Sintilimab-induced acute erosive hemorrhagic gastritis as an adverse reaction of third-line therapy in a nasopharyngeal carcinoma patient: A case report

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Abstract. Immune checkpoint inhibitors (ICIs) have become an important treatment option for patients with nasopharyngeal carcinoma. With the increasing use of such agents, immune-related adverse events (irAEs) have become a concern. Identifying and managing the toxicity and side effects of ICIs is crucial, since it not only has implications for their safety but also the intensity and efficacy of subsequent use by patients. The present case report documents a 40-year-old male patient with acute erosive hemorrhagic gastritis associated with sintilimab treatment. In particular, the clinical manifestations, treatment, side effects and prognosis of this case was focused upon. The patient was diagnosed with locally advanced nasopharyngeal carcinoma (cT4N3M0 stage IVa) and developed bone metastases after 1 year of standard radiotherapy and adjuvant chemotherapy. After the first- and second-line treatments, pulmonary metastases occurred and sintilimab monotherapy was used as the third-line therapy. During the course of treatment, the optimal outcome for this patient was partial response according to the Response Evaluation Criteria in Solid Tumors (version 1.1). However, after 14 cycles of sintilimab the patient developed melena and epigastric pain and was diagnosed with acute erosive hemorrhagic gastritis, which was treated with methylprednisolone therapy. Progression-free survival with the third-line treatment was 542 days. Sintilimab-associated hemorrhagic gastritis is not fully recognized as an irAE. Therefore, early identification, diagnosis and management of irAEs are critical for subsequent therapy and progression-free survival of patients.

Introduction

With the development of immune checkpoint inhibitors (ICIs) for the treatment of various malignancies, cancer therapy has entered into a new era of immunotherapy (1). According to statistics released by the International Agency for Research on Cancer, China had the highest incidence of nasopharyngeal cancer (NPC) in 2020, with ~60,000 new cases, accounting for 46.8% of the global cases (2). Treatment regimens for the different stages of NPC vary. Early-to middle-stage NPC is typically managed by local radiotherapy or synchronous chemoradiotherapy. In advanced NPC cases, induction chemotherapy is frequently selected before chemoradiotherapy to achieve long-term survival (3-7). By contrast, programmed cell death protein-1 (PD-1) combined with chemotherapy is the standard first-line treatment for patients with distant metastases (8,9).

PD-1 is expressed on the cell membrane of various immune cells, including activated T cells, B cells, dendritic cells, activated monocytes and tumor-infiltrating lymphocytes. By contrast, its ligand programmed cell death ligand-1 (PD-L1) is expressed on the surface of tumor cells and antigen-presenting cells. PD-1 binds to PD-L1 and prevents the T cells from recognizing tumor cells, leading to tumor immunosuppression (10). However, sintilimab, a monoclonal antibody against PD-1 (11), binds to PD-1 and blocks its interaction with its ligand, thereby restoring the antitumor response of T cells (12). Sintilimab has been successfully used to treat Hodgkin's lymphoma, non-small cell lung cancer, hepatocellular carcinoma, gastric cancer and esophageal cancer (12-17). Although sintilimab has shown efficacy for the treatment of these tumors, its side effects and potential harm to patients remain an unavoidable concern. According to a previous study (11), the incidence of all-grade adverse reactions from sintilimab treatment is >58.0%, whereas the incidence of grade ≥3 adverse reactions

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is 13.0%. Among the immune-related adverse events (irAEs) of ICIs, acute hemorrhagic gastritis is rare, with only five documented cases (18-22). For irAEs such as colitis and diarrhea, relevant grading criteria and treatment guidelines have been published (23,24), but a lack of consensus concerning upper gastrointestinal adverse reactions remains.

In the present report, acute erosive hemorrhagic gastritis occurred 51 weeks after the first sintilimab injection, where the patient also developed drug-related hypothyroidism and suspected myocardial injury. The patient achieved a partial tumor response with sintilimab treatment, and the progression-free survival (PFS) was 542 days.

