Recurrence after Radiotherapy for Gastric Mucosa-associated Lymphoid Tissue (MALT) Lymphoma with Trisomy 18

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Abstract

A 36-year-old Japanese woman presented with extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the stomach. The gastric lesions only partially improved after eradication therapy for Helicobacter pylori. A fluorescence in situ hybridization analysis revealed no fusion genes of API2-MALT1, although trisomy of chromosome 18 was identified. Radiation therapy was initiated to treat the gastric lymphoma lesions, resulting in complete remission. However, MALT lymphoma recurred in the stomach 16 months later. This case indicates that intensive follow-up is required for MALT lymphoma associated with chromosomal aberrations in order to detect early relapse.

Key words: extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, MALT lymphoma, gastric lymphoma, trisomy 18


Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is a neoplasm originating from marginal zone B cells that primarily or secondarily involves the gastrointestinal tract, lungs, salivary glands, thyroid, ocular adnexa, liver and skin (1, 2). Among these sites, the stomach is the most frequently involved in cases of MALT lymphoma. Several genetic alterations are reportedly associated with the pathogenesis of this disease. Representative chromosomal translocations include t(11;18)(q21;q21)/API2-MALT1, t(1;14)(p22;q32)/IGH-BCL10, t(14;18)(q32;q21)/IGH-MALT1 and t(3;14)(p14;q32)/IGH-FOXP1 (1-5). In addition, aneuploidies, such as trisomy 3 and trisomy 18, have been reported in patients with both gastric and extragastric MALT lymphoma. For example, patients with thymic MALT lymphoma with trisomy 18 and rectal MALT lymphoma with trisomy 3 have been documented in addition to gastric cases (5-9). Previous studies have suggested that trisomy 3 and 18 are associated with a shorter duration of disease progression and/or recurrence (5-7). However, the details of the clinical course of MALT lymphoma with trisomy 3 and/or 18 have rarely been reported.

We herein describe the case of a patient with primary gastric MALT lymphoma with trisomy 18. Eradication therapy for Helicobacter pylori resulted in only partial regression of the lymphoma lesions and radiotherapy was thus initiated. Although complete remission was achieved with the radiotherapy, the lymphoma recurred in the stomach 16 months later. This case indicates that intensive follow-up is required for MALT lymphoma associated with chromosomal aberrations in order to detect early relapse.

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therapy regimen, recurrence in the stomach was detected 16 months after the completion of treatment. This case underscores the importance of providing intensive follow-up in cases of MALT lymphoma with trisomy 18, even after complete remission is achieved.

Case Report

A 36-year-old Japanese woman underwent an upper gastrointestinal series at her family clinic as part of a health check-up. Ulcers were documented, and subsequent esophagogastroduodenoscopy showed multiple erosions, ulcers and ulcer scars in the gastric body. All biopsy specimens obtained from the ulcers in the anterior and posterior wall of the lower gastric body and erosions in the lesser curvature of the upper gastric body revealed lymphoma cell infiltration, and immunohistochemistry confirmed the diagnosis of gastric MALT lymphoma. *H. pylori* infection was positive, and successful eradication therapy with lansoprazole, clarithromycin and amoxicillin was administered. Although the gastric lesions improved endoscopically, a biopsy examination performed six months after *H. pylori* eradication revealed residual MALT lymphoma cells in the stomach. The patient was therefore referred to Okayama University Hospital for further investigation and treatment.

The patient’s history included gynecological surgery for an ovarian cyst; however, she had no history of gastrointestinal or hematological diseases. A physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. All laboratory findings, including the levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R), were within the normal ranges. An esophagogastroduodenoscopic examination showed a reddish, slightly elevated lesion in the greater curvature of the upper gastric body (Fig. 1) in addition to the ulcer scar in the lesser curvature of the lower gastric body. There were no other lesions suggestive of residual lymphoma. A magnifying observation demonstrated a lack of gastric pits and the presence of abnormal vessels. A histopathological study of biopsy samples of the gastric lesions showed the monomorphic proliferation of plasma cell-like neoplastic cells expressing immunoglobulin light chain lambda (Fig. 2). These cells were positive for CD138 and negative for CD3, CD20, CD5 and CD10, indicative of plasma cell-like characteristics. In addition, amyloid deposition was detected, which presented as an amorphous eosinophilic substance on hematoxylin and eosin staining and direct fast scarlet staining (Fig. 2H). The diagnosis of amyloid was confirmed based on apple-green birefringence under polarized light (Fig. 2I). Immunoglobulin light chain production by the neoplastic cells was

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**Figure 1.** Esophagogastroduodenoscopy images. A reddish, slightly elevated lesion was detected in the upper gastric body (A, B). A magnifying observation with Fuji intelligent chromoendoscopy (FICE) imaging showed a lack of gastric pits and the presence of abnormal vessels (C). The border of the reddish lesion was emphasized after indigo carmine spraying (D).
considered to be the cause of the amyloid deposition. Lymphoepithelial lesions were absent, and a fluorescence in situ hybridization (FISH) analysis for t(11;18)(q21;q21) translocation revealed no fusion genes of API2-MALT1, although extra copies of MALT1 were identified in 39.0% of the lymphoma cells (Fig. 3A). In addition, a FISH analysis with a chromosome 18-specific probe detected trisomy of chromosome 18 in 30.0% of the lymphoma cells (Fig. 3B), and chromosome banding of the bone marrow aspirate showed a normal karyotype of 46, XX, indicating no congenital chromosomal abnormalities.

