CLINICAL VIGNETTE

Colitis after Treatment of Melanoma

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Case Presentation

A 67-year-old man with a history of gout and melanoma presented with a seven-day history of diarrhea and rectal bleeding. His symptoms began with 10 episodes per day of watery diarrhea. He later developed four episodes of bright red blood in the stool with occasional mucus. His prior baseline was 1 to 2 formed, brown bowel movements per day. He did not have abdominal pain but reported nausea without vomiting as well as subjective fevers at home. He was receiving ipilimumab treatment for stage IIIB melanoma. Symptoms began seven days after his second dose of ipilimumab. He tried to manage symptoms at home with loperamide with some improvement in the frequency of bowel movements.

His only other medication was allopurinol and he was not taking nonsteroidal anti-inflammatory medications. He had no history of prior abdominal surgery and had never had a colonoscopy. There was no family history of gastrointestinal malignancy or inflammatory bowel disease.

Upon presentation, he was hemodynamically stable with a blood pressure of 139/78 mmHg and pulse of 83 beats per minute. Abdominal exam revealed a soft, non-distended, non-tender abdomen with normo-active bowel sounds. The remainder of his physical exam was unremarkable.

Laboratory findings included a white cell count of 12.7/L, hemoglobin and hematocrit of 11.5 g/dL and 36.1%, respectively, blood urea nitrogen of 13 mg/dL, creatinine of 0.7 mg/dL as well as aspartate aminotransferase of 190 IU/L, alanine aminotransferase of 158 IU/L, alkaline phosphatase of 225 IU/L and bilirubin of 1.5 mg/dL. INR was 1.2. Stool testing was negative for bacterial pathogens, as well as *Clostridium difficile*, ova and parasites.

CT scan in the emergency room showed moderately diffuse colonic wall thickening and surrounding fat stranding, consistent with diffuse colitis.

Gastroenterology was consulted and colonoscopy revealed pancolitis with ulcerations, edema, erythema and loss of vascular pattern. There was no involvement of the terminal ileum. Representative images are seen in Figures 1-3.

Pathological examination revealed preserved crypt architecture with acute cryptitis, crypt abscesses with focal ulceration (Figures 4-6). Overall, findings were consistent with ipilimumab-induced colitis.

Discussion

Ipilimumab is an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) monoclonal antibody which potentiates T-cell activation and proliferation. Indications include the treatment of metastatic or unresectable melanoma.[1] A phase 3 study of ipilimumab, with or without glycoprotein 100 (gp100) peptide vaccine, for previously treated metastatic melanoma showed an overall survival of 10 months compared to 6.4 months for gp100 alone.[2]

Unfortunately, immune-mediated adverse reactions occur and affect the gastrointestinal tract, liver, skin, and endocrine systems, among others. Overall incidence of immune-related adverse events is 60-77% while grade 3-4 events occur in 10-15% of patients.[1,3] In this article, we will cover the gastrointestinal and hepatic adverse reactions.

Diarrhea occurs in 37% with 6.9% having grade 3-4 events. Time to adverse event is 2-16 weeks. Colitis will occur in 8% with 4.9% being grade 3-4. Other associated symptoms may include abdominal pain, abdominal cramping, nausea, vomiting, ileus, fevers, fatigue, gastrointestinal bleeding, dyspepsia and rarely perforation or peritoneal signs.[3,4]

Pathogenesis of the gastrointestinal effects involves CTLA-4 blockade potentiating Th17-mediated autoimmunity. Th17 cells play a role in gastrointestinal mucosal immunity. The subsequent cytokine IL-17 increase correlates with development of colitis.[3]

Diagnosis can be made clinically but if there is uncertainty regarding the diagnosis or severity, colonoscopy should be performed.

Management of mild gastrointestinal symptoms (<4 stools/day) involves supportive care with fluids and loperamide. Mild-to-moderate symptoms or more persistent symptoms can be treated with oral budesonide. Moderate symptoms (4-6 stools/day) can be managed with supportive care and holding of ipilimumab. Ipilimumab can be resumed after symptoms improve. Severe symptoms can be managed with supportive care, withholding of ipilimumab and systemic corticosteroids. For

severe persistent symptoms (≥7 stools/day), rectal bleeding, abdominal cramping, peritoneal signs or fevers, the recommendation is to permanently discontinue ipilimumab and treat with systemic corticosteroids. Treatment with infliximab can also be considered. Infliximab is usually administered in patients who have symptoms lasting over 7 days despite steroids.[3,5]

