Concurrent ipilimumab and CMV colitis refractory to oral steroids

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Immune checkpoint inhibitors, including anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA4) and anti-programmed cell death protein-1 (anti-PD-1) antibodies, have demonstrated clinical and survival benefits in a variety of malignancies, which has led to an expansion in their role in oncology. In melanoma, the anti-CTLA-4 antibody, ipilimumab, has demonstrated a survival benefit in patients with advanced metastatic melanoma and in patients with resectable disease with lymph node involvement.[1,2]

Ipilimumab exerts its effect by binding CTLA-4 on conventional and regulatory T cells, thus blocking inhibitory signals on T cells, which leads to an antitumor response.[3] The increased immune response counteracts the immune-evading mechanisms of the tumor. With increased use of these agents, immune-related adverse events (irAEs) have become more prevalent. The most common irAEs secondary to ipilimumab are skin rash, colitis/diarrhea, hepatitis, pneumonitis, and various endocrinopathies.[4] In a phase 3 trial of adjuvant ipilimumab in patients with resected stage III melanoma, grade 3 or 4 adverse events occurred in 54.1% of participants in the ipilimumab arm, the most common being diarrhea and colitis (9.8% and 6.8%, respectively).[2]

Recognition and management of irAEs has led to the implementation of treatment guidelines.[4,5] Management of irAEs includes checkpoint inhibitor discontinuation and reversal of the immune response by institution of immunosuppression with corticosteroids. Here we present the case of a patient with stage IIIB, BRAF V600E-positive melanoma, who developed colitis refractory to standard therapy after treatment with ipilimumab and whose clinical course was complicated by cytomegalovirus (CMV) reactivation and bowel perforation.

Case presentation and summary

A 40-year-old white woman with stage IIIB BRAF V600E-positive melanoma presented with diarrhea refractory to high-dose prednisone (1 mg/kg BID). She had recently undergone wide local excision and sentinel node biopsy and received her inaugural dose of ipilimumab (10 mg/kg).

The patient first presented with loose, watery stools that had begun 8 days after she had received her first dose of adjuvant ipilimumab. She was admitted to the hospital, and intravenous methylprednisolone was initiated along with empiric ciprofloxacin (400 mg, IVPB Q12h) and metronidazole (500 mg, IVPB Q8h) as infectious causes were concurrently ruled out. During this initial admission, the patient's stool was negative for *Clostridium difficile* toxin, ova, and parasites, as well as enteric pathogens by culture. After infectious causes were excluded, she was diagnosed with ipilimumab-induced colitis. Antibiotics were discontinued, and the patient ultimately noted improvement in her symptoms. On hospital day 7, she was experiencing only 2 bowel movements a day and was discharged on 80 mg of prednisone twice daily.

After discharge the patient noted persistence of her symptoms. At her follow-up, 9 days after discharge, the patient noted continued symptoms of low-grade diarrhea. She failed a trial of steroid tapering due to exacerbation of her abdominal pain and frequency of diarrhea. Further investigation was negative for *C. diff* toxin and a computed-tomography scan was consistent with continuing colitis. The patient's symptoms continued to worsen, with recurrence of grade 3 diarrhea, and she was ultimately readmitted 17 days after her earlier discharge (36 days after her first ipilimumab dosing).

On re-admission, the patient was again given intravenous methylprednisolone and experienced

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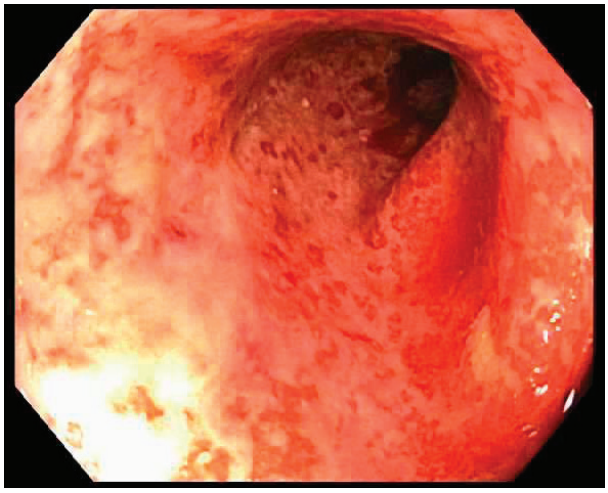

FIGURE 1 Representative image taken from sigmoidoscopy demonstrating severe inflammation by its edematous, erythematous, friable, and granulation tissue. Biopsy returned with immunohistochemical staining positive for cytomegalovirus.

