

Once in a Blue Moon, the Bone Marrow Aspiration and Biopsy Has Clinical Impact for Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

Hye Kang Kim and Dae Young Cheung

Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Korea

See "Limited Role of Bone Marrow Aspiration and Biopsy in the Initial Staging Work-up of Gastric Mucosa-Associated Lymphoid Tissue Lymphoma in Korea" by Byung-Hoon Min, et al, on page 637, Vol. 8. No. 6, 2014

The indolent and favorable clinical course of extranodal B cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) of stomach is well known. For both physician and patient, one of the most fearful parts for gastric MALT lymphoma must be the bone marrow aspiration and biopsy (BMAB) rather than the disease itself. Guidelines from authorities still does not reach to a concurrence on the role of BMAB in the initial staging work-up of gastric MALT lymphoma (Table 1).¹⁻³ National Comprehensive Cancer Network and European Gastro-Intestinal Lymphoma Study state BMAB "useful in selected

cases,"^{1,2} however, European Society for Medical Oncology do "should-be done."³ The article "Limited role of BMAB in the initial staging work-up of gastric mucosa-associated lymphoid tissue lymphoma in Korea" by Min *et al.*⁴ is timely and provides practical information which is compatible with Korean physician's experiences.

This study aimed to evaluate the distribution of gastric MALT lymphoma according to stages and analyze the clinical characteristics through a retrospective analysis. A total of 194 patients were enrolled. Considering the low incidence, this number is

Table 1. Guidelines' Statements for BMAB for Initial Staging Workup of Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

Guideline	Specialty of authors	Statement about bone marrow aspirate and biopsy	Level of evidence and strength of recommendation
NCCN (2014) ¹	Multidisciplinary team including gastroenterology, pathology, hemato-oncology	Useful in selected cases	Based upon low level evidence, there is uniform consensus that the intervention is appropriate.
ESMO (2013) ²	Hemato-oncology and pathology	Recommended	Based on retrospective cohort studies or case-control studies. Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
EGILS (2011) ³	Gastroenterology	Should be done in the case of failure of lymphoma regression after <i>Helicobacter pylori</i> eradication and before initiating oncological treatment.	

BMAB, bone marrow aspiration and biopsy; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; EGILS, European Gastro-Intestinal Lymphoma Study.

Correspondence to: Dae Young Cheung

Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea College of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea

Tel: +82-2-3779-1519, Fax: +82-2-3779-1331, E-mail: adagio@catholic.ac.kr

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl14367>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

quite big for a gastric MALT lymphoma study. In results, 97.4% of gastric MALT lymphoma was confined to gastric wall. Abdominal lymph node metastasis was found in 2.6% (n=5). Bone marrow involvement was present in only one patient (0.5%) who had metastatic abdominal lymph nodes. Authors concluded that, in Korea, bone marrow involvement was rare for gastric MALT lymphoma and BMAB could be selectively performed in patients with high risk factors such as *Helicobacter* infection negativity and extragastric metastasis.

Lymphoma is a hematologic malignancy and has the property, so called homing, to disseminate into bone marrow. Non-Hodgkin's lymphoma has various tendency of bone marrow involvement. Small cell lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, and splenic B cell marginal zone lymphoma are found to involve bone marrow in over 80% of cases. Contrarily, diffuse large B cell lymphoma (DLBCL) involves bone marrow in 30%. To decide the treatment strategy and predict the clinical course, it is important to determine whether bone marrow is involved or not. Considering the better-tempered clinical characteristics of gastric MALT lymphoma, questions arise regarding the BMAB for initial baseline workup.

From literatures, the bone marrow involvement is reported to range from 4.6% to 14.6% for gastric MALT lymphoma.^{5,6} These rates seem far from the experiences in Korea. Studies from Western often did not separate gastric from non gastric MALT lymphoma. Non-gastric MALT lymphoma is more aggressive and involves bone marrow in up to 49%.⁷ Enrolled patients were possibly symptomatic and in advanced stages in Western studies. However, in Korea, screening endoscopy is prevalent in asymptomatic population and neoplasms are detected in earlier stage. Early gastric cancer overtakes the advanced cancer, and it must be true for gastric MALT lymphoma. Literatures from Korea and Japan, gastric MALT lymphoma is mostly stage IE and bone marrow involvement is rare.^{8,9} This article also reported 0.5% of bone marrow involvement. When the probability of event is very low, the cost of generalization outweighs the benefit. We need more selective strategy to make the cost-benefit balance more reasonably.