Hepatotoxicity is in the form of immune-related hepatitis which can manifest with elevated transaminases and hyperbilirubinemia. Monitoring should be performed prior to each dose of ipilimumab. For moderate elevations (AST or ALT >2.5 to ≤5.0 x ULN, total bilirubin >1.5 to ≤3.0 x ULN), hold ipilimumab and resume when AST or ALT is ≤2.5 x ULN and bilirubin is ≤1.5 x ULN. For severe elevations of AST or ALT >5.0 x ULN or total bilirubin >3.0 x ULN, administer corticosteroids and monitor. A slow taper of steroids is advised once the tests show sustained improvement.[5]

Conclusion

Our patient was treated with oral prednisone in addition to discontinuation of ipilimumab. He improved quickly but given the severity of symptoms, ipilimumab was not resumed.

Ipilimumab used to treat metastatic or unresectable melanoma can lead to immune-mediated gastrointestinal and hepatic adverse events. Treatment frequently involves holding or discontinuing ipilimumab, along with supportive care and sometimes corticosteroids and/or infliximab. Depending on the severity of initial adverse event and response to treatment, resumption of ipilimumab can be considered in the appropriate setting.

Figures

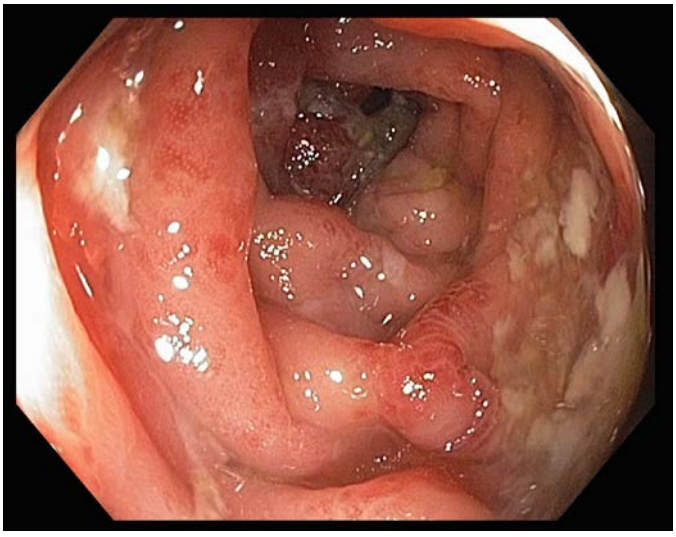
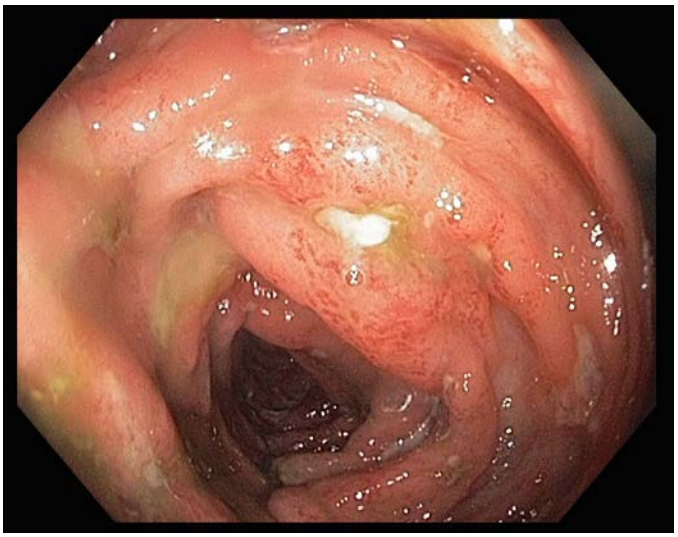


