Abstract

Immune checkpoint inhibitors (ICIs) have improved the outcome and overall survival of patients with cancer. However, predicting the efficacy of immunotherapy remains difficult. The DNA mismatch repair (MMR) system is vital for identifying and repairing mismatched nucleotides during genetic recombination. Cancers with defective MMR involve thousands of mutations and are defined as having microsatellite instability (MSI) and demonstrate a high immunotherapy response rate. Therefore, MSI could be a biomarker for predicting the response to ICIs. Herein, we present two patients with MSI-high gynecologic malignancies who demonstrated a complete response to ICI treatment, but along with panuveitis, a rare immunotherapy-related adverse event in one of the cases.

Keywords: Defective mismatch repair, immune checkpoint inhibitor, microsatellite instability, panuveitis

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are widely used for cancer treatment. A durable response greatly improves outcome and survival in certain patients. However, predicting the efficacy of ICIs remains difficult.\(^1\)

DNA mismatch repair (MMR) is a crucial mechanism for identifying and repairing mismatched nucleotides during genetic recombination.\(^2\) Cancers with defective MMR (dMMR) exhibit thousands of mutations located mostly in monomorphic microsatellites and thus have microsatellite instability (MSI). Therefore, MSI can be used as a dMMR marker and a potential biomarker to predict the response to immunotherapy.\(^1\)

ICI treatment may cause immune-related adverse events (irAEs), different from those caused by chemotherapy or targeted therapy. IrAEs can affect any tissue or organ, particularly the lungs, liver, skin, and endocrine system. Therefore, understanding the efficacy and safety of these drugs is necessary.\(^3\)

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How to cite this article: Kuo MC, Liu CT. Effect of immune checkpoint inhibitors in gynecologic cancer associated with defective mismatch repair and a rare immunotherapy-related adverse event. J Cancer Res Pract 2021;8:73-7.
Herein, we report two patients with MSI-high gynecologic malignancies who demonstrated a complete response to ICI treatment. One of the patients, however, exhibited panuveitis, a rare irAE.

**Case Reports**

**Case 1**

In October 2014, a 34-year-old woman complained of lower abdominal pain that had persisted for 2 months. Magnetic resonance imaging (MRI) revealed a right ovarian tumor with compression of bilateral ureters. Fertility-sparing right salpingo-oophorectomy exhibited clear cell carcinoma in the pathology report (AJCC 7th Edition, pT1aN0, Stage IA). Adjuvant chemotherapy with four cycles of carboplatin (target area under the concentration [AUC], 5 mg/mL/min) and paclitaxel (175 mg/m²) was administered. Recurrence at the left ovary with lymph node metastases and tumor seeding at the abdominal wall were resected in September 2015 (AJCC 7th Edition, rpT2bN0Mx, Stage IIIB). Moreover, salvage chemotherapy with six cycles of bevacizumab (7.5 mg/m²), carboplatin (target AUC, 5 mg/mL/min), and PEGylated liposomal doxorubicin (30 mg/m²) was administered. A partial response was noted after the salvage chemotherapy, with a residual tumor in the lower abdominal wall that was resected in April 2016.

Tumor recurrence was noted in the abdominal wall in October 2016, which was resolved using cisplatin-based concurrent chemoradiotherapy (60 Gy). However, lymph node metastases at the bilateral neck, mediastinum, left axilla, and upper retroperitoneum were confirmed in March 2017 which were refractory to the regimen of bevacizumab, carboplatin, and PEGylated liposomal doxorubicin. Reevaluation of the tumor pathology demonstrated dMMR with aberrant loss of MLH1 and PMS2 and increased PD-L1 expression (tumor proportion scores [TPS]: 100%, Dako 22C3 IHC assay). Triweekly pembrolizumab (2 mg/kg) was administered, and a complete response to this treatment was obtained after six cycles [Figures 1 and 2]. However, progressive blurred vision, conjunctival congestion, and keratic precipitates were noted. Grade 3 panuveitis was diagnosed by an ophthalmologist. She then received systemic steroid treatment with methylprednisolone at a dose of 32 mg per day. However, this failed to resolve the symptoms, and therefore, pembrolizumab was discontinued. After 12 months of ceasing of pembrolizumab, tumor recurrence occurred at the retroperitoneal and pelvic lymph nodes, refractory to subsequent chemotherapy. Finally, hospice care was provided to the patient because of her poor performance status.

