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CASE SERIES

Upper gastrointestinal tract immune-related adverse events: Two cases of obstructive complications occurred in immune consolidation therapy after sequential chimeric antigen receptor T cell therapy with autologous hematopoietic stem cell transplantation for refractory/relapsed diffuse large B cell lymphoma

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Key Clinical Message

Immune checkpoint inhibitors are a very popular method of treating malignant tumors. But its side effects cannot be ignored. This study revealed obstructive complications during immune consolidation therapy following sequential chimeric antigen receptor T cell therapy with autologous hematopoietic stem cell transplantation in two patients with diffuse large b cell lymphoma (DLBCL). Both our patients had the same symptoms of vomiting and inability to eat due to pyloric obstruction, it should be highlighted that this is a relatively rare and irreversible complication of upper gastrointestinal caused by immune consolidation therapy.

Abstract

Immune checkpoint inhibitors (ICIs) have become the standard therapy for many malignant tumors.However, ICIs are associated with unique immune-related adverse events (irAEs) caused by dysregulated immune activation and associated complications have been observed in patients. Here, we report two cases of patients with pyloric obstruction and duodenal ulcers induced by the use of sintilimab, which provides some guidance for the widely used anti-programmed death-1 therapy. During the entire treatment progression for such patients, the correct differential diagnosis of adverse effects and the use of immunosuppressive agents such as glucocorticoids are essential to facilitate early prevention and intervention of irAEs.

KEYWORDS

chimeric antigen receptor T cell therapy, duodenal ulcers, immune checkpoint inhibitor, sintilimab, upper gastrointestinal tract irAE

1 | BACKGROUND

Immunization checkpoint (IC) is an important immunomodulator that maintains immune homeostasis and prevents autoimmune diseases. However, some IC proteins expressed by tumor cells can disturb the body's antitumor immunity and promote the growth and proliferation of malignant cells.[1] Therefore, blocking the immune checkpoint pathway using immune checkpoint inhibitors (ICIs) is an important method for treating malignant tumors. Among all ICIs, anti-programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) antibodies have been studied the most. ICIs are associated with unique immune-related adverse events (irAEs) caused by immune activation disorders.

Sintilimab is a monoclonal antibody against PD-1, it can relieve immunosuppression and enhance T cells' immune monitoring and killing ability against tumors.[2,3] The first indication is relapsed or refractory classical Hodgkin lymphoma after second-line chemotherapy.[2] Although sintilimab has shown strong therapeutic effects in treating tumors, its side effects are inevitable. Here, we present two patients who suffered from pyloric obstruction and duodenal ulcer induced by the use of sintilimab and expect to provide insights into the therapeutic strategy for such patients.

