Analysis of complications of giant gastric ulcers induced by hepatic arterial infusion chemotherapy or combined immunotherapy: A report of three cases

SHENG CHEN[1], NAN ZHAO[2], XIANGRONG LI[1] and DEDONG CAO[2]

[1]Department of Oncology, Xiaogan Hospital Affiliated to Wuhan University of Science and Technology, Xiaogan, Hubei 432000; [2]Department of Oncology, Renmin Hospital of Wuhan University, Wuhan, Hubei 430000, P.R. China

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Abstract. Primary liver cancer is a major public health issue in China, with high incidence and mortality rates. Notably, progress has been made in improving the surgical methods and hepatic arterial infusion chemotherapy (HAIC) regimens of liver cancer and the combination of HAIC with immunotherapy is expected to further increase the surgical conversion rate or objective response rate. However, patients with liver cancer often have underlying cirrhosis, which may lead to complications, such as esophageal varices and high-pressure gastric diseases. The present study describes three cases of giant gastric ulcers that occurred during the process of HAIC or combined immunotherapy. Notably, the causal relationship between HAIC and immunotherapy is unclear. In patients with tumors receiving immunotherapy, gastrointestinal adverse reactions are common, and some may develop serious complications, such as gastrointestinal perforation. The present study provides a detailed analysis of this issue and emphasizes the need for further clarification of its mechanisms and effective treatment methods.

Introduction

Primary liver cancer ranks sixth in incidence among malignant tumors and third in mortality, representing a significant global public health issue (1). According to statistics, it is currently the fourth most common malignant tumor and the second leading cause of tumor-related deaths in China, posing a serious threat to the life and health of the Chinese population (1,2). In recent years, improvements have been made to the surgical methods and hepatic artery infusion chemotherapy (HAIC) regimens of liver cancer. The FOLFOX regimen, based on oxaliplatin, has significantly improved tumor response rates, with high disease control rate and objective response rates (3-6). Furthermore, the combination of HAIC and immunotherapy has been suggested to further increase the surgical conversion rate and objective response rate (7-11).

Patients with liver cancer often have underlying liver cirrhosis, which is commonly associated with portal hypertension and complications, such as esophageal varices and high-pressure gastric diseases. In the Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China), three cases of giant gastric ulcer complications occurred during the process of HAIC or combined immunotherapy, with clinical manifestations of abdominal pain and severe nausea and vomiting, which were discovered upon re-examination by gastroscopy. In addition, patients with tumors receiving immunotherapy may also experience gastrointestinal adverse reactions, including nausea, vomiting, loss of appetite, bloating, constipation, diarrhea and abdominal pain (12-14). A small number (<1%) of patients may develop serious complications, such as gastrointestinal perforation (12). The cause of the adverse reactions in this case needs to be further identified, to determine whether it is due to HAIC or immunotherapy. The present study provides a detailed analysis of this issue.

Case report

Case 1. A 54-year-old male patient was admitted to Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China) in October 2021, due to multiple liver lesions found 4 years after liver cancer surgery. During a routine medical examination in March 2017, liver MRI revealed a space-occupying lesion, which was subsequently treated with left hepatectomy and microwave-assisted liver tumor ablation at another hospital in April 2017. The details of the surgery are unknown (the patient could not provide details). The patient

Correspondence to: Professor Xiangrong Li, Department of Oncology, Xiaogan Hospital Affiliated to Wuhan University of Science and Technology, 215 Huancheng Road, Xiaonan, Xiaogan, Hubei 432000, P.R. China
E-mail: 541514657@qq.com

Professor Dedong Cao, Department of Oncology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuchang, Wuhan, Hubei 430000, P.R. China
E-mail: caodedong123@whu.edu.cn

