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Case Report

A case of perforated immune-related colitis complicated by cytomegalovirus infection during treatment of immune-related adverse effect in lung cancer immunotherapy

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ABSTRACT

Although immune checkpoint inhibitors (ICIs) can be used for lung cancer treatment, the activated immune response may cause immune-related adverse effects (irAEs). We present here a case of cytomegalovirus (CMV) enterocolitis during steroid therapy for an irAE. A 70-year-old man diagnosed with small-cell lung carcinoma (limited disease) received radiotherapy plus two chemotherapy cycles of cisplatin and etoposide. The tumor exhibited complete response but recurred after 3 years. After treatment with two cycles of carboplatin, etoposide, and atezolizumab, an inhibitors of programmed cell death receptor-1, he was switched to atezolizumab every 3 weeks for maintenance therapy. Diarrhea occurred after nine atezolizumab doses. With a strong suspicion of ICI-induced colitis, we administered methylprednisolone 500 mg for 3 days, followed by oral prednisolone 40 mg/day. Total colonoscopy during the treatment revealed mucosal inflammation of the total colon, suggesting immune-related colitis. Biopsies from the ulceration revealed crypt abscess with highly infiltrative plasma cells and lymphocytes. Furthermore, immunohistochemical staining showed positivity for CMV. With no improvement in watery diarrhea, the prednisolone dose was increased to 80 mg/day on the 11th day, and ganciclovir was additionally administered twice daily on the 26th day. On the 28th day, the patient had abdominal pain, and abdominal computed tomography revealed free air, resulting in the diagnosis of colon perforation. He underwent subtotal colectomy followed by ileostomy as emergency surgery. A colon specimen revealed colitis with CMV infection. We describe colon perforation in a patient with CMV enterocolitis complicated by refractory immune-related colitis.

Abbreviations: AIDS, Acquired immunodeficiency syndrome; ICI, Immune checkpoint inhibitors; CMV, Cytomegalovirus.

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Authorship statement

All authors met the International Committee of Medical Journal Editors authorship criteria. MN, YK, SH and SM wrote the original draft. MN, YK, KS, MM, SK, HM, MS, TU, AY, MT, and KU were involved in patient care. All authors reviewed the manuscript and approved the final version of the manuscript.

1. Introduction

Immune checkpoint inhibitors (ICIs) are increasingly used for the treatment of advanced solid malignancies owing to their high efficacy and acceptable side effect. ICIs, such as programmed cell death protein-1 (PD-1)/programmed death protein ligand-1 (PD-L1) inhibitors selectively target PD-L1 and prevent interaction with PD-1. ICIs reverse T-cell suppression and enhance antitumor activity. However, they also cause immune-related adverse events (irAEs), including immune-mediated inflammation, due to autoimmune mechanisms. Atezolizumab is a completely humanized monoclonal antibody to PD-L1. Immune-mediated colitis is a well-reported gastrointestinal complication associated with ICIs, including atezolizumab, and has been treated using immunosuppressive drugs, such as corticosteroids. Limited evidence indicates that cytomegalovirus (CMV) reactivation might be involved in the pathogenesis of refractory gastrointestinal irAEs. We describe a case of colon perforation in a patient with refractory immune-related colitis by CMV enterocolitis.

2. Case presentation

A 70-year-old man diagnosed with small cell lung cancer with a primary lesion in the lower right lobe and hilar and mediastinal lymph node metastasis (limited disease) in November 2018, underwent concurrent radiotherapy plus chemotherapy with cisplatin (80 mg/m^2) and etoposide (1st cycle, 80 mg/m^2; 2nd cycle, 60 mg/m^2 because of grade 4 neutropenia) (Fig. 1 A–E). After two cycles of treatment, the tumor was confirmed to exhibit complete response according to the response evaluation criteria in solid tumors (Fig. 1F). Then the patient received prophylactic cranial irradiation in April 2019. However, in September 2020, he demonstrated lung cancer recurrence (Fig. 1G and H). He underwent two cycles of chemotherapy with carboplatin (area under the concentration–time curve (AUC) 5), etoposide (80 mg/m^2), and atezolizumab (1200 mg), which are the inhibitors of programmed cell death receptor-1, after which he was switched to atezolizumab (1200 mg) every 3 weeks for maintenance therapy from December 2020. After the 9th course of atezolizumab (June 2021), he began to complain of non-bloody diarrhea. In July 2021, he was admitted to the hospital with prolonged diarrhea, fever, and abdominal pain. His blood pressure was 131/83 mmHg; pulse rate, 93 beats/min; respiratory rate, 20 breaths/min; oxygen saturation, 97% on room air; and body temperature, 37.4 °C. Upon admission, the laboratory examination revealed a poor nutritional status, with total protein and albumin levels decreasing to 6.3 and 3.2 g/dL, respectively. There was mild renal dysfunction with a urea nitrogen level of 17.0 mg/dL and a creatinine level of 1.12 mg/dL. The C-reactive protein level was high at 10.65 mg/dL, indicating an inflammatory reaction. The white blood cell count was 9300/μL (neutrophils, 77.7%); hemoglobin concentration, 11.4 g/dL; and platelet count, 25.4 × 10^4. Computed tomography revealed wall thickening of the sigmoid colon and rectum.

