

Immune-related acute and lymphocytic gastritis in a patient with metastatic melanoma treated with pembrolizumab immunotherapy

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Summary

Here, we present a case of acute and lymphocytic gastritis related to therapy with pembrolizumab for metastatic melanoma. After an asymptomatic phase with moderate histological inflammation (observed at 9 months of immunotherapy), gastritis became symptomatic and severe on repeated biopsies (13 months after the beginning of pembrolizumab). Symptoms and histological lesions both improved with proton pump inhibitor and steroid therapy, as well as interruption of pembrolizumab. The interest of this case lies in the relative rarity of gastritis over small and large intestinal inflammatory lesions caused by immune checkpoint inhibitors as well as in the features of the inflammatory infiltrate, which may be purely lymphocytic (mainly T-cells, with a prevalence of CD8+ over CD4+ lymphocytes) or mixed lymphocytic and granulocytic, requiring the exclusion of other causes of disease. To our knowledge, only 7 cases of immune-related gastritis have been previously documented in the current literature, of which 4, included the current one, were exclusively associated with pembrolizumab therapy.

Key words

Immune checkpoint inhibitors • Immune-related adverse events • Pembrolizumab-related gastritis • Cancer therapy • Oncology

Background

Immune checkpoint inhibitors, such as the Programmed Death-1 Receptor (PD-1) inhibitor pembrolizumab, have been shown to be effective in primary or metastatic malignancies, including advanced melanoma ¹.

The side effects of immune checkpoint inhibitors are referred to as immune-related adverse events (irAEs) and may affect several organs.

Colitis and diarrhea are among the common gastrointestinal (GI) adverse events. Upper GI symptoms (i.e. nausea and vomiting) are also possible, but have rarely been reported.

Immunotherapy with monoclonal antibodies targeting Cytotoxic T-Lymphocyte-associated Antigen 4 (CTLA4) as well as PD-1 inhibitors, both blocking the interaction between PD-1 and its ligands (PD-L1 and PD-L2), has become the standard of care

for an increasing number of indications, including melanoma, for which it is indicated regardless of the PDL-1 immunohistochemical score. Depending on the immune checkpoint targeted, the incidence of toxicity varies. The most frequently occurring irAEs affect the skin, colon, endocrine organs, liver, and lungs ². Clinical manifestations in the GI tract, range from asymptomatic to severe life-threatening complications (e.g., perforation).

A retrospective study published in 2017 includes a consecutive series of 909 adult patients who received anti-PD-1 or anti-PD-L1 therapy, 19 of whom had a suspected gastrointestinal irAE (GI-irAE) related to anti-PD-L1 therapy administered between 2013 and 2016, and suggests that GI-irAEs associated with anti-PD-1 or anti-PDL-1 inhibitors are much less frequent than those associated with CTLA-4 inhibitors (1-3% vs 8-20%). The authors described four distinct

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clinical presentations, each with different features and outcomes, the most frequent ones being acute colitis and microscopic colitis and, rarely, ulcerative gastritis and fecal impaction ³.

A clinicopathologic study of 20 patients treated with immune checkpoint inhibitors reported characteristic findings of gastroenterocolitis, including prominent intra-epithelial lymphocytes and crypt rupture, essentially focused on histologic findings in the colon rather than in the stomach ⁴.

We could only identify seven case reports of upper GI disorder induced by immune checkpoint inhibitors ⁵⁻¹¹. Two cases were associated with cytomegalovirus (CMV) or *Helicobacter pylori* (HP) infection ^{8,11}. Of the remaining five cases, two were observed after therapy with nivolumab ^{9,10} and the other three after therapy with pembrolizumab ⁵⁻⁷ (Tab. I). All these patients were symptomatic with abdominal/gastric pain or symptomatic gastroesophageal reflux disease (GERD). Symptoms started one to few months after initiation of immunotherapy. In one case, thoraco-abdominal CT imaging revealed extensive thickening and edema in the wall of the upper GI tract ⁵. In another case, an esophagogastroduodenoscopy showed severe hemorrhagic antral gastritis ⁷. Histologically, all cases showed an active and lymphocytic gastritis in which the infiltrate was mainly composed by CD8+ T cells. The clinical and histological findings for gastritis induced by nivolumab were comparable. The histological findings in our case are similar to a previous report, but in

contrast our patient was asymptomatic when gastric inflammation was already observed histologically. Treatment included short-term steroid therapy and treatment for concomitant pre-existing GERD.

