippel-Lindau (VHL).[2] VHL is a genetic disorder associated with mutations in the tumor suppressor *VHL* gene that causes VHL protein (pVHL) to be nonfunctional.[3] In normal oxygen condition, pVHL binds and degrades hypoxia-inducible factor 1 alpha (HIF1 alpha).[3] Without the regulation of pVHL, active HIF1 alpha leads to activation of multiple downstream genes.[3] Surgical resection of CNS hemangioblastomas is considered the standard of care. We report a 17-year-old patient who has early onset and severe manifestations of VHL. She has a rare c.337C>T (p.Arg113Ter) mutation of the *VHL* gene. The mutation is within the binding region of pVHL to HIF1s protein. This mutation occurrence is rarely reported in the literature, and we are the first to report early onset of hemangioblastoma with multiple drop-metastases like spinal lesions to be associated with this *VHL* gene mutation.

2. Case presentation

A signed consent for publication of this report was obtained from the patient. This study is a case report that retrospectively reviewed the patient information; therefore, approval by the institutional review board or ethical committee is not required.

Our patient is a previously healthy female who presented at 17 years of age with obstructive hydrocephalus and a cystic cerebellar lesion. She had 1-month history of worsening headache. Her physical examination was unremarkable. She was alert, interactive, oriented, and able to answer questions appropriately. There was no papilledema; pupils were equally round, reactive to light and accommodation; extraocular muscles were intact. The neurologic examination showed intact cranial nerves II–XII; reflexes 2+ bilateral lower extremities, good alternating movements, and coordination.

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Her mother died at 36 years of age of colon cancer; her maternal grandmother and aunt died of a brain tumor at 50 and 18 years of age, respectively; her maternal grandfather died at an unspecified age from colon cancer. No one in her family was tested for familial cancer predisposition.

On imaging, computed tomography (CT) scan of her head showed obstructive hydrocephalus with slight periventricular effusion and no calcification. Her head magnetic resonance imaging (MRI) revealed a large cystic mass with enhancing mural nodule involving the left cerebellar hemisphere, measuring $4 \times 3 \times 3.1$ cm. There were associated small enhancing lesions scattered throughout the cerebellar hemispheres bilaterally involving the medulla and cerebellar vermis. Differential diagnoses of the lesions include pilocytic astrocytomas with seeding, hemangioblastoma, or parasitic lesions (Fig. 1). The large cerebellar mass resulted in midline shift from left to right, creating a mass effect upon the 4th ventricle with associated moderate hydrocephalus and a small amount of transependymal migration of cerebrospinal fluid. Spinal MRI revealed additional satellite lesions throughout the cervical and thoracic spine with the appearance of drop metastasis (Fig. 2A, B).

Suboccipital craniotomy and complete cerebellar tumor resection were performed next day. Immunohistochemistry was positive for inhibin but not cytokeratin CAM 5.2 or EMA. This was supportive of the pathologic diagnosis of hemangioblastoma (World Health Organization Grade 1). Due to the diagnosis and significant family history of cancer, our patient received genetic counseling and later tested for VHL. This revealed a pathogenic nonsense mutation c.337C>T (p.Arg113Ter) in the *VHL* gene. One month later, she underwent another surgery for removal of her large enhancing cervico-thoracic tumor. Postsurgical MRI showed complete removal of the tumor (Fig. 2C). The intraoperative view of this tumor revealed to be an exophytic lesion (Fig. 3). The pathologic examination was again supportive of hemangioblastoma (World Health Organization Grade 1).

Five months later, the patient was found to have retinal capillary hemangioblastoma and preretinal fibrosis in both eyes. There was a limited serous detachment of the left eye. An external cryopexy was performed at that time. However, after a few months, she developed tractional retinal detachment with vitreous hemorrhage of the left eye then posterior subcapsular cataract of the left eye. Follow-up MRI of the brain and spinal cord did not show any new lesions.

Two years after last follow-up, she presented with neck and back pain that radiated to the right shoulder and breast without weakness or other pain. A brain MRI showed a cystic lesion with enhancing foci in the superior portion of the cerebellum and multiple enhancing lesions in the medulla and inferior portion of the cerebellar hemispheres. Her spinal MRI showed enlarging thoracic and cervical lesions ranging from 3 to 6 mm. Her abdominal MRI showed a 14-mm enhancing nodule in the left lobe of the liver and multiple cysts throughout the pancreas. In addition, she had progressive retinal hemagioblastomas in the right eye. She underwent implantation of nitric oxide into her right eye. Surgical resection/biopsy of all visible lesions was deemed too morbid and oral Everolimus was started to treat her systemic disease.

