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【 CASE REPORT 】

Gastric Mucosa-associated Lymphoid Tissue Lymphoma That Relapsed after 11 Years Subsequent to Achieving Complete Remission

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Abstract:
A 38-year-old Japanese man was diagnosed with extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue in the stomach (gastric MALT lymphoma). Fluorescence *in situ* hybridization analysis revealed the absence of t(11;18)(q21;q21) translocation but the presence of extra copies of MALT1, indicating tetrasomy 18. *Helicobacter pylori* eradication led to complete remission (CR). However, the gastric MALT lymphoma relapsed after 11 years old. This case underscores the need for long-term observation (>10 years) of patients with gastric MALT lymphoma. Further investigation is warranted to elucidate the correlation between trisomy/tetrasomy 18 and the recurrence propensity.

Key words: gastric MALT lymphoma, *H. pylori*, relapse

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Introduction

Extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue in the stomach (gastric MALT lymphoma) is the predominant subtype among non-Hodgkin's lymphomas occurring in the gastric region. This variant is commonly associated with persistent infection caused by *Helicobacter pylori* (1). *Helicobacter pylori* colonizes the stomach lining and causes chronic gastritis and peptic ulcers as well as plays a significant role in the development of gastric MALT lymphomas.

The reported prevalence of *H. pylori* infection in patients with MALT lymphoma is 80-90% (1-3). The intricate connection between *H. pylori* infection and gastric MALT lymphoma involves immune stimulation, eliciting lymphoid tissue growth, and, in select cases, malignant transformation. Treatment of gastric MALT lymphoma usually entails combined antibiotic therapy to eliminate *H. pylori*, with subsequent monitoring to assess the response. Successful eradication often results in lymphoma regression or complete remission. Given the strong association of *H. pylori* infection with gastric MALT lymphoma, *H. pylori* eradication plays a critical role in treatment strategies, commonly leading to favorable patient outcomes.

When gastric MALT lymphoma shows remission following *H. pylori* eradication, relapse is generally rare. We herein report a case of gastric MALT lymphoma that achieved remission after *H. pylori* eradication but relapsed after a prolonged period.

Case Report

A 38-year-old Japanese man presented with no symptoms and was referred to our hospital for further investigation after an incidental finding of elevated lesions suspected in the gastric fornix on routine gastric radiography performed for screening. He had no significant medical history, including gastrointestinal or hematological disorders. A physical examination revealed no abdominal symptoms, hepa-

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Table. Laboratory Data.

White blood cells	7,250 /μL	Creatinine	0.66 mg/dL
Neutrophils	69.2 %	Uric acid	7.9 mg/dL
Lymphocytes	18.0 %	Sodium	139 mmoL/L
Red blood cells	4.37×10^6 /μL	Potassium	3.9 mmoL/L
Hemoglobin	14.8 g/dL	Chloride	106 mmoL/L
Platelets	41.3×10^4 /μL	IgG	743.0 mg/dL
Total protein	6.9 g/dL	IgA	206.7 mg/dL
Albumin	4.1 g/dL	IgM	63.4 mg/dL
AST	36 U/L	C3	151.1 mg/dL
ALT	36 U/L	C4	37.6 mg/dL
LDH	207 U/L	RF	<1.5 U/mL
ALP	346 U/L	ANA	Negative
γGTP	120 U/L	ACPA	<0.6 U/mL
Total bilirubin	0.45 mg/dL	CRP	2.35 mg/dL
BUN	9.8 mg/dL	s-IL2R	230 U/mL

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, IgG, A, and M: immunoglobulin G, A, and M, C3, 4: complement 3, 4, RF: rheumatoid factor, ANA: anti-nuclear antibody, ACPA: anti-cyclic citrullinated peptide antibody, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor

tosplenomegaly, or lymphadenopathy. Blood tests revealed elevated levels of gamma-glutamyl transpeptidase (120 U/L), uric acid (7.9 mg/dL), C-reactive protein (2.35 mg/dL). Other parameters, including lactate dehydrogenase and soluble interleukin-2 receptor levels, were within the normal ranges (Table).

