Accepted Manuscript online: 2022-04-28 Article published online: 2022-07-15

Severe immune checkpoint inhibitor-associated gastritis: A case series and literature review

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submitted 5.1.2022
accepted after revision 28.4.2022
published online 28.4.2022

Bibliography
Endosc Int Open 2022; 10: E982–E989
DOI 10.1055/a-1839-4303
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Supplementary material is available under https://doi.org/10.1055/a-1839-4303

ABSTRACT

Background and study aims Recent advances in cancer treatment have involved the clinical application of immune checkpoint inhibitors (ICIs) for various type of cancers. The adverse events associated with ICIs are generally referred to as immune-related adverse events (irAEs). Gastrointestinal irAEs are a major disorder, but gastritis is not frequently observed. The aims of this study were to elucidate the clinical, endoscopic, and histological characteristics of irAE gastritis.

Patients and methods Information on patients treated with ICIs were collected from a single institute over 3 years. IrAE gastritis was identified based on the clinical course and endoscopic and histopathological findings. Of the 359 patients treated with ICIs, four cases of irAE gastritis were identified in clinical records from the endoscopy unit. The endoscopic and histopathological findings were analyzed, and further immunohistochemical studies with immune subtype markers and programmed cell death ligand-1 (PD-L1) antibody were conducted.

Results Among four patients with irAE gastritis, the remarkable endoscopic characteristics were network-pattern erosion, erythematous and edematous mucosa with thick purulent discharge, and fragile mucosa. Corresponding histological features were fibrinopurulent exudate, severe inflammatory cell infiltration, and epithalaxia, respectively. The PD-L1 expression rate was ≥ 1 % in the gastric tissue of all patients with gastritis. These patients were treated with prednisolone (PSL) and their symptoms improved within a few days to 2 weeks.

Conclusions IrAE gastritis were characterized by specific endoscopic findings. The appropriate endoscopic diagnosis may lead to effective treatment with PSL.

Introduction

Immune checkpoint inhibitors (ICIs) represent a major advance in treatment of many types of cancers and have dramatically changed the cancer therapeutic strategy. The efficacy of ICI treatment has been confirmed, and real-world clinical experience with its application has been gained. However, a wide spectrum of accompanying immune-related adverse events (irAEs) have been reported, with caution advised by expert oncologists [1]. These irAEs are driven by the immunologic mechanisms responsible for the therapeutic effects of ICIs [2, 3].

Gastrointestinal disorders are particularly common irAEs, and most patients develop severe inflammation in the colon [4, 5]. IrAE gastritis was first reported in 2017 [6], with more case reports on gastritis published later [7–14]. All reports described the severity and rarity of this gastritis. However, details concerning the clinical features of irAE gastritis remain sparse.

Symptoms in patients with irAE gastritis are non-specific. An accurate diagnosis should be made, based on a combination of a patient's clinical course and endoscopic and histopathological findings [13, 14]. Therefore, we retrospectively collected cases and reviewed the relevant literature to assess the characteristics of irAE gastritis, focusing on endoscopic findings and results of histopathological analyses.

Patients and methods

We conducted an observational retrospective study to collect information on patients with irAE gastritis. Three hundred and fifty-nine patients were treated with ICIs in Asahikawa Medical University Hospital from October 2018 to October 2021. Among them, 10 patients underwent esophagogastroduodenoscopy (EGD) due to complains of gastrointestinal symptoms after administration of an ICI. Severe gastritis was observed in four patients. IrAE gastritis was identified based on the clinical course and endoscopic and histopathological findings. Detailed information was collected about the patients with irAE gastritis, including their symptoms, current treatments, and later immune therapy. The diagnostic criteria for irAE gastritis were onset of upper gastrointestinal symptoms while a patient was receiving ICIs, and the exclusion of other causes endoscopically and/or histologically.

Endoscopic findings were evaluated with conventional endoscopy, chromoendoscopy, and narrow-band imaging using gastroduodenoscopy (GIF-H290Z, GIF-HQ290 or GIF-1200N, Olympus Optical Co., Ltd., Tokyo, Japan). Biopsy specimens were collected from the antrum and corpus of the stomach for histological diagnosis in patients suspected of having irAE.

