의학석사 학위논문

Bone marrow is rarely involved with superficial gastric mucosa-associated lymphoid tissue lymphoma

침범 깊이가 얕은 점막 연관 림프조직형 위 림프종에서의 낮은 골수 침범률

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박 재 용

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Bone marrow is rarely involved with superficial gastric mucosa-associated lymphoid tissue lymphoma

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The Department of Clinical Medical Sciences,

Seoul National University

College of Medicine

Jae Yong Park

Abstract

Introduction: The initial staging work-up of gastric mucosa-associated lymphoid tissue (MALT) lymphoma includes bone marrow (BM) examination. Since gastric MALT lymphoma is mostly detected in early stage with national cancer screening program in Korea, BM is rarely involved with tumor. The aim of this study was to investigate the incidence of BM involvement in gastric MALT lymphomas and the role of BM examination for an initial staging work-up.

Methods: Patients diagnosed as gastric MALT lymphoma at Seoul National University Hospital from January 2005 to July 2014 were enrolled. Clinical databases of the patients were retrospectively reviewed.

Results: Out of 105 patients, 91 (86.7%) were classified as stage IE1. Among these patients, 78 patients with *Helicobacter pylori* infection underwent eradication therapy, and complete remission was achieved in 74 cases (94.9%). Twelve out of 13 patients (92.3%) without *Helicobacter pylori* infection underwent radiotherapy or surgery and all achieved complete remission. BM involvement was proven in only one patient (1.0%).

Conclusions: BM involvement was rare in patients with only superficial gastric MALT lymphoma without extragastric invasion.

Further studies are warranted to identify the risk factors of BM involvement in gastric MALT lymphoma.

Keywords: MALT lymphoma; bone marrow; staging

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MALT, mucosa-associated lymphoid tissue; BM, bone marrow; CT, computed tomography; EUS, endoscopic ultrasonography; PET-CT, positron emission tomography-computed tomography; IHC, immuno-histochemistry; PPI, proton pump inhibitor; *H. pylori, Helicobacter pylori*; CR, complete remission; PR, partial response; CI, confidence interval; RT, radiotherapy; Op, operation; LN, lymph node

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphoma accounts for 7% of all the non-Hodgkin lymphomas. Gastrointestinal tract is involved in 50-60% of MALT lymphomas and stomach is the most commonly involved organ.[1] Although the incidence is increasing recently, primary gastric lymphoma including gastric MALT lymphoma is a rare disease entity comprising less than 5% of primary gastric malignancy.[2]

Low grade B cell gastric MALT lymphoma is mostly detected at its early stage and progresses very slowly, so it often remains a localized lesion for years.[3] And long term prognosis is relatively good, with 5-year survival rate of 80-95%.[1, 4, 5] Since upper endoscopy as national cancer screening program is recommended biennially for the population over 40 years of age in Korea, gastric MALT lymphoma tends to be detected more frequently in its early stage before any symptom develops. While there have not been much data about the portion of disseminated diseases at the time of diagnosis, some small group studies have revealed that only 6.5-7.7% of patients with gastric MALT lymphoma showed dissemination initially. According to former researches, bone marrow (BM) involvement by tumor is assumed to be present in 1-8%, but the exact rate is arguable due to the scarcity of the disease itself.[3, 6, 7]

Currently, initial staging procedures of gastric MALT lymphoma include BM examination, just as in other lymphomas. However, this increases the risk of

complication related to the procedure such as pain, bleeding, infection, as well as additional medical cost due to the necessity of admission to the hospital for the procedure.[8, 9] The purpose of this study was to investigate the rate of BM involvement by tumor and the role of BM examination as part of initial diagnostic work-up among patients with gastric MALT lymphoma.

MATERIALS AND METHODS

1. Patients and diagnostic criteria

We retrospectively reviewed 112 patients diagnosed as primary low grade B cell gastric MALT lymphoma in Seoul National University Hospital from January 2005 to July 2014. The patients were all pathologically confirmed as low grade B cell gastric MALT lymphoma according to the criteria of Isaacson and the scoring system of Wotherspoon et al.[10] Since 7 patients who did not undergo bone marrow examination due to poor general condition or rejection were excluded from the analysis, 105 patients were finally included in the study. Clinical and laboratory characteristics, endoscopic findings, histopathologic findings, imaging results, treatment algorithm and follow-up results of the patients were reviewed. The study was approved by the institutional review board of Seoul National University Hospital in accordance with the Helsinki Declaration.

