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Metastasis of Renal Cell Carcinoma to Spinal Hemangioblastoma in a Patient with von Hippel–Lindau Disease: A Case Report

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Abstract

von Hippel–Lindau (VHL) disease is characterized by neoplastic and cystic lesions, such as central nervous system (CNS) hemangioblastoma and clear cell renal cell carcinoma (RCC), arising in multiple organs. Here, we report a case of an RCC that metastasized to a spinal hemangioblastoma in a patient diagnosed with VHL disease. This is a unique case study because visceral neoplasms rarely metastasize to the CNS. The patient had undergone posterior fossa surgery for the removal of hemangioblastomas in the right cerebellar hemisphere as a child. He was diagnosed with RCC at the age of 20 years, and he underwent partial nephrectomy at the age of 35 years. The patient underwent surgical removal of a spinal tumor from Th8, which was also diagnosed as a hemangioblastoma at the age of 40. However, the residual spinal tumor rapidly regrew within 1.5 years. A second surgery was performed due to progressive leg motor weakness. The resected tumor from the second surgery had two distinct components between the tumor center and the margin. Immunohistochemistry of CD10, PAX 8, and inhibin A demonstrated the predominant region of the tumor was RCC. Pathological findings confirmed tumor-to-tumor metastasis of the RCC migrating into residual spinal hemangioblastoma. It can be challenging to distinguish hemangioblastoma from RCC in neuroimaging. We suggest that tumor-to-tumor metastasis should be considered as a differential diagnosis if benign tumors grow rapidly, even if the pathological diagnosis does not initially confirm malignancy. The biological mechanisms of RCC migrating into residual hemangioblastoma are discussed.

Keywords von-Hippel–Lindau disease, hemangioblastoma, renal cell carcinoma, tumor-to-tumor metastasis

Introduction

von Hippel–Lindau (VHL) disease is an autosomal-dominant neoplasia syndrome. A germline mutation of the VHL tumor suppressor gene causes visceral and central nervous system (CNS) neoplasms.[1–6] VHL disease is characterized by neoplastic and cystic lesions arising in multiple organs, such as CNS hemangioblastoma, clear-cell renal cell carcinoma (RCC), renal cysts, pheochromocytomas, pancreatic cysts, islet cell tumors, retinal angioma, and epididymal cystadenomas.[1–6] Visceral neoplasms rarely metastasize into the CNS. Here, we report a case of an RCC that metastasized into a spinal hemangioblastoma in a patient with VHL disease.

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Case Report

This case involves a 40-year-old male who was diagnosed with VHL disease 30 years ago. At the age of 10 years, the patient underwent posterior fossa surgery to remove hemangioblastomas in the right cerebellar hemisphere as well as radiation therapy (47.5 Gy/25 fractions) for a surgically inaccessible medullary hemangioblastoma. At the age of 20 years, two newly appeared cerebellar hemangioblastomas were surgically removed, and he was further diagnosed with RCC during the tumor screening process. At the age of 35 years, the patient underwent a tumor removal procedure for a newly appeared cerebellar hemangioblastoma. The tumor located close to the medulla oblongata was treated with stereotactic radiosurgery. He underwent partial nephrectomy, and radiofrequency ablation was performed. Pathological assessment of the renal mass confirmed RCC. Magnetic resonance imaging (MRI) screening of any spinal lesions revealed spinal cord tumors at C7 and Th8, with syrinx (C4-Th8). However, the patient was asymptomatic. At the age of 40 years, he presented with weakness and spasticity in the right leg, which had rapidly progressed. MRI revealed that the spinal cord tumor at Th8 had grown (Figs. 1A–1C). Furthermore, the MRI indicated several cerebellar hemangioblastomas, which were asymptomatic (Figs. 1E–1F). He underwent surgery to remove the spinal cord tumor. Surgical studies displayed abundant vascularization in the tumor. The tumor was removed sub-totally because of the decreased amplitude of the transcranial motor evoked potential during surgery (Fig. 2A). Pathological findings confirmed hemangioblastoma. The postoperative course was uneventful, and his symptoms improved. One and a half years after the surgery, he complained of a rapid increase in pain in the left leg, numbness, and spasticity. MRI demonstrated a regrowth of the residual spinal tumor (Figs. 2B and 2C).

