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EDITORIAL

Immune checkpoint inhibitor-associated gastritis: Patterns and management

Jing Lin, Zhong-Qiao Lin, Shi-Cheng Zheng, Yu Chen

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Abstract

Immune checkpoint inhibitors (ICIs) are widely used due to their effectiveness in treating various tumors. Immune-related adverse events (irAEs) are defined as adverse effects resulting from ICI treatment. Gastrointestinal irAEs are a common type of irAEs characterized by intestinal side effects, such as diarrhea and colitis, which may lead to the cessation of ICIs. Although irAE gastritis is rarely reported, it may lead to serious complications such as gastrorrhagia. Furthermore, irAE gastritis is often difficult to identify early due to its diverse symptoms. Although steroid hormones and immunosuppressants are commonly used to reverse irAEs, the best regimen and dosage for irAE gastritis remains uncertain. In addition, the risk of recurrence of irAE gastritis after the reuse of ICIs should be considered. In this editorial, strategies such as early identification, pathological diagnosis, management interventions, and immunotherapy rechallenge are discussed to enable clinicians to better manage irAE gastritis and improve the prognosis of these patients.

Key Words: Immunotherapy; Immune checkpoint inhibitor; Immune-related adverse events; Immune checkpoint inhibitor-related gastritis

Core Tip: Immune checkpoint inhibitor (ICI)-related gastritis is rare but may lead to serious complications such as gastrorrhagia. Biopsy under esophagogastroduodenoscopy is the gold standard for diagnosis. Specifically, this article discusses strategies for treating ICI-related gastritis, including early recognition, pathological diagnosis, management interventions, and rechallenge with immunotherapy, providing clinicians with valuable consultations to enable cancer patients to benefit early from treatment.

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INTRODUCTION

Immunotherapy has been shown to have great efficacy in treatment of multiple kinds of cancers by inhibiting the downregulation of T-cell-mediated destruction and promoting the patient's immune system to target and destroy cancer cells. Immune checkpoint inhibitors (ICIs), which are programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors, are common pharmacotherapeutics for immunotherapy and improve survival across a range of malignancies. While the inhibition of these proteins reinvigorates the host antitumor immune response, broad inhibition of these central immune regulators leads to a unique spectrum of immune-related adverse events (irAEs), and gastrointestinal (GI)-irAEs are among the most common toxicities of current ICIs. The side effects affecting the distal gastrointestinal tract, including colitis and diarrhea, are well recognized. However, gastritis induced by immune checkpoint inhibitors has also been described. Gastritis is a broad category of diagnosis that stems from inflammation to the gastric mucosa that can lead to nausea, vomiting, abdominal pain, and weight loss. This editorial focuses on early identification, pathological diagnosis, management interventions, and immunotherapy rechallenge of irAE gastritis to enable clinicians to better manage irAE gastritis and improve the prognosis of these patients.

INCIDENCE, TIME-TO-ONSET AND SEVERITY

Overall, GI-irAEs occurred in approximately 6.5% to 8.4% of patients receiving monotherapy ICIs[1,2]. ICI-related gastritis has a lower occurrence. Several retrospective studies based on large samples have reported an incidence of approximately 0.35%-1.46%[3-6]. The time-to-onset is highly variable, with a wide range of 2 wk to 156 wk, and the median time was calculated as 29.3 wk[7]. The incidence of GI-irAEs of ICI combined therapy occurred at 6-8 wk after the start of ICI treatment, which was much earlier than ICI monotherapy[8]. Furthermore, combined therapy with anti-PD1/PD-L1 and anti-CTLA-4 agents led to higher rates of GI-irAEs than anti-PD1/PD-L1 or anti-CTLA-4 monotherapy (15% *vs* 4% and 12%, respectively)[9-13]. There was also a positive association between increasing doses of ICIs and the incidence and severity of GI-irAEs, especially in anti-CTLA-4 monotherapy and combined therapy of anti-PD1/PD-L1 and anti-CTLA-4 agents[14-17]. The severity grades of ICI-related gastritis are based on the Common Terminology Criteria for Adverse Events (CTCAE)[18]. In patients with grade 1 gastritis, upper gastrointestinal symptoms are not obvious and are often detected inadvertently. ICI-related gastritis of CTCAE grade 2-3 has been reported most often (more than 75%), requiring the cessation of ICIs and steroid intervention[19].

