 doi: 10.2176/jns-nmc.2023-0058

NMC Case Report Journal 10, 235-239, 2023

Surgical Treatment for Metastatic Brain Tumor in the Cerebellar Hemisphere from Small-cell Neuroendocrine Carcinoma of the Urinary Bladder: A Case Report and Review of the Literature

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Abstract

We performed surgical treatment for cerebellar metastasis of relatively rare small-cell neuroendocrine carcinoma (SCNC) of the urinary bladder. On preoperative imaging, the lesion was solitary, and the edema around the tumor was unremarkable; thus, other differential diagnoses besides a metastatic brain tumor were also considered preoperatively. Intraoperatively, the tumor was soft, and the circumference brain and boundary were indistinct and easily hemorrhagic. The tumor was grossly totally removed, and postoperative radiotherapy was added. The clinical symptoms of the patient were relieved, and he was discharged on foot. Thus far, relatively few reports have described surgical treatment of brain metastases of SCNC of the urinary bladder. We herein report a case of metastatic brain tumor due to SCNC of the urinary bladder that required surgical treatment, along with a review of the previous literature regarding its clinical features and the characteristics of intracranial lesions related to surgery, such as imaging and intraoperative findings.

Keywords: metastatic brain tumor, small-cell neuroendocrine carcinoma

Introduction

Among extrapulmonary small-cell carcinoma, small-cell neuroendocrine carcinoma (SCNC) of the bladder is a representative location; however, it is relatively rare. Despite its histological similarity, brain metastasis of SCNC of the urinary bladder is less common than that of small-cell carcinoma of the lung; however, it is known that brain metastasis of SCNC of the urinary bladder causes a higher rate than that of transitional cell carcinoma of the urinary bladder.

Of note, only a few reports have described surgical treatment for metastatic brain tumors due to extrapulmonary SCNC.[1-3] All three case reports stated that it is highly vascular-rich and hemorrhagic, has strong invasiveness to the brain parenchyma, and has an unclear border with the brain.

Case Report

An 80-year-old man presented to his previous physician with a chief complaint of dysuria, and computed tomography (CT) revealed a pelvic mass lesion extending from the prostate to the bladder. He had a medical history of hypertension and COPD. At the previous hospital, he underwent transurethral resection of the bladder tumor (TUR-BT) and was referred to the urology department of our hospital for a detailed examination and medical treatment. The result of the pathological diagnosis was SCNC.

Imaging studies suggested the involvement of the lungs, bilateral adrenal glands, and pelvic nodules, and the tumor markers were elevated with NSE 201.0 ng/mL and ProGRP 91.4 pg/mL. From the month of surgery, cisplatin (CDDP) plus etoposide (ETP) therapy was started. After 3 courses

