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CASE REPORT

Immune checkpoint inhibitor therapy associated enteritis mimicking celiac disease

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ABSTRACT

A 68-year-old man with a previous history of lung cancer presented with deteriorating appetite and weight loss. Imaging revealed significant retroperitoneal lymphadenopathy, as well as liver and bone lesions consistent with widespread metastatic carcinoma. Biopsy results from the liver lesions confirmed the diagnosis of metastatic non-small cell lung carcinoma. A PDL-1 immunostain, performed on the initial lung resection specimen, showed a combined positive score (CPS) of 15 and pembrolizumab treatment was initiated. The patient presented with diarrhea three weeks after starting therapy and duodenal biopsies obtained at this time displayed intact villous architecture with an increase in intraepithelial lymphocytes (IELs). The colon biopsies exhibited lymphocytic colitis, characterized by significant thinning of the surface epithelium, a higher mixed inflammatory infiltrate within the lamina propria, and diffuse increase of IELs (greater than 30 per 100 epithelial cells). These findings collectively raised the differential diagnosis of celiac disease with lymphocytic colitis or immunotherapy-associated enterocolitis. Further serological testing for celiac disease, including anti-tissue transglutaminase antibodies, yielded negative results. Consequently, a final diagnosis of immune adverse event associated with immunotherapy was established. Cases reported in literature as celiac disease occurring soon after immunotherapy are likely misdiagnosed cases of immunotherapy enteritis.

Keywords: Non-small cell lung carcinoma, Celiac disease, Pembrolizumab, Duodenal biopsy.

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Introduction

The histological differential diagnosis of celiac disease is broad and includes medication associated mucosal injury (1). We report a patient with pembrolizumab (Immune checkpoint inhibitor) associated enteritis that is a pitfall that may lead to misdiagnosis of celiac diseases.

Case report

A 68 year old man with a past history of lung cancer presented with worsening appetite and weight loss. Imaging showed marked retroperitoneal lymphadenopathy and liver and bone lesions consistent with widely disseminated metastatic carcinoma. Biopsy of the liver lesions confirmed the diagnosis of metastatic non-small cell lung carcinoma. A PDL-1 immunostain performed on the original lung resection specimen showed a combined positive score (CPS) of 15 and the patient was started on pembrolizumab. The patient presented with diarrhea three weeks after initiation of immunotherapy and upper and lower endoscopy was performed.

Upper endoscopy showed a normal esophagus and stomach. The duodenum showed mild, non-specific alterations with patchy erythema. Similarly, colonoscopy showed a normal rectum and sigmoid with small foci of erythema and erosions scattered throughout the remainder of the colon. Multiple biopsies were obtained from the gastrointestinal tract.

The esophageal and gastric biopsies showed a normal microscopic appearance. The duodenal biopsies showed intact villous architecture with increased intraepithelial lymphocytes (IELs). Peak IEL count was 35 per 100 epithelial cells (Figure 1a-b). The intraepithelial lymphocytosis was predominantly seen in the villous

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compartment of the mucosa with relative sparing of the crypt epithelium. Foci of active (neutrophilic) intraepithelial infiltration or prominent lamina propria eosinophils were not identified. The colon biopsies showed a lymphocytic colitis pattern of injury with marked attenuation of the surface epithelium, increased mixed inflammatory infiltrate in the lamina propria and diffusely increased IELs (>30/100 epithelial cells). The constellation of findings raised the differential diagnosis of celiac disease with lymphocytic colitis versus immunotherapy associated enterocolitis. Additional serological workup for celiac disease, including anti-tissue transglutaminase antibodies, was negative and a final diagnosis of immune adverse event in the setting of immunotherapy was established.

Discussion

The past decade has seen increasing use of immunotherapy in the management of cancer patients. Treatment with immune checkpoint inhibitors has been shown to prolong disease-free survival, and also durable curative responses in a subset of patients (2). The immune checkpoint inhibitors are antibodies that are targeted to block regulatory signals dampening the immune response. This counteracts the immune suppression in the tumor microenvironment and thereby promotes tumor-reactive T lymphocytes to mount an anti-cancer response. Ipilimumab targets cytotoxic T lymphocyte antigen-4 (CTLA-4) and was first approved for management of advanced malignant melanoma (3). Currently, the FDA-approved immune

