Metastatic Renal Cell Carcinoma to the Brain: A Contemporary Clinicopathologic Analysis With Comparison of Immunohistochemical Profiles to Selected Primary Brain Tumors With Clear Cell Features

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Abstract: Brain metastases from renal cell carcinoma (RCC) are associated with significant morbidity and mortality. However, there are only few large series in the pathology literature specifically analyzing the clinicopathologic and immunohistochemical features in comparison with primary brain tumors with clear cell features. We identified 34 cases of metastatic RCC to the brain from the Urologic Pathology and Neuropathology files of 2 institutions between 2000 and 2018. Mean patient age at diagnosis of primary RCC was 59 years (range: 37 to 82 y). The mean size of 34 primary RCC was 7.9 cm (range: 2.5 to 19.5 cm). Twenty of 34 (59%) cases of brain metastases had primary RCC categorized as pT3. Brain imaging showed a solitary, well circumscribed, enhancing lesion in 18 of 34 (53%) patients and multifocal lesions in 16 of 34 (47%) patients. The mean size of metastatic RCC to the brain was 2.3 cm (range: 0.3 to 5.5 cm). Fifteen of 34 (44%) cases had isolated brain metastases and 19 of 34 (56%) cases had concomitant extracerebral metastases. The histologic subtypes were clear cell RCC 29 of 34 (85%) cases, RCC unclassified 4 of 34 (12%) cases, and papillary RCC 1 of 34 (3%) cases. We also included primary brain tumors with clear cell features including hemangioblastoma (30 cases), microcystic meningioma (11 cases), and clear cell meningioma (3 cases). The utility of an immunohistochemical panel that includes PAX8, carbonic anhydrase IX, SST2Ra, and inhibin is very useful in the distinction of these entities in a subset of patients.

Key Words: renal cell carcinoma, brain metastasis, synchronous, metachronous, anatomic distribution, latency, clear cell, hemangioblastoma, meningioma immunohistochemistry

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MATERIALS AND METHODS

A search was made through a bi-institutional electronic database of Urologic Pathology and Neuropathology files and consult cases for patients with metastatic RCC to the brain from 2000 to 2018. Hematoxylin and eosin (H&E)-stained sections and available immunohistochemical stains of each case were reviewed and the original diagnosis was confirmed. Patient demographics, clinical presentations, tumor radiologic features, location, focality, and size of primary RCC and brain metastases were obtained. Brain metastasis was subclassified into 2 categories (synchronous and metachronous) based on the period elapsed between the
primary RCC diagnosis and the emergence of detectable metastatic brain lesions. Synchronous brain metastasis was defined as metastases <3 months following the initial RCC diagnosis while metachronous brain metastasis was beyond 3 months of the primary diagnosis of RCC. In addition, primary brain tumors that are mimickers of clear cell RCC (hemangioblastoma: 30 cases, microcystic meningioma: 11 cases, and clear cell meningioma: 3 cases) were included in the study for comparison of immunohistochemical profiles. This study was completed following the guidelines of and with approval from Institutional Review Boards of our institutions.

RESULTS
Search of databases retrieved 1752 nephrectomy (radical and partial) cases and 342 metastatic RCC cases, and identified 34 patients with brain metastasis. Twenty-nine cases were from the routine surgical pathology/neuropathology services and 5 cases were from the expert consultation services. All brain metastasis cases were tumor biopsy or resection specimens.

Patient Demographics
Demographically, all 34 patients with brain metastasis were adults at time of primary RCC diagnosis with a mean age of 59 years (range: 37 to 82 y). There were 20 (59%) male patients and 14 (41%) female patients. There were 18 white patients, 14 African American patients, and 2 Asian patients. All primary tumors were unilateral with 19 (54%) right-sided and 15 (44%) left-sided. The metastatic RCCs in brain were 18 (53%) right-sided, 14 (41%) left-sided, and 2 (6%) bilateral.

Tumor Staging of Primary RCC
Twenty-two patients had undergone radical or partial nephrectomy. The mean size of primary RCCs was 7.9 cm (range: 2.5 to 19.5 cm). One of 34 (3%) cases was categorized as pT1a; 20 of 34 (59%) cases were categorized as pT3 with 18 cases of pT3a and 2 cases as pT3b; 1 of 34 (3%) cases was categorized as pT4a; 12 of 34 (35%) cases were diagnosed in the setting of biopsies. The final pathologic nodal status (pN) distribution of the 34 cases is as follows: 9 of 34 (26%) cases were without nodal metastasis (pN0) and 25 of 34 (74%) cases did not have lymph node status available (pNx). The metastatic status of primary RCC at diagnosis is as follows: 7 of 34 (21%) cases had no distant metastasis (M0); 12 of 34 (35%) had tumor spread to other organs (M1), and 15 of 34 (44%) had unknown metastatic status (Mx).

