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# Multiple Gastric Carcinomas Associated with Epstein-Barr Virus and *Helicobacter pylori*: A Thought-Provoking Case

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Statistical Analysis C  
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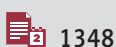
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Conflict of interest: None declared

**Patient:** Male, 60-year-old  
**Final Diagnosis:** Gastric carcinoma  
**Symptoms:** Asymptomatic  
**Medication:** —  
**Clinical Procedure:** Surgical resection  
**Specialty:** Gastroenterology and Hepatology

**Objective:** Rare co-existence of disease or pathology**Background:** Epstein-Barr virus (EBV) and *Helicobacter pylori* (HP) infections are associated with gastric carcinoma (GC). We present a thought-provoking case of multiple GCs associated with EBV and HP infections.

**Case Report:** HP infection was incidentally detected in an asymptomatic 60-year-old man. Upper endoscopy revealed gastric “kissing” ulcers. The lesions were located in the body of the stomach and measured 25 and 27 mm, respectively. They were diagnosed on pathology as moderately differentiated tubular adenocarcinoma. Imaging revealed no enlarged lymph nodes or distant metastatic lesions. Distal gastrectomy with lymphadenectomy was performed and surgical cure was obtained. The multiple GCs were categorized on pathology as infβ ly0 v0 pT1b(SM)UL1NOM0H0POCY0 pStage IA according to the Japanese classification and as T1bN0M0 Stage IA according to the tumor, node, metastasis classification. Pathological examination revealed remarkable lymphocytic infiltration into the stroma, as shown by in situ hybridization of EBV. These lymphocytic infiltrations were observed only at the sites of GC. In the immunohistochemical examination, in situ hybridization of EBV was positive for EBV-encoded small ribonucleic acid. The patient’s postoperative course was uneventful. Hence, an unexpected relationship between EBV infection and multiple GCs was suggested by pathology. Quantitative determination of EBV DNA in peripheral blood was normal postoperatively. Adjuvant chemotherapy was not recommended. HP eradication therapy was successful. The patient remained asymptomatic and developed no recurrence or metastasis for 3 years after surgery.

**Conclusions:** This thought-provoking case suggests that coinfection with EBV and HP increases GC occurrence.**Keywords:** *Helicobacter pylori* • Herpesvirus 4, Human • Neoplasms • StomachFull-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/931668>

