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Endoscopic findings of checkpoint inhibitor–induced ileitis with use of the latest advanced endoscopic optical diagnosis: near-focus narrow-band imaging

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Cancer immunotherapy with the use of checkpoint inhibitors, ipilimumab (anti-cytotoxic T lymphocyte antigen) or nivolumab, pembrolizumab, and atezolizumab (anti-programmed death-1) may induce colitis, an increasingly

recognized immune-mediated adverse event (IrAE). The spectrum of endoscopic findings at colonoscopy has not been defined comprehensively; Crohn's-like and ulcerative colitis-like changes have been described.^{1,2} Colitis is most

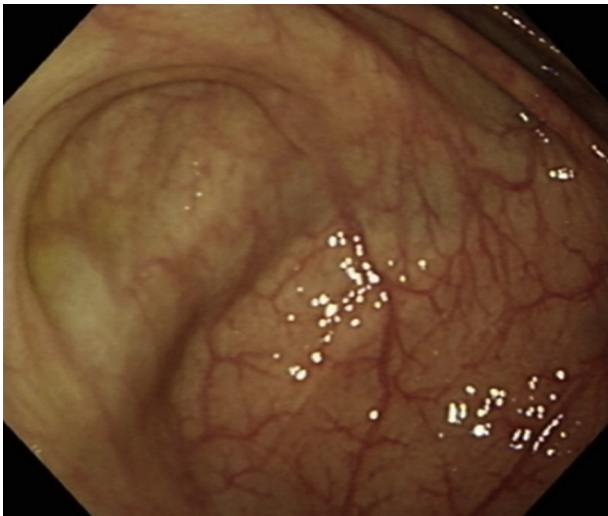


Figure 1. Normal appearance of the cecum under high-definition white-light endoscopy.

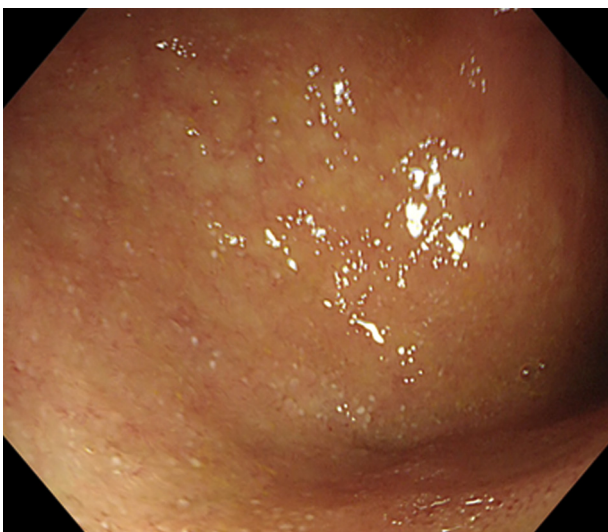


Figure 2. High-definition white-light colonoscopic view showing granular and nonspecific appearances of the ileal mucosa.

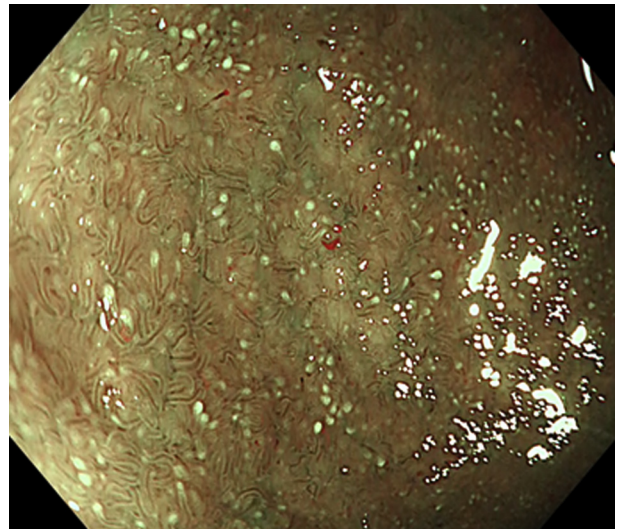


Figure 3. Narrow-band image easily showing microerosions and hypertrophy of the villi.

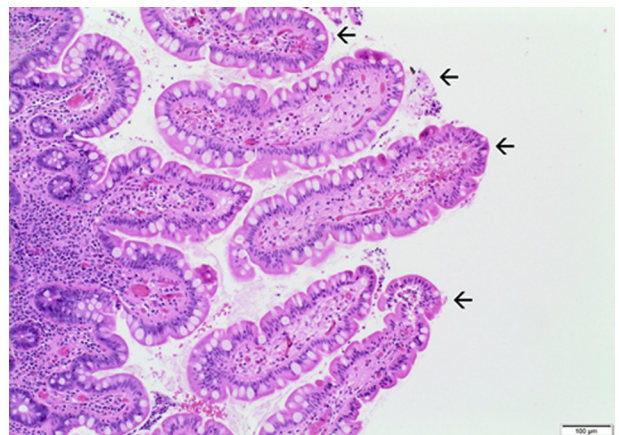


Figure 4. Biopsy specimens from the ileum showing congested and edematous villi with otherwise preserved architecture (H&E, orig. mag. $\times 100$).

