Renal cell carcinoma presenting with brain metastasis from a 1.6 cm primary tumor

Heather J. Chalfin, MD, Grzegorz T. Gurda, MD, Hans-Joerg Hammers, MD, George J. Netto, MD, Trinity J. Bivalacqua, MD

James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

CHALFIN HJ, GURDA GT, HAMMERS H-J, NETTO GJ, BIVALACQUA TJ. Renal cell carcinoma presenting with brain metastasis from a 1.6 cm primary tumor. *Can J Urol* 2013;20(5):6964-6967.

Small renal cell carcinoma (RCC) tumors are believed to have a negligible risk of metastasis. We report on a 77-year-old man presenting with extremity weakness who was found to have a 2.5 cm brain metastasis from a subsequently discovered 1.6 cm clear cell RCC primary tumor. We review what is known about synchronous and metachronous metastasis from small renal tumors and prognostic features informing treatment for such lesions.

Key Words: clear cell renal cell carcinoma, brain metastasis, synchronous metastasis

Introduction

In the past, small renal cell carcinoma (RCC) tumors were believed to have a negligible risk of metastasis. This has been verified with case series of kidney tumors < 3 cm reporting a 0.1% chance of metastasis at any time during the natural history of the primary cancer. Here, we present the first report of a synchronous brain metastasis from an RCC primary < 7 cm. Notably, the primary in the present report is 1.6 cm. We review what is known about synchronous and metachronous metastasis from small renal tumors and prognostic features informing treatment for such lesions.

Accepted for publication August 2013

Address correspondence to Dr. Heather Chalfin, 733 N Broadway/ BRB 137, Baltimore, MD 21205 USA

Case presentation

A cachexic 77-year-old man with right-sided weakness presented to our institution with a newly discovered 2.5 cm enhancing hemorrhagic mass of the left frontal lobe with extensive surrounding edema. Hemangiopericytoma versus meningioma was suspected, Figure 1. An additional 7 mm enhancing nodule in the right frontal lobe raised concern for metastatic disease, though the patient had no known primary. Exam was notable for mild cognitive slowing and orientation x1 to self. Laboratory analysis revealed normocytic anemia that was attributed to his hypothyroidism. The patient had multiple other comorbidities including hypertension, atrial fibrillation, and diabetes mellitus with 30-pack-years, alcohol and illicit drug abuse, as well as medication non-compliance. After counseling, craniotomy was

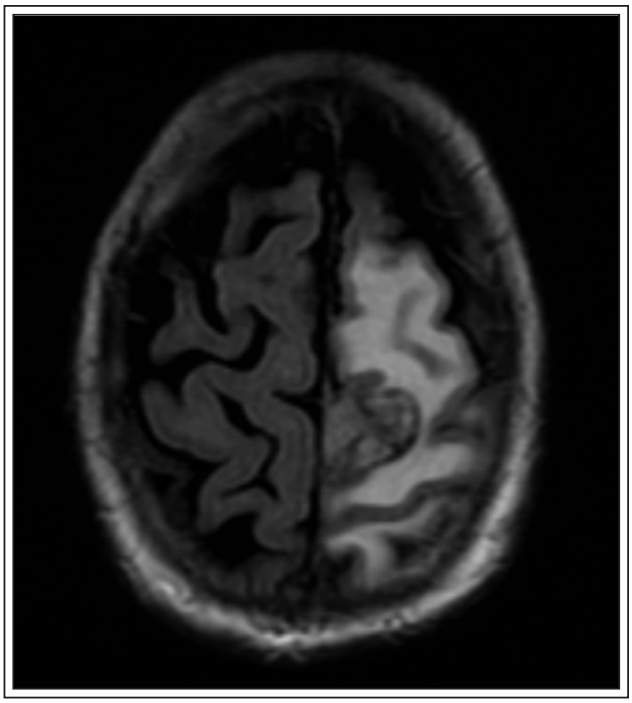

Figure 1. Axial flair T2 MRI.

planned with the understanding that it may not represent definitive treatment.