Case report

A 40-year-old man with a mass on the right side of his neck was first diagnosed with poorly differentiated squamous cell carcinoma of the nasopharynx and cervical lymph node metastasis (cT4N3M0; stage IVa) at Mianyang Central Hospital (Mianyang, China) in May 2017. As a result, radical radiotherapy, image-guided radiotherapy (IGRT) [planning target volume (PTV)-gross tumor volume of nasopharyngeal carcinoma, 74 Gy/33 F; PTV-gross tumor volume of lymph node, 70 Gy/33 F; PTV-clinical target volume, 60 Gy/33 F] and four cycles of adjuvant chemotherapy [paclitaxel injection 210 mg on day 1 + cisplatin injection 30 mg on days 1-4, repeated every 3 weeks (Q3W)] were initiated in May 2017.

Single metastases in the right iliac crest with pain presented on May 2018, for which the patient received palliative radiotherapy (IGRT, dose 54 Gy/18 F) followed by four cycles of first-line chemotherapy starting in July 2018 (gemcitabine 1.2 g on days 1 and 8 + nedaplatin 100 mg on day 1, repeated Q3W).

In September 2019, the patient showed general disease progression and metastatic sites in the left lungs and right iliac crest. Subsequently, 15 days later (October 2019), the patient was scheduled for six cycles of chemotherapy (gemcitabine 1.6 g on days 1 and 8 + cisplatin 30 mg on days 1-3, repeated Q3W). The tumor was controlled during this treatment, but metastatic lesions developed ~11 months later in August 2020.

In September 2020, intravenous (IV) sintilimab (200 mg on day 1, repeated Q3W) was initiated as the third-line of regimen. Prior to the ICI injection, the patient was tested for thyroid hormones, adrenal hormone, myocardial injury marker and other immunological tests, all of which returned normal result. Fatigue and bilateral anterior tibial edema developed ~137 days after sintilimab injection. The thyroid function tests of the patient showed free triiodothyronine levels of 1.50 pg/ml, free thyroxine levels of 0.40 ng/dl and thyroid-stimulating hormone levels of 87.4909 μIU/ml. Based on thyroid reports, the patient was diagnosed with drug-induced hypothyroidism and was prescribed thyroxine tablets 25 μg orally once a day in January 2021. Thyroid hormone levels were monitored during treatment and the dose of thyroxine tablets was adjusted according to the thyroid hormone level. The changes in thyroid hormone levels are shown in Fig. S1.

On day 167, the patient's creatine phosphokinase-MB, a myocardial injury marker, and myohemoglobin levels were 8.33 and 128.8 μg/l, respectively. Echocardiography revealed no abnormalities and a diagnosis of immune myocarditis

was considered. Since the patient did not have any related symptoms, no additional treatments were administered at the time. In total, 10 days later, creatine phosphokinase-MB and myohemoglobin were retested, where the results were 6.74 and 144.4 μg/l, respectively.

On day 329, the patient experienced subxiphoid pain and developed melena (treatment protocol detailed in Fig. 1). A gastroenterologist advised treatment using omeprazole [20 mg orally (p.o.) per day (qd)], trimebutin maleate [0.2 g p.o. 3 times a day (tid)] and chewable magnesium aluminum carbonate tablets (1 g p.o. tid). The antitumor treatment, scheduled for 1 week later, was suspended.

However, 1 month after the initiation of acid suppression treatment, the symptoms did not improve, and gastroscopy was performed. Gastroscopy indicated diffuse swelling with scattered bleeding and a pale pseudomembrane covering the surface of gastric mucosa (Fig. 2A). Contrast-enhanced abdominal CT revealed that a large area of the stomach wall was thickened and edematous (Fig. S2). The gastroenterologist adjusted the patient's treatment regimen with somatostatin [3 mg IV every 12 h (q12 h)] and esomeprazole sodium (40 mg IV q12h) during hospitalization. At 2 weeks after this infusion treatment, gastroscopy showed diffuse mucosal swelling with a pale pseudomembrane on the surface and scattered blood exudation, similar to the previous gastroscopy results (Fig. 2B). The gastroenterologist did not adjust the treatment plan and continued with the original infusion treatment for another week. The subsequent gastroscopy suggested that the gastric mucosal bleeding had worsened (Fig. 2C).

