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CASE REPORT PEER REVIEWED | OPEN ACCESS

Complete response of metastatic cervical adenocarcinoma treated with chemoradiotherapy followed by pembrolizumab: A case report

Wolfram Samlowski, Mark Chang, Raul Meoz, Amin Hedayat

ABSTRACT

Introduction: Metastatic adenocarcinoma of the uterine cervix is challenging to treat, particularly if there is persistent disease following surgery and chemoradiotherapy. In recent years, advances in checkpoint inhibitor-based immunotherapy have shown promise in patients in a variety of cancers. Only limited information is available concerning treatment of cervical adenocarcinoma with checkpoint inhibitors.

Case Report: This case report details a patient with metastatic cervical adenocarcinoma with persistent disease following surgical resection. Subsequent treatment with cisplatin, paclitaxel, and bevacizumab therapy with concurrent radiotherapy resulted in a partial response. The patient was subsequently treated with pembrolizumab. After 3 cycles of treatment the patient achieved a stable radiologic complete remission, which continues after treatment discontinuation.

Conclusion: This result suggests that chemoradiotherapy with either concurrent or sequential administration of a PD-1 antibody, such as pembrolizumab, may have significant activity as treatment of metastatic or unresectable cervical adenocarcinoma. Further prospective clinical testing appears warranted.

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INTRODUCTION

Invasive carcinoma of the uterine cervix is an uncommon neoplasm. In 2020, it is estimated that there will be 13,800 cases in the United States, resulting in 4290 deaths [1]. The most common cervical cancer histology is squamous cell carcinoma, which is frequently associated with evidence of human papillomavirus (HPV) infection [2, 3]. Less than 10% of cervical carcinomas have an adenocarcinoma histology, which may associate with maternal diethylstilbestrol usage during pregnancy [4]. Far less is known about treatment options for cervical adenocarcinoma in comparison to the more common squamous cell histology tumors. Due to lack of more specific information, cervical cancers of both histologic types are treated in a similar fashion.

Traditionally localized cervical cancer has been treated with surgery, when feasible [3]. While chemotherapy and radiotherapy individually can play a role in the management of regionally advanced cervical cancer, concurrent chemoradiation therapy has become the standard treatment for locally advanced or metastatic cervical cancer for over the last three decades [5]. Addition

of the angiogenesis inhibitor bevacizumab appears to increase survival [6]. Despite a survival improvement with an addition of concurrent chemotherapy to radiation, significant rates of local and distant failures (17% and 18%, respectively) are still encountered [6]. Patients who have persistent disease or relapse following chemoradiotherapy have a particularly poor outlook. New therapeutic approaches for persistent or recurrent cervical cancer are badly needed. Cancer immunotherapy with checkpoint inhibitor monoclonal antibodies has shown promise in many cancers, including cervical cancer. Based on this experience we treated a patient with persistent metastatic cervical adenocarcinoma with pembrolizumab after partial response to chemoradiotherapy. This approach resulted in a complete remission.

CASE REPORT

A 42-year-old woman with a history of cervical adenocarcinoma status for posthysterectomy three years previously presented oncologic consultation for progression of cervical cancer. At age 39, she was initially found to have locally invasive disease measuring 3.2 × 2.7 × 2.0 cm staged as T1b1, N0, M0 cervical adenocarcinoma (Figure 1A). She was treated with radical hysterectomy. Surgical and radiologic staging showed no evidence of metastasis. Adjuvant chemotherapy and radiation therapy were discussed, but not administered due to the patient's choice.

In January 2019 (27 months later), she noticed an enlarging mass in her right inguinal and pelvic region which was soft, rounded, and raised. She also experienced worsening pain in her right upper thigh which was worse in all activities and positions including standing, walking, and lying down. She had 2-month history of nausea, vomiting, and night sweats. She also noted a 50-pound weight loss over a 6-month period due to poor appetite. Clinical exam showed a right groin mass and lymphedema of the right leg.

In January 2019, radiographs were performed and a positron emission tomography/computed tomography (PET/CT) revealed a 9.7 × 7.5 × 7.5 cm mass with standardized uptake value (SUV) 17.2 in the right pelvis in association with the right iliopsoas muscle (Figure 2A). Additional adenopathy was noted in the pelvis. The patient underwent a biopsy and attempted resection of the pelvic mass, which revealed metastatic adenocarcinoma compatible with her previous cervical cancer (Figure 1B). Tissue sample from this biopsy was sent to the laboratory for next-generation oncogene testing (Foundation Medicine, Cambridge, MA) testing which revealed 5% PDL1 expression, an intermediate tumor mutational burden (9/Mb), with BARD1 loss, and STK11 Q37* truncation.

