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Single Case

Diffuse Metastatic Melanoma in the GI Lumen Following Immune Checkpoint Inhibitor Colitis Treatment

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Keywords
Immune-mediated colitis · Melanoma · Immunosuppressants

Abstract
We describe the unique case of a 73-year-old man who developed diffuse metastatic melanoma throughout the GI tract following potent immunosuppressive treatment for his immune-mediated colitis. Diagnosis of his metastatic GI luminal disease was confirmed with colonoscopy and EGD biopsies. Immunosuppressive therapy including corticosteroids and vedolizumab is the mainstay treatment for immune-mediated colitis and has generally been thought to have a safe toxicity profile. This unique case of diffuse luminal metastasis of melanoma after intensive immunosuppressant treatment raised the concern of their long-term safety on the cancer outcome and the need for safer alternatives.

Introduction

Immune-mediated diarrhea and colitis (IMDC) is one of the more frequent toxicities of immune checkpoint inhibitors (ICIs) that is often treated with potent immunosuppressant therapy (e.g., vedolizumab or infliximab) in cases of steroid-refractory disease [1]. Similar immunosuppressive treatments (TNF-alpha blockers) for inflammatory bowel disease (IBD) have already been shown to increase the risk of malignancy after long-term use in IBD patients [2]. Independently, adding concurrent corticosteroids was also found to decrease clinical

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benefit of ICI therapy and shorten patient survival [3]. These associations raise the concern for an increased risk of worse cancer outcomes among IMDC patients treated with immunosuppressants.

Case Report/Case Presentation

Our patient is a 73-year-old man with a significant cancer history which includes squamous cell carcinoma, basal cell carcinoma of the skin, bladder cancer, lymphoma, kidney cancer, and most recently ocular melanoma. He was in remission for 3 years following brachytherapy until 2–3 years ago when metastatic melanoma was found in his liver. He underwent electroporation and was placed on nivolumab monotherapy. After nine doses, he was switched to dual nivolumab and ipilimumab for cancer progression. Days after the only dose of dual ICI therapy, he presented to the emergency department with 10–15 watery bowel movements per day. An infectious workup came back negative and colonoscopy revealed diffuse inflammation characterized by altered vascularity, congestion, erythema, friability, and granularity throughout the entire colon, suggestive of immune-mediated colitis (Fig. 1). Pathology confirmed active cryptitis and crypt abscesses. EGD showed gastric polyps and active duodenitis. Thereafter, the ICI was withheld due to this adverse event as well as poor cancer response.

The IMDC was treated with intravenous methylprednisolone followed by 5 weeks of a tapering dose of oral prednisone and vedolizumab add-on. His IMDC achieved clinical remission with histologic remission after 5 doses of vedolizumab, which was then stopped. Five months after, he underwent radioembolization procedure for liver metastasis. Cancer remained stable for the following 4 months until another acute onset of episodes of 5–10 bloody, watery stools daily, fatigue, weakness, and nausea. Abnormal lab values upon admission included mild anemia, creatinine of 1.5 mg/dL, albumin 2.1 g/dL, ALP 314 U/L, and AST 71 U/L. CT imaging revealed new diffuse enterocolitis and increased ascites compared with prior CT scan, with otherwise stable pulmonary and hepatic metastatic disease. Upper endoscopy and colonoscopy identified new metastatic melanoma throughout the GI lumen, including stomach, duodenum, ileum, and colon (Fig. 2). Unfortunately, our patient expired within 1 month of these findings due to cancer progression.

Discussion/Conclusion

Immunosuppressive IBD treatments have a small but statistically significant increased risk of malignancy with both thiopurine and anti-TNF monotherapy [2]. Vedolizumab works by blocking the interaction between α4β7 integrin on T lymphocytes and MAdCAM-1

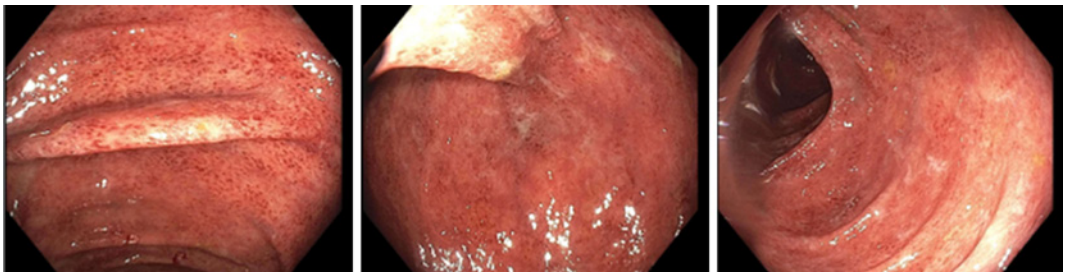

Fig. 1. Colonoscopy illustrating IMDC.