Immunohistochemical analyses were further conducted for patients with irAE gastritis. Immune subtype markers, including CD4 (1F6; Leica Microsystems, Wetzlar, Germany) and CD8 (C8/144B; Agilent Technology, Santa Cruz, CA, USA), and programmed cell death ligand-1(PD-L1) antibody (SP263; Ventana Medical Systems, Tucson, AZ, USA) were used for immunohistochemistry. Expression of PD-L1 was evaluated as the positive rate (%) in total cells including epithelial cells and infiltrating

▲ **Table 1** Characteristics of patients with immune-related gastritis.

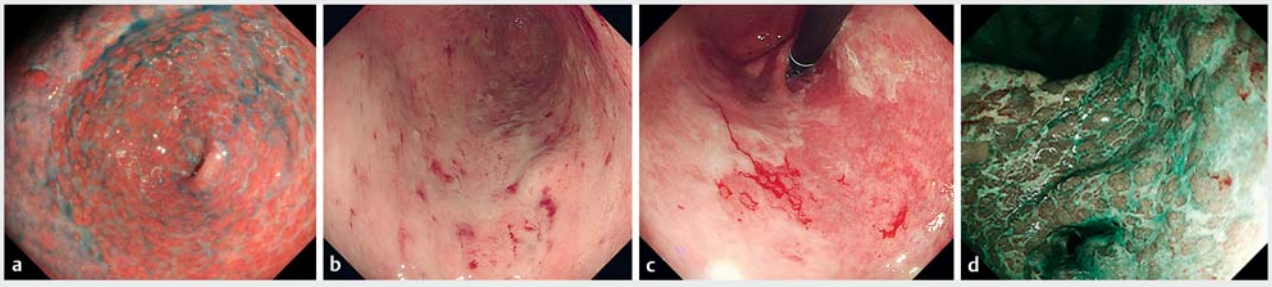
Case	Age	Sex	Cancer type	ICI past history	ICI medication	Time to onset for symptoms (weeks)	Symptoms			CTCAE grade	Prednisolone treatment	Time to improvement	ICI rechallenge	Relapse of gastritis
							Nausea/vomiting	Loss of appetite	Other					
1	84	M	Melanoma	Pembrolizumab	Nivolumab/ipilimumab	1	+	+	–	3	Div (0.5 mg/kg)	A few days	Nivolumab	+
2	75	F	Melanoma	–	Pembrolizumab	40	+	+	Fatigue	3	Div (0.5 mg/kg)	A few days	–	–
3	65	F	Lung cancer	Pembrolizumab	Pembrolizumab	15	+	+	Heartburn	3	P.O. (0.5 mg/kg)	2 weeks	–	–
4	62	M	Gastric cancer	–	Nivolumab	24	+	+	–	2	P.O. (0.5 mg/kg)	A few days	Nivolumab	+

ICI, immune checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events

▶ **Table 2** Endoscopic and histological findings and PD-L1 expression in patients with immune-related gastritis.

Case	Endoscopic findings			Histological findings				Immunohistochemical findings
	Erythematous and edematous mucosa	Network-pattern erosion in the antrum	Fragile mucosa	Severe inflammatory cell infiltration in the lamina propria	Fibrinopurulent exudate	Epithalaxia	Apoptosis	PD-L1 (%)
1	+	+	+	+	+	+	–	10%<
2	+	+	+	+	–	+	+	10%<
3	+	+	+	+	–	+	–	10%<
4	+	–	+	+	–	+	+	1%<

PD-L1, programmed cell death ligand-1; mCPS, modified combined positive score.



▶ **Fig. 1** Endoscopic features of immune-related adverse event (irAE) gastritis. **a** The network-pattern erosion and ulcer in the antrum are collectively termed a "spiderweb-like appearance." **b** Erythematous and edematous mucosa is covered with excessive whitish purulent discharge in the whole stomach. **c** The fragile mucosa easily bleeds on washing with water spray. **d** The spiderweb-like appearance is clearly enhanced with narrow-band imaging.

immunocytes. Cytomegalovirus (CMV) antibody (DDG9+CCH2, DAKO Agilent, Carpinteria, California, United States) was used for CMV immunohistochemistry. Warthin-Starry staining was performed to investigate *Helicobacter pylori* infection.

