Nivolumab-Induced Fulminant Immune-Related Colitis Despite Infliximab in a Patient With NSCLC

To the Editor:

A 63-year old male (former smoker) was diagnosed with a stage IV metastatic pulmonary adenocarcinoma with carcinomatous meningitis. *ALK* receptor tyrosine kinase (*ALK*) and *EGFR* mutations were negative. He showed progressive disease after cranial irradiation and 3 cycles of palliative chemotherapy, cisplatin-pemetrexed, for which his therapy was changed to nivolumab.

After 16 months of nivolumab, the patient developed immune-related colitis grade 2. He was started on methylprednisolone 32 mg twice daily, with moderate improvement. Five days later, he suddenly deteriorated with bloody diarrhea 10 to 15 times a day and night sweats. A computerized axial tomographic scan showed mild colitis, no free intraperitoneal fluid, nor gas. Stool cultures were negative. The patient was hospitalized and was started on high-dose intravenous methylprednisolone 120 mg/d. Sigmoidoscopy showed a normal mucosa, with no intraluminal blood. Biopsy specimens were negative for cytomegalovirus. After 3 days, the patient kept slowly deteriorating. Consequently, infliximab 5 mg/kg was administered.

Two days later, the patient woke up from increasing abdominal pain. An acute abdomen with imminent septic shock was diagnosed. Urgent laparoscopy showed a diffuse fecal peritonitis with a large perforation on the descending colon and an inviable looking transverse and ascending colon with a small perforation of the cecum. A total colectomy with terminal ileostomy was performed. The anatomopathological analysis of the colectomy was consistent with fulminant ischemic type colitis with multifocal ulceration, focal transmural ischemic necrosis, perforation, and purulent peritonitis (Figs. 1 and 2).

The postoperative course was complicated by pneumonia and multiple abdominal abscesses, the two largest of which were drained. Despite in vitro sensitivity and a trial of class-switching, the inflammatory markers remained very high and the patient gradually deteriorated. He eventually succumbed to infectious complications 35 days after his total colectomy.

In advanced NSCLC, immune-related colitis is the third most frequent high-grade immune-related adverse event with the use of programmed death 1/programmed death ligand 1 inhibitors, affecting 0.4% of patients.[1] In extreme cases, immune-related colitis can lead to bowel perforation, although only one other case report describes this in a patient treated with nivolumab for NSCLC.

The European Society of Medical Oncology recently published guidelines for managing toxicities from immunotherapy.[2] Even though programmed death 1/programmed death ligand 1 inhibitors are increasingly used in oncology, the management of immune-related colitis is mainly based on clinical experience and low-grade evidence drawn from the experience with the anti–cytotoxic T lymphocyte associated protein 4 (CTLA4)–antibody ipilimumab. According to the European Society of Medical Oncology guidelines, patients with steroid-refractory colitis after 72 hours "require infliximab and usually have an excellent response."[2] Data regarding the proportion of patients with refractory colitis despite infliximab-use are scarce to nonexisting.

Herein, we describe the first case of fatal colitis despite infliximab in nivolumab-induced immune-related colitis.

Despite the largely positive clinical effect of corticosteroids and infliximab, other therapies are warranted. In that

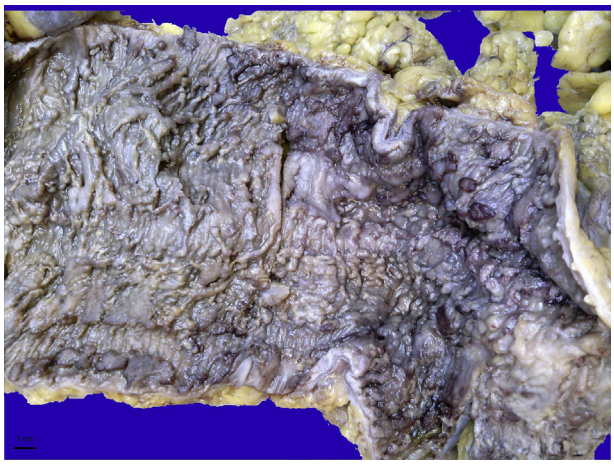

Figure 1. Macroscopy shows a well-defined zone of diffuse, continuous destruction extending from the cecum over 65 cm, including a perforation with diameter 2 cm at the transverse colon.

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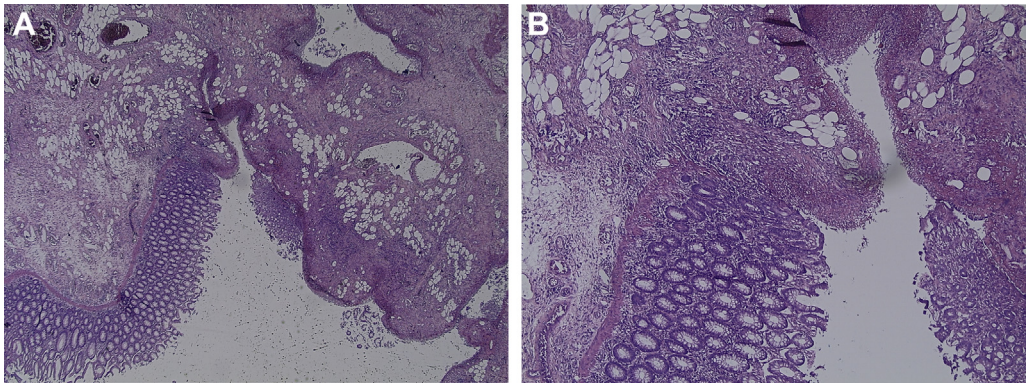

Figure 2. Histologic sections confirming the presence of multiple mucosal, sharply demarcated deep ulcerations surrounded by reactive colonic epithelium. There are dilated congested vessels and prominent fibrosis in the lamina propria and submucosa. No hemosiderophages are identified (Hematoxylin-eosin stain, original magnifications ×16 [*A*] and detail ×50 [*B*]).

regard, we remark the positive results of case reports in which vedolizumab, mesalamine, cyclosporine, and others were used.[3-5]

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Safety and Efficacy of Alectinib in a Patient With Advanced NSCLC Undergoing Hemodialysis

To the Editor:

A 52-year-old male former smoker was diagnosed with mesangial proliferative glomerulonephritis at 12 years of age, with this condition ultimately necessitating hemodialysis at age 31. He was diagnosed with unstable angina at age 45 years. At 50 years of age, he was diagnosed with lung adenocarcinoma (pT1aN2M0, stage IIIA) and underwent middle and lower lobectomy of the right lung. Analysis of the resected tumor tissue revealed positivity for an anaplastic lymphoma kinase (*ALK*) fusion gene (immunohistochemistry score, 3+; fluorescence in situ hybridization status, 74%). Although his Eastern Cooperative Oncology Group performance status was grade 0, the patient did not undergo postoperative adjuvant chemotherapy because of the high risk of complications due to his comorbid disease. Two years after surgery, a positron-emission tomography–computed tomography scan revealed enlargement of a positive hilar lymph node and multiple right pleural nodules, leading to a diagnosis of recurrent metastases (Fig. 1*A*). Treatment with alectinib (600 mg daily) was initiated with written informed consent. An asymptomatic elevation of creatine phosphokinase of

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