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Case report

Cutaneous metastasis of PD-L1 positive cervical carcinoma

Chrissy Liu [a,*], Nancy Zhou [b], Daniel Levitan [c], Juan Coca Guzman [c], Julia Fehniger [d]

[a] State University of New York (SUNY) Downstate Health Sciences University, Department of Obstetrics and Gynecology, Brooklyn, NY, United States
[b] State University of New York (SUNY) Downstate Health Sciences University, Division of Gynecologic Oncology, Brooklyn, NY, United States
[c] State University of New York (SUNY) Downstate Health Sciences University, Department of Pathology, Brooklyn, NY, United States
[d] Legacy Health, Gynecologic Oncology, Portland, OR, United States

1. Introduction

Cutaneous metastasis from cervical carcinoma is rare with an incidence of 0.1 to 2% and typically presents as a terminal event (Alrefaie et al., 2019). The interval between initial cancer diagnosis to skin metastasis is variable. The average time to presentation ranges from 16.9 to 20.7 months, but has been reported as late as 19 years (Alrefaie et al., 2019; Agrawal et al., 2010). Common morphologic presentations include nodules, plaques, or inflammatory telangiectasias. The lesions tend be ulcerated and can resemble cellulitis (Alrefaie et al., 2019). The most common metastatic sites include the abdominal wall, vulva, and lower extremities. The prognosis of patients with of cutaneous metastasis is poor, with reported overall survival of 6–12 months (Imachi et al., 1993). Here we report a rare case of programmed death ligand 1 (PD-L1) positive cervical cancer with cutaneous metastases.

2. Case

This patient is a 68-year old Black Caribbean woman with a remote history of locally advanced cervical cancer treated with radiation in the 1988. In August 2019, the patient presented for routine pelvic exam and biopsy of a necrotic cervical mass demonstrated recurrent squamous cell carcinoma (SCC). Positron emission tomography (PET) scan showed increased metabolic activity only at the level of the cervix without evidence of metastatic disease. The patient was offered pelvic exenteration, but declined. She elected to proceed with chemotherapy and completed five of six planned cycles of cisplatin, paclitaxel, and bevacizumab. The sixth cycle was omitted due to progressive toxicity despite dose reduction. PET scan following completion of chemotherapy demonstrated resolution of the previously seen avid lesion in the cervix.

The patient remained without clinical evidence of disease for six months, when she presented to the emergency room with hematochezia in October 2020. A CT scan showed two 1–2 cm exophytic soft tissue masses abutting the descending colon. CEA was elevated at 201 ng/mL, and a colonoscopy was performed but was negative for intraluminal masses. New areas of necrotic tissue were seen on pelvic exam at this time. Biopsy at the vaginal apex (Fig. 1) confirmed recurrent PDL-1 positive SCC (PD-L1 IHC 22C3 pharmDx, CPS = 2). PET scan showed diffuse metastatic disease with new hypermetabolic para-aortic lymphadenopathy, a 2.5 cm liver mass, and multiple peritoneal nodules.

The patient began treatment with pembrolizumab but developed cutaneous lesions on her vulva and bilateral lower extremities after three cycles. There was initially concern for grade 1 immune-mediated toxicity and the patient was initiated on clobetasol cream 0.05% twice daily. However, given the atypical appearance of the lesions, appearing as violaceous papules and plaques with overlying scales (Fig. 2), she was referred to dermatology for further evaluation. Multiple biopsies demonstrated metastatic SCC morphologically similar to her prior vaginal biopsies; immunohistochemistry was strongly and diffusely positive for p16 and CK7, and negative for p40 and CK5/6 (Fig. 3). The patient started treatment with pemetrexed, given its acceptable safety profile and overall response rate of 31% (Network NCC). There was notable improvement in erythema and induration seen after three cycles, along with decreased pain related to her cutaneous metastases, but unfortunately, she developed progressive disease. The patient died 11 months after being diagnosed with recurrent disease.

