Case Report

Clear-cell renal cell carcinoma and glioblastoma multiforme coexistence: Double primary malignancy, does it have a causal relationship?

Kevin Ariel Tiopan Simanjuntak1, Asra Al Fauzi1, Ayu Yoniko Christi1, Perthdyatama Syifaq Budiono1, Rahadian Indarto Susilo1, Irwan Barlian Immodoel Haq1, Nur Setiawan Suroto1, Dyah Fauziah2, Wahjoe Djatisoesanto3

Departments of 1Neurosurgery, 2Anatomical Pathology, and 3Urology, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

E-mail: Kevin Ariel Tiopan Simanjuntak – kevinarielts@gmail.com; *Asra Al Fauzi - asra.al@fk.unair.ac.id; Ayu Yoniko Christi - ayuyoniko@gmail.com; Perthdyatama Syifaq Budiono - perthdyatama@gmail.com; Rahadian Indarto Susilo - Rahadian-i-s@fk.unair.ac.id; Irwan Barlian Immodoel Haq - immodoelhaq@gmail.com; Nur Setiawan Suroto - setiawan.dr@gmail.com; Dyah Fauziah - dyah-f@fk.unair.ac.id; Wahjoe Djatisoesanto - wahjoe.djatisoesanto@fk.unair.ac.id

*Corresponding author:
Asra Al Fauzi,
Department of Neurosurgery,
Universitas Airlangga –
Dr. Soetomo General Academic
Hospital, Surabaya, Indonesia.
asra.al@fk.unair.ac.id

Received : 04 July 2022
Accepted : 28 July 2022
Published : 12 August 2022

ABSTRACT

Background: Multiple primary malignancies (MPMs), especially coexistence of renal cell carcinoma (RCC) and glioblastoma multiforme (GBM), are rare. The most likely clinical diagnosis in patient with tumor in another organ is metastatic brain tumor. Although GBM is the most common brain tumor, it is rarely coexistent with other malignancies.

Case Description: A 64-year-old female presented with headache and dizziness, along with abdominal pain for 2 weeks before being admitted. The abdominal computed tomography (CT) scan showed a kidney tumor. The patient developed left hemiplegia, and the brain CT scan showed an intracranial tumor. The patient suggested for radical nephrectomy and craniotomy tumor removal. Histopathology of the kidney and brain tumor revealed two different features, which showed RCC and GBM. Immunohistochemistry result confirmed the diagnosis of GBM and IDH1 wild type; coexistent with clear cell RCC.

Conclusion: The coexistence of carcinoma and glioma should be regarded as coincidental cases if it did not accomplish the criteria for tumor-to-tumor metastasis or proven to be a genetic syndrome. This case report provides an addition to the literature about double primary malignancy in a single patient. More studies are needed to confirm whether they have causal relationship or merely coincidental findings.

Keywords: Case report, Coexisting malignancy, Glioblastoma multiforme, Malignancy, Renal-cell carcinoma

INTRODUCTION

Multiple primary malignancies (MPMs), especially renal cell carcinoma (RCC) and glioblastoma multiforme (GBM) coexistence, are rare. About 90% of kidney cancers are diagnosed with RCC which originated from renal epithelium.10,12 The risk factors affecting RCC rates are smoking, obesity, hypertension, and genetic.13 The advancement in histopathology and molecular characterization of RCC has already made a huge development in the classification of RCC.21 The clinical findings on patients with brain metastases have significantly increased in number.
for over two decades.\textsuperscript{[5]} Brain metastases on RCC are reported on 2–4\% cases found at diagnosis in which 4–17\% will develop metastases through the disease’s progress.\textsuperscript{[5,20]} The most common brain metastases of RCC are ventricular metastases, comprised 36\% up to 64\%, and approximately 50\% affected choroid plexus. GBM is the most common malignant primary brain tumor.\textsuperscript{[2,17]} The incidence rate of GBM is 3.19 cases/100,000 people per year and poor prognostics with 4–5\% in 5-year survival rate, also GBM accounts for 82\% cases of malignant glioma.\textsuperscript{[17]} Intrinsic and environmental factors contribute to the development of malignant glioma, as well as rare hereditary syndromes, such as Turcot syndrome (TS), Li-Fraumeni syndrome (LFS), neurofibromatosis Type 1 and 2, and other types of hereditary syndrome associated with an increased risk of developing glioma.\textsuperscript{[15]} The coexistence of two tumors is commonly found as a coincidental finding that was diagnosed after pathology examination.\textsuperscript{[8]} A case report on the existence of two tumors or metastases from a cancer turned to be another highly malignant cancer is relatively rare, especially from carcinoma and GBM cases. The phenomenon of cancer to cancer is a rare case to be documented and reported. In this article, we presented a rare case of clear cell RCC with suspected brain metastases which were proven to be GBM. Written consent was obtained from the patients’ families for publication of this case report and accompanying images.

