case reports

Renal Cell Carcinoma With Urinary Bladder Metastasis: A Case Report With Metachronous Genomic Analyses

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BACKGROUND

Renal cell carcinoma (RCC) is among the most frequently diagnosed malignancies in the United States, with an estimated annual incidence of more than 73,000 new cases in 2020.[1] Nearly one in three of patients with RCC has metastatic disease at diagnosis, and another one in four of patients with localized RCC will go on to develop metastatic disease.[2,3] RCC tends to metastasize to a variety of distant organs, the most common of which are the lungs, bones, and lymph nodes.[4,5] We report a rare case of RCC with metachronous metastasis to the bladder after cytoreductive nephrectomy and systemic immunotherapy.

CASE PRESENTATION

An 83-year-old man with no past medical history presented with a complaint of hematuria for one month. Computed tomography (CT) urogram revealed a 4.6 × 8.1 cm left renal and collecting system mass. Chest CT showed multiple bilateral lung nodules suspicious for pulmonary metastasis, the largest of which measured 14 mm in size. Nuclear medicine bone scan was negative for metastasis. Kidney biopsy confirmed clear cell RCC with sarcomatoid features that extended to the perinephric fat and renal pelvis. GEM ExTra, a Clinical Laboratory Improvement Amendments–certified next-generation sequencing tumor or normal exome and tumor RNA sequencing assay, exhibited a frameshift deletion in von Hippel-Lindau (*VHL*) tumor suppressor (Y112fs) and a stop gain alteration in polybromo 1 (*PBRM1*).

The patient underwent a robotically assisted cytoreductive nephrectomy after which he began treatment with the immune checkpoint inhibitors (ICIs) nivolumab and ipilimumab. Imaging after 3 months on therapy showed regression of his pulmonary tumors, and the patient continued with nivolumab maintenance therapy. Three months later, the patient was noted to have interval increase in the size of his mediastinal nodes, but an apparent decrease in the size of multiple pulmonary nodules and therefore remained on nivolumab.

After 14 months on systemic therapy, the patient presented to the emergency room with gross hematuria and failure to thrive. CT of the abdomen and pelvis revealed a new 2.5 cm lytic lesion in the left ischium and a new 3.7 × 1.4 cm right bladder wall lesion (Fig 1). Urologist performed a transurethral resection of the bladder tumor, which was pathologically confirmed as metastatic RCC (Fig 2). In addition to known derangements in VHL and PBRM1, genomic analysis of the metastatic bladder lesion revealed a new missense mutation in the mammalian target of rapamycin (*mTOR*) and a new frameshift mutation in additional sex combs-like 1 (*ASXL1*). Although we were prepared to offer the patient combination therapy with the mTOR inhibitor everolimus plus lenvatinib, a vascular endothelial growth factor-tyrosine kinase inhibitor, the patient decided not to undergo any further treatment and opted instead for hospice care.

DISCUSSION

The urinary bladder is one of the least common sites of RCC metastasis, accounting for < 2% of patients with advanced disease.[6] A recent review found that metachronous metastasis is more common than synchronous metastasis (77% *v* 23%), and isolated bladder lesions occur more often than disseminated disease (62% *v* 38%).[7] Although the underlying pathway for bladder metastasis has not been clearly elaborated, there are at present three prevailing theories: hematogenous dissemination, lymphatic spread, and urothelial transit.

Due in large part to its high degree of vascularity, RCC frequently metastasizes through the bloodstream. With respect to bladder metastasis, researchers have posited that left renal vein thromboses can induce retrograde flow through the left gonadal vein and to the bladder.[8,9] Another proposed mechanism entails RCC extension through the pelvic lymphatic system, which communicates with the bladder by way of numerous interconnections with nearby vascular channels.[10] This mechanism has largely been attributed to cases of synchronous disseminated metastases.[11] Finally, anterograde flow through the urothelial tract, also termed drop metastases, postulates that cancer cells are capable of directly seeding through the bladder mucosa.[12,13] Drop metastases have