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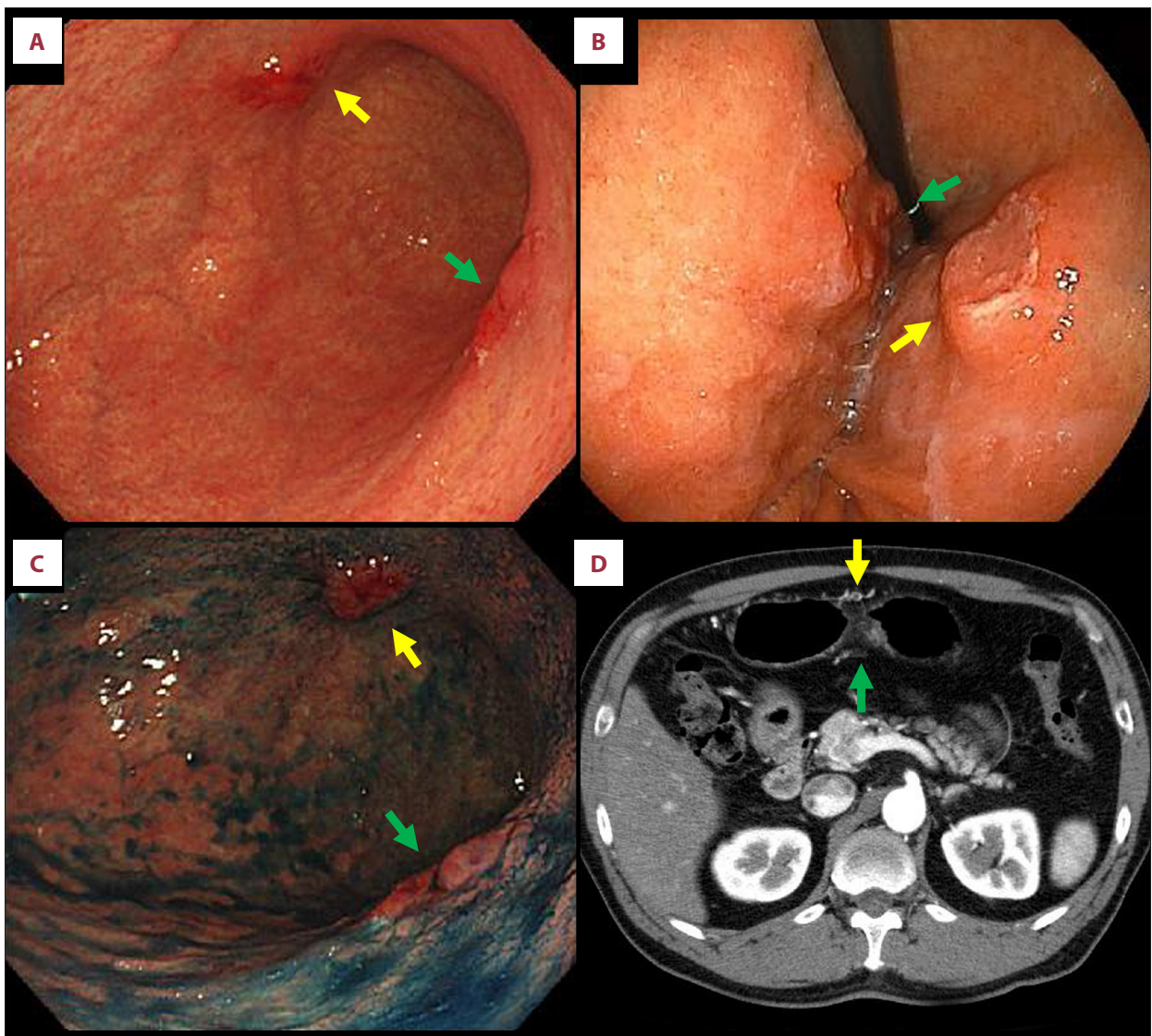
## Background

Gastric carcinoma (GC) is the fifth most commonly diagnosed cancer [1] and the third leading cause of cancer-related death in both sexes worldwide [1]. Epstein-Barr virus (EBV) was the first oncogenic virus to be identified in humans [2-4]. EBV infection is closely associated with various human cancers [5,6], and it can induce GC with unique genomic aberrations [2,7]. GC associated with EBV is typically poorly differentiated adenocarcinoma with lymphoid stroma. *Helicobacter pylori* (HP) infection causes gastroduodenal ulcers, chronic atrophic gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and GC [8-10]. HP infection is significantly associated with GC