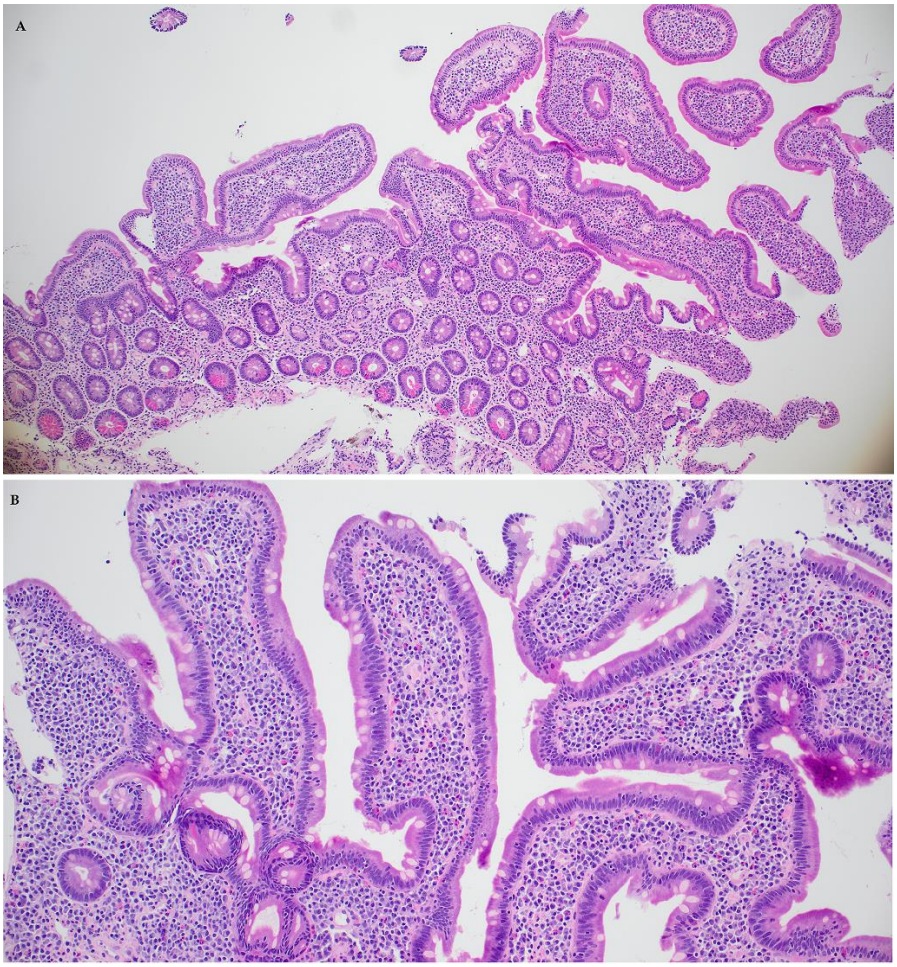

Figure 1. The duodenal biopsy shows normal villous architecture (a) and a closer look at slightly higher magnification shows increased intraepithelial lymphocytes (b) that were formally counted and showed a peak count of 35 per 100 epithelial cells. The differential diagnosis includes celiac diseases versus its many mimics on histology. The final diagnosis in this case was immunotherapy associated enteritis.

check point inhibitors fall in to two major categories: (i) those targeting the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) axis (nivolumab, pembrolizumab and atezolizumab); (ii) those targeting the cytotoxic T lymphocyte antigen-4, i.e., CTLA-4-CD28 axis (anti-CTLA-4 antibodies). The immune check point inhibitors have been proven to be effective in the management of metastatic melanoma, and carcinomas of lung, ovary, kidney, and prostate origin and other solid tumors (4). However, approximately 70% of patients receiving immune check-point inhibitors experience side effects, which are often referred to as immune-related adverse events. These side effects can involve one or multiple organs. The most affected organs include skin, gastrointestinal tract, liver, lung, and endocrine glands (5-7).

Gastrointestinal manifestations of immunotherapy toxicity vary by site. Esophageal involvement is uncommon manifests as superficial erythematous erosions or diffuse mucosal nodularity that on microscopy shows patchy peri papillary increase in intraepithelial lymphocytosis with scattered necrotic epithelial cells (8,9). Gastric involvement is relatively more common compared to the esophagus, and patients usually present with nausea and vomiting. This is more commonly seen with patients receiving combined CTLA-4 and PD (L)1 inhibitor (25%) than monotherapy with CTLA-4 inhibitor (19%) or PDL1 inhibitor (12%) alone (7). The gastritis pattern of injury mainly falls in to two categories, diffuse chronic active gastritis pattern and focally enhanced gastritis pattern. Most patients show a diffuse chronic gastritis pattern

