Immune-Mediated Colitis with Novel Immunotherapy : PD1 Inhibitor Associated Gastrointestinal Toxicity

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To the Editor

T-cell checkpoint blockade is showing great promise in treatment of advanced melanoma and noncell lung cancer [NSCLC]. Nivolumab is a monoclonal antibody that selectively inhibits programmed cell death one [PD1], a coinhibitory receptor allowing immune system to mount an effective antitumor response (1). Other immunomodulatory antibodies like Ipilimumab, a CTLA4 inhibitor have also been used to enhance immune system. Although therapeutic advances have improved prognosis of advanced melanoma, immune-related adverse events [AE] of gastrointestinal [GI] tract are commonly seen. While studies have reported GI toxicities with Ipilimumab, very few cases of Nivolumabinduced colitis are reported. We report a biopsy confirmed case of PD1 inhibitor toxicity in a 42 year old woman with metastatic melanoma. A 42 year old woman with stage IIIc metastatic melanoma presented with 2 weeks of watery diarrhea and fevers. She was recently treated with amoxicillinclavulanic acid for suspected streptococcus infection and Valacyclovir for possible viral mastoiditis. She took these for 2 days as symptoms resolved and patient stopped taking more doses. As adjuvant immunotherapy, she also received three doses of Nivolumab every two weeks. Further Nivolumab was withheld due to worsening diarrhea. At the time, Clostridium difficile PCR was positive and oral metronidazole was started. Diarrhea still worsened and she was transitioned to oral vancomycin. Symptoms persisted and she presented to emergency room. Physical exam was unremarkable. White cell count 14.9, lactate 2.2, with renal and liver function tests normal. Infectious workup negative including blood and stool cultures, and PCR for CMV and HSV. Patient was admitted and treated for severe Clostridium difficile infection with intravenous vancomycin and metronidazole. She then underwent a colonoscopy, which showed left sided colitis with diffusely friable mucosa and multiple large superficial ulcerations with serpiginous borders (Fig. 1).

Pathology showed colonic mucosa with patchy crypt dropout, lymphoplasmacytic expansion of lamina propria, and conspicuous apoptotic bodies. These findings can be seen in CMV colitis, graft versus host disease, and immunemodulating drug toxicity. Given our context, no transplant history or additional histologic and clinical evidence of CMV colitis, these findings are consistent with PD1 inhibitor toxicity (Fig. 2A, 2B). The presumptive diagnosis was immunemediated colitis of grade 3 or 4 and intravenous steroids were started. Diarrhea improved and patient was discharged on oral steroids and tapering dose of vancomycin. She was seen in clinic 10 days later. Diarrhea was lessening with only 12 formed bowel movements, scored as grade 1. Decision was made for no further PD1 inhibitor therapy based on severity of her colitis. By disrupting PD1 pathway, Nivolumab leads to enhanced immune-mediated tumor killing in advanced stage melanoma and NSCLC (2,3). A phase1 trial as well as a study by Topalian SL et al demonstrated increased survival rates in patients with advanced melanoma as well as an overall acceptable safety profile for Nivolumab (2). Although these drugs are improving survival, associated immune related AE should not be overlooked. Several studies have examined the AEs of Nivolumab alone and as synergistic treatment with Ipilumumab (Table 1). Established current treatment is glucocorticoids for diarrhea of more than 5 days or grade 3 colitis, plus withholding immunotherapy for grade 2, 3 and to permanently discontinue it for grade 4 colitis. Previous trials have shown Nivolumab to have a favorable safety profile with low rates of diarrhea and colitis. Nonetheless physicians should keep immunemediated colitis a possible cause of diarrhea in this group. We advise early colonoscopic evaluation with biopsies to identify immune colitis and rule out other infectious etiologies. Early recognition is crucial for directed treatment with glucocorticoids and depending on the grade of AEs, might warrant permanent withdrawal of immunotherapy.

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Table 1.