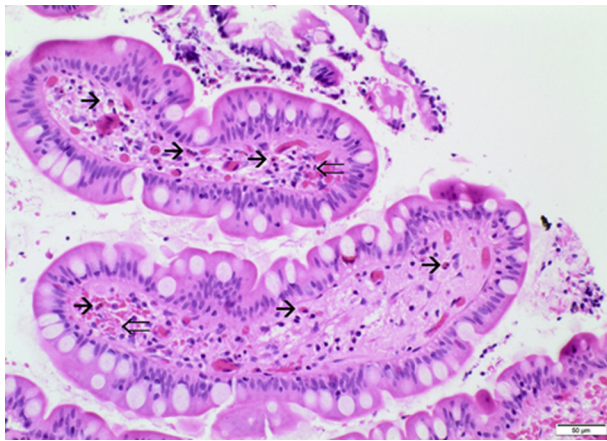


Figure 5. Biopsy specimens from the ileum showing edematous villi with extravasated red blood cells (\Rightarrow) and scattered eosinophils (\rightarrow) (H&E, orig. mag. $\times 200$).

commonly described, although ileoscopy is not always conducted. IrAEs are more common with ipilimumab than with anti-PD1 monoclonal antibodies, although increasingly, patients are being exposed to a combination or sequential use of both classes of immunotherapy.

We report a patient presenting with diarrhea after treatment with ipilimumab and nivolumab with subtle ileal changes visible only by electronic virtual chromoendoscopy after white-light endoscopy did not detect abnormalities (Video 1, available online at www.VideoGIE.org).

A 44-year-old woman with metastatic melanoma, treated with intravenous nivolumab 1 mg/kg and intravenous ipilimumab 3 mg/kg weekly, developed diarrhea. Flexible sigmoidoscopy showed macroscopically normal tissues, but biopsy specimens demonstrated apoptotic nuclear debris in the superficial lamina propria. She was treated for immune-related colitis with oral prednisolone (1 mg/kg), but when she was weaned from the prednisolone, her diarrhea worsened, with watery stools (up to 7 per day) requiring hospital admission. A repeated colonoscopy showed a normal colon with no perceptible changes under high-definition white-light endoscopy and narrow-band imaging (Olympus Evis Lucera Elite CB290 series; Tokyo, Japan) (Fig. 1). Further examination of the terminal ileum with narrow-band imaging (with and without near focus) revealed mild to moderate ileitis with microerosions and hypertrophy of villi for at least 30 cm (Figs. 2 and 3).

Biopsy specimens from the ileum and colon showed mild edema, congestion of villi with patchy borderline increase in eosinophils within the lamina propria, and prominent Peyer's patches in the terminal ileum (Figs. 4 and 5). A mild increase in eosinophils in cecal biopsies may represent checkpoint inhibitor microscopic colitis (Fig. 6). These abnormalities were distinct and different from a Crohn's disease-like appearance of the distal ileum.

Nivolumab is an anti-PD1 antibody and is a checkpoint inhibitor. A case series of 20 patients with immune-mediated

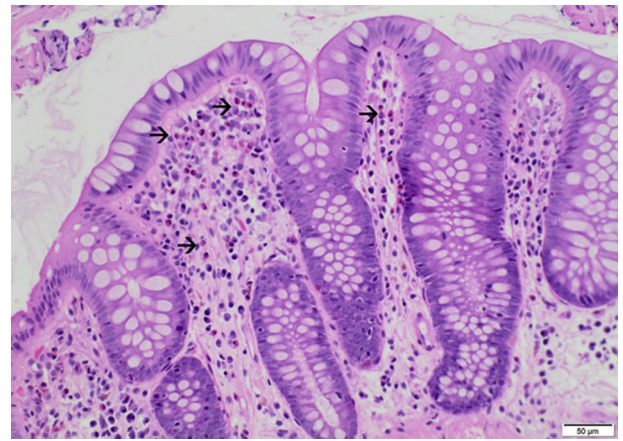


Figure 6. Biopsy specimens from the cecum showing a mild increase in eosinophils (\rightarrow) (H&E, orig. mag. $\times 200$).

gastroenterocolitis associated with PD-1 inhibitors summarizes the endoscopic findings that can be encountered.³ Endoscopic features may include normal mucosa, mild erythema, focal erosions, congested/granular mucosa, and ulceration. These features can be patchy, with apparent distal sparing of the disease. Two patients from the case series had ileitis without colonic involvement.³ It has been suggested that checkpoint-inhibitor colitis may represent a distinct type of inflammatory bowel disease; Bertha et al⁴ described a case of ipilimumab-induced colitis transforming into a Crohn's colitis-like phenotype with severe deep ulceration and skip lesions. Although the endoscopic and clinical features may be similar to those of inflammatory bowel disease, there are key differences histologically, with an acute inflammatory histologic profile associated more with checkpoint-inhibitor-associated colitis.³ As in our case, although the ileum was involved, the histologic appearance was not consistent with Crohn's disease. The endoscopic appearance of the ileum did not have aphthous ulcers, linear ulcers, cobblestoning, or vascular pattern changes.

Diarrhea and colitis can be delayed after checkpoint inhibitor treatment; therefore, a low index of suspicion should be maintained.² Endoscopic assessment can help predict response to treatment because the presence of ulcerations predicts a poor response to steroids.⁵ Although limited examinations with rectosigmoidoscopy may allow endoscopic assessment and biopsies with less-intensive bowel preparation, clinicians need to be mindful of not missing cases of ileitis without colonic involvement. This case illustrates the importance of using advanced endoscopic imaging with electronic chromoendoscopy and thorough colonoscopic examination of patients with suspected GI side effects as an IrAE, including ileal intubation to enhance mucosal abnormalities allowing targeted biopsies. We have shown that the endoscopic changes may be subtle and appear different from those of Crohn's disease.

DISCLOSURE

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Abbreviation: IrAE, immune-mediated adverse event.

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