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Case report

Off-label use of paclitaxel and pembrolizumab in a case of platinum refractory epithelial ovarian cancer and extensive thromboembolism

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1. Introduction

1.1. Subject

In this case report, we discuss the use of weekly paclitaxel and pembrolizumab to achieve disease remission in a patient with epithelial ovarian cancer who was determined not to be a candidate for debulking surgery due to multiple deep vein thromboses (DVT) and pulmonary emboli (PE).

1.2. Case

The patient is a 46 year old G2P2002 with MSH2 mutation and no other significant past medical history who initially presented with a new diagnosis of bilateral DVTs and PEs (Fig. 1). Computed tomography (CT) scan of the abdomen and pelvis demonstrated a heterogeneous pelvic mass measuring 8.4 × 6.1 cm, small amount of free fluid, and no evidence of peritoneal carcinomatosis. CT-guided core biopsy of the pelvic mass was performed and confirmed the diagnosis of adenocarcinoma of Mullerian origin (Fig. 1a and 1b). The patient subsequently received three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel given once every three weeks. The CA-125, an ovarian cancer tumor marker, was initially 2,162 (units) at the time of diagnosis and decreased to 918 (units) prior to evaluation for an interval cytoreductive surgery. Patient was deemed a poor candidate for interval cytoreductive surgery after cycle 3 of carboplatin and paclitaxel when she was noted to have new pulmonary emboli within bilateral lower lobes with evolving pulmonary infarct, nonocclusive clot within left femoral vein, and occlusive clot within the left femoral vein within the proximal left thigh with suspicion of clot extending into the left greater saphenous vein despite receiving anticoagulation with dalteparin 12,500 units SQ daily. After her third cycle of neoadjuvant chemotherapy, the patient was switched to apixaban, an inferior vena cava (IVC) filter was placed, and decision was made to forego interval debulking surgery and continue carboplatin and paclitaxel for a total of six cycles. Following her six cycles of chemotherapy, she had a follow-up CT thorax, abdomen and pelvis showing a new DVT extending up to the left external iliac vein and a new thrombus within the intrahepatic portion of the IVC, cephalad of a thrombosed IVC filter with thrombosis surrounding the filter for a length of approximately 7.2 cm. Of note, the pelvic mass appeared to be mildly decreased in size. Patient was admitted to the hospital to receive high-dose Heparin and TPA infusion with Interventional Radiology and was subsequently switched to Dabigatran. Her case was presented at tumor board and a consensus was reached that she was not an appropriate surgical candidate due to new clots and large central PE. The patient completed a total of nine cycles of carboplatin and paclitaxel until CT scan performed 3 weeks later showed progression of disease, at which point, the tumor was felt to be platinum-refractory. CA-125 at that point

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was 909.3 (units). Pegylated liposomal doxorubicin (PLD) was initiated and continued for a total of seven cycles with follow-up CT scan showing increasing size of the pelvic mass and signs of increasing peritoneal and omental disease (Fig. 2a). CA-125 increased to 1034 (units). Given suboptimal response to the platinum-based regimen and PLD, patient was started on a combination regimen of pembrolizumab intravenous every three weeks with weekly paclitaxel. After sixth cycle, her CA-125 normalized and CT scan after seventh cycle showed interval decrease in the size of pelvic mass (Fig. 2b) and almost full return of functional status. The patient has been maintained on this regimen for 16 months and has completed 20 cycles with no evidence of disease progression and ECOG 0 (Fig. 2c). At this time, the patient is on enoxaparin 100 mg BID and demonstrates no evidence of new DVT/PE with most recent imaging showing stable clot burden. There are no current plans to remove the pelvic mass as the patient is asymptomatic.