Bone marrow aspiration and a biopsy also showed no infiltration of lymphoma cells. Furthermore, contrast-enhanced computed tomography (CT) scanning of the neck, chest, abdomen and pelvis demonstrated no lymph node enlargement or organ involvement other than the stomach, while positron emission tomography (PET) disclosed no tracer uptake and a colonoscopic examination revealed no involvement in the colorectum. Taking all of these findings together, we diagnosed the patient as having primary gastric MALT lymphoma with trisomy 18 exhibiting prominent plasma cell differentiation. The Wotherspoon score was 5, and the Groupe d’Étude des Lymphomes de l’Adulte (GELA) histological score was classified as ‘no change’ (NC). The clinical stage was considered to be stage I, based on the Lugano staging system for the classification of gastrointestinal tract lymphomas (10, 11).

Radiation (30 Gy in 20 fractions) was administered as curative therapy, and the regimen was completed without any adverse events. Esophagogastroduodenoscopy performed four months after the completion of treatment revealed the disappearance of the lymphomatous lesions in the stomach (Fig. 4). A histological evaluation of the biopsied specimens of the gastric mucosa also confirmed complete remission. The gastric MALT lymphoma remained in complete remission 10 months after radiation. However, esophagogastroduodenoscopy performed 16 months after the therapy revealed the emergence of a new slightly depressed, whitish lesion in the posterior wall of the gastric body (Fig. 5A, B). Although the initial lesion remained as a scar-like whitish lesion (Fig. 5C), biopsy specimens of both the new and initial lesions showed the recurrence of MALT lymphoma.

**Figure 2.** Histopathological images. Biopsy samples of the gastric lesion showed the infiltration of plasma cell-like neoplastic cells (A, B: Hematoxylin and Eosin staining) in addition to the deposition of an amorphous eosinophilic substance (A). On immunostaining, the neoplastic cells were negative for CD3 (C) and CD20 (D) but positive for CD138 (E). A FISH analysis revealed that these cells expressed only immunoglobulin light chain lambda (F), without a light chain kappa expression (G), indicating the monomorphic proliferation of cells with plasma cell-characteristics. Amyloid deposition was confirmed on direct fast scarlet staining (H) and observed as apple-green birefringence under polarized light (I). Original magnification, A, C-G: ×4, B: ×40, H, I: ×10
Figure 3. FISH images of the neoplastic cells. In the FISH analysis for t(11;18)(q21;q21) translocation, the API2 gene is visualized as a green signal, MALT1 as a red signal and fusion genes of API2-MALT1 as yellow signals. The results showed no fusion genes, although extra copies of MALT1 were noted in 39.0% of the lymphoma cells (A). A chromosome 18-specific probe detected three signals of chromosome 18 in 30.0% of the lymphoma cells, leading to the diagnosis of trisomy 18 (B).

Figure 4. Endoscopy images after radiation. Radiation therapy (30 Gy in 20 fractions) resulted in complete remission of the lymphomatous lesions in the stomach. Esophagogastroduodenoscopy performed four months after the completion of treatment showed only a scar in the gastric body (A, B). Complete remission was also confirmed histologically.

(Fig. 5D-F). CT and PET scanning, bone marrow aspiration and biopsy and a colonoscopic examination were subsequently performed for restaging, showing no involvement other than the stomach. Bendamustine was administered; however, the lymphoma lesions remained unchanged for 16 months after recurrence.

Discussion

The current patient presented with primary gastric MALT lymphoma accompanying trisomy 18. As eradication treatment for H. pylori resulted in only partial remission, radiation was administered. Generally, H. pylori eradication results in complete regression in cases of gastric MALT lymphoma without chromosomal aberrations (1, 2). In contrast, t(11;18)/API2-MALT1, the most frequently observed structural rearrangement in patients with MALT lymphoma, is a representative trait indicative of resistance to H. pylori eradication. The relationship between aneuploidy and the response to H. pylori eradication treatment has not been fully clarified to date.

