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EDITORIAL

Helicobacter pylori eradication in gastric diffuse large B cell lymphoma

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Abstract

Diffuse large B cell lymphoma (DLBCL) of the stomach is a heterogenous disease. There are tumors without histological evidence of mucosa-associated lymphoid tissue (MALT) lymphoma, which are classified as pure or *de novo* DLBCL and those with evidence of MALT, which are classified as DLBCL (MALT). The association between *Helicobacter pylori* (*H. pylori*) and gastric MALT lymphoma and remission with *H. pylori* eradication was shown in the 1990s. In recent years, scientists from Taiwan and others have shown that high-grade gastric lymphomas may be dependent on *H. pylori* and eradication of this microorganism is effective in these cases. This entity is biologically distinct from *H. pylori* (-) cases and has a better clinical outcome. There are sufficient data about the complete remission in some of these cases with brief treatment with antibiotics. With this strategy, it is possible to save some of these cases from the harmful effects of standard chemotherapy. It is time to treat these cases with *H. pylori* eradication. However, strict histopathological follow-up is crucial and histopathological response must be evaluated according to the scoring system proposed by Groupe d'Etude des Lymphomes de l'Adulte. If there is no sufficient response, chemotherapy must be given immediately. These results suggest that *H. pylori* dependency and high-grade transformation in gastric MALT lymphomas are distinct events.

Key words: *Helicobacter pylori*; Eradication; Gastric diffuse large B cell lymphoma

Core tip: The association between *Helicobacter pylori* (*H. pylori*) and gastric mucosa-associated lymphoid tissue lymphoma has a long history and *H. pylori* eradication is the standard of care in these cases. In recent years, it has been shown that high-grade, early-stage gastric lymphoma may be dependent on *H. pylori* and eradication of this microorganism may be curative in some of the cases with gastric diffuse large B cell lymphoma. However, chemotherapy is a standard approach in cases unresponsive to *H. pylori* eradication.

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Diffuse large B cell lymphoma (DLBCL) of the stomach is a heterogenous disease entity and includes lymphomas with or without mucosa-associated lymphoid tissue (MALT) features in WHO classification[1]. Tumors without histological evidence of MALT lymphoma, dense infiltration of centrocyte like cells in the lamina propria, and typical lymphoepithelial lesions are classified as pure or *de novo* DLBCL and those with evidence of MALT are classified as DLBCL (MALT)[2,3]. The association between *Helicobacter pylori* (*H. pylori*) and gastric MALT lymphoma and remission with *H. pylori* eradication (HPE) is an old story. In recent years, this association has been shown in *de novo* gastric DLBCL and HPE is effective in this disease. There are sufficient data about HPE in these cases and it is time to treat these cases with 2 wk antibiotics and to save these cases from the harmful effects of standard chemotherapy. For this aim we can use large-scale data about HPE for MALT and we must be ready to draw an analogy from gastric MALT lymphoma for gastric DLBCL.

In the early 1990s, a high incidence of *H. pylori*-related gastritis was described by Wotherspoon in patients with gastric MALT lymphoma. Complete histological remission of gastric MALT lymphoma by HPE was detected in five of six cases in 1993[4,5]. In the past 20 years, complete pathological response (pCR) in *H. pylori (+)* gastric MALT lymphoma has been reported in 47%-100% of these patients[6-9]. The most important factors in response to HPE are tumor stage, depth of invasion, and localization, as well as geographic region[8-10]. Lymphoma regression has been reported in > 80% of cases confined to the submucosa, and in about 50% of cases with deeper invasion. Distal lesions are more responsive to HPE than proximal lesions (92% *vs* 76%). A higher response rate has been found in Asian than western populations (84% *vs* 74%). These factors may also determine the response to HPE in gastric DLBCL. Another important point is the use of highly heterogenous pathological response criteria after HPE in MALT lymphoma studies. Scoring for histopathological response proposed by Groupe d' Etude des Lymphomes de l'Adulte, which is European Gastro-Intestinal Lymphoma Study consensus report, is the recommended system for MALT lymphomas and this scoring system must be used also for gastric DLBCL[9,11].

