Quadruple therapy for gastric high-grade B-cell lymphoma

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ABSTRACT

Most low-grade gastric lymphomas arising from the mucosa-associated lymphoid tissue (MALT) are directly related to *Helicobacter pylori* infection. Most cases of MALT lymphoma limited to the stomach can be cured with *H. pylori* eradication and remain in remission for years. In contrast, high-grade lymphomas of the stomach, although potentially related to *H. pylori*, do not usually respond to *H. pylori* eradication. Here, we present the case of a woman with high-grade diffuse large B-cell lymphoma who achieved complete remission following *H. pylori* eradication.

KEYWORDS Diffuse large B-cell lymphoma; *Helicobacter pylori*; mucosa-associated lymphoid tissue; lymphoma; remission

It is estimated that *H. pylori* is directly responsible for approximately 75% of stomach cancers and 5.5% of all cancers internationally.¹ Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare condition attributed to chronic *H. pylori* exposure. The incidence of MALT lymphoma is estimated at 0.38 per 100,000 people in the United States and 0.3 to 0.8 per 100,000 people in Europe.² The mainstay of treatment for MALT lymphoma remains *H. pylori* eradication therapy, while a more aggressive approach with chemotherapy is implemented for treatment of gastric diffuse large B-cell lymphoma (DLBCL). DLBCL with areas of MALT lymphoma, or DLBCL(MALT), formerly called high-grade MALT lymphoma, is a transitional phase from low-grade MALT lymphoma to high-grade DLBCL. Given that DLBCL(MALT) is thought to be *H. pylori* independent and is categorized together with pure (de novo) DLBCL, current guidelines recommend combination chemotherapy with rituximab as the initial therapy for DLBCL(MALT).^{3,4} The data on DLBCL remission following *H. pylori* eradication are limited, as gastric high-grade lymphoma (DLBCL) is a rare condition that traditionally has not been associated with good outcomes. Here, we present the case of a woman diagnosed with DLBCL who attained complete remission following *H. pylori* eradication.

CASE DESCRIPTION

A 59-year-old white woman presented to our outpatient clinic for evaluation of epigastric pain with radiation to her upper back associated with nausea and vomiting, which was ongoing for over 6 weeks. She also complained of left lower quadrant pain with altered bowel movements over the last 2 months. She denied any other associated symptoms. Computed tomography of the abdomen without contrast was significant only for diverticulosis. Prior proton pump inhibitor treatment did not improve her epigastric pain. Her past medical history was significant for hypertension, with no prior surgeries. Esophagogastroduodenoscopy (EGD) showed a 25 mm nonbleeding cratered gastric ulcer with pigmented material at the incisura of the stomach (*Figure 1a*). Biopsies at the incisura revealed high-grade B-cell lymphoma, and biopsies in the stomach and antrum were positive for *H. pylori*. On microscopy, high-grade neoplastic cells with elevated nuclear-to-cytoplasmic ratios were seen in the stomach, with nests and sheets of cells infiltrating into and around the glands. Ki-67 was over 90% positive, and CD20 was diffusely and strongly positive. Neoplastic cells were negative for keratin AE1/AE3 but the surrounding epithelial cells were positive. Fluorescence in situ hybridization was negative for *MYC*, *IGH-BCL2*, and *BCL6* gene rearrangements.

Positron emission tomography/computed tomography showed diffuse fluorodeoxyglucose uptake along the lesser curvature of the stomach corresponding to the known area of

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Figure 1. (a) Ulcer at incisura of stomach. (b) Incisura 4 months after *Helicobacter pylori* treatment.

lymphoma. There was no evidence of metastatic disease. A trial of *H. pylori* eradication therapy was given, as the patient was apprehensive about starting combination chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). She was treated with a 14-day course of pantoprazole 40 mg orally twice daily, bismuth subsalicylate 524 mg orally four times daily, metronidazole 250 mg orally four times daily, and tetracycline 500 mg orally four times daily.

