

## Treatment Outcome for Gastric Mucosa-Associated Lymphoid Tissue Lymphoma according to *Helicobacter pylori* Infection Status: A Single-Center Experience

Kwang Duck Ryu, Gwang Ha Kim, Seong Oh Park, Kwang Jae Lee, Jung Youn Moon, Hye Kyung Jeon, Dong Hoon Baek, Bong Eun Lee, and Geun Am Song

Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

**Background/Aims:** *Helicobacter pylori* eradication therapy has been used as a first-line treatment for *H. pylori*-positive gastric mucosa-associated lymphoid tissue (MALT) lymphoma. However, the management strategy for *H. pylori*-negative MALT lymphoma remains controversial. Therefore, the aim of this study was to examine the success rate of each treatment option for *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas. **Methods:** In total, 57 patients with gastric MALT lymphoma diagnosed between December 2000 and June 2012 were enrolled in the study. The treatment responses were compared between *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas. **Results:** Of the 57 patients, 43 (75%) had *H. pylori* infection. Forty-eight patients received *H. pylori* eradication as a first-line treatment, and complete remission was achieved in 31 of the 39 patients (80%) with *H. pylori*-positive MALT lymphoma and in five (56%) of the nine patients with *H. pylori*-negative MALT lymphoma; no significant difference was observed between the groups ( $p=0.135$ ). The other treatment modalities, including radiation therapy, chemotherapy, and surgery, were effective irrespective of *H. pylori* infection status, with no significant difference in the treatment response between *H. pylori*-positive and *H. pylori*-negative MALT lymphomas. **Conclusions:** *H. pylori* eradication therapy may be considered as a first-line treatment regardless of *H. pylori* infection status. (Gut Liver 2014;8:408-414)

**Key Words:** Lymphoma, B-cell, marginal zone; Stomach; *Helicobacter pylori*; Eradication; Radiotherapy

### INTRODUCTION

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare extranodal marginal zone B cell lymphoma that originates in the stomach, accounting for 40% to 50% of primary gastric lymphomas, 20% to 40% of extranodal lymphomas, 4% to 9% of all malignant lymphomas, and 1% to 6% of all gastric malignancies.<sup>1,2</sup> Gastric MALT lymphoma is difficult to diagnose because of its nonspecific symptoms and various endoscopic findings.

*Helicobacter pylori* infection is suggested to be causally associated with primary gastric MALT lymphoma.<sup>3,4</sup> Therefore, *H. pylori* eradication could be an effective therapeutic option in cases of early-stage, low-grade gastric MALT lymphoma.<sup>5,6</sup> In a recent study in Japan, complete remission (CR) was achieved in 77% of 420 patients with gastric MALT lymphoma, with 5- and 10-year overall survival rates after *H. pylori* eradication of 99% and 95%.<sup>7</sup> In addition to *H. pylori* eradication, chemotherapy or radiotherapy has been demonstrated to have a curative potential for gastric MALT lymphoma in some retrospective studies.<sup>8-10</sup> Surgery was also considered a treatment option for gastric MALT lymphoma in the pre-*H. pylori* era.

Unlike that for *H. pylori*-positive MALT lymphoma, the management strategy for *H. pylori*-negative MALT lymphoma remains controversial. A study reported that only 11.1% of patients with *H. pylori*-negative MALT lymphoma responded to eradication therapy.<sup>11</sup> Therefore, the aim of the present study was to examine the success rate of each treatment option for *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas.

Correspondence to: Gwang Ha Kim

Department of Internal Medicine, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, 179 Gudeok-ro, Seo-gu, Busan 602-739, Korea

Tel: +82-51-240-7869, Fax: +82-51-244-8180, E-mail: doc0224@pusan.ac.kr

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## MATERIALS AND METHODS

### 1. Patient population

Between December 2000 and June 2012, gastric MALT lymphoma was diagnosed in 65 patients from Pusan National University Hospital (Busan, Korea). The diagnosis was based on morphological and immunophenotypic analyses of biopsy specimens obtained from gastric lesions identified on esophago-gastroduodenoscopy. The medical records of the patients were reviewed retrospectively. Of the 65 patients, eight were excluded, four being lost to follow-up, and four being followed up after *H. pylori* eradication. Finally, the data from 57 patients were included in the comparison of treatment results for gastric MALT lymphoma with and without *H. pylori* infection (Fig. 1). Clinical stage was determined on the basis of the Lugano staging system, a modification of the Ann-Arbor classification.<sup>12</sup>

This study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital.