Esophagogastroduodenoscopy revealed 2 contiguous elevated lesions resembling subepithelial lesions, measuring 15-20 mm in the gastric fornix (Fig. 1A). Partial redness and depression were observed along with partly dilated capillaries on the surface. Endoscopic ultrasonography revealed that the primary lesion was located in the mucosal layer, demonstrating local thickening and a hypoechoic homogeneous echo pattern (Fig. 1B). Furthermore, mild mucosal atrophy was observed in the gastric angle and antrum. A histopathological examination of the gastric lesion biopsy specimen confirmed proliferation of lymphoid cells, forming aggregates primarily in the deep layers of the mucosa. Immunostaining revealed infiltration of small- to medium-sized lymphoid cells into the gastric mucosa (Fig. 2A, B). The neoplastic cells were positive for CD20 (Fig. 2C) and negative for CD3 (Fig. 2D), CD5 (Fig. 2E), and CD10 (Fig. 2F). The Ki-67 proliferation index was low (Fig. 2G). Although a lymphoepithelial lesion was absent, a diagnosis of MALT lymphoma was made based on an immunohistochemical analysis. Fluorescence *in situ* hybridization (FISH) revealed no t(11;18)(q21;q21)/BIRC3-MALT1 translocation; however, extra copies of MALT1 were identified, indicating tetrasomy 18 (Fig. 3). In addition, a gastric biopsy confirmed *H. pylori* infection.

Computed tomography (CT) was inconclusive for detecting the tumor, including the gastric fornix. A cystic lesion suggestive of osteonecrosis of the right femoral head raised suspicion of arthritis. Positron emission tomography showed the uptake of tracer in the gastric fornix (Fig. 4). Additionally, the tracer uptake was observed in the right hip joint, thus indicating inflammation, which was considered to be the cause of elevated levels of C-reactive protein. Subsequently, the patient was referred to the Department of Orthopedic Surgery, where further investigations confirmed a diagnosis of idiopathic osteonecrosis of the femoral head. Once the patient abstained from alcohol for subsequent surgery for idiopathic osteonecrosis of the femoral head, the liver function normalized, suggesting alcohol-related liver dysfunction.

Based on the aforementioned findings, the patient was diagnosed with *H. pylori*-positive MALT lymphoma localized to the stomach, corresponding to stage I, according to the Lugano International Conference classification (4). As a treatment approach, eradication therapy for *H. pylori* was administered using amoxicillin, clarithromycin, and lansoprazole. However, the primary eradication was unsuccessful. As the gastric lesions became less discernible macroscopically during endoscopic examinations (Fig. 1C), a period of observation was chosen instead of immediate secondary eradication therapy. However, histologically, the lymphoma cells were still observed at 40 years old. At the patient's request, secondary eradication therapy using amoxicillin, metronidazole, and rabeprazole sodium was administered. The results of the urea breath test following secondary eradication were negative, indicating successful eradication. Five months after successful eradication (41 years old), endoscopy (Fig. 1D) and a biopsy confirmed histological remission of gastric MALT lymphoma. Subsequently, annual esophagogastroduodenoscopy and periodic CT were performed on a yearly or biennial basis.