2. Initial staging procedures

The initial staging procedures included a complete physical examination, chest x-ray, abdominal computed tomography (CT) scan, endoscopic ultrasonography (EUS) and BM examination. In addition, Chest CT was done in 39 patients and positron emission tomography (PET/CT) in five patients initially or during the treatment period. The depth of tumor invasion of gastric

MALT lymphoma was evaluated by EUS, and involvement of abdominal lymph nodes or distant extranodal involvement was determined by CT. Superficial gastric MALT lymphoma was defined as MALT lymphoma confined to the gastric mucosa or submucosa without any evidence of extragastric involvement, which was confirmed with full diagnostic studies including above mentioned modalities, only except BM examination. The Ann Arbor staging system modified by Musshoff and Radaszkiewicz was used for staging.[11] Bilateral BM aspiration and biopsy were routinely performed. Wright-stained BM aspirate smears and hematoxylin and eosin-stained trephine biopsy sections were reviewed by hematopathologists. Presence of lymphoid aggregates was determined in BM aspirate smears and biopsy sections. Immunohistochemical (IHC) staining was performed for CD3, CD20 and CD79a in all BM biopsy sections, and additional staining was applied according to the IHC staining results of the primary gastric lesion if needed.

3. *H. pylori* infection status

H. pylori infection status was determined as positive, if any of these test results was positive; rapid urease test (CLO® test; Kimberly-Clark, UT, USA), 13C-urea breath test, histologic examination from the antrum and body with modified Giemsa staining.

4. Treatment algorithm

Patients with low grade B cell gastric MALT lymphoma without evidence of dissemination (stage IE1) underwent eradication therapy as initial treatment if *H. pylori* infection was present, and received radiotherapy in *H. pylori*-negative cases. For *H. pylori* eradication, triple therapy with a standard dose of proton pump inhibitor (PPI), amoxicillin (1 g) and clarithromycin (500 mg) was administered twice daily for 7 days. If *H. pylori* eradication failed with triple therapy, quadruple therapy with two standard doses of PPI, three doses of metronidazole (500 mg), four doses of bismuth (120 mg), and four doses of tetracycline (500 mg) was administered for 7 days as secondary regimen. For the *H. pylori*-positive patients with stage IE2/IIE disease, eradication therapy was initially performed and radiotherapy was added when complete remission (CR) was not achieved. If *H. pylori* was negative, radiotherapy was considered preferentially. Systemic chemotherapy was considered in patients with more advanced disease (stage IIIE/IVE). If CR of gastric MALT lymphoma was not achieved in a year after successful *H. pylori* eradication, radiotherapy was applied as second-line treatment modality. If relapse occurred during the follow-up, further treatment was chosen according to the clinical status of the patient.

5. Response evaluation and follow-up

Patients were followed with upper endoscopy at 3 months after initial treatment. If endoscopic and pathologic CR were achieved, follow-up with endoscopy was performed at 6 months and then annually. If endoscopic or pathologic CR was not achieved, follow-up was performed every 3 months till

1 year. If CR was not achieved within 1 year after *H. pylori* eradication, additional radiotherapy was performed.

CR was defined as no evidence of tumor, clinically, endoscopically and histologically, and two sequential follow-up gastroscopies without evidence of tumor were required to assume CR. Partial response (PR) was defined as a 50% or greater reduction of tumor. Histological response assessment was done using Groupe d'Etude des Lymphomes de l'Adulte (GELA) histologic grading system.[12]

6. Statistical analysis

Only descriptive statistics were used in this study. Continuous variables were presented as median (range), and categorical variables were presented as number of cases (n) and percentage of occurrence (%). The percentage and their 95% confidence intervals (CIs) of positive BM involvement rate were calculated. All statistical analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Clinicopathological characteristics of the patients

