

Case Report

# Supratentorial Collision Tumor of Hemangioblastoma and Metastatic Clear Cell Renal Cell Carcinoma in a Patient with von Hippel-Lindau Disease

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## Keywords

Collision tumor · von Hippel-Lindau disease · Hemangioblastoma · Clear cell renal cell carcinoma

## Abstract

Collision tumors are rarely reported in patients with von Hippel-Lindau (VHL) disease, even though VHL patients often present with multi-organ tumor syndromes, like hemangioblastoma and renal cell carcinoma (RCC). Hemangioblastoma is rarely located in a supratentorial location, and intracranial lateral ventricular is also not a common site of metastasis for RCC. It is extremely rare for the two tumors to collide in the supratentorial area. We report a 64-year-old man with a history of clear cell RCC who presented with a sudden headache. The brain magnetic resonance imaging revealed that there was a cystic-solid mass in the intracranial lateral ventricular trigone. Histopathologically, the tumor consisted of two distinct components, most of which showed the typical morphology of hemangioblastoma. However, there were a few acinar structures composed of clear cells scattered in hemangioblastoma, and these acinar structures were subsequently confirmed as clear cell RCC. The genetic testing confirmed that the patient had VHL disease with de novo somatic mutation. Based on our case report, we systematically reviewed the characteristics of collision tumor composed of hemangioblastoma and metastatic RCC in VHL patients. The special growth site of our case is the first report of this kind of collision tumor, and can also help enrich our understanding of VHL disease and collision tumor.

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## Introduction

Collision tumor refers two or more different types of tumor occurring in the same site or organ, which originated from different tissues. Tumors are intertwined rather than adjacent to each other. The most common type of collision tumor is tumor-to-tumor metastasis, which is the type discussed here. Collision tumors can happen in a variety of organs, such as the stomach, kidney, and pituitary [1–3]. In the central nervous system (CNS), meningioma tends to be one of the most common component of collision tumors (as recipient tumor), which also include pituitary adenoma and schwannoma [3, 4]. The other component is often malignant tumors, like glioblastoma, breast cancer, lung cancer, and so on.

von Hippel-Lindau (VHL) disease is an autosomal dominant genetic disease caused by a mutation in *VHL* tumor suppressor gene located on chromosome 3 (3p25-26), and it is one of the most common multisystem familial cancer syndrome with the incidence of 1 in every 36,000 live births [5]. The patients present with tumors and/or cysts of multiple system organs, like hemangioblastoma of the retinal and/or CNS, renal cell carcinoma (RCC), pheochromocytoma, pancreatic neuroendocrine tumors, pancreatic and renal cysts, epididymal and parametrial cysts, and tumors of the inner ear. Currently, tumors associated with VHL syndrome are mainly treated with surgical resection or ablation, which aims to reduce the risk of metastatic disease and decrease the lingering effects [6]. In 2021, belzutifan was approved by the US Food and Drug Administration (FDA) for the adult patients with VHL-associated RCC, CNS hemangioblastoma, or pancreatic neuroendocrine tumors without immediate surgery, thus providing a medical option [7, 8]. However, for patients with VHL syndrome who have developed metastatic tumors, the focus of therapy is mainly on the metastatic tumors. RCC is the most common VHL-associated metastasizing tumor and one of the leading causes of death in patients with VHL syndrome [9]. In recent years, the targeted therapy and immunotherapy have provided novel approaches for the treatment of advanced or metastatic RCC, in which immune checkpoint inhibitor in combination with tyrosine kinase inhibitor have become the first-line treatment [10–12]. Rizzo et al. [11] summarized 1,769 patients with advanced or metastatic RCC in three phase 3 randomized controlled trials and demonstrated that the immune checkpoint inhibitor-tyrosine kinase inhibitor combination treatment provided survival benefit for patients with metastatic RCC, independent of several clinicopathological features. Nevertheless, in the age of immuno-oncology, there is still an urgent need to explore prognostic and predictive biomarkers for immunotherapy in metastatic RCC, as well as to systematically evaluate the effect of therapy on the quality of patients' life [13–16].