This observational study protocol was approved by the Asahikawa Medical University Research Ethics Committee (No. 210769). A written informed consent was obtained from each patient with irAE gastritis.

Results

Patient characteristics

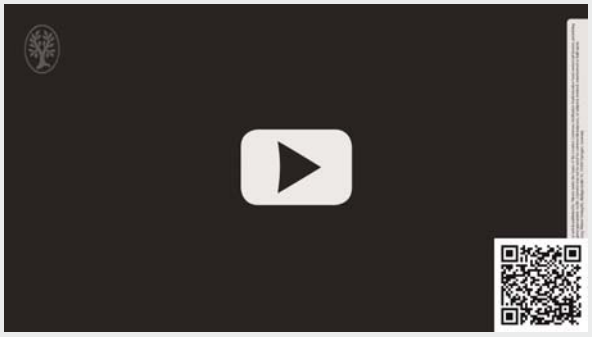
Ten patients underwent EGD due to complains of gastrointestinal symptoms after the administration of an ICI. Severe gastritis was observed in four of 359 patients (1.1%). These adverse events (AEs) were graded >2 because all patients were treated with prednisolone (PSL). Three patients were admitted to the hospital, and the incidence of grade 3 irAE gastritis was found to be 0.84% (3/359).

All four of these patients were finally diagnosed with irAE gastritis, and their clinical information is shown in ▶ **Table 1**. These four patients were two males and two females, with a median age of 70 years (range 62–84), treated with ICIs due to malignant melanoma (n=2), lung cancer (n=1), and gastric cancer (n=1). Pembrolizumab had been administered to the melanoma patient and the lung cancer patient, nivolumab to the gastric cancer patient, and nivolumab/ipilimumab to the melanoma patient. Symptoms of irAE gastritis occurred 1 to 40 weeks after administration of ICIs. Among the affected patients, two patients had a history of ICI treatment and they did not develop irAE during the treatment. Common gastrointestinal symptoms, such as nausea, vomiting, and loss of appetite, occurred in all patients, and fatigue and heartburn were observed in one patient.

Endoscopic and histopathological findings at the diagnosis

Endoscopic and histopathological findings from patients with irAE gastritis are shown in ▶ **Table 2**. EGD revealed various findings, such as network-pattern erosion or ulceration in the antrum (▶ **Fig. 1a**), erythematous and edematous mucosa with whitish purulent discharge (▶ **Fig. 1b**), and fragile mucosa (▶ **Fig. 1c**). The whitish discharge was remarkably increased by