The patient was admitted for another surgery. His symptoms worsened for 2 weeks after admission. He presented with leg pain, numbness, and motor weakness. Following this, his consciousness deteriorated. MRI showed two new lesions: one on the right cerebellar hemisphere and one on the dorsal side of the left pons. Additionally, the lateral ventricles were enlarged (Figs. 2D–2F). No tumor cells were detected in the cerebrospinal fluid. A ventriculoperitoneal shunt was placed, and the spinal cord tumor was removed. The tumor was reddish, hypervascularized, and well-circumscribed as in the first surgery. The tumor was sub-totally removed. Postoperative MRI demonstrated a small residual tumor at the Th8 (Figs. 3A and 3B).

Pathological examination revealed a compound tumor with hemangioblastoma at the periphery and a predominant region consisting of cells with a clear cytoplasm. This was different from the resected tumor in the first surgery. The resected tumor from the second surgery consisted of stromal cells with an oval nucleus and a foamy cytoplasm and had two distinct regions between the tumor center and the margin (Figs. 4A and 4B).

Immunohistochemistry revealed that the predominant tumor cells were positive for CD10 (Figs. 4C and 5A), PAX8 (Fig. 5B), vimentin, and AMACR in the inner tumor, which findings were compatible with RCC. The Ki-67 index was 20% in the tumor. However, the tumor cells were negative for CD31, CD34 (Fig. 5C), CK7 (Fig. 5D), and inhibin A (Figs. 4D and 5E), which findings indicated that the inner tumor was not hemangioblastoma. The outer tumor cells were partially positive for inhibin A (Fig. 4D); however, negative for CD10 (Fig. 4C). Pathological findings confirmed that the RCC had metastasized into a residual spinal hemangioblastoma. The patient's consciousness improved after ventriculoperitoneal shunt implantation. His pain, numbness, spasticity, and weakness of the lower extremities also improved, and he was able to walk with spinal orthosis and assistance. In addition, we clinically diagnosed rapidly growing cerebellar tumors, which could have metastasized from RCC. Stereotactic radiosurgery was performed for cerebellar metastases. He developed multiple peritoneal dissemination from RCC. We administered ipilimumab and nivolumab for systemic control of metastases from RCC. The patient was stable during the 1-year follow-up period.

Discussion

The following criteria for diagnosing tumor-to-tumor metastasis were developed by Pamphlett in 1984: (1) the metastatic nidus must be at least partially enclosed by a rim of histologically distinct primary tumor tissue; (2) the existence of primary carcinoma must be proven; and (3) the metastatic tumor must be demonstrated as compatible with the primary carcinoma through morphological or immunohistochemical methods.[1)] All the criteria for tumor-to-tumor metastasis were met in this case. There have been 18 reported cases of RCC metastasizing into hemangioblastoma in patients with VHL disease.[1–9)] The patients were aged between 28 and 60 years. Ten patients had spinal hemangioblastoma. The cervical and thoracic spinal cord regions were the most commonly affected sites in the spinal cord. Most previous reports demonstrated the coexistence of two distinct tumors in one lesion. As yet, cancer