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underwent regular follow-up examinations and was diagnosed with a slightly hyperechoic nodule in the right anterior lobe of the liver measuring 2.08x1.91 cm by color Doppler ultrasound during an outpatient visit at the Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China) in December 2020. The nodule was considered to be a proliferative nodule, but it was not given much attention when it was found to have grown larger in subsequent regular follow-up examinations every 3 months as the nodules were not significantly enlarged at the time and were considered hyperplastic, they were not considered non-malignant. In October 2021, a color Doppler ultrasound revealed a slightly hyperechoic nodule in the right anterior lobe of the liver measuring 4.76x4.33 cm. A subsequent liver CT scan with contrast enhancement showed multiple low-density lesions in the right anterior lobe of the liver, with the largest one measuring 5.0x4.4 cm and the smallest one measuring 2.2x2.1 cm. The lesions were enhanced during the arterial phase and showed decreased density during the delayed phase. The branch of the portal vein in the right anterior lobe of the liver was poorly displayed, and the possibility of multiple malignant tumors in the right anterior lobe of the liver was suspected.

The patient underwent a bone scan and chest CT, but no metastases were found. Esophagogastric gastric varices and ulcers were not observed by gastroscopy. The patient then underwent a CT-guided liver biopsy of the right lobe liver mass. The pathological results of the biopsy showed liver cancer consistent with hepatocellular carcinoma. The results of immunohistochemistry (IHC) (Fig. S1) showed that Alpha-fetoprotein (AFP; Fig. S1A) was negative, Hepatocyte exhibited focal positivity (Fig. S1B), Arg-1 displayed weak positivity (Fig. S1C), was positive for CD34 (Fig. S1D), negative for CK19 (Fig. S1E), p53 exhibited a mutated pattern (Fig. S1F), and Ki-67 labeling index of ~10% (Fig. S1G). After excluding contraindications, the patient underwent transarterial chemoembolization (TACE). The procedure was successful, but the patient experienced pain in the liver area, mild liver dysfunction and gastrointestinal symptoms, such as nausea and vomiting, after the surgery. Supportive treatment was given, and the condition of the patient improved.

A follow-up examination with abdominal pain and contrast-enhanced CT in December 2021 showed that the lesion had decreased in size compared with previous examinations. The patient underwent hepatic arterial angiography and placement of a hepatic artery catheter after exclusion of contraindications. Subsequently, the patient received continuous HAIC with FOLFOX4 regimen [day 1: oxaliplatin (100 mg/m^2) over 2 h, calcium folinate (200 mg/m^2) over 2 h, 5-fluorouracil (5-FU; 400 mg/m^2) over 15 min and 5-FU (600 mg/m^2) over 22 h; day 2: calcium folinate (200 mg/m^2) over 2 h, 5-FU (400 mg/m^2) over 15 min and 5-FU (600 mg/m^2) over 22 h]. The chemotherapy was well-tolerated, and the patient did not report any significant discomfort. However, 7 days after the procedure, the patient experienced paroxysmal upper abdominal pain without any clear triggering factor, which did not improve with self-administration of proton pump inhibitor (PPI) and prokinetic drugs (specific medications unknown). After 10 days, a follow-up abdominal CT scan showed postoperative changes in the liver, liver cirrhosis, left hepatic duct dilation and bilateral kidney stones.

A gastroscopy performed 3 days later revealed a big irregular ulcer of ~3.0x8.0 cm on the anterior wall of the gastric body and angle, with a foul exudate-covered base and mucosal edema and congestion in the gastric fundus (Fig. 1A). Multiple biopsies were taken, and the pathological report indicated ulcerative changes. The patient was treated with pantoprazole sodium 40 mg administered intravenously twice daily, famotidine 20 mg intravenous infusion before bedtime and rebamipide 0.1 g orally three times daily, resulting in significant symptom improvement. The patient was discharged and continued treatment with oral pantoprazole sodium capsules 40 mg orally twice daily, famotidine 20 mg orally before bedtime, and rebamipide sodium 0.1 g orally three times daily for treatment. A follow-up gastroscopy conducted in February 2022, revealed that the size of the big irregular ulcer on the anterior wall of the gastric body and angle had decreased to ~3.0x1.5 cm (Fig. 1B). Subsequent gastroscopy performed in April 2022 showed that the ulcer had healed, leaving behind a scar (Fig. 1C).

