

A case of *API2-MALT1*-positive gastric MALT lymphoma with concomitant diffuse large B-cell lymphoma

Akashi Fujita¹, Masahiro Tajika², Tsutomu Tanaka², Makoto Ishihara², Yutaka Hirayama², Nobumasa Mizuno¹, Kazuo Hara¹, Susumu Hijioka¹, Hiroshi Imaoka¹, Tsukasa Yoshida¹, Nozomi Okuno¹, Nobuhiro Hieda¹, Takashi Hirayama¹, Hitoshi Shibuya¹, Hisashi Kondo¹, Hirotaka Suzuki¹, Kazuhiro Toriyama¹, Yasushi Yatabe³, Kenji Yamao¹ and Yasumasa Niwa²

¹Departments of Gastroenterology, Aichi Cancer Center Hospital

²Departments of Endoscopy, Aichi Cancer Center Hospital

³Departments of Pathology and Molecular Diagnosis, Aichi Cancer Center Hospital

ABSTRACT

API2-MALT1 translocation-positive gastric marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) lymphoma is thought to transform to diffuse large B-cell lymphoma (DLBCL) rarely. A 69-year-old man presented with epigastralgia. Esophagogastroduodenoscopy showed multiple ulcerations in the stomach. Endoscopic biopsies revealed MALT lymphoma, with *Helicobacter pylori* infection. The patient underwent eradication therapy with no improvement, and was thereafter followed without additional therapy at his request. Twelve years after initial diagnosis, follow-up computed tomography (CT) showed multiple nodules in bilateral lungs, and a needle biopsy revealed MALT lymphoma, the same as in the stomach and *API2-MALT1* translocation was found. Because he again refused additional therapy, follow-up was continued. 15 years after initial diagnosis, CT showed lymphadenopathy at the splenic hilum. At first we suspected disease progression of gastric MALT lymphoma, however a needle biopsy revealed DLBCL without *API2-MALT1*. Thus, the tumor at the splenic hilum was finally diagnosed as a de novo DLBCL as a second malignancy. Although treatment with rituximab given his age and his wishes was attempted, he died of DLBCL 15 years after the initial diagnosis. We experienced an *API2-MALT1*-positive gastric MALT lymphoma with concomitant DLBCL, not transformed to DLBCL over a 15-year clinical course.

Key Words: MALT lymphoma, Second malignancy, *API2-MALT1*, DLBCL

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

Helicobacter pylori (*H. pylori*) plays a causative role in the development of gastric MALT lymphoma, and the eradication of *H. pylori* leads to complete remission (CR) of lymphoma in 50–90% of cases.¹⁻³ In a systematic review of data from 32 publications, CR was achieved in 78% of 1408 patients with localized gastric MALT lymphoma treated by *H. pylori* eradication.¹

Received: January 5, 2017; accepted: February 21, 2017

Corresponding author: Masahiro Tajika, MD., Ph.D.

Department of Endoscopy, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

Tel: +81-52-762-6111, fax: +81-52-764-2942, E-mail: mtajika@aichi-cc.jp

Based on these findings, the EGILs (European Gastro-Intestinal Lymphoma Study) European Consensus Report of 2011 recommends eradication therapy of *H. pylori* as the first-line treatment in all patients with gastric MALT lymphoma, irrespective of stage and *H. pylori* status.⁴⁾ The most common chromosomal translocation in MALT lymphoma is t(11;18)(q21;q21), which generates a functional *API2-MALT1* fusion protein that activates nuclear factor (NF)- κ B, and leads to development of this tumor.⁵⁾ The presence of the *API2-MALT1* fusion transcript has been linked to resistance of the gastric MALT lymphoma to *H. pylori* eradication, as well as absence of transformation to diffuse large B-cell lymphoma (DLBCL) phenotype.^{6,7)}

Recent studies have shown that patients with gastric MALT lymphoma have a higher risk of second malignancies, such as gastric cancer and hematological malignancies.^{8,9)} Differentiating DLBCL that evolved from MALT lymphoma from de novo DLBCL as a second malignancy is difficult. A unique case of *API2-MALT1* translocation-positive gastric MALT lymphoma with concomitant nodal DLBCL that had not transformed from the *API2-MALT1*-positive gastric MALT lymphoma over a clinical course of 15 years, which was demonstrated by immunochemistry and molecular analysis, is reported.