3. Discussion

We describe a rare case of PD-L1 positive cervical carcinoma with cutaneous metastases. PD-L1 plays a crucial role in programmed cell death and maintains the homeostasis of the immune response. It is normally expressed on immune cells, and upon binding to its receptor, the immune response is inhibited. In the context of cancer, elevated PD-L1 expression inhibits T-cell activity and favors a state of immune resistance, thus preventing cell-mediated lysis. Approximately 35% of cervical squamous cell carcinomas and 17% of cervical adenocarcinomas express PD-L1. High-risk human papilloma virus (HPV)

* Corresponding author at: Department of Obstetrics and Gynecology, SUNY Downstate Health Sciences University, 450 Clarkson Ave, Brooklyn, NY 11203.
E-mail address: chrissy.liu@downstate.edu (C. Liu).

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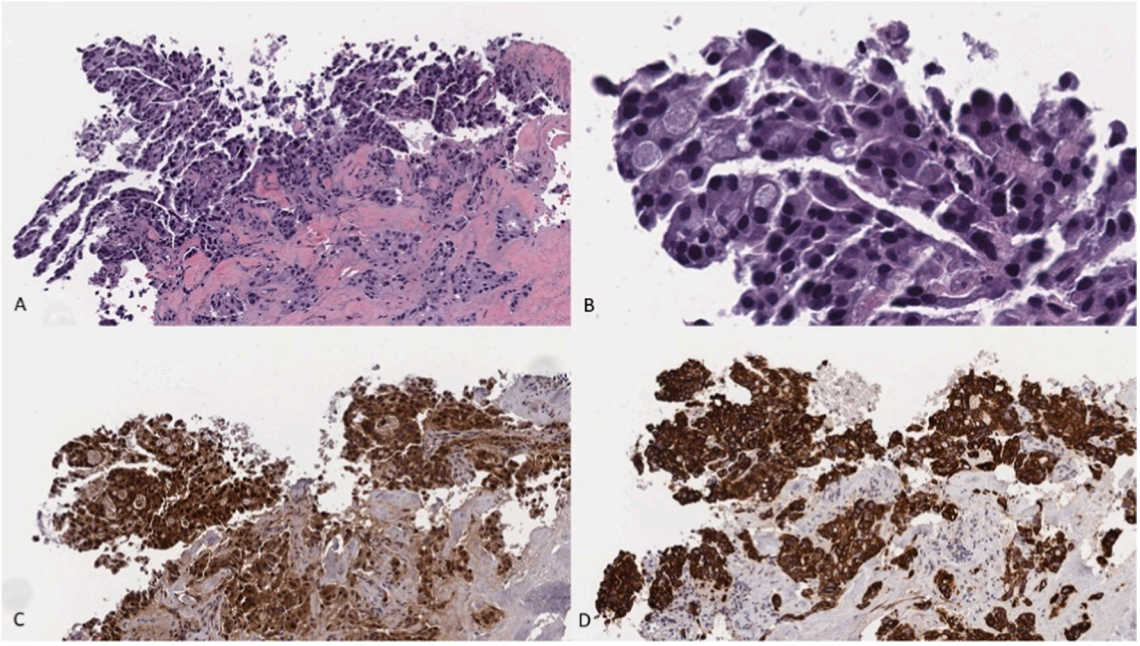

Fig. 1. Biopsy specimen from vaginal apex. A. Invasive poorly differentiated carcinoma with necrosis. B. Tumor cells have pleomorphic and hyperchromatic nuclei and a few cells show intracellular vacuoles. C. Immunostains demonstrate the tumor cells are strongly and diffusely positive for p16; and D. CK7; but negative for CK20, PAX8, p40 and CK5/6 (not shown). The findings are consistent with a poorly differentiated carcinoma of the cervix.