2. Discussion

Pembrolizumab is a humanized monoclonal IgG4-kappa isotype antibody against programmed cell death protein 1 (PD-1). PD-1 and its ligands, programmed cell death ligand 1 (PD-L1) and 2 (PD-L2) act through an inhibitory effect, allowing cancer cells to evade the immune response. Preclinical studies show PD-1 blockade leading to tumor growth suppression and decreased metastasis (McDermott and Jimeno, 2015). Pembrolizumab has been studied in various cancer types, including cervical cancer, non-small cell lung cancer, melanoma, gastric cancer, and colorectal cancer (McDermott and Jimeno, 2015). There is limited data on the use of pembrolizumab in ovarian cancer patients. In the KEYNOTE-028 study, twenty-six patients with PD-L1 positive ovarian cancers who had failed previous first-line therapies received pembrolizumab. The primary end point was confirmed objective response rate (ORR) per RECIST 1.1 criteria with 11.5% achieving ORR and 26.9% achieving stable disease. Median progression free and overall survival were 1.9 (95% CI, 1.8–3.5) and 13.8 (95% CI, 6.7–18.8) months, respectively (Varga et al., 2019). Of the twenty-six patients, only one achieved a complete response (Varga et al., 2019). A phase II, multicenter clinical trial, KEYNOTE-100, evaluated the use of pembrolizumab as a monotherapy in patients with recurrent epithelial ovarian cancer and demonstrated an 8% ORR with higher PD-L1

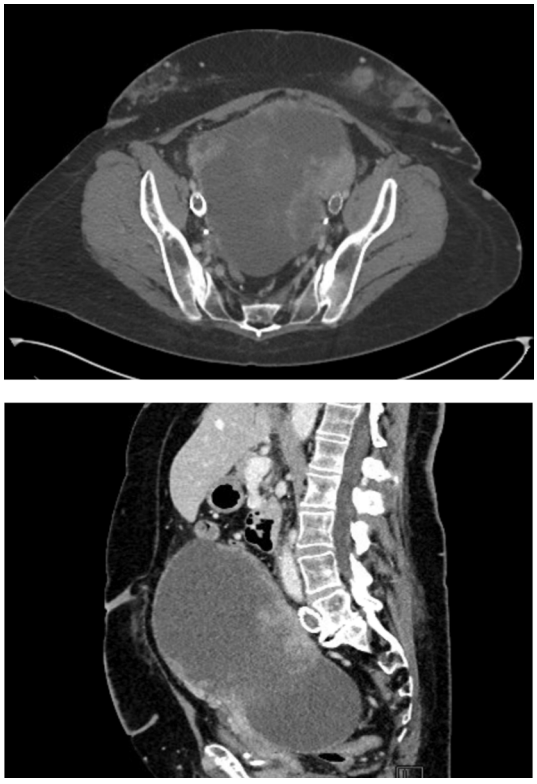

Fig. 2a. Axial and sagittal views of enlarging pelvic mass despite treatment with Doxorubicin.