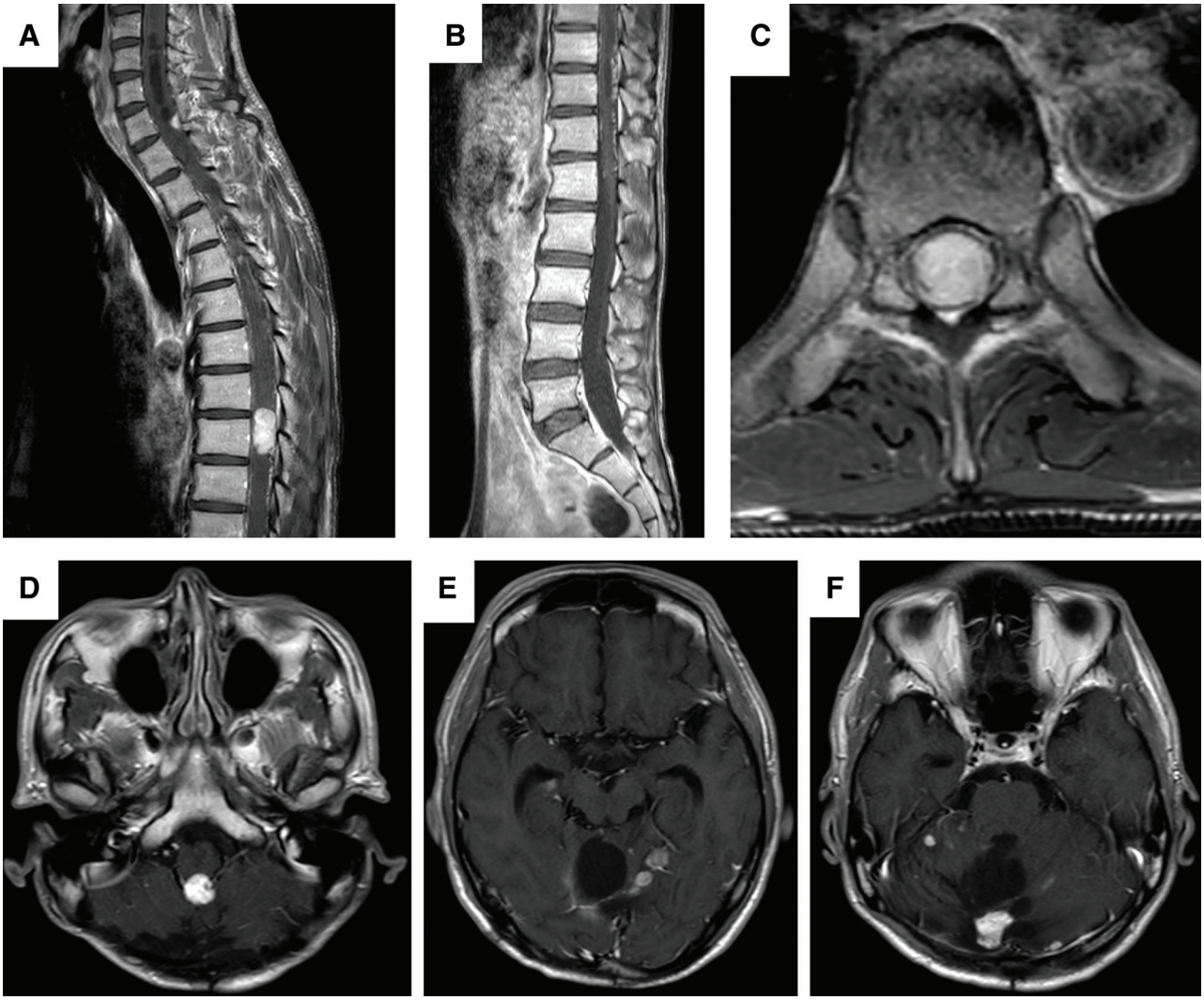

Fig. 1 Preoperative MRI scan. Gd-enhanced spinal MRI revealing that tumors with syrinx are located at the C7 and Th8. Sagittal image of the (A) cervicothoracic and (B) lumbar region. (C) An axial image of Th8. (D–F) Gd-enhanced brain MRI demonstrating tumors in the cerebellar hemisphere and close to the medulla oblongata. Gd: gadolinium, MRI: magnetic resonance imaging.

migration into the tumor bed of the residual tumor has not been reported. To our knowledge, this is the first case in which metastasis was discovered during the second surgery.

