CLINICAL VIGNETTE

Immunotherapy Induced Colitis

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Case Presentation

An 82-year-old male with metastatic melanoma to the lung, pleura, and lymph nodes was started on dual immunotherapy infusions, with ipilimumab and nivolumab. After his second infusion, he complained of fatigue and diarrhea.

He received his third infusion, and 1 week later, started to have worsened diarrhea. He was seen in the emergency room, and stool culture, clostridium difficile, ova and parasite, and CT of abdomen and pelvic were unremarkable. He was discharged home but had to return to the hospital for intractable diarrhea.

His diarrhea occurred every 15 minutes, with small volumes, without blood, but no fever or chills. He had crampy abdominal pain, associated with diarrhea. Loperamide, did not control his diarrhea and repeat stool studies were unremarkable, except for hemoccult positivity.

He underwent colonoscopy, which revealed diffuse inflammatory mucosa, with edema, and exudate, sparing the terminal ileum. Multiple biopsies revealed diffuse acute colitis with marked ulceration, lymphoplasmacytic infiltrates, crypt abscesses, without crypt distortion. Acid Fast Bacteria, CMV, and fungal stain were negative.

He was presumed to have immunotherapy induced colitis and was started on prednisone 60 mg/day. His diarrhea persisted on steroids, and he had to be hospitalized for weakness and dehydration. Infliximab infusion was recommended for his colitis, however because of his bad experience with "infusion therapy", he deferred. He was treated with mesalamine 4.8 gram orally daily but diarrhea was not controlled with prednisone and mesalamine

After his 8th hospital day, he agreed to infliximab at 5 mg/kg. Four days after his infliximab infusion, his diarrhea decreased to 3-4 times a day and his steroid dose was reduced. He was discharged from the hospital 3 days later.

Discussion

The use of immune-checkpoint inhibitors in cancer treatment is increasingly common. Immunotherapy induced colitis a serious and difficult to manage side effect of immunotherapy. Our patient was treated with nivolumab, an Anti-PD-1 Monoclonal antibody, and ipilimumab, an Anti-CTLA-4 antibody. These are immune-checkpoint inhibitors and block the inhibitory signal by binding to the inhibitory receptor or its ligand and enhance the immune response against the tumor.[1] This also leads to inflammatory side effects known as immune-related adverse events. These events typically target the gastrointestinal, hepatic, skin, and endocrine systems.[2] The most common presenting symptom is watery diarrhea. Abdominal pain, bloody diarrhea, nausea, vomiting and fever are less common.[3]

The National Cancer Institute's common terminology criteria for grading adverse events: for diarrhea and colitis[4] (See Table 1). Hodi et al reported diarrhea in 30% of 376 patients studied. Grade 3-4 diarrhea occurred in 12% of patients. Of those with colitis, 61% had grades 3/4.[5] For grade 1 diarrhea, the immunotherapy can be continued with careful follow up and symptomatic treatment with loperamide. For grade 2 or above, the immunotherapy should be discontinued.[3]

Diagnostic evaluations for patients who develop diarrhea include stool culture for enteric pathogens, clostridium difficile, and CMV. Colonoscopy is the diagnostic standard for immunotherapy-induced colitis. It is recommended for persistent grade 2 or higher diarrhea.[3] Inflammatory changes such as granularity, loss of vascular pattern, exudates, and ulceration can be seen. Endoscopic appearance can be similar to those in inflammatory bowel diseases. Biopsies should be obtained in normal appearing mucosa. Cytomegalovirus infection should be ruled out by immunohistochemical staining.

Histopathological examination can reveal active colitis characterized by marked mixed inflammatory cell infiltrates in the lamina propia neutrophils, lymphocytes, and eosinophils.[3] Foci of neutrophilic cryptitis, crypt abscesses, glandular destruction and erosions of the mucosal surface can also be seen.

Treatment of grade 1 diarrhea, includes anti-diarrhea agents such as loperimide. For grade 2 and higher diarrhea, oral prednisone 1 mg /kg should be started. O'Connor et al reported 50% response with glucocorticosteroids treatment.[6] They have reported 100% success rate with 5mg/kg infliximab infusion. Mesalamine has also reduced the severity of immunotherapy induced colitis with improvement in the frequency of diarrhea and endoscopic findings.[7]

For those refractory to glucocorticosteroid and infliximab therapy, fecal microbiota transplantation has resulted in complete

resolution of clinical symptoms, with return to normal bowel function.[8]

Reinduction should be considered on a case-by case basis when benefits outweigh the risks. In general, reinduction is not recommended in anyone who has experienced grade 3 or 4 colitis.

Summary

Our patient with metastatic melanoma involving multiple organs developed debilitating diarrhea and colitis on immunotherapy. He did not respond to the oral prednisone therapy and was reluctant to try infliximab infusion. After unsuccessful trail with mesalamine, he reluctantly agreed to infliximab infusion, which finally controlled his diarrhea.

Table 1.

Adverse effect	Grade				
	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4–6 stools per day over baseline; IV fluids indicated <24 h; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; hospitalisation; interfering with ADL	Life-threatening consequences (e.g. hemodynamic collapse)	Death
Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain; fever; change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g. perforation, bleeding, ischaemia, necrosis, toxic megacolon)	Death

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