What if the bone marrow involvement was found in patient with gastric MALT lymphoma? Treatment for gastric MALT lymphoma unresponsive to *Helicobacter* eradication proceeds to involved-site radiotherapy (ISRT) or chemotherapy. Two treatments are equally effective to achieve disease control, and radiotherapy has an advantage in aspects of tolerability and easiness. Recent consensus agrees to choose ISRT for regional gastric MALT lymphoma and save chemotherapy for disseminated disease. Therefore, before initiating ISRT, bone marrow involvement has to be excluded. However, it is extremely unlikely that gastric MALT lymphoma confined to gastric wall, especially confined to mucosa and submucosa, has bone marrow involvement, we may safely postpone bone marrow evaluation after extragastric metastasis is found or remission of gastric

MALT lymphoma is not achieved with *Helicobacter* eradication.

The trephine aspiration and biopsy of iliac crest is the conventional method for bone marrow evaluation and accepted as gold standard of bone marrow examination. The weak point of the trephine technique lies on that it is blind technique and represent only a spot of bone marrow volume. The accuracy and reliability of the trephine technique cannot be judged due to the absence of comparable method. It is well known that both aspiration and biopsy yields better diagnostic rate than single method only and bilateral examination yields better than unilateral examination. This suggests possibility of false negative with BMAB. Recently, investigation of bone marrow using fluorescence *in situ* hybridization technique was reported.¹⁰ Micrometastasis presented as subtle CD20+ cell cluster in bone marrow of MALT lymphoma patients whose BMAB did not found involvement. Fortunately, the presence of micrometastasis seems not influence the survival and prognosis and we still do not have to concern about this. Positron emission tomography using ¹⁸F-deoxy-glucose (FDG-PET) is a candidate modality for bone marrow investigation of lymphoma involvement. Investigations using FDG-PET in patients with Hodgkin's disease and DLBCL were reported accurate and complimentary to BMAB.¹¹ Though some investigators reports that gastric MALT lymphoma with plasmacytic histology was better detected with FDG-PET, we still have no evidence to support the use of FDG-PET in gastric MALT lymphoma.

This article gives us meaningful evidences. In Korea, it is once in a blue moon that gastric MALT lymphoma involves bone marrow. Patient with bone marrow involvement has abdominal lymph node metastasis, even without mediastinal lymph node metastasis. *Helicobacter* infection negativity is related with abdominal lymph node metastasis and possibly be with bone marrow involvement. We need properly adjusted Korean guideline of gastric MALT lymphoma based on Korean database. Absence of *Helicobacter* infection, t(11;18)(q21;q21), depth of invasion, abdominal lymph node metastasis should be considered risk factors for bone marrow involvement. The cost and benefit of BMAB should be balanced, and the scale of ours seems to be tipped in favor of "doing in highly selected cases."

CONFLICTS OF INTEREST

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

REFERENCES

1. Zelenetz AD, Gordon LI, Wierda WG, et al. Non-Hodgkin's lymphomas, version 2.2014. J Natl Compr Canc Netw 2014;12:916-946.
2. Ruskoné-Fourmestreaux A, Fischbach W, Aleman BM, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lym-

- phoma of MALT. *Gut* 2011;60:747-758.
3. Zucca E, Copie-Bergman C, Ricardi U, et al. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi144-vi148.
 4. Min BH, Park JY, Kim ER, et al. Limited role of bone marrow aspiration and biopsy in the initial staging work-up of gastric mucosa-associated lymphoid tissue lymphoma in Korea. *Gut Liver* 2014;8:637-642.
 5. Raderer M, Wöhrer S, Streubel B, et al. Assessment of disease dissemination in gastric compared with extragastric mucosa-associated lymphoid tissue lymphoma using extensive staging: a single-center experience. *J Clin Oncol* 2006;24:3136-3141.
 6. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000;95:802-806.
 7. Zucca E, Conconi A, Pedrinis E, et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003;101:2489-2495.
 8. Ryu KD, Kim GH, Park SO, et al. Treatment outcome for gastric mucosa-associated lymphoid tissue lymphoma according to *Helicobacter pylori* infection status: a single-center experience. *Gut Liver* 2014;8:408-414.
 9. Nakamura S, Sugiyama T, Matsumoto T, 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.
 10. Won D, Park CJ, Shim H, et al. Subtle CD20 positivity in the bone marrow of a patient who has a mucosa-associated lymphoid tissue lymphoma should not be regarded as evidence of involvement in the bone marrow. *Histopathology* 2013;62:397-405.
 11. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood* 2013;122:61-67.