Brain Metastasis Characteristics
Ten of 34 (29%) cases had synchronous brain metastases at primary RCC diagnosis, whereas 24 of 34 (71%) cases developed brain metastases after initial diagnosis with a time interval of 39 months (range: 4 to 300 mo). In synchronous brain metastases, 9 of 10 (90%) patients had brain metastasis at initial diagnosis of primary RCC and 1 of 10 (10%) of patients had brain metastasis diagnosed at 2 months of initial diagnosis. In metachronous brain metastasis, 8 of 24 (33%) patients had brain metastasis within <1 year, 5 of 24 (21%) patients had brain metastasis within 1 to 3 years, 5 of 24 (21%) patients had brain metastasis within 3 to 7 years, 2 of 24 (8%) patients had brain metastasis within 7 to 10 years of, and 3 of 24 (13%) patients had brain metastasis >10 years after initial diagnosis. The longest metastatic latency period was 25 years.

Clinically, the majority of patients 27 of 34 (79%) were symptomatic at diagnosis of brain metastasis with the most common symptoms being headache, ataxia, and confusion. Motor deficits were present in 19 of 34 (56%) patients, sensory deficits were present in 12 patients, aphasia in 6 patients, visual impairment in 12 patients, cerebellar ataxia in 3 patients, and frontal lobe disorder in 3 patients. All patients had a magnetic resonance imaging performed, which showed a solitary, well circumscribed, enhancing lesion in 18 of 34 (53%) patients (Fig. 1A) and multifocal lesions in 16 of 34 (47%) patients. Three patients had spontaneous intratumoral hemorrhage and 10 patients had peritumoral edema. The mean size of the metastatic RCCs to the brain was 2.3 cm (range: 0.3 to 5.5 cm). Regional distribution of brain metastases of RCC was as follows: frontal lobe (27%) and parietal lobe (27%), temporal (18%), cerebellum (9%), occipital (3%), pontine (3%), pineal (3%), basal ganglia (3%), and periventricular area (6%). For synchronous brain metastases, 8 of 10 (80%) lesions presented as a solitary mass located in the frontal, temporal, or parietal lobe.

For metachronous metastases with a latency beyond 7 years, 4 of 5 (80%) lesions presented as a solitary mass in periventricular areas including septum pellucidum, third ventricle, pineal space, and basal ganglia. Other metachronous brain metastases were either solitary or multifocal with no significant distribution patterns. Fifteen of 34 (44%) cases had isolated brain metastases and 19 of 34 (56%) cases had concomitant extracerebral metastases. The most common extracerebral sites were lung 11 of 19 (58%) cases and bone 3 of 19 (16%). Other extracerebral metastases included ipsilateral adrenal gland, liver, pancreas, retroperitoneum, and thyroid. Most patients with a solitary lesion had a craniotomy while patients with >1 lesion received radiosurgery. Eleven (32%) patients received systemic chemotherapy.

Microscopic Features of Metastatic RCC to Brain and Immunohistochemical Distinction From Primary Brain Tumor Mimickers
Histopathologic examination of the brain lesions showed metastatic carcinoma involving the brain parenchyma, and extended to the leptomeninges and dura in some cases. The histologic subtypes were clear cell RCC 29 of 34 (85%) cases, including 4 (12%) cases of clear cell RCC with sarcomatoid differentiation, papillary RCC 1 of 34 (3%) cases, and RCC unclassified 4 of 34 (12%) cases. Most cases were WHO/ISUP grade 3 (71%) or 4 (26%). Metastatic clear cell RCC often exhibited solid nests of clear cells with vacuolated cytoplasm separated by a prominent delicate vascular network (Figs. 1B, C [primary], D). However, these morphologic features are often nonspecific and also raise differential diagnosis of other metastatic malignancies such as clear cell melanoma as well as primary brain tumors such as
FIGURE 1. A, MRI imaging of synchronous brain metastasis of conventional clear cell RCC showing an enhancing mass centered in the anterior left temporal lobe with significant surrounding edema and local mass effect. B, Microscopic correlate of (A), metastatic clear cell RCC with adjacent brain tissue (×200). C, Corresponding primary clear cell RCC with adjacent renal parenchyma. D, Metastatic clear cell RCC with adjacent brain tissue (×400). E, Metastatic clear cell RCC with sarcomatoid differentiation and adjacent brain tissue (×200). F, Corresponding primary clear cell RCC with sarcomatoid differentiation and adjacent renal parenchyma. G, Metastatic clear cell RCC with sarcomatoid differentiation and adjacent brain tissue (×400). H, Metastatic papillary RCC with blood, fibrin, and adjacent brain tissue (×200). I, Corresponding primary papillary RCC and adjacent renal parenchyma. J, Metastatic papillary RCC (×400). MRI indicates magnetic resonance imaging; RCC, renal cell carcinoma.
hemangioblastoma, microcystic and clear cell meningiomas, oligodendrogliomas, and less commonly clear cell ependymoma and central neurocytoma. Metastatic clear cell RCC with sarcomatoid differentiation typically displayed hypercellular spindle cells with marked nuclear pleomorphism, increased mitotic figures and tumor necrosis (Figs. 1E, F [primary], G). Metastatic papillary RCC showed prominent papillary architecture with pseudostratified cells, abundant eosinophilic to occasionally clear cytoplasm, atypical nuclei, and prominent nucleoli (Figs. 1H, I [primary], J). Confirmation of the diagnosis by immunohistochemical stains is essential in challenging cases, to ensure the appropriate therapeutic strategy. Expression of cytokeratin, PAX2, PAX8, CK7, carbonic anhydrase IX (CAIX), P504S, CD10 were utilized in a subset of cases to confirm a diagnosis of metastatic RCC (Figs. 2A–C). Somatostatin receptor 2a (SSTR2a), CAIX, and inhibin were also performed in some cases, to exclude a primary brain tumor with clear cell features (Table 1 and Figs. 3A–5C).

