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CASE REPORT

Cerebellar Hemangioblastoma with Leptomeningeal Spread and a Fatal Outcome: A Rare Case Report with *MDM2* and *EGFR* Alterations

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Abstract: Hemangioblastoma (HB) is a Central Nervous System (CNS) tumor with a generally favorable behavior and prognosis, classified as WHO grade 1. Sporadic HB is not related to any inherited disease, and it usually appears in a single location. Sporadic or VHL-related HBs show variable patterns of growth velocity. Cases of growing HB can cause mild symptoms such as headache, but some cases develop serious complications such as accumulation of cerebrospinal fluid in the brain with secondary neurological damage sometimes being irreversible when early treatment is not started. Our case showed some clinical characteristics more frequently observed in VHL-related HB rather than sporadic HB, and the presence of alterations in *MDM2* and *EGFR* that could be related to the oncogenesis of these tumors. Even when the treatment of choice for HB is surgery, the presence of these genetic alterations could open a new window for research aimed at assessing the possibility of new therapies with TKIs-*EGFR* and anti-*MDM2* inhibitors in those HB cases with multifocal recurrences or cases with an adverse clinical behavior.

Keywords: haemangioblastoma, mouse double minute 2, epidermal growth factor receptor, hydrocephalus, immunohistochemistry, fluorescence in situ hybridization

Introduction

Hemangioblastomas (HB) are neoplasms originating in the central nervous system (CNS) with a generally good clinical course and prognosis. They represent 1.5–2.5% of all intracranial neoplasms and 7–12% of posterior fossa tumors.[1] In about 30% of cases, HB are associated with von Hippel-Lindau syndrome (VHL), an autosomal dominant disorder characterized by lesions in different tissues, although most arise sporadically.[2]

Various molecular alterations have been described in HB, not only mutations in VHL (substitutions, deletions, insertions, and duplications), but recurrent DNA copy-number losses of chromosomes 6q and 6, and somatic gain-of-function EPAS1 (HIF2A). Various cell signaling mechanisms are upregulated in CNS HB, including *EGFR* (HER1), *TGFα, FGFR3, PDGFRA*, and Notch signaling pathways or receptors.[3,4]

We present a case of sporadic cerebellar HB that recurred eight years after diagnosis, with multifocal leptomeningeal seeding and a fatal outcome, describing the clinical and radiological characteristics as well as the immunohistochemical and molecular alterations in *MDM2* and *EGFR* genes.

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Materials and Methods

Detailed methods are freely available in the Data Availability Statement section (see the https link in Data Availability Statement) including the following:

- Clinical and radiological data.
- Histological characteristics
- Immunohistochemistry methods and analysis
- Copy Number Alterations by Fluorescence in Situ Hybridization methods and analysis.

Results

Clinical History and Imaging

A 42-year-old man who complained of suboccipital headaches, which gradually transformed into holocranial headaches. At clinical examination he declared 10 kilogram weight loss, dizziness, unsteady gait, and behavioral disturbances in the last six weeks. He also declared a previous history of human immunodeficiency virus (HIV) infection, diagnosed when he was 35 years old, treated with Efavirenz, Emtricitabine, and Tenofovir disoproxil. Undetected viral load was confirmed in every HIV serology test performed after treatment.

Brain Magnetic Resonance Imaging (MRI) with contrast, revealed an intra-axial mass located in the middle line of the posterior fossa, centered in the cerebellar Vermis, which showed two different well-defined components: one was solid and the other was cystic. The solid component was hypervascular, predominantly located on top. The cystic component, on the lower part of the tumor, showed a T2 high signal intensity and T1 hypointense signal (Figure 1A–C and E). Both tumor components together measured 48x40x35 mm in three dimensions. The mass caused obstructive hydrocephalus with significantly enlarged lateral ventricles (Figure 1B and C), obliteration of the cerebellopontine angle cistern, and tonsillar herniation. The diffusion-weighted magnetic resonance imaging (DW-MRI) as well as the apparent diffusion coefficient (ADC) map, did not show signal restriction on the solid component of the tumor (Figure 1F). Nevertheless, hypervascular areas were exclusively present in the solid component of the tumor. The radiological diagnosis proposed a differential diagnosis including hemangioblastoma (HB), astrocytoma, and metastasis.