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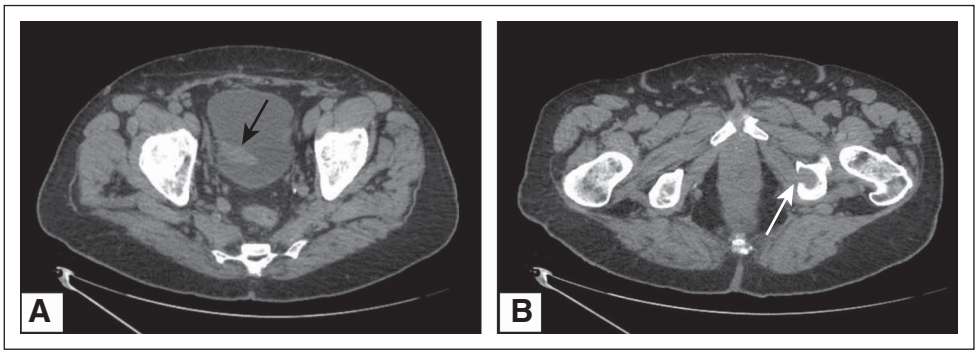

FIG 1. (A) CT of abdomen and pelvis with contrast reveals a 37 × 14 mm amorphous hyperattenuating lesion within the right aspect of the urinary bladder lumen (black arrow). (B) CT of abdomen and pelvis with contrast demonstrates a 25 mm lytic lesion in the left ischium with cortical breakthrough medially (white arrow). CT, computed tomography.

particularly gained traction as the route by which isolated bladder metastasis occurs.[14–16] For our patient, the development of isolated contralateral bladder metastasis in the absence of renal vein thrombosis supports the drop metastasis hypothesis.

In recent years, genomic data registries have begun to elucidate the putative mechanics of RCC. From these efforts, del(3p) has emerged as a sentinel event that is followed by three temporally distinct clusters of tumor evolution: del(14q), del(1p)/del(6q), and VHL/PBRM1.[17] Our patient's primary tumor possessed mutations in *VHL* and *PBRM1*, aligning him with the latter cluster.

PBRM1 is a tumor suppressor gene that codes for a component of the SWI/SNF chromatin remodeling complex.[18,19] *PBRM1* contributes to oncogenesis by upregulating tumor metabolism and facilitating tumor migration via disruption of cell adhesion.[20] Although correlative studies have found that patients with *PBRM1* mutations are more likely to derive a clinical benefit with ICIs,[21–23] emerging data suggest that *PBRM1* loss may also increase the risk for ICI resistance by reducing tumor immunogenicity.[24] One possible explanation for this heterogeneity may be due to differences in downstream tumorigenesis.

As previously mentioned, our patient developed interval *mTOR* and *ASXL1* mutations within his bladder lesion. Somatic *mTOR* mutations occur in 28% of patients with RCC, and they enhance cancer cell proliferation and angiogenesis.[25,26] Preclinical models have established that

