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Single Case

Progression of Primary Gastric Diffuse Large B-Cell Lymphoma after *Helicobacter pylori* Eradication

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Keywords
Gastric lymphoma · Diffuse large B-cell lymphoma · *Helicobacter pylori* eradication

Abstract
In *Helicobacter pylori*-positive, localized primary gastric diffuse large B-cell lymphoma (DLBCL), an increasing number of reports have recently been published on the effectiveness of *H. pylori* eradication (HPE). However, HPE treatment strategies for gastric DLBCL, including its indications, have yet to be examined. No detailed report has been published on a case of gastric DLBCL unsuccessfully treated by HPE. A 64-year-old female and a 70-year-old male were pathologically diagnosed with chronic active gastritis and mucosa-associated lymphoid tissue lymphoma, respectively. Both patients were positive for *H. pylori*, so HPE was employed. The disease progressed within 1 year, and both patients were pathologically diagnosed with DLBCL by endoscopic biopsy. On reviewing the first pathology slide, both patients were diagnosed with DLBCL. That is, the 2 patients had primary gastric DLBCL; however, they exhibited progressive disease after HPE. This failure of HPE treatment may be due to the initial lymphomas being multiplex ulcerative lesions. In both cases, complete remission was achieved by chemotherapy (plus radiation therapy) without recurrence for more than 3 years.

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Introduction

Most primary gastric lymphomas are divided into mucosa-associated lymphoid tissue (MALT) lymphomas and diffuse large B-cell lymphomas (DLBCLs) [1, 2]. Additionally, two types of primary gastric DLBCL have been identified: DLBCL (MALT), which progresses from MALT lymphoma, and *de novo* DLBCL, which develops de novo without detectable MALT lymphoma components [1]. *Helicobacter pylori* eradication (HPE) leads to localized gastric MALT lymphoma regression and reported long-term clinical control in 77% of patients, including *H. pylori*-negative cases [3]. Accordingly, HPE has now become the first treatment for gastric MALT lymphoma [4]. On the other hand, there have been other case series suggesting the effectiveness of HPE for localized *H. pylori*-positive primary gastric DLBCL with or without concomitant MALT lymphoma [5–10]. However, evidence demonstrating the middle/long-term effectiveness of HPE for gastric DLBCL is still lacking. There have been no detailed reports that examined cases of primary gastric DLBCL that did not respond to HPE treatment. We herein report two cases of primary gastric DLBCL that progressed within 1 year following eradication of *H. pylori*.

Case Presentation

Case 1

A 64-year-old Japanese female presented with epigastralgia and underwent esophagogastroduodenoscopy (EGD) at a nearby hospital. Several erosions and small ulcers were found at the anterior wall and the lesser curvature of the gastric corpus (Fig. 1a, b), and a biopsy was performed to exclude gastric cancer. At that time, the patient was histopathologically diagnosed with "chronic active gastritis associated with *H. pylori* infection" and underwent HPE treatment. Subsequently, her hospital visits were discontinued.

The results of reviewing the first pathology slide are shown. Large CD20-positive atypical lymphocytes were diffusely infiltrated (Fig. 2a, b). The Ki-67 labeling index was 30–40% (Fig. 2c). She was diagnosed with DLBCL instead of chronic active gastritis.

Eight months after HPE treatment, the patient presented with epigastralgia again and underwent EGD at the same hospital. Multiple ulcerative lesions were found in the anterior wall and the lesser curvature of the gastric corpus, which were deeper and more spread out than the primary lesions (Fig. 1c, d). A biopsy was performed, the patient was histopathologically diagnosed with DLBCL without *H. pylori* infection. Following this diagnosis, the patient was referred to our department and hospitalized. Through positron emission tomography (PET)/computed tomography (CT), it was found that the lymphoma lesions were restricted to the stomach (Lugano stage I). The patient underwent 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, and complete remission (CR) was achieved. Consecutively, involved-field radiation therapy (30 gray/15 fractions) was performed. Since then, the patient has maintained CR for more than 3 years without recurrence.

Case 2

A 70-year-old Japanese male presented with epigastralgia and underwent EGD at a nearby clinic. Two ulcerative lesions were detected in the antrum and around the pylorus of the stomach (Fig. 3a, b). A biopsy was performed. *H. pylori* was confirmed to be positive, and the patient was histopathologically diagnosed with "MALT lymphoma partially combined with

DLBCL components." Subsequently, HPE was conducted. Three months later, both lymphoma lesions regressed (not shown). Histopathological confirmation was not obtained by biopsy, but the patient was endoscopically evaluated as being in remission.

