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Pembrolizumab-induced cytokine release syndrome with severe encephalopathy in the setting of clear cell vaginal carcinoma: A case report

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1. Introduction

The programmed cell death protein 1 (PD1) is an intracellular protein that helps to regulate immune system responses. PD1 is commonly expressed on effector T cells and its ligand PDL1 is expressed on tumor cells. The binding of PD1 with PDL1 results in negative feedback to T-cells, which allows tumor cells to evade immune system response. The blockade of PD1 is a powerful immunotherapeutic approach for the treatment of cancer. An example of this has been the increasing use of the immune checkpoint inhibitor Pembrolizumab (anti-PD1 antibody) in the treatment of many solid organ malignancies (Kwok et al., 2016). Keynote 028 and Keynote 128 support the use of Pembrolizumab in PDL1-positive cervical cancers (Frenel et al., 2017; Chung et al., 2019), and this has been followed by studies supporting its use in endometrial malignancies as well (Eskander et al., 2023; Mirza et al., 2023). This has led to wide use of pembrolizumab in the treatment of gynecologic malignancies. The side effects of immune therapy are primarily due to upregulation of T cell activity which can cause wide-ranging autoimmune mediated toxicities which can include hepatitis, diarrhea, rash, hypothyroidism or hyperthyroidism, among others (Robert et al., 2015). The side effect of encephalitis is more rare; however, there are documented cases of pembrolizumab-induced encephalitis in the treatment of renal cell carcinoma (Sharma et al., 2023), metastatic melanoma (Galmiche et al., 2019), and non-small cell lung carcinoma (Vico et al., 2021; Niki et al., 2019). To our knowledge, there has not yet been a published case of pembrolizumab-induced encephalitis in the treatment a primary gynecologic malignancy.

Here, we present a case of pembrolizumab-induced encephalitis in a woman with a history of cervical cancer undergoing treatment for vaginal clear cell carcinoma.

2. Case report

The patient is a 57-year-old female with a remote history of stage IIIC cervical adenocarcinoma who developed a vaginal mass 24 years after primary radiation with sensitizing chemotherapy. Pathology of the vaginal mass revealed clear cell carcinoma. Her stage 3 vaginal clear cell carcinoma was treated initially with 6 cycles of carboplatin and paclitaxel chemotherapy with bevacizumab given concurrently, followed by whole pelvic radiation and brachytherapy. The patient declined maintenance bevacizumab. Her disease had initially responded to treatment, but PET scan 6 months after completion of radiation revealed new areas of increased uptake in the posterior endometrial canal and a nodule in the pouch of Douglas. CT-guided biopsy revealed recurrent clear cell carcinoma, and surgical management with a pelvic exenteration was discussed. The patient declined the operation due to the significant morbidity and quality of life concerns. She instead elected to proceed with Pembrolizumab, as her tumor was PDL1 positive with CPS score of 60. She was receiving pembrolizumab every 3 weeks and her treatment course was complicated by a pulmonary embolism, transaminitis related to alcohol consumption, and hypothyroidism. She had responded well to treatment and PET CT showed decreasing tumor burden aside from an increase in anterior mesenteric nodule.

The patient was found to be somnolent when presenting to the infusion suite for her fourteenth cycle, and was sent to the emergency room for evaluation. Per family's report, the patient had become more

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unsteady, confused, and tired in the preceding days. Upon arrival to the emergency room, she was afebrile and oriented only to self. She was somnolent and only able to follow simple commands with repetitive painful stimuli and then would quickly become non-responsive. She was evaluated in the ED by the ICU team and due to stable vitals with good oxygen saturation, she was admitted to the gynecologic oncology floor. A broad workup was initiated, but shortly after admission there was concern that the patient could not protect their airway with a new oxygen requirement. After admission to the ICU, she was subsequently intubated and EEG was performed which demonstrated no seizure activity but suggested encephalopathy. Neurology, Allergy/Immunology and Neuroimmunology teams were consulted due to her profound encephalopathy and potential for immune-mediated encephalitis. The infectious workup was notable for an ESR of 51 and CRP of 2.1, but otherwise negative. A brain CT and brain MRI did not show evidence of leptomeningeal spread. CSF studies were unremarkable except for an increased IGG index and oligoclonal bands, indicating CNS inflammation.

Due to concern for pembrolizumab-induced encephalitis, with a negative workup for other causes, she was started on 1 mg/kg/day of IV methylprednisolone for 1 day, followed by 1 g per day for 4 days, followed by a slow taper. IVIG infusion was started at the recommendation of neuroimmunology and continued for 4 days. Her status improved with ability to wave, smile, and look at family. Extubation was attempted, however the patient failed due to continued concerns for airway protection and was re-intubated the following day. MRI was repeated with intubation, and periaqueductal grey T2 hyperintensity was noted concerning for possible Wernicke's encephalitis. She was given 3 days of high dose IV thiamine due this concern given poor nutritional status over past months, but this was not thought to be contributory to her obtunded state. A tracheotomy was performed for prolonged intubation.