The clinicopathological characteristics of the patients are summarized at Table 1. A total of 105 patients were enrolled (41.9% males, median age 57 years, range 11-80). *H. pylori* infection was present in 89 patients (84.8%). Endoscopic findings are separately shown in Table 2. Endoscopic appearances of primary gastric lesions are classified according to an updated endoscopic classification of gastric MALT lymphoma.[13] Ulcerative type (72.4%) and hypertrophic type (22.9%) were the two most common types of lymphoma lesion. The lesion was limited to the distal part of the stomach in 79 cases (75.2%). EUS was performed in every patient, and the depth of tumor invasion was confined to the mucosa and submucosa in 96 patients (91.4%). There was only one patient who showed lymphoma involvement in distant organs on abdominal CT scan. No one showed any lesion suggesting distant localization, among the 39 patients who underwent chest CT and among the five patients who underwent PET/CT. BM involvement by tumor was proved in only one patient (1.0%; 95% CI, 0-2.8) by means of BM aspiration and biopsy.

In 100 patients (95.2%) who had lesions confined only to the stomach, 91 patients (86.7%) had only superficial gastric lesions without evidence of extragastric involvement (Modified Ann Arbor stage IE1). Among 2 patients

(1.9%) with disseminated disease (stage IV), the site of lymphoma involvement other than stomach was BM in one patient, and transverse colon in the other one.

Table 1. Baseline characteristics of the patients with gastric mucosa-associated lymphoid tissue lymphoma (*n* = 105)

Variables	No. (%)
Age, median (range), years	57 (11-80)
Gender, male	44 (41.9%)
H. pylori infection	
Present	89 (84.8%)
Absent	16 (15.2%)
Depth of invasion on EUS	
Mucosa or submucosa	96 (91.4%)
Muscularis propria or subserosa	9 (8.6%)
Serosa	0 (0%)
Abdomen CT	
Localized in the stomach	100 (95.2%)
Regional lymph nodes	4 (3.8%)
Metastasis to distant organs in abdomen	1 (1.0%)
Chest CT (N=39)	
Metastasis	0 (0%)
No lesion suggesting metastasis	39 (100.0%)
Bone marrow involvement	
Present	104 (99.0%)
Absent	1 (1.0%)
PET/CT (N=5)	
Metastasis	0 (0%)
No lesion suggesting metastasis	5 (100.0%)
Stage (Modified Ann Arbor staging)	
IE1	91 (86.7%)
IE2	8 (7.6%)
IIE	4 (3.8%)
IVE	2 (1.9%)

Values are presented as median (range) or as numbers (%).
Abbreviations: *H. pylori*, *Helicobacter pylori*; EUS, endoscopic ultrasonography; CT, computed tomography; PET/CT, positron emission tomography-computed tomography

Table 2. Endoscopic findings of primary gastric lesions (*n* = 105)

Variables	No. (%)
Endoscopic appearance	
Single/multiple ulcerations or erosions (Ulcerative type)	76 (72.4%)
Large gastric fold/nodular mucosa (Hypertrophic type)	24 (22.9%)
Irregular or polypoid mass (Exophytic type)	3 (2.9%)
Multiple mucosal petechial hemorrhage (Petechial hemorrhage type)	0 (0%)
Absence of macroscopic lesions (Normal type)	2 (1.9%)
A combination of more patterns (Mixed type)	0 (0%)
Location of the lesion	
Proximal	26 (24.8%)
Distal only	79 (75.2%)

2. Treatment course and initial response

A summary of treatment course and outcome in 105 patients with gastric MALT lymphoma is shown in Figure 1. Some of the patients were treated differently from the treatment algorithm mentioned in the method section according to their performance status or preferences.

