An Unusual Etiology of Celiac Duodenopathy

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Abstract

Immune checkpoint inhibitors (ICPI) are an evolving therapy for treating various malignancies. However, as their use increases in medical management, the associated side effects become more prominent. These immune-related adverse events can include gastrointestinal complications and exacerbation of autoimmune disorders. Diarrhea is a commonly reported side effect in the literature, and colitis or enterocolitis are also frequently noted. Although current management is mainly symptomatic treatment, discontinuing immunotherapy is necessary if symptoms become severe. This case report presents a patient who started on Pembrolizumab therapy and subsequently developed abdominal pain and nausea. Endoscopic biopsy findings suggest Celiac duodenopathy; treatment with steroids and dietary modifications helped improve symptoms. It is important to note that ICPIs can induce autoimmune phenomena, including those affecting the small bowel. Therefore, a high index of suspicion is necessary when patients present with gastrointestinal symptoms during or after ICPI therapy. Close monitoring of patients on ICPI therapy is crucial to identify and manage any potential side effects promptly.

Introduction

Cancer cells have unregulated division as a characteristic. One mechanism by which they achieve this is through the downregulation of inhibitory ligands/receptors such as Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed Cell Death Receptor 1 (PD-1), and Programmed Death Ligand 1 (PD-L1), leading to unsuppressed proliferation [1]. Immune Checkpoint Inhibitors (ICPI) are effective anti-cancer drugs that enhance T-cell mediated killing of cancer cells by blocking these checkpoints. ICPIs may cause immune-related adverse events (irAEs). As their popularity and efficacy increase, the incidence of these adverse events becomes more prominent [2]. Currently, seven ICPIs targeting three different checkpoints are available: Ipilimumab and Tremelimumab for CTLA-4; Pembrolizumab and Nivolumab for PD-1; Atezolizumab, Avelumab, and Durvalumab for PD-L1 [3]. Diarrhea is a commonly reported gastrointestinal (GI) side effect of immunotherapeutic drugs [4]. It is essential to closely monitor patients on ICPI therapy for potential irAEs. Timely recognition and management of these adverse events are crucial to ensure patient outcomes.

Case Presentation

A 79-year-old male with metastatic melanoma to the left distal humerus, on therapy with Pembrolizumab, presented with nausea, vomiting, and fatigue. The patient reported a sweet taste with a dry mouth, hesitancy to swallow solids, loss of appetite, and weight loss over a week. The symptoms began when he started Pembrolizumab. Initial labs were notable for TSH of 59 mIU/L, otherwise unremarkable. The anti-thyroid peroxidase antibody was negative. The patient was started on Synthroid 50 mcg daily. He eventually underwent an esophagogastroduodenoscopy (EGD) for persistent symptoms. EGD showed diffuse mucosal edema and scalloping-like erosions in the duodenum, with severe esophagitis and mild gastritis. Duodenal biopsy revealed lymphocytic infiltration of the small bowel mucosa associated with atrophy and blunting of the villous border at the lumen of the bowel mucosa, suggesting celiac enteropathy. TTG and IgA antibodies were negative. The patient was treated with steroids and a gluten-free diet for suspected Celiac disease on biopsy findings resulting in improved symptoms.

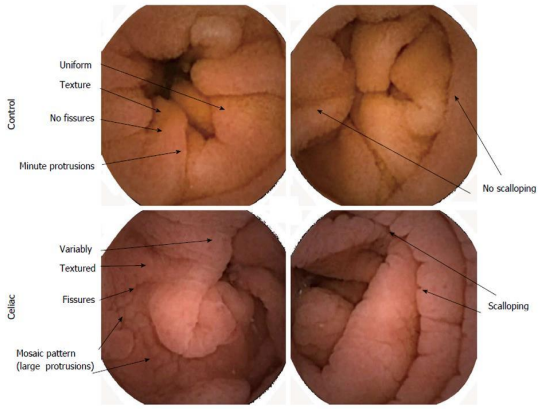

Figure 1: Figure depicting features of Celiac disease that can be observed on endoscopic visualization [5].

Discussion

Immunotherapeutic medication regimens have various indications, but one of great importance is treating malignancies. These drugs stimulate the body's immune system to attack cancer cells rather than directly targeting the tumor cells [4]. Unfortunately, as the body learns to attack these tumor cells, it may also attack healthy mucosa. Immune checkpoint receptors such as Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and Programmed Cell Death 1 (PD-1) receptors inhibit T cell function. Monoclonal antibodies targeting these checkpoints can stimulate cell death in tumor cells, thus improving therapeutic outcomes. Targeted pharmacotherapy against these receptors has effectively treated various cancer subtypes [6].