Although tumors of multiple organs may happen in patients with VHL disease, the development of collision tumors is still rare, especially in the brain. Here, we report a supratentorial collision tumor composed of hemangioblastoma and metastatic clear cell RCC in a patient with VHL disease. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000531876>).

## Case Presentation

The patient was a 64-year-old man who presented with a sudden headache mainly on the left side for 2 days in December 2019. Previously, he had underwent left radical nephrectomy for clear cell RCC in 2016 without adjuvant therapy, and he had no other recurrence of clear cell RCC during regular follow-up within 3 years. The latest magnetic resonance imaging screening revealed that there was a cystic-solid mass in the intracranial lateral ventricular

trigone. On enhanced scan, most of the mass was enhanced distinctly, while there were multiple round non-enhanced areas of different sizes in the mass (Fig. 1a–c). The mass was completely removed by craniotomy without postoperative radiotherapy or chemotherapy. Intraoperatively, the mass was located in the white matter of the intracranial lateral ventricular trigone, and had unclear boundary with the surrounding brain tissue. Part of the mass grew along the choroid plexus to the lateral ventricle, and the mass was completely removed.

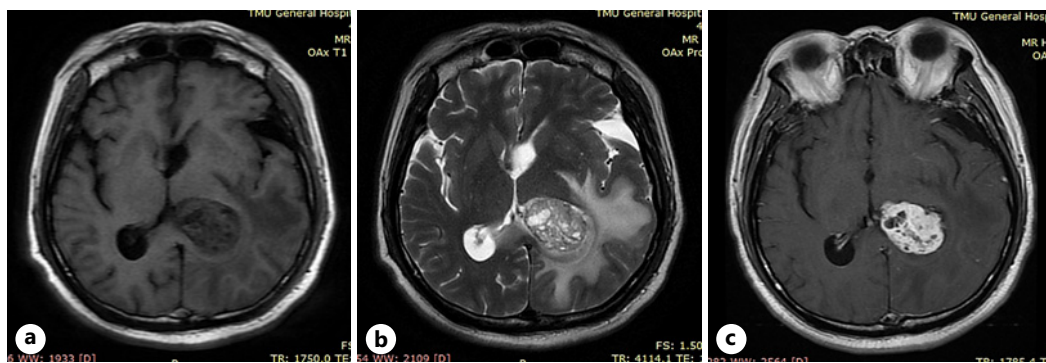
Pathological hematoxylin-eosin staining revealed that the tumor was mainly composed of abundant stromal cells and capillary networks. The cytoplasm of the stromal cells was rich, lightly stained, and in the form of vacuole or ground glass. The stromal cells were mild in appearance and surrounded by many proliferative small blood vessels. These small blood vessels had thin walls and were close together to form capillary networks, which were reactive vascular components. To sum up, the hematoxylin-eosin staining showed a typical hemangioblastoma (Fig. 2a). The immunohistochemical staining showed that the reactive vascular components were positive for CD34 and factor VIII-related antigen (F8) (Fig. 3a, b). The stromal cells had focal staining for NSE (Fig. 3c). Unfortunately, the inhibin A was negative with nonspecific staining of only a few cells (Fig. 3d). There were a few acinar structures composed of clear cells scattered in the hemangioblastoma, without mitotic and necrosis activity (Fig. 2b–d). Given the patient's medical history, the acinar structures were confirmed to be clear cell RCC by immunohistochemistry which showed positive staining for keratin, EMA, CD10, CAIX, and PAX8 (Fig. 3e, f, h–j) but showed negative staining for CD34, F8 (Fig. 3a, b), and vimentin (Fig. 3g). Combined with the histological morphology and immunohistochemical staining, the case report was diagnosed as a collision tumor of hemangioblastoma and metastatic clear cell RCC.