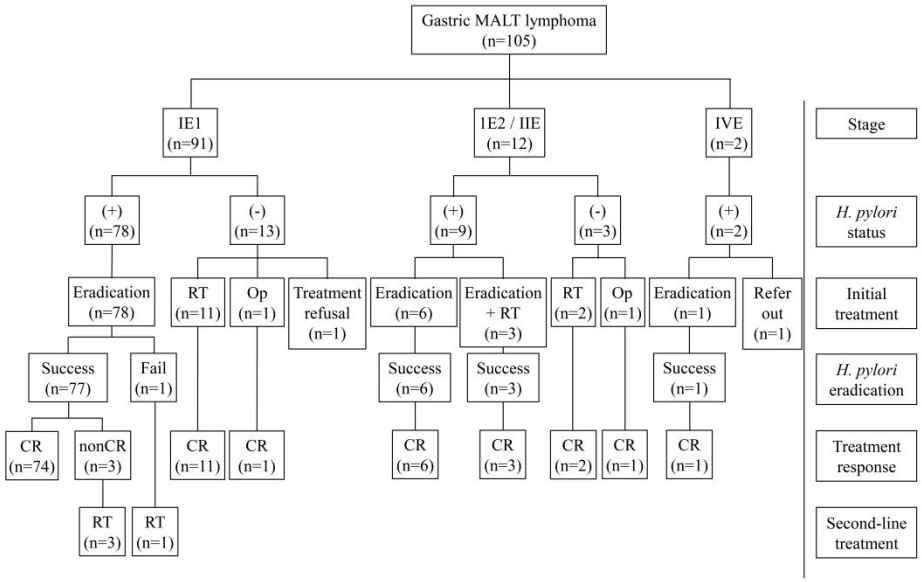

Figure 1. Treatment course and response in the patients with gastric mucosa-associated lymphoid tissue lymphoma

H. pylori, *Helicobacter pylori*; RT, radiotherapy; Op, operation; CR, complete remission

Out of 89 patients with *H. pylori* infection, all of whom underwent eradication therapy, successful eradication within two therapeutic attempts was achieved in 87 patients (97.8%). One patient attained eradication at the third attempt, while the other one failed lastly. Among the 88 patients with successful eradication, 81 patients (92.0%) achieved CR with eradication therapy only, including 74 cases of stage IE1, 3 cases of stage IE2, 3 cases of stage IIE, and 1 case of stage IV lymphoma.

Among 91 patients with stage IE1 disease, eradication therapy was done to all 78 patients (85.7%) who had *H. pylori* infection, with eradication success rate of 98.7% (77/78). Out of 77 patients with successful eradication, CR was achieved in 74 patients (96.1%). Four patients who failed to obtain CR with eradication therapy underwent radiotherapy, and CR was achieved in all of them. Among 13 patients with stage IE1 disease and *H. pylori*-negativity, radiotherapy was performed in 11 cases. Of the two remaining patients, one underwent surgery and the other one rejected to receive treatment. CR was achieved in all 12 patients who underwent treatment. (Table 3) There were 12 patients with stage IE2/IIE disease, and *H. pylori*-positive patients (9/12) all had successful eradication and achieved CR. Among these 9 patients, 3 patients underwent concurrent radiotherapy also, for they had lymphoma invasion as deep as gastric muscle layer, and complained of epigastric soreness or discomfort in common. Since they wanted rapid symptom control, considering the depth of gastric invasion, radiotherapy was simultaneously performed, in addition to eradication therapy. Meanwhile, the other 3 patients without *H. pylori* infection also obtained CR with radiotherapy (2/3) or

surgery (1/3).

Table 3. Response to initial treatment and follow-up results of the patients with stage IE1 gastric mucosa-associated lymphoid tissue lymphoma (*n* = 91)

	H. pylori status	
	Positive (*n* = 78)	Negative (*n* = 13)
Median follow-up (range) (months)	51.3 (6.5-113.0)	22.5 (8.5-75.5)
CR (%)	74 (94.9%)	12 (92.3%)
Time to get initial CR (range) (months)	9.0 (6.0-30.0)	8.0 (6.0-14.5)
Relapse (%)	2 (2.6%)	1 (8.3%)

Values are presented as medians (range) or as numbers (%).
Abbreviations: CR, complete remission; *H. pylori*, *Helicobacter pylori*

Only one patient had lymphoma involvement at BM, which was the only extragastric site with lymphoma invasion. This patient was *H. pylori*-positive and had gastric lesion confined to the mucosa on EUS and abdominal CT scan, so received eradication therapy first. (Case 1 in Table 4) For she did not complain of any symptom at initial presentation and had a good performance status, after *H. pylori* eradication, 'watch and wait' strategy with short term follow-up with EGD and BM examination was adopted as initial treatment plan. The follow-up EGD and biopsy performed in 3 months showed endoscopic & pathologic CR. After a month, repeated bilateral BM examination revealed positive-to-negative conversion of BM involvement by tumor. (Figure 2) Without any evidence of remnant disease, the patient was regularly followed-up according to the protocol. During the follow-up period

of 42 months in this patient, clinical and pathologic CR has been maintained. The other patient with stage IVE disease had lymphoma involvement in transverse colon, and systemic therapy was considered. After staging work-up, she was referred to a local hospital near her residence for treatment due to her preference.