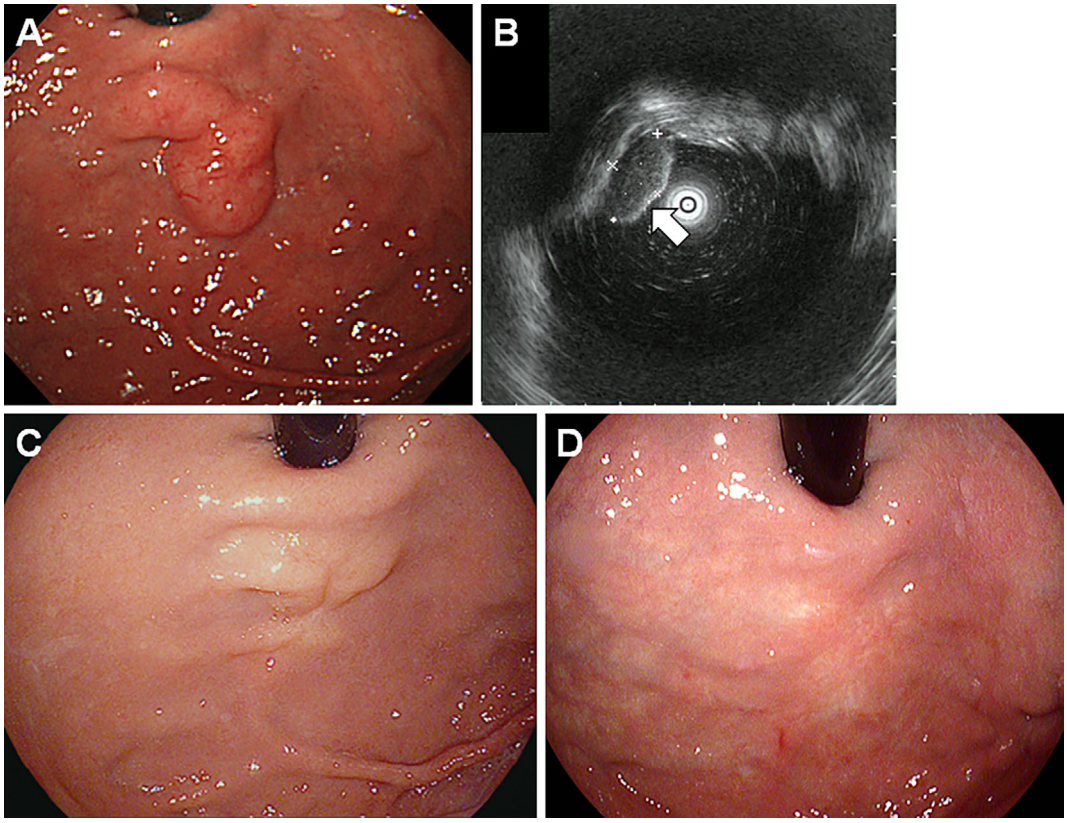

Figure 1. **Endoscopic images. Esophagogastroduodenoscopy revealed two contiguous elevated lesions in the gastric fornix (A). Endoscopic ultrasonography showed a hypoechoic, homogeneous echo pattern in the mucosal layer (B). Although the gastric lesions became less discernible spontaneously (C), lymphoma cells were still observed histologically. Five months after successful eradication, endoscopy (D) and a biopsy confirmed histological remission of gastric mucosa-associated lymphoid tissue lymphoma.**

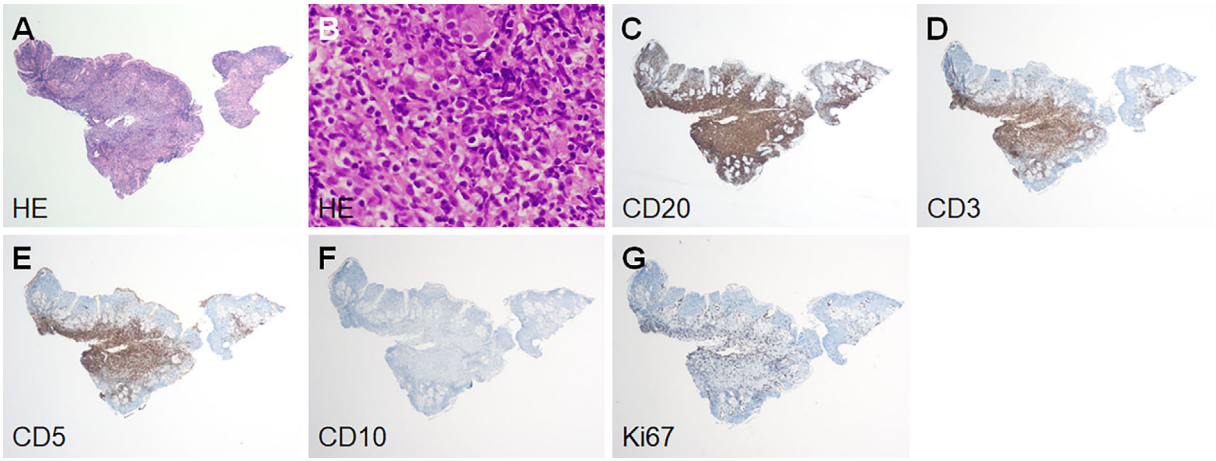

Figure 2. **Pathological images. Biopsy specimens from the gastric lesion confirmed the proliferation of small- to medium-sized lymphoid cells (A, 4×; B, 40×). The neoplastic cells were positive for CD20 (C) but negative for CD3 (D), CD5 (E), and CD10 (F). The Ki-67 proliferation index was low (G).**