Case 2. A 58-year-old male patient initially presented to Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China) with 1-week epigastric pain in March 2021, during which a CT scan revealed a mass with a cross-sectional diameter of approximately 6.4x5.6 cm in the lower segment of the right posterior lobe and caudate lobe of the liver. The mass showed heterogeneous moderate enhancement in the arterial phase and decreased enhancement in the delayed phase. Esophagogastric fundal varices and ulcers were not found by gastroscopy in early March. The patient underwent TACE followed by three rounds of immunotherapy with camrelizumab and lenvatinib. Camrelizumab injection, 200 mg, was administered in March, April and May, 2021. Lenvatinib, 8 mg, was orally administered once daily as targeted therapy. The patient was diagnosed with liver tumor with multiple intrahepatic metastases during a laparoscopic exploration and tumor biopsy under general anesthesia, ultrasound and endoscopy in June 2021. The postoperative pathology indicated necrosis of tumor cells, and the patient was discharged after recovery.

Between June 2021 and November 2021 (21 days between treatments per cycle), the patient underwent eight cycles of targeted immunotherapy with oral lenvatinib (12 mg) and intravenous camrelizumab (200 mg). In December 2022 the patient's tumor progression was assessed, and they subsequently underwent a hepatic artery angiography and left hepatic artery catheterization the next day (Fig. 2C). An endoscopy 26 days later revealed a large ulcer with uneven and edges that had irregular, hole-like patterns (~3.0x4.0 cm) covered in pus in the lesser curvature of the gastric antrum, with the surrounding mucosa forming a ramp-like bulge that was hard and brittle. Eight biopsies were taken, and pathology results showed gastric ulceration with partially high-grade dysplasia (data not shown), indicating that adenocarcinoma could not be excluded. Further examination via ultrasound endoscopy in January 2022 revealed a thickened and irregular heterogeneous hyperechoic lesion with an interrupted mucosal layer and unclear boundaries, with the intrinsic muscle layer at the site of the gastric lesion (Fig. 2A). The pathology revealed a gastric ulcer

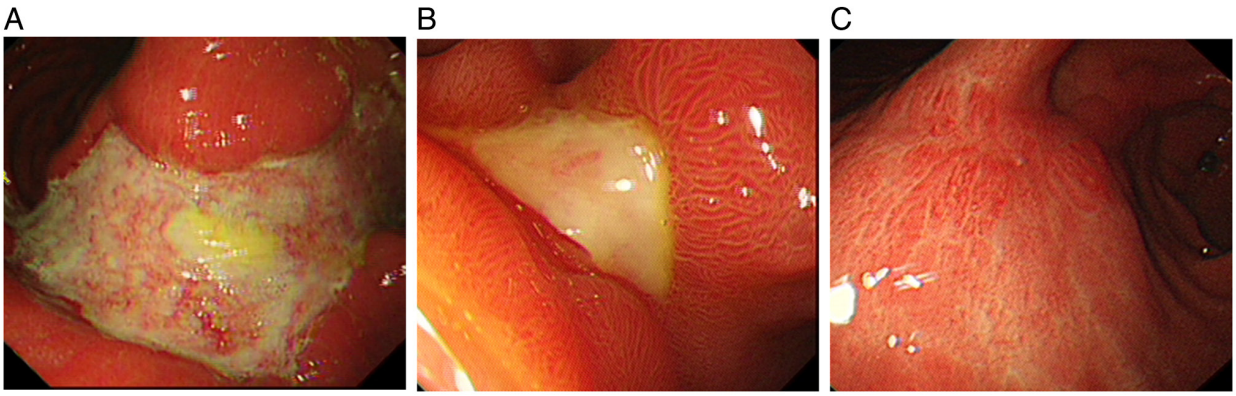

Figure 1. Gastroscopy results in (A) December 2021, (B) February 2022 and (C) April 2022.