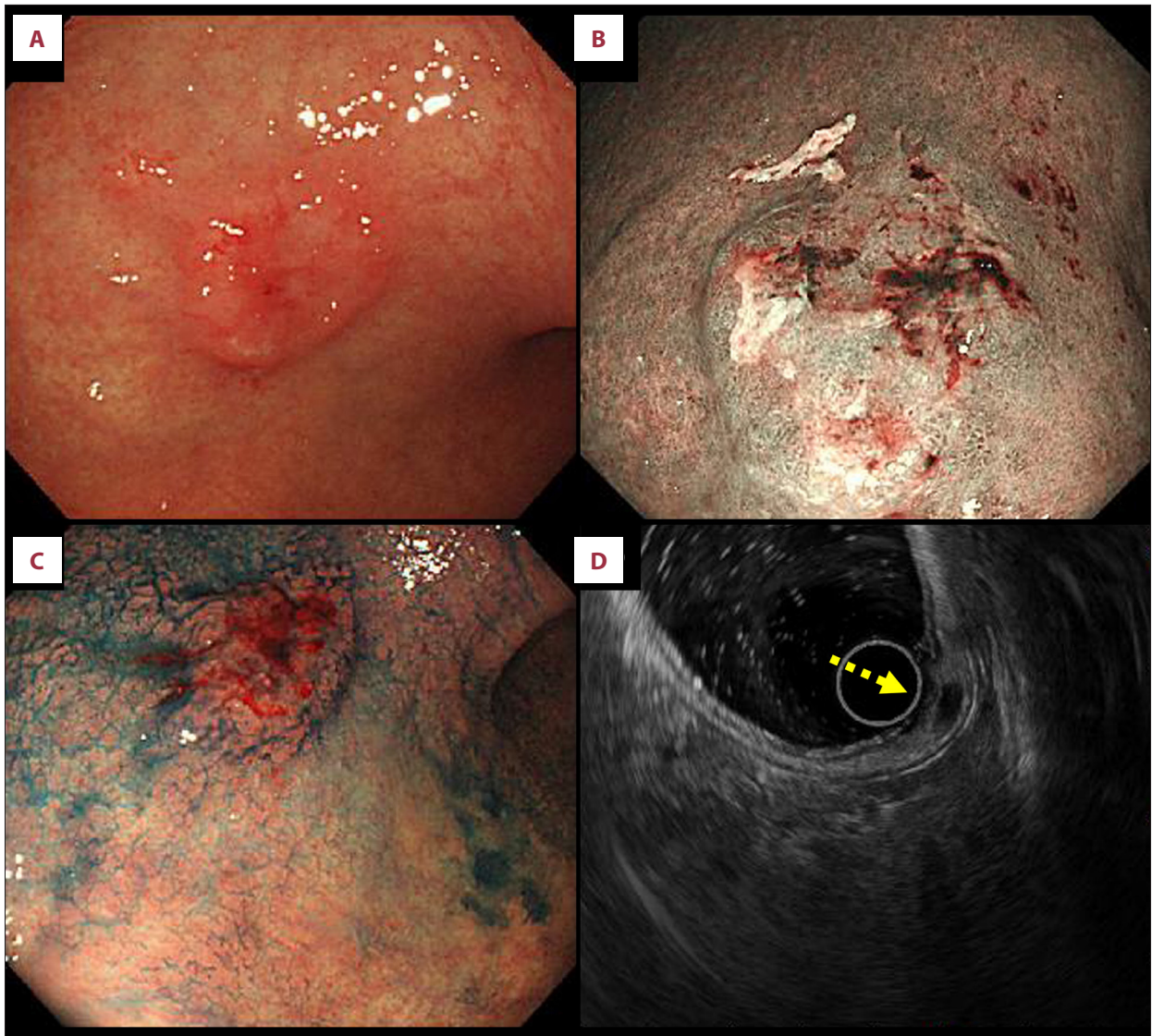
development [8-10] and accounts for more than 95% of gastric cancers [11]. Eradication therapy has proven effective for HP infection. We present a thought-provoking case of multiple GCs associated with EBV and HP infections, which suggests that coinfection may be associated with gastric carcinogenesis, as is discussed in our literature review.

The data presented were retrospectively evaluated and the patient provided written informed consent authorizing the use and disclosure of his protected health information.

The present report was approved by the Institutional Review Board of Shiga General Hospital, Moriyama, Japan.



**Figure 1.** Multiple gastric carcinomas. (A-C) “Kissing” lesions were observed in the stomach. The 2 lesions (yellow and green arrows) were located in the anterior (yellow arrow) and posterior walls (green arrow) of the gastric body. They were pathologically diagnosed as moderately differentiated tubular adenocarcinoma. (D) Both lesions (yellow and green arrows) were detected with dynamic computed tomography. GC – gastric carcinoma.