At 52 years old, 11 years after confirming histological remission, follow-up endoscopy revealed the emergence of a pale-colored, elevated lesion measuring 15 mm in the gastric fornix, slightly distal to the previous scar (Fig. 5A, B). Endoscopic ultrasonography confirmed that the lesion was located in a deeper layer of the mucosa, demonstrating a hypoechoic echo layer (Fig. 5C). A biopsy confirmed relapse of MALT lymphoma. FISH revealed no t(11;18)(q21;q21)/BIRC3-MALT1 translocation, but trisomy and tetrasomy 18 were identified (Fig. 3B). Endoscopic biopsies obtained

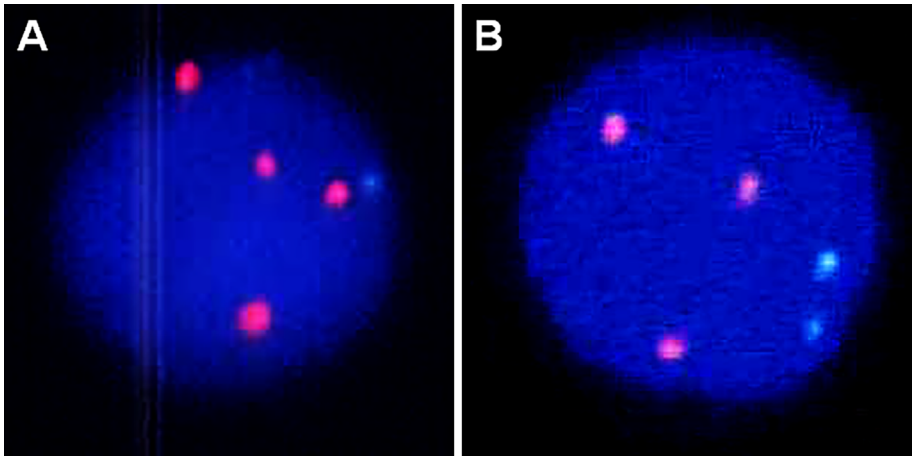

Figure 3. **Results of fluorescence *in situ* hybridization (FISH). At 38 years old, FISH revealed no t (11; 18)(q21; q21)/BIRC3-MALT1 translocation but identified extra copies of MALT1 (four red signals), indicating tetrasomy 18 (A). At recurrence (age of 52 years), FISH revealed trisomy 18 (B, three red signals) in addition to tetrasomy 18.**

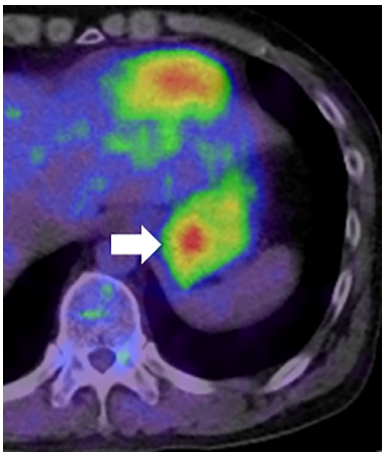

Figure 4. **Positron emission tomography images. The uptake of tracer was detected in the gastric fornix on positron emission tomography (arrow).**

from the gastric antrum and the greater and lesser curvatures of the gastric body revealed the histological absence of *H. pylori*. In addition, the urea breath test yielded negative results. Furthermore, the findings of atrophic gastritis on endoscopy remained consistent with the endoscopic findings prior to primary *H. pylori* eradication. In addition, colonoscopy, capsule endoscopy, contrast-enhanced CT, positron emission tomography, and a bone marrow biopsy were performed, all of which showed no abnormalities. Based on these findings, relapse of MALT lymphoma localized to the stomach was diagnosed, and radiation therapy was administered. Following radiation therapy, the lesion regressed macroscopically (Fig. 5D), and remission was confirmed histologically.