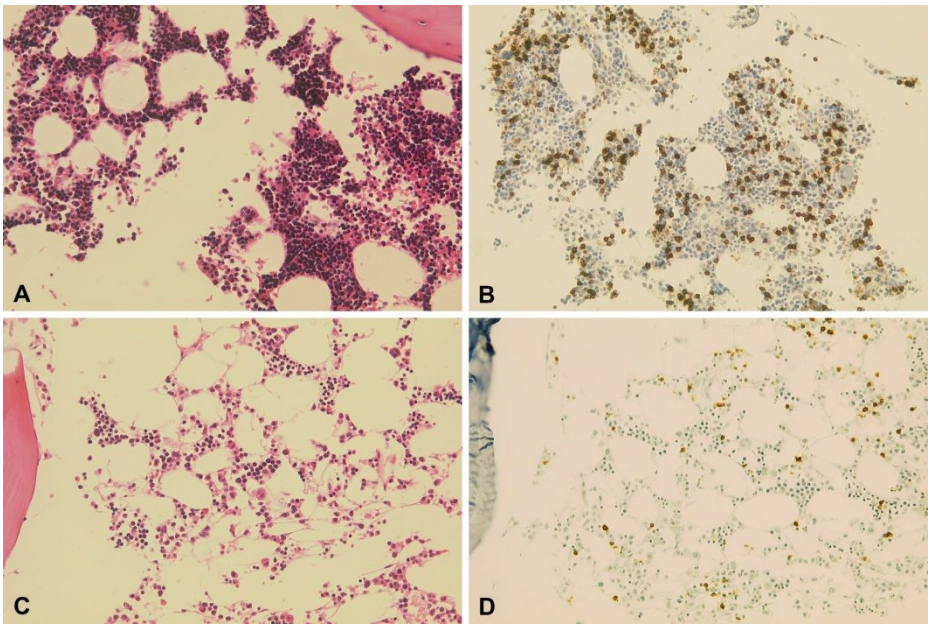

Figure 2. Changes in the bone marrow findings of the only patient with bone marrow involvement by gastric mucosa-associated lymphoid tissue lymphoma

(A) This bone marrow trephine biopsy section shows dense infiltration of lymphoid cells. (H&E stain, ×200). (B) Aggregated lymphoid cells are positive for CD20 (Immunohistochemical stain, × 200). (C) After eradication therapy, abnormal lymphoid aggregates in the bone marrow have disappeared.

(H&E stain, ×200). (D) Also, abnormal lymphoid cells positive for CD20 are not found in the bone marrow section (Immunohistochemical stain, × 200).

Table 4. Result of initial staging work-up of the patients who showed bone marrow involvement by tumor initially or during the follow-up period

Patient	Age	Sex	*H. pylori*	Depth on EUS	Abdomen CT	BM	Stage	Initial treatment	Response
Case 1	61	F	(+)	Mucosa	No intra-abdominal LN or metastasis	(+)	IVE	*H. pylori* eradication	CR
Case 2	58	M	(+)	Mucosa	No intra-abdominal LN or metastasis	(-)	IE1	*H. pylori* eradication	CR → relapse

Abbreviations: *H. pylori*, *Helicobacter pylori*; EUS, endoscopic ultrasonography; CT, computed tomography; BM, bone marrow; LN, lymph node; CR, complete remission

3. Follow-up and disease recurrence

Overall, the median duration of follow-up was 50.5 months (6.5-106.5), and CR was achieved in 99 patients (94.3%) with first-line treatment. Among these patients, the median interval to CR was 9.0 months (6.0-30.0).