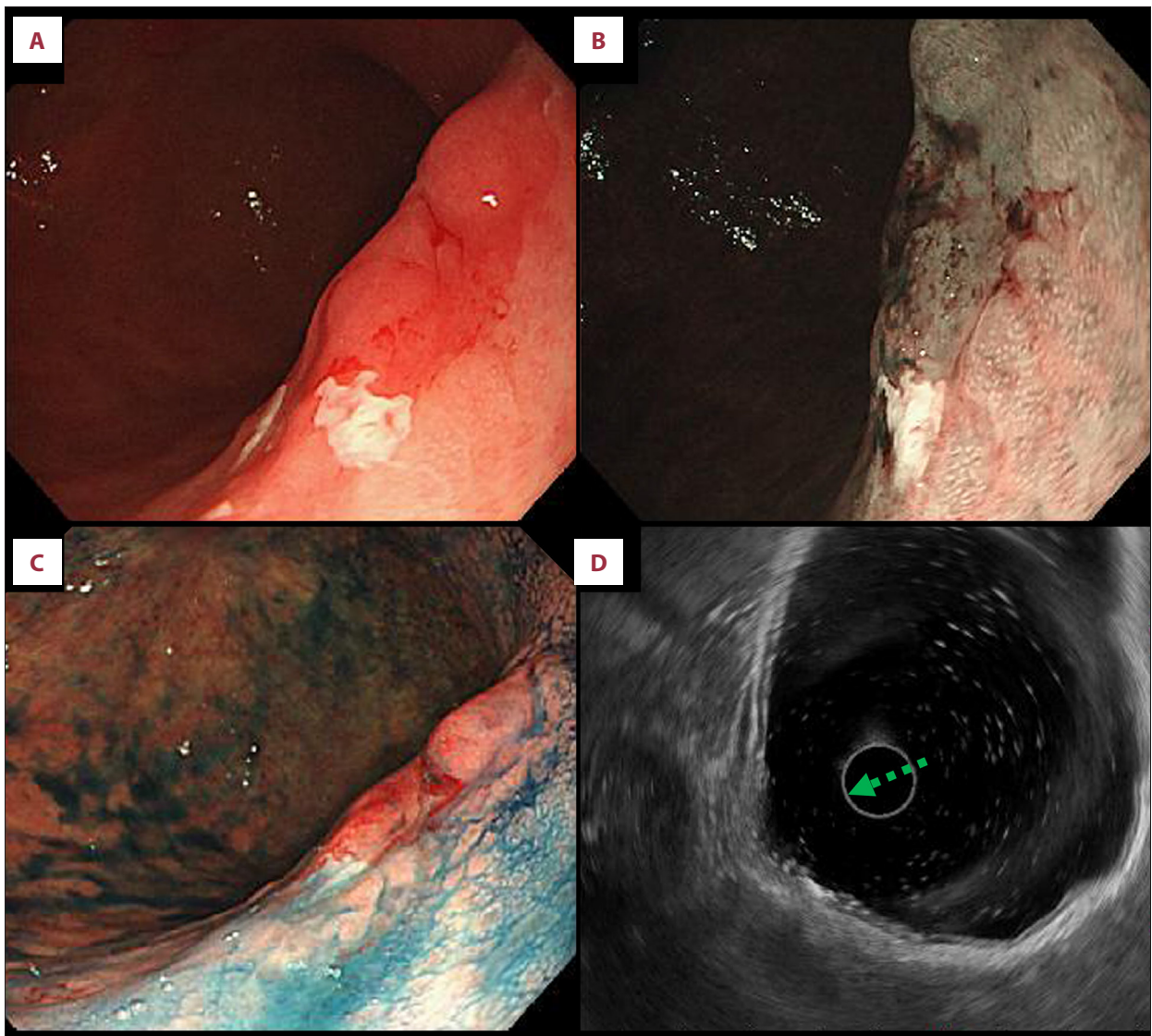


**Figure 2.** Gastric carcinoma (GC) in the anterior wall of the gastric body. (A-C) The GC lesion in the anterior wall of the gastric body measured 27 mm. (D) Endoscopic ultrasound (dotted yellow arrow) revealed that the carcinoma had invaded the submucosal layer. GC – gastric carcinoma.