The patient underwent a surgical approach by neuronavigation with cranial nerve monitoring. A suboccipital incision and craniotomy in the left occipital region, near the foramen Magnum, were performed, continuing with a "Y"-shaped durotomy. The tumor was resected from the cerebellar vermis region, bleeding easily during the procedure. A microdissection of the IV ventricle's floor to achieve a complete tumor removal, was necessary. No early post-surgical complications were reported, nevertheless after a few months, 10th cranial nerve palsy was diagnosed, requiring tracheostomy and percutaneous endoscopic gastrostomy (PEG).

Eight years later, a tumoral recurrence with supra and infratentorial involvement with multifocal spinal cord and leptomeningeal seeding was found on MRI (Figure 1A and D). Secondary hydrocephalus necessitated various surgical interventions.

Ventriculoperitoneal shunt was needed. After that, ventriculitis was diagnosed. Cerebrospinal fluid (CSF) cytology showed lymphocytic pleocytosis, however tumor cells or pathogenic microorganisms were not reported. The patient was hospitalized due to a respiratory infection (septicemia caused by *Pseudomonas aeruginosa*) and bacteremia caused by *Staphylococcus aureus*. The respiratory symptoms disappeared with antibiotics, however neurological status worsened. Brain-CT was performed urgently. Hydrocephalus and intracranial hypertension were observed. After the external ventricular drain, the patient died within a few hours.

Pathological Findings

Gross description: the tumor presented well-defined solid and cystic areas. The largest tumor diameter was 48mm with well-circumscribed and smooth margins. Cut surface showed brown color with hemorrhagic areas.

Microscopically, it consisted of a monotonous component of stromal cells with clear to vacuolated cytoplasm, and small round to oval nucleus intermingled with abundant delicate capillary vessels (Figure 2A).

