Case Lesson nr. *29*

Early cured Renal Carcinoma as a sentinel for recurrent multiple brain hemangioblastomas in Von Hippel–Lindau disease.

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Introduction

Von Hippel–Lindau (VHL) disease is an autosomal dominant tumor predisposition syndrome caused by germline mutations in the *VHL* tumor suppressor gene located on chromosome 3p25. Its estimated incidence is approximately 1 in 36,000–40,000 individuals. VHL predisposes patients to a variety of benign and malignant tumors, CNS hemangioblastomas and clear cell renal cell carcinoma (ccRCC) being the most prominent[2,5].

In VHL, RCC is due to loss of VHL protein function, leading to stabilization of hypoxia-inducible factors (HIFs) and downstream activation of angiogenic pathways, such as VEGF and PDGF. Interestingly, hemangioblastomas also exhibit coexpression of erythropoietin (EPO) and its receptor, a pattern similarly observed in RCC—indicating a shared HIF-driven pathogenesis[1,2,3,4].

We report a case with cured renal carcinoma, with multifocal brain hemangioblastomas consistent with VHL disease after 25 years [2,3,5].

Key words: Von Hippel–Lindau (VHL), hemangioblastoma (HB), clear cell renal cell carcinoma (ccRCC),VEGF, PDGF

Case Presentation A 63-year-old female presented with a two-week history of nausea, vomiting, and gait disturbance. Her past medical history was notable for: Renal adenocarcinoma ccRCC, treated with nephrectomy and postoperative radiotherapy in 2000 (considered cured since but not followed and without genetic studies)

Cutaneous fibro epithelial papilloma, surgically excised two years prior, was not suspected for VHL syndrome.

Examination: Retrograde amnesia, Constitutional apraxia, Positive Romberg sign Mild cognitive impairment

No suspicious for melanoma on skin inspection.

Brain MRI: Two supratentorial lesions in the left and right temporal lobes ,radiological interpretation favored metastatic hemorrhagic lesions (fig 1 A,B,C)

Whole-body CT scan: No pathological findings, only the prior nephrectomy.

Intervention**:** Through bilateral temporal craniotomies ,under the same anesthesia ,with neuronavigator, two cherry like lesion were microsurgicaly removed, GTR.

Post op brain CT confirmed GTR (fig 2).

Pathology NHS: presence of tumor lesions negative for CK AE1/3, SOC10, CD10, CAIX, AMACR, ERG, and CD34, consistent with multifocal hemangioblastomas (WHO Grade I). Prof. Latifaj recommended treatment with the reference (*CNS Oncol.* 2015;4(6):387–392. doi:10.2217/cns.15.33).

Prof. G. Kaloshi, Canada, suggested spinal MRI, for spinal seeding, craniospinal radiotherapy combined with Pazopanib was recommended.