### 2. Endoscopic findings

Gross findings were classified into two types according to endoscopic features; 1) superficial type: erosive, discolored, cobblestone, IIc, fold thickening, and submucosal tumor-like features; and 2) advanced cancer-like type: ulcerative, and polypoid features.<sup>13</sup> In addition, the location and number of lesions were examined.

### 3. Diagnosis and eradication of *H. pylori* infection

*H. pylori* infection was examined using at least two of the following methods: histology, urea breath test, rapid urease test and serological test. *H. pylori* infection was regarded to be present if at least one test had positive results and absent if all the tests had negative results. The patients received *H. pylori* eradication treatment with a 1- or 2-week standard triple therapy consisting of proton pump inhibitor (PPI), clarithromycin, and amoxicillin. If the *H. pylori* eradication treatment failed, the patients received a 1- or 2-week quadruple therapy consisting of PPI, metronidazole, bismuth, and tetracycline. Success or failure of the eradication therapy was determined by histology, rapid urease test or urea breath test at least 4 to 6 weeks after the

treatment.

### 4. Other treatments

Radiation therapy was administered 17 times, with a total dose of 30.6 Gy and fraction size of 1.8 Gy. All the patients were treated with opposed anterior and posterior fields to the stomach and perigastric lymph nodes.

Chemotherapy regimens were as follows: rituximab and cyclophosphamide, adriamycin, vincristine, and prednisolone; rituximab and cyclophosphamide, vincristine, and prednisolone; and etoposide, ifosfamide, cytarabine, and cisplatin. Each regimen was administered for six cycles. In one case, the mesna, ifosfamide, mitoxantrone, and etoposide regimen was administered as second-line chemotherapy.

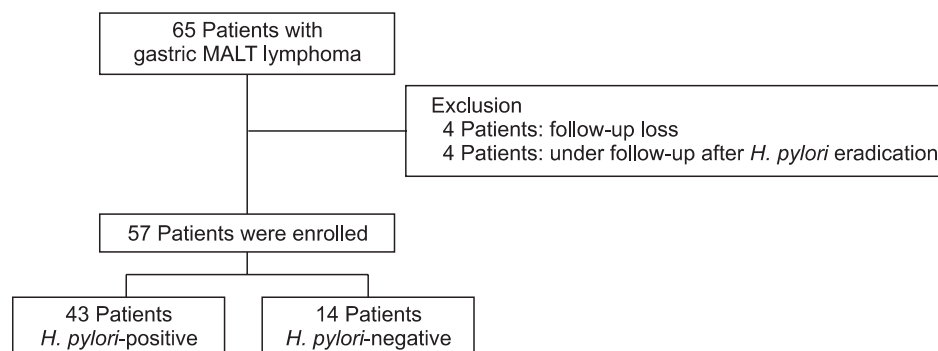
In patients treated with surgery, either wedge resection or Billroth I subtotal gastrectomy was performed.

### 5. Posttreatment evaluation

Follow-up endoscopy with multiple biopsies was performed 3 to 4 months after treatment completion to evaluate the treatment response. Thereafter, periodic follow-up endoscopy with multiple biopsies was performed every 4 to 6 months until CR was documented. CR was defined by the absence of macroscopic findings of lymphoma and negative histology in two subsequent follow-up investigations. In cases of *H. pylori* eradication therapy, further follow-up evaluation for *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphoma was performed every 4 to 6 months until at least 1 year by the watch and wait strategy. If CR was not achieved until at least 1 year after eradication, other treatments were administered.

### 6. Statistical analysis

A chi-square or Fisher exact test was performed to assess differences in baseline characteristics, endoscopic findings, and treatment response between *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas. A  $p < 0.05$  was considered statistically significant. Statistical calculations were performed using the SPSS version 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).



