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Case Report

Clinical Response to Enfortumab Vedotin and Pembrolizumab in a Patient with Vaginal Squamous Cell Carcinoma: A Case Report

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Keywords
Vaginal cancer · Enfortumab vedotin · Nectin-4 · Pembrolizumab

Abstract
Introduction: Vaginal cancer is a rare yet aggressive cancer, with unmet need for novel therapeutics. ***Case Presentation:*** In this case report, we present a patient with advanced stage, HPV-positive vaginal cancer who demonstrated clinical, radiological, and molecular response to combination treatment of antibody-drug conjugate enfortumab vedotin (EV) with pembrolizumab. ***Conclusion:*** This is the first reported response to this combination therapy in vaginal cancer in the literature. The patient had positive Nectin-4 staining on evaluation, raising the possibility for future clinical application of EV in vaginal squamous cell cancer.

Introduction

Vaginal cancer is a rare malignancy, with an estimated 9,000 cases annually [1]. The majority of vaginal cancers are squamous cell carcinoma (SCC) and classically are associated with human papillomavirus (HPV). Case series have found the incidence of HPV positivity in

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vaginal cancers to range, with most recent data estimating 50–75% [2–4]. Vaginal cancers may be difficult to distinguish from other cancers of the genital tract, particularly cervix, and diagnosis often relies on pelvic exam under anesthesia and selected biopsies [5].

While some small stage I tumors may be offered surgical excision, patients with advanced disease and infiltration of surrounding tissues are not candidates for surgery. Standard of care for these patients includes chemoradiation: retrospective studies suggest that concurrent chemotherapy (classically cisplatin or carboplatin if cisplatin-intolerant) with radiation is preferred over radiation alone with higher locoregional control [6, 7]. External beam radiation therapy is often provided in conjunction with vaginal brachytherapy, although in some instances, it can be either alone [8, 9].

Nectin-4 is a cellular adhesion molecule overexpressed in multiple cancer types including in 89% of cervical SCCs [10]. A Nectin-4 directed antibody-drug conjugate (ADC) Enfortumab vedotin (EV) was first approved by the FDA in 2019 for the treatment of advanced or metastatic urothelial cancer. Upon binding of the ADC to Nectin-4, the molecule is internalized and its microtubule-disrupting agent monomethyl auristatin E payload is released, resulting in cell death. The combination of EV with pembrolizumab (EVP) was approved by the FDA as first-line therapy in advanced or metastatic urothelial cancer in 2023. The approval was based on a randomized controlled trial (EV-302), which randomized patients to EVP versus traditional chemotherapy (cisplatin/gemcitabine or carboplatin/gemcitabine) and showed significant improvement in overall response rate (67% vs. 44%) and overall survival (31 vs. 16 months) in the EVP arm [11]. However, this combination has not been tested in other cancers of the urogenital tract, including the vagina.

Case Description

The patient is a 64-year-old female who presented initially with abdominal pain and difficulty with urination. The patient consented to the publication of her case, and the CARE Checklist has been completed by the authors for this case report and attached as an online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545141). Her medical history was notable for a total hysterectomy in 2006 for benign fibroids and splenectomy for splenic cysts. She was a former smoker with an 80-pack year history. She denied a history of abnormal pap smears or vaginal lesions, but she did not have routine gynecologic care after her hysterectomy. At her initial presentation, she underwent CT imaging, which showed a large 10.5-cm pelvic mass at the vesico-uterine junction, resulting in severe bilateral hydronephrosis. An MRI abdomen further characterized the mass at the confluence of the posterior bladder wall and the vaginal cuff, with bilateral pelvic lymphadenopathy concerning for metastasis. She had bilateral percutaneous nephrostomy tubes placed with improvement in her hydronephrosis and underwent transurethral resection of bladder tumor (TURBT), which identified a large sessile mass involving the entire posterior bladder. The pathology of the bladder tumor showed a high-grade papillary urothelial carcinoma involving the lamina propria. An FDG PET-CT scan identified a bulky, hypermetabolic mass on the posterior bladder wall with gross extension into adjacent vaginal wall, hypermetabolic foci along the descending and sigmoid colon, and a hypermetabolic lymph node in the right pelvic sidewall. There was no evidence of distant metastatic disease on the PET-CT. A ctDNA serum test (Signatera MRD) drawn prior to any therapy was positive at 97.67 MTM/mL.

