Tislelizumab-related enteritis successfully treated with adalimumab: A case report

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Abstract

BACKGROUND
With programmed death-1 (PD-1) inhibitors becoming the standard treatment for lung cancer, PD-1-related adverse reactions and treatment have gradually become prominent.

CASE SUMMARY
First reported case of tislelizumab-related enteritis successfully treated with adalimumab 40mg every 2 wk for 3 times in an advanced lung cancer patient who received first-line tislelizumab/pemetrexed/carboplatin for 4 cycles. The patient continued receiving the treatment of pemetrexed/carboplatin after symptoms, abdominal computed tomography and colonoscopy improved, significant diarrhea was not occurred.

CONCLUSION
Adalimumab can be an effective treatment option for patients with PD-1 antibody related enteritis if they do not respond well to glucocorticoid treatment.
INTRODUCTION

With programmed death-1 (PD-1) inhibitors alone or combination as first-line treatment for advanced non-small lung cancer, treatment for PD-1-related adverse reactions also becomes one of challenges in cancer treatment. Tislelizumab (TISL), a humanized monoclonal antibody against PD-1\(^1\), was launched in China in 2019. Compared with other PD-1 inhibitors, the biggest difference of TISL was modified in the constant region of the monoclonal antibody to remove its binding ability to FcγR receptor, so that it could no longer bind to type II macrophages with Fcγ receptor, thus the macrophages would no longer attack the T cells, thereby reducing the exhaustion of T cells and the potential mechanism of anti-PD-1 therapy resistance\(^1,2\). Grade 3-4 adverse events due to TISL have been reported to be about 10%, with a diarrhea incidence of < 1\%\(^3,4\). Herein, we report the first use, to our knowledge, of adalimumab (ADA) in combination with methylprednisolone for TISL-related severe enteritis. The patient's symptoms were essentially relieved with treatment and he continued to receive chemotherapy-related treatment.

CASE PRESENTATION

Chief complaints

61-year-old man with diagnosis diarrhea, who was referred to our institution on day 19 after the last treatment for lung cancer, because of symptoms were aggravated, with the frequency of diarrhea up to 20-30 times/d.

History of present illness

The patient was diagnosed with lung cancer (right lung adenocarcinoma with multiple subcutaneous muscle metastases, cT3N2M1c, stage IV, KRAS mutation (G12C), PDL-1 50%) on September 14, 2020. From September 17, 2020 to December 2, 2020, the patient was given treatment of chemotherapy (pemetrexed 900 mg and Carboplatin 600 mg) plus TISL 200 mg every 21 to 28 d for 4 cycles. The date of the fourth treatment is December 2, 2020.

Before the fourth treatment, the lung computed tomography (CT) showed that the lesion was smaller than that at diagnosis, and the subcutaneous nodule in buttock disappeared. The treatment result was assessed as partial response. On day 10 after the last treatment (hereafter day 10), the patient began to have fever \(T_{\text{max}} 39.0 \, ^\circ\text{C}\), abdominal pain, and diarrhea (watery stools, more than 10 times/d). After defecation, the abdominal pain could be relieved. The patient was suspected of gastroenteritis and received drugs for anti-infection, antidiarrheal, rehydration and other symptomatic treatment at local hospital.

History of past illness

The patient’s past medical history was unremarkable except for hypertension.

Personal and family history

No positive personal or family history.

Physical examination

The patient had stable vital signs. Abdominal examination: flat and soft, positive tenderness, negative
rebound tenderness, hyperactive bowel sounds, 6 times/min.

**Laboratory examinations**

Routine laboratory tests of a same-day showed white blood cells: $8.5 \times 10^9/L$, C-reactive protein: 80.0 mg/L, procalcitonin: 0.13 ng/mL, interleukin-6: 2.04 pg/mL, interleukin-10 (IL-10): 2.57 pg/mL. A clinical diagnosis of PD-1 inhibitors induced enteritis was made, and the patient was asked to fast and oral methylprednisolone 16 mg bid was started. Subsequent tests for cytomegalovirus DNA, bacteria cultured in blood and feces, WBC and *Clostridium difficile* in stool were negative, fecal calprotectin was significantly increased to 218.4 ug/g.