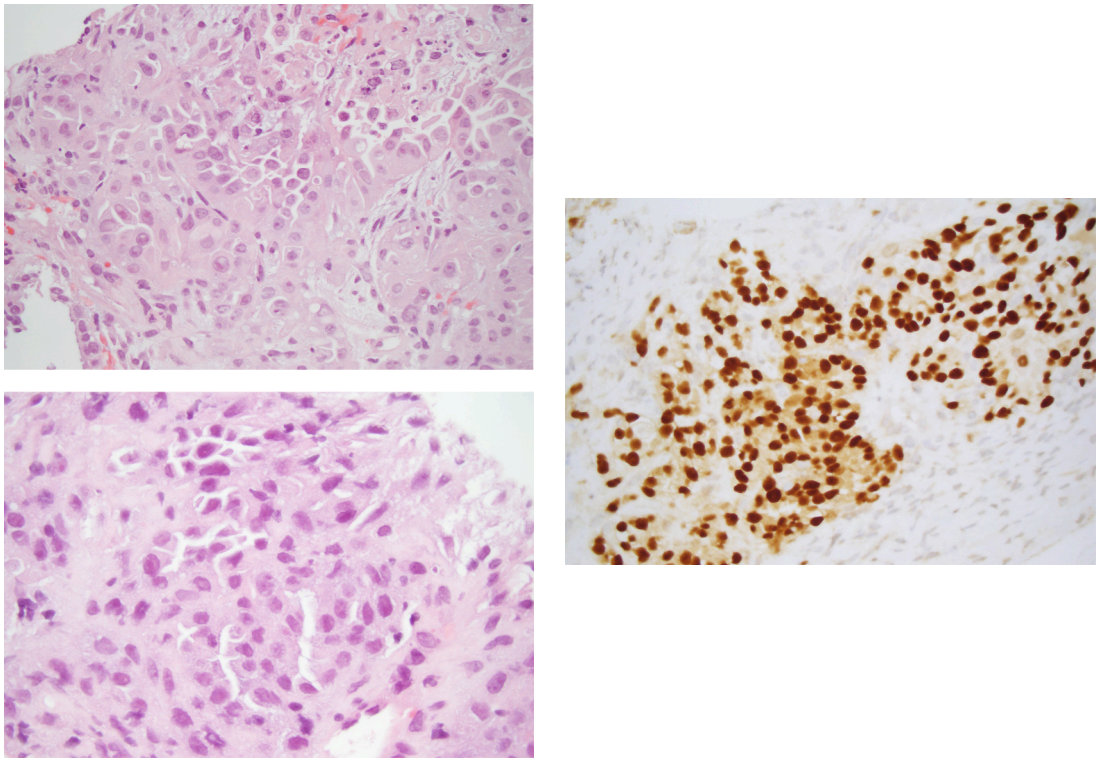

Fig. 1. a. H&E stain of CT-guided core biopsy of the pelvic mass. b. PAX8 stain of CT-guided core biopsy of the pelvic mass.

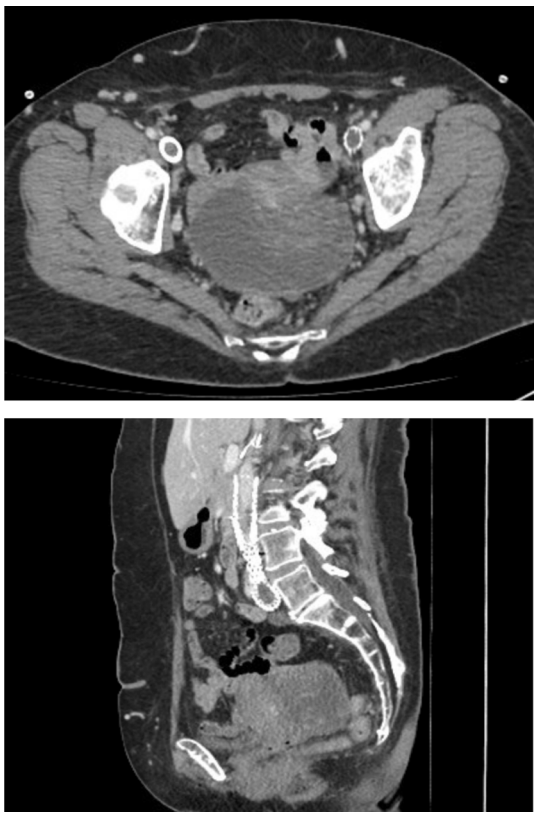

Fig. 2b. Axial and sagittal views of pelvic mass following 7 cycles of pembrolizumab/paclitaxel.

expression correlating with a higher ORR (Matulonis et al., 2019). Most recently, another phase II nonrandomized clinical trial demonstrated a clinical benefit of the combination of bevacizumab, oral cyclophosphamide, and pembrolizumab in 95%, with lasting treatment responses > 12 months in 25% of patients with recurrent ovarian cancer (Zsiros et al., 2021).

