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Severe gastritis due to pembrolizumab treatment in a lung cancer patient

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Keywords
Gastritis, immune checkpoint inhibitors, immune-related adverse events, inflammatory bowel disease, pembrolizumab.

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Abstract

Immune checkpoint inhibitors (ICIs) are known to induce gastrointestinal adverse events. Colitis occurs most frequently, and gastritis is less common. A few case reports of gastritis induced by ICIs have indicated that colitis induced by cytotoxic T-lymphocyte antigen-4 (CTLA-4) resembles inflammatory bowel disease (IBD) and that programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitor can also induce the same type of colitis. We herein encountered a case of gastritis arising after 25 cycles of pembrolizumab administration in which the pathological and endoscopic findings resembled those of IBD. ICIs may induce gastritis in a manner similar to the pathogenesis of IBD.

Introduction

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and anti-programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) inhibitors are known as immune checkpoint inhibitors (ICIs) and are widely used in different types of neoplasms, such as melanoma, lung cancer, renal cell carcinoma, Hodgkin's lymphoma, and stomach cancer [1]. However, immune-related adverse events (irAEs) involving multiple organs are observed in approximately 60–70% of patients receiving ICIs. ICI-induced gastritis can occur on rare occasions regardless of the presence of colitis, and some case reports have indicated that gastritis can develop in synchrony with cytomegalovirus or *Helicobacter pylori* infection [2,3]. Clinically, patients with gastritis typically complain of appetite loss, nausea, and vomiting. However, cases with severe ICI-induced gastritis are rare in daily practice, and little is known about the clinical features of patients with severe gastritis caused by ICIs. Here, we present a case with severe gastritis caused by an anti-PD-1 antibody in the patient with non-small cell lung cancer (NSCLC) as well as a review of the relevant literature to elucidate the clinical significance of gastritis secondary to ICIs.

Case Report

A 68-year-old woman was admitted to our hospital with appetite loss, nausea, and vomiting. She had been definitively diagnosed as having pulmonary adenocarcinoma (cT4N2M1b, stage IVA, PD-L1 90%, epidermal growth factor receptor (EGFR) negative, anaplastic lymphoma kinase (ALK) negative, ROS proto-oncogene 1, receptor tyrosine kinase (ROS-1) negative) four years previously. A laboratory investigation exhibited no abnormalities, and a physical examination was unremarkable. Therefore, she received six cycles of a combination of cisplatin, pemetrexed, and bevacizumab as induction therapy, followed by 15 cycles of pemetrexed plus bevacizumab as maintenance therapy. However, she experienced progressive disease, and pembrolizumab was initiated as a second-line treatment. After 25 cycles of pembrolizumab, she complained of appetite loss, but no obvious evidence of

any irAEs aside from the gastrointestinal symptoms was seen.

The prescription of oral betamethasone (2 mg) to reduce her symptoms was not effective; on the contrary, her symptoms worsened and she developed nausea, vomiting, and a stomach ache.

A cerebrospinal fluid test, brain magnetic resonance imaging (MRI), and some serological blood examinations did not reveal any abnormalities including cortisol, adrenocorticotropic hormone (ACTH), TSH, free T4, free T3, and sodium except for a slightly elevated C-reactive protein level. An abdominal computed tomography (CT) examination showed diffuse wall thickening in the stomach (Fig. 1), and an upper gastrointestinal endoscopy revealed findings of erythematous and inflammatory changes in the gastric mucosa, suggesting severe gastritis (Fig. 1); no evidence of any colitis was seen during colonoscopy. The pathological findings of a diagnostic biopsy of the gastric mucosa revealed erosion; multiple ulcers; the infiltration of neutrophils, plasma cells, and lymphocytes; and micro-abscesses in the fundic gland mucosa. As severe pembrolizumab-induced gastritis was strongly suspected, treatment with pembrolizumab was stopped and treatment with prednisolone (40 mg/day) was initiated. Her symptoms such as nausea and appetite loss resolved immediately. Likewise, endoscopic findings obtained two weeks later showed an improvement in the gastritis. Stomach biopsies revealed no signs of *H. pylori* infection or cytomegalovirus infection.