Figure 1.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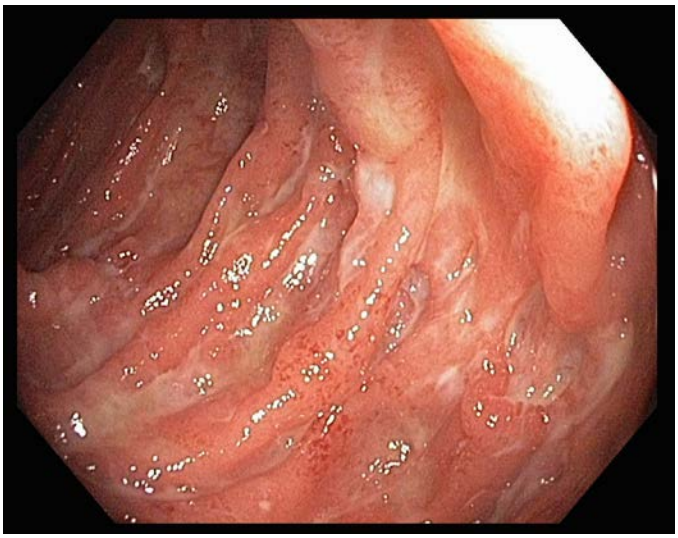
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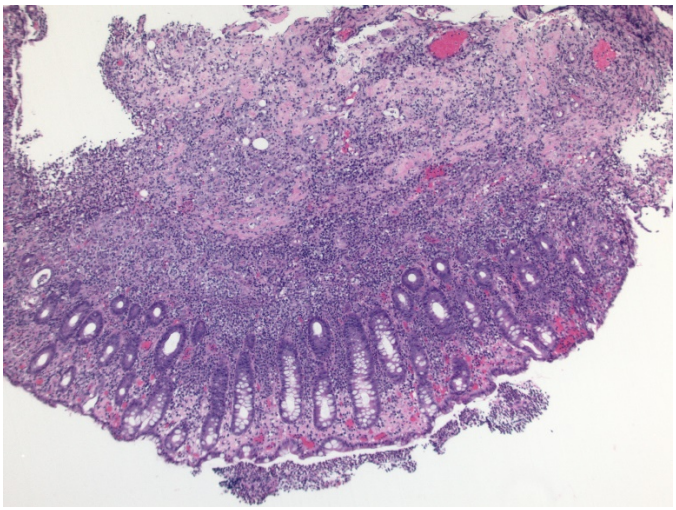
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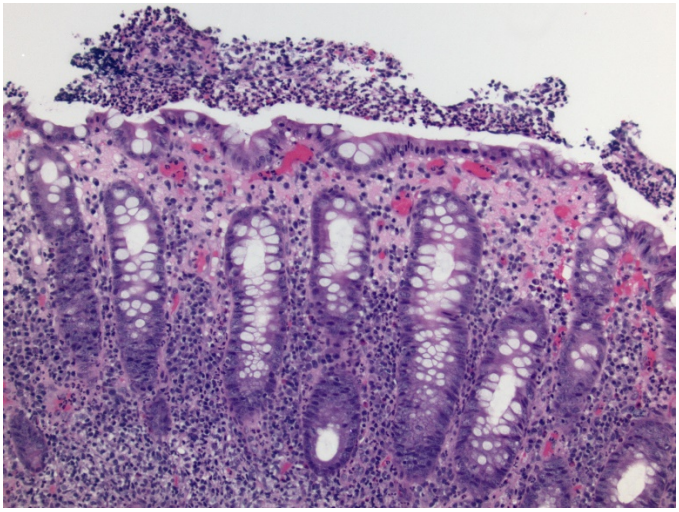

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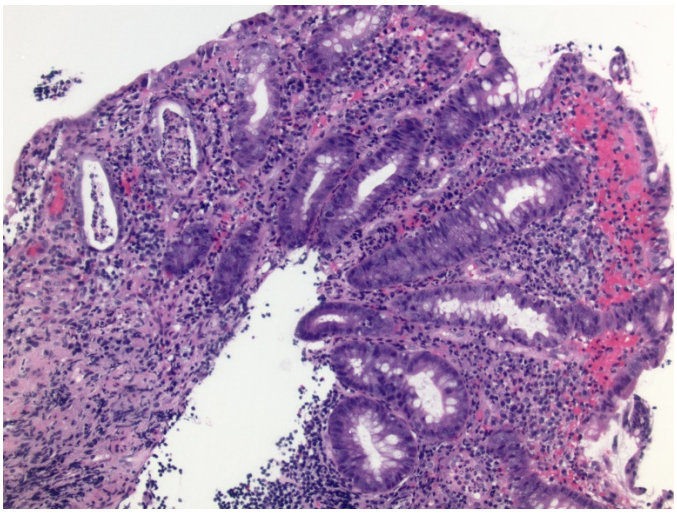

Figure 6.

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