The clinical course after admission is presented in Fig. 2. Upon admission, we strongly suspected ICI-induced colitis. Empirically, he was initially treated with antibiotic therapy (cefmetazole 4 g/day) from day 1 of hospitalization to day 7. Atezolizumab was discontinued, and intravenous methylprednisolone (500 mg/day) was administered for 3 days, followed by oral prednisolone 40 mg/day. Although his fever improved, his diarrhea and abdominal pain did not. A colonoscopy revealed diffuse severe inflammation char-

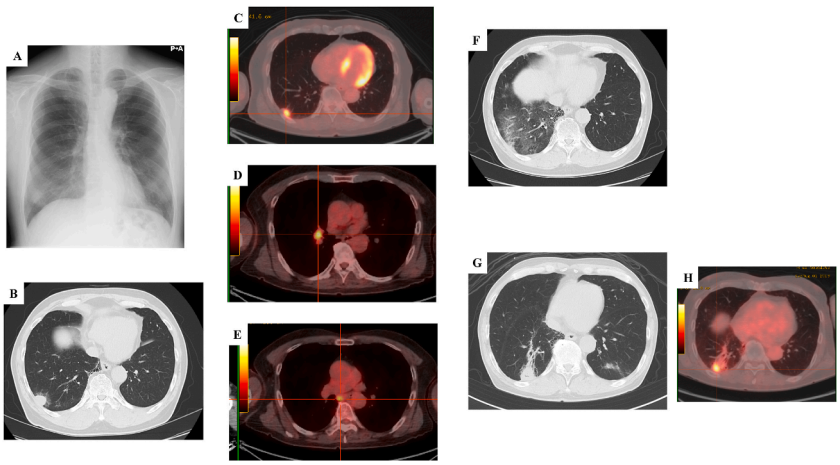

Fig. 1. Chest X-ray on initial diagnosis revealed a primary mass in the lower lung field of the right lung (A). Chest computed tomography was performed at the following time points: (B) on initial diagnosis, (F) after concurrent radiotherapy plus chemotherapy, and (G) on recurrence. 18-Labeled fluorodeoxyglucose (FDG) positron emission tomography on initial diagnosis revealed abnormal accumulation of FDG in the right lower lobe mass (C) and hilar (D) and mediastinal lymph node (E). FDG positron emission tomography performed at recurrence revealed abnormal accumulation of FDG in the right lower lobe mass (H).

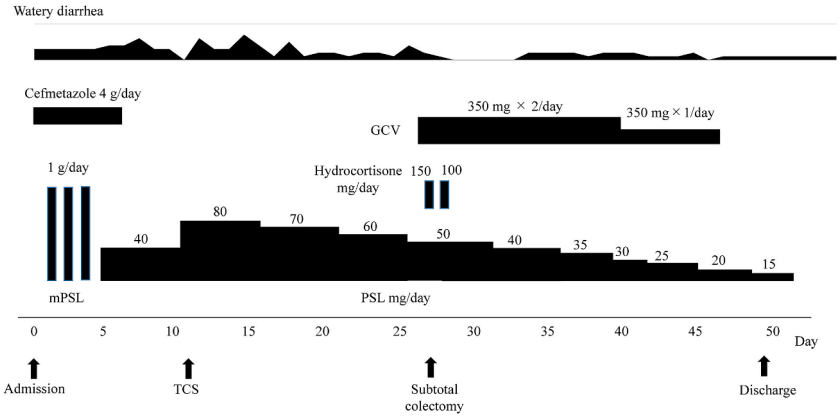

Fig. 2. Clinical course of the present case.
mPSL, methylprednisolone; PSL, prednisolone; GCV, ganciclovir; TCS, total colonoscopy.

acterized by adherent blood, erosions, erythema, friability, and confluent ulcerations throughout the entire colon (Fig. 3A). Biopsy from the ulceration revealed crypt abscess with highly infiltrative plasma cells and lymphocytes. Altogether, these findings were consistent with the diagnosis of ICI-induced colitis. On the 11th day, prednisolone dose was increased to 80 mg/day. After increasing the prednisolone dose, a gradual improvement in the patient's symptoms, including diarrhea and abdominal pain, was observed. At the same time, immunohistochemical staining of colon biopsy specimen demonstrated positivity for CMV. The CMV pp65 antigenemia test was positive (three positive cells per 50,000 cells) on day 19. The patient was diagnosed with ICI-induced colitis complicated by superimposed CMV infection. On the 26th day, we initiated ganciclovir (5 mg/kg) twice daily. After a diagnosis with CMV infection, prednisolone was tapered aggressively. On the 28th day, he began to complain of abdominal pain, and muscular defenses appeared. An abdominal computed tomography scan revealed free air, resulting in the diagnosis of colon perforation. An emergent subtotal colectomy followed by ileostomy was performed and findings from the resected specimen revealed diffuse confluent ulcerations throughout the entire colon (Fig. 3B). Specimens from the colon revealed crypt abscess with highly infiltrative plasma cells and lymphocytes (Fig. 3C and D), and immunohistochemical staining of colon biopsy specimen showed positivity for CMV (Fig. 3E and F). On the 47th day, ganciclovir was discontinued, and prednisolone was gradually tapered. The patient was shifted to medical treatment hospital for the long term care.