Since the patient's symptoms persisted, the gastroenterologist could not explain the relationship between the treatment and gastroscopy results. After consultation with an oncologist, the patient was considered to have immune-related gastritis and was recommended to be treated with methylprednisolone, an immunosuppressive agent (40 mg IV twice a day). On day 5 of treatment, the patient's abdominal discomfort was significantly relieved, and his feces turned yellow. Therefore, the dosage was reduced. In total, 10 days after the entire treatment course, the regimen was changed to oral prednisone acetate tablets (30 mg qd), which were gradually withdrawn.

On day 428, gastroscopy revealed a smooth gastric mucosa, reduced mucosal congestion and edema, with no signs of active exudation (Fig. 2D). During the exacerbation of gastric mucosal hemorrhage, the pathological examination of the gastric antrum revealed moderate chronic inflammation of the mucosa with erosion, glandular atrophy and partial dilation of glandular lumens. In addition, multiple lymphoid aggregates, plasma cells and scattered neutrophil infiltration were observed in the lamina propria. There was also intraepithelial lymphocytic infiltration accompanied by mucosal erosion (Fig. 3A). Immunohistochemical staining showed infiltration of CD3+ T cells and CD8+ T cells in the gastric mucosal epithelium, with significant infiltration of CD4+ T cells, CD8+ T cells, and CD20+ B cells in the lamina propria. The lymphoid aggregates were predominantly composed of CD20+ B cells, whilst CD8+ T cells infiltrated the epithelium and CD4+ T cells were mainly distributed between the glands. The ratio of CD4+ T cells to CD8+ T cells in the lamina propria was 1.5-2:1 (Fig. 3B). Based on the classification criteria and treatment guidelines for irAEs (25), the patient experienced a
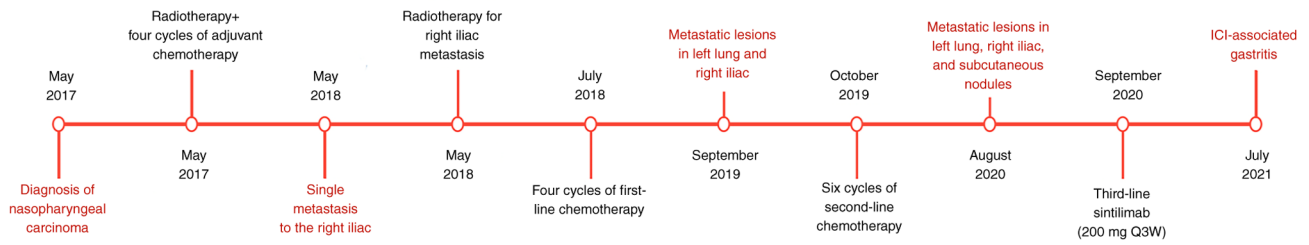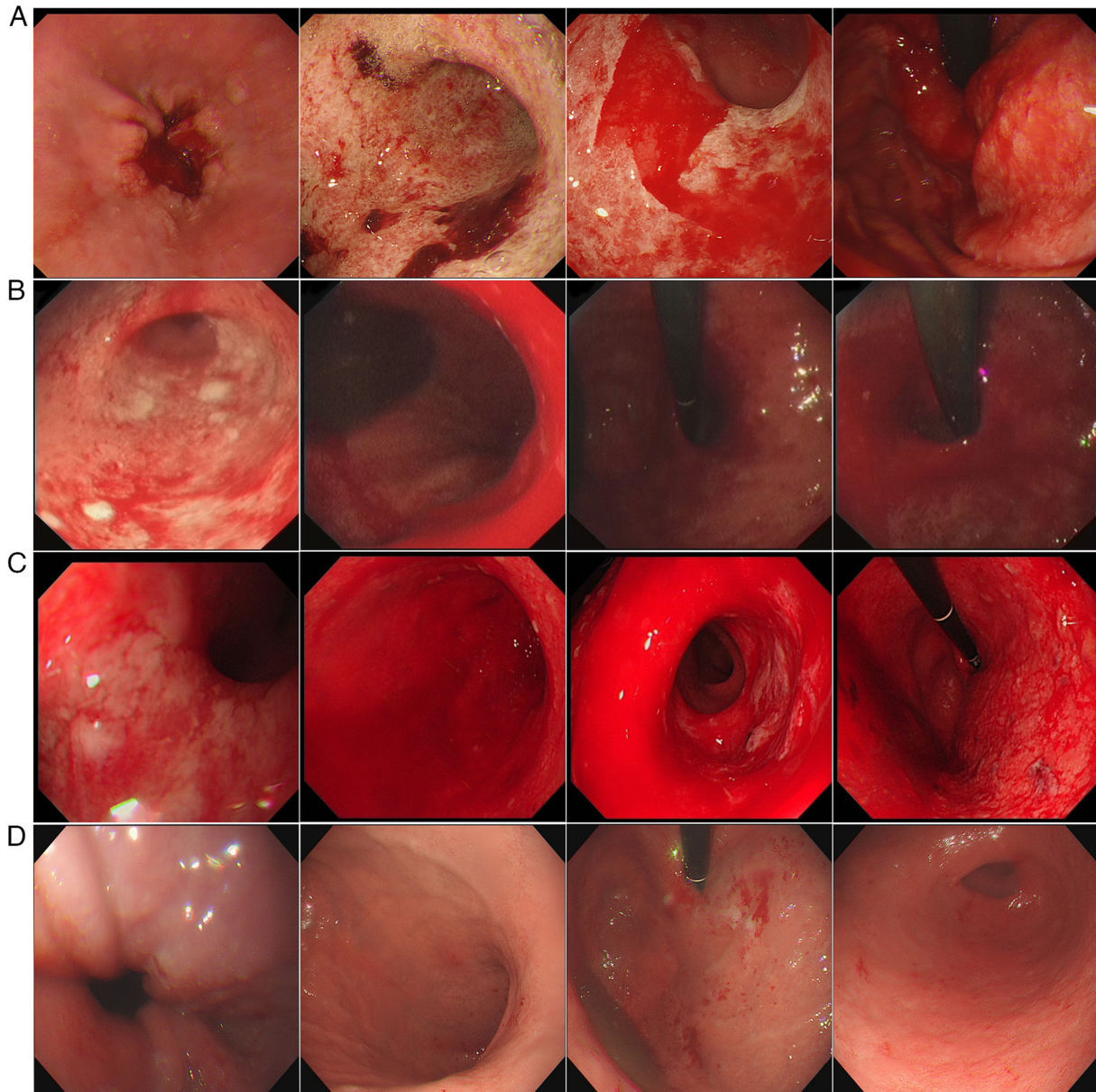
Figure 1. Timeline of the treatment course.