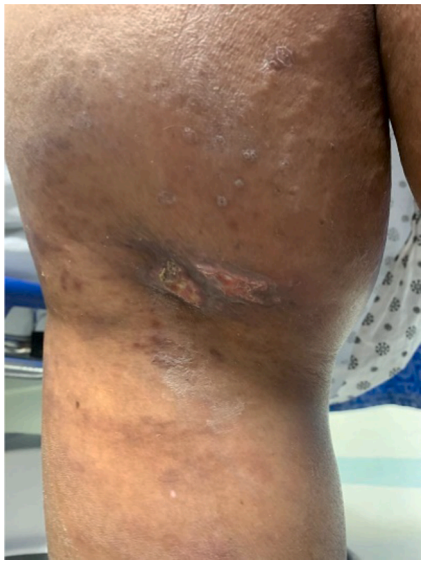

Fig. 2. Cutaneous metastasis involving the lower extremity.

oncogenes may upregulate the PD-L1 pathway (Allouch et al., 2020). The prognostic value of PD-L1 expression in cervical cancer is controversial, but may be associated with worse overall survival (OS) (Rotman et al., 2020).

Immune checkpoint inhibitors have become an important treatment modality for many cancers, such as melanoma, non-small-cell lung cancer, and breast cancer. Based on the results of KEYNOTE-158, the U. S. Food and Drug Administration (FDA) approved pembrolizumab for advanced PD-L1 positive cervical cancer patients with progression after chemotherapy in 2020 (Borcoman and Le Tourneau, 2020). This phase II trial showed an overall response rate of 14.6% in the PD-L1 + patient population (Chung et al., 2019). Overall, median PFS and OS were 2.1 months and 9.4 months, respectively (Chung et al., 2019). In the PD-L1 positive population, median PFS and OS were 2.1 and 11 months, respectively. Disease control rate was 30.6% and median duration of response (DoR) was not reached (Borcoman and Le Tourneau, 2020; Chung et al., 2019).

Pembrolizumab has a well-tolerated safety profile and only 4.1% of patients had to discontinue treatment due to adverse events. The rate of grade 3–4 severe skin reactions in KEYNOTE-158 was 1.3%. Given its duration of efficacy and safety profile, pembrolizumab became a preferred systemic therapy for PD-L1 positive recurrent cervical cancer (Network NCC). The recent publication of KEYNOTE-826 presents another opportunity to improve outcomes in this patient population (Colombo et al., 2021). The addition of pembrolizumab to platinum-based chemotherapy in persistent; recurrent; or metastatic cervical cancer improved PFS and OS for patients with PD-L1 positive tumors (Colombo et al., 2021). The addition of pembrolizumab to platinum-based chemotherapy is now first-line therapy for recurrent and metastatic PD-L1 positive cervical cancer and was FDA approved in October 2021 (Network NCC).

Despite significant advancements in the treatment of recurrent cervical cancer, the optimal treatment for cutaneous metastasis remains unknown and prior reports reflect limited survival after presentation. Treatment is mostly palliative, utilizing chemotherapy, radiation, surgical excision, and electrochemotherapy (ECT) (Basu and Mukherjee, 2013; Marty et al., 2006). ECT is the concomitant local application of a cytotoxic agent and electric impulses to facilitate better drug diffusion into cells. While ECT has been successfully used to treat cutaneous metastases from solid tumors like breast cancer, ECT use has not been described in cervical cancer. In one series, an objective response rate of 85% and complete response rate of 73% was achieved for ECT-treated tumor nodules from non-gynecologic malignancies (Marty et al., 2006).

Patients with cutaneous cervical cancer metastases reported in the literature typically experience a partial response to platinum-based chemotherapy and/or radiation (Agrawal et al., 2010; Imachi et al., 1993; Basu and Mukherjee, 2013). Complete responses, however, have also been reported (Palaia et al., 2002). Palaia et al. described a 47 year old woman who developed recurrent SCC on her abdomen, lower extremity, and gluteus after a radical hysterectomy (Palaia et al., 2002). Her skin lesions resolved with chemotherapy and she remained symptom-free for 9 months (Palaia et al., 2002).