Lymphocytic gastritis related to immune checkpoint inhibitors shows an intraepithelial and lamina propria distribution pattern of lymphoid infiltration ¹². Immunostaining identified these lymphocytes as CD 3+ T-cells, among which CD8+ predominate over CD4+. Symptoms or lesions generally manifest after several weeks of therapy, but late onset of irAEs may also occur several weeks or even months after termination of immunologic therapy. Corticosteroids are the treatment of choice for irAEs, but infliximab may also be considered in second-line. Interruption of immunotherapy should be considered only when severe clinical and/or histological inflammation is observed because of the risk of bowel perforation.

The mechanisms underlying the pathology of immune-related adverse events are not completely known yet, although several mechanisms have been proposed; they are rather extensively reviewed in the paper by Passat et al. ¹³ and include both specific (on target) and non-specific (off target) toxicity to cancerous and healthy tissues.

Tab. I. Table summarizing the four reports dealing with PD-L1 inhibitors (pembrolizumab) and related adverse gastric events.

First author, year (reference n.)	Time ^a	Symptomes	EGD ^b	Histologic features of gastric biopsies
Gaffuri, 2019	9 months (12 cycles)	Asymptomatic	Diffuse mucosal erythema	Moderate lymphoplasmocytic and neutrophilic infiltration in the lamina propria with cryptitis, crypt abscesses and increased intraepithelial T-cell (CD3+) lymphocytes with CD8+ > CD4+
	13 months (19 cycles)	Nausea, vomiting and gastric pain	Diffuse mucosal erythema	Severe active and chronic inflammatory infiltrate.
Onuki, 2018 ⁵	16 th day of the seventh cycle therapy	Fever, anorexia and abdominal pain	Erosion in gastric fundus and upper corpus and mottled reddening near the pyloric ring	Lymphocyte-dominant infiltration in the lamina propria
Yip, 2018 ⁶	1 month	Symptomatic gastroesophageal reflux disease (GERD)	Hiatal ernia	Lymphocytic gastritis with increased intraepithelial lymphocytes CD3 and CD8+
Rao, 2019 ⁷	After then cycles therapy	Intense, cramping, non radiating epigastric pain	Severe hemorrhagic antral gastritis	Florid active gastritis with dense neutrophilic infiltrate of the lamina propria and gastric glands. Prominent intraepithelial T-cell lymphocytosis CD8+ more than CD4+

^a: time passed between the first dose Pembrolizumab and the adverse event; ^b: esophagogastroduodenoscopy.

Case report

A 75-year-old white man with a previous cystectomy for a pT2 urothelial bladder carcinoma was diagnosed with a stage IB cutaneous melanoma of the back in 2013. He underwent wide skin local excision and right axillary sentinel lymphadenectomy. One year later, he was treated with surgery and adjuvant radiotherapy for a right axillary node metastasis. In 2017, a solitary lung metastasis was treated with wedge resection. On March 2018, a positron emission tomography-computed tomography (PET-CT) identified additional metastases at multiple sites (skin-soft tissues, lymph nodes, lung, pleura, bone, liver, pancreas, stomach, right adrenal gland and peritoneum) (Fig. 1A). All the metastases were from melanoma. A biopsy of the peritoneal metastasis was performed and Next Generation Sequencing (NGS) examination identified a wild type BRAF, mutation Q61K in NRAS 3 and mutation G923R in ERBB 423. In April 2018, treatment with pembrolizumab (Keytruda®) was initiated at a flat dose of 200 mg every 3 weeks.

Partial remission was observed with PET-CT after 3 months (4 cycles) of treatment, persisting after an additional 6 months (further 8 cycles), without significant side effects (Fig. 1B, C).

A third PET-CT demonstrated diffuse abnormal low-level uptake in the stomach wall, consistent with an inflammatory state (Fig. 2). This finding was not noted in the second PET-CT performed after 3 months of pembrolizumab, where no abnormal gastric uptake was observed. An esophagogastroduodenoscopy (EGD) was performed, which showed diffuse mucosal erythema, without macroscopic suspicion

of malignancy. The patient was asymptomatic and already undergoing proton pump inhibitor therapy (pantoprazole 20 mg/day) for GERD, which was already known and treated before the beginning of pembrolizumab. Biopsies of the gastric body and antrum showed moderate lymphoplasmocytic and neutrophilic infiltration in the lamina propria with cryptitis, crypt abscesses and increased intraepithelial lymphocytes (IELs). Apoptotic bodies and eosinophilia were not observed. The lymphocytic infiltrate was mainly composed of CD3+ T cells, among which CD8+ prevailed over CD4+ (Figs. 3, 4), and some CD20+ B cells. There was no histological or immunohistochemical evidence of HP or CMV infection.