Received March 16, 2023; Accepted July 10, 2023

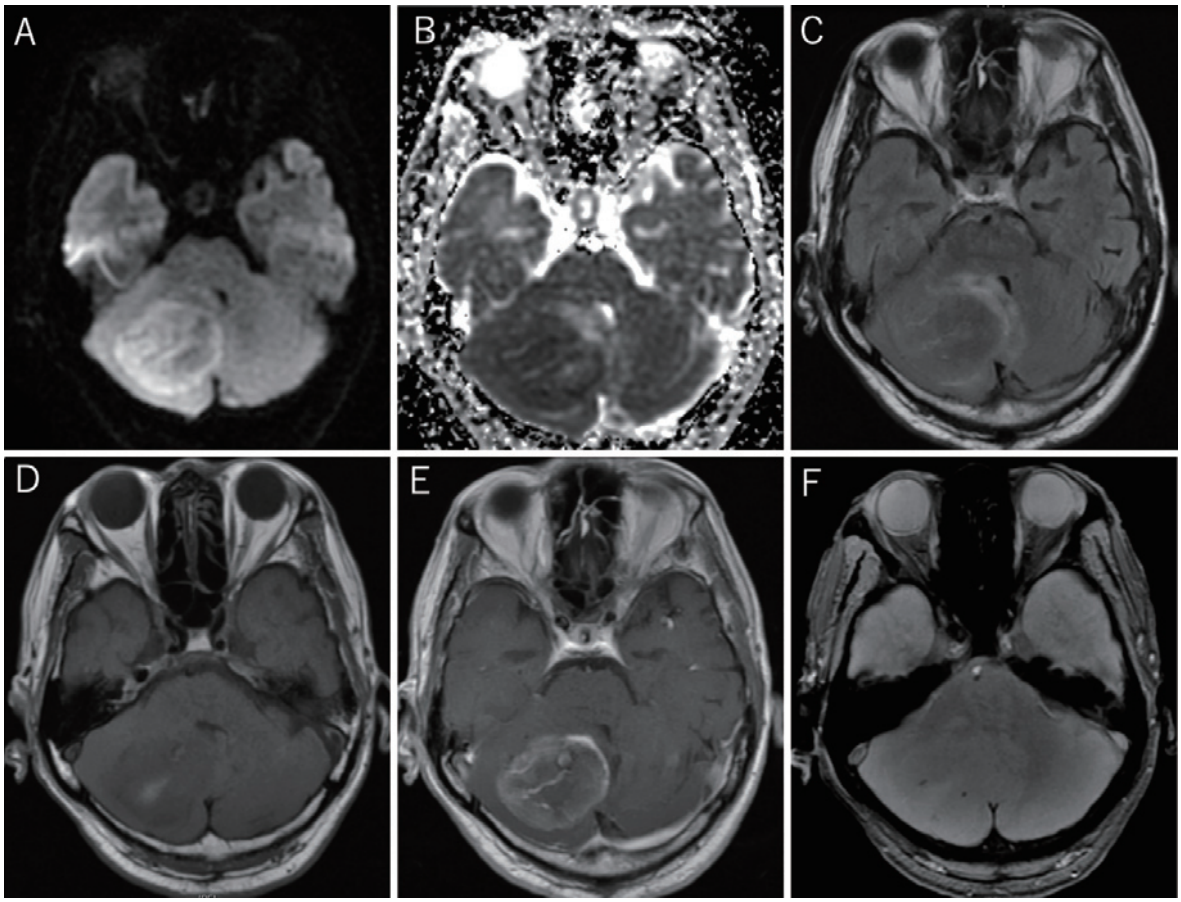

Fig. 1 Head MRI performed the day before the surgery showed a single tumor in the right cerebellar hemisphere. The tumor presented hyperintense on diffusion-weighted image (DWI) with low apparent diffusion coefficient (ADC) values. (A, B), and the contrast-enhanced image demonstrated a heterogeneously enhancing mass lesion of 46 mm in size (E). Hyperintensity on T1-weighted imaging (D) and hypointensity on T2*-weighted imaging indicated microbleeds inside the lesion (F). Peritumoral edema was not severe on FLAIR imaging (C). Enhancement of the meninges suggesting dissemination was not recognized.

of CDDP+ETP therapy, 13 courses of avelumab maintenance therapy were administered. Ten months after the initiation of treatment, he developed headache, nausea, and gait disturbance and was referred to our department of neurosurgery due to a lesion in the right cerebellar hemisphere on head magnetic resonance imaging (MRI), where he was urgently admitted.

There were slight disturbance of consciousness (E4V4M6/GCS), severe headache, gait disturbance, and dysarthria due to cerebellar ataxia dominant on the right side of the body. His presymptomatic Karnofsky performance score (KPS) was 80, and his cognitive function was good. Contrast-enhanced MRI revealed a heterogeneously enhancing mass lesion of 46 mm in the right cerebellar hemisphere. The lesion was hyperintense on diffusion-weighted image (DWI) with low apparent diffusion coefficient (ADC) values. There was evidence of microbleeds inside the mass with hyperintensity on T1-weighted imaging and hypointensity on T2*-weighted imaging. In addition, edema of the brain parenchyma around the lesion was relatively mild compared to the intensity of the lesion. The lesion was single, and the enhancement of the meninges suggesting dissemination was not recognized (Fig. 1A-F).