**Fig. 1.** Flowchart showing the selection of the patients included in the analysis. MALT, mucosa-associated lymphoid tissue; *H. pylori*, *Helicobacter pylori*.

**RESULTS**

**1. Patient characteristics**

Of the 57 patients with gastric MALT lymphoma, *H. pylori* infection was present in 43 (75%). The baseline characteristics of the 57 patients (24 men and 33 women; mean age, 57 years) enrolled in this study are presented in Table 1. The median follow-up period was 26 months (range, 3 to 125 months). Thirty-three patients (58%) had multiple lesions. In the single-lesion cases, the lesions were located mainly in the lower portion of the stomach. Most (47/57, 82%) of the gastric MALT lymphoma cases were stage I.

No significant differences in age, stage, and number of lesions were found between *H. pylori*-positive and *H. pylori*-negative MALT lymphomas. Only male gender was associated with the *H. pylori*-negative MALT lymphomas (p=0.011).

**2. Endoscopic findings of gastric MALT lymphoma**

The endoscopic findings of gastric MALT lymphoma mostly corresponded with the superficial type (49/57 [86%]; 37/43 in *H. pylori*-positive MALT lymphoma and 12/14 in *H. pylori*-negative MALT lymphoma). No significant differences in superficial types were observed between the two groups. In the *H. pylori*-positive MALT lymphoma, the erosive superficial type was predominant. In contrast, all the superficial types were similar in the *H. pylori*-negative MALT lymphoma (Table 2).

**3. Treatment of gastric MALT lymphoma**

**1) Success rate of each treatment**

Table 3 summarizes the success rate of each treatment in all

**Table 1.** Clinical Characteristics of the 57 Patients with Gastric Mucosa-Associated Lymphoid Tissue Lymphoma according to *Helicobacter pylori* Infection Status

Characteristic	<i>H. pylori</i> positive (n=43)	<i>H. pylori</i> negative (n=14)	p-value
Age, yr			0.479
≤60	23 (54)	9 (64)	
>60	20 (46)	5 (36)	
Gender			0.011
Male	14 (33)	10 (71)	
Female	29 (67)	4 (29)	
No. of lesions			0.638
Multiple	24 (56)	9 (64)	
Single	19 (44)	5 (36)	
Upper/middle/lower	3/1/15	3/0/2	
Clinical stage			0.212
I	37 (86)	10 (71)	
II or more	6 (14)	4 (29)	

Data are presented as number (%).  
*H. pylori*, *Helicobacter pylori*.

the 57 patients with gastric MALT lymphoma. Of the 48 patients with MALT lymphoma who received *H. pylori* eradication therapy as a first-line treatment, eradication was successful in 41 (85%), with the first-line standard triple therapy in 38 patients and second-line quadruple therapy in the remaining three patients. Furthermore, of the 48 patients, 36 (75%) achieved CR, with a time to CR after *H. pylori* eradication therapy of 3 to 12 months. The 12 patients who failed to achieve CR by *H. pylori* eradication therapy received additional second-line treatments as follows: radiotherapy (n=6), chemotherapy (n=5), and surgery (n=1). After treatment, 11 patients achieved CR, whereas one patient who received chemotherapy did not achieve CR. Of the nine patients who did not receive *H. pylori* eradication therapy, six patients received chemotherapy, one radiotherapy and two surgery. Of the six patients who receive chemotherapy, one did not achieve CR. Despite the additional chemotherapy in two of the patients who did not achieve CR after the first-line treat-

**Table 2.** Endoscopic Findings of Gastric Mucosa-Associated Lymphoid Tissue Lymphoma according to *Helicobacter pylori* Infection Status

	<i>H. pylori</i> positive (n=43)	<i>H. pylori</i> negative (n=14)	p-value
Superficial type			
Erosive	14 (33)	1 (7)	0.084
IIC	7 (16)	4 (30)	0.436
Discolorized	7 (16)	2 (14)	1.000
Cobble stone	6 (14)	3 (21)	0.674
SMT-like	2 (5)	2 (14)	0.250
Fold thickening	1 (2)	0	1.000
Advanced cancer-like type			
Ulcerative	5 (12)	2 (14)	1.000
Polypoid	1 (2)	0	1.000

Data are presented as number (%).  
*H. pylori*, *Helicobacter pylori*; SMT, submucosal tumor.