CASE REPORT

In 1994, a 69-year-old man presented to a previous hospital with epigastralgia. Esophago-gastroduodenoscopy (EGD) showed multiple ulcerations in his stomach. He was then referred to our hospital for further investigation and treatment. Our endoscopic findings showed multiple ulcerations with surrounding cobblestone-like mucosal appearance involving the greater curvature of the lower gastric body (Figure 1a). Biopsy specimens revealed atypical lymphocytes and typical lympho-epithelial lesions compatible with gastric MALT lymphoma (Figure 1b). Staging investigation, including CT scanning of the whole body, colonoscopy, and peripheral blood and bone marrow examinations showed clinical stage I based on the Lugano staging system. *H. pylori* was detected by culture and serology. Eradication was attempted with omeprazole 20 mg twice/day, amoxicillin 1000 mg twice/day, and clarithromycin 400 mg twice/day for 7 days as first-line therapy, but it failed. Following failure of the first regimen, *H. pylori* was eradicated with omeprazole 20 mg twice/day and ofloxacin 300 mg twice/day for 7 days as second-line therapy. The treatment success was demonstrated by culture and urea breath test respectively. Six months after successful eradication of *H. pylori*, endoscopic findings reduced ulcerations, but lymphoma cells were still seen on biopsy specimen examination. Because eradication of *H. pylori* as the first-line treatment for MALT lymphoma had failed, surgical resection or radiation therapy was recommended. However, the patient refused additional treatment, and follow-up was continued. During the follow-up period, endoscopic findings showed repeated ulcerations of the lower body of the stomach, and his stomach gradually narrowed.

In 2001, during follow-up, *API2-MALT1* translocation was found from biopsy specimen by reverse-transcription polymerase chain reaction (RT-PCR). At that time, additional therapy was again recommended, but he again refused. In 2006, follow-up CT showed multiple nodules in bilateral lungs (Figure 2a). Examination of the needle biopsy specimen taken from a nodule revealed MALT lymphoma, the same as in the stomach and *API2-MALT1* translocation was found by FISH using Dual Color Break Apart probe. (Figure 2b, 2c). Thus, MALT lymphoma that involved the lung 12 years after initial detection in the stomach was diagnosed. Because he again refused additional therapy, follow-up was continued. In 2009, the patient felt left-sided abdominal pain, and a CT scan showed lymphadenopathy at the splenic hilum (Figure 3a), although the gastric lesions and lung metastases had not progressed. Gastric MALT lymphoma was again

suspected, and a needle biopsy of the lymph node was performed for confirmation. Histological findings revealed DLBCL without *API2-MALT1* translocation (Figure 3b, 3c). Although treatment with rituximab given his age and his wishes was attempted, he died of DLBCL 15 years after the initial diagnosis.

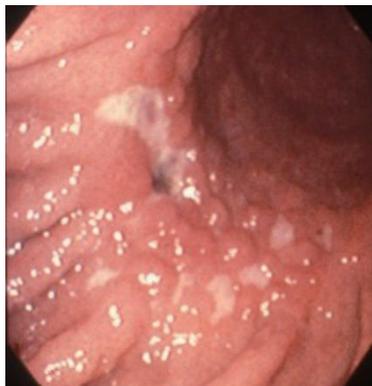


Fig. 1a

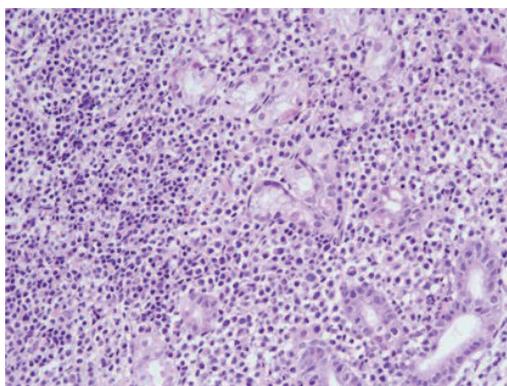


Fig. 1b

Figure 1a: Endoscopic findings show the cobblestone-like appearance with multiple ulcerations in the greater curvature of the lower gastric body.