Based on the infiltration of the tumor into several local structures as well as its nodal spread, the disease was considered locally advanced. Surgery was deferred in favor of starting EV (days 1 and 8 of a 21-day cycle) and pembrolizumab (every 3 weeks) (EVP) as standard of

care for locally advanced urothelial cancer. The patient completed 5 cycles of therapy over 4 months without significant adverse events.

Her follow-up PET-CT imaging after 5 cycles of treatment showed a favorable response, with metabolic resolution of the previously active primary mass and resolution of previously metabolic lymph nodes (Fig. 1). The decrease in tumor burden by imaging was paralleled by a significant decrease in serum ctDNA to 0.09 MTM/mL.

Routine repeat TURBT done shortly after the 5th cycle of EVP showed an invasive tumor along posterior bladder wall with numerous fistulous tracts to the vagina. Pathology identified "invasive high-risk HPV-positive carcinoma involving lamina propria" with squamous differentiation, raising the possibility of an HPV-associated SCC of gynecologic rather than urothelial origin. Features favoring the possibility of an HPV-associated tumor included prominent basaloid morphological features (characterized by nests and ribbons of hyperchromatic tumor cells with high nuclear-to-cytoplasmic ratio and frequent mitotic figures) with admixed areas of more well-differentiated squamous differentiation, in a background of squamous metaplasia (Fig. 2). The tumor was found to be HPV positive by in situ hybridization. After multidisciplinary discussion in the gynecologic oncology tumor board, and based on totality of the imaging and pathology, the consensus was that the primary tumor likely arose from the vagina.

Additional workup on this tumor included PD-L1 immunohistochemistry, which showed a combined positivity score of 1. Next-generation sequencing demonstrated microsatellite stable tumor with intermediate tumor mutation burden of 14 mut/MB. Tumor somatic mutations were found in BAP1 (M1), FGFR1 (amp), IDO1 (amp), PIK3CA (E545K), and PTEN (L57S).

The patient subsequently received external beam radiation therapy to the bladder and vagina (55 Gy over 20 fractions) with weekly cisplatin chemosensitization 20 mg/m^2 as consolidative therapy for locally advanced HPV-positive SCC of vagina. Her most recent MRI abdomen/pelvis, 4 months following CRT, demonstrated no evidence of disease. Subsequently, serum ctDNA levels have remained undetectable (0.00 MTM/mL) and 2 subsequent PET-CT scans have not shown recurrence of disease, 6 months after completing CRT.

Discussion

Here we describe a case of a patient with locally advanced vaginal HPV-related SCC with a significant clinical response to combination treatment with EV and pembrolizumab. To our knowledge, this is the first reported use of EVP in this treatment setting.

Our case presented a unique challenge as the initial pathology was consistent with a urothelial cancer and the patient was started on a regimen, only for the diagnosis to be revised on repeat biopsy. Urothelial carcinoma and SCC share overlapping morphological features, including stratified epithelium with papillary architecture; however, HPV positivity is rare in urothelial cancer (5.2%) and should alert to the possibility of a gynecologic origin [12].

Nectin-4 expression via immunohistochemistry is not commonly tested in clinical practice, but there is evidence that expression and amplification of the Nectin-4 gene correlate to response to EV [13]. The rate of moderate to high Nectin-4 staining in urothelial cancer (60%) is similar to the rate in cervical cancer (67.8%), a cancer that is similar to vaginal squamous cell cancer in its expression profile, [14, 15]. A recent published report described the efficacy of Nectin-4 ADC in patients with chemotherapy refractory cervical cancer, with an impressive overall response (40.5%) and disease control rates (89.2%) [10]. There have also been case reports documenting efficacy of EV in penile squamous cell cancers, with an ongoing phase II trial further evaluating its effect [16]. In this patient, we performed

