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Case Report

A case report of a patient with plasmacytoid urothelial cancer with significant response to HER2-targeting therapy and enfortumab vedotin

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Abstract: In this case report, we present a patient with the rare plasmacytoid variant of urothelial cancer. Notable elements of his course include: complete response to neoadjuvant paclitaxel, gemcitabine, cisplatin, development of metastatic disease to the rectum, sustained disease control with dual HER2 targeting therapy, and subsequent complete response to enfortumab vedotin. Plasmacytoid urothelial cancer accounts for just 1-3% of all urothelial cancer cases and is associated with more aggressive disease, with a propensity for intra-abdominal spread and poor response to neoadjuvant therapy. Preliminary data indicate that the variant may generally have high levels of HER2 expression. We review the history of HER2 targeting in metastatic urothelial cancer, which has included single-agent as well as combination with chemotherapy; there are ongoing biomarker-based clinical trials. Furthermore, we highlight the complete response to enfortumab vedotin. To date, this is the first report of efficacy for enfortumab vedotin in the plasmacytoid variant.

Keywords: Urothelial carcinoma, bladder cancer, plasmacytoid variant, biomarkers

Case summary

75 year-old man presented in March 2016, at age 71, with urinary symptoms. CT abdomen/pelvis showed right-sided bladder wall thickening, no enlarged lymph nodes. Transurethral resection of the bladder revealed muscle invasive poorly differentiated bladder carcinoma with plasmacytoid and signet ring features (**Figures 1** and **2**). The patient received neoadjuvant chemotherapy with paclitaxel, gemcitabine and cisplatin followed by radical cystoprostatectomy with bilateral lymph node dissection which revealed a pathological complete response. In August 2017, surveillance CT scan revealed new circumferential rectal wall thickening. FDG-PET/CT also demonstrated hypermetabolic retroperitoneal lymph nodes and peritoneal nodules (**Figure 3**). Rectal biopsy showed invasive high-grade urothelial carcinoma, consistent with prior plasmacytoid/discohesive variant. Immunohistochemistry (IHC) showed 3+ HER2 expression, without gene amplification noted on fluorescent in-situ hybridization (FISH). Targeted molecular sequencing detected RB1 deletion; subsequent whole exome sequencing revealed mutations in GNAS and ARID1A and copy number gain of HER2 (**Table 1**). The patient was enrolled on a clinical trial and treated with trastuzumab and pertuzumab. Follow-up imaging demonstrated stable disease which lasted for 20 months until April of 2019 when the patient complained of difficulty defecating and CT demonstrated new rectal wall thickening. Repeat biopsy showed high-grade urothelial carcinoma with plasmacytoid/discohesive features. HER2 expression was 2+, and no PD-L1 expression was detected. In May 2019, he received gemcitabine and carboplatin with the addition of pembrolizumab, complicated by immune-related diarrhea. Repeat imaging in July 2019 showed progression of disease in the rectum with a diminished sigmoid colon diameter and increased abdominopelvic lymphadenopathy. He underwent palliative diverting colostomy. In October, he began a course of

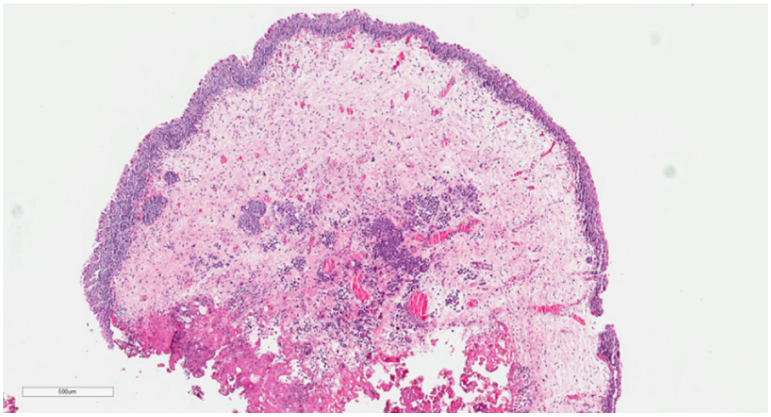

Figure 1. Bladder biopsy with normal urothelium and irregular nests of atypical cells deep within the lamina propria.