Figure 2. Representative gastroscopy images. (A) Gastroscopy showed diffuse mucosal swelling, pale pseudomembrane on the surface and scattered bleeding (day 360). (B) Re-examination of gastroscopy showed diffuse mucosal swelling with paler pseudomembrane on the surface and scattered blood oozing, with more significant oozing in the cardia area, which was not improved compared with the previous gastroscopy (day 374). (C) Gastroscopy suggested that the gastric mucosal bleeding was worse than before (day 385). (D) Gastroscopy indicated smooth gastric mucosa, significantly reduced gastric mucosal congestion and edema and no signs of active exudation (day 428).

grade 3 or higher adverse events. Therefore, further sintilimab therapy was stopped. Longitudinal changes in CT imaging findings reflecting tumor progression and treatment response throughout the therapeutic course are illustrated in Fig. S3. Following drug withdrawal, the patient was prospectively monitored until February 2022 through serial 6-month
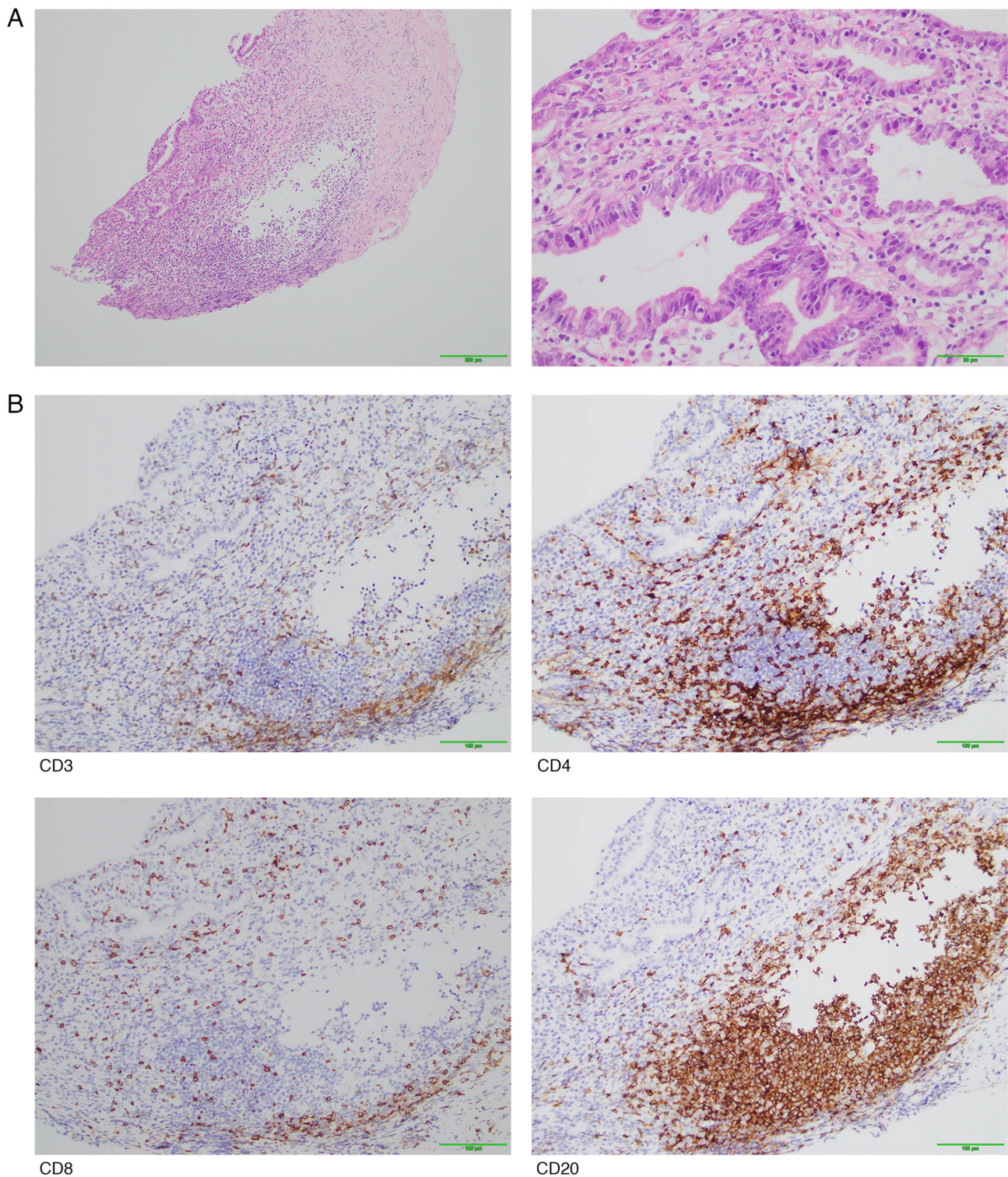
Figure 3. Pathological staining results. (A) H&E staining pictures of the gastric mucosa of the patient. Pathological findings of moderate chronic inflammation of the mucosa with erosion, glandular atrophy and partial dilation of glandular lumens. Multiple lymphoid aggregates, plasma cells and scattered neutrophil infiltration were observed in the lamina propria. There was also intraepithelial lymphocytic infiltration accompanied by mucosal erosion. Representative H&E staining of gastric mucosa (left: magnification, x100; scale bar, 200 μm; right: magnification, x400; scale bar, 50 μm). (B) Immunohistochemical staining showed infiltration of CD3^{+} T cells and CD8^{+} T cells in the gastric mucosal epithelium, with significant infiltration of CD4^{+} T cells, CD8^{+} T cells and CD20^{+} B cells in the lamina propria. The lymphoid aggregates were predominantly composed of CD20^{+} B cells, whilst CD8^{+} T cells infiltrated the epithelium and CD4^{+} T cells were mainly distributed between the glands. The ratio of CD4^{+} T cells to CD8^{+} T cells in the lamina propria was 1.5-2:1 (magnification, x200; Scale bar, 100 μm). H&E, hematoxylin and eosin.