Figure 1b: Biopsy specimens show typical lymphoepithelial lesions (H.E. stain; x400)

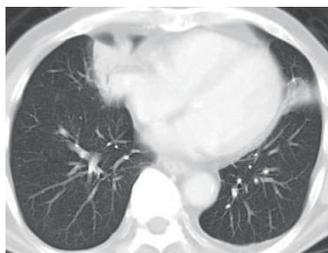


Fig. 2a

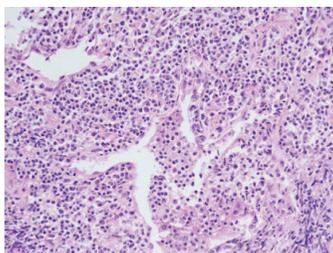


Fig. 2b

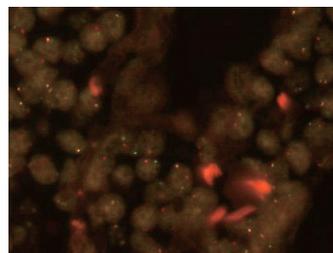


Fig. 2c

Figure 2a: Computed tomography (CT) scan shows that multiple nodules have appeared in bilateral lungs.

Figure 2b: Needle biopsy specimens show atypical lymphocytes and typical lymphoepithelial lesions with *API2-MALT1*, the same as in the stomach. (H&E stain; b: x400)

Immunochemical findings show CD3(-), CD5(-), CD10(-), CD20(+/-), BCL2(+), CCND1(-), and CXCR3(+).

Figure 2c: *API2-MALT1* translocation was found by Dual Color Break Apart probe (separated red and green signals)

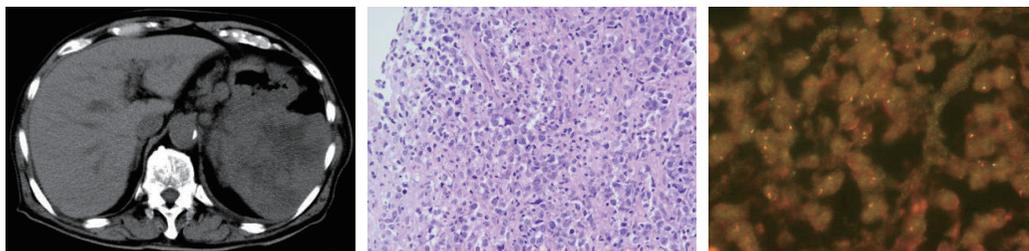


Fig. 3a

Fig. 3b

Fig. 3c

Figure 3a: CT scan shows lymph node swelling at the splenic hilum.

Figure 3b: Needle biopsy specimens of the splenic lymph node show large atypical lymphocytes without *API2-MALT1* (H&E stain; b: $\times 400$).

Immunochemical findings show CD20(+), CD10(-), BCL2(-), CD5(-), BCL6(-), MUC4/IRF4(+), CD3(-), and EBER-ISH(-).

Figure 3c: *API2-MALT1* translocation was not found by Dual Color Break Apart probe.

DISCUSSION

In the present case, gastric MALT was first diagnosed and treated in 1994; this was a very early case not only in our hospital but also in Japan. In those days, second-line therapy after failure of eradication of *H. pylori* was controversial, and choice between chemotherapy, radiation therapy, surgery, or watchful waiting was not clear. In this case the patient refused additional therapy because he was asymptomatic. In 1999, the *MALT1* gene was identified on chromosome 18q21 by analysis of $t(11;18)(q21;q21)$, a characteristic chromosomal translocation associated with MALT lymphoma.^{10,11} We analyzed and confirmed this translocation in our case in 2001. However, the treatment strategy and prognosis of *API2-MALT1* positive gastric MALT lymphoma had not yet been clarified, and although we recommended additional therapy, he refused. Thus, we could observe the natural history of *API2-MALT1*-positive gastric MALT lymphoma over 15 years.

