Metastatic renal cell carcinoma, with a radiographically occult primary tumor, presenting in the operative site of a thoracic meningioma: long-term follow-up

Case report

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Lesions metastatic to the site of a meningioma resection from a different primary tumor are rare. Metastasis of a tumor without a known primary tumor is also rare. Metastasis of a renal cell carcinoma, without an identifiable primary tumor, to the bed of a meningioma resection has not been previously reported.

The authors describe the case of a 54-year-old man who presented with decreased sensory and motor function in the lower extremities. He underwent T3–5 laminectomies and gross-total removal of an intradural, extramedullary meningioma. The postoperative course was uneventful, and the patient regained full neurological function. After a 3-year period, he developed progressive upper thoracic pain and lower-extremity paresthesias. Imaging studies showed an epidural mass at the T2–4 levels and what appeared to be blastic involvement of the T2–4 vertebrae. A metastatic workup was negative. Emergency revision laminectomies yielded a fibrous, nonvascular mass. Neuropathology was consistent with metastatic renal cell carcinoma. After 6 months, the patient’s symptoms of pain and paresthesias recurred. Repeat excision, with decompression of the spinal cord, revealed tumor cells morphologically and immunophenotypically similar to those obtained from the prior surgery. Cytogenetic analysis confirmed the presence of metastatic renal cell carcinoma.

A novel case of an epidural metastatic renal cell carcinoma, of unknown primary origin, in the same operative bed of a previously resected intradural, extramedullary meningioma of the thoracic spine is reported. (http://thejns.org/doi/abs/10.3171/2014.6.SPINE13448)

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Notably, location may also affect the rate of recurrence. Recurrence rates for spinal meningiomas are reportedly lower than those for intracranial meningiomas. According to McGovern et al., certain locations may also facilitate the recurrent growth of a higher-grade meningioma. Local postoperative tumor recurrence is well described in all realms of surgical oncology. Much less common is the growth of a completely different type of tumor in the same surgical bed. This differs fundamentally from the concept of local tumor recurrence. Such a phenomenon raises many questions including the following: the accuracy of the index pathological and radiological findings, the prospect of a mixed tumor, and the possibility that the characteristics of an operative wound augment susceptibility to metastatic seeding.

When a metastatic lesion is discovered, it is essential to search for the primary tumor. This is the case even if

Abbreviations used in this paper: EMA = epithelial membrane antigen; RCC = renal cell carcinoma.
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the new lesion arose from the same operative bed. According to the National Cancer Institute, cancers with unknown primary tumor sites account for approximately 2%-4% of all cancers. These instances of unknown primary tumor site have been reported for several cancers including squamous cell carcinoma, metastatic thoracic lymph node carcinoma, and right atrial metastatic melanoma. This phenomenon can profoundly affect the preoperative and postoperative treatment decisions.

Overall, this case report serves to represent the first known documented case of an epidural metastatic renal cell carcinoma (RCC), with an undetectable primary tumor, landing in the same operative site as a previously resected meningioma of the thoracic spine.

Case Report

Presentation and History. A 54-year-old man presented with progressive bilateral lower-extremity weakness (Grade 3–4/5) and diminished sensation below T-4. He had a history of hypertension and a completely resected benign thyroid nodule 32 years prior.

Examination. The patient had no myelopathic signs, and bowel and bladder functions were intact. Magnetic resonance imaging showed a large right-sided intradural, extramedullary mass lesion occupying approximately 80% of the spinal canal at the level of T-4 (Fig. 1).

Operation. The patient underwent T3–5 laminectomies. The tumor was dissected free from its lateral attachment to the right T-4 dura, and a gross-total removal of the tumor was accomplished. A water-tight dural repair was achieved.

Histopathological Findings. Histological examination depicted a benign transitional meningioma with meningothelial and fibroblastic appearances (Fig. 2A). Tumor cells reacted positively with immunohistochemical stains for epithelial membrane antigen (EMA) but not for SI00. The final neuropathological diagnosis was a meningioma (WHO Grade 1).