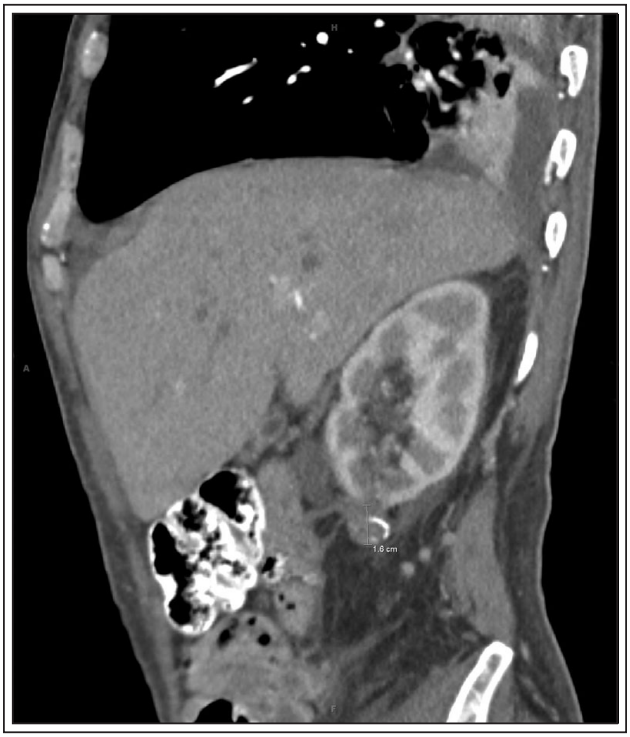

Figure 2. Renal mass - CTA abdomen w/wo contrast.

During preoperative work up, a pulmonary artery filling defect was noted on CT compatible with pulmonary embolus. Venocavogram for IVC filter placement revealed a thrombus extending from the suprarenal IVC to just below the right atrium. After subsequent CT imaging with 3D mapping, it was concluded that the IVC filling defect did not represent tumor thrombus. Furthermore, the presumed pulmonary embolus was clarified as a 2.7 cm mass encasing a lobar branch of the pulmonary artery. Finally, a complex exophytic lesion in the lower pole of the right kidney measuring 1.6 cm x 1.3 cm was noted, Figure 2.

Urology was consulted after surgical pathology revealed metastatic clear cell renal carcinoma, Figure 3. The patient denied flank pain or hematuria, although he was anemic as noted preoperatively. He was discharged to inpatient rehab and will follow up with medical oncology and radiation therapy as an outpatient.

Discussion

In the past, small RCC tumors were thought to represent negligible risk for metastasis. Any smaller than 3 cm were designated benign adenomas until 1986.[1] This "3 cm rule" referenced autopsy studies from the 1930s where only 1 of 38 small tumors metastasized versus 70 of 106 greater than 3 cm. Currently, these are not automatically considered benign, yet the link between increasing tumor size and metastatic potential has repeatedly been demonstrated.

Most notably, a 2009 report from Memorial Sloan-Kettering indicated a very low (0.1%) risk of metastasis for RCC tumors < 3 cm, based on a single synchronous event (2.9 cm primary) of 781 cases and one metachronous event (2.5 cm primary) of 720 cases.[2] Further evidence came from a report by Kunkle et al where no patient with a tumor less than 2 cm had synchronous metastasis in an 8 year period at their institution, of 110 cases of biopsy-confirmed distant metastasis.[3] Yet, one multicenter study contradicts this commonly held belief. For 609 RCC tumors < 3 cm, Klatte and colleagues found no association between size and synchronous metastasis risk.[4] However, this study considered positive nodes as metastasis in contrast to other reports that define metastasis as clinical stage M1 disease.[2-4]

In addition to size, Fuhrman grade and pathologic subtype contribute to metastatic potential. Clear cell is the most common and portends the worst prognosis. Pathologists also note differentiation patterns separately from RCC subtype. Sarcomatoid