**Table 3.** Treatment Response in Patients with Gastric Mucosa-Associated Lymphoid Tissue Lymphoma according to *Helicobacter pylori* Infection Status

	Total (n=57)		<i>H. pylori</i> positive (n=43)		<i>H. pylori</i> negative (n=14)	
	No.	Response	No.	Response	No.	Response
<i>H. pylori</i> eradication	48	36 (75)	39	31 (80)	9	5 (56)
Radiotherapy	7	7 (100)	4	4 (100)	3	3 (100)
Chemotherapy	11	9 (82)	6	5 (83)	5	4 (80)
Operation	3	3 (100)	2	2 (100)	1	1 (100)

Data are presented as number (%).  
*H. pylori*, *Helicobacter pylori*.

ment, CR was still not achieved; therefore, they received supportive care.

Among the 57 patients with gastric MALT lymphoma, seven received radiotherapy, of whom one had *H. pylori*-negative MALT lymphoma and six had eradication therapy-failed *H. pylori*-positive MALT lymphoma. The success rate of radiotherapy was 100% (7/7). Only mild adverse events such as nausea and dyspepsia were noted during radiotherapy.

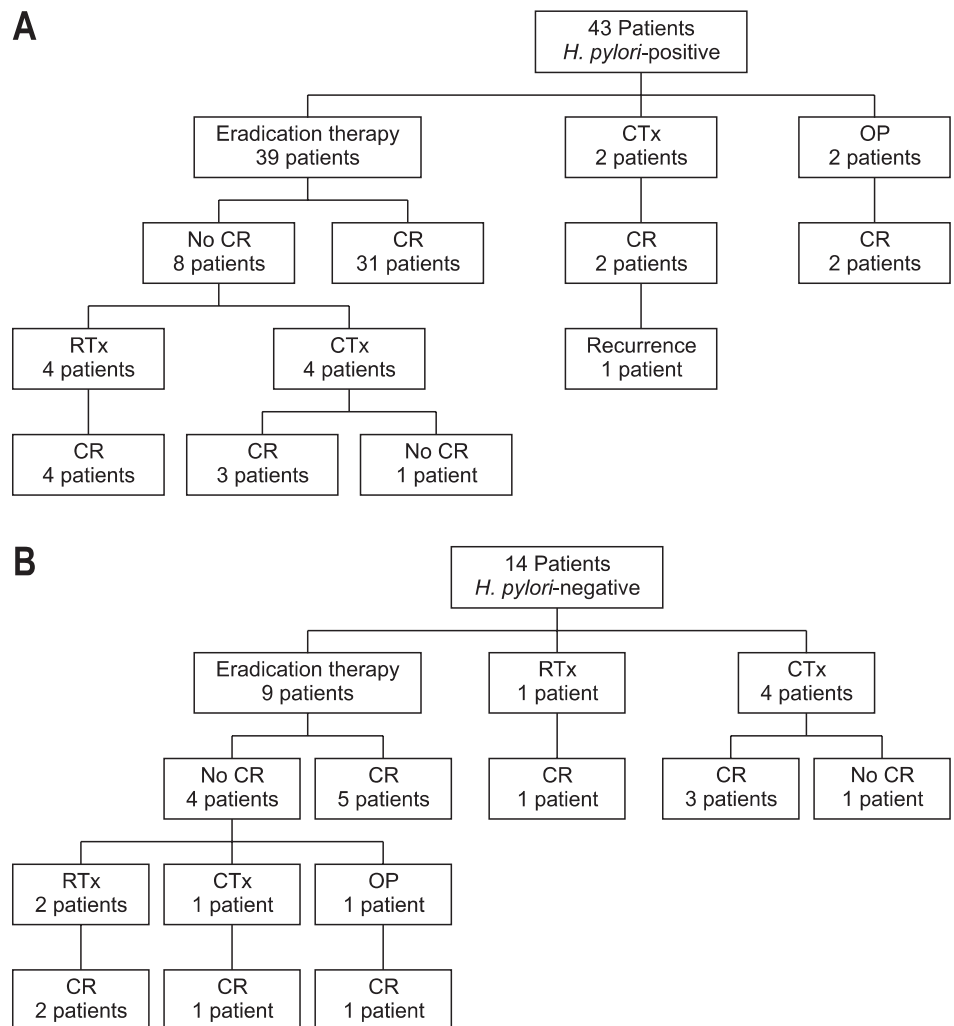
Of the 11 patients who received chemotherapy, six had *H. pylori*-negative MALT lymphoma and five had eradication therapy-failed *H. pylori*-positive MALT lymphoma. The success rate of chemotherapy was 82% (9/11). Although most of the patients who received chemotherapy had high-stage (stage II or higher) lymphoma, except one patient (stage I1E), they achieved a high CR rate. The following were the adverse events experienced by the patients who received chemotherapy; pancytopenia in one and *Pneumocystis jiroveci* pneumonia in another after chemotherapy. During the follow-up period, one patient with *H. pylori*-positive MALT lymphoma who achieved CR after chemotherapy had disease recurrence and thus received supportive care without further treatment.

