

Observational Study

***Helicobacter pylori* eradication treatment for primary gastric diffuse large B-cell lymphoma: A single-center analysis**

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Abstract**BACKGROUND**

Unlike the already established effect of *Helicobacter pylori* (*H. pylori*) eradication on gastric mucosa-associated lymphoid tissue (MALT) lymphoma, its therapeutic effect on primary gastric diffuse large B-cell lymphoma (DLBCL) is still unclear.

AIM

To clarify the efficacy of *H. pylori* eradication treatment for primary gastric DLBCL.

METHODS

We reported on 3 new cases, and added them to 3 previously reported cases. We analyzed the usefulness of *H. pylori* eradication treatment for gastric DLBCL for a total of 6 cases at our center.

RESULTS

Of the 6 patients (27-90 years old, 3 males and 3 females), all 3 patients with single lesions (one transformed from MALT lymphoma) achieved complete remission (CR) after *H. pylori* eradication. Regarding the 2 newly reported cases, CR was maintained for more than 6 years with eradication treatment alone. In contrast, none of the 3 patients with 2 lesions achieved CR. In 1 newly reported case, endoscopic CR was achieved in one lesion, while stable disease was obtained in the other lesion. Two patients with progressive disease responded to standard chemo-

therapy ± radiation and remained in CR for more than 6 years.

CONCLUSION

We believe it is worthwhile to attempt *H. pylori* eradication for elderly patients with primary gastric DLBCL in a single lesion with a small tumor burden.

Key Words: Primary gastric diffuse large B-cell lymphoma; Treatment; *Helicobacter pylori*; Eradication

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Core Tip: Unlike the already established effect of *Helicobacter pylori* (*H. pylori*) eradication on gastric mucosa-associated lymphoid tissue lymphoma, its therapeutic effect on primary gastric diffuse large B-cell lymphoma (DLBCL) is not clear. Previously, we reported 1 successful case and 2 failed cases. We report here on 3 new cases, and we considered a total of 6 cases. Three patients with a single lesion achieved complete remission, in contrast, 3 patients with multiple lesions persisted or progressed. We believe it is worthwhile to attempt *H. pylori* eradication for an elderly patient with a single lesion and a small tumor burden of primary gastric DLBCL.

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INTRODUCTION

There are several reports that explain the effectiveness of eradication treatment for early-stage primary gastric diffuse large B-cell lymphoma (DLBCL), which is positive for *Helicobacter pylori* (*H. pylori*), regardless of the presence or absence of the mucosa-associated lymphoid tissue (MALT) lymphoma component[1-5]. However, unlike the already established effect of *H. pylori* eradication on gastric MALT lymphoma[6,7], its therapeutic effect on primary gastric DLBCL is still unclear. We have placed great importance on the efficacy of this noninvasive treatment, and previously, we reported on 1 successful case (short-term)[8] and 2 failed cases[9]. However, these 3 cases were mainly reported retrospectively. This time, we report on 3 new cases as a prospective study and examine the efficacy of *H. pylori* eradication for a total of 6 cases of primary gastric DLBCL.

MATERIALS AND METHODS

Study design

This was an observational study at our center with both prospective and retrospective perspectives.

Patients

Previously, we reported 3 cases of primary gastric DLBCL treated with *H. pylori* eradication between January 2014 and June 2016. One of the patients (case A[8]) was young, 27 years old. She reached complete remission (CR) but was given the established standard treatment, rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy × 3 courses, followed by gastric irradiation (40.6 gray). One patient (70 years old, male, case B[9]) appeared to have reached CR in both the pylorus and the antrum region 3 mo after eradication treatment; however, the lesion recurred in another area (the lesser curvature of the lower corpus - ventricular angle) one year after the initial onset. The lesion had spread to the para-inferior vena cava lymph nodes (Lugano-Stage II2). The patient was administered rituximab + cyclophosphamide, pirarubicin, vincristine and prednisone chemotherapy × 6 courses, and CR was maintained for more than 6 years. In another patient (64 years old, female, case C[9]), 2 lesions in the gastric corpus were found to have enlarged (Lugano-Stage I) 8 mo after the initial onset and *H. pylori* eradication. R-CHOP chemotherapy × 3 courses followed by gastric irradiation (30 gray), and CR has been maintained for more than 6 years.