Standard chemoradiotherapy was initiated with weekly Cisplatin (25 mg/m^2), Taxol (60 mg/m^2) weekly, and Avastin (15 mg/kg every 3 weeks) for 3 cycles preceding and during radiotherapy. The patient was treated with radiotherapy to a total pelvic dose of 5040 cGy in 28 fractions over 50 elapsed days. This was followed by a boost to the right pelvic mass of 540 cGy in 3 fractions. All treatment delivered with volumetric modulated arc radiotherapy-intensity modulated radiation therapy (VMAT-IMRT) with 6 MeV photons. The patient had improvement with her groin and abdominal pain during treatment but developed neutropenia, as a side effect of her chemoradiotherapy regimen. Ultimately, chemotherapy treatment was held due to persistent neutropenia and eventually discontinued. A follow-up PET/CT scan one month after completion of chemoradiotherapy was performed in July 2019 showing persistent metabolically active right groin mass extending along the right psoas muscle measuring 5.5 × 5.4 × 9.5 cm (Figure 2B). This mass remained metabolically active with an SUV of 3.2.

Due to the persistence of a significant metabolically active mass, the patient was started on pembrolizumab at a fixed dose of 200 mg iv q 3 weeks, as salvage therapy. This was well-tolerated, without grade III or IV toxicity and the patient completed 10 cycles. In April 2020, after a 10th dose of pembrolizumab, PET/CT showed a complete metabolic response of tumor with no measurable residual tumor mass and no residual PET uptake (Figure 2C). Our patient presently remains in an ongoing radiographic remission and pembrolizumab therapy has been discontinued without recurrence, to date.

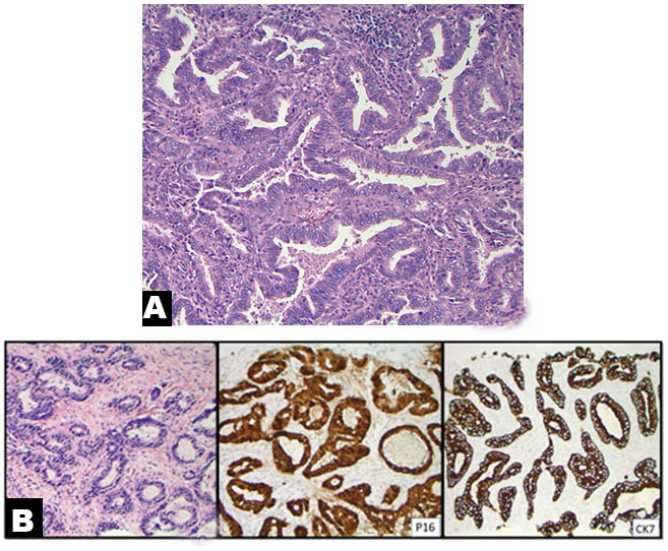

Figure 1: (A) Hematoxylin and eosin stained histology from the initial surgical resection demonstrated moderately differentiated adenocarcinoma (200×). (B) Histology and immunohistochemistry stains from pelvic mass demonstrated adenocarcinoma compatible with recurrence of a previously resected cervical adenocarcinoma (H&E, p16, CK7 as indicated) (200×).

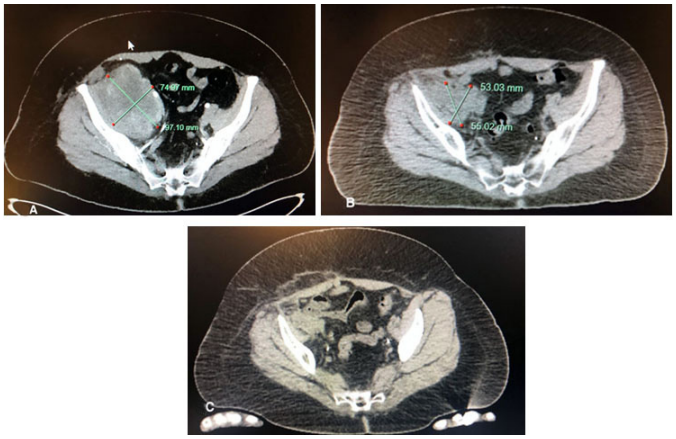

Figure 2: PET/CT evaluation of patient with cervical adenocarcinoma. (A) The initial scan demonstrated a large pelvic mass, with bidimensional measurements of 9.7 × 7.5 cm SUV 17.2. (B) After cisplatin/paclitaxel chemotherapy plus bevacizumab and concurrent radiotherapy there was improvement in the pelvic mass to 5.5 × 5.3 cm with persistently increased SUV 3.2. (C) Following 10 cycles of pembrolizumab there was no longer a measurable mass and SUV was reduced to background level.