Three patients underwent surgery: wedge resection in two and Billroth I subtotal gastrectomy in one. Of the three patients, two had *H. pylori*-negative MALT lymphoma and one had eradication therapy-failed *H. pylori*-positive MALT lymphoma; all achieved CR.

**2) Treatment outcomes according to *H. pylori* infection status**

After *H. pylori* eradication therapy, CR was achieved in 31 of the 39 patients (80%) with *H. pylori*-positive gastric MALT lymphoma and in five of the nine patients (56%) with *H. pylori*-negative MALT lymphoma (Fig. 2). *H. pylori* eradication therapy had a superior trend in the *H. pylori*-positive MALT lymphoma but made no significant difference in both groups (p=0.135).

The other treatment modalities, including radiation therapy, chemotherapy, and surgery, were effective irrespective of *H. pylori* infection, with no significant difference in treatment response between *H. pylori*-positive and *H. pylori*-negative MALT lymphomas.



**Fig. 2.** Treatment outcomes for gastric mucosa-associated lymphoid tissue (MALT) lymphoma according to *Helicobacter pylori* infection status. (A) *H. pylori*-positive gastric MALT lymphoma. (B) *H. pylori*-negative gastric MALT lymphoma. CTx, chemotherapy; OP, operation; CR, complete remission; RTx, radiotherapy.

## DISCUSSION

Gastric MALT lymphomas usually show slow progression and are localized; therefore, they are clinically characterized by long disease-free and long overall survival periods.<sup>14-16</sup> In gastric MALT lymphomas, *H. pylori* infection is generally known as an important cause of the disease, and when appropriate diagnostic methods are used, the prevalence of *H. pylori* infection is high, at nearly 90%.<sup>16</sup> Therefore, eradication therapy against *H. pylori* is universally accepted as the first-line treatment for *H. pylori*-positive gastric MALT lymphoma,<sup>6,17</sup> achieving complete lymphoma remission in 60% to 90% of patients.<sup>3,6,18</sup> In the present study, *H. pylori* infection was present in 75% of the patients and the CR rate after eradication therapy was 75%, irrespective of *H. pylori* infection.

To date, the differences in clinical findings and treatment response according to the treatment modalities between *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas are unclear. In the present study, most (82%) of the gastric MALT lymphoma were stage I and the endoscopic findings indicated various superficial types (89%). In *H. pylori*-negative gastric MALT lymphoma, male predominance was observed. No significant differences in the other clinical findings were observed between *H. pylori*-positive and *H. pylori*-negative MALT lymphomas. Based on the endoscopic findings, the predominant superficial type in *H. pylori*-positive MALT lymphomas was erosive-type, whereas no predominant superficial type was observed in the *H. pylori*-negative MALT lymphomas.

