Ataxia in a Patient With Urothelial Carcinoma: Pathologic Confirmation, Recovery, and Improved Survival

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Case Report

A 74-year-old man was diagnosed with urothelial carcinoma after he presented with urinary obstruction. He was initially diagnosed with a Green Light Photo-Selective Vaporization of the Prostate (PVP), which showed a bladder tumor that was biopsied and cauterized with the laser. Pathology showed a high-grade papillary urothelial carcinoma invading into the submucosa. He then underwent bilateral retrograde pyelography, transurethral resection of the bladder (TURB), and transurethral resection of the prostate (TURP). The pathology confirmed a high-grade urothelial carcinoma in addition to carcinoma in-situ disease that was noted throughout the bladder wall and in the prostatic urethra. Staging evaluation, which included computed tomography (CT) of the chest, abdomen, and pelvis, showed bilateral external iliac lymph nodes, the largest of which measured 1.7 cm × 3.2 cm. In addition, there was a soft tissue nodularity extending from his prostate posteriorly into his rectum. His final diagnosis was stage IV (T4bN2M0) urothelial carcinoma. He received neoadjuvant chemotherapy with gemcitabine and cisplatin for 3 cycles. After completion of neoadjuvant therapy, restaging with CT and magnetic resonance imaging (MRI) of the abdomen/pelvis showed resolution of the soft tissue focus between the prostate and the rectum, as well as resolution of the bilateral external iliac lymph nodes. There was no gross evidence of residual bladder carcinoma. The patient was offered radical cystectomy but declined. He was treated with chemoradiation 5,940 cGy with weekly cisplatin. He was observed every 3 months with laboratory data and CT of the chest, abdomen, and pelvis, which yielded no evidence of recurrent or metastatic disease. Eleven months after the completion of therapy, the patient presented to the clinic complaining of increasing unstable gait, fatigue, dizziness, as well as dysequilibrium and diplopia. MRI of the brain showed a single left vermis cerebellar mass with heterogeneous enhancement consistent with metastatic disease (Figure 1A). He was treated with resection of his

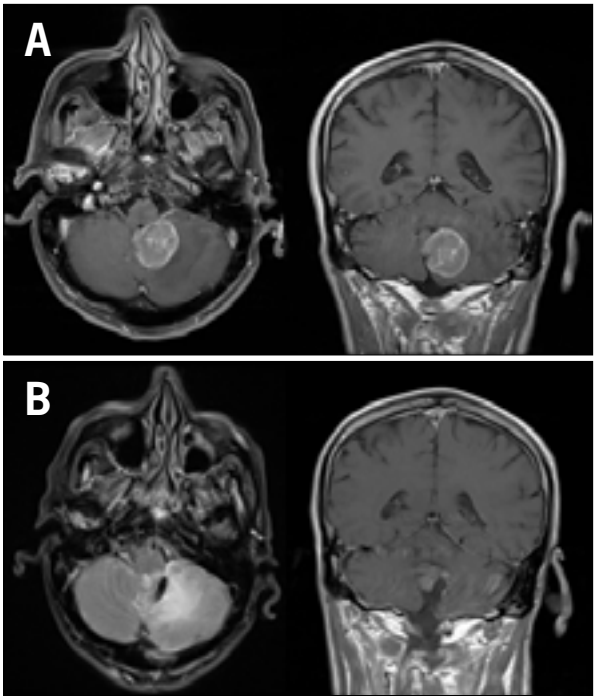

Figure 1. Axial and coronal magnetic resonance imaging (MRI) showing a 3.3 × 2.7 × 3.0 cm mass with heterogeneous enhancement in the left cerebellar hemisphere (A). There is also surrounding vasogenic edema, as well as a light mass effect on the medulla (B). Postoperative axial and coronal MRI show changes consistent with posterior fossa craniotomy and resection of the previously seen posterior fossa mass. A small hyperdense focus in the posterior fossa was believed to be consistent with residual tumor.

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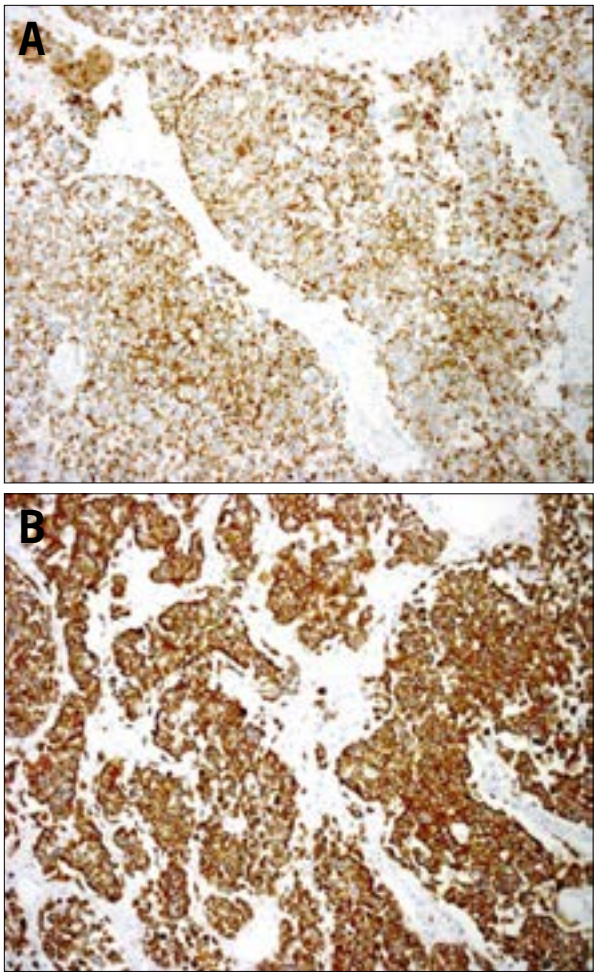