**Imaging examinations**

Abdominal contrast-enhanced CT revealed edema and thickening of the small intestine, ascending colon, transverse colon, sigmoid colon, and rectum in the middle and lower abdomen, and multiple small diverticula in the blind ascending colon (Figure 1A and B). Colonoscopy showed extensive congestion and edema of the terminal ileum and colorectal mucosa (Figure 2A and B). Intestinal mucosal pathological examination revealed chronic inflammations of the mucosa with moderate dysplasia of glandular epithelium, and chronic inflammation of the mucosa with moderate-severe dysplasia of the glandular epithelium (Figure 3A and B).

**FINAL DIAGNOSIS**

Diagnosis of PD-1 antibody induced enteritis was confirmed.

**TREATMENT**

The patient was asked to fast and oral methylprednisolone 16 mg bid was started. On day 21, methylprednisolone was increased to 40 mg q12h intravenously, montmorillonite powder and probiotic treatment also were given. On day 23, ADA (biosimilar, HS016, China) 40 mg began to administered subcutaneously every 2 wk (on days 23, 37, 51) because previous treatments were ineffective. Fasting and intravenous nutritional support were also given, as well as drugs for symptomatic treatment including mesalazine, somatostatin, and loperamide. On day 29, the frequency of diarrhea decreased and the symptom of diarrhea disappeared on day 34. The patient tried to be given a small amount of liquid diet, but abdominal pain and diarrhea symptoms repeated after eating. the symptoms were improved after giving pinaferium bromide, during which montmorillonite powder, somatostatin, mesalamine and probiotics were gradually discontinued. On day 37, Methylprednisolone began to reduce to 40 mg qd intravenously, and the patient discharged on day 47 with methylprednisolone 16 mg bid po. The treatment process would be showed in Figure 4.

**OUTCOME AND FOLLOW-UP**

The patient had no abdominal pain, diarrhea, nausea or vomiting after discharge, and underwent abdominal enhanced CT and colonoscopy again on day 64. Abdominal CT showed no significant edema compared with before, and there were multiple small diverticula in the ascending colon (Figure 1C); Colonoscopy showed that the ileal mucosa was approximately normal, the ileocecal valve was labial, congested and eroded, the ileocecal junction and the ascending and transverse colon were scattered, the whole colon and rectal mucosa were congested, swollen and brittle (Figure 2C and D), and intestinal mucosal pathological examination revealed (ileocecal junction, ascending colon, transverse colon, descending colon, rectum) mucosal epithelial detachment and erosion, inflammatory granulation tissue hyperplasia was significantly reduced compared with the previous time (Figure 3C and D). On day 65, the patient continued to receive chemotherapy, once every 3-4 wk. There was no obvious diarrhea after chemotherapy. The dose of methylprednisolone was tapered to 8 mg/d after about 3 mo, and the tapering process was uneventful.

**DISCUSSION**

The majority of adverse events (AEs) reported in clinical trials related to TISL were grade 1-2, with the most common grade 3-4 AEs being hematotoxicity, followed by pneumonitis (2%) and colitis (0.5%-1%) [2,5]. The patient developed severe diarrhea after receiving 4 cycles of TISL combined with chemotherapy. The cause of infection was excluded, and it was considered to be TISL-induced immune-
Figure 1 Abdominal contrast-enhanced computed tomography image of the patient at different stages of disease. A: Edema and thickening of the small intestine, ascending colon, transverse colon, sigmoid colon, and rectum in the middle and lower abdomen, and multiple small diverticula in the blind ascending colon; B: The small intestine and colon wall were still obviously edematous, which was similar to the computed tomography findings 10 d ago; C: No significant edema, and there were multiple small diverticula in the ascending colon.

