LETTER TO THE EDITOR

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Concerns about the Predictive Factors for Tumor Regression, Definition, and Management of Nonresponders, and Relapse of Gastric Mucosa-Associated Lymphoid Tissue Lymphoma Related to *Helicobacter pylori*

Sun-Young Lee

Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Korea

I read with interest the recent review article by Suzuki *et al*.[1] This paper helps gastroenterologists to understand the link between gastric mucosa-associated lymphoid tissue (MALT) lymphoma and *Helicobacter pylori* (*H. pylori*), but several questions remain unanswered: (i) the predictive factors for regression of gastric MALT lymphoma after *H. pylori* eradication, (ii) the characteristic endoscopic findings, (iii) how to optimize the definition and managemnet of nonresponders, and (iv) how to manage the relapse and recurrence of these tumors.

The first report in 1993[2] has been followed by numerous reports of regression of MALT lymphoma after *H. pylori* eradication. However, not all gastric MALT lymphomas regress after *H. pylori* eradication, and thus three factors related to the prediction of tumor regression need to be considered: (i) the characteristics of gastric MALT lymphoma itself, (ii) the presence of *H. pylori* infection, and (iii) factors related to the host, such as the score on the international prognostic index and blood-test results. For example, even the location of the tumor has been mentioned as a predictive factor, with gastric MALT lymphomas on the proximal side being linked to autoimmunity.[3] These proximal-side tumors progress very slowly and often fail to regress because they are linked to autoantigen responsive T cells.[3,4] In addition, histological features of MALT lymphoma are known to be unresponsive to eradication therapy.[5]

An endoscopic apperance mimiking submucosal tumors and cobblestone like elevated lesions have been classified as polypoid gastric MALT lymphoma, and characterized as *H. pylori*-negative gastric MALT lymphoma.[6,7] Although Suzuki *et al*. described this briefly in their review,[1] *H. pylori* negativity needs to be defined. Since there is no single gold-standard methods for diagnosing *H. pylori* infection, the combination of several diagnostic methods including *H. pylori* IgG antibody, histology, culture, immunohistochemistry, PCR, and the urease breath test is considered to be suitable for confirming *H. pylori* negativity.[8] In addition, the characteristics of *H. pylori*-negative gastric MALT lymphoma should be managed based on previous reports.[9] Put simply, the treatment should differ from *H. pylori* eradication in these *H. pylori*-negative gastric MALT lymphoma due to the absence of *H. pylori*. However, these lymphomas also respond to antibiotic treatment in both the stomach and other parts of the gastrointestinal tracts.[10] What mechanism underlies this phenomenon? Does this represent a clue for a false-negative diagnosis of *H. pylori* infection? What would be the possible hypothesis based on previous reports?

On the other hand, non-*H. pylori helicobacters* related to MALT lymphoma should also be considered, such as *H. helimannii* and *H. felis*.[11] Interestingly, some of these regress merely after the application of first-line *H. pylori* eradication therapy.[12] In addition, these organisms are detected in both gastric and rectal lymphomas.[13]

Optimizing the definition and management of nonresponders requires consideration of three issues: (i) the minimum observation period needed to define regression, (ii) interpretating discrepancies between the histologic and endoscopic regression, and (iii) choosing between a "wait and see strategy" and a second-line treatment such as gastrectomy, chemotherapy, and radiotherapy. Alth-

Correspondence to: Sun-Young Lee
Department of Internal Medicine, Konkuk University School of Medicine, 4-12, Hwayang-dong, Gwangjin-gu, Seoul 143-729, Korea
Tel: +82-2-2030-7747, Fax: +82-2-2030-7748, E-mail: sunyoung@kuh.ac.kr
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ough a Japanese study adressed the last issue,[14] the optimal strategy remains unclear. In addition to the definition and management, the relapse and recurrence of gastric MALT lymphoma after successful regression on *H. pylori* eradication also need to be clarified. There are some reports of the development of high-grade tumor (diffuse large B-cell lymphoma) or gastric adenocarcinoma after successful regression of gastric MALT lymphoma. What would be the mechanisms and prognostic factors in such tumors?

In summary, answers to the above questions that arose when I read the review by professor Suzuki and colleagues would be of considerable interest to readers of *Gut and Liver*. There are already several interesting published papers written by Japanese authors that strengthen our knowledge in this field, and I strongly believe that addressing the above issues would greatly increase the interest in their review article.

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