

De Novo Crohn's Disease Three Years Following Immune Checkpoint Inhibitor Therapy

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INTRODUCTION

Immune Checkpoint Inhibitors (ICIs) have become a mainstay for the treatment of multiple malignancies. Side effects related to the GI tract have been well described including an IBD-like enteritis/colitis that requires steroids or biologics. Most of these described side effects occur during or soon after the discontinuation of treatment. In this report, we describe a case of Crohn's disease arising over three years after the completion of pembrolizumab therapy.

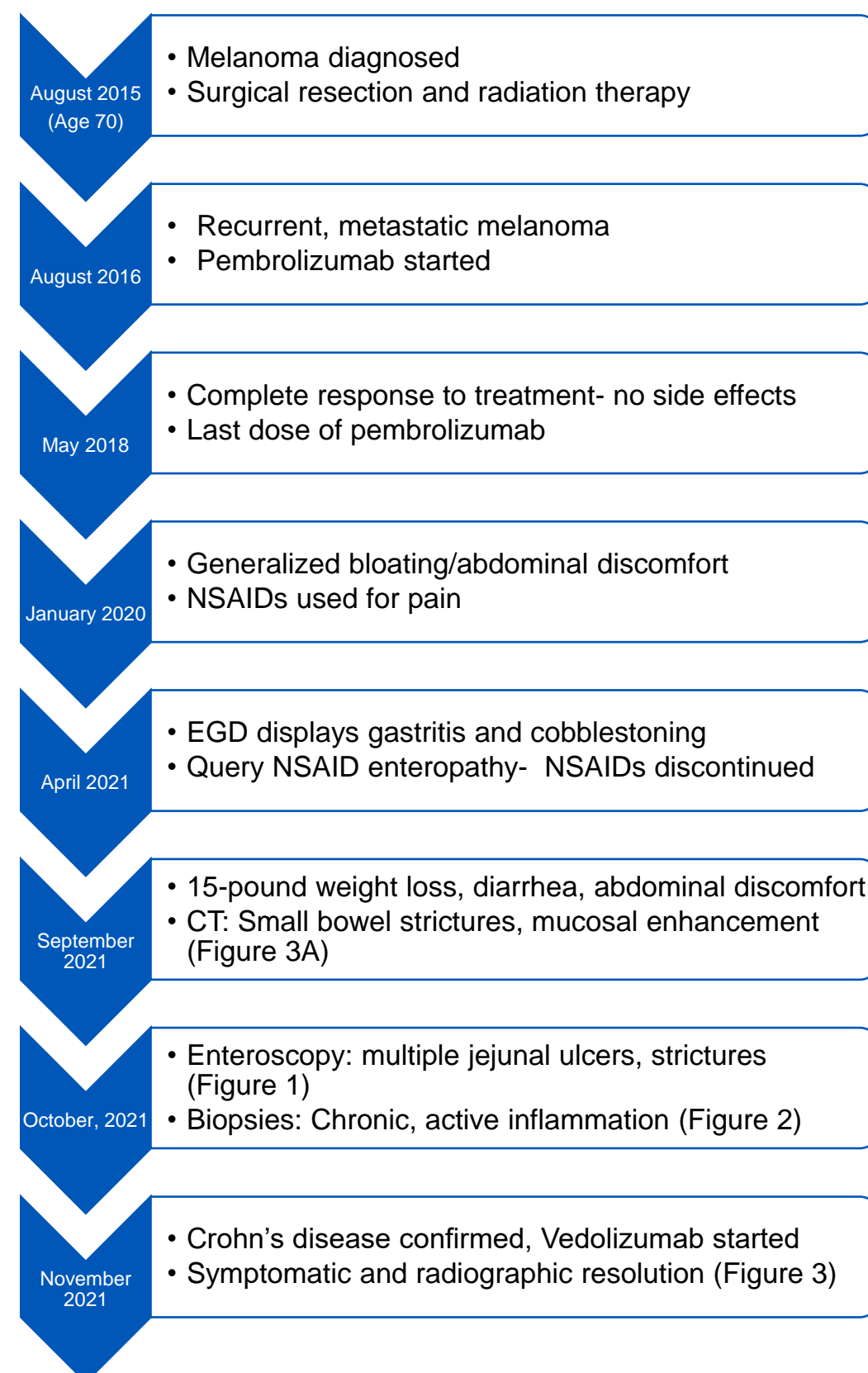
CASE DESCRIPTION

- 71-year-old male without significant medical comorbidities was initiated on pembrolizumab (August 2016) for metastatic melanoma that failed local therapies.
- Pembrolizumab therapy continued for over 18 months and was ultimately discontinued May 2018 after complete response to treatment. He never experienced any dose-limiting side effects.
- 18 months after pembrolizumab discontinuation (January 2020), he developed abdominal discomfort/diarrhea and initiated NSAIDs for pain relief.