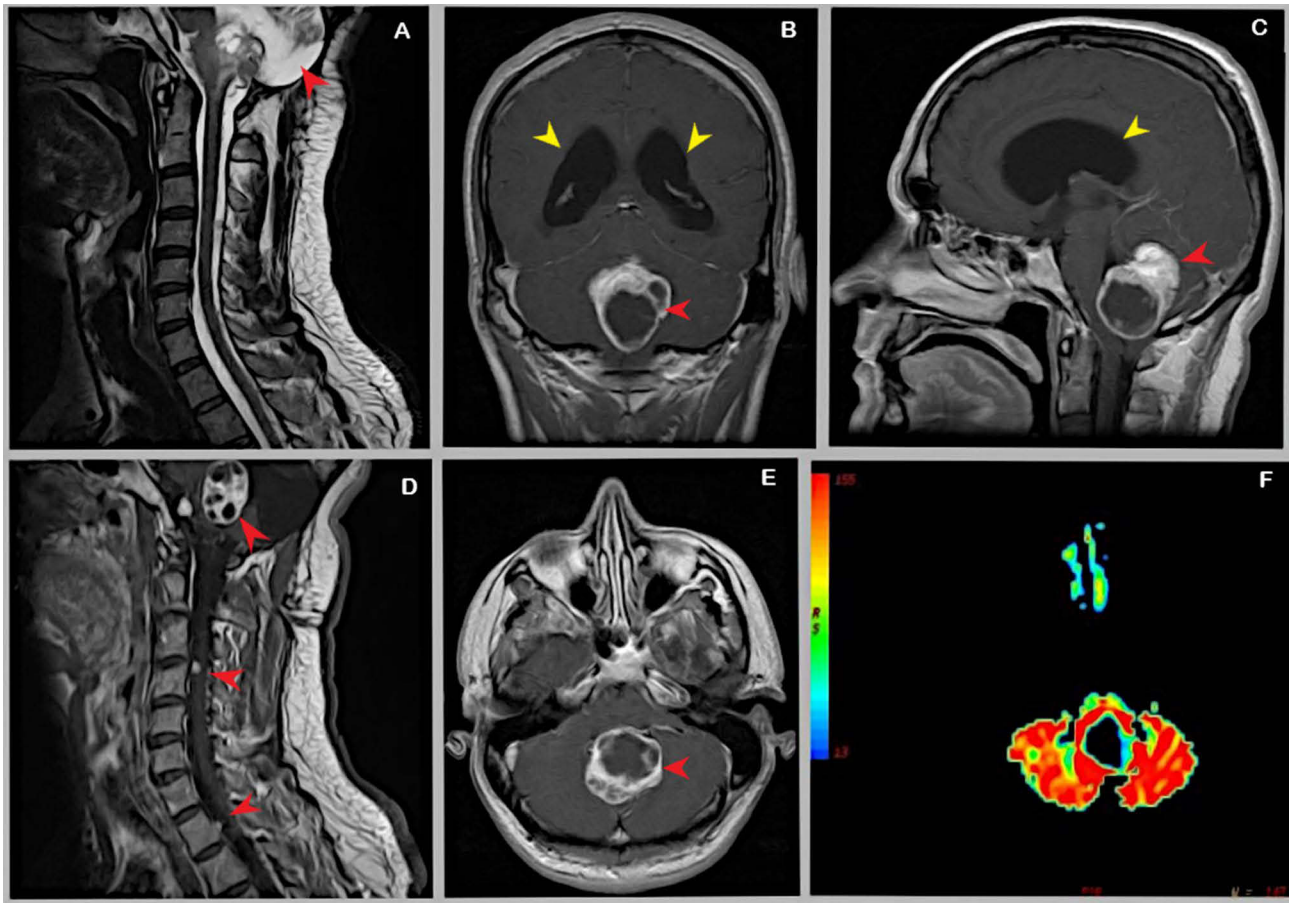

Figure 1 Brain MRI features: post contrast coronal (**B**), sagittal (**C**), and axial (**E**), T1-weighted sequences. See the obstructive hydrocephalus showing abnormally large lateral ventricles (yellow arrows on (**B** and **C**)), and the intra-axial mass located on cerebellar vermis with its solid and cystic components (red arrows on (**A, B, C** and **E**)). Cerebellar detail on axial apparent diffusion coefficient (ADC) map (**F**). Cervical spine MRI features: post contrast, sagittal T2 weighted sequences (**A**), and sagittal T1 weighted sequences (**D**). See the cerebellar mass and the multifocal spinal cord with leptomeningeal seeding (red arrows on (**A** and **D**)).

Immunohistochemical Findings

Immunohistochemically, the stromal cell component showed immunoreactivity for Inhibin alpha (Figure 2B), S100, neuron specific enolase (NSE), CD56, MDM2, and EGFR. Interestingly, PAX8 and Carbonic anhydrase IX (CaIX) were also positive. The vascular elements showed positivity for CD31, ERG, GLUT1, and VEGF (Figure 2C). Finally, EMA, CD10, PAX2, and Synaptophysin were negative (Data Availability Statement).

Fluorescence in situ Hybridization Findings

The analysis of *MDM2* and *EGFR* by fluorescent probes (FISH) revealed that 73% of stromal cells showed 5 copies (red and green signals) of *MDM2* gene (12q15) (Figure 2E); 52% of stromal tumor cells showed 5 copies (red signals) of *EGFR* gene (7p11) but polysomies were also observed in 25% of stromal tumor cells (four green signals and two red signals) (Figure 2G). Gains on these genes were also found in four more cases (from the series of 12 HB originally analyzed), (Data Availability Statement).

Discussion

Hemangioblastoma (HB) is a central nervous system (CNS) WHO grade 1, highly vascular tumor, containing neoplastic stromal cells that have clear to vacuolated cytoplasm and characteristic immunohistochemical features (eg, Inhibin alpha positivity) and molecular findings (eg, von Hippel–Lindau (VHL) alterations).[3] HB accounts for < 2% of all CNS tumors, and they may occur sporadically or in association with VHL-syndrome,[5,6] a familial predisposition to develop different