VIDEO

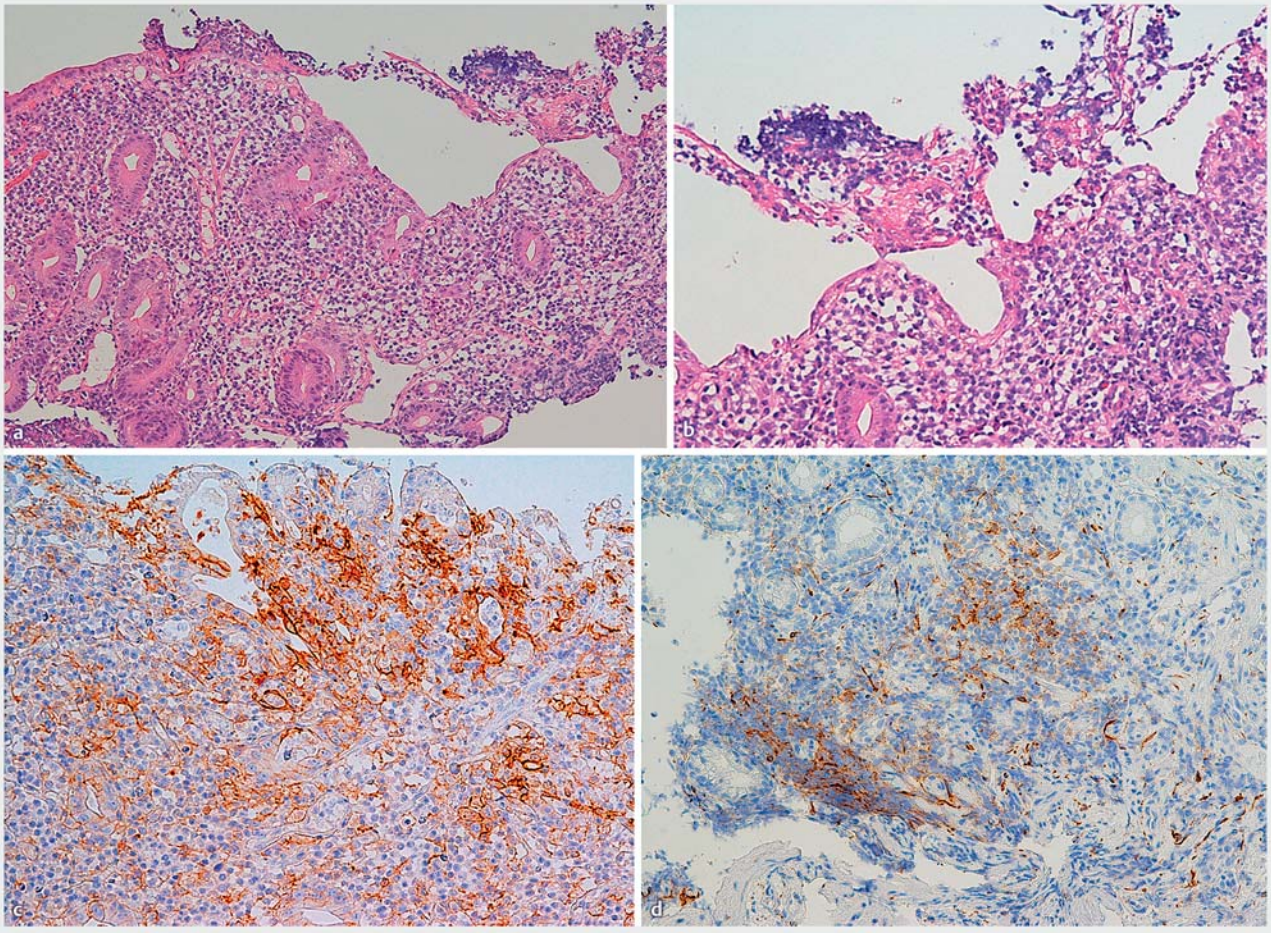


▶ **Video 1** The fragile gastric mucosa of the patient with immune-related adverse event (irAE) gastritis. The antral mucosa, which is covered with whitish purulent exudate, bleeds easily when removed by the forceps and exposed to water jet from the endoscope.

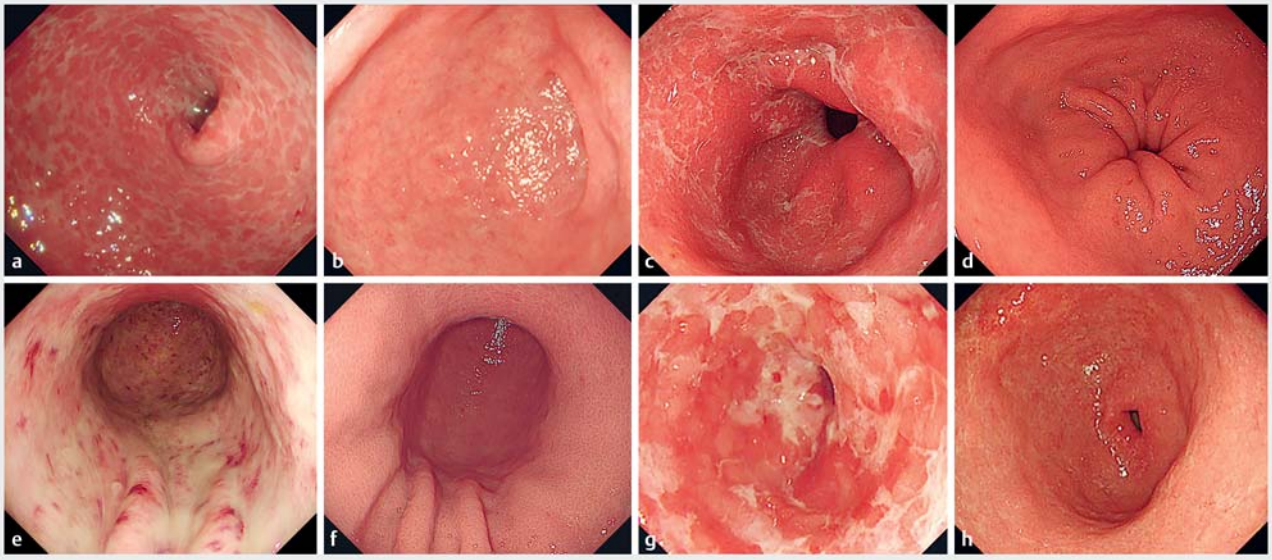
air insufflation and mechanical contact during endoscopic examination. Oozing caused by a slight touch was observed in fragile mucosa (▶ **Video 1**). Narrow-band imaging effectively enhanced erythema as a brownish area, and then contrasted between the mucosa and discharge (▶ **Fig. 1d**).

