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Letter to the Editor

Letter to the Editor regarding "Clear-cell renal cell carcinoma and glioblastoma multiforme coexistence: Double primary malignancy, does it have a causal relationship?"

Andrew Leland Waack[1], Brandon Sharkey[1], Alastair Hoyt[1], Jason L. Schroeder[1]

[1]Department of Surgery, Division of Neurosurgery, University of Toledo, Toledo, United States.

E-mail: *Andrew Leland Waack - awaack98@gmail.com; Brandon Sharkey - brandon.sharkey@rockets.utoledo.edu; Alastair Hoyt - alastair.hoyt@utoledo.edu; Jason L. Schroeder - jason.schroeder5@utoledo.edu

***Corresponding author:**
Andrew Leland Waack,
Department of Surgery,
Division of Neurosurgery,
University of Toledo, Toledo,
United States.

awaack98@gmail.com

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Quick Response Code:

Dear Editor,

We recently read with great interest "Clear-cell renal cell carcinoma (RCC) and glioblastoma (GBM) multiforme coexistence: Double primary malignancy, does it have a causal relationship?" by Simanjuntak *et al.*, who describes a case of concurrent RCC and GBM.[10] We have recently encountered a similar case in our clinical practice. We would like to describe our case of metachronous RCC and GBM, briefly summarize the existing literature regarding RCC and GBM, and comment on points raised by Simanjuntak *et al.*[10]

CASE DESCRIPTION

A 61-year-old previously high functioning woman presented with word finding difficulty, memory changes, and difficulty drawing shapes. Prior medical history included RCC treated with nephrectomy 4 years prior. Subsequent magnetic resonance imaging (MRI) revealed a 6.3 × 5.6 × 5.5 cm deep left frontal lesion, with an additional right frontal juxtacortical lesion (0.5 cm maximal diameter), and a third lesion in the right cingulate gyrus (2 cm maximal diameter); all three lesions demonstrated peripheral enhancement [Figure 1]. The patient's language and memory deficits continued to progress, and the patient developed mobility impairments and right sided hemiparesis. Due to progressive symptoms, cerebral edema, and mass effect, the patient elected to undergo surgical resection of the largest lesion. The preoperative course was complicated by bilateral lower extremity deep vein thromboses, which were treated with an inferior vena cava filter before craniotomy. The patient later underwent an uneventful resection of the largest lesion through a left superior frontal sulcus approach. Intraoperative squash prep pathology demonstrated hypercellularity and extensive necrosis, with no metastatic cancer. The final neuropathological diagnosis returned as GBM, Isocitrate dehydrogenase 1 (IDH1) wild-type, alpha thalassemia/mental retardation syndrome X-linked (ATRX) intact, epidermal growth factor receptor amplified, O6-methylguanine-DNA-methyltransferase (MGMT) nonmethylated. The postoperative course was complicated by a hematoma at the resection site. A repeat craniotomy for hematoma resection was completed, but the patient did not improve neurologically [Figure 2]. A goal of care discussion with