Although the patient did not have a family history of VHL syndrome, he had been diagnosed with clear cell RCC and intracranial collision tumor of hemangioblastoma and metastatic clear cell RCC. It was consistent with the clinical manifestations of VHL syndrome; therefore, it was necessary for the patient to carry on gene testing. The next-generation sequencing was performed on the patient's tumor tissue and peripheral venous blood. A deletion mutation of c.362\_364delATG (p.D121del) in *VHL* tumor suppressor gene was been found in the tumor tissue, which resulted in the deletion of aspartic acid at the 121st amino acid, with a mutation frequency of 9.5%. However, there was no *VHL* tumor suppressor gene mutation in peripheral venous blood. Combined with morphology, immunohistochemical staining, and genetic testing, this was a supratentorial collision tumor composed of hemangioblastoma and metastatic clear cell RCC, and the patient had the VHL syndrome with a de novo somatic mutation.

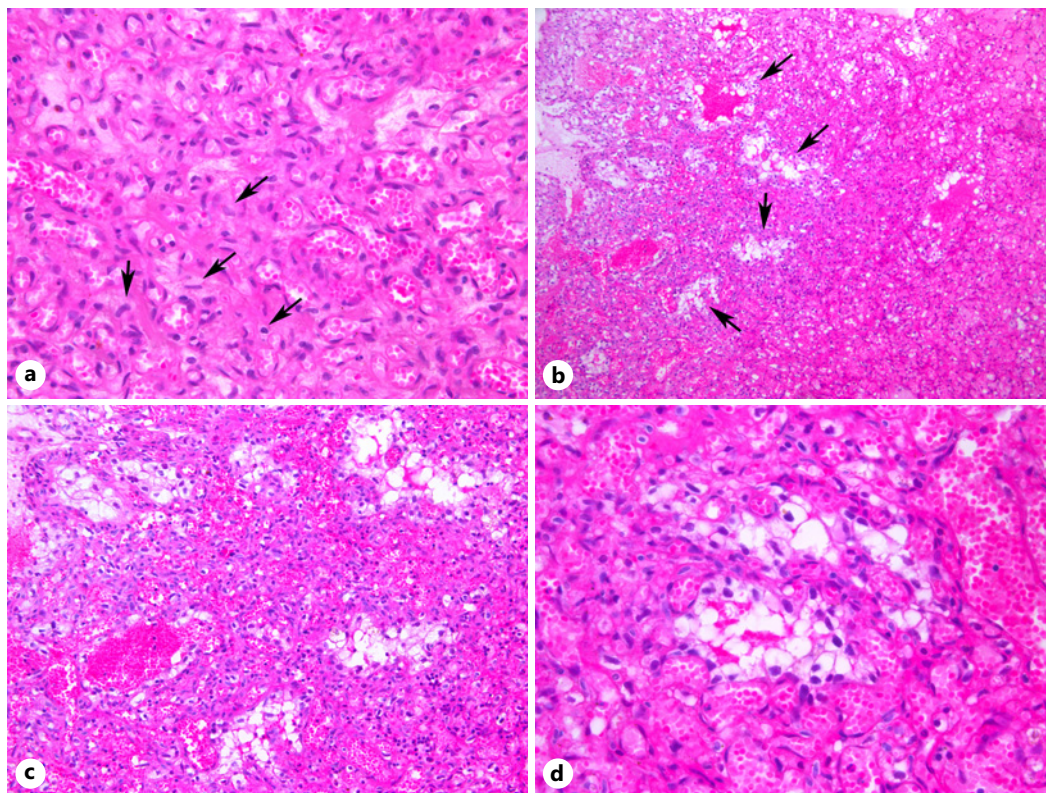
The patient did not receive any adjuvant therapy after surgery, and he was stable during the 40-month follow-up period. In April 2023, he was admitted to our hospital due to hyperosmolar nonketotic coma, and eventually died despite emergency rescue efforts.