2 | CASE PRESENTATION

2.1 | Case 1

A patient in early fifties underwent enhanced computed tomography (CT) of the upper abdomen due to abdominal distension and light stool color, suggesting uncinate process cancer of the pancreas (4.0 × 6.2 cm). The pathological diagnosis of pancreatic puncture was diffuse large b cell lymphoma-not otherwise specified (DLBCL-NOS) in 2016. Immunohistochemical staining showed the following: CD20 (+), CD3 (−), CD10 (−), Bcl-6 (+), CD5 (−), p53 (+), MUM-1 (+), CD79a (+), CD30 (−), Ki67 (approximately 70%), and In Situ Hybridization EBFR (−). Complete remission (CR) was achieved after six courses of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) regimen. The disease relapsed after 1 year, but partial remission was achieved after three cycles of chemotherapy with rituximab, ifosfamide, carboplatin, and etoposide phosphate (R-ICE) regimen, and chemotherapy with the R-modified Gemox regimen continued for one cycle. In June 2018, CR was achieved after infusion of CD19 chimeric antigen receptor (CAR)-T cells (Relmacabtagene autoleucel, Clinical Trial). However, positron emission tomography-computed tomography (PET-CT) (June 2019) indicated that the jejunum in the abdominal cavity occupied an excessively high metabolic area, which was regarded as a malignant lesion and lymphoma recurrence. Pathology showed DLBCL (non-germinal center B-cell [NGCB]). Immunohistochemical staining showed the following: CD20 (+), CD19α (+), MUM-1 (60%+), CD19 (−), CD21 (−), CD22 (−), Bcl-6 (+), Bcl-2 (approximately 80%+), c-myc (approximately 5%+), CD5 (−), Ki67 (approximately 60%), and In Situ Hybridization EBFR (−). The autologous hematopoietic stem cell transplantation (ASCT) was performed at our hospital on August 29, 2019. A total of 3.35×10^6/kg $CD34^+$ cells were infused. CAR79b (1.0×10^7/kg) and CAR20 (9.73×10^6/kg) were infused on September 4th and 5th, respectively. On September 29, the patient began to use sintilimab (100–200 mg) and chidamide (5 mg qd) every 3 or 4 weeks as consolidation treatment after ASCT combined with CAR-T cell therapy to enhance the function of CAR-T cells and prevent a recurrence. PET-CT showed CR in November 2019. Six months later, after complaining of abdominal pain, the patient was found to have a duodenal bulbar ulcer by gastroscopy, and PD-1 therapy was discontinued in September 2021. PET-CT (March 2022) showed an abnormally high nodular metabolic lesion in the antrum near the duodenal bulb. Painless gastroscopy showed gastric retention and a duodenal ulcer with stenosis. Upper gastrointestinal radiography revealed a duodenal bulbar ulcer. A duodenal bulb biopsy revealed very few abnormal cells in the denatured and necrotic tissue. The patient was treated with symptomatic and supportive treatment, such as gastric protection and improvement of intestinal flora. However, the patient again presented with epigastric pain and vomiting of bile-like contents. CT (April 2022) showed that after partial small intestinal resection, the number of peripheral lymph nodes had increased, which was consistent with lymphoma. The intestinal wall of the terminal ileum was thickened and strengthened. Thickening of the intestinal wall and stenosis of the intestinal lumen, with gastric retention, were observed in the duodenal bulb. Examination using a miniature ultrasonic probe revealed gastric retention and pyloric stenosis. Ultrasonography revealed hyperechoic thickening of the duodenal mucosa (Figure 1A). There was no organic lesion in the entire large intestine during the electronic colonoscopy (Figure 1B). Since methylprednisolone (1 mg/kg), ruxolitinib, and mycophenolate mofetil were ineffective, after consultation, the patient was transferred to the Department of Gastrointestinal Surgery and "gastrojejunostomy combined with omentectomy" was performed. Digital upper gastrointestinal angiography showed that the gastrojejunostomy was patent, and no obvious leakage of contrast agent was observed. Through telephonic follow-up, the