CASE PRESENTATION

Clinical history

A 64-year-old Asian woman presented with a headache and dizziness along with the left extremities hemiparesis for 3 days before being admitted to the hospital. In depth historical taking, the patient was admitted to another hospital 2 weeks earlier with a headache and dizziness along with abdominal pain. Patient was taken for computed tomography (CT) scan of the abdominal and was diagnosed with kidney tumor. The patient was suggested for nephrology and biopsy; however, the patient refused the surgery. The patient was discharged after the general conditions improved. Eight days later, the patient was readmitted to hospital with a headache, dizziness, and severe abdominal pain along with pain in the extremities. Given the patient’s conditions, she was undertaken for inpatient care. A couple days later, the patient developed severe headache and left-sided extremities hemiparesis as well as a decreasing consciousness with Glasgow Coma Scale (GCS) E1V2M4. Following the neurologist suggestion, the brain CT scan was subsequently performed [Figure 1], CT scan showed hyperdense intracranial lesion on the temporal region with 6 × 4 × 5 cm in size suggestive for intracranial tumor. The patient was consulted to neurosurgeon with suggestion for craniotomy tumor removal and referred to our hospital.

Patient’s consciousness improved was getting better with GCS 15 a day before being referred to our hospital.

Physical examination and radiology findings

On the initial examination, the patient was alert with GCS of 15. Her blood pressure was 136/85 mmHg which pulse was regular and strong counted in 65 times/min. The patient’s respiratory was 20 times/min and was afebrile. The patient was examined for pain scale with numeric rating scale and according to the patient, the pain score within the scale was 4 (moderate pain). Neurological examination showed diminished muscle strength with grades 2/5 for all muscle groups on the left extremities. The brain magnetic resonance imaging revealed irregular enhancing mass with intra tumoral hemorrhage on deep temporal lobe involving right basal ganglia with 6.3 × 4.2 × 5.2 cm size and adjacent edema suggesting hemorrhagic intracranial metastasis [Figure 2]. The mass caused the adjacent indentation on the right midbrain, third and right ventricle compression, also midline deviation with approximately 13 mm in length to the left side of the brain. MR perfusion showed mild increase on relative cerebral blood volume on peripheral of the mass. MR spectroscopy showed choline metabolite increase with choline/creatinine ratio = 3.27. The patient was taken for craniotomy tumor removal followed by radical nephrectomy. The intracranial tumor was removed in piece meal fashion, as much as possible.

Postoperative course

Postoperatively, the patient was admitted to intensive care unit after surgery and extubated on day 6. The brain CT scan evaluation was performed and showed residual tumor with decreased midline shift [Figure 3]. The motoric deficit was improved and her headache was resolved after surgery. She was discharged home on hospitalization day 15.

Histopathological report

Pathology examination of the left nephrectomy specimen revealed a tumor located at mid pole, measuring 4.5 × 4.5 × 4 cm. Tumor was solid and friable, with yellow and brown in color [Figure 4]. Microscopic examination depicted malignant tumor forming lobular pattern with delicate fibrovascular septa. Tumor cells showed round nuclei with mild pleomorphism, conspicuous nucleoli at × 400 magnification, abundant, and clear cytoplasm. Extra-renal extension of tumor cells and tumor emboli in renal vein and ureter was not found.