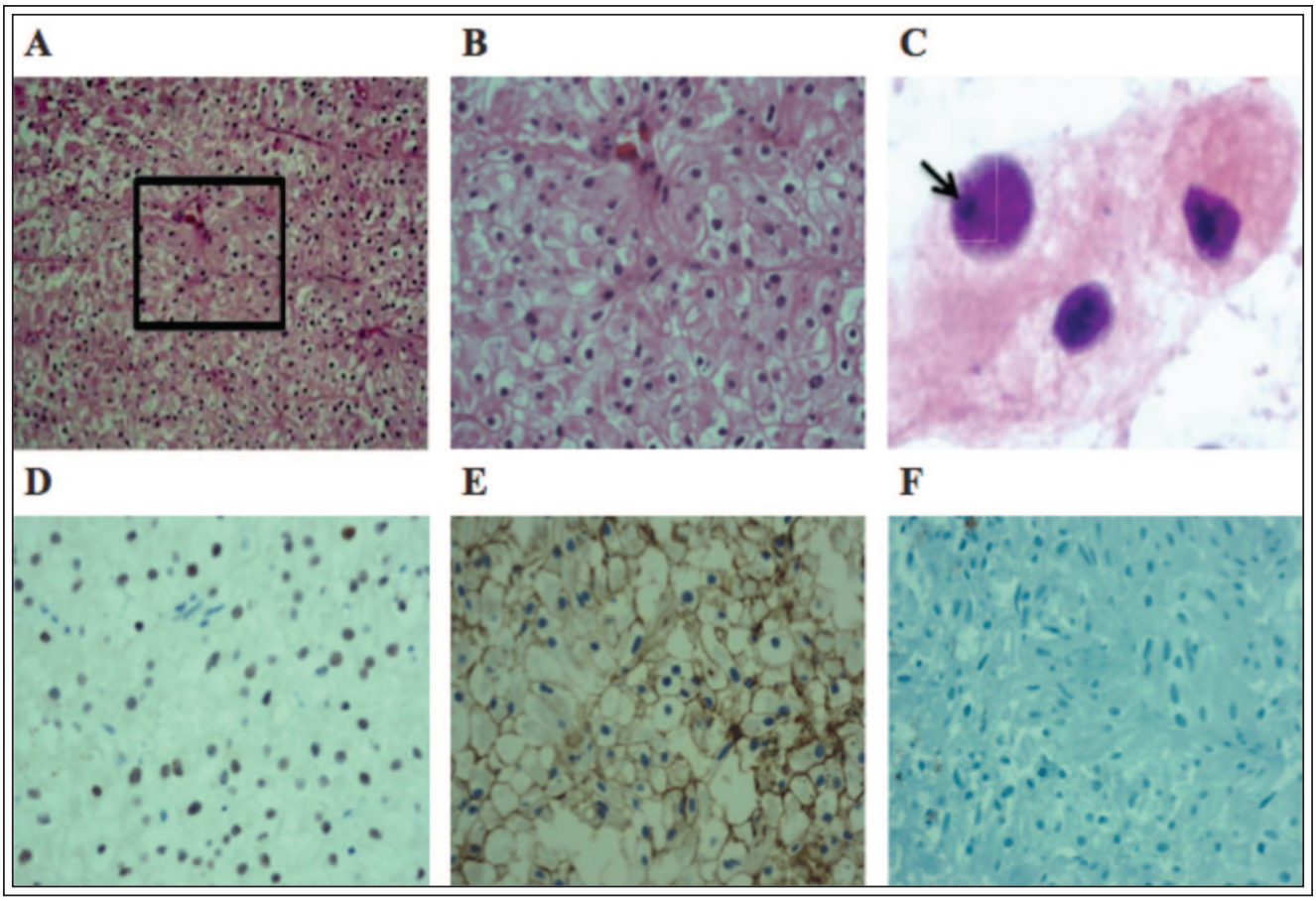

Figure 3. Histopathology for the case. A: Hematoxylin-eosin/H&E stain (100X magnification) within a viable area. Prominent vascularity was noted. **B:** H&E stain (200X within the boxed area of A). The tumor was characterized by clear-wispy pink cytoplasm, well-formed cell borders and focally prominent cytologic atypia. **C:** H&E cytologic touch preparation (400X magnification). Detailed cytologic features, including anisonucleosis and prominent nucleoli (arrow), corresponding to Fuhrman grade 3 out of 4. **D:** Immunohistochemical/IHC nuclear positivity for PAX8 in tumor cells. PAX8 is a transcription factor specific for the genitourinary (GU) tract and thyroid. **E:** IHC cytoplasmic membrane positivity for Carbonic Anhydrase IX (CAIX). CAIX is highly expressed in angiogenic clear cell tumors, including clear cell renal cell carcinoma. **F:** IHC negativity for Glial Fibrillary Acidic Protein (GFAP), a highly specific neuronal marker, to exclude an unlikely brain primary.

differentiation, present in approximately 5% of all cases of RCC, automatically garners a Fuhrman 4 grading.[5] It is associated with frequent distant metastasis and median survival of < 1 year.[1,5] An additional 5% of cases have rhabdoid morphology, another variant associated with metastasis and poor outcome.[5]

The present case study concerns a patient with clinical T1a disease, two synchronous brain metastases, and lung metastasis from a 1.6 cm primary. As such, the metastatic focus was re-examined for sarcomatoid and rhabdoid features. There was no evidence of either pathology, and it garnered a Fuhrman 3 grading. As a caveat, bipolar cautery limited adequacy of the sample for interpretation of nuclear characteristics, and more importantly, the Fuhrman grade of a metastasis cannot be extrapolated to a primary. This is illustrated in a recent study of 378 patients where metastasis and primary Fuhrman grade matched only 38.8% of the time.[6] Furthermore, it remains unknown if the primary tumor contains a sarcomatoid or rhabdoid component. However, extra immunohistochemical staining has definitively confirmed the metastatic focus as clear cell RCC, Figure 3.