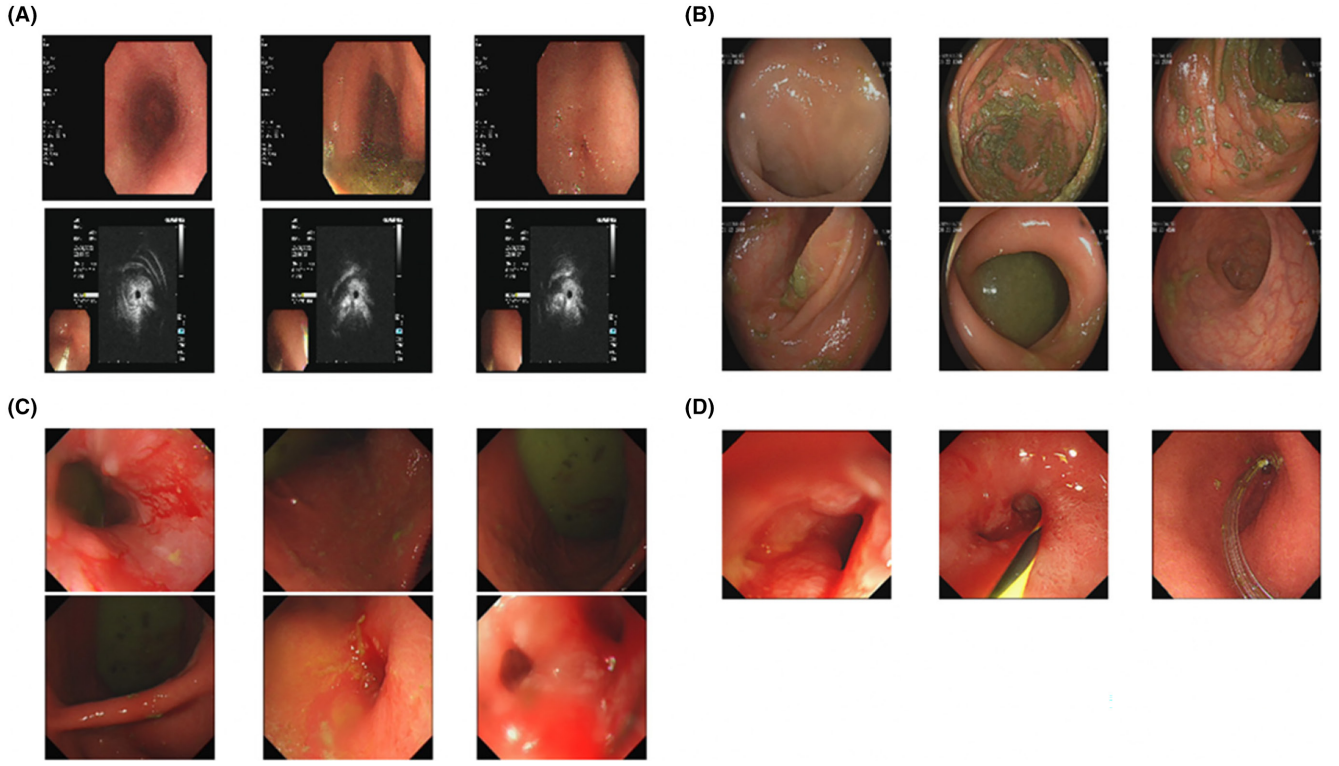

FIGURE 1 Videography results of cases. (A) The examination of miniature ultrasonic probe of case 1 revealed that gastric mucosa is smooth, and a large amount of food residues can be seen; pyloric stenosis, which can't be passed by endoscope; ultrasonography revealed hyperechoic thickening of the duodenal mucosa. (B) There was no organic lesion in the entire large intestine during electronic colonoscopy of case 1. (C) Painless gastroscopy of case 2 showed the mucosa of the lower esophagus is strip-shaped erosion, and the mucosa of cardia is scattered in sheet ulcer. A large amount of green food was found in the stomach. The pylorus is deformed, the anterior wall forms a diverticulum, the mucosa in the diverticulum is congested and edema, and the anterior wall of the pyloric canal forms an ulcer. (D) In case 2, endoscopic jejunely feeding tube placement was performed, painless gastroscopy revealed descending duodenal stenosis with pseudodiverticulum formation at the anterior wall.

patient stated that the symptoms of abdominal discomfort and vomiting had been greatly alleviated, and the results of the routine examination were all normal. Thus, the patient is very grateful for the doctors' and nursing teams' care and assistance.