## Discussion

An intracranial collision tumor is rare, and a collision tumor of hemangioblastoma and metastatic clear cell RCC is even rarer. Although patients with VHL syndrome often present with multi-organ tumor syndromes, collision tumors are rarely reported in patients with VHL disease, especially in the brain. A total of 23 patients (14 female and 9 male) with collision tumors composed of hemangioblastoma and metastatic clear cell RCC have been reported, including our patient (Table 1) [17–31]. The mean age at diagnosis of collision tumor is 47.09 years old (28–73 years), and the median age is 46 years old. A total of 22 collision tumors are located in the CNS (22/23, 96%), and only 1 is located in the eye. The spinal cord is

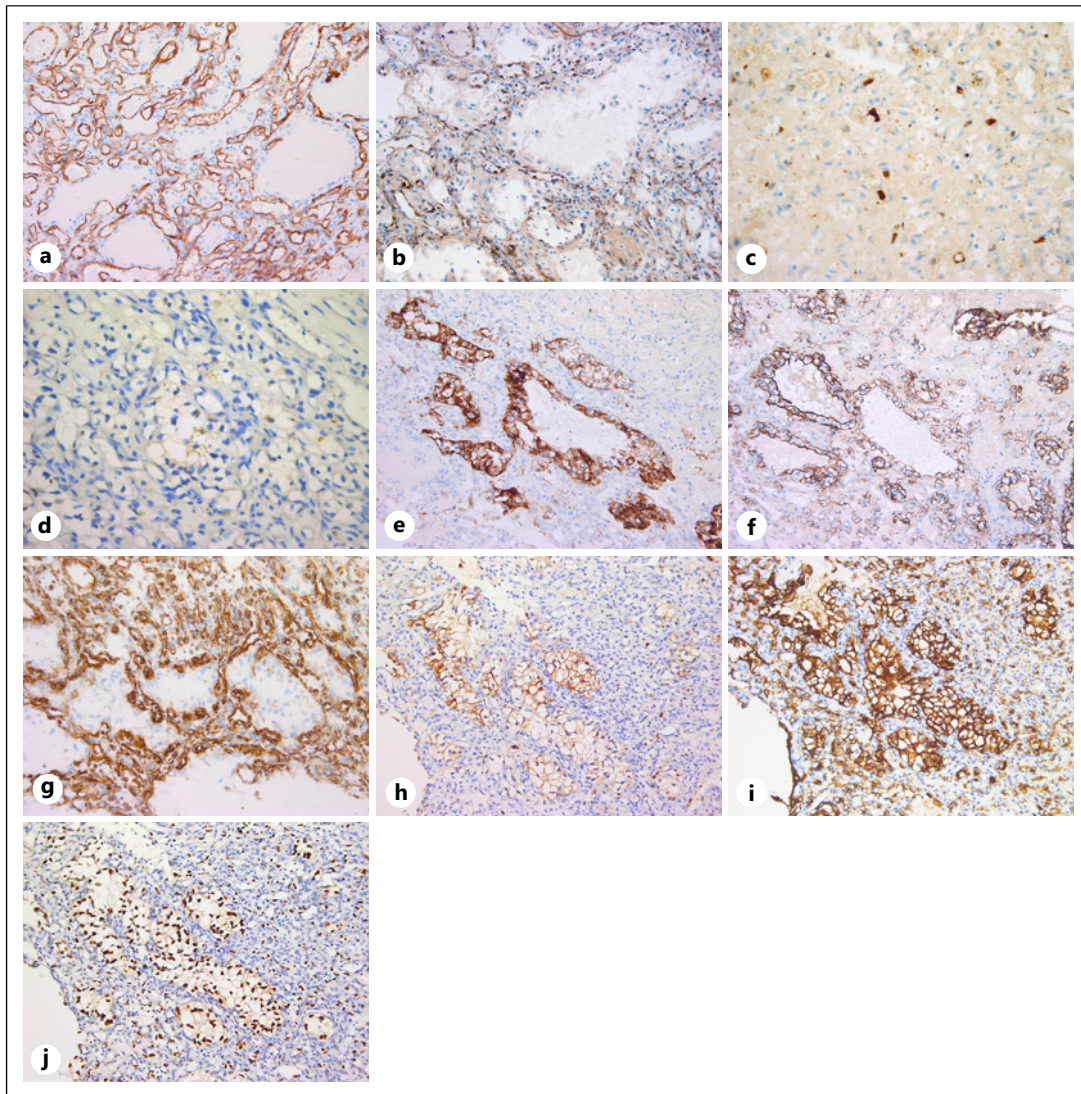


**Fig. 1.** Magnetic resonance imaging (MRI) on admission. Representative axial T1-weighted images (a), T2-weighted images (b), and contrast-enhanced images (c) showed a mass in the intracranial lateral ventricular trigone. The mass was cystic-solid, and most of the mass was enhanced distinctly with multiple round non-enhanced areas inside.



**Fig. 2.** Representative images of hematoxylin-eosin (HE) staining: clear cell RCC metastasis to hemangioblastoma. **a** The hemangioblastoma region consisting of capillary network and stromal cells with foamy cytoplasm indicated by the arrows (original magnification  $\times 400$ ). **b** Acinar structures composed of clear cells in the hemangioblastoma indicated by the arrows (original magnification  $\times 100$ ). **c** Magnification of the bright cytoplasmic region in **b** (original magnification  $\times 200$ ). **d** Acinar-like structure of clear cells in the area of metastatic clear cell RCC (original magnification  $\times 400$ ).