3. Discussion

Our patient had multiple exophytic (intradural-extramedullary) lesions throughout her spinal cord (cervical and thoracic regions) that resemble drop metastases. To our knowledge, this observation has never been reported in the literature to be associated with hemangioblastoma. Even though hemangioblastoma in patients with VHL mutation usually presents with multiple lesions that involve the retina, cerebellum, and the spinal cord,[4] the spinal lesions are rarely intradural-extramedullary. In a study of 26 patients with spinal cord hemangioblastoma, only 1 out of 26 patients was found to have an intradural-extramedullary spinal lesion.[5] Drop metastases to the spine are intradural-extramedullary spinal lesions that metastasized from intra-cranial

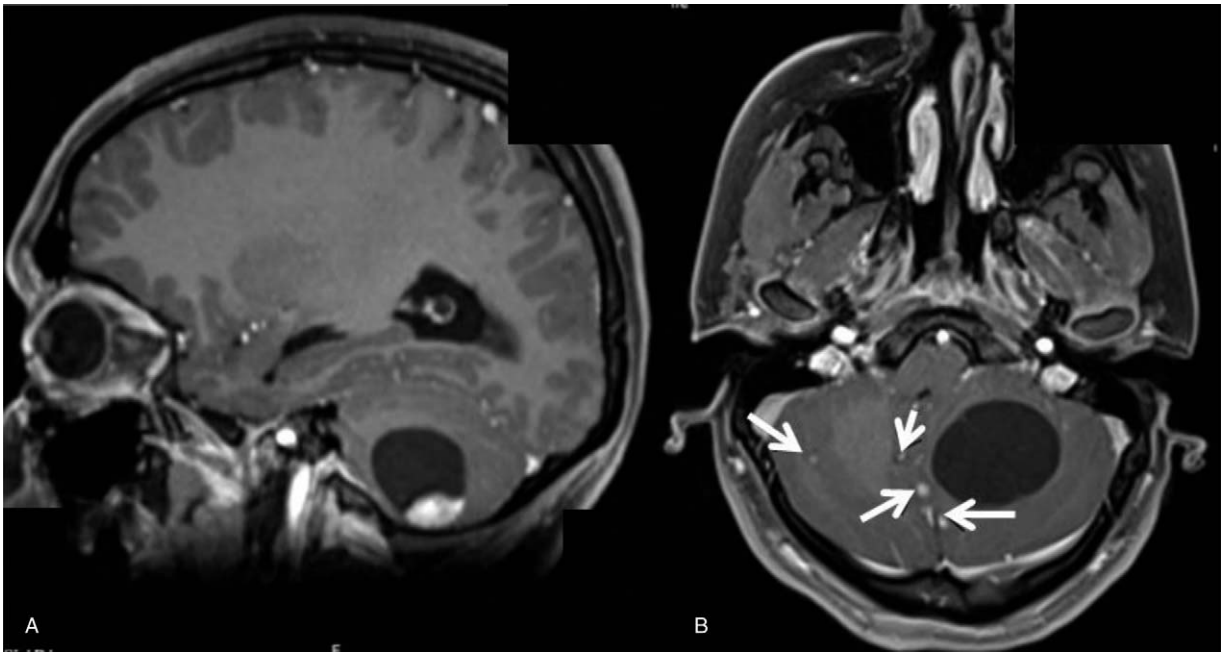

Figure 1. Magnetic resonance imaging showing a large, $4 \times 3 \times 3$ cm posterior fossa tumor within the cerebellum (A) as well as numerous satellite lesions (B, arrowheads).