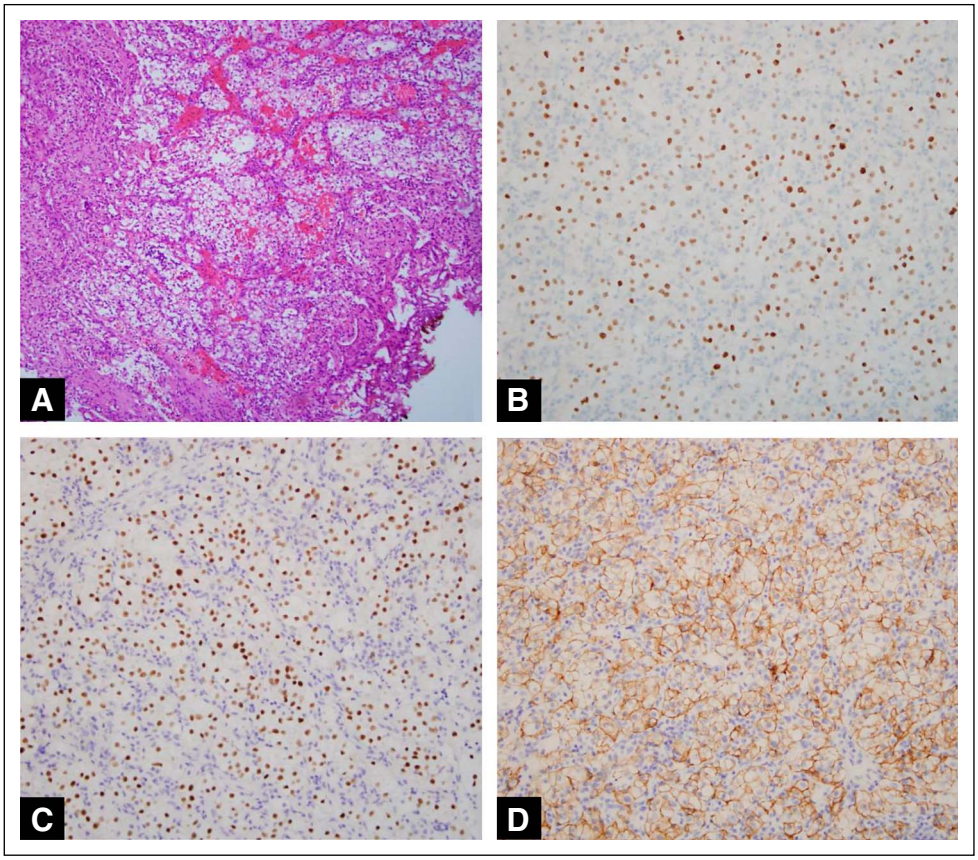

FIG 2. (A) Microscopically, there is diffuse infiltrate of neoplastic cells with clear cytoplasm within and replacing the urinary bladder wall associated with hemorrhage (H&E, 100×), and by immunohistochemistry, the tumor cells are positive for (B) Pax-8 (H&E, 200×), (C) Pax-2 (H&E, 200×), and (D) CA IX (H&E, 200×). The findings are diagnostic for a metastatic clear cell RCC. CA, carbonic anhydrase; H&E, hematoxylin and eosin; RCC, renal cell carcinoma.

mTOR aberrations are activating events in RCC that harbor *VHL* and *PBRM1* mutations.[27,28] In this respect, our patient's disease progression aligns with previously established pathogenic pathways.

In contrast, *ASXL1* is a protein that epigenetically regulates gene transcription via histone deubiquitination that is mutated in only 8% of RCC.[25,29] Although more commonly seen in isolation as a predictor of poor prognosis in myeloid neoplasms,[30,31] *ASXL1*'s functional interaction with *BAP1*—a mutation more commonly seen in RCC—makes *ASXL1* an intriguing actionable target.[32,33] For our patient, the combination of *ASXL1* and the VHL/PBRM1/mTOR axis mutations may represent a genomic variant that portends a higher risk for bladder metastasis in RCC.

One potential confounder when interpreting multiple genomic analyses is the possibility of intratumoral heterogeneity. We acknowledge that our patient's temporal changes may in fact be representative of undetected heterogenous clonality from the onset. Despite this, our case still underscores the importance of performing sequential genomic testing so that we may better elucidate the true clonal architecture of atypical sites of metastasis.

In conclusion, the urinary bladder is one of the rarest sites of RCC metastasis, the reason for which is poorly understood. In our patient, initial genomic sequencing of the primary tumor demonstrated loss of function mutations in *PBRM1* and *VHL*. Subsequent genomic analysis of his metastatic bladder lesion revealed interval mutations in *mTOR* and *ASXL1*. Performing temporal genomic assessments such as the case herein may provide further insight into site-specific clonal evolution, which may eventually inform individualized treatment strategies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.
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Huiqing Wu

Patents, Royalties, Other Intellectual Property: I am the first inventor of an active US patent (Patent #US9,771,619 B2; Patent Date, September 26, 2017): 4-miRNA signature for predicting clear cell renal cell carcinoma metastasis and prognosis. My institution (Beckman Research Institute of City of Hope) licensed the patent to NMS Labs in Pennsylvania several years ago. However, we haven't received any royalty compensation for years

Sumanta K. Pal

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