## Case Report

During a medical checkup, HP infection was incidentally detected in an asymptomatic 60-year-old man. He underwent upper endoscopy, during which gastric “kissing” lesions were observed (Figure 1A-1C). Pathological assessment of biopsy specimens revealed that the lesions were moderately differentiated tubular adenocarcinoma. The patient was referred by his physician to our hospital for a detailed work-up and surgery. Both gastric lesions were visible on dynamic computed tomography (Figure 1D), but the imaging revealed no enlarged lymph nodes or distant metastases. The patient’s serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 levels were normal. The GC lesion in the anterior wall of

his gastric body was 27 mm and categorized as 0-IIa+IIc type according to the Japanese classification [12] (Figure 2A-2C); endoscopic ultrasound revealed invasion to the submucosal layer (Figure 2D). The GC lesion in the posterior wall of the gastric body was 25 mm and categorized as 0-IIa+IIc type according to the Japanese classification [12] (Figure 3A-3C). Endoscopic ultrasound, however, suggested that this GC may have invaded the muscularis propria (Figure 3D). Both GC lesions were categorized as cT2(MP)NOM0 cStage I according to the Japanese classification [12] and as T2NOM0 Stage I according to the tumor, node, metastasis (TNM) classification [13]. In keeping with the Japanese guideline [14], distal gastrectomy with D2 lymphadenectomy and cholecystectomy was performed. Negative margins (ie, PM0 and DM0 according to the



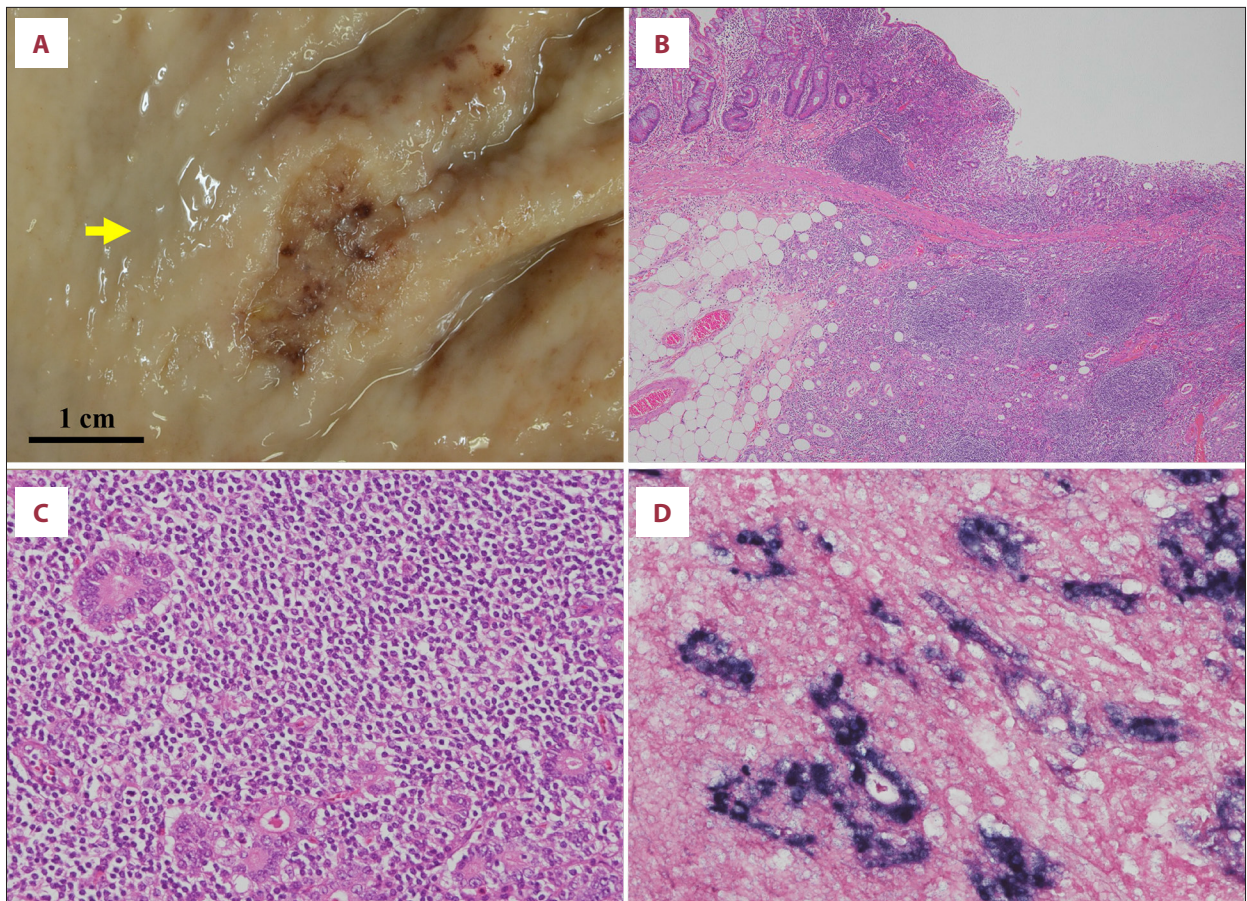
**Figure 3.** Gastric carcinoma (GC) in the posterior wall of the gastric body. (A-C) The GC in the posterior wall of the gastric body measured 25 mm. (D) Endoscopic ultrasound (dotted green arrow) suggested that the carcinoma might have invaded the muscularis propria. GC – gastric carcinoma.