- Due to the above symptoms, he underwent upper endoscopy April 2021. Biopsies demonstrated superficial gastritis, no evidence of H. Pylori, and normal villous architecture. NSAIDs were implicated and stopped.
- Symptoms progressed to more frequent diarrhea and weight loss. CT Enterography (Figure 3A) displayed small bowel strictures.
- CRP of 34.2, hemoglobin of 11.6 (MCV 88.2), and no evidence of vitamin D or B12 deficiencies. Biopsies displayed chronic, active inflammation (Figure 2).
- Over 3 years after pembrolizumab discontinuation, at the age of 76, he was diagnosed with Crohn's disease.

PATIENT DESCRIPTION

- 76 year old, Caucasian male from the Midwest
- Medical history: Hypertension and metastatic melanoma
- Medications: Lisinopril 10mg, PRN ibuprofen
- Family history: No autoimmune or IBD history
- Social History: Never smoker and infrequent alcohol use

TIMELINE



FIGURES

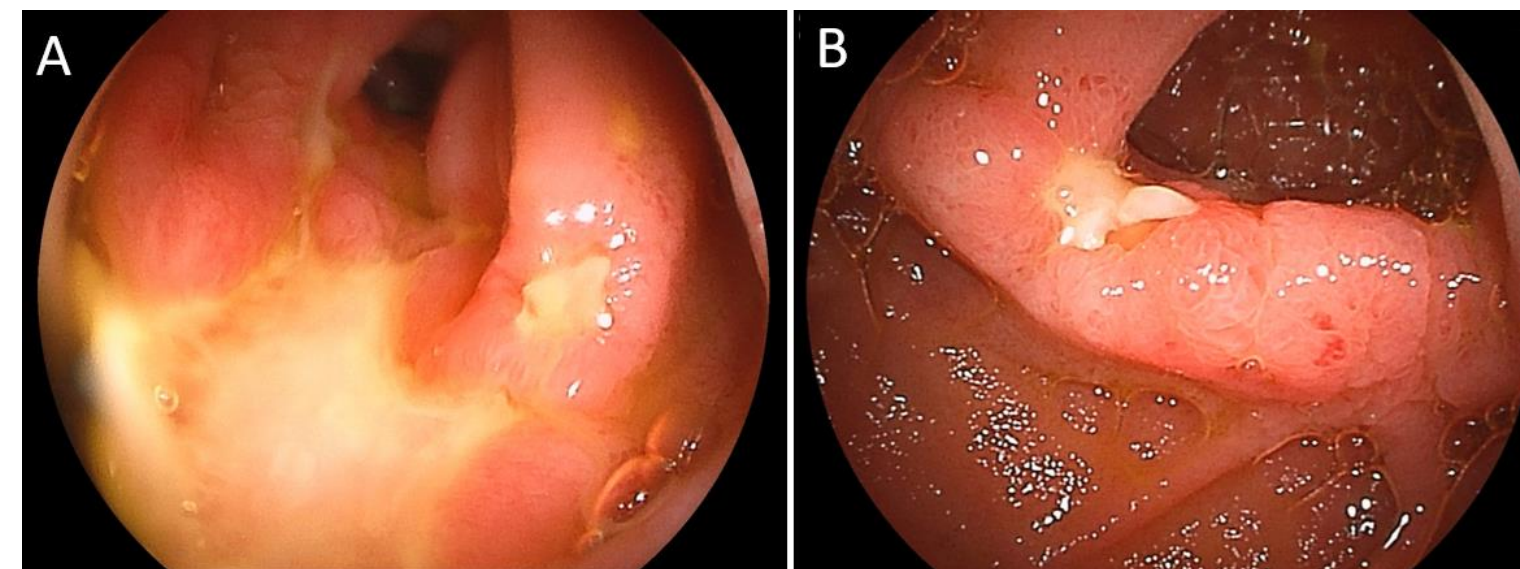


Figure 1: Images from double balloon assisted upper endoscopy displaying both stricturing (**Panel A**) and multiple ulcerations (**Panel A and B**) of the jejunum.

Figure 2: Biopsy of a proximal jejunal ulcer (conventional H&E stain) displaying mild to moderate, active, chronic enteritis with ulceration consistent with inflammatory bowel disease.