**Fig. 3.** Representative images of immunohistochemical (IHC) staining: clear cell RCC metastasis to hemangioblastoma. **a, b** The reactive capillary networks of hemangioblastoma, which was cell membrane-positive for CD34 (**a**) and cytoplasmic-positive for F8 (**b**). **c** The stromal cells of hemangioblastoma were nuclear-positive for NSE focally. **d** The nonspecific staining of inhibin A in stromal cells of hemangioblastoma. **e, f** Keratin and EMA, diffuse cell membrane-positive in the epithelial component. **g** Vimentin showed the negative clear cell RCC component surrounded by diffuse strongly cytoplasmic-positive capillary networks. **h–j** The clear cell RCC component, which was cell membrane-positive for CD10 (**h**) and CAIX (**i**) and nuclear-positive for PAX8 (**j**). The original magnification of the images was  $\times 200$ , except for **c** and **d** where it was  $\times 400$ .

the most common site of this collision tumor (12/23, 52%, 5 cervical, 5 thoracic, 1 lumbar, and 1 sacral), followed by the cerebellum (8/23, 35%), medulla oblongata (1/23), and intracranial lateral ventricular trigone (1/23). Intracranially, the collision tumor of hemangioblastoma and metastatic clear cell RCC frequently develops in the cerebellum (8/10, 80%), however, the collision tumor we reported is located in the supratentorial lateral ventricular trigone, which is extremely rare. Hemangioblastoma of the CNS is mostly located in the cerebellar hemisphere, and can also be found in midline locations such as the brain stem, spinal cord, and cerebellar vermis. Supratentorial intraventricular hemangioblastoma is extremely rare, and