Discussion

Regarding the treatment of gastric MALT lymphoma, 78% of gastric MALT lymphoma cases achieved complete remission with *H. pylori* eradication therapy (5). Consequently, existing guidelines strongly recommend the implementation of *H. pylori* eradication therapy for all patients diagnosed with gastric MALT lymphoma (6). The present patient had *H. pylori*-positive gastric MALT lymphoma confined to the stomach. Despite failure of primary *H. pylori* eradication, the lymphoma exhibited partial regression. This could be attributed to the effects of clarithromycin (7). Even though the size of the tumor was grossly reduced, complete remission could not be achieved, leading to the decision to perform secondary *H. pylori* eradication. Secondary eradication therapy was successful, and remission was achieved. However, the disease recurred after an extremely long period of time (>11 years). Prolonged recurrence is an infrequent event.

The reported relapse rates after remission vary widely, ranging from 3% to 31% (8). Concerning the time interval until relapse, a review of 4 studies conducted by Zullo et al. revealed that, among cases of MALT lymphoma that achieved remission following eradication therapy, 7.2% experienced relapse during a median follow-up period of 28 (range, 10-75) months (5). The relapse period ranged from 5.6 to 8.8 months, with an annual relapse rate of 2.2%. *H. pylori* reinfection is a plausible risk factor for relapse. Gisbert et al. reported that 6% of cases experienced relapse of MALT lymphoma following complete remission, and among these cases, 25% were associated with *H. pylori* reinfection (8). In addition, the potential involvement of non-*Helicobacter pylori* Helicobacter (NHPH), which refers to *Helicobacter* species other than *H. pylori* that infect the human stomach, has been proposed in relation to MALT lymphoma development (9). NHPH infections may also serve as a risk factor for relapse. However, in the present patient, both *H. pylori* reinfection and NHPH infection were ruled out based on a pathological analysis of biopsied specimens obtained from the stomach at the time of recurrence. Instead, trisomy 18 and tetrasomy 18 were identified in lym-

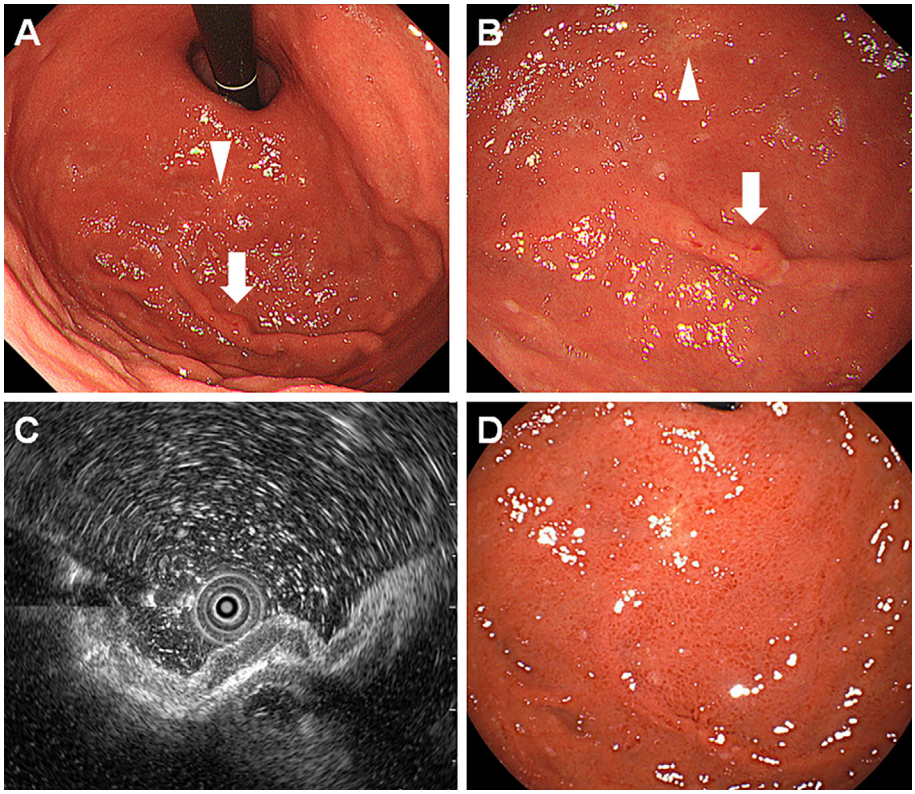

Figure 5. Endoscopy images at and after remission of mucosa-associated lymphoid tissue lymphoma. At 52 years old, 11 years after confirming histological remission, an elevated lesion became apparent at the gastric fornix (A and B, arrow), located on the greater curvature side of the scar from the initial gastric MALT lymphoma (A and B, arrowhead). Endoscopic ultrasonography confirmed that the lesion was located in the deeper layer of the mucosa (C). The lesion disappeared three months after radiation therapy (D).