We suspected that the gastric inflammation was related to pembrolizumab therapy. Therefore, although the patient was asymptomatic, he was advised to increase pantoprazole to 40 mg/day and to start oral prednisone therapy (1 mg/kg/day), to prevent the possible occurrence of symptoms or worsening of the inflammation. However, immunotherapy with pembrolizumab was not interrupted at this stage. Due to the potential risk of weight gain, the patient decided to stop prednisone after only one week. In a follow-up PET-CT, after further 6 cycles of pembrolizumab (total 18 cycles), despite general clinical improvement of the patient's conditions, an isolated progression of the lesion in the right adrenal gland was radiologically observed, which was confirmed to be metastatic melanoma upon adrenal resection.

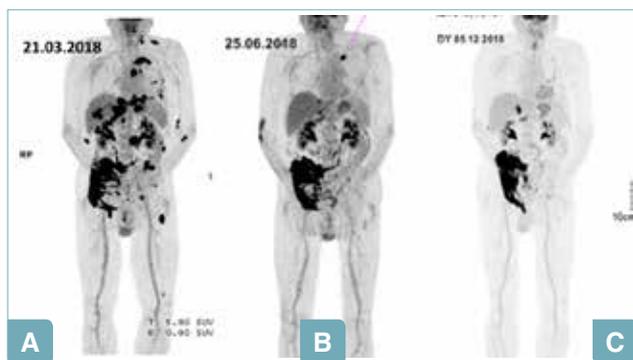


Fig. 1. (A) Initial PET-CT (March 2018) showing multiple metastatic lesions to the lymph nodes, left pleura, liver, pancreas, peritoneum, right adrenal gland, stomach, skin-soft tissues and bone; (B) PET-CT after 3 months (4 cycles); and (C) after additional 6 months (further 8 cycles, total 12 cycles) of therapy with pembrolizumab, demonstrating a very good response to therapy.

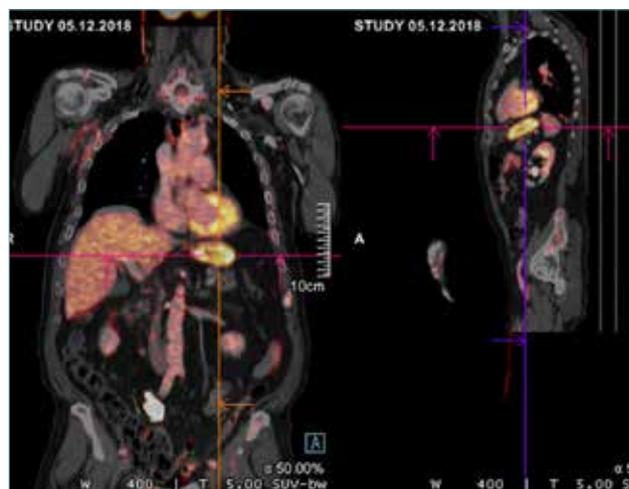


Fig. 2. PET-CT after 12 cycles showed also a diffuse abnormal low-level uptake in the stomach, consistent with an inflammatory state.

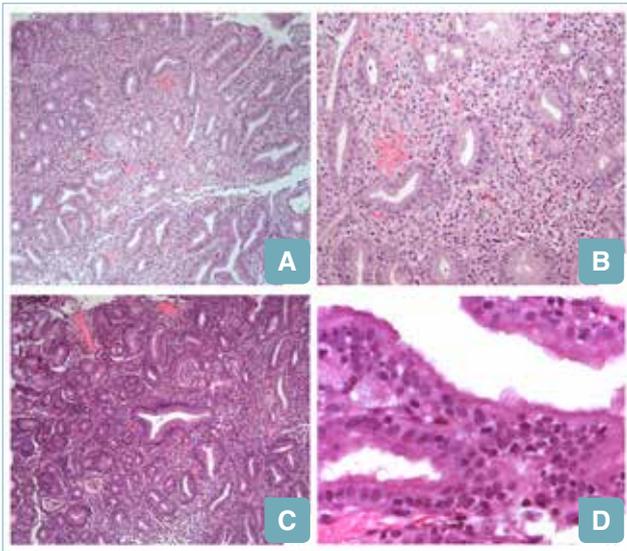


Fig. 3. Endoscopic biopsies of the gastric antrum (A) showing a moderate active and chronic inflammatory infiltrate involving both the epithelium (of glands and of surface) and the lamina propria (H. & E. 200 X). At high power magnification a florid active gastritis with cryptitis (B), crypt abscesses (C) and increased intraepithelial lymphocytes (D) was observed (H. & E. 400 X).