Japanese classification [12]) were histopathologically confirmed during surgery. An R0 resection for surgical cure, according to the Japanese classification, was completed [12]. Then, an antecolic Roux-en-Y reconstruction was performed and the jejunum of Roux-en-Y reconstruction was anastomosed to the gastric remnant in an overlapping fashion.

Pathological examination revealed that neither moderately differentiated tubular adenocarcinoma had invaded the muscularis propria (Figures 4A, 4B and 5A, 5B). Seventeen lymph nodes were harvested and no metastases were observed. Both GC lesions were categorized as inf $\beta$  ly0 v0 pT1b(SM) UL1NOM0H0PCY0 pStage IA according to the Japanese classification [12] and as T1bN0M0 Stage IA according to the TNM

classification [13]. Pathological examination showed marked lymphocytic infiltration into the stroma, as indicated by in situ hybridization of EBV (Figures 4B, 4C and 5B, 5C). These lymphocytic infiltrations were observed only at the sites of GC. On immunohistochemical examination, in situ hybridization of EBV was positive for EBV-encoded small ribonucleic acid (Figures 4D and 5D).

The patient began a normal diet 4 days after surgery. His postoperative course was uneventful and he was discharged from our hospital 12 days after surgery. Quantitative determination of EBV DNA in a blood sample was performed postoperatively because an unexpected relationship between EBV infection and multiple GCs was suggested by the pathology. However,



**Figure 4.** Macroscopic findings and microscopic assessments of the gastric carcinoma (GC) in the anterior wall of the gastric body. (A) Macroscopic findings from the GC in the anterior wall of the gastric body (yellow arrow). (B, C) Pathologic findings based on hematoxylin and eosin staining (B,  $\times 80$ , C,  $\times 200$ ). Both moderately differentiated tubular adenocarcinomas had invaded the submucosal layer. Marked lymphocytic infiltration into the stroma was seen on in situ hybridization of Epstein-Barr virus (EBV). (D) Immunohistochemical examination with in situ hybridization of EBV was positive for EBV-encoded small ribonucleic acid. EBV – Epstein-Barr virus, GC – gastric carcinoma.