In this study, we experienced 3 new cases of primary gastric DLBCL with low tumor burden that were treated with *H. pylori* eradication therapy between July 2016 and February 2021. We prospectively investigated and reported these cases here. In addition, a total of 6 cases, including the 3 cases presented above, were comprehensively examined for the efficacy of *H. pylori* eradication treatment for primary gastric DLBCL.

RESULTS

Three case reports

Case 1: A 71-year-old man underwent esophagogastroduodenoscopy (EGD) for screening at a municipal hospital while hospitalized for diabetes. An ulcerative lesion was found in the lesser curvature of the lower corpus of the stomach (Figure 1A), and a pathological diagnosis of DLBCL was made by biopsy (Figures 1B and C). Since *H. pylori* was positive by urea breath test, eradication treatment was performed at the hospital until the diagnosis was confirmed. Eradication therapy was performed by oral administration of vonoprazan fumarate, amoxicillin hydrate and clarithromycin (20 mg, 750 mg and 200 mg, respectively, twice daily) for one week. Two months later, a re-examination by EGD at our hospital revealed that the ulcerative lesion had already regressed, and no DLBCL findings were found on biopsy (Figures 1D and E). Eradication of *H. pylori* was confirmed by rapid urease test and histopathology. Computed tomography (CT) and positron emission tomography (PET)-CT did not detect any neoplastic lesions. After that, he was followed-up again at the municipal hospital with no treatment, and he was in CR endoscopically and histopathologically for more than 6 years.

Case 2: A 67-year-old woman seen at a university hospital for immunoglobulin G4-related disease, mainly affected submandibular gland, underwent EGD for screening. A reddish change was observed on the mucosal surface at the posterior wall (Figure 2A), and a raised mucosal change was observed in the corpus of the stomach (Figure 2B). A biopsy was performed for each lesion; the former was pathologically diagnosed as DLBCL (Figures 2C and D) and the latter as MALT lymphoma (Figure 2E). CT and PET-CT did not reveal gastric lesions. The patient was referred to our center. Since *H. pylori* was positive by rapid urease test and histopathological study, eradication treatment was performed using the same method as case 1. When the patient was re-examined by EGD 3 mo later, the lesions were not clear, and a biopsy was histopathologically negative for *H. pylori* (rapid urease test was also negative), with no findings of DLBCL or MALT lymphoma (Figure 2F). Since then, CR has been maintained endoscopically and histopathologically for more than 6 years.

Case 3: A 90-year-old man underwent EGD at a nearby hospital to search for the cause of his fever and was found to have a polypoid elevated lesion (Figure 3A) in the fundus and an ulcerative lesion (Figure 3B) in the greater curvature of the gastric corpus. A biopsy was histopathologically positive for *H. pylori* and revealed an MIB-1 index of 90% for both lesions. Immunostaining was positive for c-myc, and a pathological diagnosis of non-GCB-type DLBCL was made. PET-CT detected both gastric lesions, which were not apparent on CT. No lesions were found outside the stomach on those images. A screening test detected serum M-protein, it was found that this patient had monoclonal gammopathy of undetermined significance. Eradication treatment for *H. pylori* was performed at our center using the same method as case 1 and case 2. Since then, fever was no longer observed. Three months later, a fecal *H. pylori* antigen test was negative, and an EGD was performed again. The elevated lesion at the fundus was ulcerated (Figure 3C), and the ulcerative lesion at the corpus was scarred (Figure 3D). Five months after eradication treatment, CR was able to be maintained endoscopically for the latter lesion, but the former lesion was non-CR. In addition, rituximab (375 mg/m²) was administered once a week for 4 consecutive weeks. As a result, the lesions that had already reached CR were maintained in the CR state; however, the lesions that had been non-CR eventually returned to the original polypoid tumor (stable disease). The patient refused any further treatment. Nearly 2 years have passed since then, and he is still alive with the disease.