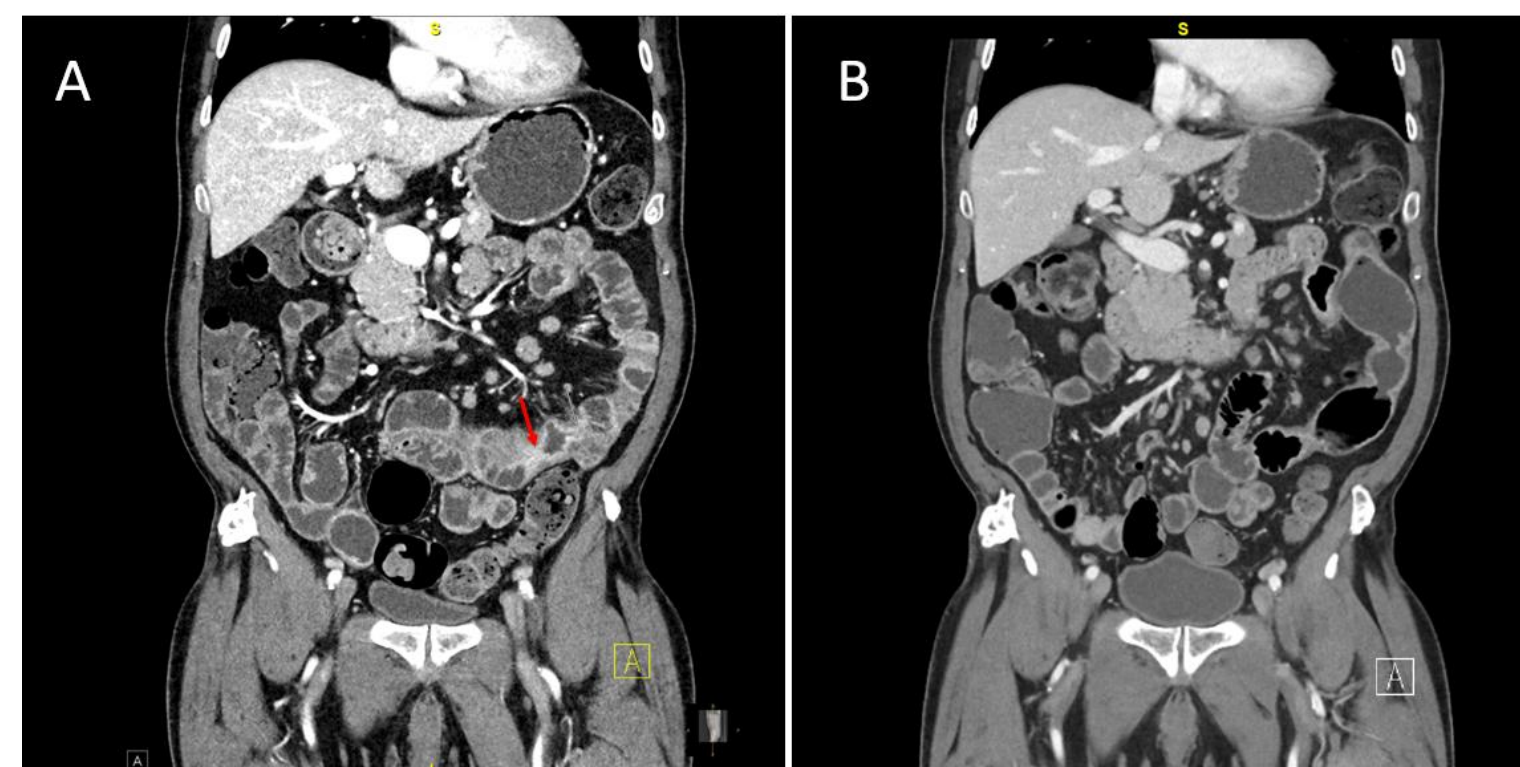
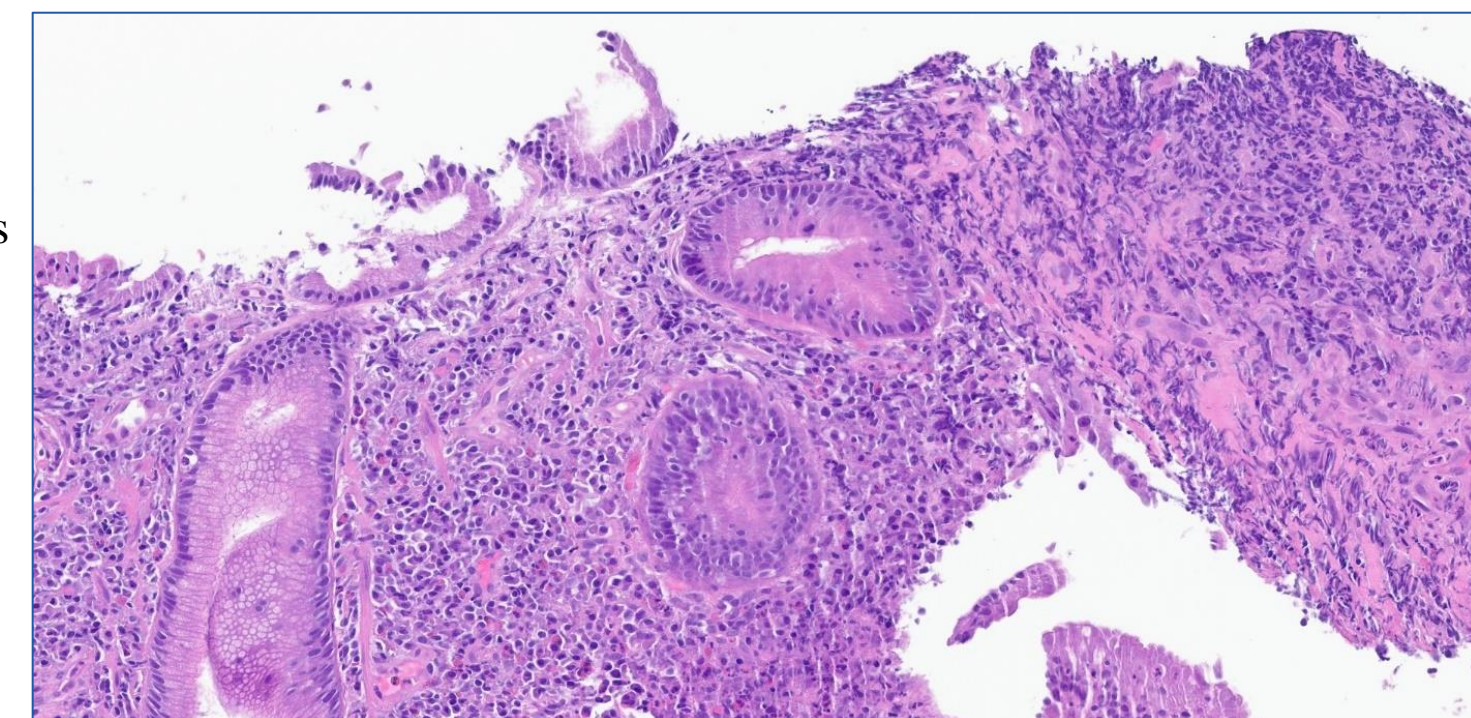