The results of reviewing the first pathology slide are shown. The growth of CD20-positive atypical large lymphoid cells was observed without any evidence of MALT lymphoma, such as centrocyte-like cells or lymphoepithelial lesions (Fig. 4a, b). The Ki-67 labeling index was 40–50% (Fig. 4c). These observations were consistent with de novo findings of DLBCL without MALT lymphoma.

Ten months after HPE treatment, the patient presented with epigastralgia again, and an EGD was conducted. It was found that the initial lymphoma lesions were still in remission (Fig. 3c); however, a new ulcerative lesion, wider and deeper than the initial lesions, was found at the angulus, which had shown no abnormalities at the initial diagnosis (Fig. 3c, d). The biopsy revealed that the patient was pathologically diagnosed with DLBCL without *H. pylori* infection. The patient was then referred to our department and hospitalized. Through contrast CT and PET/CT, in addition to the primary gastric lymphoma, lesions spreading to the para-inferior vena cava lymph node (1 cm diameter) were observed. He was evaluated to have Lugano stage II2 disease and received 6 cycles of chemotherapy: R-THP-COP (rituximab, pirarubicin, cyclophosphamide, vincristine and prednisone). CR was achieved, and the patient remained in CR for more than 3 years without recurrence.

Discussion

As noted above, the two cases were primary gastric DLBCL at initial onset but showed progressive disease (PD) after HPE treatment.

In 2012, the effectiveness of HPE treatment for localized *H. pylori*-positive primary gastric DLBCL (with or without MALT lymphoma) patients with Lugano stage IE or stage II1 disease (tumor invasion detected in regional lymph nodes), in whom the depth of lymphoma invasion in the gastric wall remained within the mucosal or submucosal layer, was high (CR rate; 86.7% [13 of 15]) [9]. As reported by Tari et al. [11], 4 of 15 Japanese patients (27%) who achieved CR after HPE treatment were endoscopically classified into the "superficial spreading" type, and the depth of lymphoma invasion was confined to the mucosal layer.

On the other hand, detailed case reports on the failure of HPE treatment for primary gastric DLBCL have not been published. Therefore, the process of PD has remained unclear. The two patients referred to here were considered eligible for HPE treatment because endoscopic observations indicated that the tumor burden of primary gastric DLBCL was originally low. Despite successful eradication of *H. pylori*, the initial DLBCL lesions progressed in the stomach within 1 year after HPE. In case 1, the primary DLBCL lesions progressed locally at the same site. In case 2, two primary lesions achieved CR but recurred at a different site, which was considered to be a result of intragastric development or multicentric onset. Considering that they did not respond to HPE, the diseases of the two patients were morphologically closer to the "ulcerative" type rather than the "superficial spreading" type, according to Tari's classification [11]. Furthermore, both patients had multiplex lesions in the stomach. In this case study, the failure of HPE may be due to the initial lymphomas being multiplex ulcerative lesions.

Unlike MALT lymphoma, HPE is not a standard treatment for primary gastric DLBCL. The indication of HPE treatment for gastric DLBCL should be carefully determined. In the future,

to accurately adapt HPE treatment for gastric DLBCL, there needs to be more focus on not only CR cases but also PD cases.

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Statement of Ethics

The research presented in the manuscript was ethically conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from each patient.

Disclosure Statement

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Author Contributions

All authors collected and analyzed the patient's clinical data. M. Saito and A. Mori managed the patient's care. K. Miyashita was involved in the endoscopic procedure. M. Saito designed and wrote the manuscript. All authors agree to be accountable for all aspects of the work.

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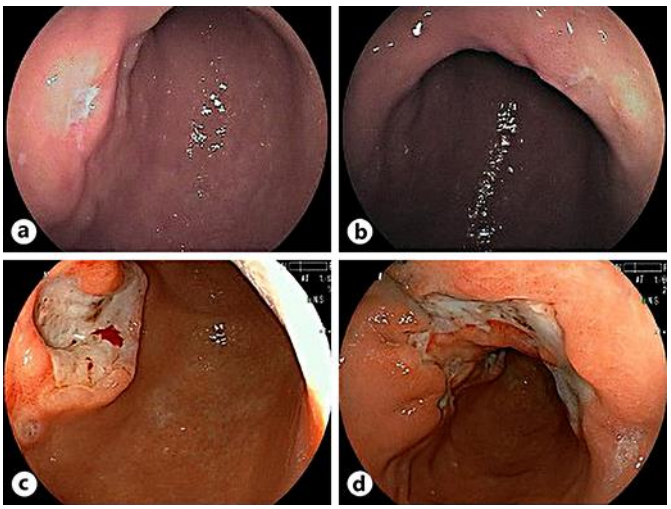

Fig. 1. Endoscopic findings (Case 1). **a**, **b** Initial onset: several erosions and small ulcers were seen at the anterior wall (**a**) and the lesser curvature (**b**) of the gastric corpus. **c**, **d** Eight months after initial onset: multiple ulcerative lesions were seen deeply and widely spreading in the anterior wall (**c**) and the lesser curvature (**d**) of the gastric corpus.