Overview of the 6 cases

Table 1 shows the clinical features of the 6 gastric DLBCL patients (27-90 years old, 3 males and 3 females) who were treated with *H. pylori* eradication. In all cases, the tumor burden was low endoscopically at the beginning of the diagnosis, and 1 patient (case 2) was found to have coexisting MALT lymphoma, suggesting transformation from MALT lymphoma. Including this patient, CR was achieved in all 3 patients with a single lesion. The patient of case A was treated with anticancer drugs early after reaching CR, so the mid- to long-term effects of eradication were unclear. On the other hand, 2 newly reported cases (cases 1 and 2) were epoch-making patients who have been maintaining CR for more than 6 years after *H. pylori* eradication treatment alone; no additional treatment was necessary.

In contrast, all 3 patients with 2 lesions were non-CR after *H. pylori* eradication treatment. In 1 new patient (case 3), both lesions had an MIB-1 index of 90% and were non-GCB-type DLBCL positive for c-myc. For 1 lesion, CR was obtained endoscopically by eradication treatment, and for another lesion, stable disease was obtained. Two cases (case B and case C) were evaluated as progressive disease; however, chemotherapy ± irradiation was effective, and CR was maintained for more than 6 years.

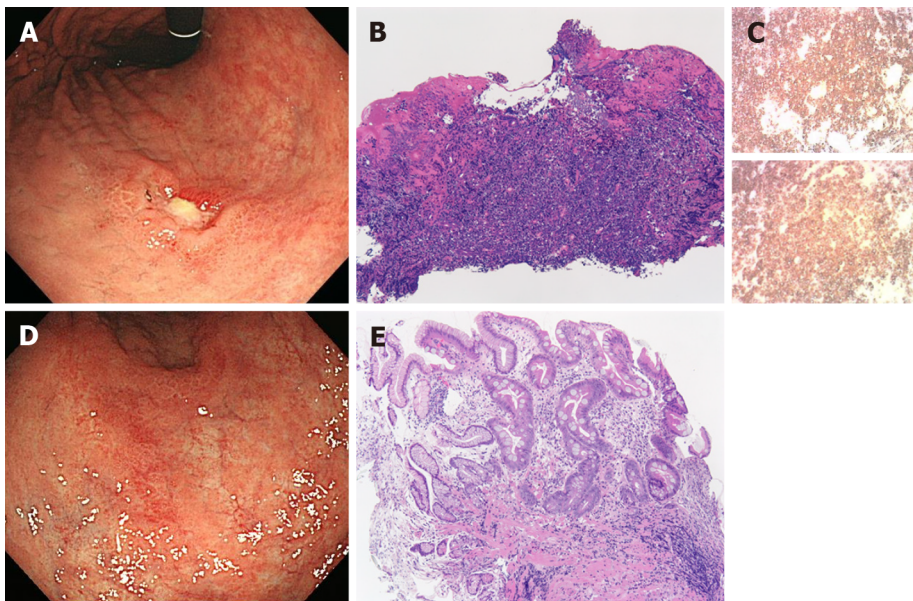
DISCUSSION

Recently, it was reported that the *H. pylori* infection rate in patients with primary gastric DLBCL was 54.7% (123/225) [10]. Another review reported that the probability of inducing CR in gastric DLBCL with *H. pylori* eradication alone was 60% (33/55) in MALT-derived DLBCL and 49.3% (40/81) in non-MALT-derived, *de novo* DLBCL; in addition, the probabilities were 50.7% (40/79) in stage I and 42.8% (6/14) in stage II [11]. Furthermore, the latter paper reported that among the 71 patients who failed to achieve remission with *H. pylori* eradication, 63 out of 64 patients (98.4%) achieved CR based on treatments including additional anticancer drugs (mainly R-CHOP) [11]. Even if the condition worsened (recurrence/progression) after *H. pylori* eradication, long-term CR could be maintained by second-line treatment, including chiefly R-CHOP chemotherapy, considering either this review [11] or our 2 successful experiences (case B and case C [9]). It is currently unknown whether eradication therapy enhances the therapeutic effect of anticancer agents.