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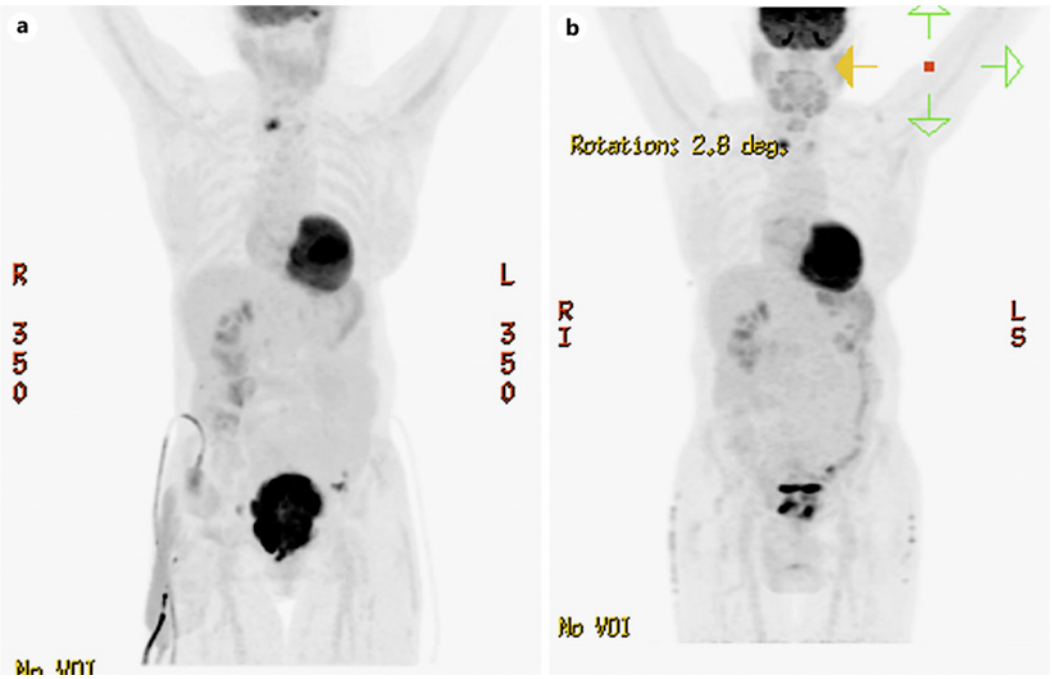

Fig. 1. PET/CT MIP 10 pretreatment imaging (**a**) to posttreatment (**b**).

immunohistochemical staining of the second TURBT specimen for Nectin-4 expression in a research lab, which was strongly positive, supporting the role of EV in her response (Fig. 3). An ongoing phase I/II trial is currently evaluating another Nectin-4 ADC, CRB-701, for use in relapsed/refractory cervical cancer (NCT06265727).

However, as with any combination therapy, it is difficult to attribute her clinical response to EV or pembrolizumab alone, an additive effect, or synergy between the agents. For example, there is evidence that she may have benefitted from pembrolizumab alone based on her histology and tumor mutational burden (14 mut/MB). A basket trial using pembrolizumab in rare histologies included 3 patients with vaginal and/or vulvar SCC, one of which had a tumor response [17]. While not standard of care in vaginal cancers, pembrolizumab is approved for the treatment of combined positive score (≥1) cervical cancers who have progressed on previous therapies based on the KEYNOTE-826 trial, which showed improved progression free survival (10.4 vs. 8.2 months) and overall response (68.1% vs. 50.2%) compared to chemotherapy alone [18]. In addition, pembrolizumab is also approved for tissue-agnostic treatment of patients with tumor mutational burden greater than 10 based on KEYNOTE-158, which enrolled 2 patients with TMB-high vaginal/vulvar cancer [19].

This case represents the 1st known patient with HPV-positive vaginal cancer with clinical, radiological, and molecular response to the combination of EV with pembrolizumab. As evidenced by EV-302, there is significant promise in the combination of ADCs and immune therapy. Researchers theorize that the ADCs prompt a more immunogenic cell death, leading to increased neoantigen presentation and immune surveillance [20]. There are several other trials using ADC-IO combinations currently under investigation (NCT05911295 and NCT04724018).

A strength of this paper is the possibility for a future avenue to treat this aggressive cancer with an unmet clinical need. We do acknowledge that while the consensus at our institution is that this represents an HPV+ vaginal cancer, we cannot rule out a HPV+ urothelial primary cancer. In addition, while there were molecular and imaging findings,