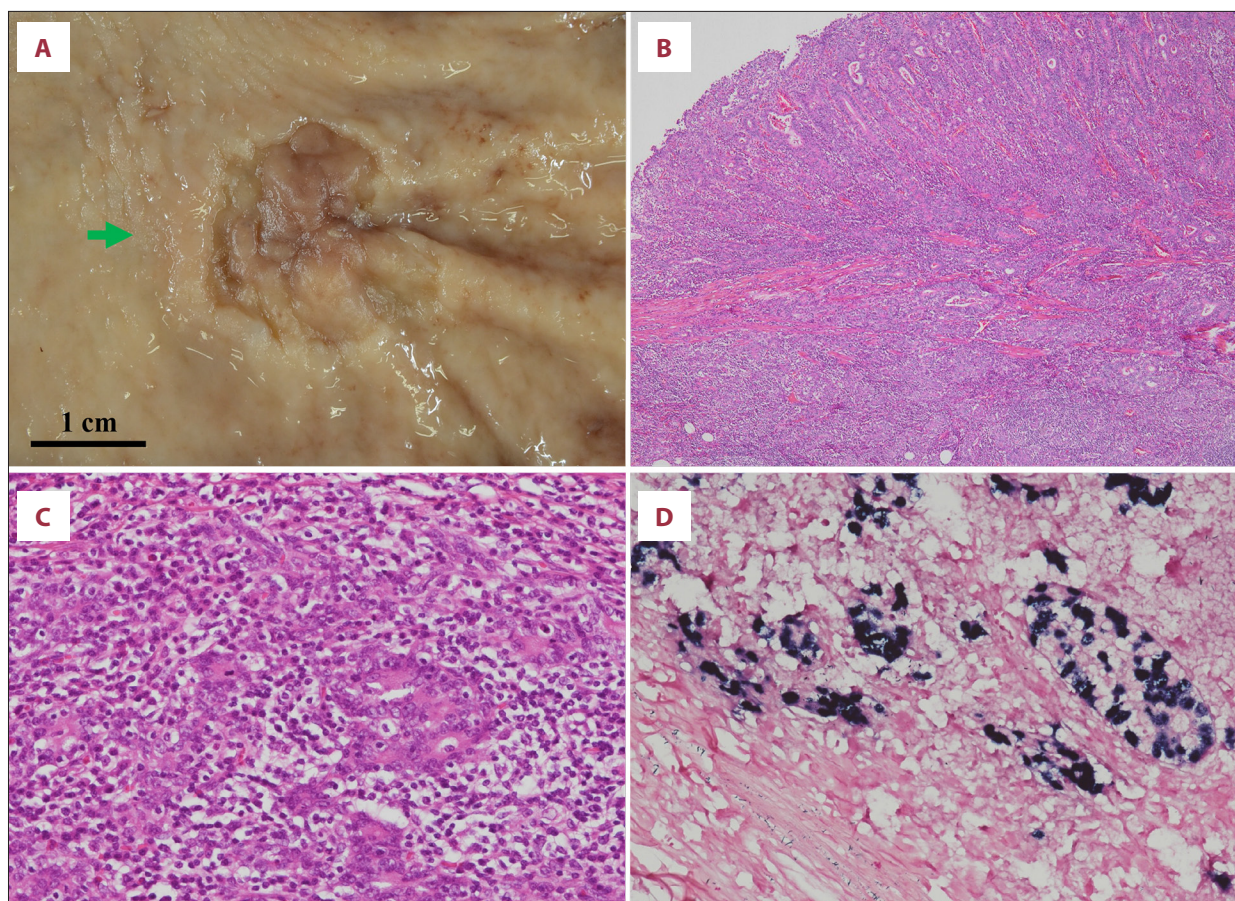
the EBV DNA level measured by polymerase chain reaction (PCR) was normal ( $<200$  copies/mL). The patient showed no clinical signs of chronic active EBV infection. According to the Japanese guideline, no adjuvant chemotherapy was necessary. HP eradication therapy was successful. At 3 years after surgery, the patient was in good health and had developed no recurrence or metastases.

## Discussion

EBV, the first human virus found to be related to oncogenesis, was initially identified in a Burkitt lymphoma cell line in 1964 [4]. More than 90% of the world's population are infected with EBV [3,4]. Most of these individuals remain asymptomatic, but EBV can be a lifelong infection [4]. In some individuals, it is involved in the development of cancer and autoimmune disease [4,7]. EBV-associated cancers are mainly

lymphomas derived from B and T cells (Hodgkin, Burkitt, and natural killer/T-cell lymphomas and post-transplant lymphoproliferative disorder) and carcinomas derived from epithelial cells (nasopharyngeal carcinoma and GC) [2]. In 1990, the EBV genome was first detected in GC by using PCR [6]. Since then, 10% of patients with GC worldwide have been found to be EBV-positive [15]. EBV-associated GC is characterized by younger patient age, less differentiated adenocarcinoma, less vascular invasion, and a good postoperative prognosis [7,16-19]. Our patient with multiple GCs also had no vessel invasion.

