Regression of gastric *de novo* diffuse large B-cell lymphoma following *Helicobacter pylori* eradication: a case report

Makoto Saito[1], Manabu Masutani[2], Katsuhiro Mabe[3], Koh Izumiyama[1], Akio Mori[1], Tatsuro Irie[1], Masanori Tanaka[1], Masanobu Morioka[1], Mishie Tanino[4]

(1) Department of Internal Medicine and Hematology, Aiiku Hospital, Japan., (2) Department of Internal Medicine, Owl Medical Clinic, Japan., (3) Division of Endoscopy, Hokkaido University Hospital, Japan. (4) Department of Cancer Pathology, Hokkaido University Graduate School of Medicine, Japan.

Abstract

We report a case of primary gastric diffuse large B-cell lymphoma (DLBCL), *de novo* DLBCL without the features of mucosa-associated lymphoid tissue (MALT) lymphoma, which regressed after Helicobacter pylori (HP) eradication. A 27-year-old Japanese female with epigastralgia was revealed to have ulcerated lesions in the angle and antral regions on gastroscopy. Biopsy specimen was consistent with a diagnosis of DLBCL without MALT lymphoma component, indicating *de novo* development. Her clinical staging on the Lugano system was Stage I. HP was positive on a rapid urease test, and she received HP eradication therapy twice, because the first therapy was not successful. On gastroscopy performed 1 month after the second HP eradication therapy, no ulcerated lesion was noted, and the lymphoma cells had regressed histopathologically. (Acta gastroenterol. belg., **2016**, 79, **367-369**).

Key words : gastric diffuse large B-cell lymphoma (DLBCL), de novo DLBCL, *Helicobacter pylori* eradication.

Introduction

More than 90% of gastric lymphomas are divided into two histologic subtypes: mucosa-associated lymphoid tissue (MALT) lymphoma (38-48 %) and diffuse large B-cell lymphoma (DLBCL) (45-59 %) (1, 2). Approximately 80-90% of patients with gastric MALT lymphoma are infected with Helicobacter pylori (HP). The effectiveness of HP eradication therapy against HP-positive, localized stage gastric MALT lymphoma is being established, that is, a complete remission (CR) rate is more than 65% and a 10-year overall survival (OS) is 83-95% (3, 4).

On the other hand, two types of primary gastric DLBCL have been identified: one is DLBCL (MALT), which progresses from MALT lymphoma, and the other is *de novo* DLBCL, which develops *de novo* without a detectable MALT component (1). HP infection rates were previously shown to be lower in *de novo* DLBCL (36 %) than in DLBCL (MALT) (75 %) ($p<0.001$) (5). Gastric DLBCL with or without concomitant MALT lymphoma component, which is an aggressive lymphoma, is frequently detected at an advanced stage (Lugano stage II2 or IV). Due to the rarity of the localized HP-positive primary gastric *de novo* DLBCL, the evidence to confirm the effectiveness of HP eradication is still lacking. Especially, in Japan, it was previously shown to be low, four of 15 (27%) gastric *de novo* DLBCL patients were achieved complete remission with eradication (6).

We herein report a case of primary gastric *de novo* DLBCL that was regressed with HP eradication.

Case report

A 27-year-old Japanese female with epigastralgia visited a nearby medical clinic. Gastroscopy revealed ulcerated lesions in the angle and antral regions (Fig. 1A). Because the background gastric mucosa was atrophic gastritis and HP was positive on a rapid urease test, she received HP eradication therapy (a combination of amoxicillin (750 mg), clarithromycin (400 mg), and lansoprazole (30 mg) twice daily) for 1 week. Biopsy-1 revealed sheets of large lymphoid cells infiltrating the lamina propria (Fig. 2A). These cells were positive for CD20, CD79a, and bcl-6, and were consistent with a diagnosis of DLBCL. The Ki-67 labeling index was over 90%.

The patient was referred to Hokkaido University Hospital. The laboratory data were unremarkable. Repeat gastroscopy and biopsy-2 were performed, and the findings obtained revealed almost no marked change from the initial presentation. Because HP was positive on the rapid urease test, she received HP eradication therapy again (amoxicillin, lansoprazole, and metronidazole (250 mg) twice daily for 1 week). A contrast enhanced CT showed a low density area in the angle-antral regions. On a PET/CT, fluorodeoxyglucose uptake was limited to the gastric wall. No abnormal findings were seen on the other imaging. She was diagnosed with primary gastric DLBCL, and the clinical staging on the Lugano system was Stage I.

