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Sprue-like Intestinal Disease Induced by Checkpoint Inhibitor Immunotherapy

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Abstract In recent years, immune checkpoint inhibitors have been increasingly used in cancer treatment with significant improvements in overall survival. A downside of these agents has been the emergence of novel intestinal diseases as reflected by development of diarrhea, sometimes severe, in at least 10%. In some, an immune-mediated enterocolitis may often develop. This may be severe, difficult to manage and result in a fatal outcome. Less well appreciated, however, are other less commonly detected forms of colitis, such as collagenous colitis, along with small bowel changes, specifically, sprue-like intestinal disease, apparently occurring as an independent inflammatory process. Taken together, these are likely to represent different pathological phenotypic expressions of treatment toxicity in the intestinal tract following management of cancer with checkpoint inhibitors.

Keywords: *celiac disease, sprue-like intestinal disease, enteritis, enterocolitis, checkpoint inhibitors, advanced malignancy, metastatic melanoma*

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1. Introduction

Over the past decade or so, immune checkpoint inhibitors have improved treatment results for some types of cancer, especially survival outcomes in melanoma, small cell lung cancer and renal cell carcinoma [1,2,3,4]. These agents promote survival of cytotoxic T-cells known to exhibit immune checkpoint proteins on their cell surface. 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. Ipilimumab (anti-CTLA-4) was initially approved for metastatic melanoma about a decade ago, followed by pembrolizumab and nivolumab (both, anti-PD-1) for melanoma and non-small-cell lung cancer. Other agents, including atezolizumab, durvalumab and avelumab (anti-PD-ligand-1) have also appeared for some types of lung, breast and urothelial cancer.

2. Checkpoint Inhibitor Intestinal Disease

Essentially, all of these agents activate a global T-cell response that can result in several immune-related adverse events, including colitis [5,6,7]. At least 10% are estimated to develop diarrhea, apparently at a dose-dependent rate for ipilimumab [8]. However, the precise mechanism for development of this inflammatory intestinal immune response in humans is not known. Other factors may play a role including the intestinal microbiome, other infectious agents (including *Clostridium difficile*, cytomegalovirus), and concomitant use of other medications, including non-steroidal anti-inflammatory agents. Increased activation of effector T-cells, increased memory T cells and increased numbers of lymphocytes in the intestinal mucosa occur [9,10]. Interestingly, in one study [11], more CD8+ T-cells were present in anti-PD-1-induced colitis whereas more CD4+ T -cells were present in CTLA-4-induced colitis. Up to 30% to 40% of these patients may develop adverse intestinal effects, more severe with anti-CTLA-4 inhibitors [12].

3. Enterocolitis

Although details are well reported and summarized elsewhere on checkpoint inhibitor colitis [6,7], small bowel inflammatory disease, or enteritis may also occur concomitantly with colitis or without colitis [12,13]. This suggests that there could be different intestinal phenotypic expressions for this type of treatment-induced toxicity. For example, one recent report [14] documented an acute inflammatory form enteritis in duodenum and ileum, but without colitis in a patient with metastatic melanoma. The enteritis was also characterized endoscopically with visible erosions and aphthoid ulcerations, especially in ileum. In this case, the intestinal disease was also associated with an immune-mediated hepatitis and arthritis and normal colonic mucosa. Resolution of symptoms resulted after treatment with steroids and 3 doses of infliximab (each, 5mg per kg). A similar case of "isolated enteritis" without colitis was also reported in an 83 year

old male with ipilimumab after 5 days of severe diarrhea [13]. Steroid management was sufficient. The authors concluded that 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. Interestingly, different inflammatory phenotypes of colitis have also been noted 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 endoscopic biopsies that showed collagenous colitis, often associated with a more chronic inflammatory process and a persistent diarrhea disorder. In this case, symptomatic management with budesonide and cholestyramine permitted continued use of pembrolizumab [14]. Similarly, a number of reports have suggested an entirely novel small intestinal disorder in this setting distinct from the usual form of enteritis, likely with a different immunopathogenesis, a so-called sprue-like enteropathy.

4. Sprue-like Enteropathy Associated 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. Figure 1 shows an example of a small bowel biopsy from a patient with diarrhea after ipilimumab. Here, no response to a gluten-free diet occurred. Interestingly, a number of other cases have been previously reported showing similar sprue-like pathological changes. Unfortunately, follow-up studies in most have failed to document the gluten-dependent nature of celiac disease with histological evidence of a gluten-free diet response.

A case of ipilimumab-associated celiac disease was first described in a 62 year old male with prostatic adenocarcinoma and an ileal conduit that eventually was treated with ipilimumab in a clinical trial [19]. After the second treatment infusion, watery non-bloody diarrhea developed that led to a visually normal colonoscopy but biopsy showed changes of increased crypt apoptosis and mild crypt distortion. No pathogens were identified nor features of collagenous or lymphocytic colitis. IgA-antibodies to tissue transglutaminase were positive without anti-endomysial antibodies. Anti-enterocyte antibodies were also negative. A duodenal biopsy showing features 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. The authors argued that the patient may have had underlying celiac disease precipitated or amplified by ipilimumab. Alternatively, sprue-like intestinal disease mimicking the biopsy changes of untreated celiac disease may also have been present.