Biopsy specimens were collected from the antrum and corpus of the stomach for histological diagnosis. Epithalaxia and severe inflammatory cell infiltration in the epithelia and lamina propria were observed on histology (▶ **Fig. 2a**). Fibrinopurulent exudate was observed on the epithelia (▶ **Fig. 2b**). Immunohistochemical analysis showed that the infiltrating lymphocytes were positive for CD3, CD4, and CD8, but negative for CD20 (Supplementary Figure). Staining was positive for PD-L1 in the immune cells and/or epithelial cells (▶ **Fig. 2c, d**). The positive rate was ≥ 10 % in three cases and ≥ 1 % in one case.

CMV was not detected by a specific antibody in any cases, and *H. pylori* was detected in the patient with gastric cancer (Case 4).



▶ **Fig. 2** Histological findings of immune-related adverse event (irAE) gastritis. **a** Epithalaxia and severe inflammatory cell infiltration in the mucosa are observed in the biopsy specimens (H&E, × 100). **b** Fibrinopurulent exudate is seeping out through the deficient of mucosa (H&E, × 200). **c** An immunohistochemical analysis of PD-L1 antibody (SP263) shows positive staining on epithelial cells and infiltrating immune cells (× 200). (d) PD-L1 is positive on the membrane of the inflammatory cells and negative in the epithelial cells (× 200).



▶ **Fig. 3** Endoscopic appearance of immune-related adverse event (irAE) gastritis before (**a, c, e, g**) and after (**b, d, f, h**) treatment with prednisolone. Four cases (Case 1: **a, b**; Case 2: **c, d**; Case 3, **e, f**; Case 4: **g, h**.) showed marked improvement in endoscopic features. Case 1 was cited from a previous publication [25].

Treatment and outcome

Treatments for irAE gastritis and the clinical outcomes are shown in ▶ **Table 1**. Corticosteroids (0.5 mg/kg) were administered orally or intravenously. Patient symptoms rapidly improved within a few days of administration. The dose was gradually tapered every 1 to 2 weeks. EGD with a histological examination after treatment with PSL revealed improvement in three cases (▶ **Fig. 3a–f**). In the other case, fragile mucosa remained in the lesser curvature (▶ **Fig. 3g, h**). While the histopathological findings remarkably improved, mild inflammatory cell infiltration persisted in all cases.

In two cases, retreatment with the same ICI was attempted to suppress the regrowing cancer, after the patient's initial epigastric symptoms had completely resolved. The patient in Case 1 (▶ **Table 1**), who had received nivolumab/ipilimumab, was administered nivolumab monotherapy. The patient in Case 4 was administered nivolumab monotherapy again. Both patients developed loss of appetite and nausea again 10 to 12 weeks after rechallenge with ICIs. EGD revealed relapse of irAE gastritis, characterized by erythematous and edematous mucosa with whitish purulent discharge, and PSL retreatment rapidly improved their symptoms.

Discussion

The number of reported cases of severe irAE gastritis has been increasing in recent years [15–20]. Previously reported cases with severe irAE gastritis are summarized in ▶ **Table 3**. These reports showed that irAE gastritis developed during administration of ICI monotherapy in most cases. Our study included three patients who developed irAE gastritis with ICI monotherapy. Incidence of irAE colitis was shown to be higher in the combination therapy group than in the monotherapy group [21]. In our study, three patients developed irAE gastritis with ICI monotherapy, while one patient developed it with ICI combination therapy. IrAE gastritis seems to develop more frequently with ICI combination therapy, as well as irAE colitis reported in a previous review [22].