During the follow-up period, relapse of lymphoma occurred in 3 patients. All of them only had had limited diseases confined to the superficial layers of stomach (stage IE1) at initial staging work-up. Two of them were *H. pylori*-positive initially, and experienced recurrence of lymphoma in 12 months and 13 months after the time of first CR, respectively. As there was no evidence of *H. pylori* reappearance at the time of disease recurrence, one patient underwent radiotherapy while the other one received chemotherapy.

Chemotherapy was performed in the latter one because involvement of multiple lymph nodes was suspected on follow-up abdominal CT scan. After receiving 6 cycles of systemic chemotherapy with rituximab, cyclophosphamide, vincristine and prednisolone, this patient obtained partial response and was followed-up regularly at the outpatient clinic. After eighteen months from the completion of chemotherapy, the patient's complete blood cell count result showed leukocytosis (12800/$\mu\ell$), low percentage of blood neutrophil (27%), high percentage of blood lymphocyte (66%), and atypical lymphocytes (4%). Since the involvement of BM by lymphoma was clinically suspected, a thorough evaluation for restaging was performed. The abdominal CT scan and PET/CT revealed numerous enlarged lymph nodes at infradiaphragmatic area and splenomegaly. BM involvement by lymphoma was histopathologically confirmed by means of BM examination. (Case 2 in Table 4) Meanwhile, in the other patient with *H. pylori*-negativity who achieved CR with radiotherapy initially, increasing mass at tongue base was found. Biopsy was done and recurrence of MALT lymphoma was histologically confirmed, while gastric lesion maintained remission status. Systemic chemotherapy was applied and additive local radiotherapy was performed sequentially.

DISCUSSION

In general, BM examination is regarded as mandatory in lymphoma staging work-up because the treatment plan and prognosis differ greatly according to the stage of the disease.[14-16] Though BM is a frequently involved site in lymphoma, the rates of BM involvement vary according to the histology of lymphoma.[17] The incidence has been reported as 39% in low grade, 36% in intermediate grade and 18% in high grade lymphomas. Association between BM involvement and poor prognosis has been well known in intermediate and high grade lymphomas.[18]

Although BM examination is also performed routinely in the patients with gastric MALT lymphoma as part of initial staging procedures, BM involvement by tumor is quite rare in gastric MALT lymphoma compared with other lymphomas, and the prognosis is relatively good due to its indolent course even in advanced cases.[6, 19] A recent study has reported that only 0.5% of the patients with gastric MALT lymphoma had BM involvement by tumor.[20]

Adverse events of BM examination itself may be problematic to consider rare incidence of BM involvement by tumor. While BM aspiration and trephine biopsy are widely performed and regared as relatively safe procedures with low complication rate, it is still unarguable that they are definitely invasive procedures. Pain, discomfort, and fear from the procedure that patients experience are also matters of importance, as well as severe

complications such as bleeding or fracture at the biopsy site.[8, 9] Increasing medical and socioeconomical costs related to the procedure itself and accompanying morbidity should be also taken into account. Considering these facts, the efficacy of BM examination in the patients with gastric MALT lymphoma might be reconsidered.

Recently, there have been different opinions about the necessity of BM examination in initial staging work-up of gastric MALT lymphoma. In the EGILS (European Gastro-Intestinal Lymphoma Study) consensus report (2011)[21], it was suggested that BM examination should only be recommended when tumor regression was not achieved with *H. pylori* eradication after an adequate time period, or when planning a loco-regional treatment. Likewise, BM examination was regarded useful in some selected cases according to NCCN guidelines (2014)[22], while it was always recommended as initial staging work-up according to ESMO clinical practice guidelines (2013).[23, 24]

There have been efforts to find out the predictive factors of BM involvement by tumor in patients with lymphoma. For Hodgkin's lymphoma, clinical prediction rule for BM involvement by tumor was developed using combination of clinical and laboratory parameters such as B symptoms, low leukocyte counts, anemia, advanced stage prior to BM biopsy, age and iliac/inguinal involvement.[25, 26] Regarding early stage diffuse large B cell lymphoma, the findings such as leukopenia, anemia and bulky disease were predictive for BM involvement by tumor.[27] Although there has been no known definite risk factor for BM involvement by tumor in MALT lymphoma,

there have been some studies about this subject. Association between the presence of monoclonal gammopathy and advanced disease with BM involvement by tumor was found in one study, and the possibility of relationship between CD5 positivity and BM involvement by tumor has also been suggested in the patients with MALT lymphoma.[18]