The optimal management of *H. pylori*-negative MALT lymphoma is still controversial. Akamatsu *et al.*<sup>11</sup> reported a lower response rate to eradication treatment in patients with *H. pylori*-negative MALT lymphoma. Although 74% of patients with *H. pylori*-positive MALT lymphoma achieved complete regression with eradication treatment, only 11% of patients with *H. pylori*-negative MALT lymphoma responded to antibiotics. *H. pylori*-negative or *H. pylori*-positive MALT lymphomas that are unresponsive to eradication therapy have been reported to show a good response to radiation therapy. In their study, 13 of 14 patients (93%) showed complete response to 30-Gy radiation therapy, although distant recurrence was observed in three patients.<sup>11</sup>

However, in the present study, despite the small number of *H. pylori*-negative MALT lymphoma (n=9), no significant difference in CR rate after eradication therapy was observed between *H. pylori*-positive and *H. pylori*-negative gastric MALT lymphomas (80% vs 56%, respectively), consistent with the results of Raderer *et al.*,<sup>19</sup> who reported a high CR rate of 83.3% (five of six patients). These findings suggest that *H. pylori* eradication therapy may be considered as a first-line treatment regardless of *H. pylori* infection. The following are two possible reasons why eradication therapy might be effective for *H. pylori*-negative

gastric MALT lymphoma: first, another infective organism such as *Helicobacter heilmannii*, might be involved in the development of gastric MALT lymphoma;<sup>20</sup> second, because of very low bacterial counts, conventional examination could not detect the organisms.<sup>13</sup>

Although MALT lymphomas can occur in any region of the stomach, they are most commonly located in the lower portion of the stomach, indicating localization of the highest concentration of colonized *H. pylori* organisms and acquired lymphoid tissue.<sup>6</sup> We also demonstrated that single-lesion gastric MALT lymphomas were mainly found in the lower portion but *H. pylori*-negative gastric MALT lymphomas were relatively more frequently found in the upper portion. The subset of *H. pylori*-negative tumors has been assumed to include autoimmune-related or autonomous tumors, which predominantly involves the corpus in contrast to *H. pylori*-induced antrum-predominant gastritis.<sup>21,22</sup>

In the pre-*H. pylori* era, localized gastric lymphomas of any histological type were commonly treated with partial or total gastrectomy, which can lead to long-term morbidity. Recently, conservative treatments that allow stomach preservation, such as radiotherapy or chemotherapy, are known to be potential treatments for gastric lymphoma. Several studies reported that CR was achieved in *H. pylori*-negative MALT lymphomas after radiotherapy.<sup>23-25</sup> In the present study, seven patients with *H. pylori*-negative MALT lymphoma or eradication therapy-failed localized gastric MALT lymphoma received radiotherapy alone and achieved CR in the absence of significant adverse effects. Therefore, radiotherapy may be considered as an effective treatment for localized gastric MALT lymphoma. Similarly, chemotherapy showed high effectiveness (82%) despite lymphoma with relatively high clinical stages; however, it caused some adverse events such as pancytopenia and opportunistic pneumonia.

Our study had some limitations. First, it was a retrospective study that assessed the treatment outcomes for gastric MALT lymphomas according to *H. pylori* infection status. Therefore, the patients were selected to undergo each treatment modality according to the clinical opinions and decisions of the medical physicians at the time of treatment. Secondly, the number of subjects, especially the number of those with *H. pylori*-negative gastric MALT lymphoma, was rather small. Thirdly, endoscopic ultrasonography and analysis for monoclonality were not performed. Finally, the translocation t(11;18)(q21;q21), which is known as a predictor of the treatment response of gastric MALT lymphoma, was not considered in this study.

In conclusion, the *H. pylori* eradication therapy achieved higher CR rates in *H. pylori*-negative as well as *H. pylori*-positive gastric MALT lymphomas. In addition, radiation therapy was effective for *H. pylori*-negative or eradication therapy-failed localized gastric MALT lymphoma. Therefore, we suggest that *H.*

*pylori* eradication therapy be considered as an initial treatment option for localized gastric MALT lymphoma regardless of *H. pylori* infection and that radiotherapy be considered as an effective second-line therapy for *H. pylori*-negative or eradication therapy-failed localized gastric MALT lymphoma. In cases of high-stage or extensive diseases, chemotherapy might be effective.

## CONFLICTS OF INTEREST

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

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