imaging evaluations-including contrast-enhanced MRI of the nasopharynx and CT scans of the chest/abdomen/neck-to continuously assess treatment response, with radiographic progression in the lung and mediastinal lymph nodes documented in Fig. S4. Sintilimab therapy achieved a PFS of 18 months. Subsequently, the patient ultimately succumbed to

disease progression in September 2023. The patient provided written informed consent for publication prior to their death.

Discussion

ICIs have changed the course of treatment for various malignant tumors. Blocking PD-1/PD-L1 binding using ICIs restores T cell-mediated antitumor immune responses and enhances tumor cell death. At present, clinically used ICIs include PD-1, PD-L1 and cytotoxic T lymphocyte-associated antigen 4 antibodies (26). The present case reports a case of sintilimab-induced hemorrhagic gastritis observed in a patient receiving third-line anti-PD-1 monoclonal antibodies. The patient experienced multi-system irAEs during drug treatment, including hypothyroidism, suspected myocardial injury and hemorrhagic gastritis. After active treatment, the patient recovered completely from hemorrhagic gastritis, where all the irAEs were well controlled. The patient achieved partial response after anti-PD-1 treatment, where the toxicity and side effects were controllable. This suggests that hemorrhagic gastritis as a result of sintilimab for the treatment of advanced NPC should be added to its list of potential irAEs.

The incidence of irAEs during immunotherapy is ~20%, where the combination of ≥2 immunotherapeutic agents or the presence of an autoimmune disease increases the risk of irAEs (27). The common manifestations of irAEs include dermatitis, fatigue, endocrine system injury, colitis, pneumonia, arthritis, musculoskeletal injury and liver injury. Rarer irAEs include gastrointestinal bleeding, cardiovascular injury, pancreatic injury, ocular injury, and neurological injury (28-30). However, the majority of irAEs are not severe, where favorable remission is frequently achieved after the discontinuation of immunotherapeutic drugs and symptomatic treatment with steroids. IrAEs may occur during any period of immunotherapy, even after the final treatment. In the present case, hypothyroidism developed 19 weeks after the initiation of immunotherapy and immune-associated hemorrhagic gastritis developed at 51 weeks.

The hallmark endoscopic features of ICI-associated hemorrhagic gastritis include diffuse gastric mucosal erythema and edema. Three distinctive patterns warrant particular diagnostic attention: i) Reticular erosions/ulcers in the antrum; ii) diffuse mucosal congestion covered by thick yellowish-white plaques; and iii) contact-induced hemorrhages upon minimal instrumentation. Patterns i) and iii) show high specificity for ICI-associated gastritis. By contrast, pattern ii) requires differentiation from *H. pylori*-induced gastritis, since heavy purulent exudates may also occur in severe infectious cases (31,32). Endoscopic maneuvers (insufflation pressure and scope contact) may artifactually exacerbate exudate formation, necessitating cautious interpretation (33).

The symptoms of ICI-associated hemorrhagic gastritis are non-specific and may mimic those of other etiologies. Consequently, clinical symptoms alone are insufficient for diagnosing ICI-gastritis. Definitive diagnosis requires integration with characteristic endoscopic findings, particularly mucosal vulnerability and reticular erosions in the antrum. The histopathology of ICI-associated hepatitis and colitis has been extensively studied (34,35). However, to the best of our knowledge, the histopathological features of gastric involvement remain poorly defined (36).

