



Pembrolizumab-induced immune-mediated fatal colitis with concurrent giardia infection

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Abstract

Advancements in medicine have enabled the use of monoclonal antibodies in the field of oncology. However, the new adverse effects of immunotherapeutic agents are still being reported. We present the first case of pembrolizumab-induced fatal colitis with concurrent *Giardia* infection in a patient with metastatic ovarian cancer. A 47-year-old woman with metastatic ovarian cancer who was being treated with pembrolizumab admitted to our clinic complaining of persisting bloody diarrhoea. Her stool antigen test was positive for *Giardia*. The patient received metronidazole. A colonoscopy with mucosal biopsy was performed upon no clinical or laboratory improvement. Colonoscopy detected deep exudative ulcers in sigmoid colon and rectum. The cytopathological evaluation revealed immune-mediated ischemic colitis. The treatment was rearranged with methylprednisolone. Upon an increase in bloody diarrhoea frequency and C-reactive protein levels, infliximab was started. However, the patient became refractory to infliximab therapy after the second dose and was deceased due to septic shock.

Keywords Cell-mediated immunity · Colitis · Colonoscopy · Drug side effects · Immunotherapy · Medical oncology

Introduction

The idea that manipulating the immune system to fight malignancy is being applied to some cancer types successfully and it was also awarded the 2018 Nobel Prize in Physiology or Medicine to Allison and Honjo [1]. Although

the immunotherapy is a breakthrough in the field of cancer, some rare adverse effects of immune checkpoint inhibitors (ICIs) hinder the application of this therapy [2]. Whereas many adverse effects are manageable, fatal events are also reported. According to a meta-analysis by Wang et al., 613 fatal ICI events were reported from 2009 through January 2018 in World Health Organization (WHO) pharmacovigilance database. 193 of deaths occurred due to anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab or tremelimumab), most were usually from colitis [135 (70%)], whereas anti-programmed cell death protein 1 (PD-1) (nivolumab, pembrolizumab)/anti-programmed death-ligand 1 (PD-L1) (atezolizumab, avelumab, durvalumab)-related fatalities were usually from pneumonitis [333 (35%)], hepatitis [115 (22%)], and neurotoxic effects [50 (15%)] [3].

Immune checkpoint inhibition with pembrolizumab, which is a humanized monoclonal antibody against PD-1, is one of the effective medications used in progressive ovarian cancer [4]. However, its adverse effects are a major clinical issue for physicians. Immune-mediated colitis is a known adverse effect of pembrolizumab; however, it occurs less than the patients receiving CTLA-4 (ipilimumab and tremelimumab)-based immunotherapy [3]. The current literature reports no pembrolizumab-induced immune-mediated fatal colitis [5]. The aim of this report is to present the first

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case of pembrolizumab-induced fatal colitis with concurrent *Giardia* infection in a patient with metastatic ovarian cancer.

Case

A 47-year-old woman was admitted to our clinic complaining of persisting bloody diarrhoea for 10 days. The patient was diagnosed with stage 4 metastatic ovarian serous adenocarcinoma in July 2019 and underwent cytoreductive surgery. Following the surgery, she had been given her first course of cancer treatment with carboplatin and paclitaxel. Pembrolizumab was added to the patient's cancer treatment on her second cycle of chemotherapy after the determination of the microsatellite instability-high (MSI-H) status of the ovarian cancer. After the fourth cycle of the chemotherapy, she received three more cycles only with pembrolizumab. Her last pembrolizumab treatment was 3 weeks prior to the admission. The patient's physical examination showed decreased skin turgor, pale conjunctiva, and oral mucosal membranes. Laboratory tests on the day of admission were significant for hyponatremia, hypoalbuminemia, lymphocytopenia, and increased C-reactive protein (CRP) (10.42 mg/dL). Her stool antigen test was negative for *Clostridium difficile* and *Entamoeba histolytica*, but positive for *Giardia*. The patient received metronidazole for the following 10 days in the inpatient setting. Since her CRP levels continued to increase and no clinical improvement was observed in 3 days, a colonoscopy together with mucosal biopsy was performed. Colonoscopy detected deep exudative ulcers in sigmoid colon and rectum (Fig. 1a). Cytopathological evaluation of the biopsy revealed cryptitis and transmucosal necrosis suggesting immune-mediated ischemic colitis (Fig. 1b, c). Pembrolizumab-induced immune-mediated colitis was considered, and the patient's medical treatment was rearranged as methylprednisolone 1 mg/kg/day. Upon an increase in bloody diarrhoea frequency and CRP levels after 3 days of the treatment, infliximab 5 mg/kg was started. The patient's acute phase reactant levels decreased after the

first dose. However, the patient became refractory to infliximab therapy after the second dose and unfortunately, was deceased due to septic shock.