In gastric MALT lymphoma, $t(11;18)(q21;q21)$ is the most frequent translocation, which is detected in 15–24% of cases. The translocation fuses the N-terminal region of *API2* to the C-terminal region of *MALT1* and generates a functional chimeric fusion, which gains the ability to activate the NF- κ B pathway.^{5,12} The *API2-MALT1* transcript has shown rare additional gene alternations¹³ and rarely transform to DLBCL, indicating that fusion-positive tumors are generally more stable than negative ones.¹⁴ However recently, several reports against these concepts have been described. Toracchio *et al.*¹⁵ had examined the frequency of chromosomal translocation $t(11;18)(q21;q21)$ in MALT lymphoma and DLBCL of the stomach, and detected the translocation in approximately equivalent proportion of gastric MALT lymphomas and DLBCLs (26% and 19%, respectively). Furthermore, they also detected the *API2-MALT1* fusion transcript in one of five DLBCLs with MALT component. In addition to their report, two of three,¹⁶ six of 46,¹⁷ and one¹⁸ gastric MALT lymphomas with $t(11;18)(q21;q21)$ translocation, transforming to DLBCL have been described. As a possible explanation for different results and conclusions from previous studies, they mentioned the different populations, classification bias, and differences in methodology.¹⁵ Hereafter, the role of $t(11;18)(q21;q21)$ translocation in MALT lymphomas and DLBCLs will be need more consideration.

In this patient, DLBCL appeared at the splenic hilum. At first, transformation from MALT lymphoma was suspected, although it is rare in *API2-MALT1*-positive gastric MALT lymphoma. However, the histological and immunological findings of the lymphocyte cells in splenic hilum

were different from those in the stomach and lung, and the DLBCL at the splenic hilum did not show *API2-MALT1* translocation. Thus, the tumor at the splenic hilum was finally diagnosed as a de novo DLBCL, as a second malignancy. Recently, several studies have shown that patients with gastric MALT lymphoma have a higher risk of second malignancies such as gastric cancer and hematological diseases compared to the general population.^{8,9)} Therefore, patients with gastric MALT lymphoma require careful follow-up not only for disease progression, but also for second malignancy.

The treatment strategy of *API2-MALT1*-positive gastric MALT lymphoma still remains to be elucidated, and these cases were considered un-responsive to *H. pylori* eradication. However, remission rates of 22.2% and 10% after *H. pylori* eradication have been reported by Zullo *et al.*¹⁹⁾ and Nakamura *et al.*,¹⁾ respectively. Thus, *H. pylori* eradication may be attempted as first-line treatment in these cases. If these patients show progressive disease or clinically evident relapse, then conventional anti-neoplastic approaches such as radiotherapy, chemotherapy, and immunotherapy with rituximab can be recommended.^{4,20)} On the other hands, the clinical course and prognosis of *API2-MALT1*-positive patients has not been clarified. Nakamura *et al.* reported their experience with 14 *API2-MALT1*-positive MALT lymphoma patients, of whom 7 were non responders to *H. pylori* eradication. Six of these 7 cases had not showed disease progression during follow-up period from 5 to 101 months, without any further treatment. They also reported that in all of 3 untreated *API2-MALT1*-positive cases showed no disease progression.²¹⁾ Furthermore, Ono *et al.* supported watch-and-wait strategy for a case with *API2-MALT1*-positive gastric MALT lymphoma.²²⁾