To obtain an accurate diagnosis, this study indicates that it is important to be alert for three characteristic endoscopic findings: 1) network-pattern erosion or ulcer in the antrum; 2) erythematous and edematous mucosa with excessive whitish purulent discharge in the whole stomach; and 3) extremely fragile mucosa. Among these findings, the first may be the most specific, and indeed, three of the four patients in our study had this finding. It was unique, enabling it to be distinguished from other etiologies, while the other finding was common findings in gastritis induced by other etiologies. For instance, the second finding can be observed in gastritis caused by severe *H. pylori* infection [23]. However, the whitish purulent discharge in irAE gastritis was exacerbated by air insufflation and endoscopic contact while performing an endoscopic examination. Furthermore, there were some patients in whom a large amount of whitish purulent discharge covered the mucosal surface, resulting in pseudo-membranous formation. This appearance was described as "fibrin-covered superficial erosions" in a previous report involving endoscopic evaluation of gastrointestinal toxicity [15, 16, 24]. Finally, the third finding was quite characteristic as well. The mucosa of our patients bled easily, even when exposed to the low-pressure water jet from the endoscope. Oozing from mucosa could be observed when the purulent discharge was removed. Endoscopic findings of irAE gastritis in previous reports are summarized in ▶ **Table 3**. Some reports described the endoscopic findings in each pa-

▶ **Table 3** Characteristics of 36 cases of ICI-related gastritis in previous reports.

Age	Median (range)		63.5 (16–93)
Sex	n	(Male:female)	20:16
Type of tumor	n (%)	Malignant melanoma	16 (44)
		Lung cancer	10 (28)
		Others	11 (31)
Type of ICI	n (%)	Pembrolizumab	14 (39)
		Nivolumab	11 (31)
		Ipilimumab + nivolumab	7 (19)
		Ipilimumab	2 (0.6)
		Nivolumab + lag3 inhibitor	1 (0.3)
		Ipilimumab + pembrolizumab	1 (0.3)
Treatment cycles	Median (range)		2.5 (1–80)
Symptoms	n (%)	Abdominal pain (epigastric pain)	19 (53)
		Nausea/vomiting	14 (39)
		Loss of appetite	11 (31)
		Diarrhea	9 (25)
		Weight loss	4 (1.1)
		No symptom	2 (0.6)
Endoscopic findings	n (%)	Erythema	16 (44)
		Erosion/ulcer	15 (43)
		Edematous	7 (20)
		White exudate	6 (17)
		Friable	8 (23)
		Normal	4 (1.1)
		Granularity	3 (0.9)
		Hemorrhagic gastritis	2 (0.6)
Histological findings	n (%)	Inflammatory cell infiltration	29(85)
		(lymphocytes, neutrophils, eosinophils, plasma cell)	
		Apoptosis	10(29)
		Decreased glands	4 (12)
Treatment	n (%)	Prednisolone (0.5–1.0 mg/kg) IV/PO	31 (89)
		Infliximab	2 (6)
		Proton pump inhibitor	1 (3)
		ICI switch	1 (3)
		No treatment	1 (3)

ICI, immune checkpoint inhibitor; IV, intravenous; PO, per oral.

tient, but only a few reports clearly discussed characteristic endoscopic findings of irAE gastritis [14, 25]. Indeed, the first finding was never mentioned in previous reports, aside from our brief case report, in which a white fibrin-like membrane was termed “spiderweb-like appearance” [25].

