



Case report

Guillain-Barre Syndrome in a patient with uterine adenocarcinoma undergoing treatment with immune-checkpoint inhibitor therapy: A case report and review of the literature

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ABSTRACT

Background: Use of immune checkpoint inhibitors in treatment of gynecologic malignancies is increasing. Rare, but potentially fatal, immune-related neurologic adverse events may occur as a result of treatment.

Case: A 72 year old female with recurrent metastatic uterine adenocarcinoma received pembrolizumab and lenvatinib combination therapy. Following her second dose of pembrolizumab, the patient developed multiple neurologic symptoms. She was ultimately diagnosed with Guillain-Barre Syndrome based on neurologic evaluation with imaging, serum studies, and cerebrospinal fluid analysis. The patient was successfully treated with high-dose intravenous corticosteroids and intravenous immunoglobulin.

Conclusion: Neurologic complications related to immune checkpoint inhibitor therapy are rare. It is imperative for gynecologic oncologists to be familiar with potentially fatal hazards of therapy to allow for rapid diagnosis and treatment.

1. Introduction

Immune checkpoint inhibitors are increasingly used in the treatment of gynecologic malignancies. Following the Food and Drug Administration's (FDA) accelerated approval in 2019 of the combination treatment pembrolizumab and lenvatinib (a novel immune checkpoint inhibitor and VEGF inhibitor combination) for recurrent metastatic uterine carcinoma, we expect to see an increase of patients on this therapy. Clinicians need to be familiar with adverse effects of this treatment, including rare, but potentially fatal events, related to auto-immune dysregulation. We present the case of a patient with metastatic uterine adenocarcinoma diagnosed with Guillain-Barre Syndrome (GBS) after initiating treatment with pembrolizumab and lenvatinib. To our knowledge, this is the first case in the literature demonstrating GBS related to pembrolizumab therapy for a gynecologic malignancy.

2. Case

A 72 year-old female was diagnosed with stage IVB uterine adenocarcinoma after initially presenting to the emergency department with several months of abdominal pain, weight loss, and abdominal

distension. Physical exam was notable for a prolapsing 4 cm polypoid uterine mass. Computed tomography (CT) demonstrated pleural effusions, ascites, omental caking, an enlarged uterus with a thickened endometrial cavity extending into the lower uterine segment to the level of the cervix, and unremarkable adnexa. Biopsy of the uterine mass showed endocervical glandular mucosa with fibrotic stroma and atypical glandular cells. Cytology from thoracentesis and paracentesis was consistent with poorly differentiated metastatic adenocarcinoma of Mullerian origin. She received neoadjuvant chemotherapy with carboplatin and paclitaxel with plans for an interval debulking procedure. The patient then developed a pulmonary embolus that precluded surgery. She completed six cycles of chemotherapy with resolution of disease by CT criteria. Serum CA-125 level decreased from 423.3 units/mL to 54.7 units/mL. Further testing of the biopsy specimen indicated the tumor was microsatellite-stable, PDL1 negative, and ER/PR positive. Surgical delay occurred again due to the COVID-19 pandemic and the patient began Tamoxifen therapy. Four months later, CT scan demonstrated progression of disease and serum CA-125 increased to 281.7 units/mL. She was started on pembrolizumab 200 mg IV every 21 days and lenvatinib 20 mg tablet/day.

Seven days after receiving her second dose of pembrolizumab, the

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patient presented to the emergency room reporting shortness of breath, pain with swallowing, progressive weakness and fatigue, diffuse body aches, inability to walk, and rash. Pertinent clinical findings were lower extremity weakness 3/5 and upper extremity weakness 4/5, inability to void, and elevated TSH (14.024 mIU/mL) with normal Free T4 (1.07 ng/dL). She was admitted hospital, started on levothyroxine, nystatin oral suspension, a tapering dose of oral dexamethasone, and supportive care.

By hospital day five, the patient reported decreased fatigue but remained unable to void, required assistance with ambulation, and developed a bilateral tremor in her hands. Neurologic examination was notable for ataxia, hyporeflexia, and tremor. Non-contrast CT of the head and magnetic resonance imaging (MRI) of the brain and lumbar spine did not reveal any abnormal findings. Lumbar puncture was performed and analysis of the cerebrospinal fluid (CSF) revealed mild albuminocytologic dissociation and mildly elevated protein level 39 mg/dL. Nerve conduction studies demonstrated mixed axonal and demyelinating features and conduction block concerning for Guillain-Barre Syndrome (GBS), also known as acute inflammatory demyelinating polyneuropathy (AIDP). Treatment consisted of methylprednisolone 1g IV daily for 5 days and intravenous immunoglobulin (IVIG) 2 g/kg over 5 days. Pembrolizumab was suspected to be the causative agent due to its known association with immune-related adverse events (irAEs), and specifically neurologic complications.

The patient regained bladder function, ambulated without assistance, and had vast improvement in other neurologic symptoms after five days of treatment. She was discharged home with plans for home rehabilitation and close follow up. Pembrolizumab and lenvatinib were discontinued, and bevacizumab was initiated during her recovery.

At follow up examination two months later, the patient continued to experience improvement in neurologic symptoms, however endorsed increasing abdominal pain and nausea. CT imaging demonstrated disease progression. Ultimately, she was readmitted to the hospital and found to have large bowel perforation. The patient was taken to the operating room and underwent exploratory laparotomy, abdominal washout, and diverting loop ileostomy. Post-operatively her condition continued to decline, and she expired 4 days later.