Paclitaxel exerts its chemotherapeutic effect by promoting the assembly of tubulin into microtubules and preventing the dissociation of these microtubules, thus blocking cell cycle progression to prevent mitosis and cell proliferation (Mikuła-Pietrasik et al., 2019). When taxanes were discovered to have high activity against epithelial ovarian cancer cells, the combination of a taxanes and a platinum-based derivative became the gold standard for epithelial ovarian cancer treatment. Data regarding the weekly administration of paclitaxel in the treatment of platinum-resistant ovarian cancer have suggested an objective response rate of approximately 10–20% (Markman et al., 2006). This favorable effect has been demonstrated in the setting of tumors not only shown to be platinum-resistant but are also clinically defined to be resistant to paclitaxel, previously delivered on a "standard" every 3-week schedule (Markman et al., 2006). A Gynecologic Oncology Group (GOG) study enrolled forty-eight patients in phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers. The overall ORR was 20.9% with two complete and eight partial responses being documented. One responding patient had previously progressed during prior paclitaxel therapy, while two patients had progressed 1–2 months after prior treatment and seven had progressed 4–6 months after. The median response duration was 3.6 months, with two patients who had not yet failed at 16.9 + and 17.1 months. Twenty two patients exhibited stable disease (Markman et al., 2006). Many studies have shown that paclitaxel directly kills tumor cells and regulates various immune cells, such as effector T cells, dendritic cells, natural killer cells, regulatory T cells, and macrophages (Bracci et al., 2014). Paclitaxel has been shown to inhibit the function of regulatory T cells and reverse the immune escape of tumors (Bracci et al., 2014). Therefore, paclitaxel combined with immunotherapy could increase the efficacy of treatment (Zhu and Chen, 2019). A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer showed a confirmed overall response rate of 23.1% (6 out of 26 patients, 95% CI: 6.9%-39.3%), with complete response in one patient and partial response in five patients. Progressive disease and stable disease were observed in 2 (7.7%) and 15 (57.7%) patients, respectively, resulting in the disease control rate of 80.7%. The median duration of response was 9.1 months (3.6–11.6 months). The median follow-up was 11.1 months and the median PFS and OS were 5.0 months (95% CI: 2.7–6.7) and 9.1 months (95% CI: 6.5–15.0), respectively (Kim et al., 2019). One case report from Jing et al. described the use of pembrolizumab in combination with nab-paclitaxel in a patient status-post initial cytoreductive surgery with recurrent, metastatic, platinum-sensitive epithelial ovarian cancer, with a complete response achieved after 6 cycles and no evidence of disease while on pembrolizumab maintenance (Jiang et al., 2020). In platinum-resistant epithelial ovarian cancers, the mainstay of treatment is non-platinum-based monotherapy or bevacizumab-based combination therapy with paclitaxel, PLD, topotecan, with generally low observed response rates of approximately 10–15% with overall survival quoted at approximately 12 months (Naumann and Coleman, 2011). Unfortunately, randomized phase III trials of second-line therapies, including taxane analogues, oral etoposide, and bevacizumab, have not shown significant survival advantages over the first-line agents mentioned above (Naumann and Coleman, 2011). A more recent Phase III randomized trial of bevacizumab in combination with single agent chemotherapy in platinum resistant setting demonstrated ORR of 27.3% and median PFS of 6.7 months (Pujade-Lauraine et al., 2014). Our weekly approach to paclitaxel administration in combination with an immune-checkpoint inhibitor is unique and can be considered if first