Following completion of quadruple therapy, repeat EGD with endoscopic ultrasound showed localized moderately erythematous mucosa without bleeding at the incisura. Biopsies were negative for neoplasia. Endosonography of the entire stomach was unremarkable. No pathologic lymphadenopathy, masses, or wall thickening was identified. Given the absence of neoplasia on repeat EGD, the patient opted to forego chemotherapy. Follow-up EGD 4 months following therapy completion showed a normal mucosal appearance of the stomach, duodenum, and esophagus. Biopsies of the incisura were negative for neoplasia (*Figure 1b*). To date, she remains asymptomatic.

DISCUSSION

The pathological findings described in this case were suggestive of an aggressive large-cell germinal center phenotype lymphoma, which is a subtype of DLBCL, consistent with a diagnosis of high-grade B-cell lymphoma, not otherwise specified, per 2016 criteria of the World Health Organization.⁵ This aggressive tumor with a high proliferation rate may arise de novo or from transformation from a MALT lymphoma. DLBCL represents about 40% to 70% of all gastric lymphomas, with guidelines recommending combination chemotherapy (e.g., R-CHOP) for optimal treatment.^{6–8} This is distinctly different from an extranodal marginal-zone lymphoma of MALT, which has a more

indolent course and may respond to treatment of *H. pylori*; these represent 50% of gastric lymphomas.⁶

DLBCL(MALT), previously referred to as high-grade transformed MALT lymphoma, is considered independent of *H. pylori*; hence, chemotherapy is recommended as the mainstay of treatment. The theory behind *H. pylori* independence of DLBCL(MALT) is largely derived from prior studies. One study showed that high-grade MALT lymphoma cells do not respond to the costimulation of *H. pylori* lysate and autologous T cells in vitro.⁹ Studies have also shown that specimens of low-grade gastric MALT lymphoma that failed to achieve remission following *H. pylori* eradication contained some degree of high-grade components within the deeper layer of the gastric wall.^{10,11} Based on these studies, in 2001 the World Health Organization renamed high-grade transformed MALT lymphoma as DLBCL with features of MALT lymphoma or DLBCL(MALT).¹²

Gastric pure (de novo) DLBCL has traditionally been treated with surgery, chemotherapy, or radiation, either alone or in combination. To date, there is no established standard management strategy for primary gastric lymphoma. Most guidelines recommend chemotherapy as the initial treatment for both gastric pure DLBCL and DLBCL(MALT).^{3,4} In contrast, most existing studies and guidelines recommend *H. pylori* eradication with antibiotics as initial gastric MALT lymphoma treatment. The efficacy of *H. pylori* eradication as DLBCL treatment has remained mostly unknown, with the exception of several anecdotal case reports. In 2009, Tari et al reported clinical remission following *H. pylori* eradication among 4 of 15 patients diagnosed with gastric pure DLBCL.¹³ A retrospective analysis by a Taiwanese group showed complete remission among 11 of 16 (69%) pure DLBCL patients following *H. pylori* eradication. A European multicenter prospective study showed similar results, where lymphoma response after eradication was complete remission in 8 of 16 (50%) patients.¹⁴ In a separate retrospective study

involving 50 patients diagnosed with de novo DLBCL, more than two-thirds of subjects achieved complete remission following *H. pylori* eradication.¹⁵ In that study, all patients with complete remission were alive and in remission at a median of 7.7 years following remission.

Despite histological remission, lymphoma recurrence remains a possibility. Relapse rates vary, with different rates being reported among those who achieved complete remission. A European prospective multicenter trial with 120 patients showed that 3% of patients (3/96) relapsed within 4 months, 5 months, and 24 months, respectively.¹⁶ In another retrospective multicenter study, 30.9% (13/42) of patients relapsed within a median time of 19 months.¹⁷ Another study described a relapse rate of 10.5%, where 4 out of 38 subjects relapsed following remission, with a median follow-up period of 51 months.¹⁸ In an analysis of 994 patients who achieved complete remission, 7.2% experienced lymphoma relapse after 3253 patient-years of follow-up, with a yearly recurrence rate of 2.2%.¹⁹ According to a 2013 study, gastric MALT lymphoma recurrence can be observed up to a period of 131 months following complete remission.²⁰ Given the data obtained from these studies, long-term, careful follow-up is needed for all patients in remission following diagnosis with either MALT lymphoma, pure DLBCL, or DLBCL(MALT).