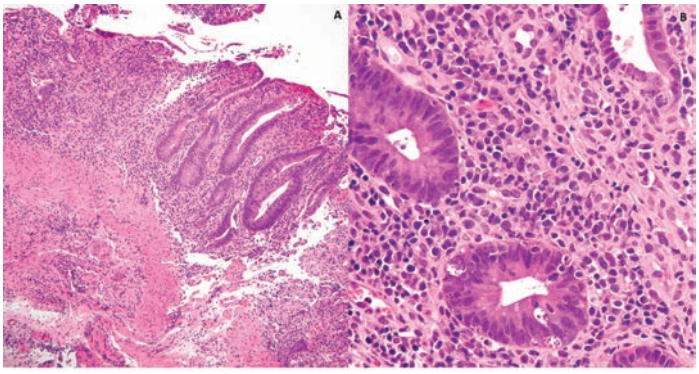

FIGURE 2 **A,** Lymphoplasmacytic expansion of the lamina propria with mild architectural disarray is present (hematoxylin and eosin, 100x). **B,** Increased intraepithelial lymphocytes and prominently increased crypt apoptosis are also identified (hematoxylin and eosin, 400x).

interval improvement in the frequency of diarrhea. A gastroenterology expert was consulted, and the patient underwent a flexible sigmoidoscopy that demonstrated findings of diffuse and severe inflammation and biopsies were obtained (Figure 1). After several days of continued symptoms, the patient received infliximab 5 mg/kg for treatment of her adverse autoimmune reaction. After administration, the patient noted improvement in the frequency and volume of diarrhea, however, her symptoms still persisted.

Biopsy results subsequently revealed findings compatible with ipilimumab-induced colitis, and immunohistochemical staining demonstrated positivity for cytomegalovirus (CMV). Specifically, histologic examination showed lymphoplasmacytic expansion of the lamina propria, some architectural distortion, and increased crypt apoptosis. Scattered cryptitis and crypt abscesses were also noted, as were rare stromal and endothelial cells with characteristic CMV inclusions (Figure 2 and Figure 3).

Serum CMV polymerase chain reaction (PCR) was also positive at 652,000 IU/mL (lower limit of detection 100 IU/mL). Induction dosing of ganciclovir (5 mg/kg IV Q12h) was initiated. The combined treatment with intravenous methylprednisone and ganciclovir led to an improvement in diarrhea frequency and resolution of blood in the stool. She was transitioned to oral prednisone, but it resulted in redevelopment of grade 3 diarrhea. The patient was therefore resumed on and discharged on daily intravenous methylprednisolone.

After discharge, the patient was started on budesonide 9 mg daily. Her serum CMV PCR level reduced and she was transitioned to oral valgancyclovir (900 mg daily) for maintenance. Another unsuccessful attempt was made to switch her to oral prednisone.

About 14 weeks after the initial ipilimumab dosing, the patient underwent another flexible sigmoidoscopy that again demonstrated severe colitis from the rectum to sigmoid colon. Biopsies were negative for CMV. Patient was readmitted for recurrence of diarrhea the following week. Treatment with IV methylprednisone (1mg/kg BID) and infliximab (5 mg/kg) again led to an improvement of symptoms. She was again discharged on IV methylprednisone (1 mg/kg BID) with a taper.

In the 15th week after her initial ipilimumab dose, the patient presented with a perforated bowel, requiring a subtotal colectomy and end ileostomy. She continued on a slow

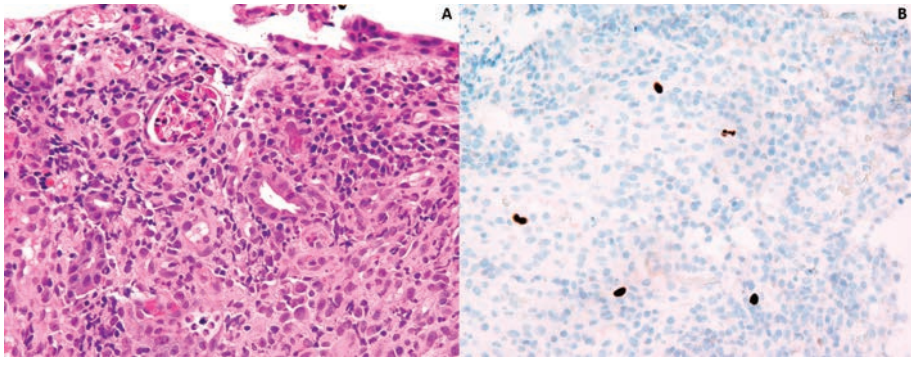

FIGURE 3 **A**, Focal crypt abscess and stromal cells with characteristic viral cytopathic effect (enlargement and cytoplasmic inclusions) are focally identified (hematoxylin and eosin, 400x). **B**, Immunohistochemical stain for cytomegalovirus highlights several scattered stromal/endothelial cells (immunohistochemical stain for CMV, 400x).

taper of oral prednisone (50 mg daily and decrease by 10 mg every 5 days).