The patient was thereafter referred to our department and hospitalized. Gastroscopy performed 1 month after the second HP eradication therapy revealed that no ulcerated lesion was noted in the angle or antral region,

Correspondence to : Makoto Saito, M.D., Department of Internal Medicine and Hematology, Aiiku Hospital. Minami4 Nishi25 Chuo-ku, Sapporo 064-0804, Japan
E-mail: ikyoku@aiiku-hp.or.jp

Submission date : 09/07/2015
Acceptance date : 30/07/2015

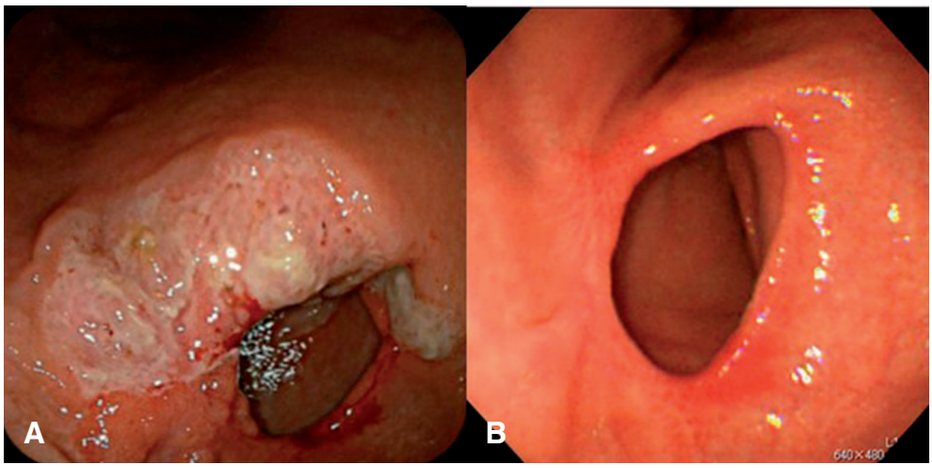

Fig. 1. — Gastroscopic findings.
(A) Before Helicobacter pylori (HP) eradication, an ulcerated lesion was revealed in the angle and antral regions.
(B) After HP eradication, the ulcerated lesion was absent in the angle or antral region.

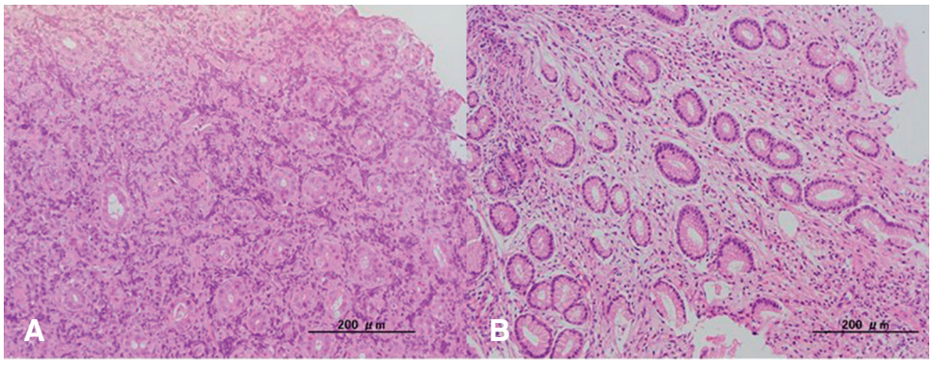

Fig. 1. — Microscopic findings (HE staining, x100).
(A) Before HP eradication, sheets of large lymphoid cells infiltrating the lamina propria were revealed.
(B) After HP eradication, the scattered infiltration of small lymphocytes in the lamina propria were seen.

with scars being the only findings (Fig. 1B). Biopsy-3 showed the scattered infiltration of small lymphocytes in the lamina propria (Fig. 2B), and the lymphoma cells were not seen. HP was negative histopathologically and on the rapid urease test. The features of MALT lymphoma such as typical lymphoepithelial lesions were not detected in any of the 3 biopsy specimens. Abdominal CT showed that the low density area in the angle-antral regions had regressed.

Discussion

The incidence of HP infection is high in the Japanese population (7), but the infection rate in individuals in their 20-29 years old was found to be low (about 15%) (8). Although our patient was young aged, healthy people apart from HP infection, primary gastric DLBCL associated HP infection still developed. Our patient was thought to be an early-onset, and an extremely rare case. In our case, Gastroscopy and biopsy were repeated 3 times, and 3 special pathologists examined the respective biopsy specimens (total 15 samples), no MALT features were observed in any specimen, indicating *de novo* development. The lymphoma lesion regressed one month after the 2nd eradication of HP, and this was consistent with previous findings in which the time to remission of *de novo* DLBCL (median time: 2.1 months) was shorter than that of DLBCL (MALT) (5.0 months) (p=0.024) (9).

In a few, small retrospective case-series, there have been sporadic reports suggesting the effectiveness of HP-eradicating antibiotic therapy for gastric *de novo* DLBCL (9, 10, 11). In case the depth of lymphoma invasion in the stomach wall remained within the

mucosal or submucosal layer, these studies reported the CR rate is more than 60% and a 5-year OS is over 90%. These findings were similar to the effectiveness of HP eradication therapy for MALT lymphoma. HP-related gastric lymphomagenesis may be a multi-step process initiated by infection and followed by chronic gastritis, and eventually develops into DLBCL through a specific common mechanism regardless of the involvement of MALT lymphoma. Barth TF et al. demonstrated that genetic aberrations, such as gains on chromosome arm 11q and losses on 6q, in the large-cell components of gastric DLBCL (MALT) overlapped with those of *de novo* DLBCL (12), and gastric DLBCL may be a blastic variant of marginal zone lymphoma (13).

