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Case Report
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A Case of High Grade Advanced Neuroendocrine Cancer of the Bladder Treated with Bevacizumab, Cisplatin, Etoposide and Cyclophosphamide-Based Chemotherapy

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Abstract

Neuroendocrine bladder cancer accounts for <1% of all bladder cancers. There is no standard treatment for neuroendocrine bladder cancer; instead therapy is mainly based on agents used in small cell lung cancer. The case report details a patient with neuroendocrine bladder cancer who had disease progression after conventional chemotherapy based on etoposide and cisplatin. During second-line chemotherapy with etoposide, cisplatin and ifosfamide the patient experienced a high-grade neurological adverse event, without any decrease in tumor burden. Third-line chemotherapy with cisplatin, cyclophosphamide, etoposide and bevacizumab was associated with an almost complete response but the patient died of hematological toxicity. The good response to the combination of cisplatin, cyclophosphamide, etoposide and bevacizumab suggests that anti-angiogenic therapies may be a treatment option for neuroendocrine bladder cancer that deserved further study.

Keywords: Small cell bladder cancer; Bevacizumab; Cisplatin; Etoposide; Cyclophosphamide; Hematotoxicity

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Introduction

Neuroendocrine bladder cancer is a very rare type of bladder cancer. As a result, there are no large prospective clinical trials investigating treatment options for this type of cancer. Instead, treatment is often based on that used in small cell lung cancer, although surgical options differ between the two cancer types [1,2]. Neuroendocrine bladder tumors show significant heterogeneity, particularly with respect to sequencing, and their pathogenesis is not well defined. The primary theory is that a multipotent common stem cell has the ability to differentiate into various cell types depending on the influence of specific expression of progression-related genes. The neuroendocrine component is frequently associated with transitional cell carcinoma within the same tumor [1,3].

Case Report

A 56-year-old woman presented with high-grade large and small cell neuroendocrine bladder cancer. Her medical history was unremarkable apart from active smoking (about 40 pack-years). Her first symptom of bladder cancer was hematuria. Cystoscopy detected a lesion on the right wall face of the bladder and the patient underwent a transurethral resection. One month later, she had loco-regional recurrence. Radiological evaluation showed a tumor located on the right wall of the bladder, which measured 63x47mm (maximum standard uptake value [SUV max]: 12.2) before initial chemotherapy; neuroendocrine biomarkers were positive. The patient was treated with preoperative chemotherapy using cisplatin and etoposide, with granulocyte colony-stimulating factor (G-CSF) support. After 2 cycles, radiological evaluation detected progressive disease (Figure 1). The tumor had increased in size to 86x59 mm (SUV max: 12.3). Chemotherapy was stopped and the patient underwent cystectomy with lymph node dissection. Histological analysis showed complete resection, but there was lymph node invasion; the tumor was ypT3N2. Next Generation Sequencing was performed, which showed 20% tumor cells. More than 500 hotspot mutation regions of 22 genes associated with lung tumor tissue were studied with the AmpliSeq Colon and Lung Cancer Panel V2 (Life Technologies). No mutations in KRAS, EGFR, BRAF, NRAS known to have therapeutic or prognostic impact were detected. Two abnormalities were identified, the predictive value of

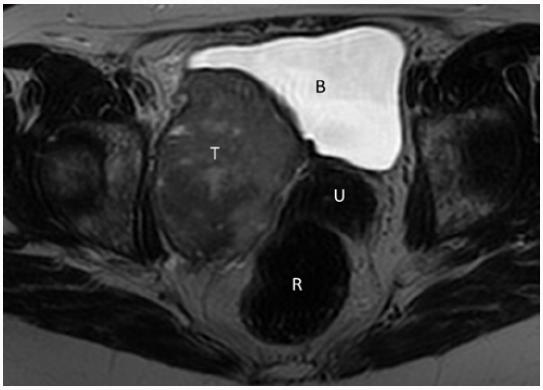

Figure 1: MRI performed during first-line chemotherapy.
T2-weighted transverse plane image showing the tumor (T) developed extrinsically from the right lateral bladder wall. The tumor presents as a mass with intermediate T2 signal, discreetly heterogeneous with spots with higher signal considered as necrosis. B: bladder, U: uterus (cervix), R: rectum.