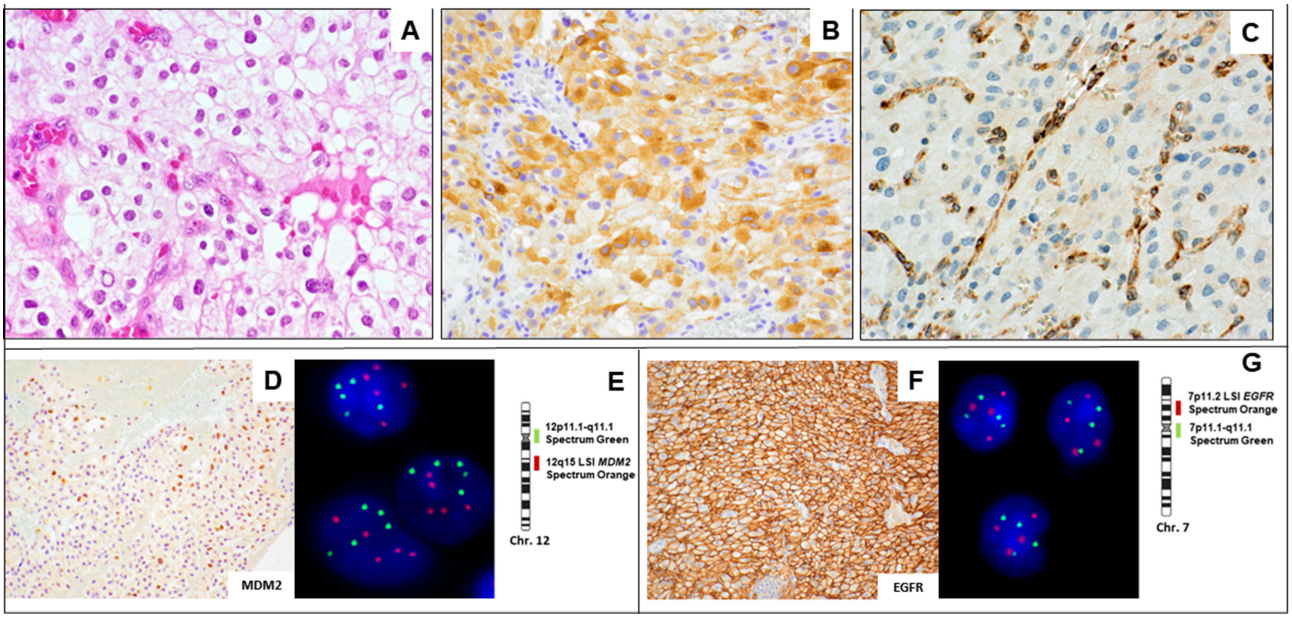

Figure 2 Histopathological, immunohistochemical, and molecular findings: stromal cells with clear to vacuolated cytoplasm and small round to oval nucleus intermingled with abundant delicate capillary vessels (**A**). Stromal cells show α-inhibin positivity (**B**). Capillary elements show VEGF positivity (**C**). MDM2 by IHC shows nuclear positivity in a high proportion of tumor cells (**D**), in accordance with the signal gains on *MDM2* gene detected by FISH (**E**). EGFR by IHC shows membranous positivity in all tumor cells (**F**), also in accordance with the signal gains on *EGFR* gene detected by FISH (**G**).

types of cancer, such as pheochromocytoma, paraganglioma, retinal- and cerebellar-hemangioblastoma, and renal cell carcinoma (RCC).[7] Our patient did not have a family history of VHL alterations. Neither somatic nor germline mutations were found on VHL molecular analysis.

Cellular subtype with clear cell aggregates may initially be misdiagnosed as metastatic clear cell renal cell carcinoma (ccRCC). Immunoreactivity for Inhibin alpha and D2-40, in addition to negative staining for RCC (antibody), EMA, CD10, and CAM5.2 antibodies, may be helpful for excluding metastatic renal cell carcinoma. PAX8 and CaIX can be positive in both, therefore we recommend not using them in differential diagnosis.[8]

Overexpression of *EGFR* in VHL-related CNS HB has been described by Liu et al.[9] They found that the expression of *EGFR* in VHL-related HB was significantly higher than that in the control group by IHC (*EGFR*, $p = 0.007$) and by RT-PCR ($p = 0.017$). Böhling et al, also found that the stromal cells in HB showed high and uniform EGFR expression by IHC.[10]

Copy-number alterations (CNAs) in various genes, including gain of *EGFR* and microdeletion of *FGFR1*, have been identified in HB.[3,11] Relevant literature studies about *EGFR* alterations in hemangioblastoma are compiled in Table 1. We found copy number gains in *EGFR* gene by FISH, in good concordance with IHC results (Figure 2F and G), (Data Availability Statement).

There are not many scientific publications about the implications of *MDM2* alteration in the oncogenesis and evolution of HB. Falconieri et al, predicted that *MDM2* is a novel direct interactor of pVHL.[14] To our knowledge, this is the first publication in English literature in which *MDM2* gene was analyzed by IHC and FISH in a series of sporadic HB cases (non VHL-related HB) and specifically in a case with a fatal outcome. We found copy-number gains in *MDM2* gene by FISH in good concordance with IHC results (Figure 2D and E), (Data Availability Statement).