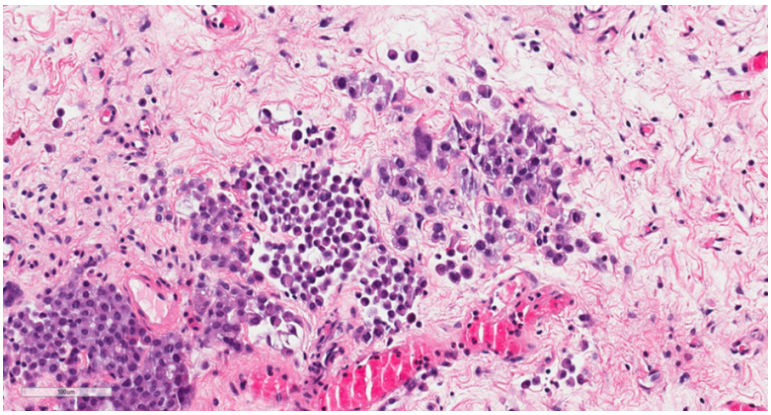

Figure 2. Discohesive carcinoma cells in clusters and dispersed singly throughout the lamina propria. The cells have eccentric round nuclei with eosinophilic cytoplasm, resembling plasma cells.

trastuzumab emtansine (T-DM1), which was complicated by rectal abscess requiring drainage and subsequently by a femoral deep vein thrombosis further complicated by rectal bleeding on anticoagulation. Imaging showed stable disease. He received five fractions of radiation to the rectal area which eliminated the bleeding. In January 2020, PET/CT demonstrated worsening lymphadenopathy. The patient was hospitalized in February for a small bowel obstruction from metastatic serosal implants and started on total parenteral nutrition.

In February 2020, he was started on enfortumab vedotin (EV). Interval CT in March showed decline in abdominal lymphadenopathy, stable rectal disease, and resolution of the bowel obstruction. He had another prolonged hospitalization in May for gallstone cholecystitis that was complicated by intra-abdominal abscess and candida fungemia. He was transitioned back to oral diet. CT of his abdomen 6/2020 showed stable disease burden. PET/CT 7/2020 showed no increased FDG uptake in abdominopelvic lymph nodes or rectum, consistent with radiographic complete response.

Background

Plasmacytoid bladder cancer represents 1-3% of all bladder cancers [1]. On histology, plasmacytoid tumors are characterized by small (2-3 times the size of a lymphocyte) nuclei that are eccentrically located in large eosinophilic cytoplasm; cells are loosely arranged, or "discohesive", and form scattered cords [2]. In each plasmacytoid bladder cancer sample, around 25-68% of the tumor has plasmacytoid differentiation [1, 2]. Recently, in a series of 69 patients, three distinct patterns associated with the plasmacytoid variant. The classic group had the aforementioned features, the pleomorphic group contained larger nuclei with more cellular atypia, and the desmoplastic group was associated with a diffuse desmoplastic reaction surrounding the tumor [2].

Loss of E-cadherin has been reported in 57%-73% of all tumors [1, 2]. The loss of this cell-adhesion protein may contribute to the scattered arrangement of tumor cells and increase the cancer's capacity to metastasize [3]. E-cadherin loss stems from a truncating mutation of the CDH-1 gene [3]. In the desmoplastic subtype, more E-cadherin expression was noted, and 68% of those tumors retained the protein [2]. Other abnormalities include loss of RB protein, which has been reported in 62% of all tumors and is seen in our patient, deletion of chromosome 9p21, noted in 60% of cases, and FGFR3 mutations, noted in 60% of cases [1, 2].

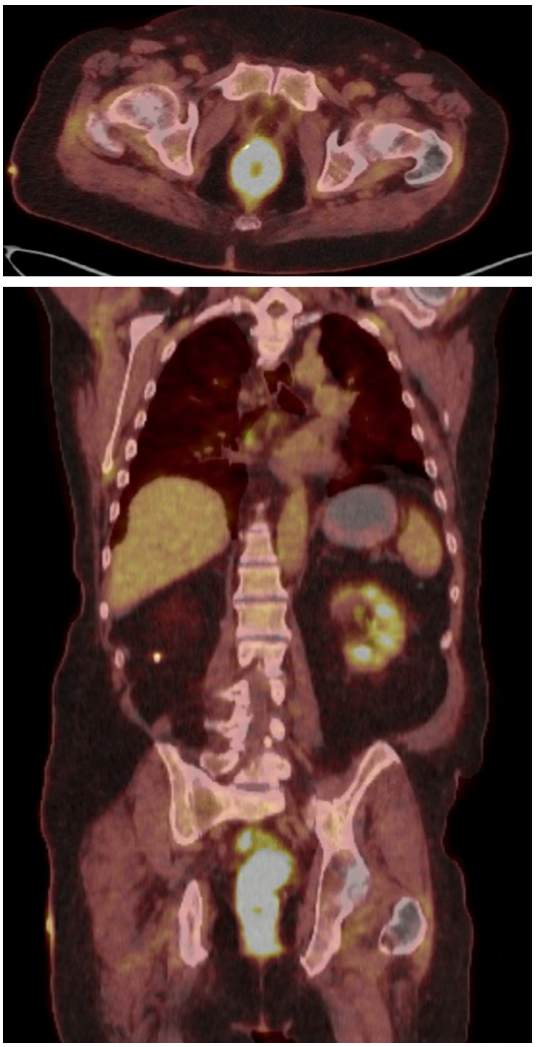

Figure 3. PET/CT demonstrating hypermetabolic rectosigmoid metastases (SUV_{max} 21.3).