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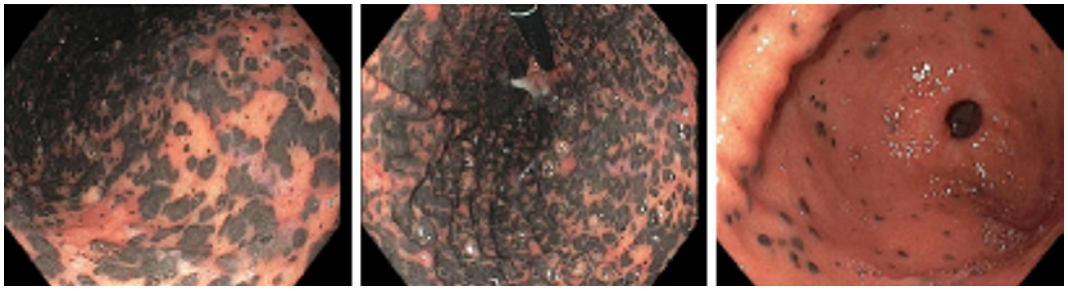

Fig. 2. Diffuse GI luminal metastatic melanoma.

on endothelial cells, ultimately reducing gut inflammation. Given its unique narrow spectrum GI immunosuppression, the risk of malignancy has not been reported. In a study of over 1,000 IBD patients treated with vedolizumab, only two developed de novo malignancies, and both of these patients had previous exposure to thiopurines [4]. Additionally, the risk of malignancy progression or recurrence from the immunosuppressive use in patients with preexisting or active cancer status is still unknown. However, corticosteroids administered with ICI therapy have been shown to decrease clinical benefit of immunotherapy [3]. Our case is a rare presentation of a delayed onset of aggressive cancer progression despite initially stable cancer status in the context of ICI colitis managed by intensive immunosuppressants.

Metastatic melanoma to the GI lumen is rarely reported. Although the current literature estimates that 50–60% of melanoma patients are found to have GI metastasis on autopsy, only 2–4% are diagnosed during the course of their disease [5]. Furthermore, one tertiary GI referral institution cited just 7 cases of melanoma metastasis to the GI lumen over a 20-year period, typically limited to one luminal location [6]. This observation was consistent with several additional case reports in various GI distributions [7–9]. Among all, the small bowel is the most common luminal location of metastasis (58%), followed by the colon (22%), stomach (20%), and rectum (5%). The esophagus and gallbladder are rare sites of melanoma metastasis [10]. Prognosis for patients with metastatic melanoma in the GI tract is poor, with a median survival duration of 12.5 months and 5-year survival of just 14% [11, 12].

The risk factors for the GI metastasis from melanoma have not been well studied due to the limited number of cases. They are presumed to be related to sex; underlying cancer biologic/genetic factors such as presence of certain cytokines and their receptors, genetic mutations, and immune profile; response to cancer therapy; and other concurrent medications. Our unusual case of diffuse GI metastasis presentation from melanoma raises several potential contributing explanations. One is the extremely aggressive cancer behavior with continuous breakthroughs even after multiple lines of cancer therapies. Another contributing factor is the potential counteracting effects of immunosuppressive therapy that he received for the ICI-related GI toxicity. Corticosteroids have been reported to diminish the benefit of ICI therapy by impeding the body's natural T-cell response. A separate study found that duration of steroid exposure for immune-related adverse events (irAEs) was directly associated with both an increased risk of cancer progression and worse survival outcomes [13]. Specifically, vedolizumab could alter the body's tumor surveillance system by inhibiting the migration of antitumor immune cells to the gut and downregulating the existing number of CD8+ cytotoxic T cells in the gut. However, clinical data are still lacking to confirm vedolizumab's safety in patients with existing cancer [14]. A recent small scale study reported the favorable safety profile among patients with preexisting GI malignancy or GI metastasis who developed GI adverse events secondary to ICI. It is still unclear if the vedolizumab use and/or steroids contributed to this patient's rapid cancer progression. The remarkable delay of

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the onset of cancer progression after completing toxicity treatment suggests the causality hypothesis may not be fully supported.

Given the theoretical counteracting effect of immunosuppressive therapies on ICI treatment, alternative safer options should be explored when treating irAEs to maximize the survival benefit. Further large-scale studies are warranted to clarify the safety of immunosuppressant treatment for irAEs on the cancer outcome.

Statement of Ethics

The MD Anderson Cancer Center Institutional Review Board granted permission for chart review, and informed written consent to publish this case including pathology images was waived (protocol PA18-0472). Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Yinghong Wang serves as a consultant for Tillotts Pharma and AzurRx Pharma. The other authors declare no conflict of interest related to the study findings.

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Author Contributions

Yinghong Wang was the senior author of the study: developed the concept, designed the study, interpreted the results, ensured that data accuracy and integrity were preserved at all stages, agreed to be accountable for all aspects of the study, was in charge of the overall direction and planning of the study, and contributed to the writing of the manuscript, with input from all the authors. Gabriel Sperling collected the data for the study, conducted and interpreted the analysis, and wrote the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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