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Case Report

Nivolumab Induced Colitis: Management of Grade III diarrhea

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Abstract

Nivolumab is a PD-1 inhibitor used for the treatment of metastatic melanoma. The use of this drug as well as other immune checkpoint inhibitors have been shown to cause inflammatory states consistent with an autoimmune process. We document a patient with metastatic melanoma treated with Nivolumab, who developed colitis and grade III diarrhea. The patient had an excellent response to a high dose course of corticosteroids.

Keywords: Colitis; Diarrhea; Nivolumab

Case Presentation

A 64-year-old Caucasian male with a history of malignant melanoma of the right foot that had metastasized to the lungs status post four cycles of Nivolumab therapy (last cycle one month ago) presented to the emergency room with an 8-day history of nausea, vomiting, and diarrhea. He described the diarrhea as watery with multiple episodes of diarrhea per day (>7 per day) but denied any associated abdominal pain. He reported having subjective fevers, chills, and reduced urine output. The patient's only home medication was 81 mg aspirin daily.

Initial vitals showed a temperature of 97.4°F, heart rate of 58 beats per minute, blood pressure of 118/87 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 91% on room air. His calculated body mass index was 18.9 kg/m^2. On exam, he appeared emaciated but alert and oriented with dry mucous membranes and cool, dry skin. Labs on admission were notable for a total white blood cell count of 16. 5 x $103/mm^3$, hemoglobin of 18.3 gm/dl, and hematocrit of 51.2%. The basic metabolic panel showed a sodium of 125 mEq/dl, potassium of 2.2 mEq/dl, chloride of 81 mEq/dl, bicarbonate of 21 mEq/dl, urea nitrogen of 57 mg/dl, and creatinine of 4.3 mg/dl.

Upon presentation, the patient received aggressive IV fluid support and electrolyte supplementation with frequent monitoring of labs. Renal failure improved with supportive fluids, but he continued to have multiple episodes of diarrhea daily. Infectious studies, including stool cultures and Clostridium difficle testing, were negative. A trial of loperamide therapy failed to control the diarrhea. Due to concerns for Nivolumab-induced colitis, methylprednisolone at 1 mg/kg was started, which resulted in the improvement of symptoms. A colonoscopy was performed after five days of steroid therapy for confirmatory evaluation.

Diagnostic tests

After 5 days of high doses of IV steroids, the patient was sedated and taken for a colonoscopy. Case reports have identified reports of Nivolumab inducing an ulcerative colitis like picture [1]. Findings on colonscopy included diffuse patchy areas of colitis (Figure 1). Random biopsies were taken of the patient. Biopsy (Figure 2) revealed patchy cryptitis, crypt abscess, and surface epithelial injury with focally increased intraepithelial apoptic bodies that are consistent with medication-induced (Nivolumab) colitis [1,2]. CMV staining was negative.

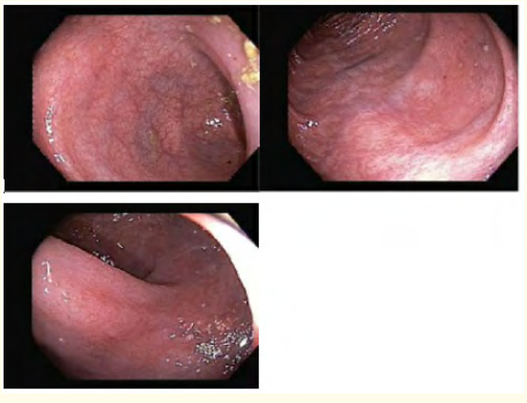

Figure 1: Colonoscopy taken 4 days post-admission in a patient with Nivolumab induced colitis. Gross imaging shows patchy areas of mucosal erythema and granularity.

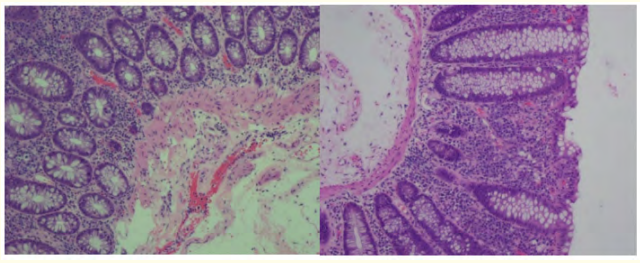

Figure 2: Histologic slides consistent with drug-induced colitis. Sections reveal patchy cryptitis (hypercellularity between glands), crypt abscesses, and surface epithelial injury/tufting. Crypt distortion is minimal. Although these findings can be nonspecific, they are consistent with medication-induced colitis (i.e. nivolumab).