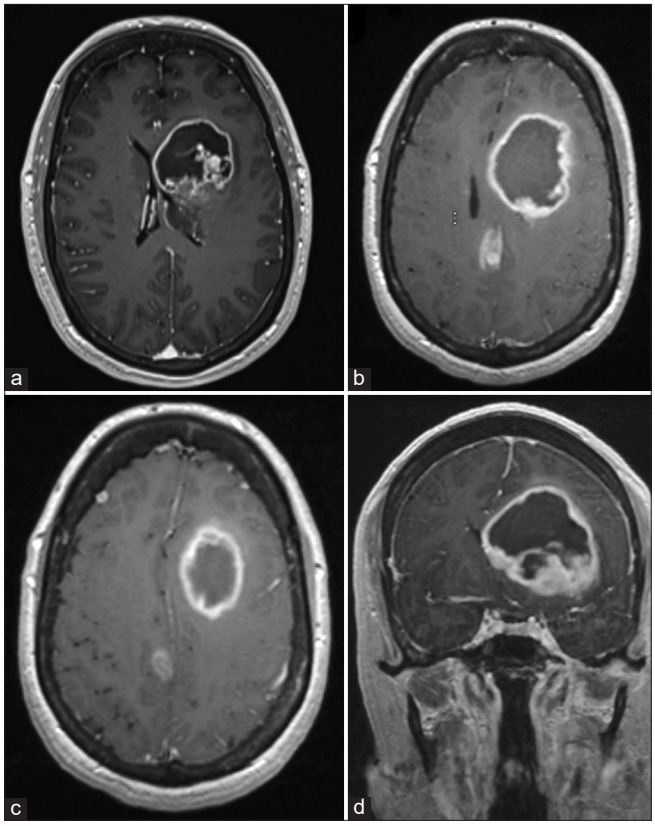

Figure 1: (a) Axial T1-weighted contrast-enhanced magnetic resonance (MR) image obtained 3 weeks before surgery. The lesion measures 4.2 × 4.5 cm. (b and c). Axial T1-weighted contrast enhanced MR image obtained 3 weeks after the MRI in (a). The tumor measured grew to 6.3 × 5.5 cm. All three tumors are visible in (c and d). Coronal T1-weighted contrast-enhanced MR image obtained 3 weeks after the magnetic resonance imaging in (a).

the family resulted in a change in code status. The patient died approximately 3-week postoperatively.

LITERATURE REVIEW

According to our literature search, our case represents the 132nd known patient with both RCC and GBM. Simanjuntak *et al.* have admirably described both their case and Franke *et al.*'s cases; we refer readers to review Simanjuntak *et al.* for a complete description of these cases.[2,10] We have subsequently identified two case reports not described by Simanjuntak *et al.*, a recently reported case series/database analysis including 126 cases of RCC followed by GBM, and an investigation of malignancies in long-term survivors (LTS) of GBM that describes one RCC arising in a patient with an existing GBM diagnosis.[4,8,9,11] A brief overview of all cases is found in Table 1.

1. Rugala describes a 56-year-old female who presented for new onset seizures, with subsequent MRI demonstrating a T2 hyperintense lesion with surrounding edema in the right temporal lobe; abdominal computed tomography demonstrated a heterogeneous hypodense lesion in the right kidney. A subsequent craniotomy was performed, followed shortly soon after by nephrectomy. Brain histopathological analysis revealed a neoplasm of glial origin, with immunohistochemistry demonstrating: casein kinase 1 (CK 1) (−), glial fibrillary acidic protein (GFAP) (+), subsequently diagnosed as GBM; the kidney tumor was diagnosed as RCC. Brain radiation and temozolomide were soon initiated. Amazingly, at the time of publication, 7 years later, the patient was reported to be neurologically intact, with follow-up imaging demonstrating only demyelinating changes in the surgical and radiation site; additionally, there was no proof either of relapse or dissemination of RCC.[9]
2. Myong and Park describe the case of a malignant glioma in a patient with Von Hippel-Lindau (VHL) syndrome with RCC and a history of multiple hemangioblastomas. At the age of 25, the patient underwent excision and subsequent radiation therapy for a large right cerebellar hemangioblastoma. The excised lesion stained positive for S100 and negative for p53 and GFAP, findings consistent with hemangioblastoma. Seven years later, the patient presented again for headache and dizziness, with subsequent MRI demonstrating a mass in the prior surgical site with irregular peripheral enhancement and a necrotic core. Abdominal MRI revealed a low-attenuating mass in the right kidney. Craniotomy and nephrectomy were performed soon after. The cranial tumor displayed markedly different morphology and staining patterns compared to the initial hemangioblastoma 7 years prior. This lesion was positive for GFAP and P53 staining and loss of p16, suggesting GBM. The patient had a rapid tumor recurrence and then underwent several episodes of excision and recurrence; the patient ultimately passed away 1 year later.[8]

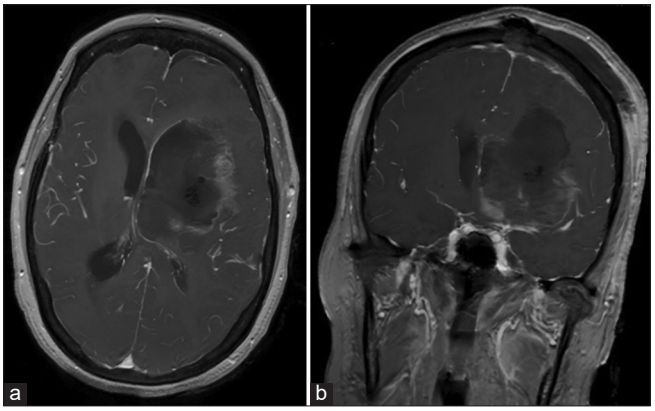

Figure 2: (a) Axial T1-weighted contrast-enhanced magnetic resonance (MR) image 10 days after surgery. (b) Coronal T1-weighted contrast-enhanced MR image 10 days after surgery.