A lumbar puncture was repeated, and IL-8, one of the cytokines that mediates the systemic inflammatory disease in cytokine release syndrome (Zhang et al., 2022), was elevated at 282. Her IV methylprednisolone was increased back to 1 mg/kg/day and she was started on tocilizumab, a monoclonal antibody that works to inhibit IL-6 mediated signaling. IL-6 is another cytokine with a large role in the immune reaction. She began to show marked clinical improvement with the ability to follow commands. Due to her appropriate response, she was given an additional dose of tocilizumab. From there, the patient continued rapidly improving. Her tracheostomy was decannulated, she was able to eat and drink on her own, and was communicating. She was discharged after 38 days in the hospital to a rehabilitation facility with a steroid taper. Unfortunately, the patient was readmitted to the hospital six weeks later with a small bowel obstruction and respiratory failure, just one week after completion of her steroid taper. She was diagnosed with recurrent autoimmune encephalitis, immune-mediated myasthenia gravis, and immune-mediated myocarditis. She again required intubation and parenteral nutrition, but was able to be extubated and weaned off of parenteral nutrition. She was treated with steroids and IVIG and was discharged to a long-term acute care hospital. Unfortunately, she was no longer a candidate for immunotherapy given her severe adverse reaction. She had further episodes of recurrent small bowel obstruction and her functional status never recovered to being able to stand or walk. Ultimately, her cancer progressed and after goals of care discussion, she transitioned to hospice and passed away.

3. Discussion

Pembrolizumab is an immune-checkpoint inhibitor (ICI) that has emerged as a promising agent in cancer therapy. Pembrolizumab is commonly used in gynecologic oncology for the treatment of PDL-1 positive cervical cancers and endometrial cancer (Frenel et al., 2017; Chung et al., 2019; Eskander et al., 2023; Mirza et al., 2023). The data in clear cell vaginal cancer is limited due to the rarity of this tumor, however vaginal cancer therapy is often extrapolated from cervical cancer literature and cases have been reported with complete and durable response to pembrolizumab therapy (Porragas-Paseiro et al., 2023). As use of ICIs continues to increase in the treatment of gynecologic cancer, so must the suspicion for ICI-related adverse effects. Rates of the more common immune related adverse effects in a phase III clinical trial of pembrolizumab include fatigue (20 %), diarrhea (14 %), rash (13 %), hypothyroidism (8 %), hyperthyroidism (3 %) and hepatitis (1.8 %) (Robert et al., 2015). Neurological effects are more rare but must be considered in the development of neurological signs and symptoms. As in the case presented above, patients may quickly become critically ill. The patient we present had elevated cytokines in her cerebrospinal fluid and encephalopathy was a manifestation of cytokine release syndrome (CRS). CRS is a systemic inflammatory condition mediated by several cytokines including IL-6 and IL-8. CRS is most commonly seen in immuno-oncology in relation to CAR-T therapy. The exact mechanism for developing CRS in the specific setting of immune checkpoint inhibitors like Pembrolizumab is not perfectly understood (Tay et al., 2022).

The treatment for neurological symptoms attributed to ICIs include discontinuing treatment with the offending agent and starting high dose steroids (either oral prednisolone (1 mg/kg) or an IV equivalent). Plasmapheresis or Intravenous immunoglobulin (IVIG) may be required if there is failure to respond to the steroid intervention (Spain et al., 2016). Tocilizumab was also used in our case, as it is a monoclonal antibody against IL6, a cytokine that plays a large role in CRS.

It is important to consider that Pembrolizumab has a long half-life of approximately 26 days that is unaffected by gender or age, and it takes approximately 5 half-lives to clear the body (Dang et al., 2016). Due to the possibility of prolonged immune mediated toxicity, providing supportive care remains an important part of the treatment. This patient spent 38 days in the intensive care unit and required respiratory and nutritional support, but was able to be discharged to a rehabilitation center with the ability to breathe and eat independently, although she never fully recovered her functional status. This emphasizes the importance of supportive care and continuous reassessment of patient and family goals during the prolonged and complicated admission a patient may have with pembrolizumab-induced cytokine release syndrome and encephalopathy.

CRediT authorship contribution statement

Samantha Metzger: Writing – review & editing, Writing – original draft. **Keely Ulmer:** Writing – review & editing. **Emily K. Hill:** Writing – review & editing, Supervision.

Informed consent

Written informed consent was obtained for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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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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