The present study compared endoscopic and histopathological findings. The biopsy specimens obtained from the whitish purulent discharge showed fibrinopurulent exudate on the epithelia in our patients. Fibrinopurulent exudate is usually observed in cases of severe gastritis, such as that induced by severe acute *H. pylori* infection, causing extensive infiltration of neutrophils. IrAE gastritis may be more destructive than *H. pylori* gastritis [26]. Presence of fibrinopurulent exudate is considered to reflect the severity of irAE gastritis. Fragile mucosa is consistent with the histological appearance of epithalaxia and gland depletion, which are caused by severe inflammatory cell infiltration and destructive response (▶ **Fig. 2a**). One of the noteworthy histological findings in gastritis was apoptosis, which is observed in irAE enterocolitis with different frequency [27–29]. Apoptosis is typically observed in gastric graft-versus-host-disease, the histological criteria for which are apoptosis and gland destruction, sparse inflammatory infiltration, and granular eosinophilic debris in the dilated gland. Therefore, the histological distinction will be useful when endoscopic features are similar to irAE gastritis. Differential diagnosis also includes gastric lesions such as in patients with ulcerative colitis. Endoscopic findings of erythematous and edematous mucosa with whitish purulent discharge may be observed in upper gastrointestinal lesions in patients with ulcerative colitis [30, 31]. On pathological examination, the lesions show severe inflammation with sloughed epithelial cells, resembling a crypt abscess. Thus, a more detailed histological comparison between ulcerative gastritis and irAE gastritis is expected in the future.

A common mechanism by which ICIs exert their effects involves activation of effector T cells by inhibition of PD-1, PD-L1, and CTLA-4 [32]. It is also proposed that the proliferation of activated T cells and increase in cytokine production, caused by a lack of self-tolerance, may result in irAEs [2, 33]. However, the detailed mechanisms underlying manifestation of irAEs remain unclear. Immunohistochemistry in our patients revealed that PD-L1 positivity in all four cases. This expression was observed on epithelial cells and mesenchymal cells. The relationship between expression of PD-L1 and irAEs needs to be evaluated in more patients. PD-L1 expression in the stomach may be associated with development of irAE gastritis. The linkage between PD-1 and PD-L1 is inhibited by ICIs, resulting in blockade of immune tolerance. T cells will actively attack antigens that are present on gastric epithelial cells. This novel hypothesis will need to be assessed in a further case-control study. While expression of tissue-based biomarkers including PD-L1 has been shown to correlate with ICI efficacy, its association with AEs remains unclear [34]. One histological analysis of a patient with encephalitis induced by ICI demonstrated prominent PD-L1 expression and robust T-cell infiltration [35].

Concerning the treatment, our patients were treated with intravenous or oral PSL 0.5 mg/kg/day, which rapidly improved their symptoms within a few days to 2 weeks after administration of PSL and the symptoms eventually disappearing. Although the time to symptom improvement was not mentioned much in previous reports, many patients had symptom improvement within a few days of PSL treatment. As with other irAEs, there were some PSL-refractory cases that needed an anti-TNFα monoclonal antibody among previous cases [36]. Therefore, we should pay attention to improvement in symptoms after administration of PSL.

One limitation associated with this case report is its retrospective nature and single-center setting. Because gastritis is a relatively rare irAE, we only analyzed endoscopic and histological findings in four collected cases. The sensitivity and specificity of the characteristic endoscopic findings, as mentioned previously, could not be estimated, because the endoscopic findings were not evaluated in this case series. A case-control study or cohort study with a sufficient number of cases would help clarify the accuracy of endoscopic findings.

Conclusions

In conclusion, we identified clinical features of irAE gastritis, including characteristic endoscopic findings, in this case series. IrAE gastritis can be induced by any ICI at any timing during administration of ICIs. Furthermore, symptoms of irAE gastritis are non-specific and can resemble those induced by other etiologies, such as disease progression and cachexia. Therefore, it is difficult to diagnose irAE gastritis based on symptoms alone. IrAE gastritis, thus, was diagnosed by characteristic endoscopic findings, and gastritis in patients was effectively treated with PSL. These results suggest that an endoscopic diagnosis is quite important, so oncologists should be aware of characteristic endoscopic findings for this entity. These findings are expected to deepen our understanding of irAE gastritis, leading to prompt diagnosis and appropriate treatment.

Acknowledgements

The authors gratefully acknowledge the technical assistance received from Yuji Uno. The authors declare that Case 1 is the same patient who was previously reported in our brief report [ref. 25; *Sugiyama Y* et al. JGH open 2021].

Competing interests

Dr. Okumura has received grant support from Ono Pharmaceutical Corp. and MSD Co., Ltd., and has received payment for honoraria from Ono Pharmaceutical Corporation. Dr. Fujiya has served as a lecturer for Ono Pharmaceutical Corporation.

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