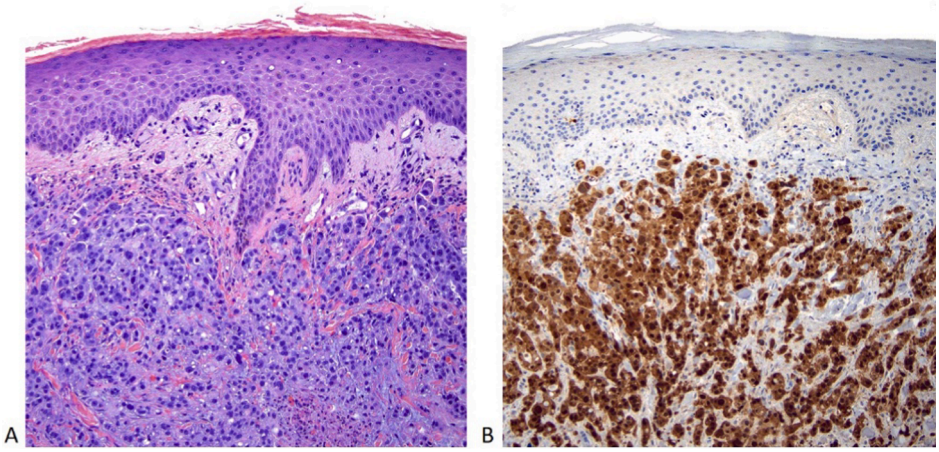

Fig. 3. Skin punch biopsy from the left mid-thigh showing metastatic carcinoma within the dermis A. Hematoxylin-eosin staining shows a relatively unremarkable epidermis with tumor below. Lymphovascular invasion is present. B. There is strong and diffuse, nuclear and cytoplasmic staining for p16, consistent with an HPV-associated carcinoma.

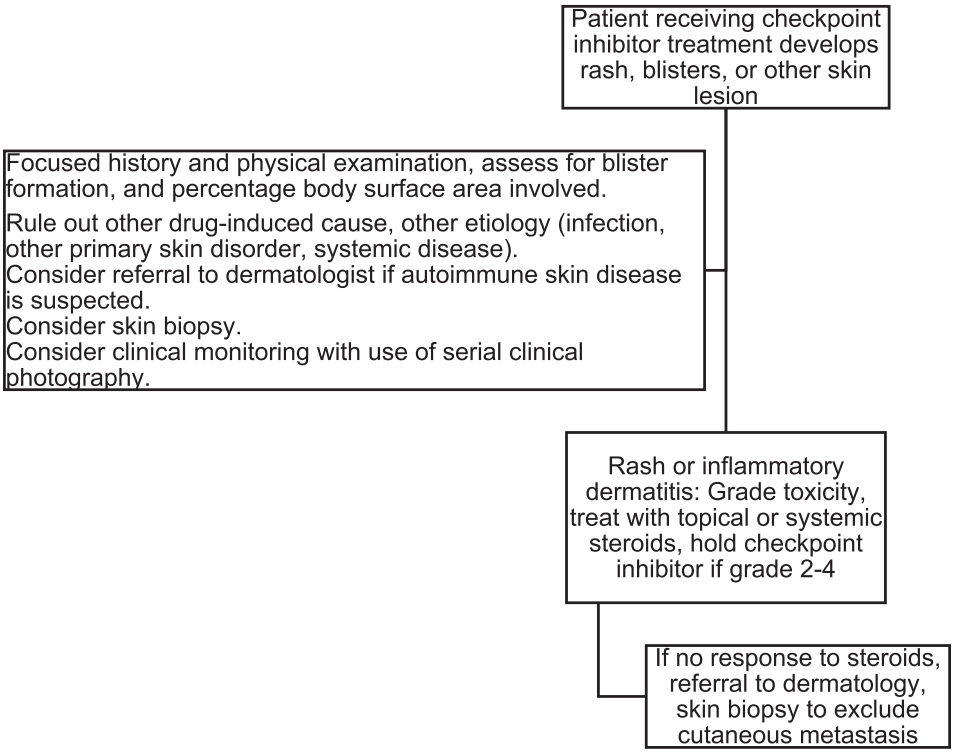

Fig. 4. Proposed diagnostic algorithm for evaluating cutaneous toxicities in cervical cancer patients on checkpoint inhibitor treatment.(Schneider et al., 2021).