Metastases from visceral neoplasms into primary intracranial tumors are extremely rare. However, this rare phenomenon has been increasingly recognized. In the CNS, meningiomas are the most common intracranial benign tumors to host metastatic cancer.[2,10,11] The majority of metastases arise from lung or breast carcinomas.[10,12,13] Other types of benign intracranial tumors, such as schwannoma and pituitary adenoma, have rarely been reported.[12] Contrastingly, RCC-to-hemangioblastoma is the most common donor–recipient tumor association among tumor-to-tumor metastasis cases.[5] The biological mechanisms of tumor-to-tumor metastasis remain unclear. However, several factors affecting metastasis have been previously reported. Metabolic characteristics, such as high collagen and lipid content, can influence metastasis because of the abundant vascularization required by the recipient tumors.[4,5] Focal disruption of the blood–brain barrier by the recipient tumor or immunocompromised patients with systemic diffusion of neoplasia might also favor the spread of cancer cells.[11] In the hemangioblastomas as a recipient tumor, the high vascularization, slow growth, and high glycogen content might be related to the metastasis of RCC.[4] Hemangioblastomas highly express vascular endothelial growth factor (VEGF).[14] Anti-VEGF agents, such as bevacizumab[15,16] and pazopanib,[17,18] have the potential to inhibit tumor growth of unresectable