Discussion

Recent treatment approaches for melanoma with metastasis have incorporated checkpoint inhibitors: anti- programmed death (PD1, e.g. Nivolumab, Pembrolizumab) and anti- cytotoxic T-lymphocyte antigen 4 (anti- CTLA- 4, e.g. Ipilimumab). The mechanism of action of these medications is to reverse the immunosuppression of T-cells and enhance their antitumor activity [3,4]. Nivolumab is a monoclonal antibody against the PD1 receptor with limited immune adverse events as compared to other checkpoint inhibitor therapies. It was approved by the FDA for melanoma in 2014 [5]. The advantages of Nivolumab over its predecessors are due to the durability of the treatment as Nivolumab or a Nivolumab combination therapy with CTLA-4 inhibitors are associated with more favorable long-term outcomes along with less immune related adverse effects, such as rash, diarrhea/colitis, hepatitis [6,7].

Due to the immune-based mechanisms by which chemotherapies exert their effects, they are often associated with a diverse array of systemic adverse events (AE). Nivolumab, along with other approved PD-1 inhibitors, however, are typically associated with a lower risk of severe treatment-related AEs as compared to treatment with CTLA-4 inhibitors [5]. The standard toxicity profile of Nivolumab includes creatinine elevation, colitis, diarrhea, hyperglycemia, hyperthyroidism, hypothyroidism, hypopituitarism, infusion related reactions, abnormal LFTs, mucosal inflammation/ stomatitis, pneumonitis, pruritis, rash, and vertigo [5,6]. However, gastrointestinal immune-related adverse effects (irAE) such as diarrhea and colitis are of particular interest when a patient is treated with PD-1 inhibitors because these side effects are thought to be associated with a higher incidence of treatment related grade 3 or 4 AE [5]. Despite these concerns, however, a recently published meta-analysis and systematic review [6] evaluating the toxicity profile of anti-PD-1 monoclonal antibodies demonstrated that the vast majority of irAEs associated with PD-1 inhibitors are low grade (grades 1 or 2) and very few cases were reported as grades 3 or 4. Diarrhea, was reported to be one of the most common irAEs in about 11.6% of patients receiving PD-1 targeted therapy, but only 1% of cases were found to have grade 3 out of 4 diarrhea and only 0.5% of cases were found to have grade 3 out of 4 colitis [6]. In our patient, the diarrhea was classified as grade 3 based on 8-14 days of loose bowel movements and the need for treatment with IV normal saline [8]. The patient's colitis was categorized as grade 3 based on neutrophil involvement in both the crypt and surface epithelium along with crypt abscesses [9]. These findings support the use of PD-1 directed therapy in appropriate patients without significant risk for clinical toxicities.

Patient outcome and management

It should be noted that management guidelines recommend cessation of Nivolumab, at least temporarily, in patients with high grade (grades 3 or 4) diarrhea. If the patient has grade 4 diarrhea, current recommendations advocate for the permanent discontinuation of the immune checkpoint inhibitor (ICI). If the patient has grade 3 diarrhea, the ICI should be withheld and only resumed when treatment with corticosteroids is tapered to <10mg/day and the patient remains symptom free [10].

If Nivolumab induced colitis and/or diarrhea is suspected, an infectious work up to rule out clostridium difficile and other bacterial causes is often done first. A CT scan may help guide the practitioner towards the diagnosis of colitis, but a colonoscopy with biopsy is definitive in uncertain presentations. For grade 1 or 2 diarrhea or colitis, use of antimotility agents and dietary modifications are considered first-line treatments. If symptoms do not improve within 3 days, enteric budenoside is often the next step. For patients with grades 3 or 4 diarrhea, systemic steroids are the choice of management. The decision to use methylprednisome IV or prednisone PO is dependent upon electrolyte abnormalities and the severity of diarrhea. If symptoms are resistant to steroids, infliximab is the choice of therapy [1,4,5,10].

Clinical pearls

- The onset of acute diarrhea within months of starting an immunotherapeutic drug could be due to an immunotherapeutic drug reaction
- Colitis due to an immune therapy drug can be treated with a course of steroids (methylprednisolone 1 mg/kg) after initial stabilization with IV fluids and electrolyte correction.

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