Patients with a history of gastrointestinal disease are more likely to develop ICI-related gastritis after immunotherapy. One study revealed that in 54 patients with ICI-related gastritis, thirteen (24%) had a history of gastroesophageal and liver disorders, and nine of thirteen had former gastroesophageal reflux disease[4]. Previous medications that potentially damage the stomach should be assessed in patients with ICI-related gastritis. In a total of 25 patients with ICI-related gastritis, 3 (12%) patients had a history of nonsteroidal anti-inflammatory drug (NSAID) use, and 11 (44%) patients had received chemotherapy, radiation, or combined therapy[3]. A shorter onset time of 2.0 wk was observed in those patients, and they all had grade-2 or higher adverse events (AEs) that required prednisolone (PSL) therapy.

SYMPTOMS AND CLINICAL EXAMINATIONS

Clinical symptoms of ICI-related gastritis are diverse; they can be covered by the delayed or cumulative effect of previous treatment lines or can be neglected when coexisting with other lower GI tract toxicities, which makes diagnosis challenging. Nausea/vomiting and abdominal pain are most commonly seen in patients with ICI-related gastritis. High-dose, short-interval administration of pembrolizumab increases the frequency of nausea and vomiting[20]. Sometimes, nausea/vomiting may be the only discomfort, digestive discomfort may be absent, so the occurrence of ICI-related gastritis should be determined in patients receiving immunotherapy under this circumstance. Dyspepsia (38%) and bloating (25%) are also observed in patients with ICI-related gastritis. Compared with patients with concomitant

enteritis/colitis, patients with isolated gastritis were less likely to have diarrhea (13% *vs* 68%; $P < 0.001$) or abdominal pain (19% *vs* 47%; $P = 0.07$)[4].

In general, serological evidence is still insufficient. Laboratory findings for most patients were not clinically significant, or they had mild anemia and malnutrition. Elevated C-reactive protein (CRP) was observed in several patients, but their WBC counts were within normal limits. However, in two reported cases, patients with severe eosinophilia and increased IgE and IL-5 levels showed eosinophilic infiltration on histology. Several serum biomarkers have been shown to predict ICI-related colitis. An increase in the serum IL-17 concentration at baseline with an exponential elevation at six weeks is a good indicator for ICI-diarrhea/colitis, and an decrease in the serum IL-17 concentration correlates with the resolution of symptoms, making it a valuable indicatior of treatment response[21]. High sCTLA-4 serum levels might predict favorable clinical outcomes and greater risk of irAEs in MM patients treated with ipilimumab[22]. Currently, there is no specific index to demonstrate ICI-related gastritis in an early stage.