**Case 2**

In December 2016, a 52-year-old woman presented with intermittent postmenopausal vaginal bleeding. An endometrial biopsy demonstrated clear cell carcinoma, and MRI confirmed an endometrial tumor with invasion of the myometrial wall and left ovary and left external iliac lymph node metastases. Debulking surgery was performed, which showed clear cell carcinoma (AJCC 8th Edition, pT3aN1, Stage IIIC1). Adjuvant chemotherapy with six cycles of carboplatin (target AUC, 5 mg/mL/min) and paclitaxel (175 mg/m²) was administered. However, tumor recurrence at retroperitoneal, para-aortic, retrocruiral, left paravertebral, and left supraclavicular lymph nodes was confirmed. Reexamination of tumor pathology confirmed dMMR with aberrant loss of MLH1 and PMS2 without PD-L1 expression (TPS: 0%). Eight cycles of triweekly pembrolizumab (2 mg/kg) were administered, accompanied by a sequential short course of radiotherapy (30 Gy) to para-aortic lymph nodes between the fourth and fifth cycle. A complete response to the treatment was demonstrated [Figure 3]. Due to economic concerns and disease-free status, the patient decided to interrupt the ICI treatment in February 2018. Recurrent lymph node metastases at the left neck, left supraclavicular, and left axillary regions were diagnosed in July 2018. A complete response to pembrolizumab rechallenge was again noted. However, grade 2 hyperthyroidism was also noted, which was controlled with methimazole and prednisolone [Figure 4]. A further thyroid function test revealed euthyroid status. The patient has remained free of disease after 2 years of pembrolizumab treatment.

**Discussion**

Cancers with dMMR can be a potential biomarker for predicting the efficacy of the response to ICI treatment. Le et al. initially reported that MMR status could predict the clinical benefits of ICIs with pembrolizumab and demonstrated a novel approach based on genetic status rather than the primary site of origin for the treatment of solid tumors. A next-generation sequencing-based review of 12,019 cancers revealed that >2% of adenocarcinomas exhibited dMMR. The most important cancer types warranting MSI testing through immunochemistry to assess MMR protein status include endometrial, colorectal, small bowel, gastric, ovarian cancer, esophageal adenocarcinoma, and glioblastoma. The hypothesis for a high response rate to ICIs could be the sensitivity of a large proportion of mutant neoantigens in dMMR cancers. A systematic review reported high TMB-high and MSI-high concordance rates in colorectal cancers (44.2%), esophagogastric adenocarcinomas (27.7%),
and endometrial cancers (31.0%). However, high concordance has not been observed between PD-L1 expression and MSI.\(^1\) Of the cases with MSI-high tumors in the current case report, Case 1 with ovarian cancer exhibited 100% TPS, while Case 2

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**Figure 2:** Complete response was noted after six cycles of pembrolizumab. The green arrows indicate mediastinal and axillary lymph nodes before treatment.

**Figure 3:** After eight cycles of pembrolizumab, complete regression of metastatic lymph nodes in retroperitoneal, para-aortic, retrocrural, left paravertebral, and left supraclavicular areas were confirmed by positron emission tomographic scan.
with endometrial cancer exhibited 0% TPS. The discrepancy in PD-L1 expression may be related to intratumor heterogeneity.\[6\] Although a high PD-L1 expression has been proven to predict the efficacy of ICI treatment in some cancer types, when a solid tumor presents with dMMR or MSI-high status, ICI treatment should be strongly recommended as systemic treatment regardless of the PD-L1 expression. Both clinical courses demonstrated the efficacy of ICIs in patients with MSI-high cancers.

Panuveitis, a rare ophthalmic irAE, was diagnosed after pembrolizumab treatment in Case 1. Few case reports have described uveitis as an irAE in patients with metastatic urothelial carcinoma, and the culprit drugs mainly included pembrolizumab and ipilimumab.\[7\] Baughman et al. also presented a case with bilateral uveitis and keratitis following a third nivolumab infusion for metastatic melanoma.\[8\] Ipilimumab-induced uveitis was also reported in a case series of four patients with metastatic melanoma, in which the ocular inflammation was resolved using systemic steroids.\[9\] The drug exposure period was <3 months in all of the previous cases. Artificial tears are recommended for all uveitis grades. Ophthalmic and systemic corticosteroids may be considered for grade 2 or higher events. In case of grade 3 or 4 uveitis, permanent ICI use is contraindicated.\[3\]

In this case report, the therapeutic efficacy of ICIs in patients with MSI-high cancers was confirmed. However, the incidence of panuveitis, a rare irAE, should also be considered a consequence of ICI therapy.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgment
We appreciated the two patients’ consent of reporting for research. We thank the multidisciplinary team of the gynecologic cancer at our hospital for their generous assistance and cooperation. This manuscript was edited by Wallace Academic Editing.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References


