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Severe ileocecal ulcers in a patient with urothelial carcinoma receiving anti-programmed death-1 agent

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Abstract

A 92-year-old man had urothelial carcinoma of renal pelvis, pIIIB, and pembrolizumab was prescribed for 8 months with acceptable disease control. This time, he was admitted due to abdominal pain and diarrhea for 5 days. Abdominal computed tomography revealed thicken bowel wall, and lower gastrointestinal endoscopy showed marked ulcers at ileocecal valve. The histology findings suggested immuno checkpoint therapy related enterocolitis. Medication with intravenous methylprednisolone, then tapped gradually to oral prednisolone, was used, and he had complete symptomatic recovery.

Keywords

anti-programmed death-1 agent; colon ulcer; immunotherapy; urothelial carcinoma.

Introduction

Immune checkpoint inhibitors (ICI), including targeting cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed death-1/ligand (PD-1/PD-L1), have become a new standard of care in several cancers. Anti-PD-1 agent, such as pembrolizumab, has been approved in melanoma, non-small cell lung carcinoma, hepatocellular carcinoma, gastric or gastro-oesophageal junction adenocarcinoma, squamous cell carcinoma of the head and neck, Merkel call carcinoma and urothelial carcinoma [1-3]. ICI enhance antitumour T-cell activity, and this might lead to result immune-related adverse effects (irAE), including involiving gastrointestinal (GI) tract [4]. In this case, we describe a patient with urothelial carcinoma having severe ileocecal ulcers after receiving treatment of pembrolizumab, an anti-PD-1 agent.

Case Report

A 92-year-old man had urothelial carcinoma of right renal pelvis and received right nephroureterectomy with bladder cuff excision. The pathologic stage was IIIB (pT3a, N2, M0 by TNM classification). He then accepted a systemic therapy with pembrolizumab 240 mg every 3 weeks for 8 months, and achieved stable disease control. This time, he was admitted to our hospital with persistent abdominal pain, nausea and diarrhea, all of which had begun 5 days before admission. He had no history of fever, chills, night sweating or body weight loss. Other medical history, travel history and family history were unremarkable. He had been brought to the hospital for treatment of the abovementioned symptoms.

On physical examination, the patient was not in distress. He had a body temperature of 36.2°C, heart rate of 83 beats/min, blood pressure of 110/63 mmHg, respiratory rate of 16 breaths/min and oxygen saturation of 99% under room air. There was no significant icteric sclera or yellowish skin. Mild abdominal tenderness was found in the right lower quadrant. No lymphadenopathy or splenomegaly was found. Laboratory work-up demonstrated a white cell count of 8.8 × 103/μL (normal, 4–11 ×103/μL), hemoglobin of 12 g/dL (normal, 11.3– 15.3 g/dL), platelet count of 306 × 103/μL (normal, 120–320×103/μL), creatine of 1.9 mg/dL (normal, 0.6–1.2 mg/dL), alanineaminotransferase (ALT) of 9 U/L (normal, 8–38 U/L) and C-reactive protein of 12.2mg/dL (normal, < 0.5 mg/dL). Prothrombin time was within normal limits (10.3 seconds). Chest X-ray showed no active lesion, but computed tomography (CT) of the abdomen revealed thicken bowel wall in the right lower abdominal space (Figure 1). Other examinations were negative for stool culture and Clostridium difficile toxin.

Lower GI endoscopy showed marked ulcers at ileocecal valve (Figure 2), and biopsy demonstrated intestinal mucosa with lamina propria edema, mixed infiltrate of leukocytes. No malignant cell, granuloma, or crypt distortion was present, and immunohistochemistry (IHC) satin for cytomegalovirus (CMV) showed neither negative. The histology findings suggested immuno checkpoint therapy related enterocolitis.

