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Arthritis Post-Immunotherapy for Endometrial Cancer: A Case Report and Review of Literature on the Acute Onset of Inflammatory Arthritis Following PD-I Inhibitor Therapy in a Patient with Recurrent Endometrial Cancer

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ABSTRACT

Since gaining FDA approval in 2014, pembrolizumab, a PD-1 immune checkpoint inhibitor, has been utilized in the management of cancers that progress following first-line therapy.1,2,5 While the pathological response to pembrolizumab is favorable, immune related adverse events (irAEs) can be elicited and require prompt diagnosis and management based on grading and severity, which can include discontinuation of immunotherapy.6,7,10,12 Our case concerns a 66-year-old female with recurrent endometrial cancer who was treated with pembrolizumab and developed inflammatory arthritis following therapy. We provide a succinct review of the pathogenesis and risk factors associated with irAEs, as well as diagnosis and management strategies.

KEYWORDS

Pembrolizumab, Immunotherapy, Immune-related adverse event, Inflammatory arthritis, Endometrial cancer, Arthralgia

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INTRODUCTION

In the United States, endometrial cancer is the fourth most common cancer among women, and there have been recent increases in its incidence and mortality rates.[1,2] Specifically, increases are noted from 49,650 cases and 8,190 deaths in 2013 to 65,620 cases and 12,590 deaths in 2020, respectively.[1,3] Endometrial cancer caught in early stages can be curatively treated with surgery, radiotherapy, or chemotherapy; however, 15% of women will have recurrence following first-line therapy.[1,2,4] Patients diagnosed with advanced stages or disease that progresses following first-line therapy have poor prognoses. With no standard therapy protocol, the 5-year survival rate for patients with lymph node metastasis is less than 50% and for patients with peritoneal or distant metastasis is less than 20%.[2]

Approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of advanced melanoma, pembrolizumab is an immune checkpoint inhibitor that interferes with the interaction between the programmed cell death protein 1 (PD-1) receptor expressed on the cells of the immune system and PD-1 ligand (PD-L1) expressed on tumor cells to prevent evasion of the immune system by tumor cells.[5,6] Studies have demonstrated favorable results among patients who have progressed following first-line treatment, or those who have no other treatment options.[1,2] However, immune related adverse events (irAEs), such as rash, colitis, and pneumonitis, are associated with this modality due to impaired self-tolerance.[5,6]

In this case, we report a 66-year-old woman with a history of recurrent endometrial cancer treated with pembrolizumab. She subsequently presented to her gynecologic-oncologist with complaints of bilateral hand joint pain and swelling and bilateral knee pain. She was referred to rheumatology and diagnosed with inflammatory arthritis related to immunotherapy. Due to the rarity of this irAE, this case provides the opportunity to discuss the pathogenesis of irAEs following treatment with immune checkpoint inhibitors, risk factors associated with irAEs, and the diagnosis and management of irAEs.

CASE PRESENTATION

The patient is a 66-year-old woman with no significant medical history who presented to her gynecolo-

gist with postmenopausal bleeding. She was referred to a gynecologic-oncologist after an endometrial biopsy revealed complex atypical endometrial hyperplasia. Following a total laparoscopic hysterectomy and bilateral salpingo-oophorectomy, she was diagnosed with stage IIIC endometrial cancer and started on adjuvant chemoradiation. Regimens included carboplatin and paclitaxel, as well as doxorubicin and carboplatin. Six years after the initial diagnosis, the patient was found to have recurrence of endometrial cancer and started on pembrolizumab.

While the immunotherapy elicited favorable oncological response, the patient began experiencing bilateral hand joint pain and swelling, as well as bilateral knee pain seven months after the first infusion. The patient was referred to rheumatology for further evaluation. Per rheumatology records, the patient complained of pain, swelling, and stiffness of bilateral hand joints, which was worse in the morning, and general fatigue. She denied any history of joint pain or similar symptoms prior to immunotherapy infusion. On physical exam, bilateral wrists, metacarpophalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints showed severe swelling, limitation of movement, and flexion deformity with incomplete fist and grip. Suspecting severe inflammatory arthritis status-post immunotherapy infusion, the patient was started on daily low-dose oral prednisone (10 mg) for symptomatic improvement. Additional work-up to differentiate inflammatory and non-inflammatory arthritis included x-ray of bilateral hands and a complete connective tissue screening profile, including rheumatoid factor (RF), anticyclic citrullinated peptide antibodies (anti-CCP), antinuclear antibodies (ANA), and C-reactive protein (CRP). The patient was advised to continue all other medications, including pembrolizumab infusions, as prescribed.

At two-week follow-up, the patient reported symptomatic improvement with the use of daily low-dose oral prednisone. On physical exam, bilateral wrists, metacarpophalangeal joints, proximal interphalangeal joints, and distal interphalangeal joints showed minimal swelling with improved range of motion and flexion deformity with improved fist and grip. Serology test was negative for RF, anti-CCP, and ANA; however, CRP was elevated. All other laboratory findings were within normal limits. Additionally, x-rays of bilateral hands revealed no erosions, but osteopenia was identified in both hands. While unable to definitively differentiate between inflammatory arthritis status-post immunotherapy infusions and seronegative rheumatoid arthritis, the patient responded to low-dose oral steroids, an indicator of appropriate response in the setting of immunotherapy usage. After a joint discussion between the rheumatologist and gynecologic-oncologist, the decision was made to taper the prednisone, in order to spare prolonged steroid use, and begin weekly methotrexate infusions. Four months following the initiation of methotrexate, the patient continued to receive pembrolizumab with limited reports of arthralgias.