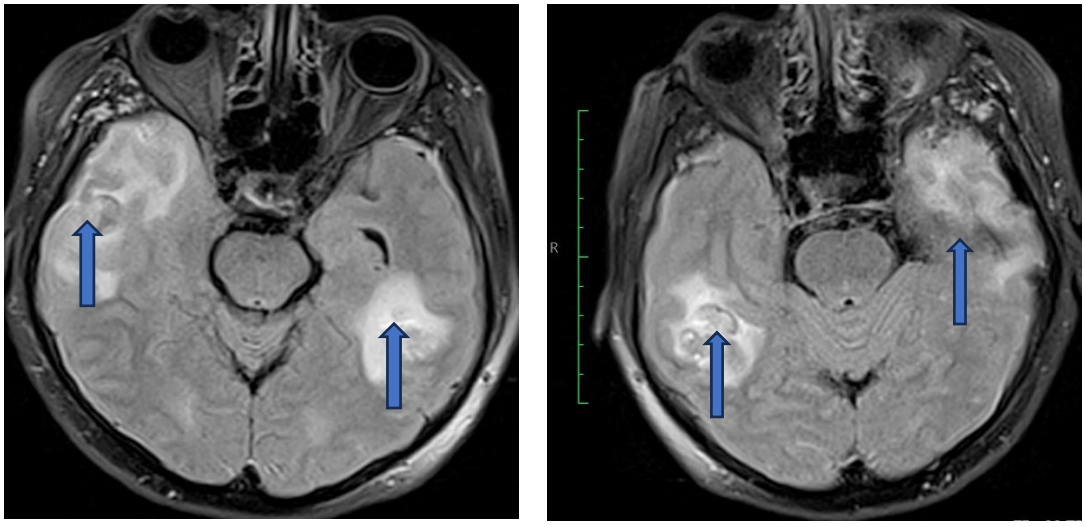

Fig 1 A: Flair T2 images: Iso- to hyperintense left and right temporal lesions (blue arrow)

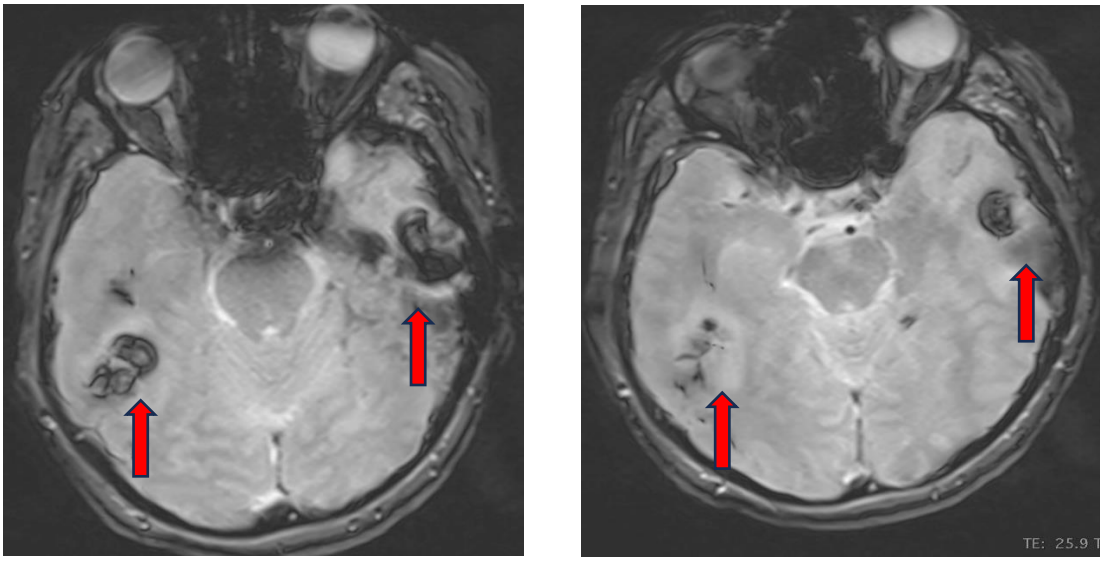

Fig 1 B: Hemo sensitive images: Presence of hemosiderin (red arrow)