The tumor was large, and brainstem compression was present, conferring a risk of obstruction of the cerebrospinal fluid outflow pathway in a short period, and the symptoms of the patient rapidly worsened. After the possible risks associated with surgery were fully explained, and informed consent was obtained, the patient urgently underwent surgical removal of the tumor with suboccipital craniotomy, and the lesion was grossly totally removed (Fig. 2A-B).

Intraoperative findings showed that the lesion was highly hemorrhagic, resulting in a loss of 410 mL of blood and requiring a transfusion of 2 units of packed red blood cell concentrate. The tumor was fragile and easily collapsed. The border between the tumor and the surrounding brain parenchyma was difficult to identify (Fig. 3). The postoperative course was stable, his clinical symptoms markedly improved, and rehabilitation was performed for

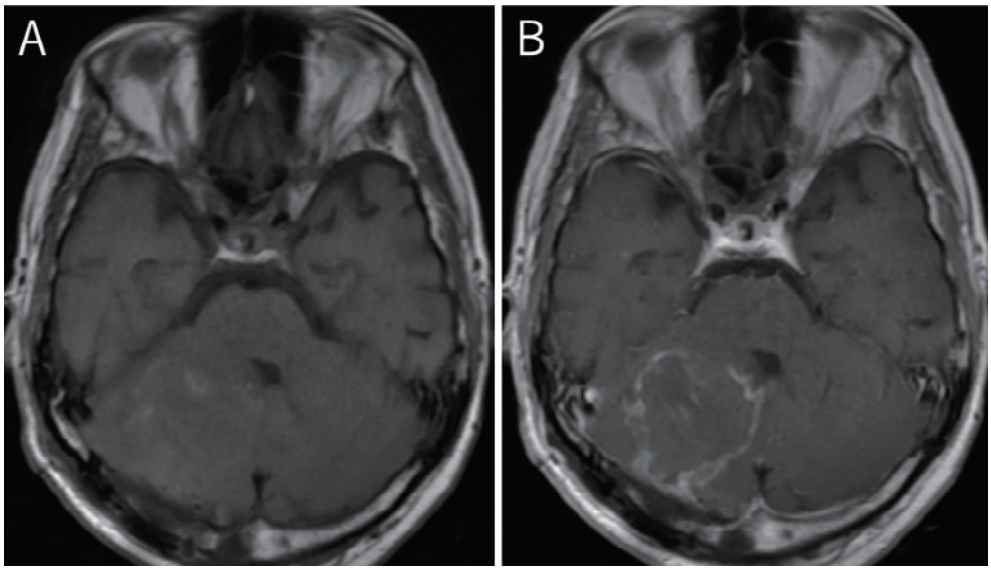

Fig. 2 Head MRI 10 days after surgery showed no tumor recurrence or dissemination except for the contrast effect surrounding the resection cavity reflecting postoperative changes (A: T1WI, B: contrast-enhanced T1WI).

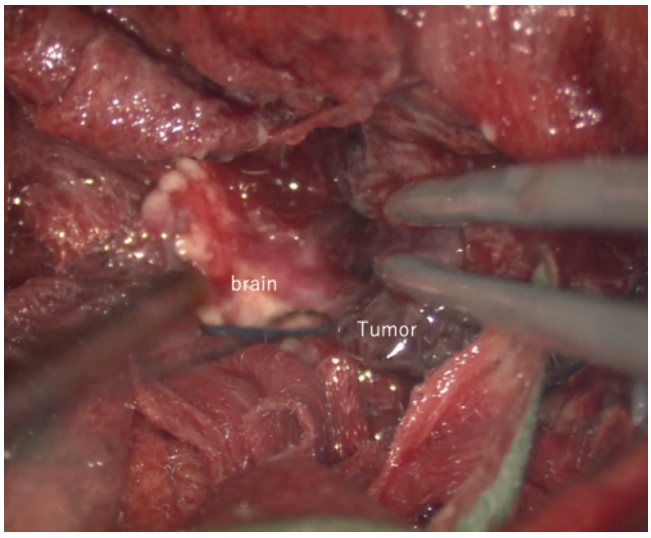

Fig. 3 Intraoperative microscopic views showed that the tumor was highly vascularized and hemorrhagic, with a fragile and collapsible nature, and the border with the brain parenchyma was extremely unclear.