At her last documented follow-up, 8 months after her first ipilimumab dose, she was having normal output from her ileostomy. She developed secondary adrenal insufficiency because of the long-term steroids and continued to take prednisone 5 mg daily.

Discussion

Diarrhea and colitis are common irAEs attributable to checkpoint-inhibitor therapy used for the treatment of melanoma. This case of ipilimumab-induced colitis refractory to high-dose oral steroids demonstrates the risks associated with management of anti-CTLA-4 induced colitis. In particular, the high-dose corticosteroids required to treat the autoimmune component of this patient's colitis increased her susceptibility to CMV reactivation.

The diagnosis of colitis secondary to ipilimumab is made primarily in the appropriate clinical setting, and typically onsets during the induction period (within 12 weeks of initial dosing) and most resolve within 6-8 weeks.[6] Histopathologically, there is lymphoplasmacytic expansion of lamina propria, increased intraepithelial lymphocytes, and increased epithelial apoptosis of crypts. One can also see acute cryptitis and crypt abscesses. Reactive epithelial changes with mucin depletion are also often seen in epithelial cells.

Findings from immunohistochemical studies have shown the increased intraepithelial lymphocytes to be predominantly CD8-positive T cells, while the lamina propria contains an increase in the mixture of CD4- and CD8-positive T cells. In addition, small intestinal samples show villous blunting. There is an absence of significant architectural distortion and well-developed basal lymphoplasmacytic infiltrates characteristic of chronic mucosal injury, such as idiopathic inflammatory bowel disease.[7] Granulomas are also absent in most series, though they have been reported in some cases.[8] The features are similar to those seen in autoimmune enteropathy, but goblet and endocrine cells remain preserved. Graft-versus-host disease has similar histologic features, however, the clinical setting usually makes the distinction between these obvious.

Current treatment algorithms for ipilimumab-related diarrhea, begin with immediate treatment with intravenous methylprednisolone (125 mg once). This is followed with oral prednisone at a dose of 1-2 mg/kg tapered over 4 to 8 weeks.[4] In patients with persistent symptoms despite adequate doses of corticosteroids, infliximab (5 mg/kg every 2 weeks) is recommended until the resolution of symptoms, and a longer taper of prednisone is often necessary.

Institution of high-dose corticosteroids to treat grade 3 or 4 irAEs can increase the risk for infection, including opportunistic infections. One retrospective review of patients administered checkpoint inhibitors at a single institution revealed that 7.3% of 740 patients developed a severe infection that lead to hospitalization or treatment with intravenous antibiotics.[9] In that patient cohort, only 0.6% had a serious infection secondary to a viral etiology, and 1 patient developed CMV enterocolitis. Most patients who developed an infection in this cohort had received corticosteroids (46/54 patients, 85%) and/or infliximab (13/54 patients, 24%).[9]

CMV is a member of the Herpesviridae family. After a primary infection, which can often go unrecognized in an immunocompetent host, CMV can persist in a latent state.[10] In a study by Bate and colleagues, the age-adjusted seropositivity of CMV was found to be 50.4%.[11] Based on those results, immunosuppression in a patient who has previously been infected with CMV can lead to a risk of reactivation or even reinfection. In the era of checkpoint-inhibitor therapy, reactivation of CMV has been described previously in a case of CMV hepatitis and a report of CMV colitis.[12,13] Immunosuppression, such as that caused by corticosteroids, is a risk factor for CMV infection.[14] Colitis caused by CMV usually presents with abdominal pain, diarrhea, and bloody diarrhea.[15] In suspected cases of CMV colitis, endoscopy should be pursued with biopsy for tissue examination. A tissue diagnosis is required for CMV colitis because serum PCR can be negative in isolated cases of gastrointestinal CMV infection.[15]

Conclusion

Despite appropriate treatment with ganciclovir and the noted response in the patient's serum CMV PCR, symptom exacerbation was observed with the transition to oral prednisone. The requirement for intravenous corticosteroids in the present case demonstrates the prolonged effects exerted by irAEs secondary to checkpoint-inhibitor therapy. Those effects are attributable to the design of the antibody – ipilimumab is a fully humanized monoclonal antibody and has a plasma half-life of about 15 days.[1,4]

By the identification of CMV histopathologically, this case, along with the case presented by Lankes and colleagues,[13] illustrates the importance of considering CMV colitis in patients who are being treated with ipilimumab and who develop persistent or worsening diarrhea after initial treatment with high-dose steroids.

Early recognition of possible coexistent CMV colitis in patients with a history of treatment with ipilimumab can have important clinical consequences. It can lead to quicker implementation of proper antiviral therapy and minimization of immune suppression to levels required to maintain control of the patient's symptoms.

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