In previous years, it was believed that MALT is dependent on *H. pylori* and this dependency is lost with high-grade transformation. However, it has been shown that low-grade MALT lymphomas and high-grade gastric MALT lymphomas remain *H. pylori* dependent and potentially can be cured by HPE only[12-14]. In an early German study, pCR by HPE was reported in seven of eight cases with high-grade gastric MALT in 2001[12]. Long-term results of HPE in early-stage gastric high-grade transformed MALT lymphoma were reported by Chen *et al*[15] in 2005. pCR was reported in 64% of cases. After these successful results about the regression of HG lymphomas with HPE, the first prospective study was reported again by Chen *et al*[14]. The study of Chen *et al*[14] reported treatment with HPE in 16 cases with stage IE, high-grade MALT lymphomas between 1995 and 2000. *H. pylori* was eradicated in 15 of the 16 cases and rapid tumor regression with disappearence of large cells was seen in 10 of these 15 cases. The response was found to be adversely affected by the depth of tumor invasion, as reported in low-grade MALT lymphomas with an attractive pCR rate (66.6%) with long duration (31.2 mo)[3]. This study suggests that high-grade transformation is not associated with loss of *H. pylori* dependency and disappearance of large cells with HPE. This finding is similar to the results of a study from Japan in which pCR was found in four of six cases with high-grade MALT lymphoma restricted to the mucosa/submucosa, but in only one of four cases with invasion beyond the muscularis propria[13]. A retrospective but larger study was published by Kuo *et al*[16] 3 years ago. Fifty patients with stage IE (tumor limited from mucosa to subserosa) or stage II1E (tumor invasion detected in regional lymph nodes) *H. pylori* (+) gastric DLBCL between 2002 and 2009 were treated by HPE. pCR was detected in more than two-thirds of the cases with *de novo* DLBCL and more than half of those with DLBCL (MALT). Importantly, all the patients achieving pCR were alive and in remission at a median of 7.7 years[16]. These studies are the cornerstone for HPE in gastric DLBCL. Additionally, an important study published last year showed different biology of *H. pylori*-dependent gastric DLBCL. It was shown that *H. pylori* (+) cases had lower international prognostic score, earlier stage disease, fewer constitutional symptoms of lymphoma, higher sensitivity to standard chemotherapy, and better 5-year event-free survival (EFS) and overall survival than *H. pylori*-independent cases. *H. pylori* negativity was seen among the six detrimental prognostic factors for EFS, and CagA expression was related to better response to chemotherapy[17].

Although *H. pylori*-dependent DLBCL has a better biology and HPE may be curative in some of these cases, we must not forget that high-grade lesions may rapidly progress if they are unresponsive to HPE. For this reason, cellular and/or molecular markers predicting *H. pylori*-independent status of newly diagnosed high-grade gastric lymphoma are important. These markers are well known for low-grade MALT lymphoma and we can make an analogy for high-grade lesions. t(11:18) is a genetic aberration predictive for no response to HPE in low-grade lymphoma[18-21]. In contrast, t(11:18) activates the nuclear factor (NF)-κB pathway[22]. Aberrant nuclear BCL10 or NF-κB is predictive of *H. pylori*-independent status in low-grade gastric MALT lymphoma with or without t(11:18)[23]. However, t(11:18) is uncommon in gastric DLBCL with or without MALT properties and the absence of t(11:18) precludes its use in predicting the response to HPE in DLBCL[21]. Kuo *et al*[16] studied

BCL10 and NF-κB in 22 cases with stage IE high-grade gastric MALT. They found aberrant nuclear BCL10 expression in seven of eight *H. pylori*-independent cases and in none of 14 *H. pylori*-dependent high-grade MALT cases. Additionally, they found NF-κB expression in all seven cases with BCL10 expression and in only two of 15 cases without BCL10 expression. These results suggest that aberrant nuclear BCL10 or NF-κB expression is highly predictive of *H. pylori*-independent status[24]. In contrast, CD86 expression is associated with *H. pylori*- dependent status in high-grade gastric MALT lymphoma[25]. Another important biological feature is CagA expression, which is more frequent in *H. pylori*-dependent cases than *H. pylori*-independent cases, and response to HPE is more rapid in cases with Cag A expression[26]. These results identify the candidate patients with gastric DLBCL for HPE without chemotherapy.

In conclusion, HPE is not limited to *H. pylori*-dependent low-grade MALT lymphoma, and it may be used in patients with high-grade DLBCL. Essential points are as follows. (1) all the patients without pCR after HPE must be immediately treated by standard chemotherapy; (2) histological sections from a minimum of six endoscopic tumor biopsies should be evaluated according to the EGIL consensus. Endoscopic ultrasound is mandatory for initial staging and CR has to be confirmed in two subsequent follow-up biopsies[16]; (3) loss of *H. pylori* dependency and high-grade transformation are distinct events in the progression of gastric lymphoma and short-term antibiotics may be effective in some cases[6]; (4) there are many molecular and biological markers predicting *H. pylori* dependency. Markers associated with *H. pylori* dependency are CD86, CD4 CD56 Treg, $p16^{INK4A}$, serum/tissue CagA protein and antibodies. Markers showing no response to HPE are t(11:18), t (1:14), aberrant BCL10 nuclear expression, CXCR3, MAD2, miR203, miR 142-5p and miR 155[6]; (5) *H. pylori* (+) gastric DLBCL, particularly with Cag A expression, is *H. pylori* related and clinicopathologically distinct from *H. pylori*-unrelated gastric DLBCL[17]; and (6) CagA (+) cases with DLBCL tend to be localized and have a lower clinical stage[17]. CagA positivity is more frequent in East Asia compared with western countries and this may be related to higher response to HPE in eastern countries[6,27].

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