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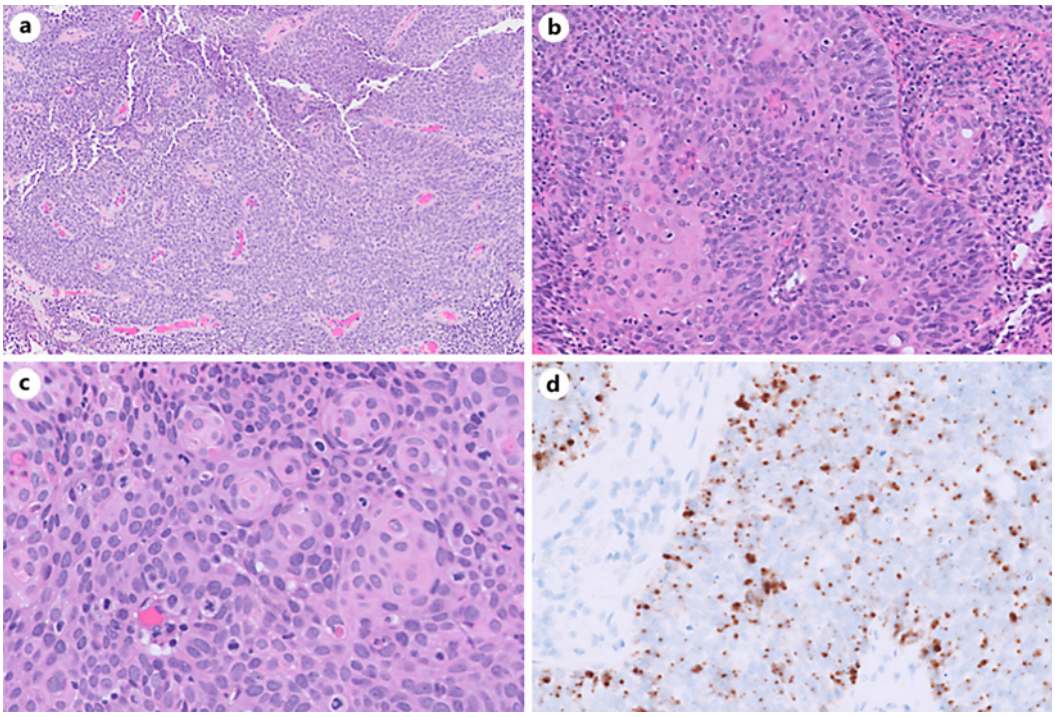

Fig. 2. Hematoxylin and eosin (H&E, **a–c**) and high-risk HPV in situ hybridization. **d** Staining of the urinary bladder transurethral resection specimen containing HPV-associated carcinoma. **a** Initial biopsy showing tumor cells surrounding apparent fibrovascular cores, mimicking papillary urothelial carcinoma, ×10. **b–c** Subsequent specimen showing invasive carcinoma in nested ribbons and sheets with basaloid features and focal squamous differentiation with individual cell keratinization and intercellular bridges, ×20 and ×40. **d** HR-HPV-ISH (Leica Bond, ACD bio; RNAscope™ 2.5 LS Probe-HPV-HR18; Cat No. 312598; automated assay for Leica Systems) demonstrating granular positivity targeting HPV E6 and E7 messenger RNA (mRNA) transcripts, providing evidence of viral DNA integration into the tumor cells, ×40.

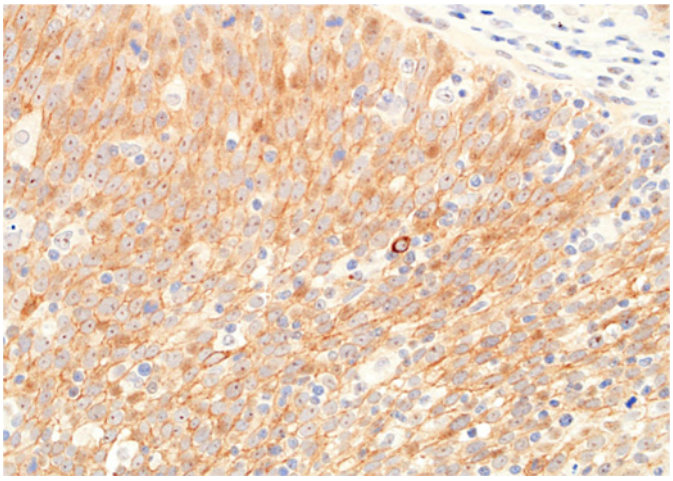

Fig. 3. Nectin-4 immunohistochemical, taken at ×40 magnification, shows a strong expression of Nectin-4 in tumor cells. The Abcam antibody was used at 1:100 dilution, using rabbit monoclonal [EPR15613-68].

showing a response to EVP, the addition of consolidative chemoradiation limits our ability to understand the durability of the response to EVP alone. Further research in this field is warranted.

Patient Perspective

I am happy that the unconventional treatment I have received to this point has worked and I am grateful to my doctors for their support.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study design: M.G., I.B., and S.A.S.; acquisition of data: M.G., I.B., A.M., C.D., and E.C.; analysis of data: M.G., I.B., O.D., E.C., and S.A.S.; and review of manuscript: all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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