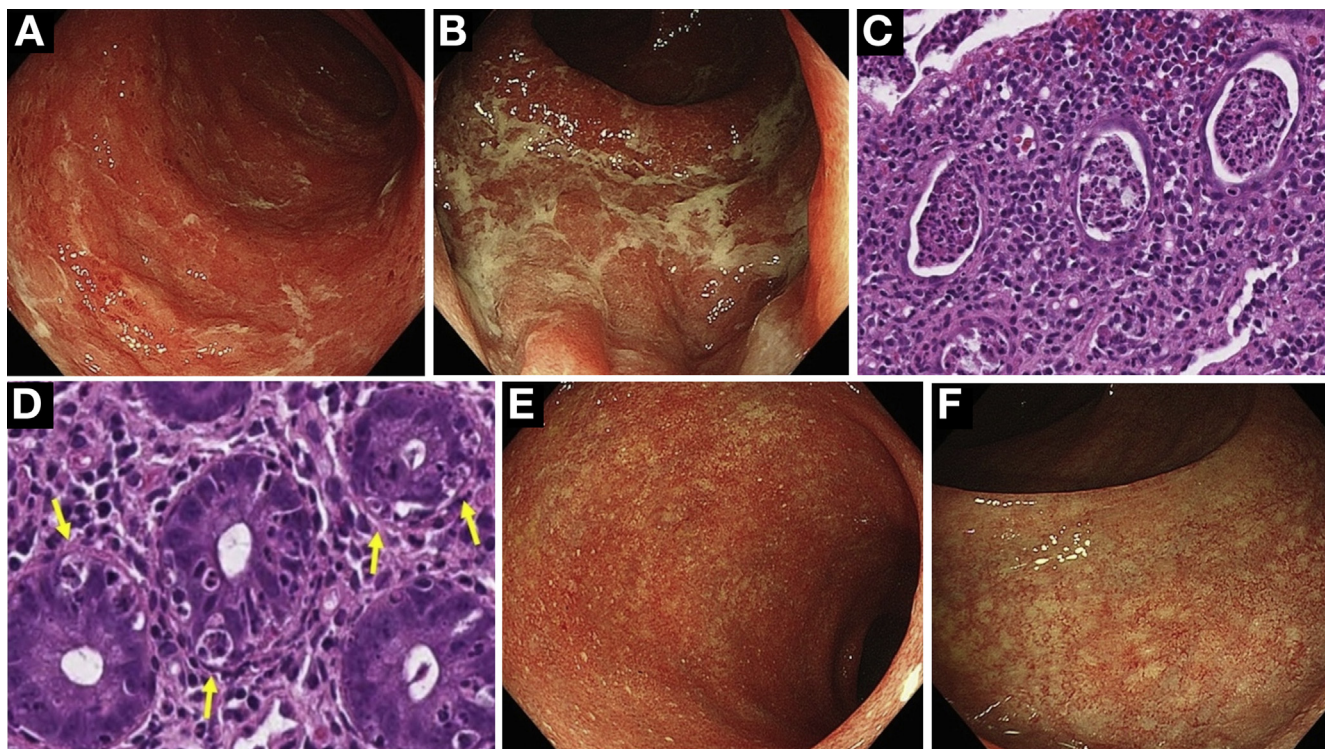


## Nivolumab-Induced Colitis Treated by Infliximab



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A 51-year-old man was admitted to our institution for abdominal pain and bloody diarrhea. The patient had been diagnosed as having uveal melanoma of the right eye 17 years previously, which had been treated by enucleation and radiotherapy. Because of the recurrent melanoma in the right orbit with multiple metastases in the liver and stomach, immunotherapy with triweekly infusion of nivolumab (200 mg, 2 mg/kg) was started. After the fourth infusion of nivolumab, he manifested abdominal pain and bloody diarrhea. The laboratory test results were as follows: white blood cell count, 5370/ $\mu$ L; hemoglobin level, 15.5 g/dL; platelet count, 180,000/ $\text{mm}^3$ ; serum protein level, 6.7 g/dL; albumin level, 4.3 g/dL; and C-reactive protein level, 3.3 mg/L (normal, 0–1.4 mg/L). The computed tomography scan showed thickening of the sigmoid colon and the rectum. Colonoscopy showed reddish, edematous mucosa with increased mucous exudate and loss of normal vascularity throughout the entire colorectum (Figures A and B).

Biopsy specimens from the colon and the rectum disclosed dense inflammatory infiltrates including lymphocytes, plasma cells, and neutrophils with crypt abscesses (Figure C), and prominent apoptosis (Figure D, arrows). Based on these findings, we diagnosed the patient as having nivolumab-induced colitis.

Because his symptoms remained unchanged after the discontinuation of nivolumab for 35 days, we treated the patient by intravenous corticosteroids (methylprednisolone, 1000 mg) for 3 days, followed by oral prednisolone (90 mg/d) for 2 weeks. However, the steroid therapy was ineffective. We therefore started intravenous administration of infliximab (5 mg/kg), which resulted in prompt resolution of his symptoms. Follow-up sigmoidoscopy 2 weeks after the initial infusion of infliximab showed mucosal healing in the sigmoid colon (Figure E) and the rectum (Figure F).

Nivolumab is an immune checkpoint monoclonal antibody against programmed cell death protein 1, which

recently was approved for metastatic melanoma and non-small-cell lung carcinoma.<sup>1,2</sup> The resultant T-cell activation by this antibody causes enhancement in the immune response, which is associated with many immune-regulated adverse events (irAEs), including nausea, abdominal pain, and diarrhea. There is a much higher incidence of diarrhea in patients receiving ipilimumab, another immune checkpoint blocker to Cytotoxic T-lymphocyte-associated antigen, than in patients treated with nivolumab.<sup>3</sup>

It should be noted that the endoscopic and histologic findings in the present case were similar to those of ulcerative colitis. In addition, prominent apoptosis in the colorectal epithelium seems characteristic of histologic findings for nivolumab-induced colitis. In our present case, infliximab was effective for corticosteroid-resistant, nivolumab-induced colitis, as has been shown previously in cases of severe colitis belonging to irAEs.<sup>4,5</sup> Although it has been reported that a certain proportion of patients who belonged to a clinical trial of nivolumab experienced colitis,<sup>1</sup> our case suggests that the endoscopic and histologic findings of the colitis are exactly the same as those of ulcerative colitis. It also has been suggested that chronic colitis seriously should be considered as one of the major irAEs with the use of immune checkpoint inhibitors.

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## Conflicts of interest

The authors disclose no conflicts.



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