Table 1 Clinical characteristics of 6 cases

Case	Age	Sex	Number of lesions	Endoscopic morphology	MALT lymphoma component	Comorbidities	Therapeutic effect	Additional treatment	Current condition	Ref.
1	71	Male	1	Ulcerative	(-)	Diabetes	CR	(-)	Maintaining CR (≥ 6 yr)	
2	67	Female	1	Superficial	(+)	IgG4-related disease	CR	(-)	Maintaining CR (≥ 6 yr)	
3	90	Male	2	Ulcerative. Elevated	(-)	MGUS	CR. SD	RTX (1/wk) \times 4 wk	Alive with disease (2 yr)	
A	27	Female	1	Ulcerative	(-)	(-)	CR	R-CHOP \times 3 courses + gastric irradiation	Maintaining CR (≥ 9 yr)	[8]
B	70	Male	2	Ulcerative (both 2 lesions)	(-)	Diabetes	CR (both lesions). Recurrence (PD)	R-THP-COP \times 6 courses	Maintaining CR (≥ 6 yr)	[9]
C	64	Female	2	Ulcerative (both 2 lesions)	(-)	(-)	PD (both lesions)	R-CHOP \times 3 courses + gastric irradiation	Maintaining CR (≥ 6 yr)	[9]

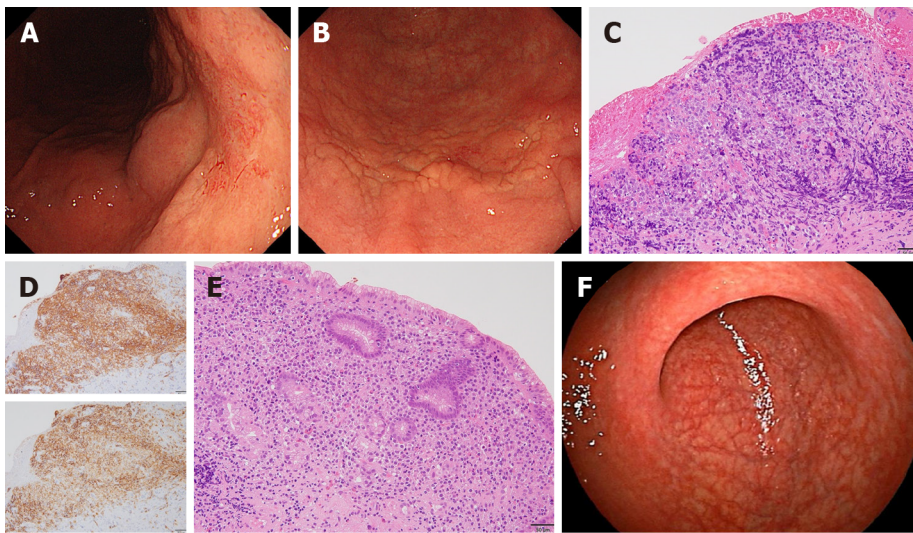
MALT: Mucosa-associated lymphoid tissue; MGUS: Monoclonal gammopathy of undetermined significance; CR: Complete remission; SD: Stable disease; PD: Progressive disease; RTX: Rituximab; R-CHOP: Rituximab + cyclophosphamide, doxorubicin, vincristine and prednisone; R-THP-COP: Rituximab + cyclophosphamide, pirarubicin, vincristine and prednisone; IgG: Immunoglobulin G.