ICI-associated gastritis includes chronic active gastritis, idiopathic lymphocytic gastritis and granulomatous gastritis, with periglandular inflammation (37). Chronic active gastritis, the most common type of gastric injury caused by ICI therapy, is characterized by increased lymphocytic infiltration of the lamina propria and increased intraepithelial lymphocytes and neutrophils, with or without neutrophilic gland abscesses. In ~80% cases of chronic active gastritis caused by ICI therapy, intraepithelial lymphocytes are increased, where these epithelial cells are predominantly CD8$^+$ T cells. Although chronic active gastritis is superficially similar to *H. pylori* gastritis in the majority of cases of ICI-associated gastritis, the former is typically more destructive and ulcerous, whilst chronic active gastritis has milder lymphatic infiltration of the lamina propria, less lymphocyte aggregation and increased intraepithelial lymphocytes. Syphilitic gastritis, although extremely rare, can manifest as full-thickness chronic gastritis with dense plasma cell infiltration. However, this diagnosis can be easily ruled out by the lack of high-risk clinical features, endarteritis and poorly formed granulomas (38). Idiopathic lymphocytic gastritis is a disease with an increase in intraepithelial lymphocytes, mainly CD8$^+$ T lymphocytes. Unlike chronic active gastritis with intraepithelial lymphocytosis, idiopathic lymphocytic gastritis is not associated with active gastritis. *Foci* of active neutrophilic inflammation can be seen in idiopathic lymphocytic gastritis, from which it may be almost indistinguishable. However, lymphocytosis is rarely associated with marked neutrophilic inflammation and apoptosis in biopsies obtained from patients with idiopathic lymphocytic gastritis. Viral-associated gastritis can also be shown with intraepithelial lymphocytosis on gastric biopsy. However, in the context of immunotherapy, the majority of common infections, such as cytomegalovirus, herpes simplex virus, adenovirus and Epstein-Barr virus, can be typically ruled out by prebiopsy microbiological testing (39). Focal-enhancing gastritis is characterized by a small collection of lymphocytes and histiocytes surrounding a small group of actively inflamed gastric pits or glands, forming focal-enhancing lesions. Periglandular inflammation is characterized by inflammation of the pit, isthmus and neck of the stomach, which is predominantly comprised of lymphocytes and granulomatous inflammation and is not associated with the rupture of the gastric glands. Focal-enhancing or perigenoidal gastritis, especially when combined with granulomas, may resemble granulomatous gastritis in infection, sarcoidosis or inflammatory bowel disease (Crohn's disease). However, in ICI-associated gastritis, histiocytes within focal-enhancing lesions are typically loosely intermingled with neutrophils and eosinophils, rather than the discrete epithelioid granulomas frequently seen in infections involving the stomach, sarcoidosis, or Crohn's disease (40,41). Finally, the diagnosis of ICI-associated gastritis is effectively a diagnosis of exclusion. On the basis of excluding other causes of gastritis, recognizing the gastroscopic manifestations and histopathological types of ICI-associated gastritis and before associating them with the time course of symptoms after treatment will be key for pathologists to make a diagnosis of ICI-associated gastritis.

To the best of our knowledge, ICI-associated hemorrhagic gastritis has been rarely reported, where there are no relevant grading criteria or treatment guidelines. The gastroscopy results of the present patient indicated an acute inflammatory reaction in the stomach, which is more frequently caused by heavy drinking or long-term drug use (42). However, the patient in the present case had no history of peptic ulcers and was not taking long-term nonsteroidal anti-inflammatory drugs or alcohol. Only sintilimab was administered during the period of hemorrhagic gastritis, making hemorrhagic gastritis caused by sintilimab highly likely. In addition, cytomegalovirus infection may also lead to hemorrhagic gastritis (43). However, the present patient did not have a cytomegalovirus infection, because viral inclusion bodies were not found in the tissue sections (44). The patient was initially treated with a proton pump inhibitor, but there was no improvement in the bleeding symptoms. Subsequently, methylprednisolone sodium succinate was administered, leading to rapid alleviation of the symptoms. This further indicates that the patient's hemorrhagic gastritis was indeed induced by ICIs rather than other causes. Due to the current lack of diagnostic criteria for ICI-associated gastritis, the diagnosis of this condition was essentially a process of elimination. After ruling out other potential causes of gastritis and considering the patient's clinical symptoms, endoscopic findings, pathological biopsy, immunohistochemical results, medical history and treatment course, it was concluded that the diagnosis of gastrointestinal bleeding induced by sintilimab occurred in the current case.