A consensus report of the EGILS (European Gastro-Intestinal Lymphoma Study) emphasized the importance of evaluating the lymphoma response after effective *H. pylori* eradication in patients with gastric MALT lymphoma.⁴⁾ And the report recommended that patients with persistent histological lymphoma (rRD; responding residual disease and no change) can be managed up to 24 months by a 'watch and wait' strategy unless progression or recurrent endoscopic lesion can be demonstrated, and the detection of rRD might encourage continuation of this strategy beyond 24 months before considering alternative oncological treatment. However, they also mentioned that the 'watch and wait' duration might be shorter in patients with more advanced disease stage, involvement of peri-gastric lymph nodes, suspected high-grade transformation lymphoma, *H. pylori*-negative status and *t(11;18)(q21;q21)* positivity as these cases are more frequently unresponsive to anti-*Helicobacter* therapy alone. The decision to continue a 'watch and wait' follow-up or to start oncological treatment should be an individually tailored multidisciplinary decision, based on clinical, histological and molecular features, the patient's preferences and data from ongoing trials. In the present patient, although *API2-MALT1*-positive MALT lymphoma had not transformed to DLBCL, the lymphoma had progressed to the lung over a 15-year clinical course. This may suggest that the prognosis of *API2-MALT1*-positive gastric MALT lymphoma is relatively good, however, needless to say that if the patient shows progressive disease or clinically evident relapse during watchful waiting period, then second line anti-neoplastic treatments should be done.

In summary, we experienced an *API2-MALT1*-positive gastric MALT lymphoma with concomitant DLBCL, not transformed to DLBCL over a 15-year clinical course. In general, the second line therapy for the patient who does not respond to *H. pylori* eradication therapy is oncological treatment regardless of the state of *API2-MALT1* transcription. However, if the patient refused to additional therapy or were poor condition, a 'watch and wait' strategy with careful observation for progressive disease and second malignancy may be a treatment option in patient with *API2-MALT1*-positive gastric MALT lymphoma.

CONFLICT OF INTERESTS

The authors declared no conflict of interests for this article.