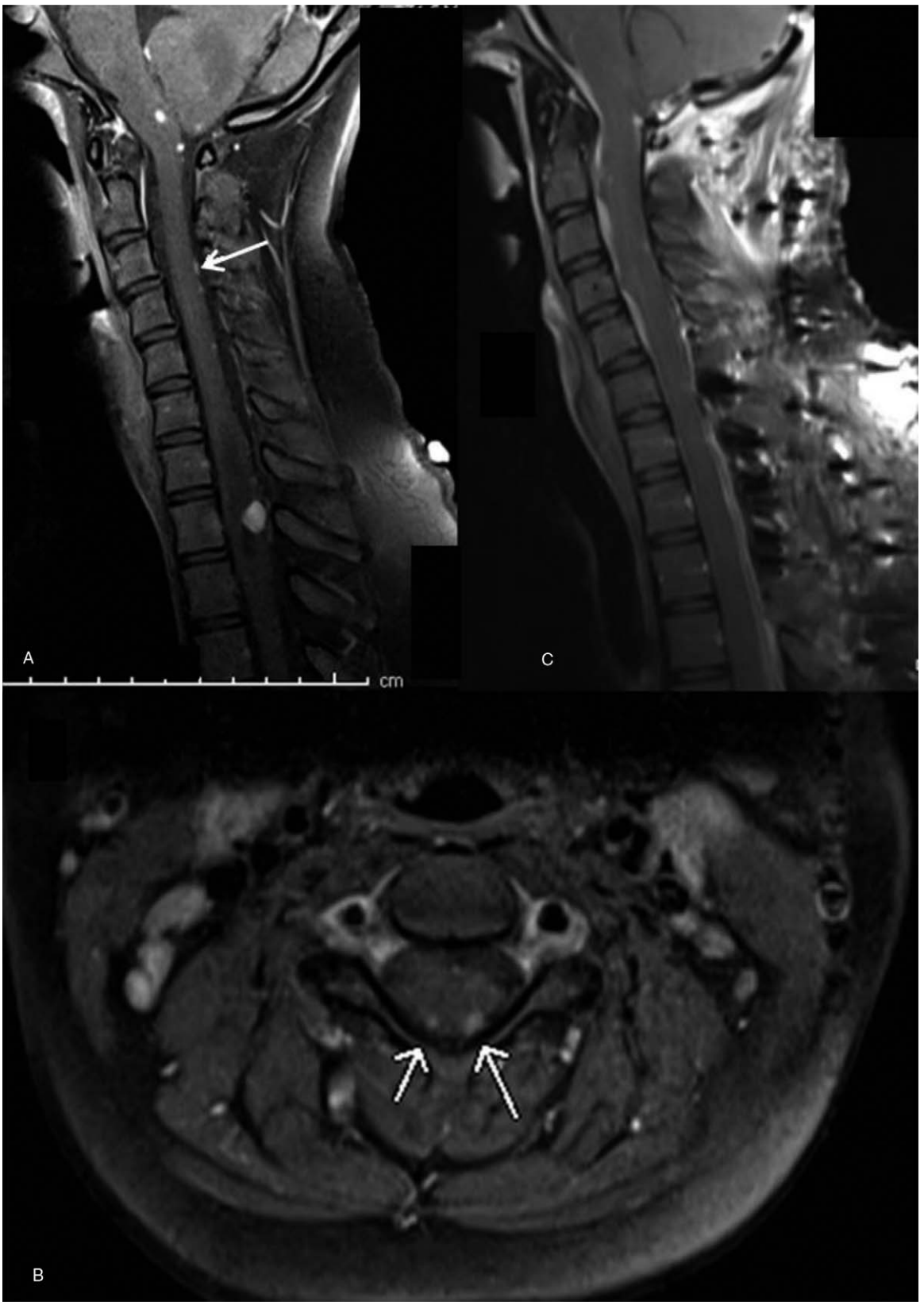

Figure 2. Magnetic resonance imaging of the cervical spinal cord showing smaller cervical spine lesions with the appearance of drop metastasis (A and B, arrowheads). Cervicothoracic enhancing mass was removed (C).