A previous study found that irAEs are associated with patient prognosis (45) and that patients who develop irAEs have longer overall survival (OS), PFS, and objective remission rates (46-50). In non-small cell lung cancer, patients presenting with multiple irAEs have prolonged OS and PFS compared with those presenting with single irAEs (51). In the present case, the patient also showed initial multi-system adverse reactions during immunotherapy. Severe adverse reactions may be associated with a superior prognosis. Gemcitabine combined with cisplatin (GP), as the standard first-line treatment for recurrent or metastatic NPC, has a median PFS of 7.0 months and a median OS of 29.1 months (52). The median PFS was 11.7 months in the toripalimab plus GP group and 8.0 months in the GP alone group [hazard ratio (HR), 0.52; P=0.0003] (8). The median PFS was 9.7 months in the combination group and 6.9 months in the GP group (HR, 0.54; P=0.0002) (9). In the present case, the PFS3 was >1.5 years and the patient remains alive. The PFS time may be associated with superior benefits for patients with ICI-related multi-system damage, as reported in the literature.

After the occurrence of hemorrhagic gastritis, according to the treatment principles of ICI-associated colitis, patients are not recommended for PD-1 antibody treatment again for irAEs grade ≥3. The present patient was followed-up regularly after improvement of the hemorrhagic gastritis. The patient's right iliac and subcutaneous nodules remained stable for 1 year whilst he was off sintilimab. However, right lung and mediastinal lymph node enlargement were present. To determine whether the patient could undergo ICI treatment again, the literature was investigated. According to a previous study, 25-33% patients who discontinued ICI therapy after their first irAE experienced recurrence of the same irAE after reinitiation of the concerned ICI. Therefore, ICI reuse may be beneficial for patients who develop irAEs and progress again after ICI discontinuation (53). In the present case, the efficacy was satisfactory and the PFS was achieved for ~1.5 years after the third-line treatment with single-drug sintilimab. However, reactivating PD-1 monoclonal antibodies was considered too high a risk for the present patient, where after the multi-disciplinary discussion, IGRT was scheduled to shrink the mediastinal lymph nodes.

In conclusion, the present report highlights a rare case of ICI-associated hemorrhagic gastritis, whereas with other irAEs, recognition and appropriate treatment of ICI-associated gastritis cannot be underestimated. When clinicians suspect ICI-associated gastritis, immunosuppressive agents, such as glucocorticoids, should be used immediately. It is hoped that the present case will increase clinician awareness of ICI-associated hemorrhagic gastritis and provide a reference for physicians in similar situations.

The present study has several limitations. The diagnosis of suspected immune myocarditis remains uncertain; although transient elevations in creatine phosphokinase-MB and myohemoglobin were observed, the absence of clinical symptoms, normal echocardiography and spontaneous resolution without intervention weaken the causal association with sintilimab. Additionally, while the management of ICI-associated hemorrhagic gastritis achieved symptomatic relief through endoscopic mucosal evaluation and glucocorticoid step-up therapy, the underlying immune mechanisms remain unclear due to the lack of systematic immunomonitoring (dynamic profiling of cytokines such as interleukin-6 and interferon-γ). It is critical to emphasize that endomyocardial biopsy-the gold standard for diagnosing immune myocarditis-is clinically underutilized due to its invasiveness. Future studies should optimize non-invasive diagnostic parameters (cardiac biomarkers, electrocardiography, echocardiography, cardiac MRI and PET/CT) to improve sensitivity and specificity. Concurrently, elucidating the immunopathology of ICI-associated hemorrhagic gastritis requires longitudinal analysis of cytokine dynamics and multi-omics investigations to characterize the evolving immune microenvironment of gastric mucosa, thereby comprehensively mapping disease pathogenesis and progression. Ultimately, constructing toxicity surveillance systems, developing personalized therapeutic strategies, and achieving precise immune homeostasis modulation will be critical to advancing immune therapy management paradigms.

Availability of data and materials

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

Authors' contributions

WT, XD and FG conceptualized the study. WT, YL, XY, KG, GF, JL, LN and YB collected the data. WT and YL wrote the original draft preparation. XD and FG wrote, reviewed and edited the manuscript. FG supervised. FG acquired funding. XD and FG 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

Ethical review and approval were not required for the report on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Patient consent for publication

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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