cerebellar ataxia with mild sequelae. Regarding the pathological diagnosis, atypical cells with enlarged hyperchromatic nuclei and scant eosinophilic cytoplasm had proliferated diffusely. Many mitotic figures and extensive necrosis were observed. It resembled the bladder tumor morphologically. Immunostaining revealed that the neoplastic cells were positive for CD56, chromogranin A, and synaptophysin, which led to the diagnosis of metastatic SCNC of the bladder (Fig. 4A-E). Cerebral stereotactic radiotherapy was started at the extraction site 2 weeks after surgery, with 30 Gy delivered in five fractions. At 3 months after the surgery, there was no evidence suggestive of recurrent lesions or leptomeningeal dissemination on the head CT; however, progression of the pelvic lesion at the primary site has been noted.

Discussion

Small-cell carcinoma (SCC) of the urinary bladder is an aggressive, poorly differentiated neuroendocrine neoplasm that is similar to SCC of the lung in clinical behavior.[4] It is also described as SCNC. SCNC of the urinary bladder is a representative type of extrapulmonary SCC, albeit a relatively rare tumor, accounting for only <1% of primary malignant tumors in the urinary bladder.[5] Bex et al. reported a literature review of symptomatic brain metastases due to SCNC of the urinary bladder,[6] and several articles have mentioned metastatic brain tumors due to SCNC of the bladder, with an estimated risk of brain metastases of around 0%-40%. Although this disease has an aggressive clinical course and a poor prognostic outcome, Bex discussed that a prolonged survival with the development of therapies may increase the number of patients with metastatic brain tumors from this disease.[6] Therefore, it would be meaningful to discuss surgical treatment for this metastatic disease.

To the best of our knowledge, only two previous reports have focused on the surgical treatment of SCNC of the urinary bladder for metastatic brain tumors thus far.[1,2] Isaka et al. reported a case involving surgery performed for a metastatic lesion in the left frontal lobe, including radiological, intraoperative, and pathological findings.[1] In that case, intense tumor staining was noted from early in the arterial phase on angiography, and there was substantial

