Gynecologic Oncology Reports 33 (2020) 100607

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Cutaneous metastasis of PD-L1 positive ovarian carcinoma

Victoria Hastings[a], Jennifer McEachron[b,*], Marguax J. Kanis[a]

[a] Division of Gynecologic Oncology, New York Presbyterian – Brooklyn Methodist Hospital, Brooklyn, NY, United States
[b] Division of Gynecologic Oncology, SUNY Downstate Medical Center, Brooklyn, NY, United States

1. Introduction

Ovarian cancer is the leading cause of gynecologic cancer deaths in the United States as it is frequently diagnosed at an advanced stage (Otsuka, 2019). Peritoneal seeding and lymphatic spread are the primary routes of metastasis, and as a result, the abdominopelvic cavity, pleura and lymph nodes are the most common sites (Otsuka, 2019; Kim et al., 2012; Ayhan et al., 2007). Direct invasion to adjacent tissue and hematogenous spread are reported, but occur significantly less frequently (Otsuka, 2019; Kim et al., 2012). Cutaneous metastasis are even more uncommon; the majority of which occur in previous incision sites and at the umbilicus as the well-known Sister Mary Joseph nodule (Otsuka, 2019; Wiechert et al., 2012; Nam et al., 2017). Although the true incidence is unknown, cutaneous metastasis is reported to occur in < 6% of all ovarian cancers. However, after excluding melanoma, leukemia and lymphoma, breast and ovarian cancer represent the most common primary tumors to metastasize to the skin. Ovarian cancer alone accounts for 10% of all reported skin metastasis (Otsuka, 2019; Cormio et al., 2003; Dauplat et al., 1987).

There is no standard treatment regimen for cutaneous metastasis, and management follows typical paradigms for advanced ovarian cancer (Otsuka, 2019; Cormio et al., 2003; Dauplat et al., 1987; Clinical, 2020). The bulk of the literature regarding specific management of cutaneous metastasis is comprised of small case series and reports which demonstrate mixed responses with surgery, chemotherapy alone, surgery plus chemotherapy and external beam radiation (Kim et al., 2012; Cormio et al., 2003); however, no published studies have included treatment with immunotherapy or targeted agents. Here, we report a case of cutaneous metastasis of ovarian carcinoma to the vulva, thighs, abdomen and chest with complete response to front-line chemotherapy followed by rapid recurrence after cessation of treatment. The tumor was found to be PD-L1 positive, and the patient subsequently received pembrolizumab.

Case:. *The patient is a 70-year-old African-American female with a past medical history of type II diabetes, osteopenia and hypertension who initially presented to her gynecologist with a complaint of right labial and lower extremity swelling. Additionally, she reported increased abdominal girth, abdominal discomfort, early satiety and mild nausea. She denied postmenopausal bleeding. Her family history was non-contributory. Physical exam was remarkable for bilateral labial edema, and a friable cervix with ectropion and superficial bleeding. A Pap smear was performed at that time which resulted as adenocarcinoma. Pelvic sonogram demonstrated bilateral complex pelvic masses and CA* 125 *was elevated at* 2140 *U/mL. She was then referred to gynecologic oncology for further management.*

Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a 4.6 × 3.7 cm pelvic mass and bulky retroperitoneal lymphadenopathy with multiple enlarged lymph nodes ranging from 1.7 cm to 3.7 cm. She had several nonspecific pulmonary nodules between 5 and 12 mm (Fig. 1). Upfront surgical debulking was recommended, however the patient was lost to follow up prior to discussion of management options.

She then presented five months later to the emergency department with progressive intra-abdominal disease new skin lesions along the thighs and lower abdomen. Lesions were biopsied and consistent with metastatic high-grade serous carcinoma of Mullerian origin confirming the diagnosis of stage IVB ovarian carcinoma. CA-125 was now elevated to 2632 U/mL. She agreed to chemotherapy and received 6 cycles of carboplatin-paclitaxel. At that time, CA-125 had declined to 163.8 U/mL and imaging demonstrated stable disease in the pelvis and resolution of pulmonary nodules. Clinically, all skin lesions had resolved. Despite recommendation for further systemic therapy, the patient desired a break from chemotherapy and declined further treatment.