phoma cells during both the initial presentation and relapse, suggesting a potential association with relapse after an exceedingly prolonged period of over 11 years.

Among chromosomal abnormalities in MALT lymphoma, t(11;18)(q21;q21) translocation is the most frequently reported, and cases with t(11;18)(q21;q21) translocation are considered resistant to eradication (10). Chromosomal numerical abnormalities, such as trisomy 18, tetrasomy 18, and trisomy 3, have also been reported in lymphoma cells. Taji et al. reported that, among 13 patients with gastric MALT lymphoma, 3 had trisomy 3, and 2 had trisomy 18. After *H. pylori* eradication, partial remission (n=1), no response (n=1), and progression (n=1) were observed in patients with trisomy 3, whereas complete remission was achieved in patients with trisomy 18 (11). Ishikawa et al. reported a case of gastric MALT lymphoma with trisomy 18 that showed only partial improvement after *H. pylori* eradication therapy and experienced gastric lymphoma relapse 16 months after radiotherapy (12). In our earlier work, we investigated 146 patients with gastric MALT lymphoma; 18.5% had t(11;18)(q21;q21) translocation, and 21.2% had trisomy or tetrasomy 18. Furthermore, although the difference was not statistically significant, the event-free survival in patients with trisomy or tetrasomy 18 tended to be inferior to that in patients without chromosomal aberrations (13). In another study, although not statistically significant, patients with stage II Lugano International Conference classification had a higher incidence of trisomy 18 than those with stage I, suggesting a possible association between trisomy 18 and the disease stage (14). Chromosomal numerical gain is also considered to be associated with transformation to diffuse large B-cell lymphoma (DLBCL) in MALT lymphoma (15).

Raderer et al. analyzed MALT lymphoma cases, including those originating outside the stomach, and found chromosomal abnormalities, including translocations and numerical chromosome aberrations, in 50% of recurrent cases (16). Although chromosomal alterations were consistent between the time of the diagnosis and relapse, no significant correlation was observed between chromosomal alterations and relapse. However, patients with t(11;18)(q21;q21) translocation had a significantly longer median duration until relapse than those without this translocation, suggesting a potential association between genetic abnormalities and relapse (17). According to Nakamura et al., a study involving 18 patients with trisomy 18 demonstrated a reduced event-free survival rate when analyzed using a Cox multivariate analysis (17). These findings suggest a potential correlation between trisomy 18 and relapse in MALT lymphomas. As reports on the relationship between chromosomal abnormalities and the treatment response or prognosis are based on a limited number

of patients, these associations have not been fully elucidated at present. Further investigations involving a larger number of cases and prospective studies are needed to evaluate the association between trisomy/tetrasomy 18 and the prognosis.

In cases of relapse of gastric MALT lymphoma, secondary treatment entails the implementation of *H. pylori* eradication therapy when *H. pylori* is detected. However, if *H. pylori* is absent, radiation therapy is the predominant modality employed, although reports have also documented the use of chemotherapy and surgical resection. Furthermore, instances have been reported wherein observation alone was employed, leading to histological disappearance (18, 19). Given the indolent nature and favorable prognosis of MALT lymphoma, a "watch and wait" strategy is also considered when the lesion remains localized. In the present patient, considering the confined relapse limited to the stomach, the decision was made to administer radiation therapy, resulting in complete remission.

In conclusion, we encountered a patient with gastric MALT lymphoma in whom relapse occurred after an extremely long period of over 11 years. This case reinforces that long-term observation (>10 years) may be required in patients with gastric MALT lymphoma. Further investigations are warranted to explore the association between trisomy/tetrasomy 18 and susceptibility to recurrence.

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

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