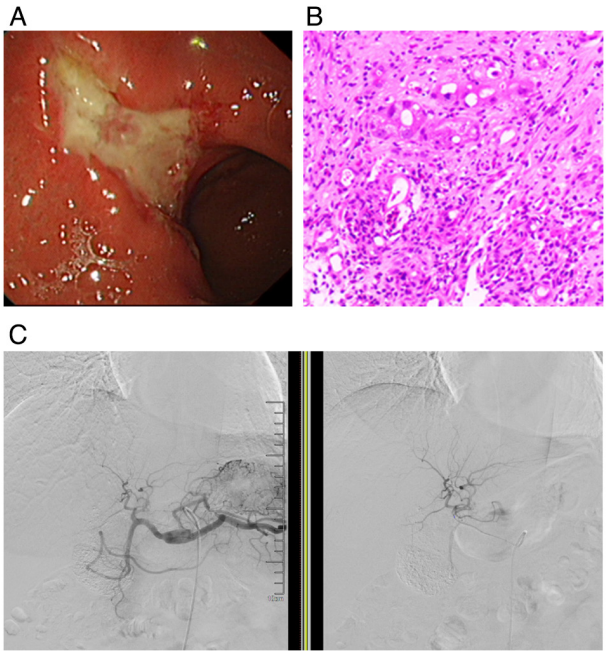

Figure 2. Gastroscopy, biopsy pathology, and hepatic artery catheterization results in Case 2. (A) Gastroscopy results in January 2022. (B) Pathological results of the biopsy. Magnification, x100. (C) Hepatic artery catheterization image with hepatic artery contrast agent.

with concavity and mucosal epithelial dysplasia, with some high-grade intraepithelial neoplasia (Fig. 2B).

In January 2022, after discussion with the multidisciplinary team and family consultation, the patient underwent a laparoscopic distal gastrectomy and a laparoscopic right hepatectomy under general anesthesia. The postoperative pathology report revealed the following findings: i) Stomach: Chronic gastric ulcer with an ulcer size of ~4.0x3.5 cm, partial glandular atypia, and no apparent surrounding mucosal or omental involvement. The lymph nodes had not been invaded by the tumor cells. ii) Liver tumor: Moderately differentiated hepatocellular carcinoma with a nodule size of ~1.8x1.8 cm. No obvious intravascular cancer embolus or significant tumor necrosis or hemorrhage was observed and no invasion into the liver capsule was noted. Gastric tissue IHC (Fig. S2) showed the following: AFP(-) (Fig. S2A), hepatocyte(+) (Fig. S2B), CK19(-) (Fig. S2C), CK8/18(+) (Fig. S2D), CD10(-) (Fig. S2E), Ki-67 labeling index (~40%) (Fig. S2F), Galectin-3(+) (Fig. S2G), Arg-1(focal +) (Fig. S2H), CD31 (vascular +) (Fig. S2I) and carcinoembryonic antigen(-) (Fig. S2J).

Case 3. A 28-year-old male patient was found to have elevated AFP during a physical examination at Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China) in April 2021. Contrast-enhanced CT of the liver revealed left lobe liver mass, with the possibility of liver cancer. The patient's serum AFP level was 1,263 ng/ml (normal range <20 ng/ml). In November 2021, the patient underwent laparoscopic left hepatic lobectomy under general anesthesia. The postoperative pathological examination showed that part of the liver resected was low-grade hepatocellular carcinoma (nodule size, 2.0x1.5 cm), with visible vascular cancer emboli, but no obvious nerve invasion or residual cancer at the margin of the cut (data not shown). IHC (Fig. S3) showed the following: AFP (+), hepatocyte (partially positive), Arg-1 (focally positive), CD34 (positive in stromal blood vessels), CD31 (positive in interstitial blood vessels), CK8/18 (+), Glypican-3 (+), PCK (+) and Ki-67 (~35%). The patient's recovery after surgery was smooth. No esophagogastric fundal varices and ulcers were observed by gastroscopy in December 2021.