2.2 | Case 2

A patient in early thirties found enlarged left cervical lymph nodes in 2016. CT indicated multiple enlarged left cervical, mediastinal, pelvic, and abdominal lymph nodes; retroperitoneal lymph nodes; and multiple space-occupying lesions in the spleen. A pathological biopsy revealed DLBCL; however, the patient refused chemotherapy and was administered oral traditional Chinese medicine. Subsequently, the lymph nodes increased gradually. In September 2016, PET-CT revealed that extensive lymph nodes invaded the spleen. The patient was diagnosed with DLBCL (Stage III B) with an alanine aminotransferase level of 216 U/L. Chemotherapy was discontinued due to a progressive transaminase increase after liver protection and anti-hepatitis B virus therapy. In April 2017, the patient had a lower back pain, received three cycles of chemotherapy with the CHOP regimen and nine cycles of chemotherapy with the R-CHOP regimen were continued. The PET/CT result (January 2018) indicated a residual tumor after the treatment of lymphoma. The patient then received radiotherapy at a DT dose of 40 Gy/20 F. Magnetic resonance imaging showed no swollen lymph nodes. In April 2018, the patient experienced pain in the left iliac region, and CT indicated multiple lymph node enlargements in the whole body. Considering the recurrence of the disease, the patient was again treated with the R-CHOP regimen. In July, the patient was diagnosed with recurrent DLBCL-NGOB, stage IIIB (recurrence, invasion of pelvic cavity, retroperitoneal lymph node, and spleen) with an international prognostic index score of 1, received 6 cycles of chemotherapy with a gemcitabine, dexamethasone, and cisplatin (GDP) regimen and lenalidomide (25 mg qd) for 3 weeks. Immunosuppression therapy (rituximab 600 mg) was initiated in February 2019. Pretreatment with the BCNU, etoposide, cytarabine, and melphalan

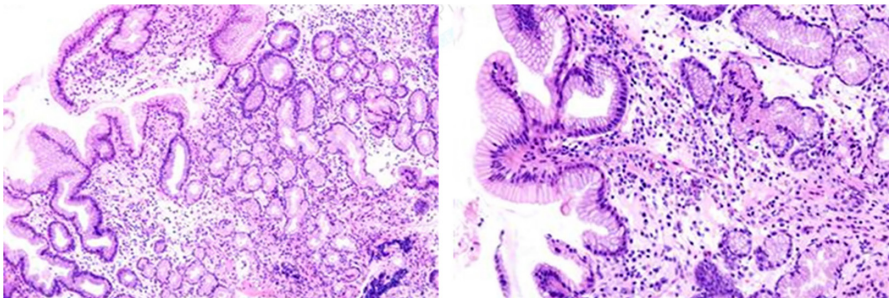

FIGURE 2 Pathologic examination showed showed (pylorus) intestinal mucosa congestion and edema, accompanied by infiltration of lymphocytes, plasma cells and a small amount of eosinophils and neutrophils, indicating chronic active inflammatory changes.

(BEAM) regimen started in May 2019, and ASCT and CAR-T cells were infused subsequently on May 23, 27, and 29 (a total of 3.7×10^6/kg of $CD34^+$ cells, 4×10^6/kg of CD22, and 2.75×10^6/kg of CD19). Sintilimab (100–200 mg) and chidamide (5 mg qd) every 3 or 4 weeks were administered in October 2020 as a consolidation treatment after ASCT combined with CAR-T cell therapy to enhance the function of CAR-T cells and prevent recurrence. PET-CT (August 26, 2021) showed that the metabolism of the lower esophagus-cardia was slightly increased. Painless gastroscopy showed reflux esophagitis (grade B), gastric retention, and pyloric obstruction with an ulcer (Figure 1C). Ultrasonography showed the disappearance of the pyloric and tube wall layers, and pathological examination showed chronic active inflammatory changes (Figure 2). Digital upper gastrointestinal radiography revealed pyloric obstruction and retention of a large amount of fluid in the stomach cavity. PD-1 therapy was discontinued, and painless gastroscopy revealed descending duodenal stenosis with pseudodiverticulum formation at the anterior wall (Figure 1D). As the patient did not respond to methylprednisolone (1 mg/kg) and mycophenolate mofetil treatment, endoscopic jejunal nutrition tube placement was performed. Subsequently, the patient underwent PET-CT re-examination and no recurrence occurred. Because the endoscopic jejunal nutrition tube could not meet the long-term demand, "gastrojejunostomy combined with omentectomy" was performed. Through telephonic follow-up, we confirmed that the patient was in good condition postoperatively. The patient told us that life has returned to normal following the operation, and there is no discomfort. That he can receive effective treatment and make a full recovery makes the patient very happy.