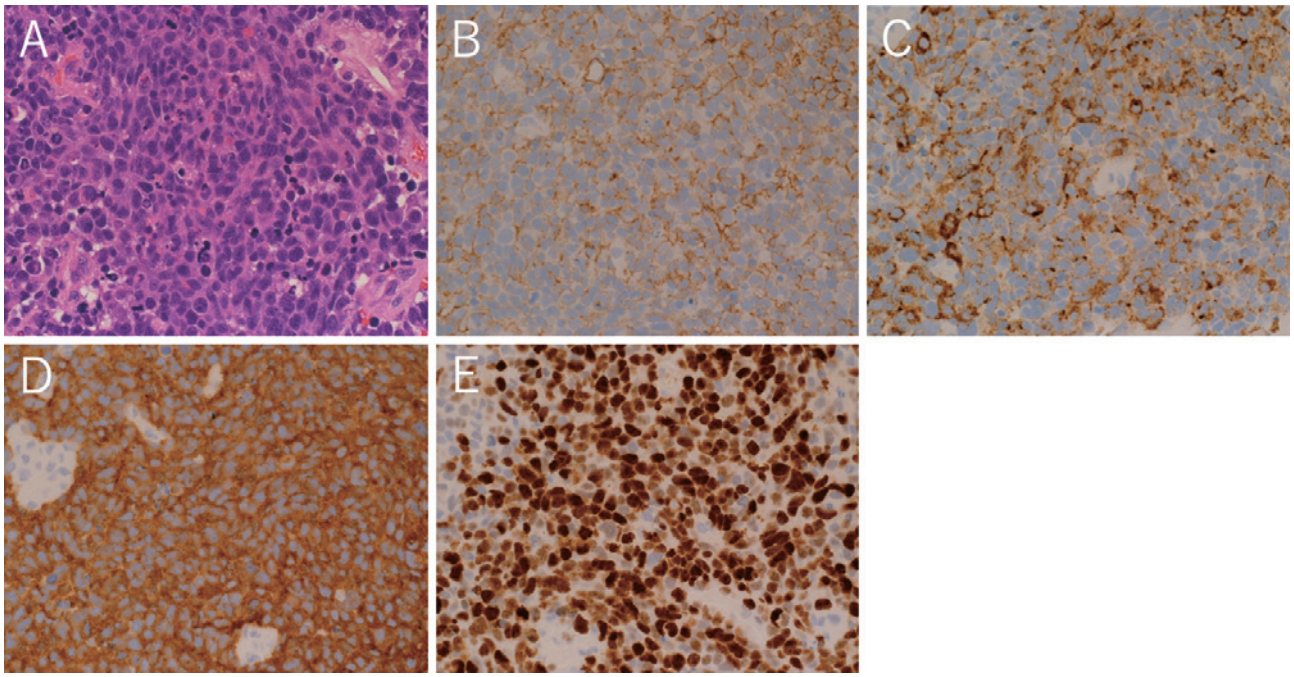

Fig. 4 Pathological microphotograph at 40× magnification.
Hematoxylin-eosin (HE) staining (A) revealed the presence of hyperchromatic nuclei with scant eosinophilic cytoplasm in neoplastic cells that proliferated in a solid pattern, exhibiting notable features of necrosis and mitotic activity. An immunohistochemical examination demonstrated CD56 positivity (B), chromogranin A positivity (C), and synaptophysin positivity (D), suggestive of neuroendocrine differentiation. The Ki-67 labeling index (E) was quite high at 90%.

intraoperative bleeding from the fine vessels consistent with this finding. In addition, the border with the brain parenchyma was exceedingly indistinct intraoperatively, and the tumor cells had diffusely infiltrated the brain parenchyma in the pathological view. Maeshima et al. presented a case of metastatic tumor of the basal ganglia that resulted in intratumoral hemorrhaging and required hematoma evacuation.[2] Moreover, Theodros et al. reported that primary small intestine tumors as extrapulmonary SCNC were highly vascularized and associated with substantial difficulty achieving hemostasis.[3] It has been reported that metastatic brain tumors derived from lung cancer are prone to bleeding,[7] and metastasis from SCNC of the bladder may have similar clinical features to small-cell lung cancer brain metastases. These reports are consistent with the present case. These features of the lesion, such as excessive bleeding, fragility, and indistinct borders, may prevent *en bloc* excision of the lesion. Since this may increase the risk of developing meningeal carcinomatosis after surgery, early initiation of postoperative adjunct therapy with radiotherapy or chemotherapy is vitally important and requires careful follow-up.

In general, massive peritumoral vasogenic edema is characteristic in metastatic brain tumors, causing increased intracranial pressure and neurological deficits;[8] however, in the present case, peritumoral edema was not remarkable. This atypical finding for a metastatic brain tumor was similar to the image findings in the cases reported by Isaka and Maeshima.[1,2] One possible explanation for this is that it has been proposed that high apparent diffusion coefficient (ADC) values in brain metastases may result in larger peritumoral edema volumes due to increased water influx into the tumor interstitium,[9] while tumors with low ADC values, as in this case, may not necessarily result in as significant peritumoral edema since ADC is an index of the magnitude of water molecule diffusion within the tumor. Although the accumulation of further cases is needed, this may be a potentially distinctive radiological finding in brain metastases of SCNC of the bladder. It is also known that decreased diffusion of the lesion is a particular finding in metastatic brain tumors due to SCC,[10] which is thought to reflect the lesion's high cellularity, as was also the case in our patient.