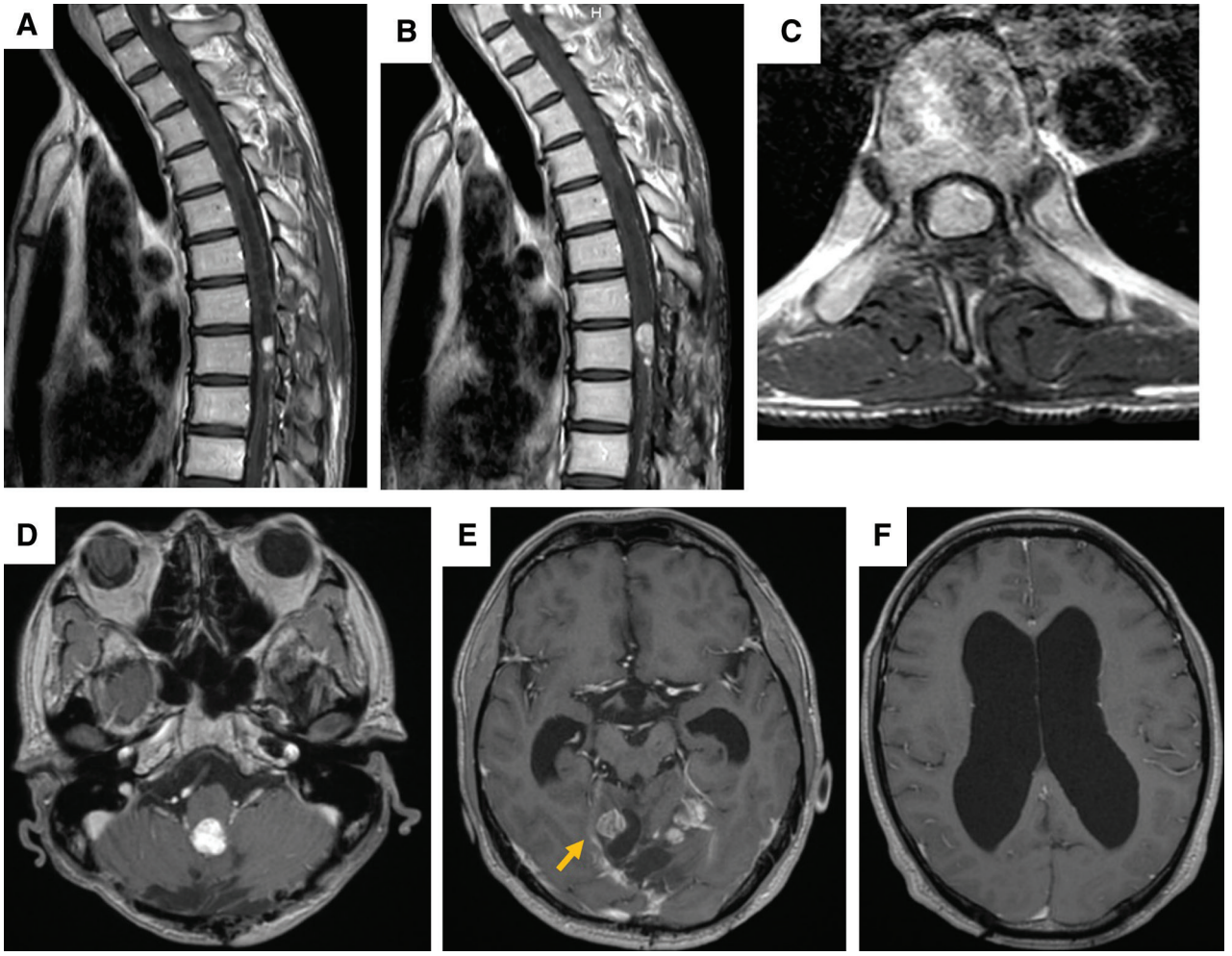

Fig. 2 (A) Postoperative Gd-enhanced MRI of the spinal cord showing a small residual tumor in the Th8 region. (B) A sagittal and (C) an axial image confirming the presence of the residual tumor 18 months post-surgery. (D–E) Gd-enhanced brain MRI showing a newly appeared tumor in the cerebellar hemisphere (indicated by an arrow) and its ventricular enlargement (F). Gd: gadolinium, MRI: magnetic resonance imaging.

hemangioblastoma in some cases. The inactivation of the VHL tumor-suppressor gene is a specific genetic change in clear-cell RCC. This may occur at an early step or the first step in the clear-cell tumorigenic pathway rather than as a late event.[19] VEGF plays a role in the activation of mitogen-activated protein (MAP) kinase signal pathways via VEGF receptors, angiogenesis, and tumor proliferation.[20] An overlap in the mechanism of tumorigenesis might contribute to a preferentially hospitable environment for RCC metastasis. In the present case, the remnant tumor became a recipient for tumor-to-tumor metastasis. Postsurgical effects, such as wound healing and revascularization, might promote the establishment of metastasis in remnant spinal hemangioblastoma because the spinal cord is capable of expressing VEGF and VEGF receptors in response to mechanical injury.[21]

The prognosis of VHL disease is strongly related to RCC. Metastatic RCC develops in 40% of patients with VHL disease.[15] Early detection of distant metastases is crucial for their survival. In tumor-to-tumor metastasis, the progress of metastasis from the primary site of cancer often remains unnoticed for a long period of time as most metastatic tumors are slow-growing.[2–5,9] It can be challenging to distinguish hemangioblastoma from RCC as they share similar characteristics under MRI. Diffusion-weighted imaging and dynamic susceptibility contrast-enhanced perfusion-weighted MRI have been demonstrated as being able to differentiate hemangioblastomas from metastases in brain lesions.[22] However, there is still a technical limitation for applying these techniques in spinal lesions. A definitive diagnosis would be required to go ahead with surgery. Immunohistochemistry is essential in discriminating between hemangioblastoma