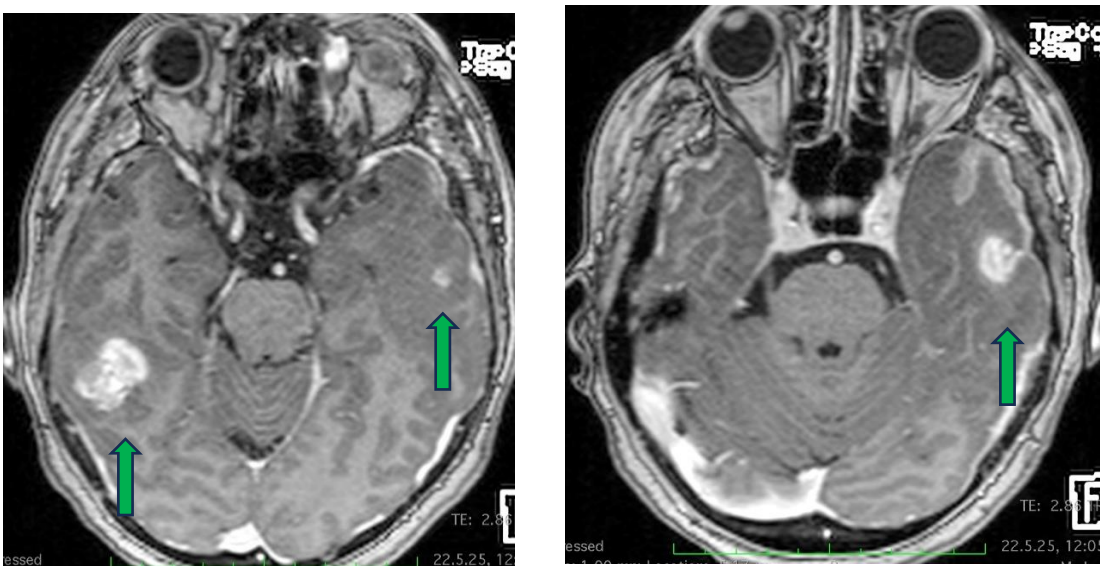

Fig 1 C With Contrast: Heterogeneous enhancement of two lesions (green arrow)

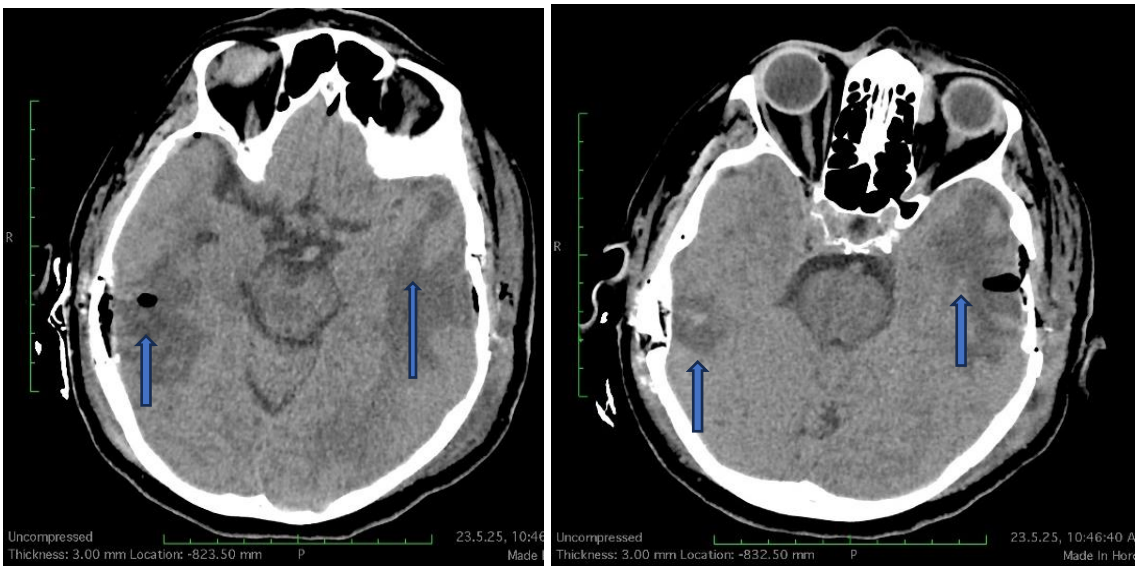

Fig 2 Brain Ct post op: GTR confirmation of both lesions (blue arrow)

Discussion

In VHL disease, both ccRCC and hemangioblastomas demonstrate HIF-dependent molecular profiles, with increased angiogenesis driven by VEGF and PDGF expression[1,3].

In our case, the initial renal tumor was treated over 25 years ago, at the relatively young age, which retrospectively appears to have been an early manifestation of VHL. The bifocal brain hemangioblastomas, confirmed histologically and occurring decades later, is a possible natural progression of VHL syndrome.

Cerebellar, spinal, and brainstem hemangioblastomas are common in VHL, supratentorial intracerebral hemangioblastomas, like in our patient, is extremely rare, some reports are on hypophyseal and optic localisation.[5] (fig 3).

VHL should be considered in very rare condition in endolymphatic sac tumor (ELSTs), as we reported in our case lessons series nr. 20 earlier.