Abdominal computed tomography (CT) is often unremarkable, with only a few patients displaying thickening of the gastric wall[7]. PET-CT can reveal diffuse fluorodeoxyglucose accumulation in the stomach wall, but it is poorly distinguished from metastasis[23-25]. Esophagogastroduodenoscopy (EGD) can reveal gastritis, duodenitis [frequently without *Helicobacter pylori* (*H. pylori*) infection], esophageal or gastric ulcers, ileitis, or enterocolitis[11]. Erythema (64%-88%) and edema (46%-52%) of the gastric mucosa are typical findings under EGD[3,26]. In patients with grade-3 ICI gastritis, hemorrhagic and fragile mucosa, network-pattern erosion or ulcers in the antrum have also been observed[6,27]. However, histological examination or endoscopic ultrasonography may show prominent characteristics of autoimmune gastritis, although there are no typical gastroscopic characteristics or clinical symptoms. Some reports have indicated a weak correlation between gastroscopic and histological findings in PD-1-induced gastritis[28,29]. Approximately 10%-20% of patients have endoscopically normal gastric tissue despite biopsy–proven ICI-related gastritis[4]. Thus, in patients with suspected PD-1-induced gastritis, a complete workup is necessary for diagnosis, especially stomach biopsy. Furthermore, patients with isolated ICI-realted gastritis exhibit a trend toward greater endoscopic severity of gastric inflammation (erosions/ulcerations/severe erythema *vs* mild erythema/normal) than those with concurrent enteritis/colitis ($P = 0.12$)[4]. Gastric biopsies in patients with endoscopic lesions often show pathohistological manifestations of active gastritis or chronic active pangastritis. Lymphoplasmacytic and granulocytic infiltration with scattered eosinophils in the lamina propria and epithelium, diffuse inflammation and crypt abscesses are usually observed[23,26,27,30-32]. Further immunohistochemical analysis demonstrated that the infiltrating lymphocytes were positive for CD3, with CD8+ prevailing over CD4+ but negative for CD20, and PD-L1 was positive in immune cells and/or epithelial cells[6,33]. The involvement of limited areas of the GI tract, such as the duodenum, stomach, ileum, or colon, suggests an underlying immune mechanism directed toward epitopes specific to this location.

Autoimmune gastritis or ICI-induced autoimmune-like gastritis need to be differentiated. A marked reduction in acid-secreting cells and destruction of the glands in the background of diffuse lymphoplasmacytic infiltration are typical manifestations of autoimmune gastritis under EGD[34]. In addition, peripheral blood is positive for B-cell antibodies, with concomitant pernicious anemia. ICI-associated immune gastritis also needs to be distinguished from *H. pylori* gastritis and cytomegalovirus gastritis. Unlike ICI-associated gastritis, *H. pylori* gastritis is characterized by significantly lower numbers of intraepithelial lymphocytes, more lamina propria inflammation, and more lymphoid aggregates[35]. However, lymphocyte phenotyping of *H. pylori* gastritis and nivolumab gastritis showed no difference in the number of lamina propria CD4+ cells or CD8+ cells[35]. A C-13 or C-14 blow test is a noninvasive method for differentiation of *H. pylori* infection. Cytomegalovirus (CMV) gastritis after immunotherapy has been reported, and a CMV inclusion body inside the cytoplasm is a hallmark[36]. Notably, autoimmune gastritis may be concurrent with *H. pylori* and/or CMV infection. For patients in whom *H. pylori* gastritis and CMV gastritis are initially excluded but symptoms worsen after steroid therapy, another EGD should be performed to exclude opportunistic *H. pylori* or CMV infection. In addition, gastric metastases can be seen as hemorrhagic, ulcer and fragile mucosa, which need to be differentiated from gastritis[37,38], and pathological biopsy to find tumor cells is well suited for identification.

POSSIBLE MECHANISM

The detailed mechanisms underlying ICI-related gastritis are poorly understood. A common view is that ICIs increase T-cell activation and proliferation, abrogate Treg functions, and possibly boost humoral autoimmunity, which results in irAEs[39]. Moreover, CTLA-4 inhibitors increase the number of circulating Th17 cells, decrease the number of circulating Tregs and contribute to irAEs[40-42]. PD-1/PD-L1 inhibitors regulate Tregs *via* deficient differentiation from Th1 cells to Treg cells, reducing the immunosuppressive effect of Treg cells and enhancing T-cell activation[33,43]. All these imbalances result in enhanced CD4+ and CD8+ T-cell activation and drive destruction of normal cells[44]. Furthermore, CTLA-4 and PD-1/PD-L1 inhibition results in increased cytokine production, such as TNF, IFN-γ and IL-17, which further leads to T-cell proliferation and activation as well as proinflammatory effects[39].