Pathology examination of brain tumor revealed cellular tumor tissue with necrosis and hemorrhages. The tumor cells showed round to oval shaped nuclei, marked pleomorphic, coarse chromatin, with high mitotic activity.
Immunohistochemistry of brain tumor was positive for glial fibrillary acidic protein (GFAP) and ATRX; yet negative for pancytokeratin, CD10, p53, and IDH1 R132H. The final conclusion was glioblastoma, IDH1 wild type, the World Health Organization (WHO) Grade 4; Coexistent with Clear Cell RCC in the left kidney, and the WHO/International society of urological pathology (ISUP) Grade 2, Stage I [Figure 5].

**DISCUSSION**

Coexistence of two malignant tumors is a very rare occurrence especially a report on simultaneous GBM existence with RCC case. Based on the research conducted by Luciani, it is estimated by the year of 2030 around 70% of neoplasm will occur at the age of 65; having stated that the patient involved in this present case was 64 years old. Warren and Gates described some criteria for MPMs they are (a) each tumor must present a definite picture of
Based on the histology characteristic and tumor formations, meningioma and clear cell RCC exhibit opposing differentiation; it is the same as another malignancy, that is, malignant glioma which is commonly undetected because it has heterogeneous composition of the neoplastic tissue. Neoplasms often act as donors in tumor-to-tumor metastasis including carcinomas, with RCC and glioma are one of many tumors that act as recipients in tumor-to-tumor metastasis. Franke et al. (1990) reported an RCC on tumor-to-tumor metastasis with the donor and glioma with the recipient; having stated that, the metastatic RCC was reported to collide with GBM. RCC tumor metastasis colliding with meningioma was reported in another case, different compared to the previous one. It described the collision of meningioma and metastatic RCC. The collision tumor is different with tumor-to-tumor metastasis, in which collision tumor are two tumors intermixed and appear close to each other compared to tumor-to-tumor metastasis which two tumors exist at the same time.

Dobbing and Campbell et al. defined tumor-to-tumor metastasis using rigorous standards: The presence of two or more distinct tumors, the recipient tumor must be a true neoplasm, and there must be an actual metastatic deposit within the neoplastic tissue of the recipient tumor. Based on the criteria, our case is not tumor-to-tumor metastasis, because both kidney and brain tumor are true neoplasms with lack of metastatic deposit within the neoplastic tissue. Since GFAP is positive in glioma cells and normal brain tissue, this can be applied to differentiate between glioblastoma and RCC. In this case, the brain tumor showed different morphological features with tumor of the kidney. However, immunohistochemistry was performed to confirm that the brain tumor and the kidney tumor were two different entities. Immunohistochemistry of the brain tumor showed negative for pancytokeratin and CD10, yet positive for GFAP. The morphology and immunohistochemistry findings supported a diagnosis of glioblastoma. Subsequent immunohistochemistry with IDH1 R132H, ATRX, and p53 established a diagnosis of glioblastoma and IDH wild type.

GFAP is the mark of intermediate filament protein in astrocyte in the central nervous system (CNS). Hence, to differ between metastatic cell carcinoma and glioma, we can use GFAP as the immunohistochemistry examination. The purpose of this examination is to detect the difference between glioma and metastatic carcinoma, so there will be no false positive or negative on the diagnostic between tumor-to-tumor metastasis and collision tumor.

A study by Budka regarding GFAP as a biomarker on glioma showed that renal carcinoma metastatic to the brain had a strong reaction in moderate cells for anti-GFAP. This result was affected by two possibilities such as immunoreactive cells might represent reactive astroglia and dense gliosis in suspected vicinity. van Asperen noticed that GFAP itself can be used as a biomarker for detecting higher grade glioma;
meanwhile, GFAP as a biomarker for low-grade glioma is not conclusive whether it is higher or lower since the incidence rate of GFAP positive is lower in low-grade brain tumors.[23] MPMs are always associated with genetic syndrome. Several genetic syndromes associated with CNS tumors especially GBM are TS, LFS, and von-Hippel Lindau (VHL) syndrome. TS is a genetic syndrome for MPM with association of primary tumors of CNS and two different forms of colorectal polyp, while TS is divided into two types; TS Type I is characterized with the presence of glial tumors with few colonic polyps, while TS Type II is characterized with thousands of colonic polyps and increased risk of medulloblastoma.[7,24] This case was not a TS because GBM presence was not followed by colorectal polyp but RCC.