Study name	Andy adverse event	Grade 3 or 4 event	Diarrhea	Colitis	Other adverse event
Topalian et al (4) (Nivolumab 1mg/kg)	49%	6%	19%	<1%	Rash (20%), pruritus (16%)
Larkin et al (5) (Nivolumab only arm)	99,4%	43,5%	19,2%	1,3%	Fatigue (34%), rash (26%), nausea (13,1%)
Postow et al (6) (Nivolumab + Ipilimumab)	91%	54%	45%	23%	Rash (41%), fatique (39%), nausea (22%), pruritus (35%)

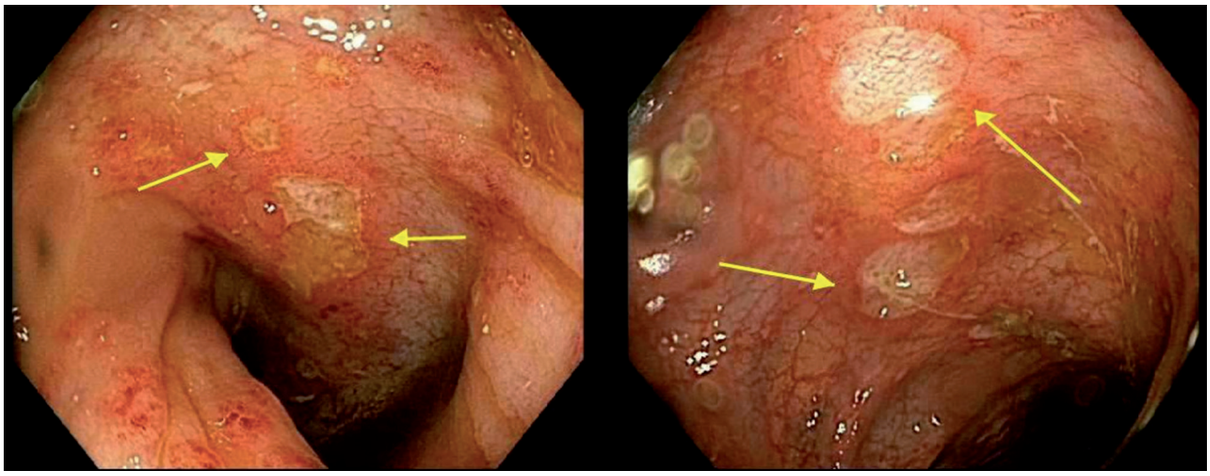

Fig. 1. — Acute colitis with diffusely friable mucosa and multiple scattered large superficial appearing ulcers covered with yellow exudate (yellow arrows)

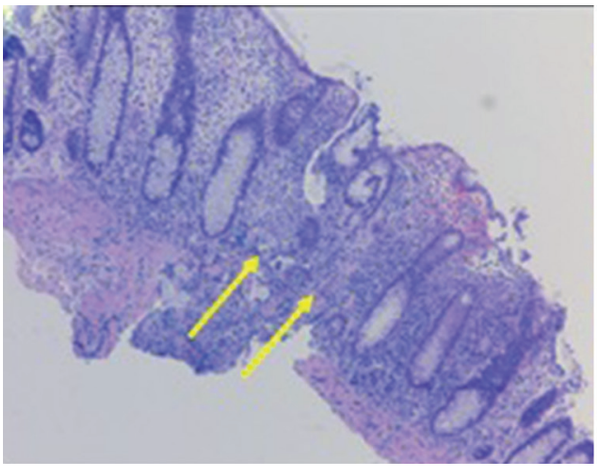

Fig. 2A. — Low power image of colonic mucosa with patchy crypt dropout (yellow arrows) and lymphoplasmacytic expansion of the lamina propria.

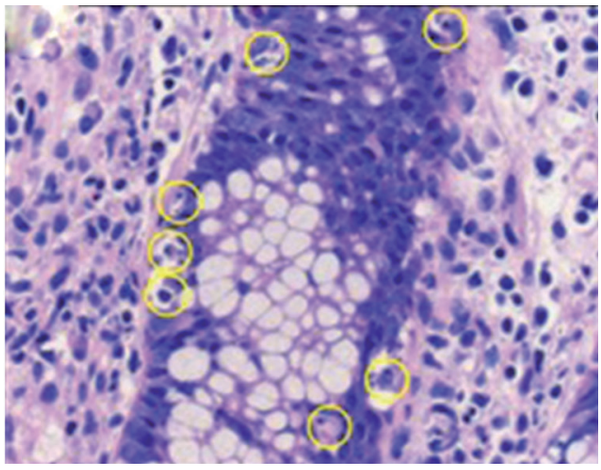

Fig. 2B. — High power image of colonic crypts with conspicuous apoptotic bodies (yellow circles). These findings are consistent with PD1 inhibitor toxicity.

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