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Review Article

Monoclonal Antibodies for Checkpoint Inhibitors and Sprue-Like Intestinal Disease

Hugh J Freeman*

Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada

***Corresponding Author:** Hugh J Freeman, Department of Medicine (Gastroenterology), University of British Columbia, Vancouver, BC, Canada.

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Abstract

Biologically active monoclonal antibodies functioning as checkpoint inhibitors have been used in cancer treatment with improved overall patient survival. Infusions may be complicated by development of diarrhea, sometimes severe. In some, an immune-mediated enterocolitis occurs, sometimes difficult to treat, occasionally with a fatal outcome. Less well appreciated are other less commonly detected forms of colitis, such as collagenous colitis, as well as alterations in the small bowel alone, including a distinctive sprue-like intestinal disease. These may all be entirely independent inflammatory processes. Together, these likely represent different phenotypic expressions of treatment toxicity in the intestinal tract following management of cancer with infused checkpoint inhibitor monoclonal antibodies.

Keywords: Celiac Disease; Sprue-like Intestinal Disease; Enteritis; Enterocolitis; Checkpoint Inhibitors; Advanced Malignancy; Metastatic Melanoma

In the past 10 years or so, immune checkpoint inhibitors have improved results of treatment for some cancers, particularly patient survival outcomes in melanoma, small cell lung cancer and renal cell carcinoma [1-4]. These biological agents, developed as monoclonal antibodies, promote survival of cytotoxic T-cells known to exhibit immune checkpoint proteins on their cell surface. For example, cytotoxic T lymphocyte-association protein 4 (CTLA-4) and programmed cell death protein (PD-1) are cell surface receptors that interact with their ligands on antigen-presenting cells. About a decade ago, ipilimumab (anti-CTLA-4) was initially approved for metastatic melanoma. Later, pembrolizumab and nivolumab (both anti-PD-1 agents) were employed for melanoma and non-small-cell lung cancer. Others, including atezolizumab, durvalumab and avelumab (anti-PD-ligand-1) have also appeared for some types of lung, breast and urothelial cancer as well as Merkel's type skin cancer.

Checkpoint inhibitor intestinal disease

All of these biological agents activate a global T-cell response that can result in several immune-related adverse events, particularly colitis [5-7]. At least 10% of patients develop diarrhea, apparently at a dose-dependent rate for ipilimumab [8] even though the precise mechanism for development of this inflammatory intestinal immune response in humans is not known. Other factors may play a role including changes in the intestinal microbiome, specific infectious agents (including *Clostridium difficile,* cytomegalovirus), and concomitant use of other medications, including non-steroidal anti-inflammatory drugs (i.e., NSAIDs). Increased activation of effector T-cells and memory T cells along with increased lymphocyte numbers in the intestinal mucosa occur [9,10]. Interestingly, more CD8+ T-cells were present in anti-PD-1- induced colitis, whereas

more CD4+ T -cells were present in CTLA-4-induced colitis [11]. Up to 30% to 40% of these patients may develop adverse intestinal effects, more severe with anti-CTLA-4 inhibitors [12].

Enterocolitis

Although colonic inflammatory disease caused by checkpoint inhibitors is reviewed elsewhere [6,7], small bowel inflammatory disease, or enteritis, may also concomitantly with colitis or independently from colitis [12,13]. Stated differently, different intestinal phenotypic expressions may occur with this form of treatment-induced toxicity. For example, acute inflammatory duodenitis and ileitis, but without colitis was reported in a patient with metastatic melanoma [14]. The small bowel disease was characterized endoscopically with visible erosions and aphthoid ulcerations, especially in ileum. Here, an associated immune-mediated hepatitis and arthritis was evident along with normal colonic mucosa. Resolution of symptoms resulted after treatment with steroids and infliximab. A similar case of "isolated enteritis" without colitis was also detailed in an 83 year old male with ipilimumab-associated severe diarrhea [13]. In this case, steroid management was provided. Thus, a normal colonoscopy may not be adequate to exclude small intestinal disease, possibly reflecting a later time-dependent appearance of the colitis, rather than a completely separate phenotype.

In addition, different colitis phenotypes have also been described with "atypical" forms of histopathologic expression. In a 68 year old female, pembrolizumab treatment was provided for stage IV melanoma. During cycle 14, development of severe diarrhea led to colon biopsies showing collagenous colitis, often associated with more persistent diarrhea. Symptomatic management with budesonide and cholestyramine even allowed continued use of the monoclonal agent [14]. Moreover, an entirely novel small intestinal disorder has been suggested in this setting distinct from the usual form of acute enteritis, likely with a different immunopathogenesis, sprue-like intestinal disease.