The prednisolone dosage was reduced gradually over a four-month period. Her condition improved, and she has not experienced any recurrence of gastritis as of four months after the cessation of steroid use. She has not received chemotherapy for lung cancer since the cessation of pembrolizumab, but tumour progression has not been observed.

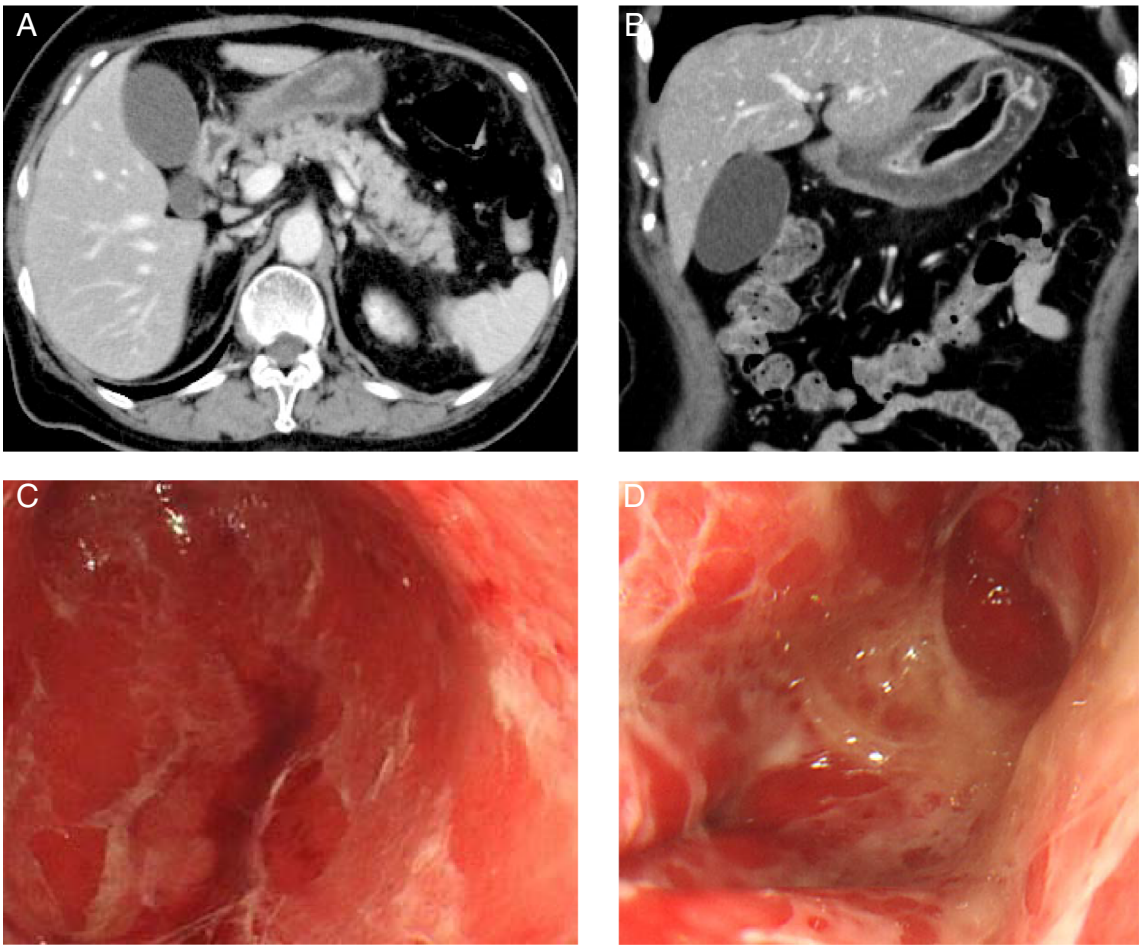

Figure 1. Computed tomography (CT) image showing gastric wall thickening (A, B) and endoscopic findings showing extensive gastric mucosa erythematous with a white coating (C: pylorus, D: antrum).

