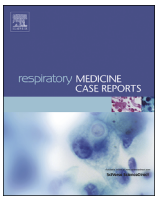
Respiratory Medicine Case Reports 39 (2022) 101720

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

An autopsy case of immune-related severe colitis due to long-term use of nivolumab in a patient with non-small cell lung cancer

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A B S T R A C T

Immune checkpoint inhibitors (ICIs) have been developed as cornerstones of cancer therapy, but the growing use of ICIs has induced immune-related adverse effects (irAEs). Immune-related colitis, which is one of the most common irAEs, generally occurs 2–4 months after ICI treatment initiation and can be life threatening. Therefore, early diagnosis and appropriate management are required. A rare autopsy case of nivolumab-related severe colitis that occurred 34 months after the start of treatment and recurred despite temporal remission with corticosteroids and infliximab is presented. Physicians should be aware of the possibility of late-onset irAEs in patients on receiving long-term ICI treatment.

1. Introduction

The introduction of immune checkpoint inhibitors (ICIs), including cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1), has dramatically improved the prognosis of patients with advanced-stage lung cancer [1]. ICIs enhance the innate immune system; therefore, off-target inflammation and autoimmunity can result in immune-related adverse events (irAEs) in various organs. The frequency of and organs affected by irAEs depend on the agents used, and the time to onset is dictated by the involved organ [1]. Colitis is one of the most frequent gastrointestinal (GI) irAEs in patients treated with anti-CTLA-4 antibody, but it occurs less in patients treated with anti-PD-1 antibody [1,2]. GI irAEs associated with anti-PD-1 antibody generally occur 2–4 months after treatment initiation [3]. Immune-related colitis can lead to serious morbidities and mortality [4]; therefore, early recognition and management are critical in patients receiving any ICIs.

A rare autopsy case of nivolumab-related severe colitis that occurred 34 months after the start of nivolumab treatment is reported.

2. Case presentation

A 59-year-old man had been diagnosed with Stage IV combined lung adenocarcinoma and large-cell neuroendocrine carcinoma, which was 3.5 cm in size, in the right upper lobe of the lung with right hilar lymphadenopathy and pleural dissemination six years earlier. Cisplatin plus irinotecan were administered as the first-line chemotherapy for stage IV large-cell neuroendocrine carcinoma. After five courses of cisplatin plus irinotecan, a partial response was observed with a 30% decrease in the sum of the diameter of mea-

Abbreviations: ICIs, Immune checkpoint inhibitors; irAEs, immune-related adverse effects; CTLA-4, cytotoxic T lymphocyte antigen 4; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CT, computed tomography.

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https://doi.org/10.1016/j.rmcr.2022.101720
Received 8 May 2022; Received in revised form 16 July 2022; Accepted 25 July 2022
Available online 2 August 2022

sured lesions. Positron emission tomography/CT scan only detected the primary lesion in the right upper lobe of the lung. The patient received radiotherapy to the remaining primary pulmonary lesion, although this was not a standard therapy. One year later, follow-up computed tomography (CT) showed mediastinal lymphadenopathy. Bronchoscopy showed recurrence of lung adenocarcinoma, negative for *EGFR* and *ALK* mutations. The patient received eight courses of pemetrexed as second-line chemotherapy, but the lymphadenopathy worsened. Third-line therapy with erlotinib was administered, but new metastatic lesions appeared in bilateral lung fields. The patient was treated with nivolumab 3 mg/kg every two weeks as fourth-line immune therapy. During this treatment, the patient's primary and pulmonary metastatic lesions maintained a long-term partial response. The levels of thyroid hormones, cortisol, glucose, transaminase, electrolytes and autoantibodies in the blood were regularly checked, and no abnormality was observed before and during nivolumab treatment. No evidence suggesting autoimmune diseases was observed.