This case highlights that a renal lesion may be identified during work up for a brain tumor. It should be considered as a possible primary with the overall likelihood 3%-11%, which historically was heavily dependent on the size of the renal mass.[7] Overall, one

third of RCC presents with synchronous metastasis, but to our knowledge no report describes a primary smaller than 7 cm.[1,7,8] As described previously, the 1.6 cm size of the primary in the present report afforded a 0.1% chance of metastasis at any point during the disease course, and is furthermore remarkable as a synchronous metastasis.

Ten year survival for all RCC patients with metastasis at any time is < 5%, and absence of prior nephrectomy is actually linked to worse cancer specific survival. Metastasectomy improves outcomes with best results when metachronous metastasis occurs > 1 year after nephrectomy.[1,8] Other favorable factors include age < 60, solitary metastasis, and tumor size < 4 cm.[1] For medical therapy, poor characteristics include brain as a metastatic site as well as synchronous and multiple lesions.[9,10] Specifically, 148 patients who received adjuvant immunotherapy reported median survival for synchronous versus metachronous metastasis as 17.1 months versus 58.4 months respectively ($p = 0.019$) and for solitary versus multiple metastasis as 55.2 months versus 15.6 months ($p < 0.001$).[10]

As outlined by the factors above, the present patient's overall benefit from metastasectomy and medical therapy is likely reduced. In addition, the small contribution of his primary tumor to the overall disease burden likely decreases the benefit from cytoreductive nephrectomy. IL-2 is a therapeutic treatment option typically reserved for younger, asymptomatic patients with excellent performance status and absent or controlled brain metastases. In this case, the safe administration of any systemic therapy, including tyrosine kinase and mTOR inhibitors, is precluded by the patient's significant decline in cognitive functioning as well as age, comorbidities, and noncompliance.

Conclusion

In conclusion, the present case report documents for the first time a synchronous brain metastasis from an RCC primary < 7 cm. Notably, the primary in this case was only 1.6 cm, or clinical stage T1a disease. □

References

1. Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia: Saunders Elsevier. 2011:1436,1475-1495.
2. Thompson RH, Hill JR, Babayev Y et al. Metastatic renal cell carcinoma risk according to tumor size. *J Urol* 2009;182(1):41-45.
3. Kunkle DA, Crispen PL, Li T, Uzzo RG. Tumor size predicts synchronous metastatic renal cell carcinoma: implications for surveillance of small renal masses. *J Urol* 2007;177(5):1692-1696.
4. Klatte T, Patard JJ, de Martino M et al. Tumor size does not predict risk of metastatic disease or prognosis of small renal cell carcinomas. *J Urol* 2008;179(5):1719-1726.
5. Aydin H, Zhou M. The changing face of renal cell carcinoma pathology. *Curr Oncol Rep* 2008;10(3):235-244.
6. Abel EJ, Carrasco A, Culp SH et al. Limitations of preoperative biopsy in patients with metastatic renal cell carcinoma: comparison to surgical pathology in 405 cases. *BJU Int* 2012; 110(11):1742-1746.
7. Taxy JB. Renal adenocarcinoma presenting as a solitary metastasis: contribution of electron microscopy to diagnosis. *Cancer* 1981;48(9):2056-2062.
8. Candiano G, Pepe P, Grasso G, Aragona F. Headache: a unique clinical presentation for renal cell carcinoma (RCC). *Arch Ital Urol Androl* 2010;82(4):184-186.
9. Gore ME, Hariharan S, Porta C et al. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. *Cancer* 2011; 117(3):501-509.
10. Kwak C, Park YH, Jeong CW, Jeong H, Lee SE, Ku JH. Characteristics of metastasis as a prognostic factor for immunotherapy in metastatic renal cell carcinoma. *Tumori* 2007; 93(1):68-74.