Plasmacytoid bladder cancers typically do not express PD-1 or PD-L1 [1, 2].

Clinically, plasmacytoid bladder carcinoma has been associated with more aggressive and advanced disease with a propensity for peritoneal spread [4-8]. In the series of 69 patients, of which 64 had localized disease at diagnosis, median survival was 18 months, with the desmoplastic variant having worse survival at 10 months [2]. For patients that underwent cystectomies, 48% had pT4 disease, and 37% had pT3 disease; 72% had nodal involvement. Median survival after cystectomy was 14 months. Compared to traditional bladder carcinoma, it was more likely to be diagnosed at a higher stage, have nodal metastasis, and have positive surgical margins [9]. 80% of patients who underwent cystectomy were upstaged to pT3 or pT4. Consequently, survival was significantly worse for patients with plasmacytoid disease, 19 months compared to at least 68 months (median not reached), and plasmacytoid disease was found to be an independent predictor of mortality (hazard ratio 2.1). These findings are corroborated by a recent comparison of 64 patients with plasmacytoid bladder cancer to a group of 418 patients with conventional disease [7]. Again, plasmacytoid disease was associated with higher stage, 65% with T3 or T4 compared to 28%, and worse median survival, 24 months compared to 154 months. However, though plasmacytoid cancer correlated with poorer survival, on multivariate analysis controlling for tumor stage, this relationship was no longer significant, suggesting that advanced stage was the main driver of outcomes.

It is noteworthy that our patient had complete response at cystectomy to neoadjuvant cisplatin, gemcitabine, paclitaxel, a combination that has been studied in both advanced and adjuvant settings [10, 11]. Prior case series have demonstrated that standard neoadjuvant chemotherapy is generally ineffective for plasmacytoid disease [2, 7, 9]. Out of 21 patients who either received dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) or gemcitabine with cisplatin (GC), only three patients had down-staging of disease [7]. Compared to those who underwent upfront surgery, there was no difference in overall survival or proportion with negative surgical margins. However, in contrast to our patient, most of the case series so far have included patients who received either MVAC or GC [2, 7, 9, 12].

HER2 in urothelial cancer

Human epidermal growth factor receptor 2 (HER2/ERBB2) is a tyrosine kinase receptor belonging to the ERBB family that has been implicated in the pathogenesis of several cancers and is a well-established target for therapy, notably in breast cancer [13-15]. In conventional urothelial cancer, expression rates vary. Among a series of 80 bladder tumors, 28% had 2+ expression by IHC [16]; in a larger group of 563 patients, 13.3% had overexpression through both IHC and FISH [17]. As in breast cancer, HER2 overexpression has been

Table 1. Whole exome sequencing results of patient's rectal metastasis

Mutations/Indels	GNAS, HOXA13, SS18L1, DAXX, MEN1, PTPRC, KMT2C, MLH1, TPM3, RNF43, ARID1A, NTRK3, CREB3L2
Broad Copy Number Gain	CDK12, SUZ12, RARA, MLLT6, LASP1, SMARCE1, TAF15, ERBB2, NF1, RNF43, HLF, ETV4, CLTC, BRCA1, COL1A1, STAT5B, STAT3, MSI2, SPOP, MYB, TNFAIP3, ECT2L
Focal Amplification	USP6, RSPO3, PTPRK

associated with higher tumor-grade in urothelial cancers, and metastatic foci have higher levels of HER2 compared to primary tumor [16, 18]. While data on HER2 expression in plasmacytoid disease is scarce, one study involving 6 patients showed that 4 cases had 3+ expression on IHC, one case had 2+ expression, and 3 cases had gene amplifications by FISH [19].

The earliest trial of trastuzumab in urothelial carcinoma, reported in 2007, involved 44 patients with metastatic disease selected based on HER2 overexpression (at least 2+ on IHC or gene amplification) [20]. Participants received trastuzumab with paclitaxel, carboplatin, and gemcitabine in 21-day cycles. Primary endpoint was cardiac toxicity. 70% of patients had responses to therapy; median progression-free and overall survival were 7.1 and 14.1 months, respectively with median 6 cycles completed. Cardiac toxicity was significant, with 22.7% of patients experiencing toxicity and 4.5% experiencing grade 3. Patients with gene amplifications had the largest response rate, 82%, though patients with only overexpression on IHC also had high response rates, 67%. In 2015, Oudard et al. compared outcomes in patients receiving gemcitabine and platinum with or without trastuzumab [17]. Inclusion criteria specified both HER2 positivity on IHC and FISH. Despite screening over 500 patients, only 61 were eligible. There were no significant differences in response rate (65.5% without trastuzumab vs 53.2% with) or survival (15.7 months without vs 14.1 months with).