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- Arfaoui D, Elloumi H, Ben Abdelaziz A. *Helicobacter pylori* and gastric adenocarcinoma. *Tunis Med*. 2009;87(4):231–236.
- Ullrich A, Fischbach W, Blettner M. Incidence of gastric B-cell lymphomas: a population-based study in Germany. *Ann Oncol*. 2002;13(7):1120–1127. doi:10.1093/annonc/mdf177.
- Zelenetz AD, Abramson JS, Advani RH, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas. *J Natl Compr Canc Netw*. 2010;8(3):288–334. doi:10.6004/jnccn.2010.0021.
- Zucca E, Dreyling M; ESMO Guidelines Working Group. Gastric marginal zone lymphoma of MALT type: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(Suppl 5):v175–v176. doi:10.1093/annonc/mdq182.
- Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375–2390. doi:10.1182/blood-2016-01-643569.
- Psyri A, Papageorgiou S, Economopoulos T. Primary extranodal lymphomas of stomach: clinical presentation, diagnostic pitfalls and management. *Ann Oncol*. 2008;19(12):1992–1999. doi:10.1093/annonc/mdn525.
- Ferreri AJ, Montalbán C. Primary diffuse large B-cell lymphoma of the stomach. *Crit Rev Oncol Hematol*. 2007;63(1):65–71. doi:10.1016/j.critrevonc.2007.01.003.
- Wöhler S, Püspök A, Drach J, Hejna M, Chott A, Raderer M. Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for treatment of early-stage gastric diffuse large B-cell lymphoma. *Ann Oncol*. 2004;15(7):1086–1090. doi:10.1093/annonc/mdh261.
- Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet*. 1993;342(8871):571–574. doi:10.1016/0140-6736(93)91408-E.
- Bayerdörffer E, Neubauer A, Rudolph B, et al; MALT Lymphoma Study Group. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. *Lancet*. 1995;345(8965):1591–1594. doi:10.1016/S0140-6736(95)90113-2.
- Neubauer A, Thiede C, Morgner A, et al. Cure of *Helicobacter pylori* infection and duration of remission of low-grade gastric mucosa-associated lymphoid tissue lymphoma. *J Natl Cancer Inst*. 1997;89(18):1350–1355. doi:10.1093/jnci/89.18.1350.
- Mitsuhashi K, Yamashita K, Goto A, et al. Gastric diffuse large B-cell lymphoma cured with *Helicobacter pylori* eradication regardless of whether it contains features of MALT lymphoma. *Intern Med*. 2014;53(7):695–698. doi:10.2169/internalmedicine.53.1603.
- Tari A, Asaoku H, Kashiwado K, 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(4):219–227. doi:10.1111/j.1443-1661.2009.00896.x.
- Ferreri AJ, Govi S, Raderer M, 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(18):3858–3860. doi:10.1182/blood-2012-06-438424.
- Kuo SH, Yeh KH, Wu MS, 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(21):4838–4844. doi:10.1182/blood-2012-01-404194.
- Wündisch T, Thiede C, Morgner A, et al. Long-term follow-up of gastric MALT lymphoma after *Helicobacter pylori* eradication. *J Clin Oncol*. 2005;23(31):8018–8024. doi:10.1200/JCO.2005.02.3903.
- Andriani A, Miedico A, Tedeschi L, et al. Management and long-term follow-up of early stage *H. pylori*-associated gastric MALT-lymphoma in clinical practice: an Italian, multicentre study. *Dig Liver Dis*. 2009;41(7):467–473. doi:10.1016/j.dld.2008.09.009.
- Kim JS, Kang SH, Moon HS, Sung JK, Jeong HY. Clinical outcome of eradication therapy for gastric mucosa-associated lymphoid tissue lymphoma according to *H. pylori* infection status. *Gastroenterol Res Pract*. 2016;2016:1–7. doi:10.1155/2016/6794848.
- Zullo A, Hassan C, Cristofari F, et al. Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*. 2010;8(2):105–110. doi:10.1016/j.cgh.2009.07.017.
- Zullo A, Hassan C, Ridola L, et al. Eradication therapy in *Helicobacter pylori*-negative, gastric low-grade mucosa-associated lymphoid tissue lymphoma patients: a systematic review. *J Clin Gastroenterol*. 2013;47(10):824–827. doi:10.1097/MCG.0b013e318286ff72.