DISCUSSION

Initial therapeutic options for metastatic cervical cancer are currently limited. There have been numerous trials of chemotherapy spanning many decades that have shown modest effectiveness in producing clinical responses with a relatively high level of side effects due to incorporation of platinum analogues in these regimens [7]. Doublet chemotherapy with cisplatin and paclitaxel proved superior to other chemotherapy doublets tested, and has become the de facto standard treatment regimen [8, 9]. Patients with prior treatment with radiotherapy or prior platinum exposure were found to have an adverse outcome with further palliative chemotherapy [10]. In the GOG-0240 study, addition of the antiangiogenic agent bevacizumab to cisplatin/paclitaxel resulted in improved response rate (48 vs 36%), modestly improved progression free survival (8.2 vs 5.9 months) and improved overall survival (17.0 vs 13.3 months) [6]. Unfortunately, the vast majority of patients in this trial eventually died of their disease. Thus, when our patient had only a partial response to platinum/paclitaxel and bevacizumab therapy, we were concerned about a potential need for effective 2nd line therapy options.

There is limited data concerning the effectiveness of cancer immunotherapy with checkpoint-inhibitor antibodies directed against PD1, PDL1, or CTLA4. These agents have shown modest activity in recurrent or metastatic cervical cancer. In clinical trials in recurrent/metastatic cervical cancer, the CTLA4 antibody ipilimumab failed to induce any significant responses [11]. One complete response was seen in a phase I trial of cemiplimab (a PD1 specific antibody) in combination with hypofractionated radiotherapy [12]. In the Checkmate 358 trial, treatment with nivolumab (another PD1-specific antibody) resulted in 1 CR and 4 PR in 19 women [13]. In the Keynote 028 phase I trial, there was a 17% response rate in the 24-patient cervical cancer cohort following pembrolizumab treatment (another PD1-directed antibody), with a median duration of response of 5.4 months [13]. This led to further testing of pembrolizumab in the Keynote 158 phase II trial [14]. In this trial, 98 women with cervical cancer were treated. Eighty-two patients had increased PDL1 expression on tumor cells (≥1%). The objective response rate was 12.2%, all in PDL1 expressing patients. There were three complete responses. The most common side effects were hypothyroidism (10.2%), decreased appetite (9.2%), and fatigue (9.2%). Grade 3–4 adverse events occurred on only 12.2% of patients. This trial included 5 women with cervical adenocarcinoma. Based on this limited experience we elected to treat our patient with persistent cervical adenocarcinoma with pembrolizumab after completion of planned cisplatin/paclitaxel/bevacizumab chemoradiotherapy. This strategy resulted in a complete remission.

There is an increasing biologic rational for combining checkpoint inhibitors with radiotherapy. Doses of radiation that induce tumor cell necrosis (>1 Gy) may stimulate immune responses through a number of different mechanisms. These include enhanced expression of Class I MHC molecules on the surface of tumor cells, increased expression of cell death receptors like Fas/CD95 and NKG2D ligand on tumor cells, and boosting T cell and NK cell recognition [15, 16]. Soluble mediators, such as chemokines and cytokines are released that increase vascular adhesion and MHC Class I antigen expression, further increasing T-cell recruitment into the tumor microenvironment [17–19]. Finally, radiotherapy downregulates inhibitory immune signals from myeloid-derived suppressor cells and regulatory T cells [20]. Thus, preclinical studies strongly support the concept that radiotherapy can create a tumor microenvironment that enhances induction of anticancer immune responses which can be increased by addition of PD1 antibody treatment [21]. Chemotherapy also can promote immunologic anticancer responses by increasing the immunogenicity of malignant cells, or by inhibiting immunosuppressive circuitries that are established by developing neoplasms [22]. This has led to successful development of effective cisplatin-based chemo-immunotherapy regimens in non-small cell lung cancer [23]. Our clinical case suggests potential for success of either concurrent or sequential chemoimmuno-radiotherapy approaches in cervical carcinoma. These approaches appear to be worthy of further evaluation in prospective clinical trial.

CONCLUSION

Addition of pembrolizumab therapy following chemoradiotherapy for metastatic cervical adenocarcinoma

induced a complete remission. Our clinical case suggests potential for either concurrent or sequential chemoimmuno-radiotherapy approaches in cervical carcinoma. This approach appears to be worthy of further evaluation in prospective clinical trials.

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Wolfram Samlowski – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mark Chang – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy

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Amin Hedayat – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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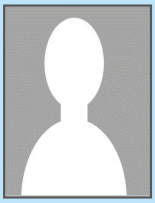

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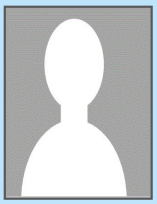

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