Three months later she returned with severe, tender, disabling vulvar edema and multiple vulvar lesions consistent with recurrence of cutaneous metastasis. At this time, cutaneous metastasis had also recurred across the lower abdomen and thighs, along with new cutaneous lesions involving the breast bilaterally (Fig. 2). She then underwent a palliative bilateral simple vulvectomy with resection of the bulkiest regions of the vulvar tumor. At this time, the patient underwent germline testing (Myriad Genetics) which was negative for a BRCA or homologous recombination defect mutation. Somatic tumor testing was also performed (Foundation One) which was negative for any actionable mutations. She then began second-line chemotherapy with liposomal doxorubicin and bevacizumab. She completed four cycles of therapy at which time cutaneous disease had overall remained stable,

* Corresponding author at: Department of Gynecologic Oncology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, United States.
E-mail address: Jennifer.McEachron@downstate.edu (J. McEachron).

https://doi.org/10.1016/j.gore.2020.100607
Received 12 May 2020; Received in revised form 17 June 2020; Accepted 27 June 2020
Available online 02 July 2020

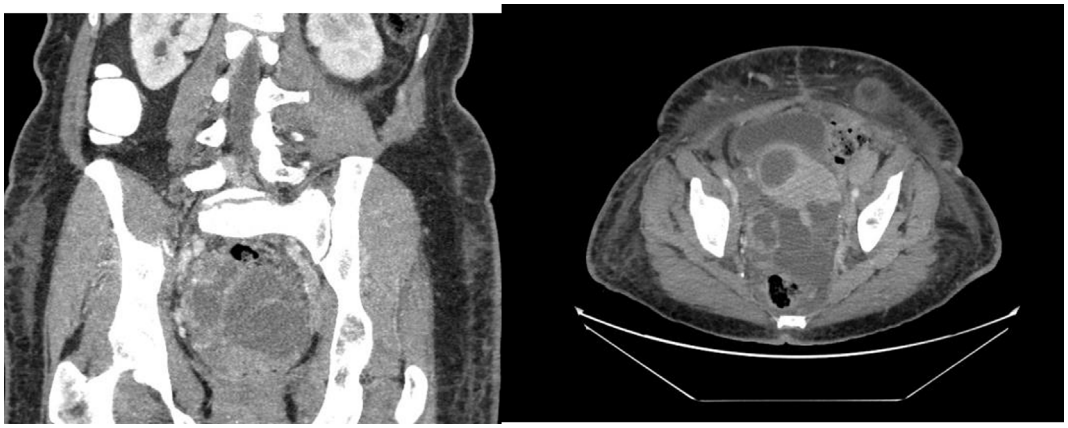

Fig. 1. Contrast enhanced computed tomography (CT) of the abdomen and pelvis performed at time of diagnosis of cutaneous metastasis which demonstrates large pelvic mass and bulky retroperitoneal lymphadenopathy with multiple enlarged lymph nodes up to 3.7 cm in size.

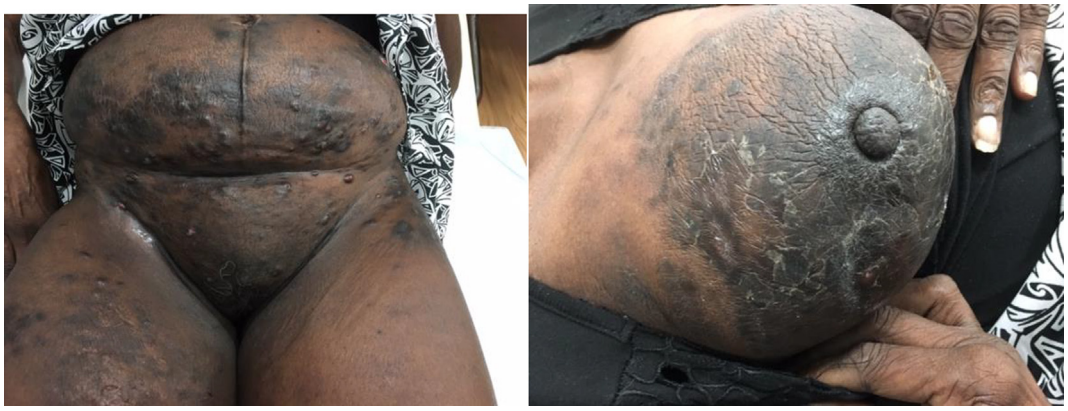

Fig. 2. Cutaneous metastasis diffusely involving the lower abdomen, breast and upper thighs.

with subtitle improvements in the breast and vulva. At this time, imaging demonstrated a partial response. The patient felt constitutionally worse from the adverse effects of treatment and experienced epithelial breakdown prompting her to discontinue this regimen.

Immunohistochemical (IHC) tumor analysis demonstrated PD-L1 positivity (CPS > 1) and it was recommended that the patient begin niraparib plus pembrolizumab. She refused niraparib because she did not want to take daily pills, but agreed to pembrolizumab. In October 2019, after receiving 2 cycles of pembrolizumab, she declined further treatment secondary to adverse side effects, most notably, fatigue, and elected to pursue palliative care. At this time, she was noted to have clinically stable cutaneous disease and no further imaging was performed. She expired 3 months later in January 2020.