**DISCUSSION**

This study represents one of the largest contemporary studies to date on the clinicopathologic findings of patients with metastatic RCC to the brain. In this case cohort, brain metastasis occurred in ~10% (34/342 cases) of patients with metastatic RCC. This rate is within the reported range of 6% to 10%.5–8 Demographically, all 34 patients with brain metastasis were adults at time of primary RCC diagnosis with a mean age of 59 years (range: 37 to 82 y). There were no significant sex, race, or laterality predominance identified for brain metastasis of RCC. Metastatic clear cell RCC was the most common subtype of RCC (85%), followed by RCC unclassified (12%), and papillary RCC (3%). Approximately one-third of patients

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>SSTR2a</th>
<th>CAIX</th>
<th>PAX8</th>
<th>Inhibin</th>
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<tbody>
<tr>
<td>Metastatic CCRCC (18)</td>
<td>0</td>
<td>18 (100)</td>
<td>18 (100)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Hemangioblastoma (30)</td>
<td>0</td>
<td>30 (100)</td>
<td>0</td>
<td>26 (87)</td>
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<tr>
<td>Microcystic meningioma (11)</td>
<td>10 (91)</td>
<td>9 (82)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clear cell meningioma (3)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
</tr>
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CAIX indicates carbonic anhydrase IX; CCRCC, clear cell renal cell carcinoma; SSTR2a, somatostatin receptor 2a.
had synchronous brain metastases at primary RCC diagnosis, whereas two-thirds of patients developed brain metastases after initial diagnosis with a median time interval of 39 months (range: 4 to 300 mo). The longest brain metastatic latency of RCC in this study was 25 years after nephrectomy. To our knowledge, this is one of the longest latency periods that has been reported so far in the literature. Clinically, at the time of the diagnosis, the majority of patients (27/34, 79%) were symptomatic at diagnosis of brain metastasis with the most common symptoms being headache, ataxia, and confusion. The majority of brain metastases had the primary RCC categorized as pT3. The lymph node status of primary RCC does not predict the likelihood of brain metastasis, because all cases with available lymph nodes were categorized as pN0. Pattern comparison between synchronous and metachronous brain metastases revealed that a substantial number of synchronous metastases and metachronous metastases having a long latency (> 7 y) tended to present as a solitary brain mass, but they exhibited different anatomic distributions. Synchronous metastases were predominantly located in the frontal, temporal or parietal lobes, while metachronous metastases with a latency > 7 years were mainly distributed in periventricular areas including septum pellucidum, third ventricle, pineal space, and basal ganglia.

The distinct anatomic distribution patterns of early and late brain metastasis appear to suggest 2 different hematogenous metastatic pathways. Cava-type spread through the lung and a backward paravertebral venous spread through the vertebrae have been proposed to explain the spread of prostate cancer to the brain.9 This mechanism may also explain the different latency periods of brain metastasis of clear cell RCC with sarcomatoid differentiation, which is one of the most aggressive clinicopathologic phenotypes of RCC. All cases of clear cell RCC with sarcomatoid differentiation in this study had multiple concomitant lung or bone metastases at diagnosis of brain metastasis. However, the hypothesis appears to be of less significance in the explanation of brain metastases of conventional clear cell RCC and its long latency because a substantial number of synchronous brain metastases and metachronous brain metastases with long latency in this study were an isolated brain mass with no

concomitant lung or bone metastases. All 3 delayed brain metastatic cases with latency >10 years in this study were conventional clear cell RCC and had primary tumor categorized as pT3, and 1 of the cases had renal vein involvement. Although the pathobiology of late brain metastasis is poorly understood, the long latency appears to be attributed to the indolent behavior of some special subsets of clear cell RCC, whose circulating tumor cells or tumor stem cells may have lower ability to disseminate and slowly home to the brain.10