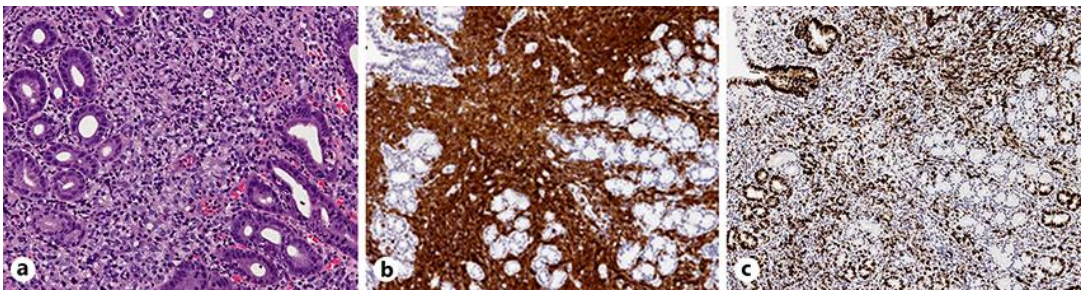

Fig. 2. Histopathological findings at initial onset (Case 1, ×100). **a** Diffusely infiltrating large atypical lymphocytes were seen in the lamina propria (HE. staining). **b** Atypical lymphocytes were CD20-positive. **c** Ki-67 labeling index was 30–40%.

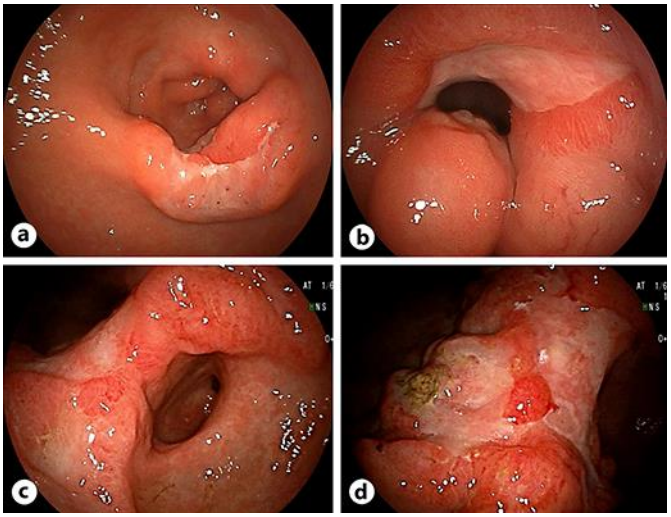

Fig. 3. Endoscopic findings (Case 2). **a**, **b** Initial onset: two ulcerative lesions were seen at the antrum, greater curvature side (**a**) and around the pylorus (**b**) in the stomach. **c**, **d** Ten months after initial onset: initial lymphoma lesions were kept in remission (**c**). A new ulcerative lesion, wider and deeper than the initial lesions, was found at the angulus (**c**, **d**).

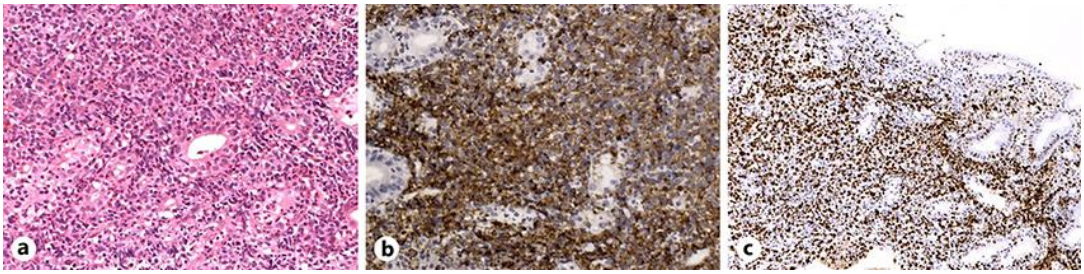

Fig. 4. Histopathological findings at initial onset (Case 2, ×100). **a** Diffusely infiltrating large atypical lymphoid cells were seen in the lamina propria (HE. staining). **b** Atypical lymphoid cells were CD20-positive. **c** Ki-67 labeling index was 40–50%.