DISCUSSION

Compared to traditional chemotherapies, pembrolizumab demonstrates superior efficacy and a better toxicity profile; however, due to inhibitory properties, it is still associated with adverse events.[7,8] The PD-1 is a transmembrane protein that is expressed on immune cells, including cytotoxic T-cells, natural killer cells, and B-cells.[4,5] Physiologically, this receptor interacts with PD-L1 during presentation of self-antigens to prevent harm to normal-functioning tissue.[4,5] Tumor cells harness this property in order to evade the immune system.

Interestingly, tumor infiltration lymphocytes (TILs) upregulate the PD-1 receptor to increase interactions with PD-L1 in order to suppress the cytotoxic effects of T-cells and other immune cells.4,5 Pembrolizumab, an anti-PD-1 inhibitor, works against tumor cells by attaching to PD-1 and blocking the site where this interaction occurs, leading to destruction of the tumor cells by immune cells.[4,6] While this results in a favorable pathologic response, the system-wide inhibition can cause infiltration of normal tissue by immune cells, resulting in autoimmunity.

Identifying risk factors associated with the development of irAEs in patients who receive immune checkpoint inhibitors helps to predict incidence of events and to make rapid diagnoses to begin management strategies.[8] Some studies have theorized that risk factors include low muscle attenuation, chronic infections, use of medications with autoimmune side effects, and various biomarkers, such as eosinophil count.[8] Kartolo et al. aimed to identify the predictors

of irAEs in patients with advanced solid cancers who were treated with immune checkpoint inhibitors. Results from the study indicate protective predictors, such as corticosteroid use prior to initiation of immunotherapy and female sex, as well as harmful predictors, such as pre-existing autoimmune disease, use of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, and poor renal function.[8]

Due to apprehension towards exacerbation of underlying autoimmune disease, there is limited research available concerning the use of immune checkpoint inhibitors in patients with pre-existing autoimmune disease, and this population is often excluded from studies.[4] Ramos et al. demonstrated successful oncological response following immunotherapy in a patient with recurrent endometrial cancer without aggravating her underlying p-ANCA vasculitis.[4] Other studies have demonstrated similar results in patients who have systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and scleroderma.[9] Therefore, patients with underlying autoimmune disease are at a higher risk for exacerbation; however, immune checkpoint inhibitors can be used in the treatment of their malignancy.

Prior to initiation of immunotherapy, clinicians must provide patients and caregivers with sufficient education to identify symptoms of irAEs and screen thoroughly at each appointment thereafter.6 In efforts to standardize screening, Lidar et al. developed a screening questionnaire to assist in identifying the onset of irAEs, including questions such as, "have you suffered from arthritis?" or "do you suffer from dryness of eyes or mouth?"10 If the patient or caregiver endorses any symptoms, it is imperative to begin therapy, such as steroids, and refer to the appropriate specialty team.[6,10]

The KEYNOTE-028 study demonstrated that 54.2% of women with advanced endometrial cancer developed irAEs following pembrolizumab therapy.[2] The American Society of Clinical Oncology provides a succinct summary of management of irAEs, including the diagnostic workup, grading, and management associated with inflammatory arthritis.[11] Per recommendations, workup should include complete rheumatologic history and examination of all peripheral joints and spine, plain x-rays to evaluate for joint damage, and autoimmune panel.[11] IrAEs are classified based on the system effected, and severity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[6,7,8] The most common irAEs include rash, pruritus, hypophysitis, colitis, hepatitis, and pneumonitis.[6,10] While most irAEs are self-limiting and mild, less than 10% are considered severe and qualify as grade three or four.8 Ott et al. reported 16.7% of women enrolled in the KEYNOTE-028 study developed grade three irAEs, and none developed grade four.[2] While the median onset for moderate to severe irAEs is approximately nine weeks, the median onset of rheumatological irAEs is approximately 11 months.[6,10]

Once the irAE has been diagnosed, management must begin promptly and is determined based on severity.[6,10] All patients, regardless of severity, should be referred to applicable specialty teams.[11] For rheumatological irAEs of mild to moderate severity, NSAIDs can be used for analgesia, and oral steroids can be used for immunomodulation.[6,10,12] If management of the irAE requires a higher dose of oral steroid, or the steroid is unable to be tapered appropriately, methotrexate can be added.[10] While tumor necrosis factor inhibitors are second-line therapy, they should be used with caution due to side effects and toxicity profile.[10,12] Lastly, pembrolizumab therapy should be stopped if the irAE is life-threatening or severe.[13]

CONCLUSION

In this report, we present the case of a patient with recurrent endometrial cancer treated with pembrolizumab and the subsequent development of inflammatory arthritis, a rarely reported irAE. We have provided a literature review in order to emphasize the pathological response responsible for development of autoimmunity, risk factors associated with the use of immunotherapy, and the need for prompt diagnosis and management. It is imperative that all healthcare workers involved in the medical care of patients receiving immunotherapy understand how irAEs present in order to diagnose and manage appropriately, including prompt initiation of immunosuppressive medications and referral to specialists for additional evaluation.

AUTHOR AFFILIATIONS

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