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Comment on “Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy”

Comment on “Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy”

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Abstract

We recently read with interest the original research article entitled "Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy". The abovementioned article is an observational retrospective cohort study, which could be of particular value to the clinicians to understand how immunotherapy affects the pre-existing enteral disease in inflammatory bowel disease patients. Although we appreciate the endeavor of Samuel Rubin *et al*, based on our in-depth analysis, we detected a potential shortcoming in this article; thus, we present our comments in this letter. In case the authors contemplate these comments in their relevant research, we believe that their contribution would be considerable for future studies.

Key Words: Inflammatory bowel disease; Immune-related adverse events; Immune checkpoint inhibitors; Immunotherapy; Malignancy

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Core Tip: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment owing to their ability to empower patients’ anti-neoplastic immune response. However, by empowering the immune system, ICIs can trigger off-site inflammation and autoimmunity, raising safety concerns every time these agents are considered for cancer patients with pre-existing autoimmune disorders such as inflammatory bowel disease (IBD). In this article, Samuel Rubin *et al* investigated how immunotherapy affects the pre-existing enteral disease in a cohort of IBD patients on ICIs; however, we detected several limitations that need further consideration. Therefore, we would like to share our views on this interesting study.

TO THE EDITOR

We read with great interest the original research article “Disease exacerbation is common in inflammatory bowel disease patients treated with immune checkpoint inhibitors for malignancy”^[1]. In this article, Rubin *et al*^[1] investigated how immunotherapy affects the pre-existing enteral disease in patients with cancer and inflammatory bowel (IBD). By retrospectively analyzing twenty years of data from cancer patients with pre-existing IBD exposed to immune checkpoint inhibitors (ICIs) at their center, the authors provided an insight into the prevalence of immune-mediated IBD exacerbation and subsequent clinical outcomes. Furthermore, the authors provided a detailed description of their entire cohort’s clinical characteristics aiming to set up the clinical phenotype of IBD patients who are at increased risk for immune-mediated IBD exacerbation and hence, are in increased need of more intensive clinical monitoring. Given the scarcity of relevant literature on ICIs in IBD, we greatly appreciate the dedication of the authors towards helping clinicians to understand the impact of

immunotherapy on IBD; however, through our in-depth reading, we came across several limitations and anticipate a discussion with the authors.

First, by carefully reviewing the methodology section, we noticed that in the absence of co-existent enteral infection, the diagnosis of IBD exacerbation was based only on several clinical features developed by IBD patients exposed to immunotherapy such as ¹new-onset bloody stool, rectal bleeding, diarrhea, and/or increased bowel movements. However, the abovementioned symptoms are not specific to IBD^[2]; hence, we believe that the addition of the endoscopic, the histologic, and the radiologic data of the study population in this article would have been of critical value for the authors to establish the diagnosis of IBD recurrence and should be supplemented.

Another methodological limitation of this study was that the authors did not make a clinical meaningful differentiation among the different causes that could have caused the development of enteral symptoms in their population. Previous studies of ICIs on IBD highlighted that the differential diagnosis in all cancer patients with pre-existing IBD should mainly include infections and immune-mediated colitis (IMC)^[3]. Although the authors in this study excluded gastrointestinal infections following ICIs, they omitted to include IMC in their differential diagnosis. The reason behind this exclusion was not mentioned by the authors; however, we believe that it is of particular value. Previous studies showed that IMC could occur at any time following immunotherapy complicating the management of cancer patients^[4]. The reported incidence ranges from 3 to 21% for mild and 5 to 17% for severe cases^[5]. Clinically, IMC is characterized by enteral symptoms that range in severity from mild diarrhea to severe enterocolitis with lethal complications, including perforation, ischemia, necrosis, bleeding, toxic megacolon, and death, mimicking IBD and making difficult the clinical differentiation between IMC and true IBD; however, colonoscopy with biopsy was highlighted by early studies in ICIs on IBD as a sensitive method to differentiate IMC from IBD exacerbation and should be considered for persistent or severe cases^[6-7]. Given the distinct nature of IMC, by not including IMC in the differential diagnosis of this study population, we believe that the study results are vulnerable to the misclassification

between IMC and true IBD, and we suggest the study results should be interpreted with caution.

However, despite the abovementioned limitations, we believe that this article can be a valuable reference study, helping clinicians holistically understand how immunotherapy affects the pre-existing enteral disease in inflammatory bowel disease patients. Thus, we offer our evidence-based considerations on this article to expand the value of the research basis that this article sets, leading to more comprehensive future studies.

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