Survival outcomes range from 3 to 16 months, with an average of 8.5 months from diagnosis of skin metastases to death (Alrefaie et al., 2019; Agrawal et al., 2010; Imachi et al., 1993). Similar to our case, Agrawal et al. described a 66 year old woman who developed cutaneous metastases on her lower abdomen, vulva, and perineum after treatment with chemoradiation for cervical SCC (Agrawal et al., 2010). She received six cycles of chemotherapy, but subsequently progressed and died 6 months after the appearance of her recurrent disease (Agrawal et al., 2010). Prolonged survival up to 4 years, however, has been reported (Imachi et al., 1993; Ozmen et al., 2009). Ozmen et al. described a 32 year old patient with cervical SCC status post a radical hysterectomy and radiation who developed a subcutaneous mass, nodular skin lesion, and anterior abdominal wall mass 5 years after initial treatment (Ozmen et al., 2009). Surgical excision followed by chemoradiation was performed, and the patient survived 4 years recurrence-free (Ozmen et al., 2009). Likewise, Imachi et al. performed surgery and chemoradiation on a 75 year old patient with a chest wall and scalp recurrence, who survived 37 months (Imachi et al., 1993). These cases suggest that with isolated metastases, surgical resection in addition to chemoradiation may prolong disease-free survival.

Cutaneous metastasis from cervical cancer can vary in clinical appearance and should remain in the differential diagnosis until proven otherwise. With the increased use of immune checkpoint inhibitors, which are known to carry the risk of cutaneous toxicity, the interpretation of skin disease can be challenging. Dermatologic manifestations of immunotherapy-related adverse events can include pruritus, maculopapular rashes, and lichenoid reactions (Geisler et al., 2020). Treatment depends on the severity of toxicity and typically utilizes topical or

systemic steroids and possible treatment interruption (Fig. 4). With any atypical lesions, biopsy should be performed to exclude cutaneous metastases over a drug-related reaction. Unfortunately, despite the promising results seen in the use of immune checkpoint-inhibitors for recurrent cervical cancer, our patient's disease progressed following anti-PD-L1 treatment and she died 6 months after the development of cutaneous metastases.

4. Conclusion

In advanced, recurrent, and metastatic cervical cancer, identification of PD-L1 expression is important to guide treatment. Results from recent studies of anti-PD-L1 therapies represent new opportunities to improve patient outcomes. In this case of a recurrent PD-L1 positive cervical cancer whose cutaneous metastases developed while receiving treatment with pembrolizumab, limited benefit was seen with immune checkpoint inhibitor use. However, treatment of other cutaneous malignancies with pembrolizumab is well established and has led to a durable response in patients with squamous cell skin cancer (Grob et al., 2020). Further studies are warranted to improve outcomes in patients with this rare manifestation of recurrent cervical cancer. With the increasing utilization of immunotherapy in recurrent, advanced cervical cancer, this report highlights the importance of ruling out cutaneous metastases for patients on checkpoint inhibitors who develop dermatologic toxicity that is unresponsive to steroids.

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The patient has been made aware in advance that photographs were taken. Per the Elsevier website, formal consents are not required for the use of entirely anonymized images from which the individual cannot be identified. The image and pathology slides we included are not identifiable.

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CrediT authorship contribution statement

Chrissy Liu: Writing – original draft, Writing – review & editing. **Nancy Zhou:** Conceptualization, Methodology, Writing – review & editing. **Daniel Levitan:** Writing – review & editing. **Juan Coca Guzman:** Writing – review & editing. **Julia Fehniger:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

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

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