Table 1: Case descriptions of GBM and RCC in the same patient.

Case	Patient demographics (Age, Sex)	GBM-RCC Temporal Relationship	GBM Location	Treatment	Outcome	Miscellaneous
Franke *et al.*[2] 1990	74, F	Concurrent (RCC incidental at necropsy)	Left temporal lobe	Craniotomy and chemotherapy, second craniotomy for GBM recurrence 2 months later	Death 2 months after second craniotomy	Tumor collision between GBM and RCC brain metastases
Myong and Park[8] 2009	32, M	Concurrent	Right cerebellum	Craniotomy and nephrectomy, three subsequent craniotomies for GBM recurrence	Death 1 year after initial GBM diagnosis	VHL syndrome, GBM occurred secondary to radiation of right cerebellum hemangioblastoma
Rugała[9] 2018	56, Not specified	Concurrent	Right temporal lobe	Craniotomy and nephrectomy, followed by Stupp protocol	Patient neurologically intact at time of reporting, 7 years later	Patient alive 7-year postcraniotomy and nephrectomy
Kim *et al.*[4] 2019	62, M	RCC 11.5 years following GBM	Not specified	Craniotomy and brain radiotherapy, nephrectomy	Death from GBM	Long-term survivor of GBM who later developed RCC
Simanjuntak *et al.*[10] 2022	64, F	Concurrent	Right temporal lobe	Craniotomy and nephrectomy	Patient discharged home 15-day postoperative at time of reporting	
Zhang *et al.*[11] 2023 Case #1	76, M	GBM 4 years after RCC	Not specified	Renal surgery and Stupp protocol	Death from GBM 11 months after diagnosis	*TERT* mutation; no IDH1/2 mutation, 1p/19q codeletion, or ATRX loss
Zhang *et al.*[11] 2023 Case #2	66, F	GBM 2 years after RCC	Not specified	Renal surgery and Stupp protocol	Death from GBM 3 months after diagnosis	*TERT* mutation, *EGFR* amplification, *EGFR* variant III; no IDH1/2 mutation, 1p/19q codeletion or ATRX loss
Zhang *et al.*[11] 2023 Case #3	62, F	GBM 7.5 years after RCC	Not specified	Renal surgery+IL2 and Stupp protocol	Death from GBM 15 months after diagnosis	*TERT* mutation; no IDH1/2 mutation, 1p/19q co-deletion, or ATRX loss
Zhang *et al.*[11] 2023 Case #4	49, M	GBM 4.5 years after RCC	Not specified	Renal surgery+IL2 and Stupp protocol	Death from GBM 14 month after diagnosis	*TERT* mutation; no IDH1/2 mutation, 1p/19q co-deletion, or ATRX loss
Zhang *et al.*[11] 2023 SEER database review	63.5 mean age, 88 M, 34 F Composite analysis of 122 cases	GBM mean 4 years after RCC	Not specified	Not specified	Death from GBM mean 6 months after diagnosis	
Current case 2023	61, F	GBM 4 years after RCC	Left frontal lobe	Nephrectomy and craniotomy	Death 2 weeks after craniotomy	Three brain lesions seen on imaging

RCC: Renal cell carcinoma, GBM: Glioblastoma, VHL: Von Hippel Lindau, *TERT*: Telomerase reverse transcriptase, IDH1: Isocitrate dehydrogenase, *EGFR*: Epidermal growth factor receptor, ATRX: Alpha thalassemia/mental retardation syndrome X-linked

3. Zhang *et al.* report a series of four cases of metachronous RCC and GBM, as well as an analysis of the SEERS database, identifying 122 cases of RCC followed by GBM. Similar to our reported case, the average GBM occurred approximately 4 years after the diagnosis of RCC. The four GBMs Zhang *et al.* describe in the case series all had a *TERT* gene promoter mutation; none of the patients demonstrated *IDH1/2* mutation, 1p/19q codeletion, or ATRX loss. Two of the four had *TP53* mutations. In the analysis, patients with GBM following RCC had a worse prognosis compared to "control" GBM; Zhang *et al.* hypothesize the average higher age of GBM and the molecular profiles of these tumors (TERT positive) are likely responsible for the worse outcomes.[11]
4. Kim *et al.* report a case series of malignancies occurring in LTS of GBM. They describe 155 LTS of GBM, with 17 subsequent cancers occurring in 13 patients; most later cancers occurred in the field of radiation for GBM. These cancer types included skin cancer, leukemia, low-grade glioma, and scalp sarcoma. The remaining subsequent cancers reported included melanoma, prostate cancer, bladder cancer, endometrial adenocarcinoma, basal cell carcinoma, and one RCC. The reported RCC occurred 12 years after the initial GBM; this patient's GBM was managed by gross total resection and radiotherapy, but not temozolomide. The authors did not elaborate on potential mechanisms of RCC induction or the relationship between RCC and GBM.[4]