Between December 2021 and May 2022 (21 days between treatments per cycle), the patient underwent five cycles of HAIC + liver arterial infusion chemotherapy + sintilimab immunotherapy (FOLFOX4). Specifically, the dose was oxaliplatin (130 mg) + 5-FU (600 mg) x 2 days + 5-FU (1,950 mg) x 2 days + sintilimab (200 mg). During the fifth HAIC, the patient experienced significant gastrointestinal reactions, such as nausea and vomiting, which improved after symptomatic treatment. On the fifth day after HAIC, they experienced epigastric pain at home without any obvious reason for induction, and were treated with esomeprazole 20 mg orally once daily and famotidine 20 mg orally once daily for acid suppression, but the result was not satisfactory. Gastroscopy in May 2022 showed: mucosal congestion and edema in the lesser curvature of the stomach, along with a large ulcer of 5.0x4.0 cm. Multiple biopsy samples were taken. (Fig. 3A). Endoscopic gastric biopsy pathology indicated chronic superficial atrophic gastritis (Fig. 3B). Gastroenterology consultation recommended the addition of pantoprazole sodium injection 40 mg orally twice daily and rabeprazole sodium 0.1 g orally three times daily for anti-ulcer treatment for one week. The

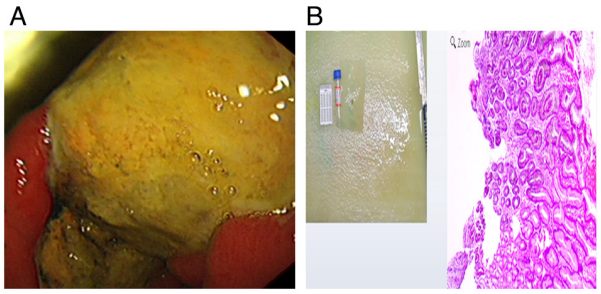

Figure 3. Endoscopic and pathological results in Case 3. (A) Endoscopic results in May 2022. (B) Pathological results of gastroscopic biopsy. Magnification, x100.

symptoms improved after treatment, and the patient continued to take the above medications for 3 months thereafter.

Histopathological review of tissues. All IHC primary antibodies were from Beijing Zhongshan Jinqiao Biotechnology, Co., including arginase-1 mouse monoclonal antibody (cat. no. ZM-0328, clone number OT1IH4), CD34 mouse monoclonal antibody (cat. no. ZM-0046, clone number 10C9), hepatocellular mouse monoclonal antibody (cat. no. ZM-0131, clone number OCH1E5). Chromogenic reagents included improved iodine oxidation for activating horseradish peroxidase (HRP), diaminobenzidine (DAB) + substrate buffer, DAB + chromogenic agent and DAB enhancer.

Paraffin sections were placed in fresh xylene and soaked for 10 min x 3 times. Excess liquid was removed and the sections placed in absolute ethanol and soaked for 3 min x 3 times. Excess liquid was removed and the sections placed in 95% ethanol, soaked for 3 min x 2 times and then soaked for 3 min x 2 times in 75% ethanol, rinsed with distilled water for 1 min and then place in PBS buffer solution at room temperature.

The slide was placed in 0.01 M citrate buffer (PH 6.0), and microwaved at 100˚C. After natural cooling at room temperature for ~20 min, no additional methods such as ice were used to accelerate the cooling process. After reaching room temperature, the slides were removed and rinsed with PBS buffer for 5 min 3 times for 10 min at room temperature.

An appropriate amount of endogenous peroxidase blocking agent was added to the sections, which were incubated at room temperature for 10 min and rinsed with PBS buffer solution for 3 min x 3 times.

The thickness of the tissue sections was between 4-6 μm, with a diameter of ≤2 centimeters. Then, 100 μl of primary antibody was added and incubated at 37˚C for 60 min and rinsed with PBS buffer solution at room temperature for 3 min 3 times.

Then 100 μl of enzyme-labeled goat anti-mouse IgG polymer was added and incubated 37˚C for 20 min and rinsed with PBS buffer solution at room temperature for 3 min 3 times.

An appropriate amount of freshly prepared DAB or AEC chromogenic solution was added and incubated at room temperature for 5-8 min.

The sections were rinsed with tap water, incubated in hematoxylin staining solution for 20 sec, differentiated and rinsed in running tap water until blue. The sections were dehydrated as aforementioned, cleared and sealed

The staining results were observed and interpreted under an optical microscope by qualified pathologists from Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China).