Future molecular studies including gene expression profiling of these tumors may play a role in unraveling the metastatic mechanisms, and accurately predict the likelihood of patients who are at increased risk of developing brain metastasis. Irrespective of the unclear metastatic pathways and pathobiology, our findings have several significant implications for both clinicians and pathologists. First, it is important for clinicians to be aware that a solitary brain mass on imaging does not exclude metastatic RCC in a patient with a remote history of RCC, which should always be included in the differential diagnosis of brain tumors, especially in the setting of very long disease-free survival following nephrectomy. Furthermore, a solitary metastatic RCC to the brain may appear very similar radiologically to a primary brain tumor. Therefore, a complete histopathologic and immunophenotypic assessment of the lesion in challenging cases following biopsy or excision is essential to avoid potential diagnostic pitfalls. Although different histologic subtypes of RCC were found to metastasize to brain in this study, conventional clear cell RCC was the most common (73%), and often exhibited solid nests of clear cells with vacuolated cytoplasm separated by a prominent delicate vascular network. However, these morphologic features are often nonspecific and depending on the anatomic location may raise the differential diagnoses of hemangioblastoma, microcystic and clear cell meningioma, and other mimickers with a clear cell phenotype.11,12

To aid the histopathologic distinction of primary and metastatic clear cell neoplasms involving the brain, an immunohistochemical panel that includes SST2Ra, PAX8, CAIX, and inhibin was performed in a subset of patients in this cohort (Table 1). In a study of 62 cases addressing the
immunoprofile of brain tumors with a clear cell phenotype that included 18 cases of metastatic clear cell RCC, we found that SSTR2a immunoreactivity is highly sensitive and specific for meningioma, including variants with clear cell features (both clear cell and microcystic meningioma subtypes). Recently, SSTR2a has arisen as the most sensitive meningioma marker.2,14 PAX8 and inhibin were sensitive and specific for metastatic clear cell RCC and hemangioblastoma, respectively. CAIX strongly and diffusely labeled all metastatic clear cell RCCs, hemangioblastomas, most microcystic meningiomas, and a small proportion of clear cell meningiomas, limiting its use in differentiating among brain tumors with a clear cell phenotype.13 Others have noted similar expression patterns with CAIX immunohistochemistry.15,16

Although papillary RCC is the second most common type of RCC, it tends to metastasize to lymph nodes and liver. Metastasis to the brain is very rare.17 In our case cohort, a single case of brain metastasis of papillary RCC was also identified. The case was in a 47-year-old Asian male with a 5.8 cm, left occipital brain mass.Clinically, the patient complained of constant headache and transient visual obscuration for ~2 to 3 months. He had a past history of papillary RCC of the left kidney and underwent a left radical nephrectomy and adrenalectomy 5 years before the brain symptoms. He was found to have metastatic disease in his liver and lungs, and received chemotherapy 2 years following the initial diagnosis of RCC. Magnetic resonance imaging revealed a left occipital homogeneously enhancing mass concerning for metastatic spread to the brain, which was excised. Histopathologic examination of the tumor revealed a prominent papillary configuration. The tumor cells had eosinophilic cytoplasm and prominent nucleoli. The morphologic and immunohistochemical findings were consistent with metastatic papillary RCC, type 2 subtype. Other tumors with papillary features such as collecting duct carcinoma, FH-deficient RCC, translocation-associated RCC, etc. were excluded.

In conclusion, metastatic RCC should always be included in the differential diagnosis of brain tumors in the setting of a solitary brain mass in patients with a remote clinical history of RCC. Conventional clear cell RCC is the most common variant of RCC to metastasize to the brain, and may have similar morphologic features as primary brain tumors with clear cell features. Both clinicians and pathologists should

FIGURE 5. A, Clear cell meningioma (hematoxylin and eosin, ×100). B, Negative expression of carbonic anhydrase IX in clear cell meningioma. C, Negative expression of PAX8 in clear cell meningioma.
be aware that late brain metastases may occur, even decades after the initial diagnosis of RCC. A complete histopathologic and immunophenotypic assessment of the brain lesion following biopsy or excision is essential to avoid potential diagnostic pitfalls.

REFERENCES