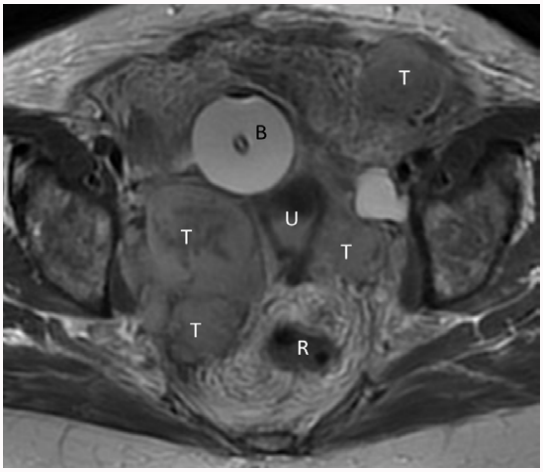

Figure 2: MRI showing recurrence after surgery.
T2-weighted transverse plane image showing the multiple tumor nodules (T), including in the anterior left pelvic wall, right and left pelvic lateral walls, with intermediate T2 signal. B: bladder (with a urinary catheter), U: uterus (cervix), R: rectum.

which was unknown. There was a gain-of-function mutation of TP53 (p.E285K, c.853G>A, allelic ratio 75%) that is often associated with poor prognosis [4], and a nonsense mutation of SMAD4 (p.GIn245*, c.733C>T, allelic ratio 29%) meaning that the TGF-beta pathway was impaired. One month later, the patient had an aggressive loco-regional recurrence. The patient had severe abdominal pain, treated with opioids. There were several tumor nodules in the pelvis, one of 95mm (SUV max: 19) and another of 77mm (SUV max: 18.3) (Figure 2). Mesenteric lymphadenopathy measuring 16mm and 9mm was also detected. Second-line chemotherapy with cisplatin (20mg/m^2/day for 5 days), etoposide (75mg/m^2/day for 5 days) and ifosfamide (1200mg/m^2/day for 5 days) with G-CSF was given. Unfortunately, the patient developed ifosfamide-induced encephalopathy at the start of treatment with this regimen. Magnetic resonance imaging (MRI) did not find any brain metastasis. Neurological symptoms resolved after treatment with methylene blue, thiamine, and albumin. However, inclusion of chemotherapy including ifosfamide was deemed too risky, especially as the disease remained progressive on radiological evaluation (+18%): 106mm (vs. 95mm), 85 mm (vs. 77mm), 23mm (vs. 16mm) and 18mm (vs. 9mm). A decision was made to initiate

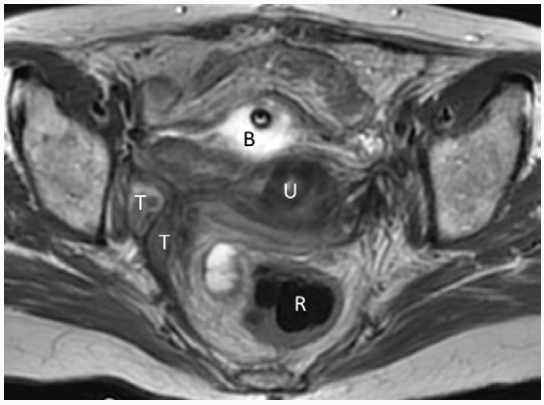

Figure 3: MRI showing a very good response after the addition of bevacizumab to chemotherapy.
T2-weighted transverse plane image showing a single nodule remaining (T) on the right pelvic lateral wall, having partly lost its intermediate T2 signal. The anterior and left pelvic wall nodules have completely disappeared. B: bladder (with a urinary catheter), U: uterus (cervix), R: rectum.

third-line chemotherapy with cisplatin (20mg/m^2/day for 5 days), etoposide (75mg/m^2/day for 5 days), cyclophosphamide (400mg/m^2/day for 3 days) and bevacizumab (15mg/kg on day 1), plus G-CSF. There was evidence of a partial response on radiological evaluation: 96mm (vs. 106mm), 84mm (vs. 85mm), 17mm (vs. 23mm) and 14mm (vs. 18mm) (i.e. a 10% response). The patient developed a number of high-grade chemotherapy-related toxicities, including daily vomiting, fever, anemia, and thrombopenia requiring platelet transfusion. A second cycle of the same chemotherapy regimen was given, but with a 20% dose reduction. At that time, the patient had no abdominal pain and was able to interrupt analgesics. Radiological evaluation showed a partial response: 79mm (vs. 96mm), 60mm (vs. 84mm) and no adenopathy (i.e. a 40% response). The patient required another platelet transfusion but developed HLA alloimmunization, which limited the treatment options available. A third cycle of third-line chemotherapy was given at the same reduced dosages used in cycle 2. Radiological evaluation showed an 59% response: 52mm (vs. 79mm), 44mm (vs. 60mm) and no adenopathy (Figure 3). Unfortunately, the patient developed thrombopenia complications, including digestive tract and brain bleeding, resulting in death secondary to treatment toxicity.