Postoperative Course. Postoperatively, the patient did well, experiencing a return of normal motor and sensory functions by 6 weeks. No postoperative adjuvant therapy (radio- or chemotherapy) was used.

Second Presentation and Examination. Following an uneventful 3-year period, the patient presented with progressive upper thoracic pain and paresthesias at the T-4 level. He had preserved motor function, as well as bladder and bowel functions. Magnetic resonance imaging revealed a hypointense, heterogeneously enhancing epidural mass in the spinal canal at T2–4, extending into the associated neural foramen bilaterally (Fig. 3). There was also enhancement in the T2–4 vertebral bodies. A CT scan demonstrated sclerotic or blastic changes, without destruction of the bony architecture, at the involved levels (Fig. 4). Contrast-enhanced CT scanning of the chest, abdomen, and pelvis did not demonstrate any evidence of a primary lesion or lymphadenopathy. However, the CT scans did reveal the presence of a 9 x 9-mm central nodule within the left adrenal gland, likely an adenoma. Moreover, a 1.5-cm, nonenhancing cyst was revealed within the lower pole of the right kidney along with multiple, subcentimeter, low-density, nonenhancing cystic lesions within both kidneys consistent with renal cysts. A urinalysis was negative and prostate-specific antigen was within normal limits.

Second Operation. At this juncture, with no primary lesion having been detected, the patient underwent a laminectomy of T-2 and revision T3–5 laminectomies. The epidural tumor, which had minimal vascularity, was subtotally resected. Of note, all bony structures that were visible from this posterior approach appeared grossly to be normal. Once again, the patient’s neurological status normalized postoperatively.

Histopathological Findings. Histological findings were consistent with metastatic carcinoma. There were regions with an epithelial appearance; furthermore, tumor cell nuclei had large, prominent, occasionally multiple nucleoli, with moderately copious cytoplasm (Fig. 2B). Immunohistochemistry revealed tumors cells that reacted positively with antibodies to EMA, vimentin, cytokeratins AE1/AE3, CD10, PAX-8 and RCC antigen (Fig. 2C and D). Furthermore, various other primary sites, including the lungs, gastrointestinal tract, and thyroid, as well as squamous cell carcinoma, were ruled out based in part on negative reactions with antibodies to CD31; CD34; cytokeratins 7, 20, 19, and 5–6; the melanoma marker HMB-45; TTF-1; p63; and the TFE-3 immunostain. As such, immunohistochemistry ruled out the recurrence of any meningioma or mixed tumor. To ensure a correct diagnosis, a second opinion was obtained from a neuropathologist at an independent institution as well. The pathological diagnosis was confirmed as an epidural metastatic RCC.

Given the lack of evidence for a primary tumor on contrast-enhanced CT scans, PET scans were obtained. These scans did not demonstrate uptake in the kidneys or adrenal glands to suggest the presence of a primary tumor. Radiographically, a primary tumor could not be detected.

Third Operation and Postoperative Course. After 6 months, the patient’s symptoms of pain and paresthesias recurred. Recurrence of the tumor with spinal cord compression demonstrated on MRI warranted an additional decompressive surgery. A fusion was performed to prevent postoperative vertebral instability, following a significant resection of bone, including partial facetectomies (Fig. 4). Pathological examination of the resected tumor was compatible with a primary renal origin. Tissue sections were morphologically and immunophenotypically similar to those obtained from the previous resection. Cytogenetic analysis yielded a male karyotype with an additional chromosome 7 and a loss of chromosome Y. The final diagnosis was an epidural metastatic RCC with an undetectable primary origin.