Discussion

HAIC is a major treatment for advanced primary liver cancer, with proven efficacy (15). There have been numerous reports on the occurrence of gastric and duodenal mucosal lesions after HAIC treatment (16); however, to the best of our knowledge, no cases of HAIC or combined immunotherapy leading to giant gastric ulcers have been reported. Notably, the mortality rate of peptic ulcers in patients with cirrhosis has been reported to be five times higher than that of the general population (17). However, the mechanism is not well understood. Different factors are said to be involved, such as altered serum gastrin levels, decreased gastric acid secretion, gastric mucosal blood flow and gastric mucosal prostaglandin production, in addition to a correlation with *Helicobacter pylori* infection. However, in all three cases, gastric ulcers were excluded by preoperative gastroscopy.

Mucosal lesions of the gastric and duodenal mucosa caused by simple HAIC are mostly due to vascular variations. The gastric and duodenal arteries mainly supply blood to the greater curvature of the stomach, while the right gastric artery supplies blood to the lesser curvature. The affected areas are mainly located in the pyloric region and angle of the stomach, the greater curvature of the stomach body and the upper portion of the duodenal bulb and descending portion, which is consistent with the blood supply range of the gastric and duodenal arteries (18). In ~50% of the population, the gastric and duodenal arteries originate from the midpoint between the origin of the hepatic artery from the celiac trunk and its division into the left and right hepatic arteries (19,20). With this anatomical structure, placing the catheter outside the stomach and duodenum, and entering the appropriate hepatic artery should be the ideal choice for HAIC. In 25% of the population, the intrahepatic artery is very short (<1.0 cm) or absent (19,20), which makes it possible to inadvertently insert the catheter into the right or left hepatic artery. However, this is clearly not suitable for patients with lesions in both the left and right liver. For example, in case 2 (Fig. 2C) it was found that the gastroduodenal artery originated from an intermediate position between the beginning of the common hepatic artery in the abdominal trunk and the division of the common hepatic artery into the right and left hepatic arteries. This anatomical variation was not emphasized, in order to perfuse the entire hepatic tissue, and the catheter was placed in the common hepatic artery. Consequently, during the administration of chemotherapy drugs via the hepatic artery catheter, inadvertent perfusion of the gastroduodenal artery occurred,. In addition, there are variations in the length of the hepatic artery (20), making it difficult to insert the conventional hepatic arterial catheter into the right (or left) branch of the hepatic artery or the intrahepatic artery. During first treatment, due to the abundant blood supply to the tumor most of the chemotherapy drugs enter the tumor; however, during retreatment the reduced blood supply

to the tumor makes it easier for the chemotherapy drugs to enter the gastric and duodenal arteries or the right gastric artery, resulting in loss of drugs. In addition to the aforementioned factors, direct damage to the gastroduodenal mucosa by anticancer drugs is an underestimated factor, particularly the damage caused by 5-FU and/or stress ulcers induced by other anticancer drugs. During treatment, the possibility of this serious complication must be highly suspected if upper abdominal pain persists for a prolonged period, especially if accompanied by epigastric tenderness and abdominal distension. Acute gastroscopy examination should be performed immediately, and abdominal CT, gastrointestinal angiography or upright abdominal radiography and abdominal puncture should be conducted if necessary, to exclude perforation. Routine use of gastromucoprotective agents and H2 receptor blockers, such as chewable aluminum magnesium carbonate tablets, famotidine, omeprazole enteric-coated capsules or rabeprazole, is recommended following HAIC treatment to protect the gastroduodenal mucosa. Adequate hydration to promote the excretion of anticancer drugs is also crucial. It is important to identify and avoid these abnormal arteries (those that deviate from the vast majority), such as the gastroduodenal artery, right gastric artery or pancreaticoduodenal artery, during HAIC treatment, and to perform appropriate ligation to prevent damage to non-target organs. Additionally, when inserting a catheter, it is preferable to select the hepatic artery or its branches as precisely as possible (18).

Although the colon is the most common site for immune-related adverse events, inflammation related to immune checkpoint inhibitors (ICIs) may also occur in the upper gastrointestinal tract (13). Symptoms, such as nausea, vomiting and abdominal pain, typically coexist with gastrointestinal symptoms and are generally lacking in specificity. Reports of upper gastrointestinal involvement take the form of esophagitis, gastritis and duodenitis, often as case reports (16).