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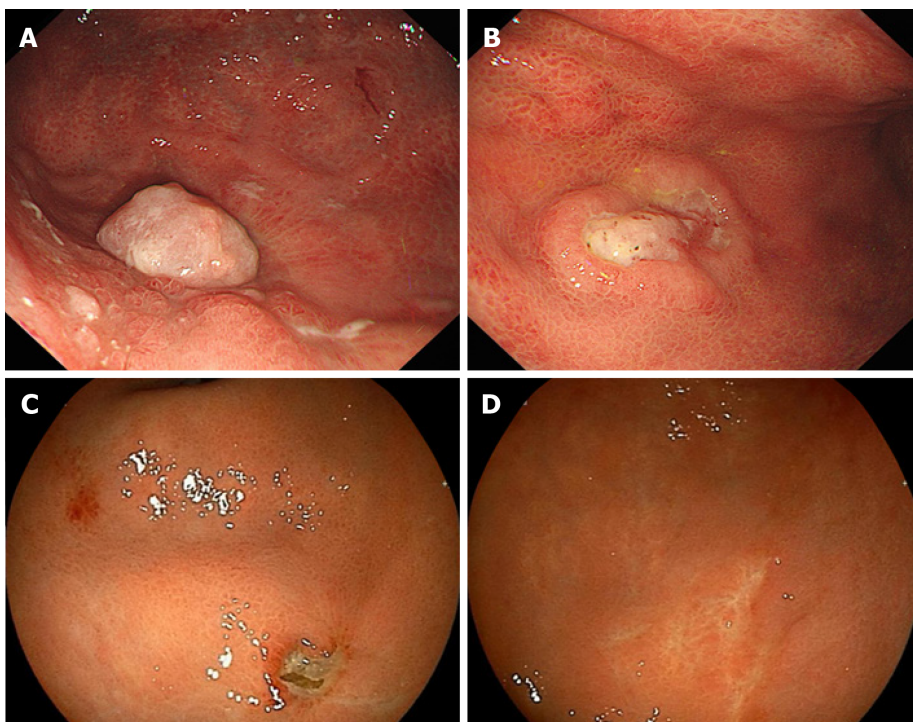
Figure 1 Case 1. A: An ulcerated lesion was revealed in the lesser curvature of the lower corpus; B: Abnormal lymphoid cells were densely proliferating in the lamina propria; C: The upper panel shows CD20 immunostaining, and the lower panel shows CD79a immunostaining. Both were clearly positive; D: Seven months after *Helicobacter pylori* eradication, the ulcerated lesion regressed; E: Scattered infiltration of small lymphocytes in the lamina propria was observed. A and D: Endoscopic findings of the stomach; B, C, and E: Microscopic findings (B and E; hematoxylin eosin staining, scale bar = 100 μ m).

The efficacy of *H. pylori* eradication in patients with DLBCL may be related to the depth of tumor invasion. As an indication for *H. pylori* eradication treatment for primary gastric DLBCL with or without the MALT lymphoma component, the depth of the lesions into the gastric wall is important, and it is essential to stay at the mucosa[12] or sub-mucosa[1]. In addition, previous reports have indicated that it takes a median of 2.1 (0.6-3.7) mo for *de novo* DLBCL and a median of 5.0 (2.8-7.5) mo for DLBCL with MALT lymphoma from eradication treatment for *H. pylori* to pathological CR [1]. In the current 3 cases, EGD was performed 2-3 mo after eradication therapy, and the therapeutic effect was evaluated.



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Figure 2 Case 2. A: The surface layer of the mucosa on the posterior wall side changed to reddish; B: A subtle ridged change in the mucosa was observed; C: Neoplastic lymphoid cells were densely proliferating in the lamina propria; D: The upper panel shows CD20 immunostaining, and the lower panel shows CD79a immunostaining. Both were clearly positive; E: Atypical lymphoid cells were proliferating in the lamina propria; F: Fourteen months after *Helicobacter pylori* eradication, a white scar was observed on the posterior wall where diffuse large B-cell lymphoma was present. A, B, and F: Endoscopic findings of the stomach; C-E: Microscopic findings (C and E; hematoxylin eosin staining, scale bar = 100 µm).