After adrenal surgery, the patient received the nineteenth cycle of pembrolizumab followed by complaints of nausea, vomiting and gastric pain. A gastroscopy was repeated which demonstrated a worsened diffuse mucosal erythema. The biopsy samples taken from the gastric corpus and antrum both demonstrated a severe active and chronic inflammatory infiltrate, characterized by lymphoplasmocytic expansion of lamina propria with some eosinophils, crypt abscesses, erosion of the mucosal surface, and focal thinning of the of the gastric glandular epithelium, though intraepithelial lymphocytosis was no longer observed (Fig. 5).

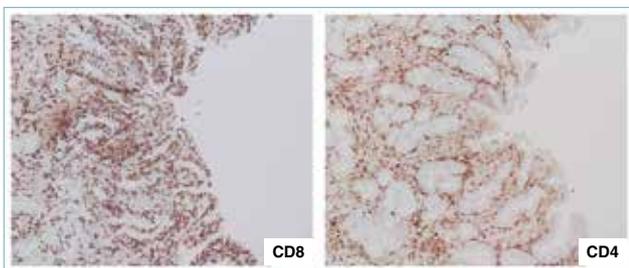


Fig. 4. Intraepithelial and lamina propria CD8+ T cells infiltrate with few CD4+ T cells restricted to the lamina propria (Immunoperoxidase, 200 X).

Due to the worsening of gastritis and the presence of symptoms, pantoprazole was increased to 120 mg/day and prednisone 0.5 mg/kg/day was introduced with resolution of symptoms.

Since symptoms and inflammation related to the second episode of gastritis were more severe, pembrolizumab treatment was terminated. Seven weeks later, in June 2019, a PET-CT was performed again showing a complete remission of the metastatic disease and disappearance of the abnormal gastric uptake (Fig. 6). Repeated gastric biopsies performed in the same days confirmed an improvement of the inflammatory state, with only some moderate chronic inflammation left with focal gland atrophy, without an acute infiltrate and/or intraepithelial lymphocytosis (Fig. 7).

Differential histopathological diagnosis

An increase in the number of gastric IELs can occur in association with a variety of conditions, including HP infection, celiac disease, Human Immunodeficiency Virus (HIV) infection, Ménétrier’s disease, Crohn’s disease and lymphocytic or collagenous colitis. Lymphocytic gastritis is diagnosed when the gastric surface and foveolar epithelium are infiltrated by at least 25 IELs per 100 epithelial cells, regardless if an additional lympho-plasmocytic expansion of the lamina propria is present or not. These lymphocytes

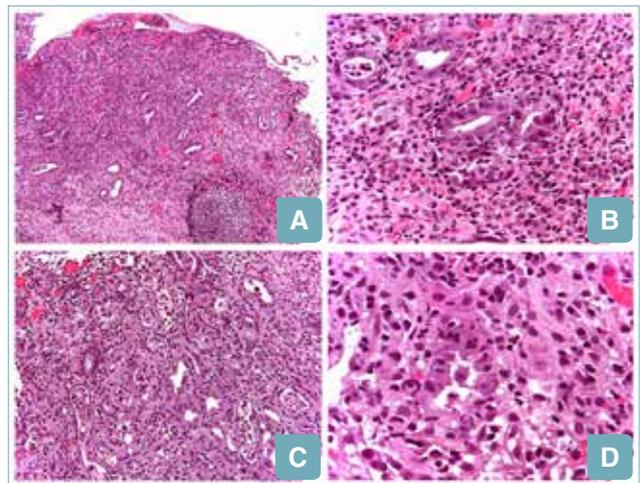


Fig. 5. Gastric biopsies taken 13 months (May 2019) after initiation of immunotherapy. (A-B) antrum (H & E, 100x and 400x); and (C-D) corpus (H & E, 100x and 400 x) both showing an important active and chronic inflammatory infiltrate, with some eosinophils, crypt abscess and erosion of the mucosal surface. The epithelial lining of the gastric glands often present a thinned aspect.