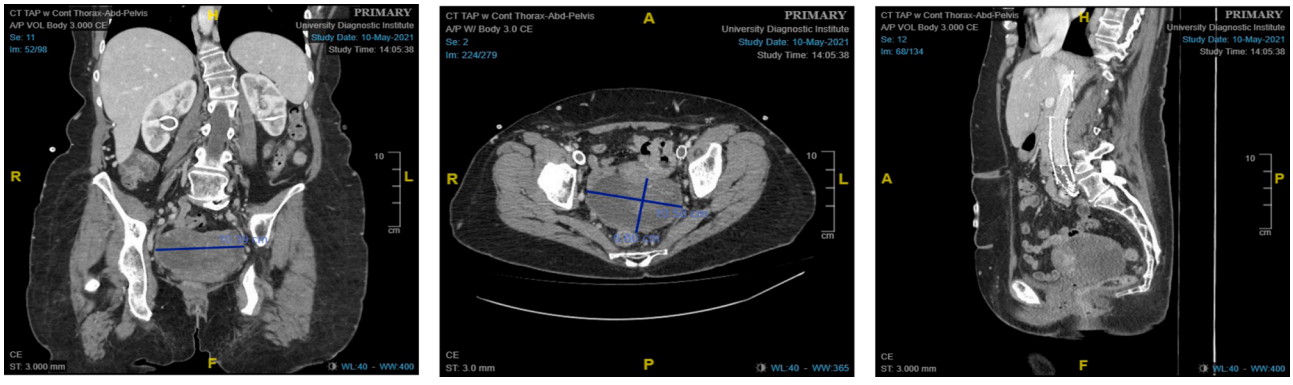

Fig. 2c. Coronal, axial, and sagittal views of stable pelvic mass after treatment with pembrolizumab and paclitaxel.

line-agents, such as bevacizumab, are contraindicated. Additionally, this patient has DNA mismatch repair (MMR) deficiency that is predicted by her MSH2 (Gln662) mutation noted on germline genetic testing. Treatment with immune-checkpoint inhibitors in the setting of MMR deficiency may have also complimented overall efficacy of weekly paclitaxel. Given the lack of a randomized environment, it is not clear if this particular patient responded to the weekly paclitaxel alone or if there was significant contribution from the addition of pembrolizumab. Authors recognize this as a limitation of this descriptive case report.

Cancer-associated thromboses (CAT) are a major cause of morbidity and mortality in cancer patients, with cancer patients having up to a 20% risk of developing a venous thromboembolic event (Metcalf et al., 2014). Ovarian cancer patients in particular have one of the highest incidences of VTE among patients diagnosed with solid organ cancers, with an overall VTE rate of 4.1% (Khorana et al., 2007). The molecular basis for this hypercoagulable state seen in ovarian cancer is thought to be related to an overexpression of tissue factor, which promotes procoagulant activity in cancer cells (Uno et al., 2007). Chemotherapy agents have been observed to promote a prothrombotic, proinflammatory milieu through endothelial injury, direct platelet activation, reduced fibrinolytic activity, and release of procoagulant materials from dying tumor cells, thus further increasing risk of VTE in cancer patients (Wood et al., 2010; Adess et al., 2006). Because immune checkpoint inhibitors (ICIs) such as pembrolizumab result in a sudden onset of T-cell proliferation, the risk of CAT is potentially equivalent to other anticancer agents that have previously been investigated in VTE risk (Ando et al., 2020). Our case report demonstrates the morbidity caused by CAT and highlights the unique treatment challenges that arise with increasing VTE incidence. We cannot demonstrate whether there is an increased risk of thrombosis in our combination therapy of pembrolizumab and paclitaxel given the inherent limitation of a case report.

Management of ovarian cancer typically involves cytoreductive surgery in combination with a platinum and taxane chemotherapy regimen followed by maintenance therapy. In this particular patient, who was neither a surgical candidate nor was her disease responsive to platinum-based chemotherapy, we sought to explore the effects of a combination of pembrolizumab and weekly paclitaxel based on the limited data presented above. In this case, the patient failed both first line carboplatin/paclitaxel and second line PLD and ultimately achieved appreciable tumor response with normalization of tumor markers with pembrolizumab and weekly paclitaxel.

This case report suggests pembrolizumab and weekly paclitaxel as a possible treatment option in patients whose disease would otherwise be deemed refractory to treatment in the setting of poor surgical candidacy and lack of response to platinum-based chemotherapy. Existing studies have examined the response of platinum-resistant ovarian cancer to these agents either as monotherapy or in combination with other drugs. The longest median progression-free survival was described in Zsiros et al. which reported a median PFS of 10 months with a regimen of pembrolizumab, bevacizumab, and cyclophosphamide, in comparison to our case report which demonstrates a current PFS of 16 months (Zsiros et al., 2021). Few studies have looked at the effect of pembrolizumab and weekly paclitaxel on progression-free survival specifically in platinum-resistant ovarian cancer. Overall, in our patient, this combination was well tolerated in off label application with durable response. Our findings present a potential area for further research into the efficacy and safety of this regimen.

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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