2. Discussion

While cases of ovarian carcinoma with cutaneous metastases have been previously reported, this case highlights the first report of PD-L1 positive ovarian carcinoma with cutaneous metastasis (Otsuka, 2019). The most commonly reported sites of cutaneous metastasis are at previous surgical incisions and paracentesis sites, related to iatrogenic tumor spread (Otsuka, 2019; Kim et al., 2012). Cutaneous metastasis at non-incisional locations is much less common, and the most frequently reported sites are the abdomen and chest wall (Cormio et al., 2003). The vulva is a rare site of cutaneous metastasis, with only two reported cases in the literature (Wiechert et al., 2012; Cormio et al., 2003). There are several proposed mechanisms for the development of cutaneous metastasis, the most accepted theory is hematogenous (Otsuka, 2019; Hu et al., 2009). The majority of ovarian cancer patients with cutaneous metastasis harbor concurrent metastasis at other known hematogenous-spread sites, including the bone, lung and other extra-abdominopelvic sites (Cormio et al., 2003).

The symptoms of cutaneous metastasis vary, but most reports cite visible lesions, mild pain and pruritus as the most common presenting signs. Additionally, several reports detail extreme discomfort at the affected site, including an intractable “burning” sensation, leading patients to seek treatment (Kim et al., 2012; Wiechert et al., 2012). The vast majority of cutaneous metastasis will present in the recurrent setting. The interval of time from initial diagnosis of ovarian cancer to occurrence of skin metastasis ranges widely. We identified 16 individual patients reported in the literature. The mean time to diagnosis of skin metastasis was 28-months (range 4–84) (Oh et al., 2017; Lee et al., 2007; Kim et al., 2012; Ayhan et al., 2007; Wiechert et al., 2012; Nam et al., 2017; Cormio et al., 2003). In all cases, patients were treated according to standard protocols. Skin metastasis at time of initial diagnosis is extremely uncommon with only one reported case in the literature (Cormio et al., 2003). In our patient, cutaneous metastasis appeared five months after her initial diagnosis; however, given that the patient declined initial treatment, this represented progression of her disease rather than recurrence.

The optimal treatment of cutaneous metastasis is unknown. A series of nine patients reported median survival of 35-months in patients treated with surgical resection plus chemotherapy compared to only 2-months in patients treated with chemotherapy alone (Cormio et al., 2003). Besides disease eradication, surgical resection often offers symptomatic relief. In the current case, our patient was treated with multiple chemotherapeutic agents in addition to surgical resection with palliative intent and survived 15-months from diagnosis of skin metastases. After first-line carboplatin and paclitaxel, the rationale for treatment with liposomal doxorubicin and bevacizumab in this case

arose from the fact that her disease appeared to be located primarily within the lymph nodes and cutaneous epithelium, as well as her platinum-resistant disease status.

The patient strongly desired to stop chemotherapy, and PD-L1 positivity led to the recommendation of both niraparib and pembrolizumab. To our knowledge, this is the first report of targeted therapy use in ovarian cancer with cutaneous metastasis. Oh et al. describes a BRCA-1 mutation carrier with cutaneous metastasis developing late in her disease course. However, based on available evidence at that time, the patient was treated with 5th-line chemotherapy and shortly after succumbed to her disease (Oh et al., 2017). In our case, the rationale for treatment with niraparib, poly-ADP ribose polymerase (PARP) inhibitor, plus pembrolizumab combination is based on the recently published KEYNOTE 162/TOPACIO trial examining this regimen in platinum resistant epithelial ovarian cancer. The authors observed an overall response rate of 18% in a heavily pre-treated platinum resistant population. Notably, patients were treated without regard to PD-L1 or BRCA status (Konstantinopolous et al., 2019). The theory behind the positive results observed with this combination is due to PARP-inhibitor enhancement of intra-tumoral immune cell infiltration, increasing the efficacy of anti-PD-L1 therapy. Therefore, in our known PD-L1 positive patient, this synergistic relationship should theoretically enhance the existing immunogenicity of the tumor cells.

PD-L1 binding to its receptor leads to an inhibitory signal that reduces apoptosis and decreases activation of antigen-specific T-cells, allowing cancer cells to evade the immune system. Pembrolizumab, a monoclonal antibody against PD-L1, demonstrates high objective response rates across a spectrum of solid tumors expressing PD-L1 (Chung et al., 2019; Le et al., 2017). Although immunotherapy is widely utilized in both cervical and endometrial cancer with positive outcomes, the activity of single agent immunotherapy has failed to produce significant response rates in ovarian cancer (Konstantinopolous et al., 2019; Chung et al., 2019; Le et al., 2017). There was an overall response rate of only 8% among recurrent ovarian cancer patients in the KEYNOTE 100 and 11.5% in the KEYNOTE-028 (Matulonis et al., 2019 Jul 1; Varga et al., 2019).