Figure 2 Colonoscopy manifestations of patients at different stages of disease. A and B: Extensive congestion and edema of the terminal ileum and colorectal mucosa, and necrosis and shedding on day 20; C and D: On day 64 showed that the mucosa in the venue was approximately normal, and there was still congestion and swelling of the whole colon and rectal mucosa, which was significantly improved than before.

related enteritis (Adverse Drug Reaction Probability Scale[6] score was 7). For the management of severe immune checkpoint inhibitor–induced enteritis, the guidelines[7,8] recommend prednisone/methylprednisolone at 1-2 mg/kg/day for 2 d, followed by the infliximab (IFX) and its analogues or vedolizumab for poor response. At that time, we could not obtain vedolizumab quickly, therefore considered the use of anti-tumor necrosis factor-α (TNF-α) monoclonal antibody. In contrast to
Figure 3 Pathological sections were examined by colonoscopy. Intestinal mucosal pathological examination revealed chronic inflammation of the mucosa (ileum, ascending colon, and descending colon) with moderate dysplasia of the glandular epithelium, and chronic inflammation of the mucosa (transverse colon and rectum) with moderate-severe dysplasia of the glandular epithelium. A: For the ileocecal junction on day 20; B: For the descending colon on day 20, mucosal epithelial sloughing erosion were not significant compared with the previous colonoscopy, but were still accompanied by moderate atypia and crypt abscess; C: For the ileocecal junction on day 64; D: For the descending colon on day 64.

Figure 4 Treatment of tislelizumab-related enteritis. The 25% murine chimeric monoclonal antibody of infliximab (IFX), ADA is a fully human monoclonal antibody that binds TNF-α. ADA has been approved with about 17 indications worldwide, including Crohn’s disease, ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis. ADA (biosimilar, HS016, China) is approved in China for rheumatoid arthritis, ankylosing spondylitis and psoriasis. Although the pathophysiology of immune checkpoint inhibitor-mediated immune-related adverse events (irAEs) were not yet fully understood, the role of immune checkpoint pathways in autoimmune diseases provides some clues: irAEs may be caused by some combination of autoreactive T cells, autoantibodies, and/or inflammatory cytokines, such as interleukin-17[9,10]. One potential mechanism is T-cell activity against antigens present in tumor cells and healthy tissues[11,12]. Inflammation in other
normal tissues may result from increased levels of inflammatory cytokines that are downstream effects of T cell activation\[13,14\]. It has been shown that the intestinal lamina propria of PD-1 inhibitor-induced enteritis is characterized by CD8+ T cell infiltration, accompanied by a certain concentration of TNF-\(\alpha\), and Treg cells predominate similar to inflammatory bowel disease\[15\]. ADA can prevent the significant decrease in intestinal mucosal epithelial resistance caused by TNF-\(\alpha\) and prevent the internalization of tight junction proteins after cytokine exposure, and can also reverse the TNF-\(\alpha\)-induced down-regulation of connexin-1, claudin-2, claudin-4, occludin and the activation of PI3K signaling in T-84 cells, thereby preventing barrier dysfunction induced by TNF-\(\alpha\) at the functional and structural as well as at the signaling level\[16\].

The patient received subcutaneous injection of ADA 40 mg once every two weeks after poor response after treatment with 1-2 mg/kg methylprednisolone for 2 d. The symptoms began to improve 6 d after the first injection of ADA, the dose of methylprednisolone was gradually reduced after the second injection because of the symptoms gradually improved. The second colonoscopy and pathological sections also confirmed that the mucosal epithelial detachment and erosion were significantly improved than before. This case is the first report of enteritis caused by PD-1 inhibitors treated with ADA, and there has been a previous case of arthritis caused by pembrolizumab treated with ADA\[17\].

CONCLUSION

PD-1 inhibitor may also cause other colonic diseases than enteritis, for example acute diverticulitis\[18\], whether colonoscopy and pathological examination were important to distinguish enteritis and acute diverticulitis cause by PD-1 inhibitor. In addition, the duration of glucocorticoid therapy after the development of severe immune checkpoint inhibitor-induced enteritis can be as long as several months, during which clinical experts should be alert to the possibility of infection with various opportunistic pathogens\[19\], especially cytomegalovirus. With the advent of the era of immunotherapy, both physicians and pharmacists need to be more familiar with the judgment and treatment of irAEs, especially the selection and management of various immunosuppressive agents or monoclonal antibodies when serious adverse reactions occur.

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