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Bone marrow involvement is rare in superficial gastric mucosa-associated lymphoid tissue lymphoma

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ABSTRACT

Background: The initial staging work-up of gastric mucosa-associated lymphoid tissue (MALT) lymphoma includes bone marrow examination. Since gastric MALT lymphoma is mostly detected in early stages with the national cancer screening programme in Korea, bone marrow is rarely involved.
Aims: To investigate the incidence of bone marrow involvement in gastric MALT lymphomas and the role of bone marrow examination for an initial staging work-up.
Methods: Patients diagnosed with 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 *H. pylori* infection underwent radiotherapy or surgery and all achieved complete remission. Bone marrow involvement was proven in only one patient (1.0%).
Conclusion: Bone marrow involvement was rare in patients with only superficial gastric MALT lymphoma without extragastric invasion. Further studies are warranted to identify the risk factors of bone marrow involvement in gastric MALT lymphoma.

1. 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 malignancies [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 is recommended biennially by the national cancer screening programme 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 symptoms develop. While there have not been much data about cases with disseminated disease 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 tumour 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 complications 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 tumour and the role of BM examination as part of initial diagnostic work-up among patients with gastric MALT lymphoma.

2. Materials and methods

2.1. 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

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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]. Seven patients who did not undergo bone marrow examination due to poor general condition or rejection were excluded from the analysis, and 105 patients were finally enrolled. 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.

2.2. 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 tumour 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 [11,12]. Bilateral BM aspiration and biopsy were routinely performed. Wright-stained BM aspirate smears and haematoxylin 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.

2.3. 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.

2.4. 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.

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

Variables	No. (%)
Median age (years)	57 (11–80)
Male gender	44 (41.9%)
H. pylori infection	89 (84.8%)
Depth of invasion on EUS	
Mucosa or submucosa	96 (91.4%)
Muscularis propria or subserosa	9 (8.6%)
Serosa	0
Abdominal CT	
Localized to stomach	100 (95.2%)
Regional lymph nodes	4 (3.8%)
Distant abdominal organs	1 (1.0%)
No metastasis at chest CT ($N = 39$)	39 (100.0%)
Bone marrow involvement	1 (1.0%)
No metastasis at PET/CT ($N = 5$)	5 (100.0%)
Stage (Modified Ann Arbor staging)	
IE1	91 (86.7%)
IE2	8 (7.6%)
IIE	4 (3.8%)
IVE	2 (1.9%)

H. pylori, *Helicobacter pylori*; EUS, endoscopic ultrasonography; CT, computed tomography; PET/CT, positron emission tomography–computed tomography.

2.5. 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 tumour, clinically, endoscopically and histologically, and two sequential follow-up gastroscopies without evidence of tumour were required to define CR. Partial response (PR) was defined as a 50% or greater reduction of tumour. Histological response assessment was done using Groupe d'Etude des Lymphomes de l'Adulte (GELA) histologic grading system [13].

2.6. 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).

3. Results

3.1. Clinicopathological characteristics of the patients

The baseline characteristics of patients are summarized in 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 [14]. 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 tumour invasion was confined to the mucosa and submucosa in 96 patients (91.4%). There was only one patient who