Discussion

The Food and Drug Administration approved the use of pembrolizumab for solid cancers with MSI-H status in 2017 [6]. In a review in 2020, administration of immunotherapy in ovarian cancer, albeit not definitive, pointed to encouraging results [7]. Pembrolizumab, which is an anti-PD-1 humanised monoclonal antibody could cause some immune-related adverse effects including pneumonitis, gastritis, and neurotoxic events [5]. The severity of colitis is classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (Table 1). Pembrolizumab-induced colitis is rare. However, grade 3 and 4 colitis have been reported as an adverse effect in some clinical trials with a mean incidence of 2%. Furthermore, grade 5 colitis, in other words, death due to pembrolizumab-induced colitis, has not been recorded until now [8].

Immune-mediated colitis requires prompt diagnostic evaluation and true management [9]. In the case of diarrhoea and abdominal pain, infection should be first ruled out. If an infection exists, then the appropriate antibiotic treatment should be given [10]. Another important point in

Table 1 The severity of colitis is classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events

Grade	Colitis—clinical presentation
1	Asymptomatic
2	Abdominal pain, mucus, blood in stool
3	Severe pain, fever, peritoneal signs
4	Life-threatening consequences such as perforation, ischemia, necrosis, bleeding, toxic megacolon
5	Death

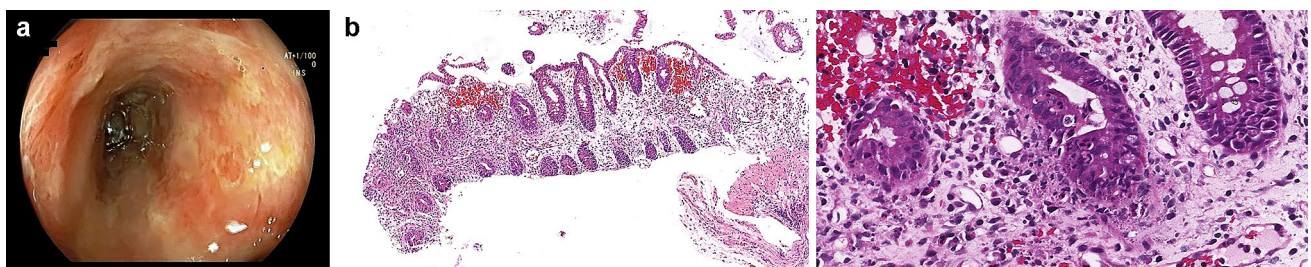


Fig. 1 a Colonoscopy image of the sigmoid colon showing exudative ulcers. b There is significant active inflammation with extensive crypt loss. They are observed as decreased in size and number, in association with the mucin loss of the crypt epithelia. These findings

are consistent with ischemic-like colitis (haematoxylin and eosin). c Prominent neutrophil and eosinophil infiltration and increased apoptosis are observed in the crypt epithelia (haematoxylin and eosin)

patients with malignancy is the exclusion of the metastasis and metastasis-related complications in the gastrointestinal system, such as perforation or bleeding [11–13].

The gold standard of immune-mediated colitis is colonoscopy and biopsy, including the examination of the ileum. In addition, the biopsy should be evaluated by an experienced pathologist since it could be difficult to distinguish from the inflammatory bowel diseases [14]. The management of immune-mediated colitis mainly consists of immunosuppressive agents according to the severity of the colitis [9]. In cases such as the presented one, meaning grade 3 or more severe colitis, the immune checkpoint inhibitor drug should be stopped, and systemic corticosteroids should be initiated. One-third to two-thirds of patients could be refractory to steroid treatment [15]. Then, the second-line treatment infliximab is initiated and mainly successful [16]. If the patient does not improve, the next step is vedolizumab, which is an antibody against the $\alpha 4\beta 7$ -integrin on the surface of CD4+ T cells. The usage of vedolizumab is written in a few clinical reports, but there are no clear treatment algorithms for this therapy [17, 18].

Anti-PD-1 antibodies mostly cause immune-related adverse events (irAEs) occur within the first 6 months of the treatment and fatal outcomes occur more frequently and earlier if the patients receive ICI combination therapy [19]. Due to the growing use of ICIs in oncology, clinicians are facing with irAEs; thus, awareness of this complications needs to be raised regarding the clinical presentation, early diagnosis and appropriate management of these toxicities, to have a better survival rate in cancer patients [20].

Conclusion

Although the *Giardia* infection was treated and the severity of immune-mediated colitis tried to be reduced with proven strategy: first, corticosteroid and then infliximab, the patient became refractory to these treatments and was deceased before the third-line medication (vedolizumab) could be administered. To our knowledge, this is the first reported case of pembrolizumab-induced colitis with concurrent giardia infection, resulting in death despite the appropriate treatment. This case demonstrated that immune-mediated colitis could be very severe, even fatal, and further research is needed for better treatment options for this clinical situation.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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