Discussion

Neuroendocrine bladder cancer is a very rare tumor and has poor prognosis. There is currently no large prospective clinical trial data and no standard treatment. Radiotherapy may be an option for palliative or curative care. Surgery is another approach, especially when the neuroendocrine tumor is associated with urothelial carcinoma of the bladder, although results are controversial. Chemotherapy is the main treatment, especially in the neoadjuvant setting, because neuroendocrine bladder cancer is very sensitive to chemotherapy and is often diagnosed at advanced stage: 90% of patients present with stage II disease and 25% are stage IV [1,5]. Chemotherapy regimens described in retrospective series for locally advanced (as neoadjuvant chemotherapy) or metastatic disease are: cisplatin and etoposide; ifosfamide, doxorubicin, etoposide and cisplatin; ifosfamide, etoposide and cisplatin; etoposide, cisplatin, cyclophosphamide, vincristine and doxorubicin; and methotrexate, vinblastine, cisplatin and doxorubicin [1,2,6,7]. There is one prospective phase II study in neuroendocrine bladder cancer [8]. It

assessed the benefit of an alternating doublet of chemotherapy with ifosfamide plus doxorubicin and cisplatin plus etoposide during 4 cycles as neoadjuvant chemotherapy for resectable disease, or up to 2 cycles beyond maximal response for metastatic disease. Eighteen patients with locally advanced disease up to T4aN0M0 were enrolled, of whom 78% had a major response (defined as a down-staging up to pT1N0M0). Overall survival was 58 months. In the twelve enrolled patients who had metastatic disease, the overall response rate was nearly 100%; median overall survival was 13.3 months. Neutropenic fever occurred in 7/30 patients (23%) [8]. Bevacizumab has not been formally studied in neuroendocrine bladder cancer. However, over expression of the vascular endothelial growth factor receptor (VEGFR) on endothelial cells has been documented in this type of tumor [1]. For patients with advanced small cell lung cancer, adding bevacizumab to conventional first-line chemotherapy (cisplatin and etoposide) was associated with progression-free survival of 4.7 months, overall survival of 10.9 months and an overall response rate of 63.5% [9]. The most common adverse event was neutropenia, which occurred in 57.8% of patients [9]. Another randomized phase II study in advanced small cell lung cancer compared bevacizumab to placebo in combination to cisplatin or carboplatin plus etoposide as first-line therapy. Progression-free survival was 5.5 and 4.4 months, respectively, in the bevacizumab and placebo groups (hazard ratio 0.56, 95% confidence interval 0.32–0.86); corresponding values for median overall survival were 9.4 and 10.9 months, median duration of response were 4.7 and 3.2 months, and grade ≥3 toxicity were 75% and 60% [10]. Our patient showed a good response to bevacizmab-containing chemotherapy, but unfortunately died from treatment-related toxicity. The number of platelet transfusions with pooled platelets appears to be the only risk factor for alloimmunization in this case. To date, there is no data to suggest that bevacizumab or the type of chemotherapy play a role in the development of anti-HLA antibodies. Abnormal signaling pathways that have been described in both small cell lung cancer and neuroendocrine cancer of the bladder include expression of c-kit, c-MYC amplification, EGFR mutations that activate RAS-RAF-MAPK pathways, over expression of BCL2, and TP53 mutation [1,6]. Over expression of p53 doesn't appear to correlate with prognosis, while over expression of p16 may be an early and necessary event. Expression of p63 may be helpful for differentiating neuroendocrine bladder cancer from urothelial bladder cancer because it is inactivated in the former (92.8%) and expressed in the latter (81.3%) [11].

Conclusion

Although this patient died from treatment-related toxicity, she showed an almost complete response to third-line chemotherapy containing bevacizumab. Given the lack of data on treatments for neuroendocrine bladder cancer, our experience suggests that a phase II study assessing the benefit of adding bevacizumab to conventional chemotherapy in this setting appears to be warranted.

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