The patient lived an additional 6 months following this third surgery before ultimately succumbing to diffuse metastatic cancer. No further surgical procedures had been performed and no adjuvant treatment had been administered following this final surgery.
Discussion

The rarity of a new tumor in the same operative site as a previously resected tumor is evident, but unfamiliarity may lead to an increase in misdiagnoses. Treatment options and prognosis can drastically change based on whether the diagnosis is a benign meningioma or a metastatic tumor. As Tagle et al. suggested, the ability to efficiently diagnose a meningioma versus a metastasis can have profound prognostic relevance.23

Fig. 1. Preoperative Gd-enhanced MR images. Sagittal (left) and axial (right) images showing a large right-sided intradural extramedullary mass lesion, consistent with a meningioma, at the level of T-4. No blastic or lytic changes were observed in the vertebrae.

Fig. 2. A: Classical appearance of a WHO Grade I meningioma. H & E, original magnification ×200. B: Malignant neoplasm with epithelial appearance, large nuclei with prominent and occasionally multiple nucleoli, and abundant cytoplasm. H & E, original magnification ×200. C: Immunohistochemistry showing nuclear reactivity of the neoplastic cells with a PAX-8 antibody. Original magnification ×100. D: Immunohistochemistry showing cytoplasmic reactivity of the neoplastic cells with an RCC antibody. Original magnification ×100.
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In general, a thoracic meningioma is usually a benign tumor originating in the spinal meninges. Spinal meningiomas can be found in intradural, epidural, or in both intradural and epidural locations. Case reports have also documented tumors having both intradural and epidural components without an obvious dural breach. In the present report, the initial tumor, a benign meningioma, was intradural and extramedullary. Advanced imaging scans revealed typical characteristics of a meningioma. Pathological evaluation of the tumor revealed that the meningioma was classified as Grade I, benign and noncancerous, reacting positively with EMA, but not S-100. Schnitt and Vogel demonstrated that EMA immunoreactivity is a characteristic feature of meningiomas, while positive reaction with S-100 was an indicator of schwannomas.

As a result of the detection of a new lesion following a 3-year symptom-free interval, the presence of epidural tumor led to a metastatic workup. No primary lesion was detected. Subtotal resection to decompress the cord led to marked resolution of symptoms. Neuropathological examination ruled out meningioma, and the diagnosis of metastatic RCC was made. However, this tumor exhibited numerous characteristics that were very atypical of RCC: 1) the tumor was relatively avascular; 2) contrast-enhanced CT scans of the chest, abdomen, and pelvis were negative; 3) a PET scan was negative; 4) sclerotic or blastic changes, not present 3 years earlier, were observed in the T2–4 vertebrae; and 5) a urinalysis was negative. Furthermore, prostate-specific antigen was within normal limits.

As a result of the tumor recurrence after the gross-total excision of the original intradural meningioma, the possibility of a meningioma recurrence with epidural components was considered. With MRI demonstrating an extradural lesion, with heterogeneous enhancement that was not consistent with the previous meningioma, recurrent meningioma was placed low on the differential diagnosis. As a result of appreciable mass effect on the spinal

![Fig. 3. Sagittal (left) and axial (right) MR images revealing a hypointense, heterogeneously enhancing epidural mass in the spinal canal at the T2–4 levels, extending into the associated neural foramina bilaterally.](image)

![Fig. 4. A: At the time of the initial surgery, a CT scan demonstrated no sclerotic or blastic changes. B: Three years later, a preoperative CT scan demonstrated sclerotic or blastic changes, without destruction of the bony architecture, at the associated levels. C: Postoperative CT scan acquired after the third surgery.](image)
cord, the second decompressive surgery was performed to alleviate the neurological symptoms.