3. Discussion

It is known that ICIs cause various irAEs, including complications of the gastrointestinal tract, endocrine glands, skin, and liver [1]. The variable presentation of irAEs makes the diagnosis difficult. The present case highlights the management of a patient with colitis that occurred following atezolizumab therapy and was complicated by superimposed CMV infection.

ICI-related colitis is one of the most widely reported irAE [1]. Diarrhea occurs in 8%–10% of patients treated with ICIs [2]. Corticosteroids have been used for treating ICI-related colitis [1]. In corticosteroid-resistant cases, an increase in the dose of corticosteroids

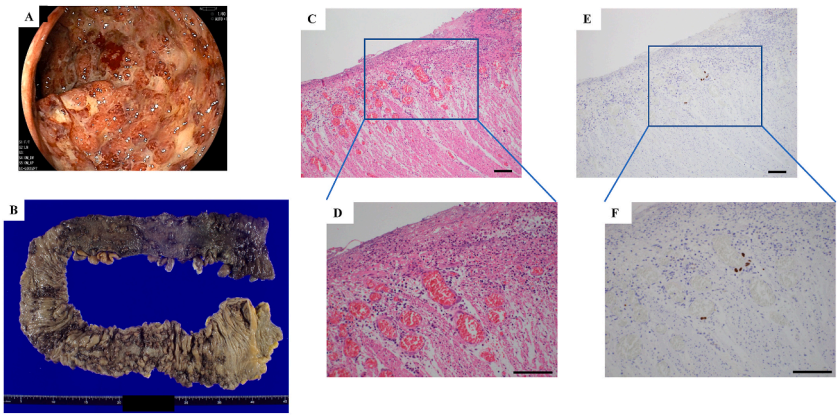

Fig. 3. Endoscopic evaluation revealed ICI-related colitis complicated by CMV infection. The entire colon exhibited diffuse severe inflammation characterized by adherent blood, erosion, erythema, and confluent ulcerations throughout the entire colon (A). Findings from the resected specimen (B) indicated multiple ulcerations. Histological examination of the resected specimen revealed crypt abscess and inflammatory cell infiltration (hematoxylin and eosin staining) (C and D). Scale bar, 100 μm. Immunohistochemistry for cytomegalovirus revealed a positive result (E and F). Scale bar, 100 μm.
CMV: Cytomegalovirus, ICI: immune checkpoint inhibitor.

has been recommended. Nevertheless, increasing the dose of corticosteroids poses a risk for superimposed CMV infection development. CMV infections are opportunistic in patients with immunosuppressive diseases, such as acquired immunodeficiency syndrome (AIDS), and in those receiving immunosuppressive therapy or chemotherapy [3].

The literature reports two cases of CMV enterocolitis in patients with refractory immune-related colitis. One case of metastatic melanoma treated with ICIs, nivolumab/ipilimumab, developed severe immune-related colitis. After treatment with high-dose steroids and infliximab, CMV reactivation was detected in the colon [4]. The second report was a case of malignant melanoma treated with ICI ipilimumab, which induced immune-related colitis, and during corticosteroid therapy, CMV reactivation was detected in the colon [5]. A systemic review reported that intestinal perforation is affected by CMV infection in patients with AIDS [6].

In the present case, the surgical specimen revealed that the mucosa of the large bowel segment was vulnerable, and several perforations were detected. Moreover, histological findings from the large bowel segment indicated severe inflammation, despite the administration of the high-dose steroid. The vulnerable bowel caused by ICI-related colitis may cause perforation due to additional CMV infection. Generally, CMV infection is diagnosed based on the presence of inclusion bodies on histopathology. Biopsy with immunohistochemistry using monoclonal antibodies against CMV is considered as the diagnostic standard [7]. Although we needed time until the definitive diagnosis for CMV infection by the pathology, the patient might not have suffered from intestinal perforation if the CMV treatment had been earlier. We take CMV enteritis into consideration, and the early administration of the antiviral agent is important.

To the best of our knowledge, this is the first report of gastrointestinal tract perforation caused by irAE-related colitis complicated by CMV infection. For a long period of severe immunosuppression with treatment for irAE, we suppose that early diagnosis and treatment initiation are important for CMV infection. In conclusion, CMV reactivation should be considered as a complication in the case of an irAE-related colitis for immunosuppressive therapy escalation.

4. Conclusion

- Gastrointestinal tract perforation is caused by irAE-related colitis, which is complicated by CMV infection.
- Early diagnosis and treatment initiation are important for CMV infection.
- This case reports emphasizes the need to consider CMV reactivation as a complication in the case of an irAE-related colitis for escalating immunosuppressive therapy.

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Ethics approval and consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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