After the 68th nivolumab administration, the patient was admitted to our hospital because of a high fever and bloody and watery diarrhea occurring more than 10 times daily for 4 days. Laboratory data showed a white blood cell count of 3700/μL, hemoglobin of 11.8 g/dL, platelet count of 5.4×10^4/μL, C-reactive protein of 37.69 mg/dL, creatinine of 6.4 mg/dL, and D-dimer of 17.1 μL/dL. Blood culture was negative for bacteria and fungi. Stool culture was negative for *Clostridium difficile* antigen and toxin, and anaerobic bacteria. Abdominal CT showed an edematous and thickened colonic wall (Fig. 1). The presumptive diagnosis was grade 3 immune-related colitis according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0[5], with dehydration, acute renal failure, and disseminated intravascular coagulation. Two hours after admission, the patient lost consciousness due to hypovolemic shock. The patient was intubated, mechanically ventilated, and transferred to the intensive care unit. Fluid boluses, vasopressors, high-dose prednisolone (1 mg/kg/day), and antibiotics were administered according to the American Society of Clinical Oncology (ASCO) guidelines [6]. Continuous hemodiafiltration was started. Since high fever and diarrhea persisted, the dose of prednisolone was doubled (2 mg/kg/day) on the 4th day after admission. Despite this, high fever and diarrhea persisted. On the 5th day, infliximab 5 mg/kg was administered intravenously for steroid-refractory colitis. The patient's high fever and diarrhea improved markedly, and the patient was extubated on the 7th day. Subsequently, the dose of prednisolone was gradually reduced by 10% every 5–7 days, according to the ASCO guidelines that suggested corticosteroid tapering over 4–6 weeks.

On the 24th day, colonoscopy was performed and showed scattered ulcerations and loss of the vascular pattern of the sigmoid colon. The mucosal biopsy specimens showed infiltration of inflammatory cells, but no infection with cytomegalovirus, *Entamoeba histolytica*, or herpes simplex virus. These findings were consistent with ICI-associated colitis.

The patient had a high fever on the 40th day. Sputum, blood, and urine cultures were negative. On the 44th day, watery diarrhea recurred, but stool culture was negative for *Clostridium difficile* toxin and anaerobic bacteria. The dose of prednisolone was 50mg daily. On the 46th day, the patient's chest X-ray showed infiltration of bilateral upper lung fields, and chest CT showed persistent consolidation limited to the radiation field in the right upper lobe of the lung and new ground-glass opacites in bilateral upper lobes of the lungs (Fig. 2). The patient lost consciousness due to respiratory and circulatory failure and was intubated and mechanically ventilated again. Despite treatment with fluid boluses, vasopressors, intravenous methylprednisolone pulse therapy (1 g daily for 3 days), and antibiotics, the patient died on the 50th day.

A pathological autopsy was performed within 24 hours after death to evaluate the cause of the pulmonary infiltration and diarrhea. Macroscopic evaluation showed pulmonary edema (Fig. 3a). Neither primary nor metastatic pulmonary lesions were identified. There was only left hilar lymph node metastasis of lung adenocarcinoma. Multiple ulcerations were observed from the jejunum (Fig. 3b) to the colon (Fig. 3c). Histologically, bilateral lungs showed diffuse alveolar damage with hyaline membrane formation (Fig. 4a), suggesting the possible diagnosis of immune-related pneumonia. Inflammatory infiltration and ulceration of colonic mucosa were observed (Fig. 4b), suggesting immune-related colitis.

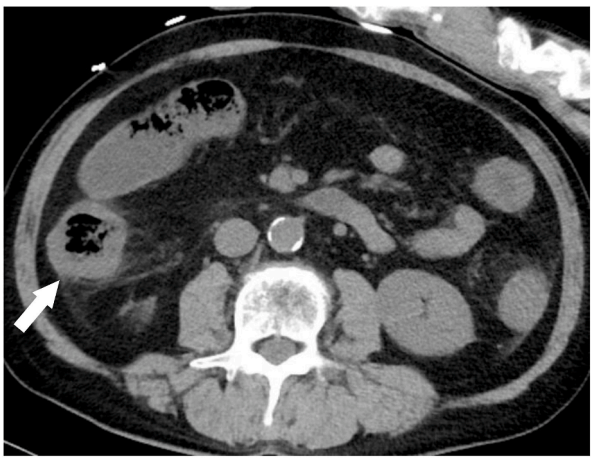

Fig. 1. Abdominal computed tomography (CT) on admission shows edematous and thickened walls of the ascending colon (white arrow).