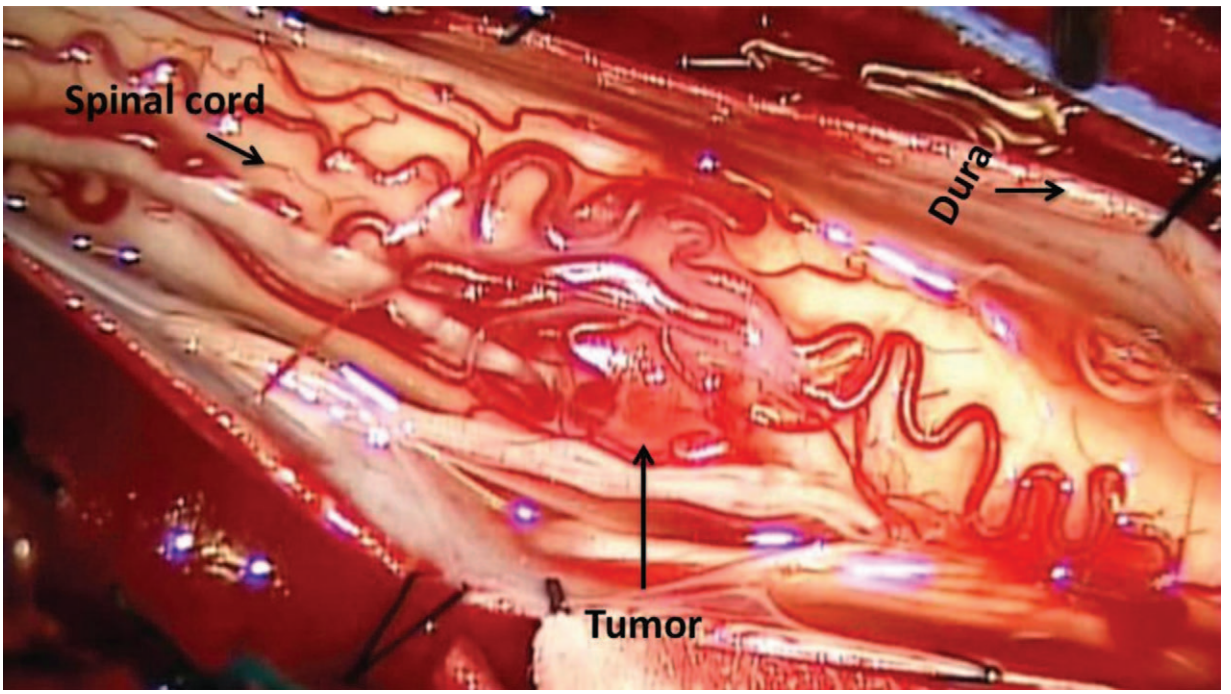

Figure 3. Intraoperative view of the cervicothoracic lesion confirms the tumor to be exophytic (intradural-extramedullary).

tumors by spreading through the spinal fluid.[6] Our patient's presentation of multiple intradural-extramedullary spinal lesions supports that her spinal lesions could be metastases from her cerebellar mass. Moreover, multiple satellite lesions throughout the tentorial surface of the cerebellum and a lesion in the midbrain suggest that her tumor might have also spread locally. Sporadic hemangioblastoma tends to be single and localized, but multiple lesions can be seen in the case of patients with *VHL* mutation.[7] Our unique clinical observation and early onset of hemangioblastoma could be attributed to the genetic makeup of our patient's *VHL* gene.

Our patient has a nonsense mutation c.337C>T (p. Arg113Ter) in the *VHL* gene. This mutation is rarely reported in the literature. Only a few articles in literature have described the c.337C>T nonsense mutation in patients with VHL syndrome. Martucci et al looked at the association of paragangliomas with mutations in *SDBH* and *VHL* genes and found only 1 out of 27 patients to have c.337C>T mutation in *VHL* gene.[8] Peyre et al described 2 patients with endolymphatic sac tumors in which 1 patient carries the c.337C>T mutation.[9] Association of this mutation and early onset of hemangioblastoma with multiple drop-metastases spinal lesions has not been reported in the literature. However, we speculate this association to be biologically plausible. The c.337C>T mutation is within the β-pleated sheet domain of pVHL (residues 63–154, encompassing both exons 1 and 2) which binds the α-subunits of hypoxia-inducible factor (HIF 1α–3α) at residues 65 to 117 in the process of targeting HIFs for degradation.[10] Therefore, a mutation within this region might affect the regulation of HIF alpha by pVHL and leads to the more severe onset of the disease. Interestingly, sequencing of oncogenic mutations in our patient showed that she also has a C.7987A mutation of neurofibromin 1 (*NF1*) gene. The pathogenic nature of this mutation has not been reported in the literature; however, concurrent mutation of both *VHL* and *NF1* gene might have contributed to the remarkable disease manifestation of our patient.

Hemangioblastomas are benign, capillary-rich neoplasms of the CNS. Severe and early onset can be seen in patients with VHL syndrome. However, there are no standard systemic chemotherapeutic treatment available beside surgery for patients with aggressive and recurrent hemangioblastomas. Our patient had an early presentation with multiple drop-metastases like spinal lesions, her hemangioblastomas relapsed after surgical treatment and her systemic disease warranted innovative approach. We selected Everolimus as a systemic therapy based on limited evidence suggesting effectiveness of Everolimus in VHL disease with multiple organ involvement.[11] Our patient has tolerated Everolimus for the last 3 months with no signs of disease progression. Due to the short follow-up, we are unable to validate or refute the evidence suggesting a role for Everolimus as a systemic therapy in aggressive multisystem disease in patients with VHL.

Our anecdotal observation is intriguing but may not be unique. Genotype-phenotype correlation has been conducted but minimal information to link disease aggression with specific mutations in *VHL* gene exist. A large scale review of patients with VHL can delineate the need for early screening and intervention. Furthermore, collaborative clinical trials utilizing biotherapy should be conducted to help patients with targetable DNA defects and aggressive disease avoids repeated morbid interventions.

Author contributions

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Writing – review & editing: Thinh H. Nguyen, Teresia Pham, Muhittin M. Belirgen, Mohamad M. Al-Rahawan.

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