Figure 3: Panel A: CT Enterography, performed prior to treatment initiation, with evidence of jejunal stricture (red arrow) with associated wall thickening and inflammation. **Panel B:** CT Abdomen with IV contrast, performed three months after the initiation of vedolizumab, with evidence of interval improvement of jejunal wall thickening and mucosal hyperenhancement

DISCUSSION

- The progression of symptoms after NSAID discontinuation and improvement with vedolizumab therapy support the IBD diagnosis.
- The patient had minimal IBD risk factors. This presentation raises the hypothesis that exposure to ICIs may have triggered de-novo IBD, although causality cannot be ascertained.
- Cases of de novo IBD following ICI therapy have been reported. However, previous cases have been accompanied by treatment-induced, GI-related side effects.
- This appears the first reported case of ICI-induced IBD occurring outside the framework of an acute treatment-induced colitis/enteritis.

CONCLUSION

- This case serves as an example of potential long-term autoimmune implications of ICI therapy, even in patients who do not develop acute side effects

REFERENCES

- Akel R, Anouti B, Tfayli A. Late-Onset Inflammatory Bowel Disease-Like Syndrome after Ipilimumab Therapy: A Case Report. *Case Rep Oncol.* 2017;10(2):456-461.
- Bellaguarda E, Hanauer S. Checkpoint Inhibitor-Induced Colitis. *Am J Gastroenterol.* 2020;115(2):202-210.
- Bertha M, Bellaguarda E, Kuzel T, Hanauer S. Checkpoint Inhibitor-Induced Colitis: A New Type of Inflammatory Bowel Disease? *ACG Case Rep J.* 2017;4:e112.
- Loftus EV, Jr., Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gastroenterology.* 1998;114(6):1161-1168.