Pathological evaluation of the resected tissue included immunohistochemistry testing, which revealed tumor cells that reacted positively with antibodies toEMA, possibly indicative of meningioma; however, positive reactions with cytokeratins AE1/AE3, CD10, RCC, and PAX-8 indicated an immunoprofile that was most consistent with a metastatic lesion arising from the kidney. Furthermore, various other primary sites, including the lungs, gastrointestinal tract, and thyroid, as well as squamous cell carcinoma, were able to be ruled out based in part on negative reactions with an assortment of antibodies. As such, immunohistochemistry ruled out the recurrence of any meningioma or mixed tumor. These findings are significant because several case reports have demonstrated the recurrence of meningiomas or even a metastasis of RCC to a spinal meningioma. In each prior case report involving metastatic RCCs and meningiomas, a primary lesion was able to be detected in the kidney. In the case presented here, the pathological evaluation confirmed the diagnosis of an epidural metastatic RCC.

Cytogenetic analysis was performed to corroborate the neuropathological and radiological findings. Cytogenetics yielded a male karyotype with an additional chromosome 7 and a loss of chromosome Y. Trisomy 7 and the loss of chromosome Y are frequently seen in papillary RCCs. These results are consistent with the presence of metastatic RCC in the epidural region.

The etiology of tumor recurrence following resection has been proposed as a direct inoculation of the wound by exfoliated cancer cells, hematogenous seeding, or traumatization of tissues. As such, tumor recurrence in the same operative site is an anticipated phenomenon; however, such is not the case for a lesion from a novel cell type. Rosenthal et al. reported a case of metastatic brain adenocarcinoma growing in the surgical site of a completely resected hemangioblastoma. In meningiomas that host metastatic cancer, the highly vascular architecture of meningiomas have been implicated in the facilitation of seeding. In a similar fashion, changes in the microvasculature induced by resection are thought to also facilitate seeding of metastatic cells. Disruption of the blood-brain barrier by surgery increased mitotic ability induced by a previous lesion and immunological changes induced by a previous tumor have all been proposed as etiologies for the seeding of a metastatic tumor in an operative bed.

While the seeding of metastatic tumor in the site of a resection is rare, the inability to detect a primary tumor represents the novelty of this case. The authors of most published cases of tumors report a readily identifiable primary tumor; however, in our patient’s case, a primary tumor for the metastatic RCC was undetectable using numerous radiological examinations. Though observed in only 2%–4% of all cancers, metastatic lesions with an unknown primary tumor have been cited. Proposed etiologies indicate that the primary site may either have a slow growth rate or it may involute, thereby revealing only an “invisible” primary.

Treatment options for meningiomas, even recurrences, differ widely from recommended therapy options for metastatic RCC. Preferably, meningiomas are treated by a complete or maximal resection; however, radiation may be delivered in cases of recurrent growth. In contrast, RCC demonstrates resistance to radio- and chemotherapy. Conventional cytotoxic chemotherapy agents and hormonal treatments have not significantly improved the prognosis of patients with metastatic RCC. Unfortunately, as observed in the present case, metastatic lesions of an unknown primary origin have historically been treated with chemotherapy, but RCCs show resistance to chemotherapy. Still, some studies have demonstrated that spinal radiosurgery can be a successful therapeutic modality for the delivery of large-dose single-fraction irradiation to RCC spinal metastases that are often poorly controlled with conventional external-beam radiation therapy modalities. In the case presented, the metastatic tumor displaced the spinal cord, making radiosurgery not feasible.

Conclusions

This report demonstrates a novel case of a patient with a metastatic RCC, with an undetectable primary origin, found at the operative site of a resected thoracic meningioma. Although most published cases of metastatic cancer report a readily identifiable primary tumor, in this case report, a primary tumor was radiographically undetectable. Moreover, the shift of tumor location from intradural meningioma to epidural metastatic RCC augments the novelty of this case. Ultimately, the ability to recognize an aberrant clinical presentation of new tumor growth, after a resection, can have an appreciable impact on overall patient care.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Heary, Agarwal. Acquisition of data: Heary, Agarwal. Analysis and interpretation of data: Heary, Agarwal, Barry, Baisre. Drafting the article: Heary, Agarwal, Baisre. Critically revising the article: all authors. Statistical analysis: Heary. Administrative/technical/material support: Heary. Study supervision: Heary.

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