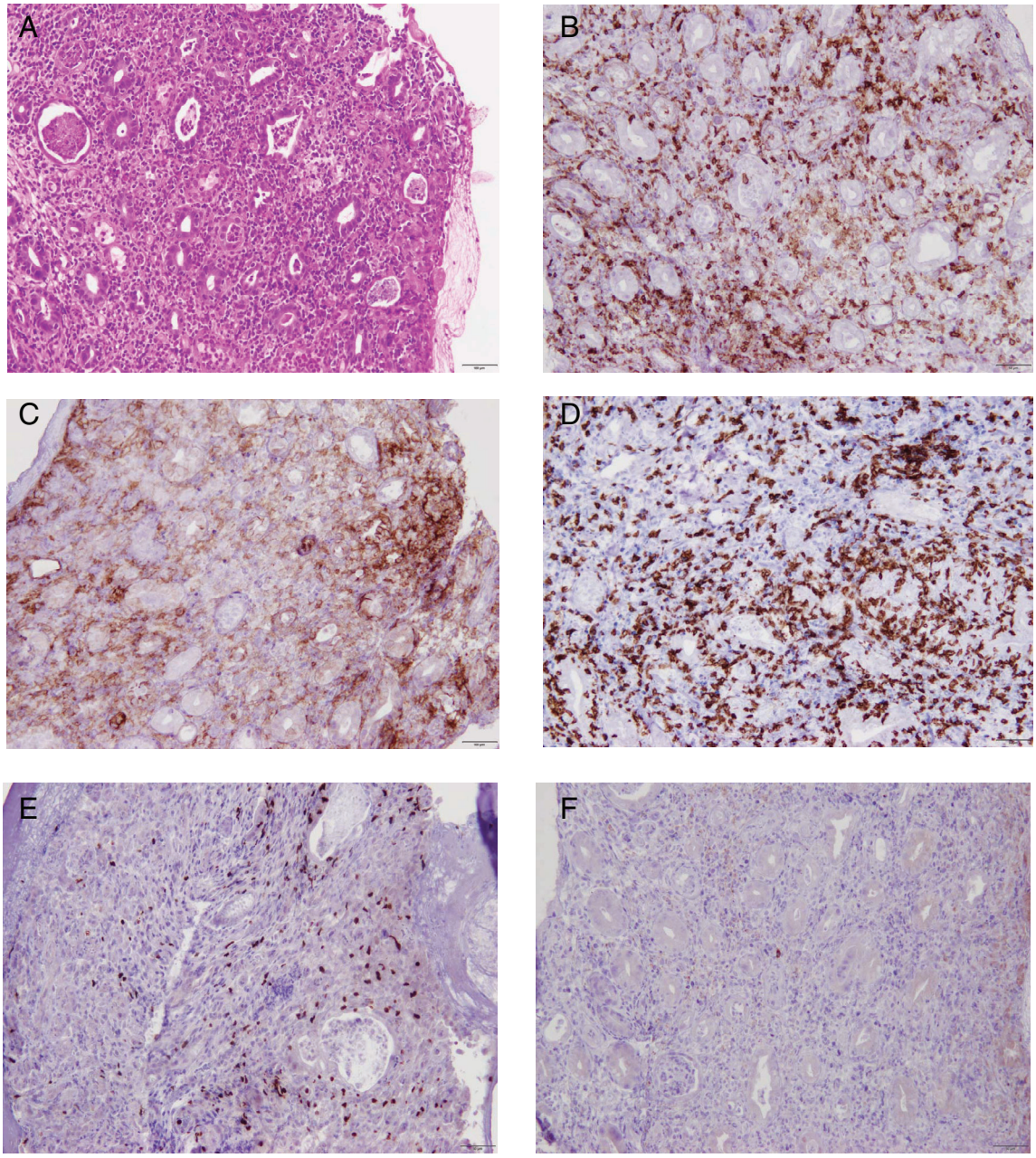

Figure 2. Pathological findings of the gastric mucosa biopsy specimen showing erosion, multiple ulcers, and the infiltration of neutrophils, plasma cells, and lymphocytes (A: haematoxylin–eosin stain). Immunohistochemically, the specimen was positive for programmed death ligand-1 (PD-L1) (SP142) (B), CD4 (C), and CD8 (D), the accumulation of Foxp3 was relatively low (E), and the specimen was negative for vascular endothelial growth factor receptor (VEGFR2) (F).