The prognosis of HB is generally excellent after a complete excision. Early treatment is highly recommended to avoid permanent neurological deficits.[15] Sporadic HB has a better prognosis compared to VHL-associated ones, among other reasons, because the latter shows multifocality. Features that impact prognosis include age, size, growth pattern, treatment, multifocality, and location.[16]

Thus, our case presents some unusual characteristics rarely found in sporadic HB, such as the leptomeningeal spread, local recurrence, and complication with a fatal outcome, being more frequently found in VLH-related forms of HB.

Table 1 Relevant Literature Studies about *EGFR* Alterations in Hemangioblastoma

Authors	Article	Journal	Year
G Reifenberger et al[12]	Coexpression of transforming growth factor-alpha and épidermal growth factor receptor in capillary hemangioblastomas of the central nervous system	American Journal of Pathology	1995
T Böhling et al[10]	Expression of growth factors and growth factor receptors in capillary hemangioblastoma	Journal of Neuropathology and Experimental Neurology	1996
Gregory J Chen et al[13]	Overexpression and activation of epidermal growth factor receptor in hemangioblastomas	Journal of Neuro-Oncology	2010
Ruty Mehrian-Shai et al[11]	Identification of genomic aberrations in hemangioblastoma by droplet digital PCR and SNP microarray highlights novel candidate genes and pathways for pathogenesis	BMC Genomics	2016
Zhen Liu et al[9]	Overexpression of EGFR and TGFα in von Hippel–Lindau-Related Central Nervous System Hemangioblastomas	Frontiers in Oncology	2020

There is not enough scientific evidence, to date, that allows us to conclude that the *EGFR* and *MDM2* findings observed in our case induced a clinically worse and fatal outcome. This requires a deeper molecular investigation with a large prospective series to shed light on the role of protein expression on IHC, and CNAs on FISH, in *EGFR* and *MDM2* genes, in the oncogenesis of HB and its potential significance in therapy and prognosis.

Abbreviations

HB, hemangioblastoma; CNS, central nervous system; *VHL-gene*, von Hippel-Lindau gene; VHL-syndrome, von Hippel-Lindau syndrome; pVHL, von Hippel–Lindau protein; FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; CNAs, copy number alterations; RT-PCR, reverse transcription-polymerase chain reaction; *EGFR*, epidermal growth factor receptor; *MDM2*, murine double minute 2; TKIs-EGFR, EGFR tyrosine kinase inhibitors; *EGFR1*, epidermal growth factor receptor 1; *HER1*, human epidermal growth factor receptor 1; *EPAS1*, Endothelial PAS Domain Protein 1; *HIF2A*, hypoxia-inducible factor 2-alpha; *TGF-α*, transforming growth factor-alpha; *FGFR3*, fibroblast Growth Factor Receptor 3; *PDGFRA*, platelet Derived Growth Factor Receptor Alpha; CD56, cluster of differentiation 56; CD31, cluster of differentiation 31; CaIX, carbonic anhydrase IX; PAX8, paired box gene 8; PAX2, paired box gene 2; VEGF, vascular endothelial growth factor; ERG, erythroblast transformation-specific [ETS]-related gene; GLUT-1, glucose transporter 1; EMA, epithelial membrane antigen; CD10, cluster of differentiation 10; HIV, human immunodeficiency virus; MRI, Magnetic Resonance Imaging; DW-MRI, diffusion-weighted magnetic resonance imaging; ADC, apparent diffusion coefficient; Brain-CT, computed tomography of the brain; PEG, percutaneous endoscopic gastrostomy; WHO, World Health Organization.

Data Sharing Statement

The data are publicly available in the following link:
https://github.com/LMCT-Repository/MDM2-and-EGFR-Alterations-in-HaemangioblastomaHemangioblastoma.git.

Ethics Approval Statement

This manuscript has been reviewed and authorized by the ethics committee of the University Hospital of Salamanca. No private personal data of the patient have been revealed in this manuscript.

Patient and Patient's Family's Consent Statement

The patient's family authorized and consented to the publication. The informed consent signed by the patient's family included in the clinical data contemplates the scientific disclosure of relevant findings if the privacy of personal data is respected.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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