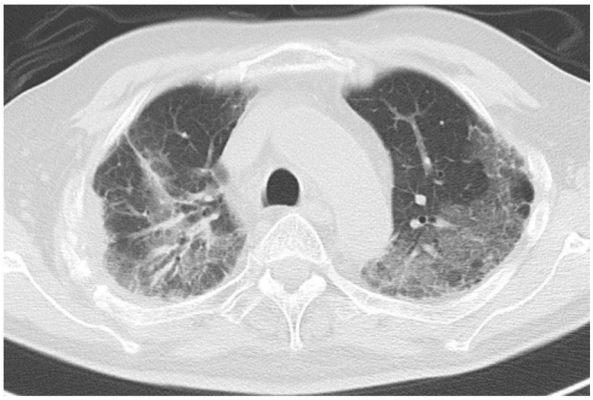

Fig. 2. Chest CT on the 46th day shows ground-glass opacities in bilateral upper lobes of the lung.

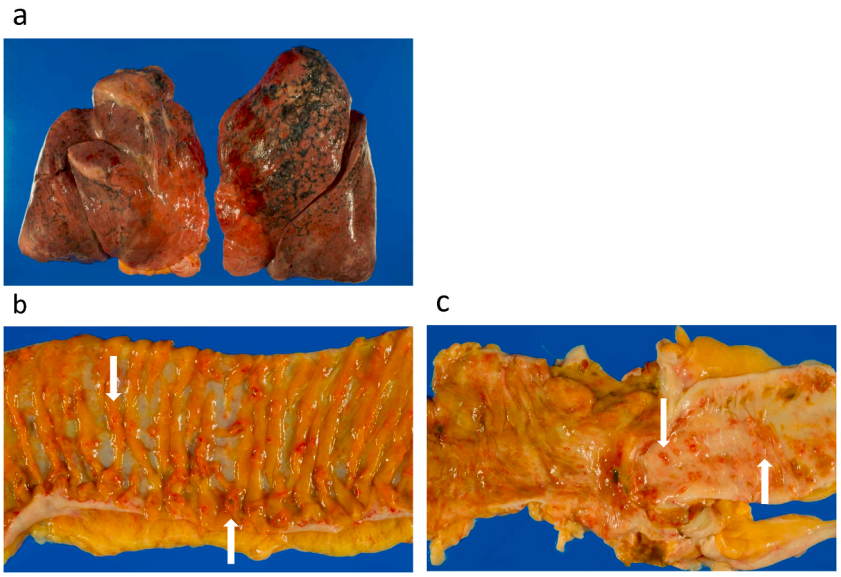

Fig. 3. Macroscopic evaluation shows pulmonary edema (a), multiple ulcerations (white arrows) of the jejunum (b) and of the colon (c).

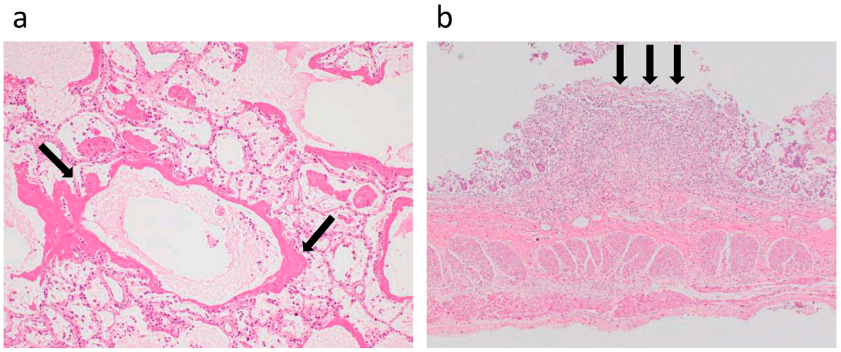

Fig. 4. Histopathologic findings of bilateral lungs show diffuse alveolar damage with hyaline membrane formation (black arrow) (hematoxylin-eosin stain, 100 ×) (a). Those of the jejunum show inflammatory infiltration and ulceration (black arrows) (hematoxylin-eosin stain, 40 ×) (b).

3. Discussion

An autopsy case of nivolumab-related severe colitis that occurred 34 months after nivolumab treatment initiation was described. The present case was rare because of the late-onset immune-related colitis and recurrence despite temporary remission with corticosteroids and infliximab.

Immune-related colitis can be life-threatening [4]. Therefore, early diagnosis and management based on grading are critical. In patients with grade 2 colitis, symptoms, blood, stool, and CT imaging are recommended as the diagnostic work-up [5,6]. In patients with severe grade 3/4 colitis, endoscopic evaluation, as well as the aforementioned diagnostic work-up lists, is recommended [5,6]. Endoscopy has the advantages of distinguishing immune-related colitis from other causes of colitis and of providing information on disease severity, which can be used to decide whether to continue immune therapy [2]. On the basis of the diagnostic work-up lists, the present patient was diagnosed with grade 3 immune-related colitis on the day of hospitalization.