EBV can induce oncogenesis in its host cell by activating various signaling pathways [2], and EBV-associated GC has a unique cancer immune microenvironment [7,16-20]. In our case, marked lymphocytic infiltration was clearly distinct from the typical findings of carcinoma with lymphoid stroma. Hence, unexpected EBV infection and EBV-associated GCs were diagnosed based on pathology, and limited lymphocytic infiltration



**Figure 5.** Macroscopic findings and microscopic assessments of gastric carcinoma (GC) in the posterior wall of the gastric body. (A) Macroscopic findings from the GC in the posterior wall of the gastric body (green arrow). (B, C) Pathologic findings based on hematoxylin and eosin staining (B,  $\times 80$ , C,  $\times 200$ ). Both moderately differentiated tubular adenocarcinomas had invaded the submucosal layer. Marked lymphocytic infiltration into the stroma was seen on in situ hybridization of EBV. (D) Immunohistochemical examination with in situ hybridization of Epstein-Barr virus (EBV) was positive for EBV-encoded small ribonucleic acid. EBV – Epstein-Barr virus, GC – gastric carcinoma.

into the GC sites suggested that the infection was associated with development of the multiple GCs.

Infectious mononucleosis is clinically characterized by various manifestations, including fever, pharyngitis, lymphadenopathy, and hepatitis [3]. Chronic active EBV infection is a rare syndrome characterized by prolonged infectious mononucleosis-like symptoms and an elevated peripheral blood EBV DNA load [3]. Our patient was asymptomatic and the EBV DNA level in his peripheral blood was normal postoperatively.

HP was first isolated in 1983 [21] and one-half to two-thirds of the world's population is infected with it [10]. Patients often acquire HP during childhood and the infection persists throughout life if untreated [8,9]. HP is strongly associated with many non-neoplastic conditions (eg, peptic ulcer disease and chronic atrophic gastritis) and neoplastic conditions (eg, GC and gastric mucosa-associated lymphoid tissue lymphoma [so-called

MALToma]) [8-10]. Hence, the World Health Organization categorized HP as a definite carcinogen in 1994 [8,9]. Early diagnosis of HP infection and successful eradication cures chronic atrophic gastritis and can reduce the risk of long-term complications [8-10]. Eradication therapy with vonoprazan, amoxicillin, clarithromycin, and proton pump inhibitors has been proven effective [11]. In our case, eradication therapy was successful after surgery and the state of the gastric remnant was followed up with annual endoscopy.

The present case raises to a simple question: How did coinfection with EBV and HP cause GC? Although much research has been carried out about EBV and HP separately, very few reports are available about coinfection with these 2 pathogens [22]. Coinfection is known to be associated with gastric disorders [23,24] and it is likely that approximately 45% of the world's population is infected with both pathogens [22,24]. Approximately 180 individuals per 100 000 population develop

GC, along with many gastric abnormalities [22-25]. This makes GC the third leading cause of cancer-related death worldwide [1,22]. Recent studies suggest that EBV and HP coinfection increases the occurrence of GC [22,24,25]. EBV-driven epigenetic modifications are known to be enhanced in the presence of HP, and, more specifically, in the presence of antigens to a cytotoxin-associated gene that are secreted by HP [25]. EBV-associated GC is characterized by less differentiated adenocarcinoma [7,16-19], whereas HP infection causes both differentiated and undifferentiated adenocarcinoma [26]. In our patient, coinfection with EBV and HP caused differentiated adenocarcinoma, but the reasons underlying that are unclear. We should never forget that EBV and HP infections are strongly associated with carcinogenesis of GC. The present thought-provoking case provides a timely reminder of that for gastroenterologists and gastrointestinal surgeons.

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## Conclusions

We have documented multiple GCs associated with EBV and HP coinfection in our patient. This thought-provoking case supports the hypothesis that coinfection with EBV and HP increases the occurrence of GC.

## Conflict of Interests

None.