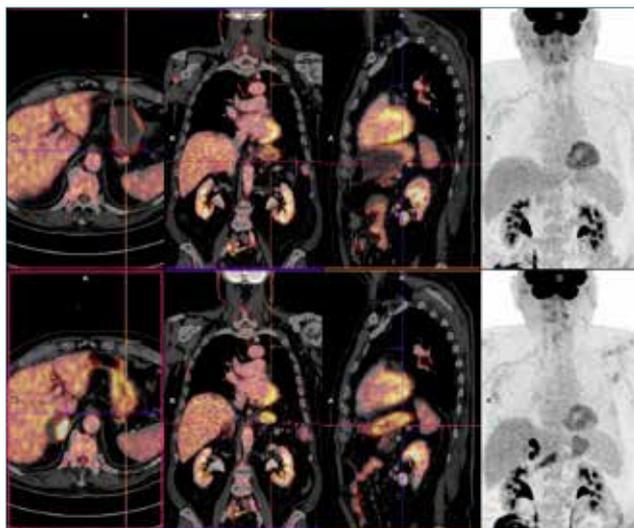


Fig. 6. PET-CT performed 7 weeks after interruption of pembrolizumab showing complete remission of the metastatic disease and absence of the abnormal gastric uptake.

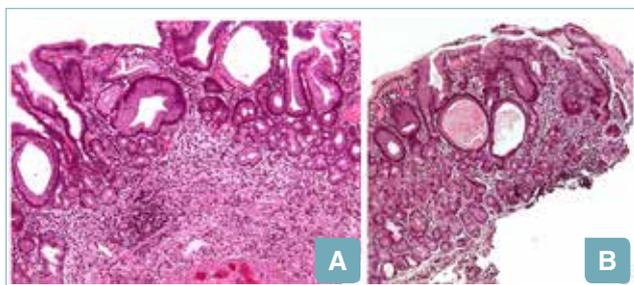


Fig. 7. Gastric biopsies taken in June 2019, 7 weeks after interruption of pembrolizumab, showing only moderate chronic gastritis in antrum (A) and corpus, which also presented slight glandular atrophy (B) H & E, 100x and 400 x. Note that active neutrophilic inflammation is completely resolved.

have been characterized as mainly CD8+ T cells. Similarly to lymphocytic colitis, lymphocytic gastritis can also be caused by some drugs, especially non steroidal anti-inflammatory drugs (NSAIDs) and immune checkpoint inhibitors¹². The correct diagnosis in a given case, therefore, results from clinical and pathological correlations.

Discussion

In this report, we described a case of acute and lymphocytic gastritis occurring in the setting of pembrolizumab immunotherapy for metastatic melanoma.

Upper GI tract immune-related adverse events (irAEs) seem to be much rarer in comparison to those observed in the lower GI tract. The type of the inflammatory infiltrate in both localizations does not differ significantly, it can be chronic and/or acute, with or without intraepithelial lymphocytosis. Clinicians should be aware of the occurrence of gastritis related to pembrolizumab and histopathological findings should be in accordance with those described in the literature. Immunotherapy withdrawal should be considered only when strictly necessary (i.e. in case of severe histological inflammation, because of the risk of perforation) in patients with widespread malignancies.

TAKE HOME MESSAGES

The side effects of immune checkpoint inhibitors are referred to as immune-related adverse events (irAEs) and may affect several organs. Colitis and diarrhea are common gastrointestinal adverse events, but upper gastrointestinal events also exist and have rarely been reported.

Gastritis related to PD-1 inhibitors treatment may be suspected by abnormal gastric uptake in PET-CT even in asymptomatic patients. Gastric biopsies can be performed to confirm the presence of gastric inflammation and to appreciate his intensity.

Histologically immune-related gastritis is characterized by acute and/or chronic inflammation with intraepithelial lymphocytosis.

Gastritis related to immunotherapy can be diagnosed only when other causes of gastritis (HP, CMV, sprue, other drugs especially NSAIDs) have been excluded. Late-onset irAEs may also happen several weeks or months after completing or suspending immune checkpoint inhibitors¹⁴.

Immunotherapy discontinuation should be considered only when strictly necessary in patients with widespread malignancies (i.e. in case of severe histological inflammation, because of the risk of perforation).

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