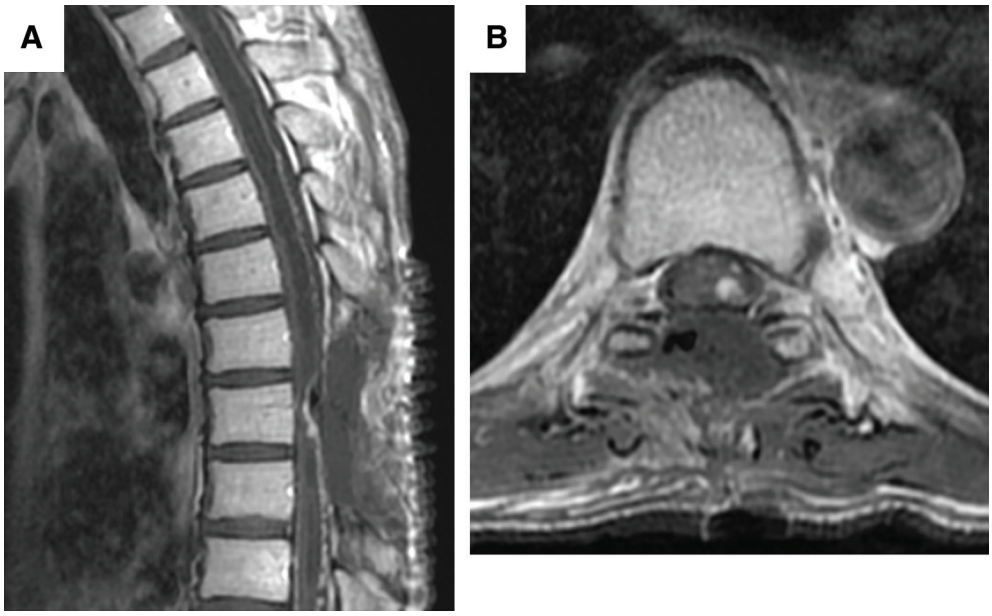

Fig. 3 Gd-enhanced MRI of the spinal cord demonstrating a small residual tumor in the Th8 region. (A) A sagittal and (B) an axial image.

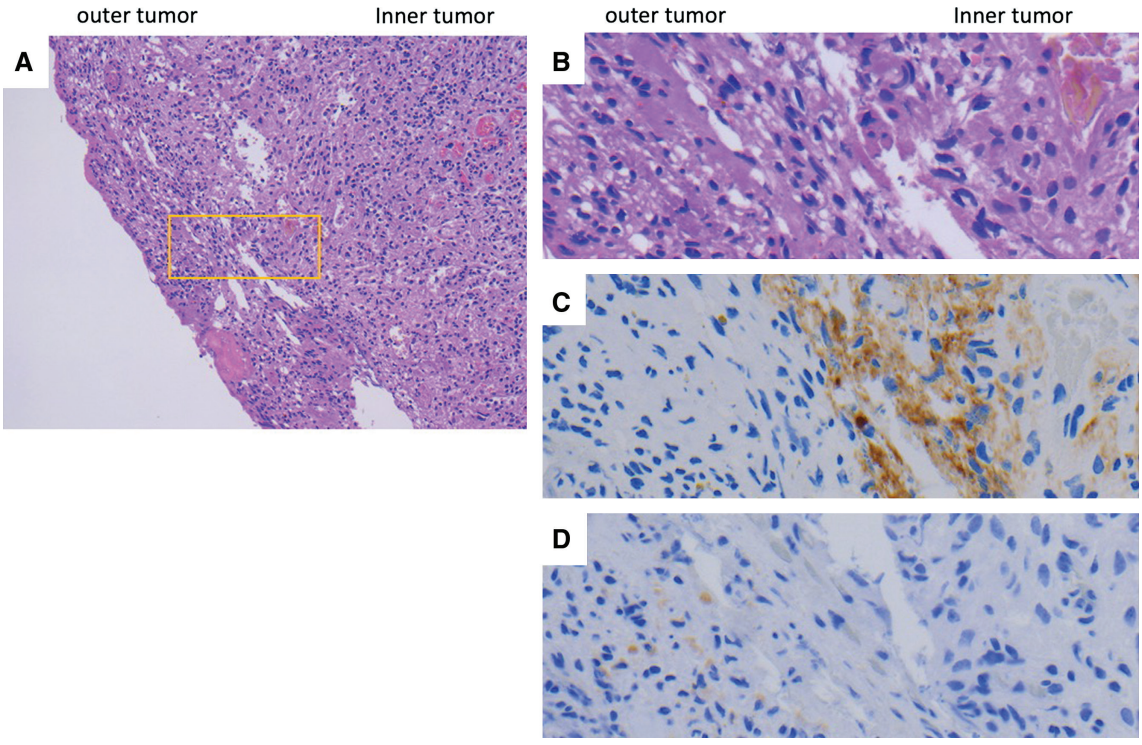

Fig. 4 Pathological studies. (A) Hematoxylin–eosin stained tumor from the second surgery, demonstrating the margin between the inner and outer tumor (×100). (B) The magnified photo in the yellow rectangle in A, ×200). (C) Immunohistochemical studies demonstrated that staining for CD10 (C) and inhibin A (D). The inner portion of tumor was positive for CD10 and negative for inhibin A. The outer portion demonstrated opposite immunoprofile (CD10 negative and inhibin A positive).