3. Discussion

To our knowledge, this is the first described case of GBS/AIDP due to immune checkpoint inhibitor (ICI) therapy in a gynecologic malignancy. A variety of irAEs have been attributed to ICI therapy: dermatologic reactions, colitis, hepatitis, endocrinopathies, pneumonitis, and rheumatologic complications (Han et al., 2020; Kao et al., 2018). Several case reports and case series detail neurologic adverse events of ICI use in other cancers, most commonly melanoma and lung cancer, but also renal cell carcinoma, glioblastoma, and Hodgkin lymphoma (Han et al., 2020; Fellner et al., 2018; Ong et al., 2018).

ICIs are relative newcomers to gynecologic oncology. These monoclonal antibody agents have produced promising results with improved response rates, prolonged survival rates, and tolerability in other solid tumors (Levinson et al., 2019). The two main pathways targeted by ICIs are cytotoxic lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1, or its ligand PDL-1) inhibition. CTLA-4 and PD-1/PDL-1 are both negative regulators of the immune system; inhibition of these pathways may increase immune activity against tumor cells (Hottinger, 2016; Manam et al., 2018). The complementary role of these pathways is in preventing autoimmunity. This mechanism is hypothesized to reduce peripheral tolerance of self-antigens, promoting cross-reactivity through molecular mimicry by tumor cells and resulting in autoimmune events (Fellner et al., 2018; Ong et al., 2018; Psimaras et al., 2019).

CTLA4-targeting pathway results in earlier, more severe, and more frequent adverse effects than the PD-1/PDL-1 pathway (Levinson et al., 2019). Reported rates of low grade neurologic adverse events are 3.8%

with anti-CTLA4 and 6.1% with anti-PD1 antibodies. Symptoms include headache, dysgeusia, sensory impairment, and dizziness (Fellner et al., 2018; Anderson et al., 2019). High grade neurologic complications are diverse, affecting both the central and peripheral nervous system. Though high grade events account for <1% of neurologic complications due to ICI monotherapy, they can be life threatening, and this effect may be compounded in doublet regimens targeting both CTLA4 and PD-1 pathways. Neurological events including myasthenia gravis, GBS, chronic immune demyelinating polyneuropathy, encephalitis, myositis, neuritis, and enteric neuropathy have all been associated with ICIs (Kao et al., 2018; Fellner et al., 2018; Hottinger, 2016; Manam et al., 2018; Wang et al., 2018). Early suspicion and prompt diagnosis are paramount, as, unmanaged, these complications may lead to death due to respiratory failure, colitis, myositis, or myocarditis (Kao et al., 2018; Wang et al., 2018).

A diagnostic algorithm has been proposed for evaluation of suspected neurologic irAEs. Serum studies, consultation with Neurology, MRI, electromyography (EMG), nerve conduction studies (NCG), and LP for CSF analysis are recommended. Differential diagnosis includes metastatic disease progression, paraneoplastic disease, or infectious etiologies. To establish the diagnosis of GBS, CSF should demonstrate albuminocytologic dissociation and protein elevation, while EMG and NCS can delineate GBS variant (Fellner et al., 2018; Anderson et al., 2019).

While mild neurologic symptoms may be treated with oral corticosteroids, any grade 3 or 4 toxicity based on the common criteria for adverse events (CTCAEs) should be managed in the hospital. Clinical consensus for frontline treatment includes IV corticosteroids, IVIG, and plasmapheresis (Han et al., 2020; Ong et al., 2018; Levinson et al., 2019; Hottinger, 2016; Manam et al., 2018; Anderson et al., 2019). Prolonged corticosteroid therapy up to 2–3 months is reasonable based on the long half-lives of ICIs (approximately 3 weeks). If patients fail to improve on front line treatment, some clinicians have demonstrated success with immune suppressants (Psimaras et al., 2019). Re-challenging a patient with an ICI after resolution of irAEs is becoming more common in practice, though there is no standardized approach (Fellner et al., 2018; Psimaras et al., 2019).

The field of ICI therapy is broad and promising in gynecologic oncology. Numerous monoclonal antibodies have been developed against PD-1, PDL-1, and CTLA4, and are currently under investigation in gynecologic malignancies. Combination modalities such as dual ICI, ICI with PARP inhibitor, and ICI with antiangiogenic hold therapeutic potential to be explored (Levinson et al., 2019).

The bulk of data currently available on neurotoxicity from ICIs comes from melanoma and lung cancer research (Wang et al., 2018). We have presented a unique case of GBS in a patient with uterine adenocarcinoma treated with pembrolizumab and lenvatinib. Though neurologic complications related to this regimen are rare, clinicians must be cognizant of potential associated toxicities. As ICIs become increasingly utilized in gynecologic oncology, it is imperative for gynecologic oncologists to be familiar with potentially fatal hazards of therapy, allowing for rapid diagnosis and treatment.

Author contributions

Bogna N. Brzezinska: Organized data, drafted the written report.

Robert V. Higgins: Contributed to written report.

Bunja Rungruang: Provided gynecologic oncology care for the patient, recognized the educational value of publishing the case, and highlighted key teaching points.

Patient consent

Patient consent was obtained for publication of this case report.

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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