EDITORIAL

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Helicobacter pylori Eradication Therapy, the Reasonable First Line Therapy for Gastric Mucosa-Associated Lymphoid Tissue Lymphoma Irrespective of Infection Status and Disease Stages

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See "*Helicobacter pylori* Eradication Therapy Is Effective as the Initial Treatment for Patients with *H. pylori*-Negative and Disseminated Gastric Mucosa-Associated Lymphoid Tissue Lymphoma" by Eun Jeong Gong, et al. on page 706, Vol. 10. No. 5, 2016

It seems very interesting and also strange that a malignant disease can be treated with antibiotics and acid suppressant combination therapy, rather than chemotherapy or radiotherapy. Infectious agents such as hepatitis B virus and hepatitis C virus, Epstein-Barr virus, *Helicobacter pylori*, and herpes simplex virus are well known causative agents for chronic inflammation associated cancers including hepatocellular carcinoma, stomach cancer, and cervical cancer. Even though the very early event of carcinogenesis starts from the chronic persistent infection status, once established cancers must be treated with chemo- and radiotherapy. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is the only exception from the rules.

Gastric MALT lymphoma is a shortened name of extranodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue of stomach and typically a low-grade malignancy. In addition to B cell monoclonality, this is characterized by a dense lymphoid infiltrate mainly composed of small-size lymphocytes that invade and destroy the gastric epithelium, configuring the lymphoepithelial lesion which is pathognomonic of MALT lymphoma diagnosis.[1]

The discovery of the strong relationship between *H. pylori* infection and gastric MALT lymphoma naturally suggested *H. pylori* eradication to treat lymphoma. The effectiveness of eradication has been well accepted and both hematology and gastroenterology international guidelines currently advise *H. pylori* eradication as first-line therapy for gastric MALT lymphoma.[2-4] It is more interesting that *H. pylori* eradication therapy is also indicated as a first line to *H. pylori* negative gastric MALT lymphoma and lymphoma in advanced stage.

The article by Gong *et al*.,[5] titled as "*Helicobacter pylori* eradication therapy is effective as the initial treatment for patients with *H. pylori*-negative and disseminated gastric mucosa-associated lymphoid tissue lymphoma" provides an additional evidence for this interesting clinical phenomenon. A total of 345 cases of gastric MALT lymphoma who had received eradication therapy as their first line treatment were enrolled by using medical record retrospectively. *H. pylori* positivity was 91.9% and *H. pylori* eradication therapy achieved complete remission in 82.3% for *H. pylori*-positive patients and 57.1% for *H. pylori*-negative patients (p=0.001). In this study, investigators claimed that the complete remission rates were comparable, 74.4% for stage IE2 or above and 83.3% for stage IE1 disease after administration of *H. pylori* eradication treatment (p=0.167). Because *H. pylori* negative patients were relatively small in number (28/345) and patients in stage IE2 or above also occupied a limited proportion (39/345), degree of effectiveness of *H. pylori* eradication on the gastric MALT lymphoma in stage IE2 or above should be interpreted carefully. Nonetheless, it is definitely true that, considering the low cost and risk of *H. pylori* eradication regimen, eradication therapy as a first line is worthwhile as a first step to gastric MALT lymphoma treatment regardless of the *H. pylori* status and disease stage.

How dose *H. pylori* eradication treatment work on patients with *H. pylori* negative gastric MALT lymphoma? The first

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explanation is the possibility of false negativity of *H. pylori* infection. All diagnostic tests have limitations in the detection power and hostile intragastric environments including severe inflammation and mucosal atrophy can reduce or even remove *H. pylori* colonization. As an intrinsic limitation of a retrospective study, investigators cannot control the quality of diagnostic tests and false negative cases cannot be corrected with additional steps including serology, polymerase chain reaction, and so on. The second is a hypothesis of non-*H. pylori* intragastric bacterial contribution to gastric MALT lymphoma.[6] Beyond traditional culture based research, recent investigations on gastric microbiota employ immunologic, molecular and genetic tools. The presence of *Helicobacter heilmannii*-associated gastritis was reported in Korea and Japan and the possible association to MALT lymphoma was claimed also in animal model.[7] However, we have no evidence of any microbe other than *H. pylori* in human. *H. pylori* associated gastric MALT lymphoma need specific *H. pylori* strain which can interact with specific interleukin-2 producing T cell and result in proliferation of B cell expression IL-2 receptor.[8,9] If there is other microbe which can induce MALT lymphoma, it may need research in strains level, not species.

It is more difficult to answer the mechanism of *H. pylori* eradication on advanced stage gastric MALT lymphoma in which lymphoma expands beyond mucosa to deep gastric wall structure, regional lymph nodes, distant organ and even to bone marrow.[10] At now, we have no clear explanation. During the disease progression, gastric MALT lymphoma is considered to go through the *H. pylori* dependent period and then *H. pylori* independent period. If advanced disease responds to the *H. pylori* eradication therapy, the transit between these two periods must be not a break but be connected with a smooth overlapping. Even more, data regarding the etiological role of *H. pylori* for diffuse large B cell lymphoma (DLBCL) is accumulating, there are several reports about remission achievement in DLBCL after *H. pylori* eradication therapy.

Negative predictive factors for lymphoma remission after *H. pylori* eradication includes advanced stage disease, deeper invasion of lymphoma into gastric wall, presence of the t(11;18) API2-MALT1 translocation, proximal location of lymphoma in stomach and the Western ethnicity. What if we fail in remission achievement with *H. pylori* eradication? Although no specific guidelines on the management of these patients are available, the European Society of Medical Oncology (ESMO) recommends the use of conventional antineoplastic therapeutic approaches.[3] In ESMO clinical practice guideline for gastric MALT lymphoma, radiotherapy or chemotherapy are reserved for symptomatic lymphoma or lymphoma with other treatment indications including overt progression, deep invasion or nodal involvement, presence of t(11:18) translocation, bulky disease, impending organ damage, and patient preference.[3] At present, failure to remission induction with *H. pylori* eradication therapy does neither mean delayed administration of definite anticancer therapy nor increase the risk of disease progression. Possibly, we need finer stratification of gastric MALT lymphoma according to the remission induction failure risk of *H. pylori* eradication and the disease progression risk if not treated earlier with antineoplastic therapy. The clinical evidences definitely support the *H. pylori* eradication as a first line therapy for gastric MALT lymphoma, irrespective of *H. pylori* infection status and disease stage.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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