In this study, BM involvement by tumor was confirmed in only one patient at initial staging work-up, and the involvement rate was 1.0% (1/105). The patient did not show any finding indicating advanced stage at other work-up procedures such as EUS and radiologic imaging, and the prognosis was good. Patients with only superficial gastric MALT lymphoma (stage IE1) achieved CR by initial treatment in more than 90% of the cases, showing relapse rate of lower than 3%. Interestingly, there was one patient who newly showed markedly abnormal findings at complete blood cell count test during the follow-up period, and relapsed disease with BM involvement by tumor was confirmed. With these findings, considering the low prevalence of BM involvement by tumor and relatively good prognosis in gastric MALT lymphoma, it would be reasonable to perform BM examination in only selected cases.

It is interesting that the prevalence of stage IV disease was only 1.9% among 105 patients in our study, which is much lower than the prevalence of 8.9%, previously reported in a systematic review of 438 patients with gastric MALT lymphoma.[28] Probably, these divergent results between the studies might be partly due to the nationwide health examination system in Korea. As biennial upper endoscopic examination is recommended regardless of gastrointestinal

symptoms in the populations over 40 years of age, patients with gastric MALT lymphoma might have a lot more chances to be detected in earlier stages of disease.

There were some limitations in this study. First, designed as a single-center, retrospective study, the result of this study should be interpreted with caution. The upper limit of 95% CI of BM involvement rate was 2.8% in this study. The possibility of underestimating BM involvement rate could not be ruled out. Second, there was only one patient with BM involvement by tumor at initial staging work-up, and subgroup analysis for identifying risk factors for of BM involvement by tumor could not be feasible. Third, the proportion of patients who underwent chest CT and PET/CT were 37.1% (39/105) and 4.8% (5/105), respectively. So the results of these exams were only restrictively adopted.

In conclusion, this study shows that the frequency of BM involvement by tumor was substantially low in the patients with gastric MALT lymphoma. Considering the low incidence of BM involvement by tumor, relatively good prognosis and indolent course of the disease itself, performing BM examination in the initial staging work-up might be deferred in selected gastric MALT lymphoma patients who present with only superficial gastric lesion and no evidence of extragastric involvement. Abnormalities in the complete blood cell count could be regarded as a good alarm sign indicating BM examination. Further large-scaled studies are warranted to find out the risk factors that favor BM involvement by tumor, which will help establishing

a guideline for indications of BM examination in staging of gastric MALT lymphoma.

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국문 초록

서론: 현재 위 말트종의 초기 병기설정을 위한 검사에는 골수 검사가 포함되어 있다. 하지만 우리나라에서는 국가 암 검진 사업이 널리 행해지고 있기 때문에 위 말트종이 대부분 조기 병기에서 발견되고 있어 골수 침범을 보이는 경우는 드물다. 위 말트종에서 골수 침범의 빈도를 파악하고 초기 병기설정에서 골수검사의 필요성을 알아보고자 본 연구를 계획하였다.

방법: 서울대학교병원에서 2005 년 1 월부터 2014 년 7 월까지 위 말트종으로 진단받은 환자들을 대상으로 하였고, 임상 자료에 대한 후향적 의무기록 분석을 시행하였다.

결과: 전체 105 명의 환자 중 91 명 (86.7%)의 병기는 IE1 이었다. 이들 중 78 명에서 헬리코박터 파일로리 양성 소견을 보여 제균치료를 시행하였고, 74 명 (94.9%)에서 완전 관해가 확인되었다. 헬리코박터 음성이었던 13 명 중 12 명 (92.3%)에서는 방사선 치료나 수술을 통해 완전 관해에 도달하였다. 골수 침범은 1 명 (1.0%)에서 확인되었다.

결론: 위 외 침범이 배제된 표재성 위 말트종 환자에서 골수 침범은 드물었다. 위 말트종에서 골수 침범이 호발하는 위험인자들을 판별하기 위해서는 추가적인 연구가 필요하다.

주요어 : 말트 림프종, 골수 검사, 병기 설정

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