**Table 1.** Collision tumor composed of hemangioblastoma and metastatic RCC

Case report: author, year	Gender	Age, years	Location of collision tumor	Other sites of metastatic RCC	Other tumors	Treatment	Time to death after diagnosis, months
1 Holanda et al. [17], 2022	Female	59	Cervical	Lung	None	Surgery	>2
2 Wakita et al. [18], 2021	Male	40	Thoracic	None	Cerebellum hemangioblastoma	Surgery, radiotherapy, chemotherapy	>12
3 Dessauvagie et al. [19], 2015	Female	54	Cervical	Bone, lung	None	Surgery	24
4 Dessauvagie et al. [19], 2015	Male	28	Cerebellum	None	None	Surgery	>12
5 Rai et al. [20], 2015	Female	73	Eye	Sacrum	Cerebellum hemangioblastoma	Surgery	>5
6 Xiong et al. [21], 2010	Male	38	Medulla oblongata	None	Cerebellum and thoracic spine hemangioblastoma	Surgery	Not described
7 Martin et al. [22], 2009	Female	41	Cerebellum	None	Cerebellum hemangioblastoma	Surgery	Not described
8 Polydorides et al. [23], 2007	Female	52	Cervical	None	None	Surgery	Not described
9 Jarrell et al. [24], 2006	Female	36	Sacral	None	None	Surgery	>40
10 Jarrell et al. [24], 2006	Female	60	Cerebellum	None	Pheochromocytoma	Surgery	>20
11 Jarrell et al. [24], 2006	Female	46	Cerebellum	None	Retinal hemangioblastoma	Surgery	>12
12 Jarrell et al. [24], 2006	Female	44	Thoracic	None	Retinal hemangioblastoma	Surgery	>12

**Table 1** (continued)

Case report: author, year	Gender	Age, years	Location of collision tumor	Other sites of metastatic RCC	Other tumors	Treatment	Time to death after diagnosis, months
13 Jarrell et al. [24], 2006	Male	41	Thoracic	None	None	Surgery	4
14 Jarrell et al. [24], 2006	Female	50	Lumbar	None	Pheochromocytoma, pancreatic neuroendocrine tumor	Surgery	Not described
15 Altinoz et al. [25], 2005	Male	43	Thoracic	Adrenal gland, lung, cerebrum	None	Surgery, chemotherapy, radiotherapy	>96
16 About-Hamden et al. [26], 2003	Male	39	Cervical	None	Cerebellum hemangioblastoma (presumed)	Surgery	>4
17 Hamazaki et al. [27], 2001	Female	46	Cerebellum	None	Spinal cord hemangioblastoma	Surgery	12
18 Hamazaki et al. [27], 2001	Female	47	Thoracic	None	Cerebellar hemangioblastoma, retinal angioma	Surgery	>24
19 Mottolese et al. [28], 2001	Male	46	Cerebellum	None	Retinal angioma	Surgery	Not described
20 Fakih et al. [29], 2001	Female	37	Cervical	Lung	None	Surgery, chemotherapy, radiotherapy	23
21 Bret et al. [30], 1999	Male	50	Cerebellum	None	Retinal and conus medullaris hemangioblastoma	Surgery	Not described
22 Jamjoom et al. [31], 1992	Female	49	Cerebellum	None	None	Surgery	3
23 Author's report, 2023	Male	64	Left ventricular triangle	None	None	Surgery	40

only 8 patients of lateral ventricle hemangioblastoma have been reported in English literature, and 7 patients are confirmed to be associated with VHL syndrome [32, 33]. On the other hand, more than 80% of intracranial metastases occur in the junction of the cerebral cortex and white matter, occasionally seed along ventricular walls. In our case report, the next-generation sequencing reveals the *VHL* tumor suppressor gene mutation in patient's tumor tissue but not in peripheral blood. These results indicated that this is a de novo somatic mutation of VHL syndrome. In addition, the location of this collision tumor is very special, which is helpful to enrich our understanding of VHL syndrome and collision tumor.

Collision tumor is mostly the fusion growth of a benign tumor and a malignant tumor, and the most common type is tumor-to-tumor metastasis. As a recipient, the benign tumor is often characterized by slow growth and rich blood vessels, thus becomes a potential metastatic site over a long time. In the collision tumors of CNS, the most common recipient tumor is meningioma, while schwannoma, pituitary adenoma also have been reported. Ashizawa et al. [34] summarized 131 patients with intracranial collision tumors from 1976, including collision with metastatic carcinoma, among whom meningioma were more common in primary intracranial collision tumors (39/57; 66.6%), and most of them were recipient tumor. In patients with VHL syndrome, the most common benign tumor was hemangioblastoma. About 60–80% of patients with VHL syndrome develops hemangioblastoma in the CNS, which is most commonly diagnosed during the third decade of life [35]. VHL patients may develop hemangioblastoma repeatedly or at multiple sites. Hemangioblastoma grows slowly and has a high incidence and recurrence rate in patients with VHL syndrome. These characteristics provide favorable conditions for becoming a recipient tumor in collision tumors. Therefore, we speculate that hemangioblastoma is most likely the best recipient tumor for collision tumors in patients with VHL syndrome.