A common histological feature is an increase in CD8+ T cells but a decrease in CD4+ T cells. Hence, there is a hypothesis that PD-1 inhibitors promote gastritis through weak expression of CD4+ Treg cells and disturbed immune tolerance; strong expression of CD8+ T cells enhances the effect of cytotoxic T lymphocytes in attacking autologous organs[33]. Additionally, as PD-L1 is expressed in immune cells and/or epithelial cells, a novel hypothesis is that T cells actively attack antigens present on gastric epithelial cells, which exacerbates gastritis, but this needs to be assessed in a case-control study[6].

TREATMENTS FOR ICI-RELATED GASTRITIS

Because of the scarcity of prospective trials on drug immunosuppression in the setting of ICI-related gastritis, no guidelines exist for management, and clinicians can only seek information from small series studies and case reports on how to handle these challenging cases. Treatment decisions for ICI-related gastritis are based on individual clinical presentations. A wait and watch approach can be used for patients with EGD without symptoms[45]. Immunotherapy is often stopped after ≥ grade 2 gastritis occurs[7,46]. In several patients with isolated gastritis, symptoms have improved after PPI treatment alone[4]. However, in most cases, steroids are the first-line empirical agent. Indeed, early use and high doses of prednisone (1-2 mg/kg/d) lead to a favorable prognosis, with only 16.7% clinical recurrence[19]. Steroids can attenuate the CD28 signaling pathway and CD80 co-stimulation that partly impairs T-cell function[47]. With ICI cessation, use of prednisone and proton pump inhibitors, symptoms of ICI-related gastritis can rapidly subside within a week, but complete resolution under EGD will take months[3,31,48,49], and the longest remission is reported at 66 wk [50]. The use of steroids, most commonly prednisone, begins to taper when clinical symptoms reduce to grade 1, and *Pneumocystis Carinii* pneumonia and *Fungal* infections should be necessarily prevented for long-term steroid therapy (≥ 4 wk)[51-53]. For patients who have concomitant CMV infection, symptom improvement can be achieved with active antiviral treatment[49]. If no improvement is noted within 2 to 3 d on intravenous steroids (1-2 mg/kg/d), immunosuppression agents, such as TNF-α (*e.g.*, infliximab) or integrin blockers (*e.g.*, vedolizumab), can be used for this type of steroid-resistant gastritis. Retrospective data from a large cohort study of cancer patients administered ipilimumab reported that 103 (35%) of 298 patients received corticosteroids to manage an irAE and that 29 (10%) of 298 needed additional immunosuppressive drugs[54]. Vedolizumab can be used in treating steroid-refractory GI-irAEs. One study showed that 24 of 28 patients with steroid-resistant ICI-related colitis who received vedolizumab achieved clinical remission; 12 patients with EGD monitoring had nonulcerative inflammation or no signs by the last repeat EGD[55]. Patients with GI-irAEs who were initiated on infliximab within 14 d of starting steroids had good resolution, and the average time to infliximab response was 17 d[56]. Infliximab has been reported to be effective against steroid-resistant gastritis in several case reports[23,26,57], such as one patient whose symptoms did not resolve after 6 d of high-dose steroid treatment but improved significantly after 2 doses of infliximab (2-wk regimen)[23]. The duration of therapy with a TNF-α blocker (infliximab) or an integrin blocker (vedolizumab) is not clearly defined. Evidence supports use of up to 3 doses (at weeks 0, 2, and 6) to reduce risk of recurrence and increase the likelihood of endoscopic/histologic remission [58]. In addition, active parenteral nutrition, such as water and electrolyte balance and energy supplementation, preventive anti-infection treatment when needed, and symptomatic management, are important.

Despite the lack of prospective data, retrospective studies have shown that the use of steroids and immunosuppressants after irAEs does not reduce the efficacy of ICIs[53]. In 54 patients with ICI-related gastritis, the overall response rate and disease control rate were 52% and 74%, respectively, after immunotherapy[4]. Patients who developed GI-irAEs experienced a better response to ICI therapy than those who did not develop GI-irAEs (41% *vs* 27%, $P = 0.003$)[32]. Development of GI-irAEs was also associated with better overall survival[5]. However, for ICI-related gastritis, it is still unclear whether the occurrence of ICI-related gastritis correlates positively with better outcomes. Nevertheless, there was no clear correlation between the endoscopic severity or extent of inflammation and the response to ICIs ($P = 0.85$ and $P = 0.44$, respectively)[4]. More evidence is needed for better support.