The incidence of colitis ranges from 5.7% to 22% in patients on anti-CTLA-4 antibody and from 0.7% to 1.6% in patients on anti-PD-1 antibody [7]. Another review [2] showed that the incidence of colitis was 8.2%–11.6% in patients on CTLA-4 antibody, 0.9%–3.6% in patients on PD-1 antibody, and 2% in patients on PD-L1 antibody. Anti-PD-1 antibody-related colitis generally occurs 2–4 months after treatment initiation [3]. Late-onset irAEs during anti-PD-1/PD-L1 treatment occur less frequently than early-onset irAEs in patients with advanced cancer [8]. To the best of our knowledge, there has been only one report of a patient who presented with late-onset colitis 32.5 months after starting nivolumab [9]. Taken together with the present and the previous reports [9], physicians should pay attention to the possibility of late-onset irAEs.

Regarding the management of immune-related colitis, the ASCO guidelines state that, in patients with grade 3 colitis, ICIs should be temporarily discontinued, and corticosteroid treatment (initial dose of 1–2 mg/kg/day of prednisone or equivalent) should be given [6]. If symptoms persist for ≥3–5 days, intravenous corticosteroids or biologic therapy with infliximab or vedolizumab should be administered [6]. In the present patient, infliximab was administered for corticosteroid-refractory colitis on the 5th day, and the colitis improved markedly. Despite temporal remission with corticosteroids and infliximab, immune-related colitis recurred on the 44th day. In a review of patients with immune-related colitis, 19% of patients developed recurrence of colitis after immunosuppressive therapy and weaning from corticosteroids [10]. Risk factors for recurrence of colitis included: 1) needing multiple hospitalizations; 2) experiencing steroid-tapering failure after immunosuppressive therapy; 3) receiving infliximab rather than vedolizumab; 4) receiving fewer than 3 infusions of immunosuppressive therapy; 5) having higher fecal calprotectin levels after immunosuppressive therapy; and 6) receiving a longer course of steroids, hospitalization, and colitis symptoms [10]. Patients with active histological inflammation and high-risk endoscopic features, such as colonic ulcers or extensive colitis, were corticosteroid-refractory [11] and had more recurrences [12]. In such patients with high-risk features for corticosteroid resistance, there is a rationale for rapid corticosteroid withdrawal and completing infliximab induction (5 mg/kg at weeks 0, 2, and 6) to mitigate the risk of symptomatic relapse during rapid corticosteroid tapering [13]. The present patient with steroid-tapering failure showed high-risk endoscopic features for corticosteroid resistance, but nevertheless received a single infusion of infliximab alone. Taking into consideration these risk factors, we believe that infliximab should either have been completed (5 mg/kg at weeks 0, 2, and 6) as initial treatment or have been re-administered immediately after the recurrence of colitis. Completing infliximab induction could mitigate the recurrence of colitis during corticosteroid tapering. Because the optimal cycle of infliximab infusion and the optimal strategy for corticosteroid withdrawal have not yet been clarified, future studies are needed to determine them.

In the patients in both the present report and the previous report [9], a long-term partial response of lung cancer was achieved during nivolumab therapy. In the majority of ICI clinical trials, patients have been treated for up to 2 years [14]. The United States' Food and Drug Administration approved the use of ICIs for up to 2 years or until the disease progresses or unacceptable toxicity occurs [14]. Meanwhile, the risk of late-onset irAEs was shown to increase with the duration of therapy in melanoma patients who had been treated with anti-PD-1 monotherapy for at least 2 years [15]. So far, the optimal duration of ICI therapy has not yet been determined. Physicians should consider the risk-benefit balance when deciding whether to continue ICI therapy, especially in responders. Future studies are needed to identify the optimal duration of ICI therapy.

4. Conclusion

An autopsy case of immune-related severe colitis due to long-term use of nivolumab in a patient with lung cancer was described. Physicians should be aware of the possibility of late-onset irAEs. Further studies are needed to elucidate the optimal duration of ICI treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

Conflicts of interest

The authors have no conflict of interest to declare.

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