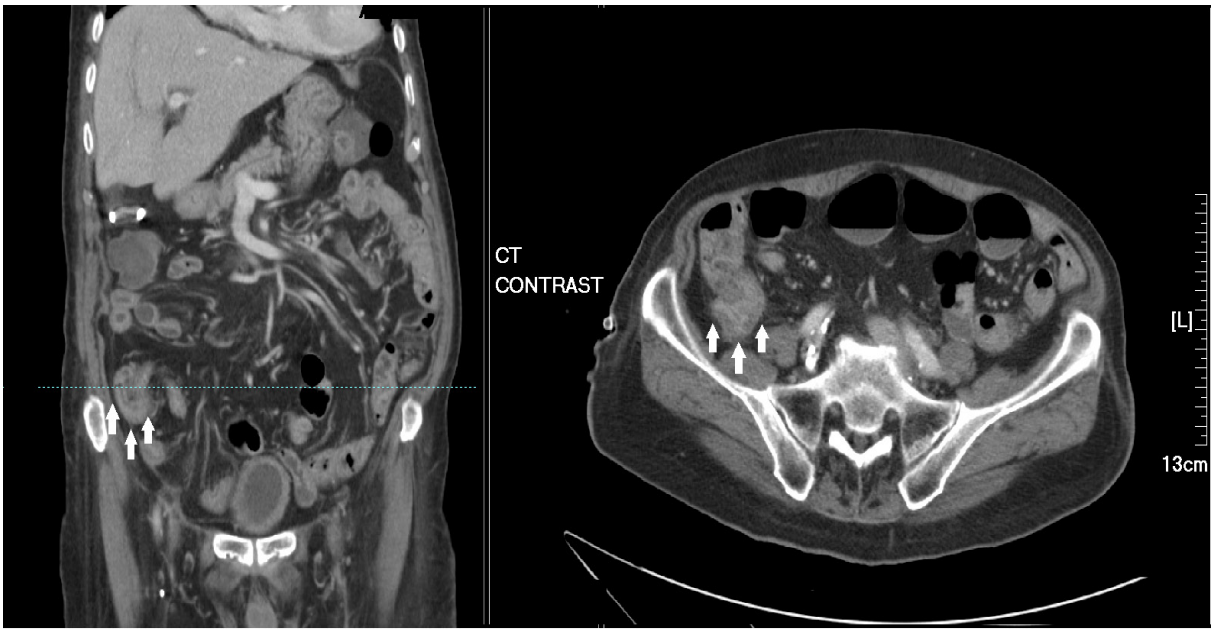

Figure 1: Computed tomography (CT) of the abdomen showed thicken bowel wall in the right lower abdominal space. (arrow)

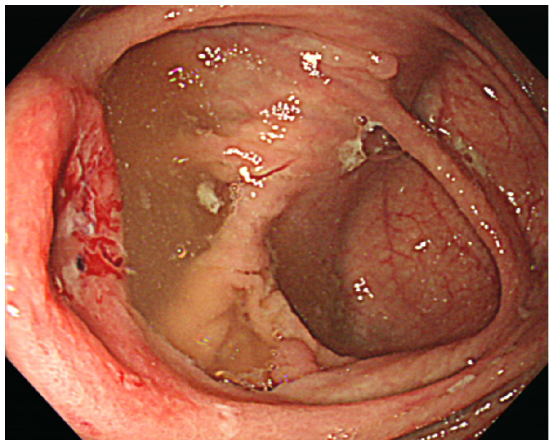

Figure 2: Lower gastrointestinal (GI) endoscopy showed marked ulcers at ileocecal valve.

The immunotherapy was discontinued. Medication with intravenous methylprednisolone 1 mg/kg/day was adapted and symptomatic recovery occurred. The dosage of steroid was tapped gradually with one-week interval, and shifted to oral prednisolone 20 mg per day at last. The patient was later discharged from hospital and received clinical follow-up.

Discussion

To date, there are 7 approved ICIs that target 3 main checkpoints, including CTLA-4 (ipilimumab and tremelimumab), PD-1 (pembrolizumab and nivolumab), and PD-L1 (atezolizumab, avelumab, and durvalumab). ICIs have become the standard of care for a number of cancers [1].

With a remarkable breakthrough in the treatment of several malignancies, several irAEs that affect multiple body systems have been recognized, [5,6] including upper and lower GI. The incidence of GI irAE ranges from 0.3% to 7%, depending on different kinds of ICIs [7-9]. For example, GI irAE induced by anti-CTLA-4 are frequent and severe, whereas those induced by PD-1 blockade seem to be less frequent and clinically more diverse.8 The relative risk of colitis for patients treated with anti-PD-1 monotherapy is 0.20 (95% CI 0.07 to 0.62; p=0.005) as compared with patients treated with anti-CTLA-4 monotherapy.10 In fact, incidence of pembrolizumab-related colitis in phase 2 KEYNOTE 224 was 1% only [3].

The median time to onset of GI irAE associated with anti-PD-1 therapy is later and generally occurs 2–4 months after treatment initiation [8]. To our patient, the severe lower GI irAE occurred 8 months after initiation of anti-PD-1 therapy.

Histological finding of anti-PD-1 agent related LGI irAE included acute colitis and microscopic lymphocytic colitis [11,12]. Colonic mucosal lymphocytes are predominantly CD8+ T cells in anti- PD-1-induced colitis, which differs from the predominance of CD4+ T cells observed in anti-CTLA-4-induced colitis [12,13].

Most patients respond to corticosteroids, including up to 87.5% of patients with acute colitis and 57% of patients with microscopic colitis.2 Time to resolution of GI irAE related to anti-PD-1 ranges from 1.1 to 4.2 months [14]. Our patient experienced a faster recovery course and no more relapse symptoms after steroid dosage tapped.

Conclusion

In conclusion, we have reported a patient with urothelial carcinoma having severe lower GI irAE after receiving treatment of anti-PD-1 agent. The symptoms relieved rapidly after steroid prescription. This case can help raise clinicians' awareness of the possibility of GI irAE in the subjects with treatment of ICI.

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