Sprue-like small intestinal disease with checkpoint inhibitors

Celiac disease is an immune-mediated enteropathy, often presenting with diarrhea and weight loss along with biopsy changes of untreated celiac disease [15]. Celiac disease is gluten-dependent and, usually, in most, biopsy abnormalities normalize over time with a strict gluten-free diet [16]. A number of disorders [17], particularly medications, like olmesartan, may cause a similar sprue-like enteropathy [18]. The histological changes in this drug-induced form of sprue-like enteropathy do not respond histopathologically to a gluten-free diet but can respond to drug removal.

A similar sprue-like intestinal disease has been reported following use of checkpoint inhibitors, including ipilimumab, pembrolizumab and nivolizumab, all agents causing diarrhea and weight loss. In some, but not all, underlying and undiagnosed celiac disease may have been present and precipitated by checkpoint inhibitor treatment. In some, no response to a gluten-free diet was documented. In others with similar sprue-like pathological changes, follow-up studies failed to confirm the gluten-dependent nature of celiac disease with histological evidence of a gluten-free diet response.

Ipilimumab-associated celiac disease was first described in a 62 year old male with prostatic adenocarcinoma and an ileal conduit [19]. After a second treatment infusion, watery non-bloody diarrhea developed. Colonoscopy appeared normal but histological evaluation of the colonic mucosa showed increased crypt apoptosis and mild crypt distortion. Features of collagenous or lymphocytic colitis were not present. No infectious pathogens were identified. Serum for IgA-antibodies to tissue transglutaminase were increased. Anti-enterocyte antibodies were negative. Duodenal biopsy revealed changes of untreated celiac disease (even though steroids were also concomitantly administered). After treatment with a gluten-free diet, diarrhea improved and the tissue transglutaminase assay normalized. Unfortunately, further follow-up after 20 weeks, including biopsies, was not noted. It was hypothesized that underlying celiac disease may have been present precipitated or amplified by ipilimumab. An alternative diagnosis may be that sprue-like intestinal disease may also have been present.

Similarly, a 74 year old male with metastatic renal carcinoma was also reported after treatment with a combination of ipilimumab and nivolumab [20]. Biopsies showed changes of villus atrophy and antibodies to tissue transglutaminase were elevated. While some duodenal biopsy features were thought to be atypical, a tentative diagnosis of celiac disease led to treatment with a gluten-free diet and budesonide. With continued treatment for 4

cycles of combination therapy, significant weight gain occurred but treatment had to be terminated because of evidence of disease progression. Again, repeat serological and histological studies were not reported.

In 2019, a 59 year old male with metastatic renal cell cancer was eventually required treatment with nivolumab [21]. Severe diarrhea occurred after a second parenteral dose, leading to hospitalization. Investigations showed hypoalbuminemia, decreased iron, folic acid and zinc. Impaired absorption was suggested. Calcium and magnesium levels were low. Small intestinal biopsy showed features of untreated celiac disease with subtotal villous atrophy including intra-epithelial lymphocytosis. Serological studies, however, including tissue transglutaminase antibodies, were negative. A gluten-free diet had no effect. A colonoscopy appeared to be normal. Intravenous steroids produced a dramatic positive effect with resolution of symptoms and normalization of blood studies. Six months later, another duodenal biopsy was normal. Thus, sprue-like biopsy changes developed acutely after a second checkpoint inhibitor infusion eventually responding to steroid treatment. Another case of severe diffuse sprue-like enteropathy with villous atrophy and negative celiac serological studies with collagenous colitis was described following nivolumab treatment [22]. The authors believed that this form of nivolimumab enteropathy was unusual and possibly reflecting an up-regulation of the T-cell response.

Later, a 79 year old male with metastatic melanoma treated with pembrolizumab was reported [23]. Serological studies were positive for anti-IgA-tissue trans-glutaminase and duodenal biopsy showed villous atrophy, classified as Marsh type IIIc. A gluten-free diet was provided, but not tolerated. However, symptoms resolved with cessation of pembrolizumab. Subsequent steroid treatment for the malignancy was provided and a further duodenal biopsy was not done. The authors thought that a similar up-regulation of T-cells may have occurred leading to this novel small bowel mucosal lesion. Interestingly, in this case, recurrent symptoms occurred with each monoclonal antibody infusion.

Conclusion

To conclude, these cases, taken together, suggest that a sprue-like small intestinal mucosal lesion may result from treatment with monoclonal antibodies that function as checkpoint inhibitors. In some, a clear differentiation from the changes in celiac disease were not documented. In others, unrecognized celiac disease may have preceded treatment but was precipitated or enhanced by checkpoint inhibitor infusions. Finally, in rare cases, a novel sprue-like intestinal disorder resulted that did not histologically improve with a gluten-free diet. Future studies may lead to further elucidation of the immune pathogenesis of this drug-induced small bowel lesion.

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