RECHALLENGING IMMUNE CHECKPOINT INHIBITORS

After the complete resolution of irAEs, resumption of immunotherapy is of crucial importance for treatment and patient prognosis, as is the risk of relapse of irAEs. The recurrence rate of all kinds of irAEs is reported to be 28.6% after anti-PD-1 monotherapy resumption, 47.4% after anti-CTLA-4 monotherapy resumption, and 43.5% after combination therapy resumption in patients with various cancers[59]. A retrospective study reported that a lower recurrence rate of GI-IrAEs was found in 23.1% (6/26) of patients receiving another course of ICIs, 95% (25/26) of patients treated with anti-PD-1 as second-line therapy had no relapse within 3 months, and 88% (23/26) of patients had no relapse within one year[8]. Among the six patients who relapsed with the second ICI, the recurrence severity was grade I for 2/6 (33%), grade II for 2/6 (33%) and grade IV for 2/6 (33%); the outcome was favorable with medical treatment[8]. However, the incidence of recurrent ICI-related gastritis remains uncertain. Two studies demonstrated that 5 patients who recovered from ICI-related gastritis restarted immunotherapy without any recurrence of irAEs[60,61]. There is also a report of two patients who experienced recurrence of ICI gastritis at 10 to 12 wk after rechallenge with anti-PD-1 monotherapy, and EGD findings indicated milder lesions than those occurred during the first time (erythematous and edematous vs. network-pattern erosion or ulceration and fragile mucosa)[6]. A high possibility is increased awareness of ICI-related gastritis and EGD performed at an earlier stage. Moreover, it should be noted that patients with irAEs may experience autoimmune damage in other systems after restarting immunotherapy. According to a pharmacovigilance database review, when rechallenged after ICI discontinuation for irAEs ≥ grade 2, 39% experienced another ≥ grade 2 irAE at relapse[62].

In general, whether and when to restart ICI treatment should be based on the conditions. Limited data are available to support clinicians' decisions. Available data on the timing of ICI resumption after the first irAE show that it ranges from a median of 14 d to 60 wk[63]. One study involving ten patients with ICI-related gastritis found a median time of 2.8 months (range: 1.0-35.8) between treatment discontinuation and resumption of ICIs[27]. However, as complete resolution of symptoms will require a couple of months and the longest duration for resolution of inflammation is reported to be 66 wk, a new EGD examination or biopsy needs to be performed for confirmation before resumption of ICI treatment. Furthermore, the duration of steroid tapering, severity of initial irAEs and use of additional immunosuppressants do not

predict toxicity upon rechallenge, but patients who remain on steroid therapy at the time of anti-PD-1 therapy resumption have high rates of toxicity (55% *vs* 31%, $P = 0.03$)[64]. Moreover, the time of the first appearance of irAEs may help to predict their recurrence. Compared with the nonrecurrent group, the recurrent group had a shorter average time to first irAEs (9 wk *vs* 15 wk)[65]. Fecal calprotectin and lactoferrin are good biomarkers for monitoring irAE-colitis with rechallenge ICI therapy, but there is no biomarker to predict recurrence of ICI-related gastritis at present[66].

CONCLUSION

In conclusion, ICI-related gastritis is rare and should be suspected in patients with recurrent upper gastrointestinal symptoms and a history of immunotherapy. Adopting a proactive monitoring strategy is expected to reduce the occurrence of severe immune gastritis. EGD examination and biopsy are needed to confirm ICI-related gastritis. Early and adequate glucocorticoids can improve prognosis, and recommendation for re-examination of EGD before restarting ICI therapy. Furthermore, proper management of severe irAEs requires the efficient response and concerted decision of multidisciplinary teams. Such efforts will ensure that patients with cancer benefit from the highest quality of care as immunotherapy continues to evolve.

FOOTNOTES

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