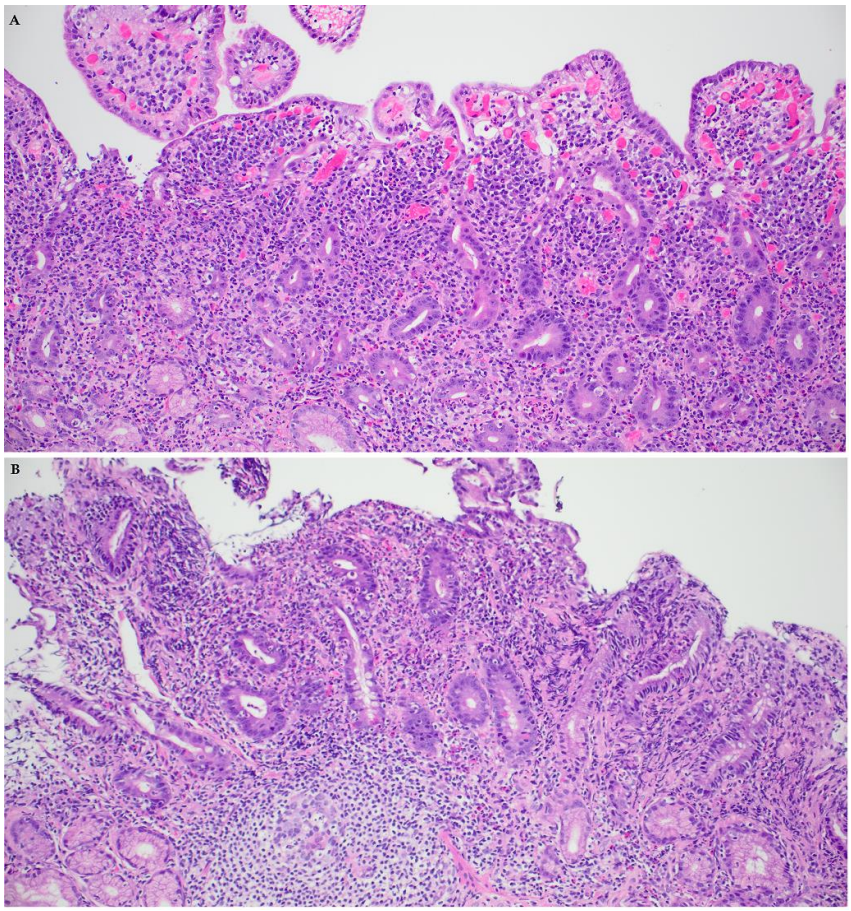

Figure 2. A different case of immunotherapy enteritis that shows marked villous blunting and increased inflammatory infiltrate in the lamina propria (a). At a cursory glance, this resembles a Marsh 3 lesion of celiac disease. However, on closer inspection there is marked cryptitis and erosion of the surface epithelium (b) which resembles duodenal involvement in inflammatory bowel disease more than celiac disease. This constellation of findings can also be seen in immunotherapy associated enteritis and in this case was due to ipilimumab therapy for malignant melanoma (12).

with active neutrophilic infiltration in the surface or pit epithelium, prominent intraepithelial lymphocytosis and apoptosis (10). These findings overlap with H. pylori gastritis but special stains for microorganisms are negative in immunotherapy gastritis and the clinical context is key in making this diagnosis. In the duodenum, immune check point inhibitor related toxicity can show erythema, erosion, ulcer, and stricture on endoscopy (11). Histologic findings span a spectrum from normal villous architecture with increased IELs mimicking celiac disease to a severe chronic active duodenitis with flat mucosa, markedly increased lamina propria inflammation, intraepithelial neutrophilic infiltration, and patchy lymphocytosis, and scattered apoptotic bodies (Figure 2a-b) (12). This combination of active inflammation, increased IELs and apoptosis has been suggested to be useful in diagnosis of immunotherapy enteritis, but all features are only present in a subset of patients (13). The villous blunting and increased IELs mimic celiac disease and lymphoplasmacytic expansion of the lamina propria leads to complete or partial villous blunting. Misdiagnosis can occur if histology alone is used to make a diagnosis of celiac disease in this setting. Some cases reported in literature as 'celiac disease' occurring soon after initiation of immunotherapy are examples of this pitfall (14, 15). Serologic testing is helpful in distinguishing immune check point inhibitor induced enteropathy from true celiac disease. Symptomatic response following gluten withdrawal alone is also insufficient for a credible diagnosis of celiac disease in this setting. Another helpful feature is presence of concurrent gastritis or colitis, which favor an immune related adverse event involving the gastrointestinal tract. This was also present in our patient described above. The colon biopsies showed a lymphocytic colitis pattern of injury that is well described in this clinical setting. Endoscopically, the colonic mucosa can show erythema, alteration of vascularity, granularity, and mucosal ulcers and on rare occasions, can be essentially normal (16). The microscopic changes range from an active colitis mimicking infection, to a chronic active colitis mimicking inflammatory bowel disease to a microscopic colitis similar to lymphocytic and collagenous colitis seen in a sporadic setting. The pattern of colitis can vary with the medication used. The anti-CTLA-4 (ipilimumab)-induced colitis usually shows a diffuse active colitis pattern of injury whereas the lymphocytic and collagenous colitis patterns of injury are more often seen with pembrolizumab (17).

The differential diagnosis of celiac disease with normal or near normal villous architecture and increased IELs (Marsh 0 or 1) is broad and includes a variety of disorders including infections, such as Helicobacter gastritis, tropical sprue, immunodeficiency disorders such as CVID, autoimmune enteropathy, Crohn's disease and drug induced mucosal injury. The anti-hypertensive medication olmesartan and immunotherapy medications mentioned above are the most recent additions to the list of drugs (18) that may cause histologic alterations mimicking celiac disease in duodenal biopsies. Pathologists should be aware of this phenomenon and ensure they gather relevant patient history and order additional work up to avoid misdiagnosis of celiac disease.

Conflict of interests

The authors declare that they have no conflict of interest.

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