Whole-brain irradiation has been the proactive approach in radiotherapy for brain metastases from SCNC of the urinary bladder. Although there is no consensus as to the most appropriate standard therapy, prophylactic whole-brain irradiation, in accordance with the approach for small-cell lung cancer, has been reported.[11-13] Considering the aggressive disease nature and high risk of postoperative meningeal carcinomatosis, it is imperative to consider the possibility of prophylactic or early postoperative radiation therapy. In the present case, our patient underwent stereotactic irradiation postoperatively rather than whole-

brain irradiation due to his strong wishes. We will consider adding whole-brain irradiation if recurrence or dissemination is suspected under close imaging follow-up.

Conclusion

During surgical treatment of metastatic brain tumors from SCNC of the bladder, hypervascularity and hemorrhaging, fragility and collapse, and unclear boundaries due to strong invasiveness into the brain are considered barriers to surgery. In addition to the prognosis of primary cancer, it is necessary to choose the treatment intervention while considering the difficulty of the operation and the possibility of postoperative meningeal carcinomatosis.

Abbreviations

CT: computed tomography
DWI: diffusion-weighted image
KPS: Karnofsky performance score
MRI: magnetic resonance imaging
SCNC: small-cell neuroendocrine carcinoma
TUR-BT: transurethral resection of the bladder tumor

Conflicts of Interest Disclosure

The authors declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1) Isaka T, Maruno M, Sato M, et al.: Brain metastasis from small-cell neuroendocrine carcinoma of the urinary bladder: A case report. *Brain Tumor Pathol* 19: 117-122, 2002
2) Maeshima K, Sasaki T, Yamoto T, Fukai J, Nishibayashi H, Nakao N: Hemorrhagic brain metastasis from small-cell carcinoma of the urinary bladder. *Surg Neurol Int* 13: 1-4, 2022
3) Theodros D, Goodwin CR, Crane GM, Liauw J, Kleinberg L, Lim M: Metastatic extrapulmonary small cell carcinoma to the cerebellopontine angle: a case report and review of the literature. *Case Rep Oncol Med* 2015: 847058, 2015
4) Ismaili N: A rare bladder cancer - small cell carcinoma: review and update. *Orphanet J Rare Dis* 6: 75, 2011
5) Choong NWW, Quevedo JF, Kaur JS: Small cell carcinoma of the urinary bladder: the mayo clinic experience. *Cancer* 103: 1172-1178, 2005
6) Bex A, Sonke GS, Pos FJ, Brandsma D, Kerst JM, Horenblas S: Symptomatic brain metastases from small-cell carcinoma of the urinary bladder: the Netherlands Cancer institute experience and literature review. *Ann Oncol* 21: 2240-2245, 2010. https://doi.org/10.1093/annonc/mdq225 [Internet]. Elsevier Masson SAS
7) Nutt SH, Patchell RA: Intracranial hemorrhage associated with primary and secondary tumors. *Neurosurg Clin N Am* 3: 591-599, 1992
8) Soffietti R, Rudā R, Mutani R: Management of brain metastases. *J Neurol* 249: 1357-1369, 2002
9) Toh CH, Siow TY, Castillo M: Peritumoral brain edema in metastases may be related to glymphatic dysfunction. *Front Oncol* 11: 725354, 2021
10) Hayashida Y, Hirai T, Morishita S, et al.: Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. *Am J Neuroradiol* 27: 1419-1425, 2006
11) Lohrisch C, Murray N, Pickles T, Sullivan L: Small cell carcinoma of the bladder: long term outcome with integrated chemoradiation. *Cancer* 86: 2346-2352, 1999
12) Lester JF, Hudson E, Barber JB: Bladder preservation in small cell carcinoma of the urinary bladder: an institutional experience and review of the literature. *Clin Oncol* 18: 608-611, 2006
13) Siefker-Radtke AO, Kamat AM, Grossman HB, et al.: Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. *J Clin Oncol* 27: 2592-2597, 2009

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