Due to the high incidence of VHL with benign and malign tumor development, it is necessary to do genetic studies of patient and family member with yearly imagining of CNS and spine according to Surveillance and Consensus Statement 2022[5].

In VHL patients and ccRCC due to improved surveillance and targeted therapies, is not considered longer the leading cause of death. Agents such as Pazopanib and other VEGF inhibitors have shown promise in both ccRCC and VHL, CNS and spine HBs lesions, leading to disease stabilization[,3,5].

Early recognition of syndromic patterns of VHL diseases could improve long-term outcomes and enable proactive care in ccRCC, HB, Endolymphatic sac tumors, Pheochromocytomas, Pancreatic neuroendocrine tumors.[1,2,5].

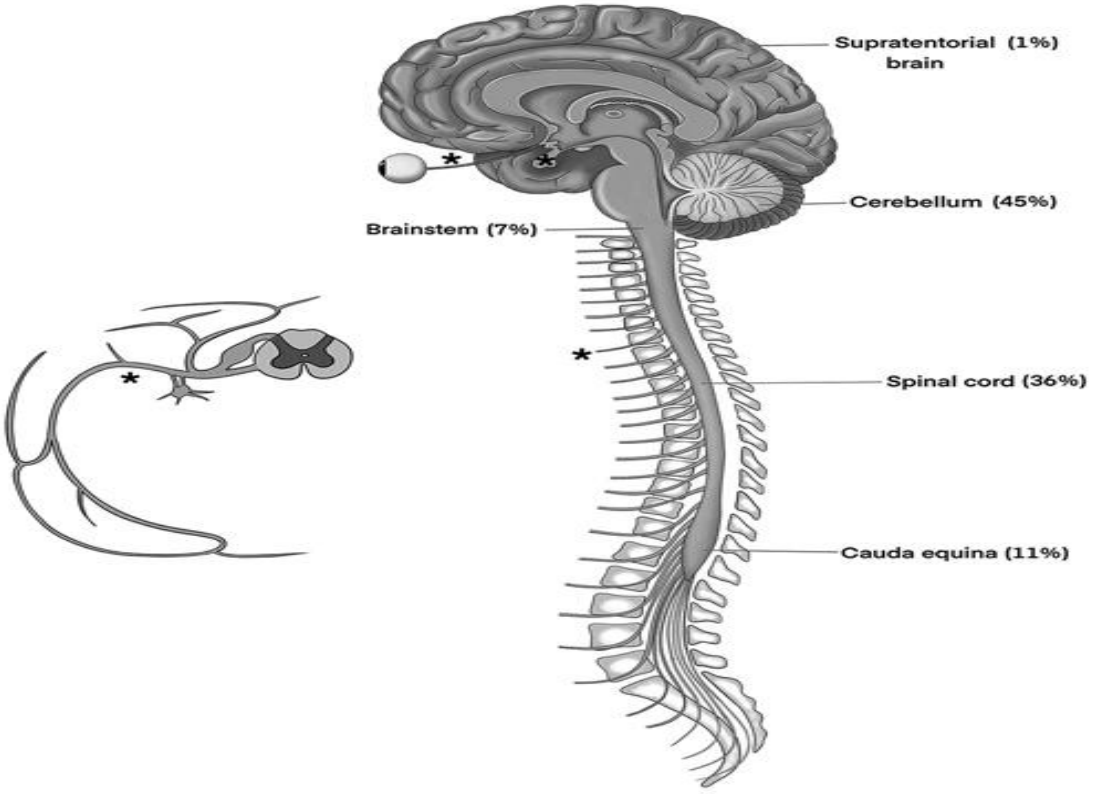

Fig 3 : Schematic of the sites and frequency of VHL-associated CNS hemangioblastomas. The image on the *left* is an axial view depicting peripheral nerve frequency. *Regions in which CNS hemangioblastomas account for < 1% of hemangioblastomas

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Conclusion

Von Hippel–Lindau disease should be considered in patients with a history of renal carcinoma when new-onset multifocal CNS and spine lesions are suspected. Genetic testing are strongly recommended for both the patient and at-risk relatives according to Surveillance and Consensus Statement 2022[5] in VHL disease in case of benign and malign tumors evidence.

Reference

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