Figure 2. Immunochemical staining of the excised cerebellar mass. The cells were positive for CD903 (A) and CK7 (B), consistent with a urothelial primary.
Figures are ×10 magnification.

isolated brain metastasis. The pathology report showed that his brain lesion was positive for CK903 and CK7, which is consistent with metastatic urothelial carcinoma (Figures 2A and 2B). Postoperative MRI of the brain did show residual disease in the left ventral nodulus in the surgical bed (Figure 1B). He was then treated with whole-brain radiation with 3,000 cGy in 10 fractions. After completion of radiation therapy, subsequent MRI showed regression of the residual disease. There was no evidence of any other metastatic lesions. The patient did well for approximately 9 months, and then developed neck pain. On imaging, he was found to have T11 to L4 leptomeningeal disease, as well as a tumor recurrence in the left ventral nodulus, with minimal deterioration of his gait. He did receive palliative radiation to the spine with improvement of symptoms. After that, he declined further treatment and was enrolled into hospice.

Discussion

Bladder cancer accounts for approximately 5% of all diagnosed cancers and 3% of all cancer-related deaths.[1] In men, bladder cancer is the 4th most commonly diagnosed cancer and the 9th leading cause of cancer-related deaths.[1] Of the newly diagnosed cases of bladder cancer, 10–30% will progress to advanced disease, with the liver (38%), lungs (36%), bones (27%), adrenal glands (21%), and intestines (13%) being common sites of hematogenous metastases.[2]

In general, brain metastases are rare events. Before the advent of cisplatin-based chemotherapy for bladder cancer, the incidence of brain metastases was noted to be low, ranging from 1–3% in case reports from the 1980s.[3,4] However, with the introduction of the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy regimen, the incidence of brain metastases has increased. In one study, there was a 16% incidence rate of brain metastases among patients who received treatment with MVAC.[5] It is thought that this increased incidence is related to the prolonged duration of remission seen with the MVAC regimen. With durable remissions, the likelihood of brain metastases, which is thought to occur later in the disease process, also increases.[5]

Few data exist on the outcome of brain metastasis from bladder cancer. However, patients with brain metastases usually have a poor prognosis, with a median survival of approximately 2–5 months.[6] Treatment for brain metastasis consists of surgery, surgery and radiation therapy together, or radiation therapy alone. A sentinel, randomized, prospective study by Hatchell and associates demonstrated that, for all cancers, patients with a single metastasis to the brain who were treated with surgical resection plus radiotherapy lived longer than those who received radiotherapy alone (40 weeks vs 15 weeks, respectively).[7] They also had fewer recurrences of cancer in the brain compared to patients treated with radiotherapy alone (20% vs 52%, respectively). Patients who received combined modalities also reported a better quality of life than those patients who received radiotherapy alone.[7]

The benefit of surgery was confirmed in another prospective clinical trial, which showed that the combined modalities of radiotherapy and surgery resulted in a longer median overall survival compared to radiotherapy alone (10 months vs 6 months, respectively). The largest difference in survival between treatment arms was seen in patients with inactive extracranial disease; there was a median overall survival of 12 months in the subgroup that received surgery and radiotherapy compared to 7 months for those patients who received radiotherapy alone.[8]

In both of these studies, the number of patients with genitourinary cancers was small. Nonetheless, one

can extrapolate that these findings would hold true for patients with brain metastases from bladder cancer. Indeed, in one retrospective study by Rothstein and colleagues, the overall mean survival time for patients with brain metastases from bladder cancer who were treated with surgery and radiation was 19 months, compared to 6 months among patients treated with radiation alone.[9]