Fukuhara et al. noted that three of their 29 patients with gastric MALT lymphoma had trisomy 3, none of whom responded to H. pylori eradication (12). In addition, Taji et al. reported that, among 13 patients with gastric MALT lymphoma, three had trisomy 3 and two had trisomy 18 (13). In that report, H. pylori eradication resulted in partial remission (n=1), no response (n=1) and progressive disease (n=1) in the patients with trisomy 3, while both patients with trisomy 18 achieved a complete response. These findings suggest that gastric MALT lymphoma with trisomy 3 is resistant to eradication therapy, whereas that associated with trisomy 18 is sensitive. However, H. pylori eradication was ineffective in the present patient, as described above. Further investiga-
The reported prevalence of trisomy 18 in patients with MALT lymphoma varies among studies, accounting for 2.3 to 27.6% of gastric cases and 12.9 to 23.4% of extragastric MALT lymphoma. In our previous report, prospective assessments of 22 patients with gastric MALT lymphoma demonstrated that treatment with 30 Gy of radiotherapy resulted in complete remission in all patients, without serious toxicities (17). The overall and relapse-free survival rates at five years after the completion of radiotherapy were 91% and 84%, respectively. Although recurrence was detected outside the field of irradiation in three cases, no patients exhibited local recurrence of lymphoma. In this context, the development of local recurrence 16 months after radiation therapy observed in the current case is considered to be rare.

Nakamura et al. reported that the presence of extra copies of MALT1, often suggestive of partial or complete trisomy 18, is significantly associated with a shorter event-free survival according to a multivariate analysis (5). Previous studies have also suggested that the accumulation of genomic alterations results in the high-grade transformation of MALT lymphoma and that numerical gains, such as that involving trisomy 3 and trisomy 18, are partly involved in the pathogenesis of histologic transformation (6, 18). Moreover, Raderer et al. revealed trisomy 18 to be a predictive factor for multi-organ involvement in cases of MALT lymphoma in extragastric organs (16). Therefore, MALT lymphoma patients presenting with trisomy 18 must be carefully followed up in order to detect early progression and relapse as well as histologic transformation and multi-organ dissemination.

The reported prevalence of trisomy 18 in patients with MALT lymphoma varies among studies, accounting for 2.3 to 27.6% of gastric cases and 12.9 to 23.4% of extragastric cases (Table) (16, 19-21). Nakamura et al. reported that in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among 195 cases (Table) (16, 19-21). Nakamura et al. reported that, in Japanese patients, 18 cases of trisomy 18 were found among

Table. Reported Incidence of Chromosomal Aberrations in Patients with MALT Lymphoma

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Sites</th>
<th>Total no. of cases</th>
<th>t(11;18) no. (%)</th>
<th>t(14;18) no. (%)</th>
<th>t(1;14) no. (%)</th>
<th>trisomy 3 no. (%)</th>
<th>trisomy 7 no. (%)</th>
<th>trisomy 12 no. (%)</th>
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<td>1995</td>
<td>19</td>
<td>stomach</td>
<td>29</td>
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<td>NA</td>
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<tr>
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<td>NA</td>
<td>4 (5.6)</td>
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<tr>
<td></td>
<td></td>
<td>extra-stomach</td>
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<td>4 (2.2)</td>
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<td>NA</td>
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<td>stomach</td>
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<tr>
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<tr>
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<td>23 (37.1)</td>
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Figure 5. Images of the relapsed lesions. Esophagogastroduodenoscopy performed 16 months after radiation therapy revealed the emergence of a new slightly depressed, whitish lesion in the posterior wall of the gastric body (A, B). The initial lesion remained as a scar-like whitish lesion (C). Recurrence of MALT lymphoma cells was histologically diagnosed in both the new lesion (D-F) and initial lesion.
71 gastric MALT lymphomas (25.3%) (5). These discrepancies in prevalence are likely based on differences in susceptibility to chromosomal aberrations among ethnic groups and the geographic variability of infectious etiologic factors, e.g., Chlamydia psittaci infection in cases of ocular adnexal MALT lymphoma, Borrelia burgdorferi in cases of cutaneous MALT lymphoma and H. pylori in cases of gastric MALT lymphoma (21). It is noteworthy that the translocations t(11;18)(q21;q21)/API2-MALT1, t(1;14)(p22;q32)/IGH-BCL10 and t(14;18)(q21;q21)/IGH-MALT1 and aneuendy are mutually exclusive, suggesting the presence of diverse pathogeneses in the development of MALT lymphoma (7, 21).

To the best of our knowledge, this is the first case report to describe the details of the clinical course of a patient with gastric MALT lymphoma with trisomy 18, as previous articles were primarily retrospective analyses of archival pathologic specimens derived from multiple patients with the aim of clarifying the etiology of chromosomal aberrations (16, 19-21). We believe that detecting abnormalities in the structure or number of chromosomes in cases of gastric MALT lymphoma refractory to H. pylori eradication is desirable, preferably before administering any therapies, as the majority of chromosomal aberrations are indicative of resistance to treatment. In the present case, the detection of extra copies of MALT1 on a FISH analysis of the API2-MALT1 fusion gene was diagnostic for trisomy 18.

In summary, we treated a patient with gastric MALT lymphoma associated with trisomy 18 in whom local recurrence was documented 16 months after the administration of radiation therapy. This case indicates that careful follow-up is required in patients with MALT lymphoma exhibiting such aneuploidies in order to detect early relapse.

The authors state that they have no Conflict of Interest (COI).

References