3 | DISCUSSION

PD-1 works by interfering with the immune mechanism; therefore, when a patient presents with gastric symptoms after treatment, it can easily be considered immune-related gastroenteritis. However, in this report, two patients developed pyloric obstruction with gastric retention after taking sintilimab. None of the two patients had a history of peptic ulcer or tumor-related diseases (especially before the use of sintilimab). The pathological results of gastroscopy revealed inflammatory lesions, no congenital lesions, and no pyloric stenosis or atresia. The patients denied the existence of diet-inducing factors such as long-term consumption of excitatory food or alcohol consumption. After excluding the common causes related to pyloric obstruction mentioned above, combined with the diagnosis and treatment, the use of sintilimab was the most likely cause of this situation in our patients.

The specific mechanism is still unclear. We found that there was obvious infiltration of lymphocytes and neutrophils in the case reports of adverse reactions caused by Nivolumab. Among them, CD3+ T cells, CD4+ helper T cells, and CD8+ cytotoxity and suppressor T cells are the main ones.[4] The infiltration of CD4+ T cells and CD8+ T cells is often found in anti-PD-1-induced colitis. The damage of cells and tissues may be caused by self-reactive CD8+ T cells, and the autoantibodies mediated by plasma antibodies produced by CD4+ T cells may also damage cells and tissues. The expression of the gene encoding integrin α4β7 increased in CD8 lymphocytes, and lymphocyte recruitment was mediated by the interaction between integrin α4β7 and mucosal addressin cell adhesion molecule-1 on intestinal endothelium,[5] so this may be an effective intervention target. In a nutshell, T cell receptors overactivation, the increase of memory T cells, lymphocyte infiltration and cytokine activation[6] promote the occurrence of adverse events, and the obstruction and contracture caused by inflammatory thickening may be the main pathophysiological mechanisms in this case.

After the diagnosis of irAE is confirmed, the patient should be advised to stop ICI therapy (to determine whether gastrointestinal decompression is needed according to the situation), and conservative drug therapy to be started immediately. In emergency cases, a jejunum feeding tube or intravenous nutrition support can be considered. If no improvement is found, surgical intervention could be performed after a multidisciplinary consultation.

In our cases, patients did not respond well either to glucocorticoids or immunosuppressants such as ruxolitinib and mycophenolate mofetil, and surgery was needed to resolve the severe pyloric obstruction.

To the best of our knowledge, ICIs PD-1 (such as nivolumab[7–9] and pembrolizumab[4])-induced gastritis and sintilimab-induced acute hemorrhagic erosive gastritis have been reported. However, irreversible complications of the upper digestive tract caused by sintilimab have not been described, and our cases had more serious consequences than that of the previously reported cases. Therefore, we believe that this case report provides a reference for preventing and treating of ICI-related gastrointestinal complications.

AUTHOR CONTRIBUTIONS

Qi Zhang: Data curation; funding acquisition; writing – original draft; writing – review and editing. **Chunrui Li:** Supervision. **Yang Cao:** Supervision. **Na Wang:** Supervision. **Liang Huang:** Supervision. **Zhen Shang:** Supervision. **Jue Wang:** Supervision. **Lifang Huang:** Supervision. **Jinhuan Xu:** Supervision. **Min Xiao:** Supervision. **Liting Chen:** Supervision. **Xiaojian Zhu:** Supervision. **Yicheng Zhang:** Supervision. **Yi Xiao:** Resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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