Gastroscopy is an effective method to confirm the occurrence of a gastric ulcer and evaluate its severity. When patients experience persistent grade 1 upper abdominal pain for >1 week, endoscopic examination should be performed. ICI-induced gastritis exhibits a variety of endoscopic features (14) and being cautious of three characteristic endoscopic findings is crucial: i) Antral erosions or ulcers; ii) mucosal erythema and edema with excessive white purulent secretion throughout the stomach; and iii) markedly fragile mucosa. Pathological examination is the gold standard for diagnosing gastritis. A previous study reporting characteristic findings in the clinical pathology of 20 patients receiving ICI treatment showed a lack of significant intraepithelial lymphocytes and crypt rupture (21). In a case report of acute erosive hemorrhagic gastritis induced by cindilimab (22), a more extensive and severe lesion was found during gastroscopy, with the entire gastric mucosa was significantly swollen and congested with opaque mucus adhesion and diffuse white plaque-like erosions, and active local bleeding was widely observed. Necrotic mucosa and large areas of shedding were found in the antrum.

Nivolumab, a monoclonal antibody against the programmed death 1 (PD-1) receptor, has been reported to induce gastritis in some cases (23-25). The appearance of ICI-induced gastric ulcers on gastroscopy may show irregular, raised or friable lesions with peripheral inflammation. By contrast, other gastric ulcers may have different features, such as well-defined margins or a more typical appearance. Gastric biopsy specimens from these studies showed marked infiltration of lymphocytes and neutrophils in the gastric mucosa. IHC identified these lymphocytes as mainly $CD3^+$ T cells, $CD4^+$ helper T cells and $CD8^+$ cytotoxic and suppressor T cells.

The exact pathogenic mechanisms of immune-related gastrointestinal adverse events are not yet fully understood, although several mechanisms have been proposed (26). It has been suggested that immune checkpoint inhibition reduces the regulation of autoreactive T cells, ultimately leading to immune-mediated adverse reactions and damage (21,27). For example, cell and tissue damage may be due to autoreactive $CD8^+$ T cells. Alternatively, self-antibodies produced by $CD4^+$ T cells mediated by plasma antibodies may damage cells and tissues. The lymphocyte composition observed in the present cases were similar to previous reports, with $CD4^+$ and $CD8^+$ lymphocytes being predominant, and IHC may aid in diagnosing upper gastrointestinal disease caused by ICIs. For patients with gastrointestinal symptoms, accurate diagnosis should be made based on the patient's clinical course, and endoscopic and histological findings.

In conclusion, HAIC combined with immunotherapy may increase the risk of gastric ulcers. Therefore, attention should be paid when selecting the appropriate placement of the HAIC catheter by identifying vascular variations. While it is important to actively screen for the cause of gastric ulcers, early detection of gastric ulcers seems to also be important, as it is the basis for early and effective treatment. In the present study, in the second of the three cases, the gastric ulcer was directly related to vascular degeneration, which was associated with the lack of relevant surgical experience in the early stage of this gastric ulcer. For the first and third cases, the causes of gastric ulcer may be related to immunotherapy, but not vascular variations as there was no vascular mutation in the Case 1 and Case 3 patients. In the three cases, gastric ulcers were found to be cured after anti-ulcer treatment, and no gastric ulcers were found after reuse of HAIC combined with immunotherapy. In the Xiaogan hospital affiliated to Wuhan University of Science and Technology (Hubei, China), there have been >30 cases of HAIC combined with immunotherapy, >10 cases of HAIC and >70 cases of simple immunotherapy combined with targeted therapy in patients with hepatocellular carcinoma since 2021, all of which have not yet developed gastric ulcers.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DC and XL conceived the present study. SC, NZ and XL performed the experiments. SC and NZ wrote the manuscript. DC and XL critically reviewed the manuscript. SC and XL confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Xiaogan Hospital Affiliated to Wuhan University of Science and Technology (approval no. XGLY2021-12-23; Xiaogan, China).

Patient consent for publication

All patients provided their written consent for the publication of their data and associated images.

Competing interests

The authors declare that they have no competing interests.

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