Immunohistochemical Finding

Using the biopsy sample of the gastric mucosa, PD-L1 (clone SP142; 1:100 dilution; Abcam, Japan), CD4 (1:200 dilution; Dako, Japan), CD8 (1:1000 dilution; Abcam), Foxp3 (1:200 dilution; Dako), and vascular endothelial growth factor receptor (VEGFR2;1:200 dilution; Abcam) were evaluated using immunohistochemistry (Fig. 2). Immunohistochemical staining was performed for these markers according to previously described procedures [4]. CD4 and CD8 were strongly stained throughout the

Table 1. Summary of the reported cases of gastritis induced by anti-PD-1 antibody.

No	Age	Sex	Types of tumour	Drug	Duration of therapy	Symptoms	Endoscopy findings of stomach	Pathological findings	CMV	*Helicobacter pylori*	Treatment
1	41	F	Melanoma	Pembrolizumab	10 cycles	Gastric pain	Severe haemorrhagic gastritis	Neutrophilic infiltration of the lamina propria and gastric glands	–	–	Oral prednisone (1 mg/kg)
2	44	M	Melanoma	Pembrolizumab	One month	Dyspepsia and GERD	No abnormality	Lymphocytic gastritis	ND	–	ND
3	43	F	Melanoma	Nivolumab	13 months	Gastric pain, anorexia, vomiting, weight loss	Ulcerative and haemorrhagic	Lymphocytic, plasma cell, neutrophils, eosinophils infiltrates	–	–	Methylprednisolone IV (1 mg/kg)
4	66	F	Colon cancer	Atezolizumab and then pembrolizumab	Five cycles	Dysphagia, gastric pain, nausea, vomiting	Erythematous and ulcerated mucosa	Mononuclear inflammatory cell infiltration in the lamina propria, crypt apoptosis	+	–	IV ganciclovir. No steroids
5	75	M	Bladder carcinoma. Melanoma	Nivolumab	13 months	Nausea, vomiting, gastric pain	Diffuse mucosal erythema	Severe active and chronic inflammatory infiltrate	–	–	Prednisone (0.5 mg/kg)
6	93	F	Lymphoma	Nivolumab	6 months	Dysphagia, diarrhoea	Thick mucosal exudates with underlying erythema	Lymphocytes and plasma cells in the lamina propria and epithelial layers	–	–	IV prednisone (1 mg/kg)
7	77	M	Lung carcinoma	Nivolumab	Four months (10 courses)	Gastric pain, haematemesis	Haemorrhagic gastritis	Lymphoplasmacytic and neutrophilic infiltration in the fundic gland mucosa	ND	ND	Prednisolone (1 mg/kg)
8	68	M	Lung carcinoma	Pembrolizumab	Seven cycles	Gastric pain	Erosion	Lymphocyte-dominant infiltration in the lamina propria	–	–	Prednisone IV (1 mg/kg)
9	56	M	Lung carcinoma	Nivolumab	Three weeks	Diarrhoea	Non-bleeding erosions	–	ND	ND	Symptoms improved without changes in treatment
10	45	F	Brest carcinoma	Pembrolizumab	ND	ND (abnormal CT scan)	Diffuse atrophy thickened pre-pylorus	Chronic active gastritis, severe inflammation, intraepithelial lymphocytes, apoptosis	–	–	Increased PPI
11	44	F	Colon cancer	Pembrolizumab	ND	Diarrhoea	Normal	Focal enhancing gastritis with granulomas	–	–	Steroid IV, infliximab
12	69	M	Melanoma	Nivolumab	ND	Nausea, vomiting, diarrhoea	Erythema, erosions	Focal enhancing gastritis	–	–	Prednisone, infliximab
13	81	F	Hodgkin's disease	Pembrolizumab	ND	Nausea, vomiting, diarrhoea	Normal	Focal enhancing gastritis	–	–	Prednisone
14	68	F	Lung carcinoma	Pembrolizumab	25 courses	Nausea, appetite loss	Erythematous with white coating	Erosion, multiple ulcer, infiltration of neutrophils, plasma cell, and lymphocyte and micro-abscess in fundic gland mucosa	–	–	Prednisolone IV (40 mg)