Only 11 patients were examined, a prospective trial demonstrated that HP eradication was feasible and effective as exclusive treatment in patients with *de novo* DLBCL (14). International, large-scale prospective studies to validate these findings are warranted, and, as HP eradication therapy has been established as the 1st-line therapy for gastric MALT lymphoma, its applicability as an exclusive treatment for localized gastric *de novo* DLBCL needs to be investigated in more detail.

References

1. KOCH P., PROBST A., BERDEL W.E., WILLICH NA., REINARTZ G., BROCKMANN J., *et al*. Treatment results in localized primary gastric lymphoma: data of patients registered within the German multicenter study (GIT NHL 02/96)., *J. Clin. Oncol*., 2005, **23** : 7050-7059.
2. PAPAXOINIS G., PAPAGEORGIOU S., RONTOGIANNI D., KALOUTSI V., FOUNTZILAS G., PAVLIDIS N., *et al*. Primary gastrointestinal non-Hodgkin's lymphoma: a clinicopathologic study of 128 cases in Greece. *A Hellenic Cooperative Oncology Group study (HeCOG). Leuk Lymphoma*. 2006, **47** : 2140-2146.
3. STATHIS A., CHINI C., BERTONI F., PROSERPIO I., CAPELLA C., MAZZUCCHELLI L., *et al*. Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type., *Ann. Oncol*., 2009, **20** : 1086–1093.
4. NAKAMURA S., SUGIYAMA T., MATSUMOTO T., IIJIMA K., ONO S., TAJIKA M., *et al*. Long-term clinical outcome of gastric MALT lymphoma after eradication of Helicobacter pylori: a multicentre cohort follow-up study of 420 patients in Japan., *Gut*. 2012, **61** : 507-513.
5. LI X., XIA B., GUO S., ZHAN Z., ZHANG L., ZHAO D., *et al*. A retrospective analysis of primary gastric diffuse large B-cell lymphoma with or without concomitant mucosa-associated lymphoid tissue (MALT) lymphoma components. *Ann. Hematol*., 2013, **92** : 807-815.
6. TARI A., ASAOKU H., KASHIWADO K., YOSHINO T., KITADAI Y., TANAKA S., *et al*. Predictive value of endoscopy and endoscopic ultrasonography for regression of gastric diffuse large B-cell lymphomas after Helicobacter pylori eradication. *Dig. Endosc*., 2009, **21** : 219-227.
7. SAITO M., MORIOKA M., WAKASA K., IZUMIYAMA K., MORI A., IRIE T., *et al*. In Japanese patients with type A gastritis with pernicious anemia the condition is very poorly associated with Helicobacter pylori infection. *J. Infect. Chemother*., 2013, **19** : 208-210.
8. KAWAI T., YAMAMOTO K., FUKUZAWA M., YAMAGISHI T., YAGI K., FUKUZAWA M., *et al*. Helicobacter pylori infection and reflux esophagitis in young and middle-aged Japanese subjects., *J. Gastroenterol. Hepatol*., 2010, **25** (Suppl 1) : S80-85.
9. KUO S.H., YEH K.H., WU M.S., LIN C.W., HSU P.N., WANG H.P., *et al*. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas., *Blood*., 2012, **119** : 4838-4844.
10. MORGNER A., MIEHLKE S., FISCHBACH W., SCHMITT W., MÜLLER-HERMELINK H., GREINER A., *et al*. Complete remission of primary high-grade B-cell gastric lymphoma after cure of Helicobacter pylori infection., *J. Clin. Oncol*., 2001, **19** : 2041-2048.
11. CAVANNA L., PAGANI R., SEGHINI P., ZANGRANDI A., PATIES C., High grade B-cell gastric lymphoma with complete pathologic remission after eradication of Helicobacter pylori infection: report of a case and review of the literature., *World J. Surg.Oncol*., 2008, **6** : 35.
12. BARTH T.F., BENTZ M., LEITHÄUSER F., STILGENBAUER S., SIEBERT R., SCHLOTTER M., *et al*. Molecular-cytogenetic comparison of mucosa-associated marginal zone B-cell lymphoma and large B-cell lymphoma arising in the gastro-intestinal tract., *Genes Chromosomes Cancer,* 2001, **31** : 316-325.
13. BARTH T.F., BARTH C.A., KESTLER H.A., MICHL P., WENIGER M.A., BUCHHOLZ M., *et al*. Transcriptional profiling suggests that secondary and primary large B-cell lymphomas of the gastrointestinal (GI) tract are blastic variants of GI marginal zone lymphoma., *J. Pathol*., 2007, **211** : 305-313.
14. FERRERI A.J., GOVI S., RADERER M., MULÈ A., ANDRIANI A., CARACCIOLO D., *et al*. Helicobacter pylori eradication as exclusive treatment for limited-stage gastric diffuse large B-cell lymphoma: results of a multicenter phase 2 trial., *Blood*., 2012, **120** : 3858-3860.