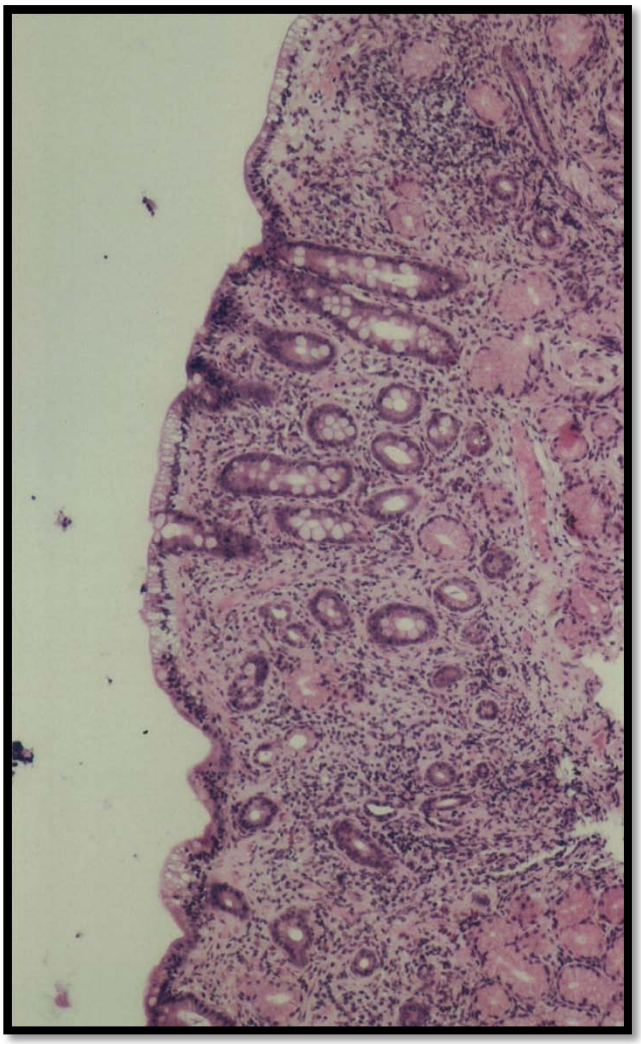

Figure 1. Hematoxylin-eosin stained duodenal biopsy showing typical histopathological "flattened biopsy" changes of celiac disease with villus atrophy with intra-epithelial lymphocytosis following ipilimumab treatment in an elderly male with metastatic melanoma. Serological studies were negative. Colonoscopy biopsies were normal. Repeat small bowel biopsies were unchanged after a gluten-free diet suggesting no histological response, characteristic of sprue-like intestinal disease

A similar case of a 74 year old male with metastatic renal carcinoma was also reported following combination 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. Weight gain resulted with continued treatment for 4 cycles of combination therapy, but treatment was 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 treated with nivolumab [21]. After the second injection, diarrhea developed requiring hospitalization. Blood studies suggested impaired absorption, including hypoalbuminemia, decreased iron, folic acid and zinc. Calcium and magnesium levels were low. An endoscopic duodenal biopsy reported subtotal villous atrophy with chronic duodenitis including intra-epithelial lymphocytosis. Serological studies, including tissue transglutaminase antibodies, were negative. Colonoscopy was normal. A gluten-free diet had no effect. Intravenous steroids produced a dramatic positive effect with resolution of symptoms and normalization of blood studies. Six months later, repeat duodenal biopsy was normal. Thus, sprue-like biopsy changes developed acutely after a second checkpoint inhibitor infusion eventually responding to steroid treatment. A similar case of severe diffuse sprue-like enteropathy with villous atrophy and negative celiac serological studies with collagenous colitis following nivolumab has also been noted [22]. Based on this information, the authors argued that this form of enteropathy with nivolimumab is unusual and differs from the usual type of enteritis with checkpoint inhibitors and may reflect an up-regulation of the T-cell response.

Most recently, a further case of a 79 year old male with metastatic melanoma was treated with pembrolizumab [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 not tolerated, but symptoms resolved with cessation of pembrolizumab and steroid treatment for the malignancy so a further duodenal biopsy was not done. The authors hypothesized that a similar up-regulation of T-cells may have occurred resulting in a novel small bowel mucosal lesion. Interestingly, the report also noted that recurrent symptoms occurred with each infusion.

5. Conclusions

Together, these cases suggest that a sprue-like small intestinal mucosal lesion may result from treatment with 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 immuno-pathogenesis of this drug-induced small bowel lesion.

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