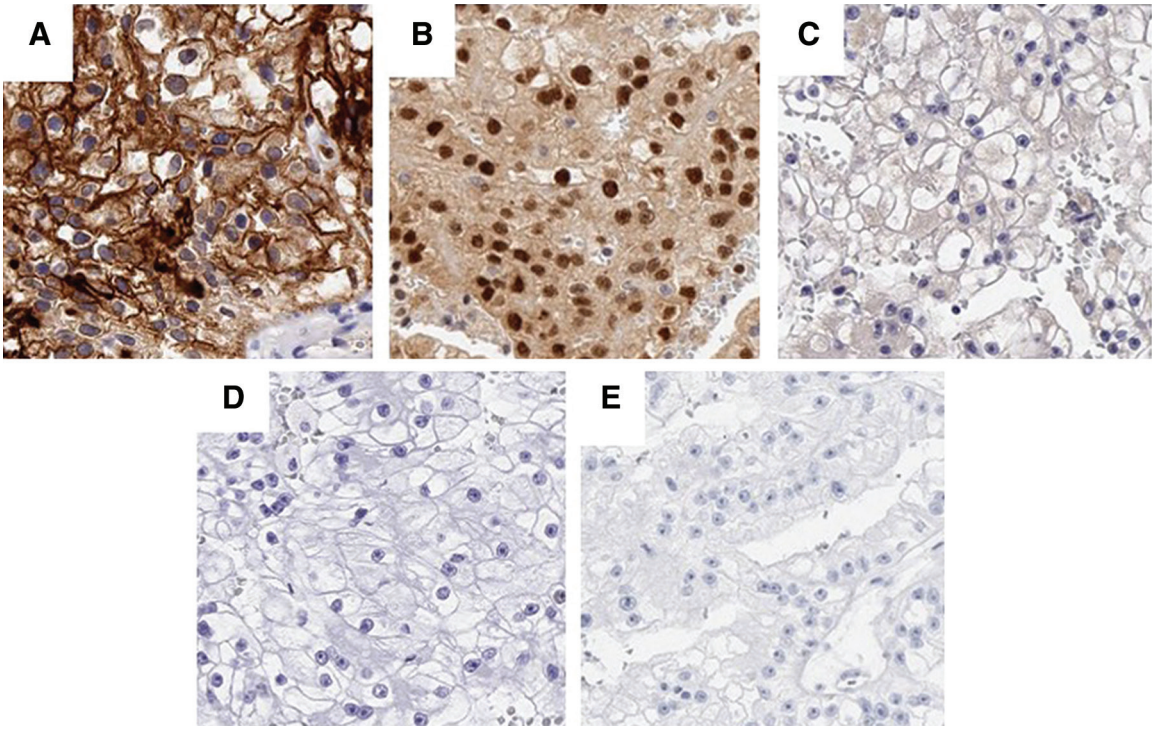

Fig. 5 Pathological studies. The inner portion indicating RCC. Immunohistochemical studies demonstrated that staining for CD10 (A) and PAX8 (B) were positive and CD34 (C), CK7 (D), and inhibin (E) negative in the inner tumor (×400). RCC: renal cell carcinoma.

and RCC due to overlapping histological characteristics.[9,23] Careful histological studies and immunohistochemical evaluation should be applied for cases of hemangioblastomas in patients with VHL disease. We suggest that when hemangioblastoma is rapidly growing, tumor-to-tumor metastasis should be considered as a differential diagnosis, even if hemangioblastoma alone was pathologically diagnosed previously.

Conclusions

We have presented a case of an RCC metastasizing into a spinal hemangioblastoma in a patient diagnosed with VHL disease. Metastasis was diagnosed during the second surgery and was not observed during the first. We should consider tumor-to-tumor metastasis as a differential diagnosis in cases where benign tumors display rapid growth, even if the pathological diagnosis does not initially confirm this.

Conflicts of Interest Disclosure

The authors report no conflict of interest concerning the materials, methods, and findings in this paper. All authors are members of The Japan Neurosurgical Society and have registered online Self-reported Conflict of Interest Disclosure Statement Forms.

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