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Figure 3 Case 3. Endoscopic findings of the stomach. A: A polypoid-like elevated lesion was found in the fundus; B: An ulcerative lesion with peripheral ridges was found in the greater curvature of the corpus; C and D: Three months after *Helicobacter pylori* eradication, the elevated lesion in the fundus was ulcerated (C), and the ulcerative lesions in the corpus became scarred (D).

It has been reported that in gastric DLBCL, the expression of BCL10, nuclear factor kappaB (p65), cytotoxin-associated gene A (CagA)[13] and CagA-signaling molecules is clinically and biologically *H. pylori*-dependent[5], or miR-200 was associated with the susceptible group for *H. pylori*[14]. Although knowledge about B-cell receptor signaling related to susceptibility to *H. pylori* eradication treatment in gastric DLBCL is advancing[15], clinical application is still difficult. In this study, molecular medical markers were not scrutinized, which was a limitation of our research.

We studied 3 new cases prospectively, which are inherently different from the 3 cases we previously reported as a retrospective study (1 successful case, but short-term observation[8], and 2 failed cases[9]). Of the current 3 patients with

4 lesions, medium- to long-term CR was obtained successfully in 3 lesions with *H. pylori* eradication alone, and stable disease was obtained in 1 lesion. However, two lesions in case 3 had a MIB-1 index of 90% and a non-GCB-type DLBCL positive for c-myc and had a high degree of biological malignancy. It is significant that CR was obtained even for 1 lesion endoscopically by eradication treatment, and this patient has been alive with the disease for approximately 2 years.

We considered the benefits of *H. pylori* eradication on gastric DLBCL with a total of 6 cases, including 3 previously reported cases. Three patients with a single lesion achieved CR, in contrast, 3 patients with multiple lesions persisted or progressed. This may be the first report showing that the number of tumors affected the efficacy of *H. pylori* eradication treatment for primary gastric DLBCL.

CONCLUSION

In conclusion, especially in elderly individuals, it is worthwhile to try *H. pylori* eradication treatment first in single primary gastric DLBCL lesions, which have a low tumor burden. The number of relevant cases is still small, and the study should be continued with more patients.

ARTICLE HIGHLIGHTS

Research background

The efficacy of *Helicobacter pylori* (*H. pylori*) eradication treatment for gastric mucosa-associated lymphoid tissue (MALT) lymphoma has been established.

Research motivation

The therapeutic efficacy of *H. pylori* eradication treatment for primary gastric diffuse large B-cell lymphoma (DLBCL) remains unclear.

Research objectives

This study aimed to clarify the efficacy of *H. pylori* eradication for primary gastric DLBCL.

Research methods

We examined the usefulness of *H. pylori* eradication treatment for gastric DLBCL in a total of 6 patients at our center, including 3 previously reported cases.

Research results

Of the 6 patients (27-90 years old, 3 males and 3 females), all 3 patients with a single lesion achieved complete remission (CR) after *H. pylori* eradication. Regarding the 2 newly reported patients (one transformed from MALT lymphoma, and the other was *de novo*), CR was maintained for more than 6 years with eradication treatment alone. In contrast, none of the 3 patients with 2 lesions achieved CR. In 1 newly reported patient, CR was achieved endoscopically in 1 lesion, while stable disease was obtained in the other lesion. Two patients with progressive disease responded to standard chemotherapy ± radiation.

Research conclusions

It is considered worthwhile to try *H. pylori* eradication first for elderly patients with a single primary gastric DLBCL lesion, which has a low tumor burden.

Research perspectives

The number of relevant cases is still small, and it is necessary to further increase the number of patients and continue the examination.

FOOTNOTES

Author contributions: Saito M designed this study; Tanei ZI and Shimizu A involved in pathological procedure; all authors made substantial contributions to acquisition of data, or analysis and interpretation of data; took part in drafting the article; and agree to be accountable for all aspects of the work.

Institutional review board statement: This study was conducted in accordance with the World Medical Association Declaration of Helsinki, and this study was reviewed and approved by the Aiiiku Hospital Clinical Research Review Board (Sapporo).

Informed consent statement: All patients provided written informed consent.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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