Although our patient only received two cycles of pembrolizumab prior to elective discontinuation, this case represents the first report of immunotherapy utilization in gynecologic malignancies metastatic to the skin. Additionally, we observed a complete resolution of all cutaneous lesions following front-line carboplatin-paclitaxel in the absence of surgical excision suggesting that the cutaneous lesions were in fact initially sensitive to platinum therapy. Short-term regrowth was likely due to the persistent abdominopelvic disease at the time the patient discontinued therapy, and this high disease burden paved the way for recurrence of cutaneous metastasis via hematogenous and lymphatic dissemination.

3. Conclusion

Cutaneous metastasis are an uncommon manifestation of ovarian cancer. Histologic confirmation of lesions to rule out other skin diseases is critical. IHC and molecular tumor profiling are key players in adjuvant therapy planning. Even in the setting of incurable disease, identification of PD-L1 positivity or other actionable mutations, expands treatment options and may allow patients to avoid toxic chemotherapy regimens, while still receiving treatment.

CRediT authorship contribution statement

Victoria Hastings: Writing - original draft, Data curation. **Jennifer McEachron:** Conceptualization, Writing - review & editing. **Marguax J. Kanis:** Conceptualization, Writing - review & editing, Project administration.

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.

References

Ayhan A, Gultekin M, Celik NY, Dursun P, Taskiran C, Aksan G, Yuce K. Occult metastasis in early ovarian cancer: risk factors and prognosis. Am J Obstet Gynecol. 2007;196(1):81. e1–6.

Chung, H.C., Ros, W., Delord, J.P., Perets, R., Italiano, A., Shapira-Frommer, R., et al., 2019. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J. Clin. Oncol. 37 (17), 1470–1478.

NCCN Clinical Practive Guidelines in Oncology: Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. Version 1.2020. Accessed May 10, 2020.

Cormio, G., Capotorto, M., Di Vagno, G., Cazzolla, A., Carriero, C., Selvaggi, L., 2003. Skin metastases in ovarian carcinoma: a report of nine cases and a review of the literature. Gynecol. Oncol. 90, 682–685.

Dauplat, J., Hacker, N.F., Nieberg, R.K., Berek, J.S., Rose, T.P., Sagae, S., 1987. Distant metastases in epithelial ovarian carcinoma. Cancer 60, 1561–1566.

Hu, S.C.S., Chen, G.S., Wu, C.S., Chai, C.Y., Chen, W.T., Lan, C.C., 2009. Rates of cutaneous metastases from different internal malignancies: Experience from a Taiwanese medical center. J. Amer. Acad. Dermatol. 60 (3), 379–387.

Kim, M.K., Kim, S.H., Lee, Y.Y., Choi, C.H., Kim, T.J., Lee, J.W., et al., 2012. Metastatic skin lesions on lower extremities in a patient with recurrent serous papillary ovarian carcinoma: a case report and literature review. Can. Res. Treat.: J Korean Can. Assoc. 44 (2), 142–145.

Konstantinopolous, P.A., Waggoner, S., Widal, G.A., et al., 2019. Single-Arm Phases 1 and 2 Trial of Niraparib in combination with pembrolizumab in patients with recurrent platinum resistant epithelial ovarian cancer. JAMA Oncol. 5 (8), 1141–1149.

Le, D.T., Durham, J.N., Smith, K.N., Wang, H., Bartlett, B.R., et al., 2017. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357 (6349), 409–413.

Lee, H.C., Chu, C.Y., Hsiao, C.H., 2007. Carcinoma erysipeloides from ovarian clear-cell carcinoma. J. Clin. Oncol. 25, 5828–5830.

Matulonis, U.A., Shapira-Frommer, R., Santin, A.D., Lisyanskaya, A.S., Pignata, S., Vergote, I., et al., 2019. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann. Oncol. 30 (7), 1080–1087.

Nam, G., Lim, Y.M., Cho, M.S., Lee, J., Kim, Y.H., 2017. Skin metastases in ovarian clear cell adenocarcinoma: a case report and a review of the literature. Obstet. Gynecol. Sci. 60 (6), 593–597.

Oh, S.R., Park, J.W., Kwon, H.Y., Rha, S.H., 2017. BRCA1-mutated ovarian cancer with skin metastasis: a case report. Obstet. Gynecol. Sci. 60 (5), 477–480.

Otsuka, I., 2019. Review: cutaneous metastases in ovarian cancer. Cancers 11 (9), 1292.

Varga, A., Piha-Paul, S., Ott, P.A., Mehnert, J.M., Berton-Rigaud, D., Morosky, A., Yang, P., Ruman, J., Matei, D., 2019. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analsysis of KEYNOTE-028. Gynecol. Oncol. 152 (2), 243–250.

Wiechert, A.C., Garrett, L.A., Lin, G., Al, G., 2012. Management of a skin metastasis in a patient with advanced ovarian cancer. Gynecologic Oncol. Case Rep. 2 (4), 124–126.