Toxicities are related to autoimmune phenomena, termed "immune-related adverse events". Gastrointestinal (GI) side effects are well known to occur with the administration of ICPI. Colitis and enterocolitis have been found in roughly 15-20% of patients on these medications who underwent endoscopy [7]. Ipilimumab, for example, is a monoclonal antibody against CTLA-4. It is associated with diarrhea in 1/3rd of patients and colitis in 7-22%. By inhibiting the regulatory function of T-cells, local erythema and inflammation can result [4].

Celiac disease is another such noted symptom that has been reported in the literature. Whether the medication precipitates the disease or exaggerates a previously asymptomatic state, both CTLA-1 and PD-1 help regulate the disease's autoimmune nature; with their effects diminished, there is decreased disinhibition of the autoimmune antibodies leading to exacerbations of the disease [8]. One case in the literature reported a patient developing nausea, diarrhea, and weight loss after a week of Ipilimumab for metastatic renal cell carcinoma (RCC). Biopsies were positive for gastritis, duodenitis, erosions, neutrophilic cryptitis, and villous atrophy; these are some characteristic findings of Celiac disease [2].

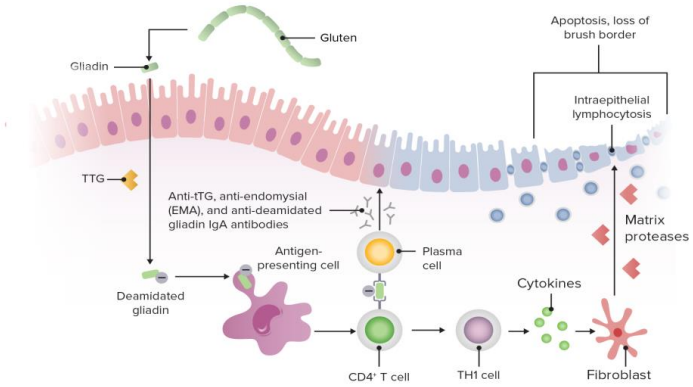

Figure 2: Figure depicting the autoimmune mechanism of Celiac disease resulting in brush border blunting [9].

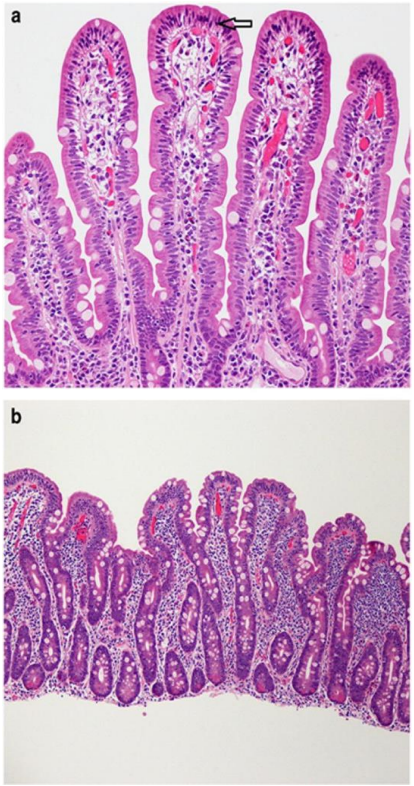

Figure 3: Typical histopathologic findings of villous atrophy and brush border blunting as associated with Celiac disease [10].

Pembrolizumab, a monoclonal antibody to PD-1 receptors, has been shown to potentiate antitumor responses in patients with advanced melanoma. To our knowledge, there have not been many specific associations between Pembrolizumab and Celiac disease, although T-cell and macrophage infiltration and antibody deposition have been hypothesized [11]. We suspect that using Pembrolizumab potentiated the clinical presentation of Celiac disease without positive serological evidence. One case was reported of a patient who developed abdominal pain and diarrhea after six months of Pembrolizumab therapy despite being concurrently treated with steroids. Biopsies were significant for erosions, lymphoplasmacytic inflammation, and elevation of intraepithelial lymphocyte count [12].

GI hemorrhage is another complication that could potentiate secondary to chronic inflammation. Very few cases of bleeding have been documented in the literature. One study noted a patient on Atezolizumab therapy for small-cell lung cancer who presented with hematemesis and abdominal pain. Emergent endoscopy revealed bleeding erosions and ulcers requiring clipping and cauterizations. Tissue biopsies showed eosinophils, lymphocyte infiltration, and plasma cells [13]. These patients should be closely monitored as the recurrent inflammation and bleeding may weaken the mucosa to the point of perforation [3].

Peripheral tolerance is part of the body's immune response to help prevent self-reactive T and B cell escape or activation. By inhibiting these checkpoints, there is the potential to exacerbate various autoimmune pathologies. Worsening hypothyroid symptoms, for example, have been noted after the immunomodulating regimen initiation [14].

Management

Interventions for patients who experience GI side effects may depend on the nature and location of the symptoms. Those who experience hematochezia and diarrhea, for example, may warrant colonoscopy. On the other hand, those who experience nausea, reflux, and dysphagia may benefit more from EGD. In both cases, biopsies are crucial in further evaluation. In one study, ~63% of patients who underwent colonoscopy for persistent diarrhea were found to have ulcerations and erythema [4].