Lapatinib, an inhibitor of both epidermal growth factor (HER1/ERBB1) and HER2, has also been studied in metastatic urothelial carcinoma. In a small study of patients with progressive disease, only one patient responded to lapatinib [21]. In the largest study to date, 232 patients with metastatic bladder cancer and HER1 or HER2+ disease were assigned to maintenance lapatinib or placebo following completion of first-line chemotherapy [22]. There were no differences in progression-free survival (4.5 months for lapatinib compared to 5.1 months for placebo) or overall survival (12.6 months for lapatinib compared to 12 months for placebo). In subgroup analyses, patients with 3+ overexpression, only HER1+, and only HER2+ did not have differential responses to lapatinib therapy.

Following disease progression on dual-HER2 targeting with trastuzumab/pertuzumab and chemo-immunotherapy, our patient received T-DM1, as part of the biomarker-based trial MyPathway (NCT02091141). Emtansine is a cytotoxic agent and microtubule inhibitor that is linked to trastuzumab. Following a 2012 study that showed efficacy in patients with metastatic HER2+ breast cancer who had progressed through trastuzumab, T-DM1 was FDA approved for advanced breast cancer [23]. In bladder cancer, Hayashi et al. has demonstrated efficacy of T-DM1 in cell lines and a murine model [24]. Currently, T-DM1 is being studied in the large biomarker-based clinical trials MyPathway, NCI-MATCH, and NCT02675829.

Enfortumab vedotin

Enfortumab vedotin is an antibody-drug conjugate. Monomethyl auristatin E, a microtubule inhibitor that induces cell cycle arrest, is linked to a monoclonal antibody targeting nectin-4, a cell-adhesion protein overexpressed in urothelial cancer [25]. EV showed significant efficacy in its phase I study, EV-101 [26]. A total of 201 patients with nectin-4 expressing tumors and advanced metastatic disease were enrolled, with a majority of patients (112) treated at the highest cohort (1.25 mg/kg). In the highest cohort, progression-free survival was 5.4 months, and overall survival was 12.3 months, with 40 patients still alive at time of publication (16.4 months follow-up). 43% responded to therapy. These encouraging results spurred a two-cohort phase II study, EV-201, that is ongoing [27]. Cohort 1 includes patients who had received both platinum-based chemotherapy and anti-PD-1/L1 therapy; cohort 2 includes patients who had received anti-PD-1/L1 therapy and are ineligible for platinum-

based chemotherapy. For the 125 patients in cohort 1, response rate was 44%, with median progression-free survival of 7.6 months. 16% remain on treatment, and 44% have ongoing responses. Based on these results, in December 2019, EV was granted accelerated approval by the FDA in patients with metastatic urothelial carcinoma previously treated with platinum chemotherapy and immunotherapy [28]. Recently, in a confirmatory global phase III trial, EV-301, EV was compared against investigator's choice of chemotherapy (docetaxel, paclitaxel, vinflunine) in patients who had progressed on platinum chemotherapy and immunotherapy [29]. 608 patients were randomized based on ECOG score, geography, and presence of liver metastases. At an interim analysis at 11 months, EV demonstrated superior overall survival (12.88 vs 8.97 months, HR 0.70), progression-free survival (5.55 vs 3.71 months, HR 0.62), and overall response rate (40.6 vs 17.9%). Due to clear benefit, the trial was terminated early. EV-103 (NCT03288545) is an ongoing trial examining EV in the neoadjuvant setting and in combination with platinum-based chemotherapies and pembrolizumab for metastatic disease, including a randomized cohort in patients who are unfit for cisplatin.

Notably, our patient responded significantly to EV. To date, there have been no direct studies commenting on EV in plasmacytoid urothelial cancer, nor have there been studies examining expression of nectin-4 in the plasmacytoid variant. However, in EV-101, expression of nectin-4 was nearly universal [26]. Furthermore, the clinical trials have permitted patients with mixed cell types on pathology. In EV-101, 12% of trial patients were classified as "urothelial carcinoma with divergent differentiation", and in EV-201, 21% were classified as "urothelial carcinoma with other histologic variants" [26, 27].

Conclusion

We present a case of the rare urothelial cancer variant, plasmacytoid with several notable aspects: complete response to paclitaxel/gemcitabine/cisplatin neoadjuvant therapy, sustained disease control with HER2-targeting therapy, and subsequent major response to EV. In patients with plasmacytoid variant, investigation into HER2 expression should be undertaken with consideration for HER2-directed therapies; enfortumab vedotin should also be considered for treatment in less selected patients.

Acknowledgements

The authors attest that they obtained signed and written informed consent from the patient to publish his medical images and medical information.

Disclosure of conflict of interest

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