RCC is an important clinical manifestation and one of the main causes of death in patients with VHL syndrome. Due to genetic defects, in addition to hemangioblastoma, patients with VHL syndrome are likely to develop clear cell RCC, accounting for about 25–45% of cases, with the frequency increasing with age [36]. 40% of RCC in VHL patients develop metastases and about one-third of metastatic RCC is fatal [31]. It had been reported that the pathological type of RCC in VHL syndrome was almost all clear cell RCC, although a few tumors contained scattered granular cells [37]. Metastatic RCC of the CNS is relatively rare, accounting for 4.3% (72/1,689), and the average age at diagnosis of metastatic RCC is 56 years old [38]. Tumor cells of RCC often metastasize to the CNS through a vascular route (arterial or venous). We speculate that in such collision tumor, the abundant blood supply of hemangioblastoma is extremely favorable for tumor cell retention and aggregation, thereby fusing with the host tumor to form an entity.

It has been found that in VHL syndrome, the *VHL* gene product is involved in the degradation of HIF-1 $\alpha$  which promotes the transcriptional activation of pro-angiogenic genes, such as VEGF, PDGF, EPO, and TGF. VHL-HIF-VEGF angiogenesis signaling pathway is important for the progression of hemangioblastoma and RCC [39, 40]. Among the 23 patients we summarized, 18 patients (78.26%) have no other metastases, except RCC metastasis to hemangioblastoma. In two autopsy patients reported by Jarrel et al. [24], 1 patient developed five CNS hemangioblastomas, two of which were collision tumors of spinal hemangioblastoma and metastatic RCC. Subsequently, he was diagnosed with recurrent RCC and metastatic RCC of the lung 1 week before his death. The other patient also developed five CNS hemangioblastomas, one of which was diagnosed as collision tumors of spinal hemangioblastoma and metastatic RCC, while he had no other metastatic tumors. In the report of Dessauvage et al. [19], 1 patient with collision tumor developed multiple RCC metastases of bony and pulmonary during follow-up. Although the number of this kind of collision tumor is limited, the metastatic RCC appears to choose preexisting hemangioblastoma as host to form a collision



tumor. Whether the same genetic defects of recipient tumor and metastasis increase the risk of collision tumor formation requires further study, and the mechanism of collision tumor formation in VHL syndrome also needs to be further explored.

Hemangioblastoma is rich in vacuolated stromal cells, which have a similar appearance to the lipid-containing cells of clear cell RCC. The two kinds of tumor cells have some confusion in histological morphology. Especially when the initial metastatic clear cell RCC is small in the collision tumor, it is easy to be ignored. Immunohistochemical staining indexes such as keratin, EMA, CD10, CAIX, and PAX8 can effectively identify the hidden lesions. For patients at high risk of VHL disease, comprehensive and systematic examination can effectively detect early lesions and provide intervention, reduce RCC metastasis, hemangioblastoma bleeding, and other fatal risks, and effectively prolong the survival of patients.

### Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. This case report did not require ethical approval in accordance with local/national guidelines.

### Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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### Author Contributions

Wenjun Luo: designed the case report and wrote the manuscript; Cuiyun Sun: provided and interpreted the histology analysis; Shizhu Yu: reviewed the histology analysis and MRI scans; and all authors revised and approved the final manuscript and agreed to be accountable for all aspects of the work.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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