Initial management can be as simple as targeting symptoms. If not severe, for example, diarrhea can be treated with antidiarrheals without having to discontinue the therapy. Medication discontinuation would be indicated when more severe, however, with episodes of greater than six watery bowel movements per day [4]. Gluten-free diets (GFD) have also decreased symptoms [2]. In one study, GFDs helped improve GI symptoms in patients with Celiac disease by up to 65.6% [15]. Further evaluation via fecal calprotectin and lactoferrin can help distinguish diarrhea and whether it has an infectious vs. inflammatory etiology, in which case appropriate therapy, for example, antibiotics vs. steroids, can be initiated [16] for those refractory to steroid therapy, Infliximab or fecal microbiota transplant may be used [3].

As various autoimmune disorders can be precipitated, cases have been known of worsening hypothyroid symptoms; treatment can be either initiation or appropriate dose adjustments of thyroid supplementation (as seen with our patient). Those with worsening acid reflux-type symptoms can also be treated with anti-emetics and Proton Pump Inhibitors (PPIs). Due to concern for ulcerations and bleeding, patients on immunomodulating medications should be counseled to minimize NSAID use.

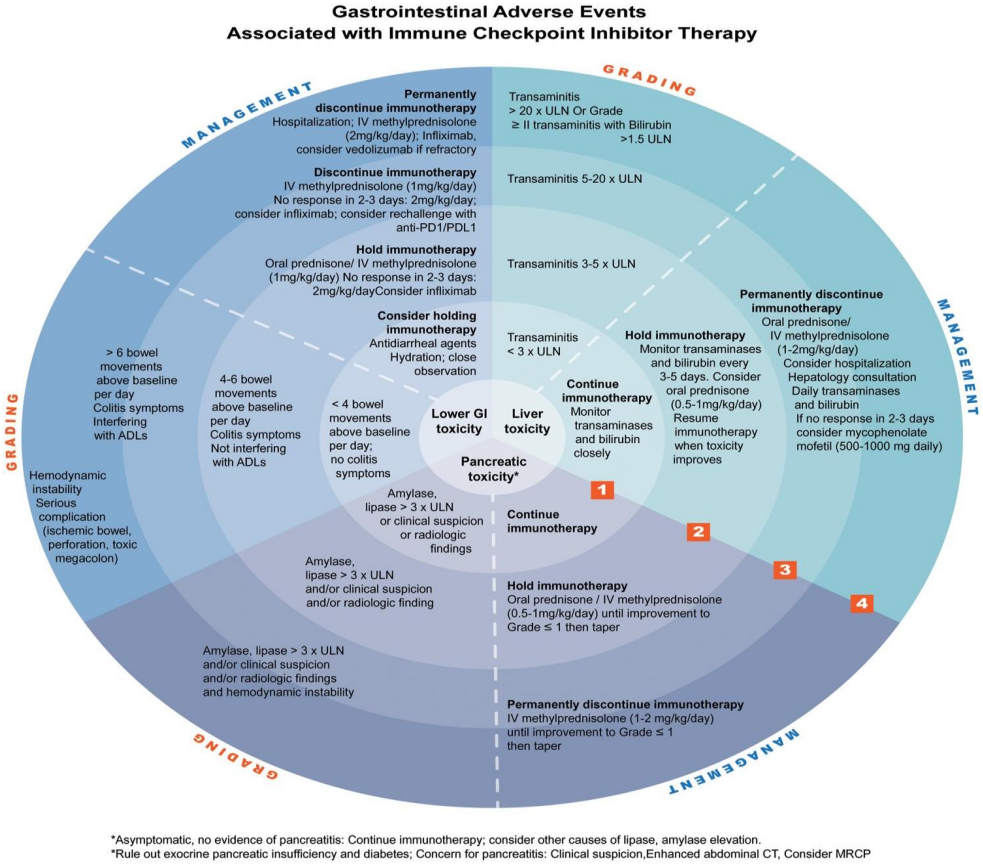

Figure 4: Figure depicting grading symptoms of various GI side effects with their associated recommended management strategy [16]

Conclusion

Immune checkpoint inhibitors have proven practical tools in managing patients with various malignancies. As their popularity increases, however, so does the occurrence of immune-related adverse events. Diarrhea is one of the most common side effects of ICPI treatment. The decreased cytotoxic regulation effect may exacerbate localized inflammation and autoimmune disorders complications. Management options for these adverse events include dietary modifications and symptomatic relief with antidiarrheals, while discontinuing immunotherapy is considered in severe cases. Celiac disease has been hypothesized to be an irAE; however, whether it is due to a new onset or worsening of a previously silent disease remains unclear. Although some cases have been overall associated, more studies need to be performed to confirm the correlation of these ICPIs with Celiac disease.

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