CMV, cytomegalovirus; CT, computed tomography; GERD, gastro-esophageal reflux disease; IV, intravenous; ND, not described; PD-1, programmed death-1; PPI, proton pump inhibitor.

Table 2. Patient characteristics.

		$n = 14$
Age		67 (41–93)
Sex		
	Male	6
	Female	8
Drug		
	Nivolumab	6
	Pembrolizumab	8
Onset		
	Within six months	7 (63%, $n = 11$)
Symptom		
	Gastric pain	6
	Nausea, vomiting	6
	Appetite loss or weight loss, dyspepsia	3
	Diarrhoea	5

whole gastric mucosa, and Foxp3 was weakly stained. There was evidence of some expression of PD-L1 within the gastric cells in the mucosa, but not VEGFR2.

Discussion

ICI-induced gastritis has been reported in some case reports and original articles. Several reports regarding gastritis resulting from CTLA-4 antibody and anti-PD-1 antibody have been published. The reported case series caused by anti-PD-1 antibody alone are listed in Table 1. The patient background characteristics are listed in Table 2. Among the previous reports, five cases had malignant melanoma and three cases had lung cancer, and no specific patient characteristics were seen. Approximately half of the previous cases experienced gastritis within six months after ICI administration, but long-term ICI use was observed in a few cases. Major symptoms included diarrhoea, appetite loss, nausea, vomiting, and stomach ache.

In our case, the patient complained of non-specific symptoms, such as appetite loss and nausea; therefore, a diagnosis of ICI-induced gastritis was initially difficult. In colitis secondary to ICI use, diarrhoea is the most common symptom; however, diarrhoea has also been reported in gastritis patients without colitis [5–7], and gastritis can occur in synchrony with oesophagitis, duodenitis, and colitis [8]. If any symptoms appear during the administration of ICIs, both an upper gastrointestinal endoscopy and colonoscopy are necessary to investigate the possibility of ICI-induced gastritis.

Endoscopic biopsy of the gastric mucosa was useful for a definite diagnosis of ICI-induced gastritis, as it can show different kinds of gastric findings such as erosion, bleeding, and ulcer. The endoscopic observation in the presently reported case suggested a similarity to the gross findings associated with ulcerative colitis, which was supported by the pathological examination. Moreover, our immunohistochemical investigation revealed that there were predominantly infiltrations of CD4 or CD8 lymphocytes [9], rather than regulatory lymphocytes such as Foxp3, and the expression of PD-L1, but not VEGFR2, was seen within the gastric cells in the mucosa. The expression of PD-L1 (SP142) was observed in the infiltrating lymphoid cells and stromal cells. The immune reaction in the gastric mucosa was relatively strong; therefore, there was obvious evidence of severe gastritis related to ICI use. To the best of our knowledge, this is the first report to present the immunohistochemical findings of immune-related gastritis.

As in the presently reported case, steroid therapy is reportedly effective in most cases of ICI-induced gastritis, but a few cases have also required immunosuppressive agents [10].

The incidence of ICI-induced gastritis is relatively rare, compared with colitis, but a massive immunoreaction caused by ICIs can induce severe gastritis. Thus, gastritis should be considered when patients taking ICIs complain of any gastrointestinal symptoms.

Disclosure Statements

Appropriate written informed consent was obtained for publication of this case report and accompanying images.
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