REFERENCE

- 1) Nakamura S, Sugiyama T, Matsumoto T, Iijima K, Ono S, Tajika M, *et al.* Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. *Gut*, 2012; 61: 507–513.
- 2) Chen LT, Lin JT, Tai JJ, Chen GH, Yeh HZ, Yang SS, *et al.* Long-term results of anti-*Helicobacter pylori* therapy in early-stage gastric high-grade transformed MALT lymphoma. *J Natl Cancer Inst*, 2005; 97: 1345–1353.
- 3) Wundisch T, Thiede C, Morgner A, Dempfle A, Gunther A, Liu H, *et al.* Long-term follow-up of gastric MALT lymphoma after *Helicobacter pylori* eradication. *J Clin Oncol*, 2005; 23: 8018–8024.
- 4) Ruskone-Fourmestraux A, Fischbach W, Aleman BM, Boot H, Du MQ, Megraud F, *et al.* EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. *Gut*, 2011; 60: 747–758.
- 5) Lucas PC, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, *et al.* Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J Biol Chem*, 2001; 276: 19012–19019.
- 6) Nakamura T, Nakamura S, Yonezumi M, Suzuki T, Matsuura A, Yatabe Y, *et al.* *Helicobacter pylori* and the t(11;18)(q21;q21) translocation in gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type. *Jpn J Cancer Res*, 2000; 91: 301–309.
- 7) Sugiyama T, Asaka M, Nakamura T, Nakamura S, Yonezumi S, Seto M. API2-MALT1 chimeric transcript is a predictive marker for the responsiveness of *H. pylori* eradication treatment in low-grade gastric MALT lymphoma. *Gastroenterology*, 2001; 120: 1884–1885.
- 8) Wundisch T, Dieckhoff P, Greene B, Thiede C, Wilhelm C, Stolte M, *et al.* Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by *Helicobacter pylori* eradication and followed for 10 years. *Gastroenterology*, 2012; 143: 936–942; quiz e913–934.
- 9) Tajika M, Matsuo K, Ito H, Chihara D, Bhatia V, Kondo S, *et al.* Risk of second malignancies in patients with gastric marginal zone lymphomas of mucosa associate lymphoid tissue (MALT). *J Gastroenterol*, 2014; 49: 843–852.
- 10) Akagi T, Motegi M, Tamura A, Suzuki R, Hosokawa Y, Suzuki H, *et al.* A novel gene, MALT1 at 18q21, is involved in t(11;18)(q21;q21) found in low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *Oncogene*, 1999; 18: 5785–5794.
- 11) Dierlamm J, Baens M, Wlodarska I, Stefanova-Ouzounova M, Hernandez JM, Hossfeld DK, *et al.* The apoptosis inhibitor gene API2 and a novel 18q gene, MLT, are recurrently rearranged in the t(11;18)(q21;q21) associated with mucosa-associated lymphoid tissue lymphomas. *Blood*, 1999; 93: 3601–3609.
- 12) Nakamura S, Ye H, Bacon CM, Goatly A, Liu H, Banham AH, *et al.* Clinical impact of genetic aberrations in gastric MALT lymphoma: a comprehensive analysis using interphase fluorescence in situ hybridisation. *Gut*, 2007; 56: 1358–1363.
- 13) Ott G, Katzenberger T, Greiner A, Kalla J, Rosenwald A, Heinrich U, *et al.* The t(11;18)(q21;q21) chromosome translocation is a frequent and specific aberration in low-grade but not high-grade malignant non-Hodgkin's lymphomas of the mucosa-associated lymphoid tissue (MALT-) type. *Cancer Res*, 1997; 57: 3944–3948.
- 14) Starostik P, Patzner J, Greiner A, Schwarz S, Kalla J, Ott G, *et al.* Gastric marginal zone B-cell lymphomas of MALT type develop along 2 distinct pathogenetic pathways. *Blood*, 2002;99:3–9.
- 15) Toracchio S, Ota H, de Jong D, Wotherspoon A, Rugge M, Graham DY, *et al.* Translocation t(11;18)(q21;q21) in gastric B-cell lymphomas. *Cancer Sci*, 2009;100:881–887.
- 16) Chuang SS, Lee C, Hamoudi RA, Liu H, Lee PS, Ye H, *et al.* High frequency of t(11;18) in gastric mucosa-associated lymphoid tissue lymphomas in Taiwan, including one patient with high-grade transformation. *Br J Haematol*, 2003; 120: 97–100.
- 17) Bernasconi B, Karamitopoulou-Diamantis E, Tornillo L, Lugli A, Di Vizio D, Dimhofer S, *et al.* Chromosomal instability in gastric mucosa-associated lymphoid tissue lymphomas: a fluorescent in situ hybridization study using a tissue microarray approach. *Hum Pathol*, 2008; 39: 536–542.
- 18) Yamane H, Ohsawa M, Shiote Y, Umemura S, Suwaki T, Shirakawa A, *et al.* Cavitory pulmonary involvement of diffuse large B-cell lymphoma transformed from extra nodal marginal zone B-cell lymphoma MALT

Gastric MALT lymphoma with *API2-MALT1*

- type. *Clin J Gastroenterol*, 2011; 4: 401–406.
- 19) Zullo A, Hassan C, Cristofari F, Andriani A, De Francesco V, Ierardi E, *et al.* Effects of *Helicobacter pylori* eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*, 2010; 8: 105–110.
 - 20) Zucca E, Dreyling M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2010; 21 Suppl 5: v175–176.
 - 21) Nakamura T, Seto M, Tajika M, Kawai H, Yokoi T, Yatabe Y, *et al.* Clinical features and prognosis of gastric MALT lymphoma with special reference to responsiveness to *H. pylori* eradication and *API2-MALT1* status. *Am J Gastroenterol*, 2008; 103: 62–70.
 - 22) Ono S, Kato M, Takagi K, Kodaira J, Kubota K, Matsuno Y, *et al.* Long-term treatment of localized gastric marginal zone B-cell mucosa associated lymphoid tissue lymphoma including incidence of metachronous gastric cancer. *J Gastroenterol Hepatol*, 2010; 25: 804–809.