COMMENTS

There is no established relationship linking RCC and GBM. Although uncommon, these cancers are not exclusive to one another, and both can occur in the same patient.[2] Different patterns of coincidental RCC and GBM have been reported, including both synchronous and metachronous presentations.[2,4,8-11] Although no clear relationship between these two cancers has been elucidated, it has been suggested that they may cooccur due to therapeutic side effects, underlying genetic syndromes, or as an unfortunate coincidence.

GBM and RCC in the same patient may occur metachronously, with the second malignancy possibly occurring due to therapy for the first malignancy.[4,11] Cranial radiation therapy and some pharmacotherapies have been shown to increase the risk of GBM, as demonstrated by Myong and Park's case (described above).[8,11] However, Zhang *et al.* were not able to confidently attribute GBM development to any specific therapeutic measure incurred during treatment for RCC, as none of the described patients received cranial radiotherapy, and the pharmacotherapy between patients was inconsistent.[11] In addition, Kim *et al.*'s description of an RCC occurring in a patient with existing GBM does not show a relationship between GBM treatment and RCC; the patient received only gross total resection and cranial radiotherapy for GBM, without concurrent temozolomide, making it difficult to link GBM treatment to the development of the RCC.[4] All malignancies that were attributed to GBM treatment were located in the radiation field.[4] In addition, temozolomide is classically linked to the development of hematologic malignancies, not RCC.[6] There is no clearly defined relationship linking the treatment of RCC or GBM to the subsequent development of the other malignancy type.

It has been suggested RCC and GBM may occur in the same patient as part of genetic syndromes, although there is no clear evidence as to which genes, alleles, or mutations are responsible.[10,11] Simanjuntak *et al.* implicate genetic syndromes, such as Li-Fraumeni syndrome, neurofibromatosis, and VHL, as possibly being involved.[10] Notably, VHL is an established predisposition to developing RCC, although it does not seem to play a role in GBM. Krieg *et al.* show that VHL-associated hemangioblastomas display distinct genetic features from GBM, and GBM displays wild-type VHL expression.[5] Furthermore, in the only identified case of GBM occurring in VHL (described above), Myong and Park posit the GBM was more likely related to prior radiation therapy and an inherited mutation.[8] Li Fraumeni syndrome, neurofibromatosis and Turcot syndrome are all syndromes that predispose to GBM.[1,3,7] However, none of these are linked to the development of RCC. We have been unable to identify a common underlying genetic syndrome linking GBM to RCC.

There are currently no concrete data demonstrating an association between RCC and GBM, and we agree with Simanjuntak *et al.* that concurrent RCC and GBM likely represents an unfortunate coincidence, although it is possible, there is an underlying relationship between the two. The literature does not indicate that any specific treatment protocol is particularly effective for these patients. Because there is no known underlying mechanism responsible for the cooccurrence of these cancers, we believe that each cancer should be treated as its own entity, in accordance with the respective standards of care.

We agree with Simanjuntak *et al.* that it is important to document these unusual cases. RCC and GBM in the same patient are likely to be underdiagnosed and underreported.[10] The true occurrence of both cancers in a single person is likely higher than currently believed and is likely to increase as outcomes continue to improve.[11] GBM in the setting of RCC is highly likely to be misdiagnosed as metastatic disease, which may profoundly impact the treatment strategy.[11] Stupp protocol, including surgical resection, should be initiated as soon as possible following the diagnosis of GBM. The rate of surgical resection of metastatic RCC is lower than GBM, suggesting that some presumed RCC metastases are misdiagnosed GBMs that do not undergo surgical resection and Stupp protocol.[11] We believe, it is important

for neurosurgeons to remain cognizant that brain lesions in the presence of systemic cancers are not necessarily brain metastases. Even in the presence of systemic cancers, we believe that GBM should be included as a differential for brain lesions, especially if only one lesion is detected. In conclusion, we commend Simantunjak *et al.* for an excellent case report describing concurrent RCC and GBM, and we would like to add a description of a similar case to the literature.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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