Another genetic syndrome associated with CNS tumor is LFS. LFS is autosomal dominant disease caused by germline mutation in gene locus 17p13 which encode Tumor Protein 53 (TP53) gene, so LFS is having a lifelong increased risk of developing multiple tumors especially intracranial malignancy such as GBM.[24] Meanwhile VHL syndrome is another genetic syndrome, an autosomal dominant disease the same as LFS, but different gene locus mutation in chromosome 3p25 which encodes tumor suppressor protein, pVHL.[24] The weakness in our case report is the lack of genetic laboratory examination for genetic syndrome, which prevented us from concluding the LFS and VHL syndrome as diagnosis in this case because there was no evidence or laboratory examination of TP53 and pVHL.

In the study attempted by Tajika et al., it was reported that in the epithelial line of the glioma from bronchial carcinoma showed immunoreactivity for cytokeratins; it had acinar and papillary patterns which were demarcated on the surrounding glioma tissue.[22] It is different from our case, which did not show any immunoreactivity for cytokeratins. Mork and Rubinstein reported three postmortem cases of suspected intracranial metastases from bronchial carcinomas, which were confirmed as glioma.[16] Thus, they concluded that the coexistence of glioma and visceral carcinoma at the same time did not have any causal relationship and should be regarded as coincidental.[16] This finding[16] is in line with our case and since there are not enough proofs to determine the causal relationship between both tumors, our case should be regarded as coincidental.

**CONCLUSION**

The coexistence of carcinoma and glioma in a single patient is rare. If the coexistence of both tumors did not accomplish the criteria for tumor-to-tumor metastasis and was not proven as a genetic syndrome, it should be regarded as coincidental finding, as seen in our case. This case report provides an addition to the literature about double primary malignancy in a single patient. However, more studies are needed to confirm whether they have causal relationship or merely coincidental findings.

**Ethical approval**

This is a case report; therefore, it did not require ethical approval from the ethics committee. However, we obtained permission from each patient’s parents to publish their data.

**Consent**

Written informed consent was obtained from each patient’s family for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Research registration**

This case report is not eligible for obtaining a research registry since it only contains a report of a known entity with no new surgical or medical interventions.

**Provenance and peer review**

Not commissioned, externally peer-reviewed.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Bao Q, Yu S, Yu X. Collision tumor of meningioma and metastatic renal clear cell carcinoma: A case report. Br J Neurosurg 2020;1-3.
2. Batash R, Asna N, Schaffer P, Francis N, Schaffer M. Glioblastoma multiforme, diagnosis and treatment; recent literature review. Curr Med Chem 2017;24:3002-9.
3. Budka H. Non-glial specificities of immunocytochemistry for the glial fibrillary acidic protein (GFAP). Triple expression of GFAP, vimentin and cytokeratins in papillary meningioma and metastasizing renal carcinoma. Acta Neuropathol 1986;72:43-54.
4. Campbell LV Jr., Gilbert E, Chamberlain CR Jr., Watne AL. Metastases of cancer to cancer. Cancer 1968;22:635-43.
5. Crisman CM, Patel AR, Winston G, Brennan CW, Tabar V, Moss NS. Clinical outcomes in patients with renal cell carcinoma metastases to the choroid plexus. World Neurosurg
Simanjuntak, et al.: Clear-cell renal cell carcinoma and glioblastoma multiforme coexistence

2020:140:e7-13.

6. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: Case report and a comprehensive review of the literature. Am J Clin Oncol 2003;26:79-83.