Another retrospective study[10] found that, for patients with brain metastases from bladder cancer who were treated with whole-brain radiation therapy (WBRT), the median overall survival time was only 2 months (range, 0.5–11 months). Patients who received both resection of the tumor followed by radiation therapy had a median survival of 7.75 months. Although the number of patients in that study was small, the results suggest that WBRT alone is not the most effective treatment modality for patients with brain metastases from bladder carcinoma. In general, WBRT is not followed by durable disease control.[10] The best treatment that results in prolonged overall survival usually requires a more aggressive approach, which includes resection of isolated brain metastasis followed by WBRT.[7,9,11] This approach is usually limited to patients with a single brain metastasis. However, for those with multiple lesions, WBRT alone remains the mainstay of treatment.[11] Most patients are given a long-course of WBRT, consisting of the standard regimen of 3,000 cGy administered in 10 fractions.[3,11] However, several studies have suggested that a hypofractionated WBRT for multiple brain metastases may be feasible. Patients who have less than 4 brain metastases and no other extracranial disease are more likely to significantly benefit from a hypofractionated course of therapy.[11]

Another recent advancement in the treatment of metastatic brain disease is stereotactic radiosurgery (SRS), a technique that was developed by the Swedish neurosurgeon, Lars Leksell. Radiosurgery is a technique that delivers single radiation treatment aimed at specific intracranial targets. It is sometimes viewed as a treatment option for patients with surgically unresectable brain metastasis.[12,13] For those patients with a solitary unresectable brain metastasis, the combination of SRS and WBRT can prolong survival. In a trial by the Radiation Oncology Treatment Group (RTOG 9508), WBRT followed by SRS improved overall survival for patients with single unresectable brain metastasis, with a median survival time of 6.5 months for the combined group versus 4.9 months for the WBRT-alone group. Additionally, patients who received SRS were more likely to have stable or improved Karnofsky performance status scores at a 6-month follow-up than those who received WBRT alone.[12]

In addition to unresectable single brain metastasis, SRS also plays a role in patients with multiple brain metastases. In a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 22952-26001), patients with 1–3 brain metastases were randomized to receive radiosurgery followed by observation or WBRT. There was no difference in the median overall survival for patients who were observed compared to those who received WBRT (median, 10.9 months vs 10.7 months, respectively). However, SRS followed by WBRT did decrease the 2-year relapse rates at the initial sites, as well as at new sites. Additionally, there were less neurologically-related deaths among patients who received WBRT after radiosurgery. Nevertheless, the addition of WBRT to SRS did not improve overall survival.[14]

Conclusion

Our patient had locally advanced urothelial cancer and was treated with neoadjuvant cisplatin-based chemotherapy, which resulted in a dramatic response. Eleven months later, he developed cerebellar symptoms. Imaging revealed evidence of a solitary left vermis metastasis. Surgical resection confirmed a diagnosis of metastatic urothelial cancer. Surgical resection was followed by WBRT, with resolution of his symptoms. Surgical confirmation of brain metastasis is rare; survival of more than 1 year and improvement of clinical symptoms are even rarer.

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Review

Ataxia in a Patient With Urothelial Carcinoma

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Urothelial carcinoma (UC) rarely metastasizes to the brain, but as Gardner and associates describe in their case report,[1] the incidence rate of brain metastases from UC has increased from 1–3% up to 16%. This increase can be attributed to the introduction of the systemic chemotherapy regimen of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC),[2-4] which results in prolonged duration of remission, with a subsequent increase in the likelihood of such cancer dissemination.[4] However, no data exist that show the comparable incidence of brain metastases in patients receiving the gemcitabine and cisplatin systemic regimen, which is more commonly used in patients with metastatic UC.

In this case report, the authors describe a 74-year-old man who was initially diagnosed with clinical T4bN2M0 UC during a Green Light Photo-Selective Vaporization of the Prostate (PVP). He underwent 3 cycles of salvage systemic chemotherapy with gemcitabine and cisplatin, and restaging studies demonstrated an excellent response. He then refused a radical cystectomy and subsequently underwent a bladder-sparing approach of chemoradiation with weekly cisplatin. Eleven months after completing this treatment, he presented with neurologic symptoms (unstable gait, fatigue, dizziness, disequilibrium, and diplopia), and a magnetic resonance imaging (MRI) of the brain revealed a solitary metastatic lesion in the left vermis. The patient underwent a resection, and the pathology was consistent with metastatic UC. He was then treated with whole-brain radiation therapy (WBRT) and did well for 9 months. Thereafter, he developed a recurrent brain tumor with leptomeningeal spread and was recommended and transferred for hospice care.[1]

As the authors point out in their discussion, the median survival for patients with UC and brain metastases is extremely poor. Current treatment options (which are dependent on tumor location and multiplicity) are limited to surgical resection, WBRT, and, more recently, stereotactic radiosurgery (SRS). However, data suggest that the survival benefit of surgical resection followed by WBRT compared to WBRT alone in patients with resectable disease is significant,[5,6] which underscores the importance of a detailed assessment, including neurologic symptoms, as part of the follow-up for patients with UC. This raises the question of whether routine brain imaging should be a part of the follow-up schedule for such metastatic UC patients and, if so, at what frequency of neurologic imaging (ie, patients who have been treated with MVAC).

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