7. Dipro S, Al-Otaibi F, Alzahrani A, Ulhaq A, Al Shail E. Turcot syndrome: A synchronous clinical presentation of glioblastoma multiforme and adenocarcinoma of the colon. Case Rep Oncol Med 2012;2012:720273.

8. Dobbing J. Cancer to cancer. Guys Hosp Rep 1958;107:60-5.

9. Franke FE, Altmannsberger M, Schachenmayr W. Metastasis of renal carcinoma colliding with glioblastoma. Carcinoma to glioma: An event only rarely detected. Acta Neuropathol 1990;80:448-52.

10. Gray RE, Harris GT. Renal cell carcinoma: Diagnosis and management. Am Fam Physician 2019;99:179-84.

11. Hol EM, Pekny M. Glial fibrillary acidic protein (GFAP) and the astrocyte intermediate filament system in diseases of the central nervous system. Curr Opin Cell Biol 2015;32:121-30.

12. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers 2018;3:1117-27.

13. Liu Z, Liu C, Guo W, Li S, Bai O. Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. PLoS One 2015;10:e0125754.

14. Luciani A, Ascione G, Marussi D, Oldani S, Caldiera S, Bozzi S, et al. Clinical analysis of multiple primary malignancies in the elderly. Med Oncol 2009;26:27-31.

15. Maher ER. Hereditary renal cell carcinoma syndromes: Diagnosis, surveillance and management. World J Urol 2018;36:1891-8.

16. Mörk SJ, Rubinstein LJ. Metastatic carcinoma to glioma: A report of three cases with a critical review of the literature. J Neurol Neurosurg Psychiatry 1988;51:256-9.

17. Omuro A, De Angelis LM. Glioblastoma and other malignant gliomas: A clinical review. JAMA 2013;310:1842-50.

18. Petraki C, Vaslamatzis M, Argyrakos T, Petraki K, Stratakis M, Alexopoulos C, et al. Tumor to tumor metastasis: Report of two cases and review of the literature. Int J Surg Pathol 2003;11:127-35.

19. Rosso S, De Angelis R, Ciccolallo L, Carrani E, Soerjomataram I, Grande E, et al. Multiple tumours in survival estimates. Eur J Cancer 2009;45:1080-94.

20. Siomin V, Lin JL, Marko NF, Barnett GH, Toms SA, Chao ST, et al. Stereotactic radiosurgical treatment of brain metastases to the choroid plexus. Int J Radiat Oncol Biol Phys 2011;80:1134-42.

21. Sun M, De Velasco G, Brastianos PK, Aizer AA, Martin A, Moreira R, et al. The development of brain metastases in patients with renal cell carcinoma: Epidemiologic trends, survival, and clinical risk factors using a population-based cohort. Eur Urol Focus 2019;5:474-81.

22. Tajika Y, Reifenberger G, Kiwit JC, Wechsler W. Metastatic adenocarcinoma in cerebral astrocytoma: Clinicopathological and immunohistochemical study with review of the literature. Acta Neurochir (Wien) 1990;105:50-5.

23. van Asperen JV, Fedorushkova DM, Robe PA, Hol EM. Investigation of glial fibrillary acidic protein (GFAP) in body fluids as a potential biomarker for glioma: A systematic review and meta-analysis. Biomarkers 2022;27:1-12.

24. Vijapura C, Aldin ES, Capizzano AA, Policeni B, Sato Y, Moritani T. Genetic syndromes associated with central nervous system tumors. Radiographics 2017;37:258-80.

25. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer 1932;16:1358-414.

26. Zhai C, Cai Y, Lou F, Liu Z, Xie J, Zhou X, et al. Multiple primary malignant tumors-a clinical analysis of 15,321 patients with malignancies at a single center in China. J Cancer 2018;9:2795-801.

How to cite this article: Simanjuntak KA, Al Fauzi A, Christi AY, Budiono PS, Susilo RI, Haq IB, et al. Clear-cell renal cell carcinoma and glioblastoma multiforme coexistence: Double primary malignancy, does it have a causal relationship? Surg Neurol Int 2022;13:361.