

[CASE REPORT]

Collision Tumors of Gastric Adenocarcinoma and Mucosa-associated Lymphoid Tissue Lymphoma

Kenichi Kobayashi¹, Kazuhiro Furukawa², Eri Ishikawa², Ayako Mitsuma³, Kohei Funasaka⁴, Naomi Kakushima², Satoshi Furune^{2,3}, Nobuhito Ito², Hirotaka Wada², Takashi Hirose², Koichi Muroi², Tomohiko Suzuki², Takahiro Suzuki², Emiko Hida², Keiko Hirai², Hiroyuki Shibata², Toshinari Koya¹, Masanao Nakamura², Hiroki Kawashima⁵, Ryoji Miyahara⁶ and Mitsuhiro Fujishiro²

Abstract:

A 65-year-old woman with a history of treatment for splenic marginal zone B-cell lymphoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma underwent esophagogastroduodenoscopy. A reddish elevated lesion was found in the fundus of the stomach. On image-enhanced endoscopy, several findings, such as glandular structures of varying sizes suggesting well-differentiated adenocarcinoma, pruned blood vessels, and dilated blood vessels in deeper mucosa suggesting MALT lymphoma, were observed. The final pathological diagnosis after surgical resection was collision tumors of well-differentiated adenocarcinoma and MALT lymphoma. The features of both tumors could be observed simultaneously with image-enhanced endoscopy.

Key words: collision tumor, double tumor, image enhanced endoscopy, gastric adenocarcinoma, mucosa-associated lymphoid tissue lymphoma

(Intern Med 60: 2419-2424, 2021)

(DOI: 10.2169/internalmedicine.6124-20)

Introduction

Gastric adenocarcinoma is the most common type of gastric cancer. Although the number of cases is declining due to a reduction in the *Helicobacter pylori* (*H. pylori*) infection rate in Japan, it is still the fifth-most common cancer in the world and has the third-highest mortality; thus, it remains a major cancer. The prognosis of gastric adenocarcinoma varies depending on the stage of the disease, and reports have shown that while stage IV has a 5-year survival rate of only 16.4%, the survival of stage IA can be as high as 91.5% (1-3). Detection of lesions using endoscopy is very important, and reports have shown the usefulness of image-enhanced endoscopy (IEE), including linked-color imaging

(LCI) (4-9).

Gastric lymphoma accounts for only 0.8%-2.0% of all gastric tumors, making it a relatively rare disease. The most common histological type of gastrointestinal lymphoma is mucosa-associated lymphoid tissue (MALT) lymphoma, accounting for approximately 52% of cases (10, 11). Gastric MALT lymphoma shows a good prognosis. Both gastric adenocarcinoma and MALT lymphoma are attributed to *H. pylori* infection.

The simultaneous presence of two histologically distinct tumor types is referred to as synchronous double tumors. Double tumors of the stomach have been reported, but they tend to be rare (12-19). When each tumor exists independently, they can often be diagnosed with conventional endoscopy or IEE (4-9, 20-22). However, few reports have de-

¹Department of Gastroenterology, Tokai Central Hospital, Japan, ²Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Japan, ³Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Japan, ⁴Department of Gastroenterology, Fujita Health University School of Medicine, Japan, ⁵Department of Endoscopy, Nagoya University Hospital, Japan and ⁶Department of Gastroenterology and Gastroenterological Oncology, Fujita Health University School of Medicine, Japan

Received for publication August 16, 2020; Accepted for publication January 12, 2021

Correspondence to Dr. Kazuhiro Furukawa, kazufuru@med.nagoya-u.ac.jp

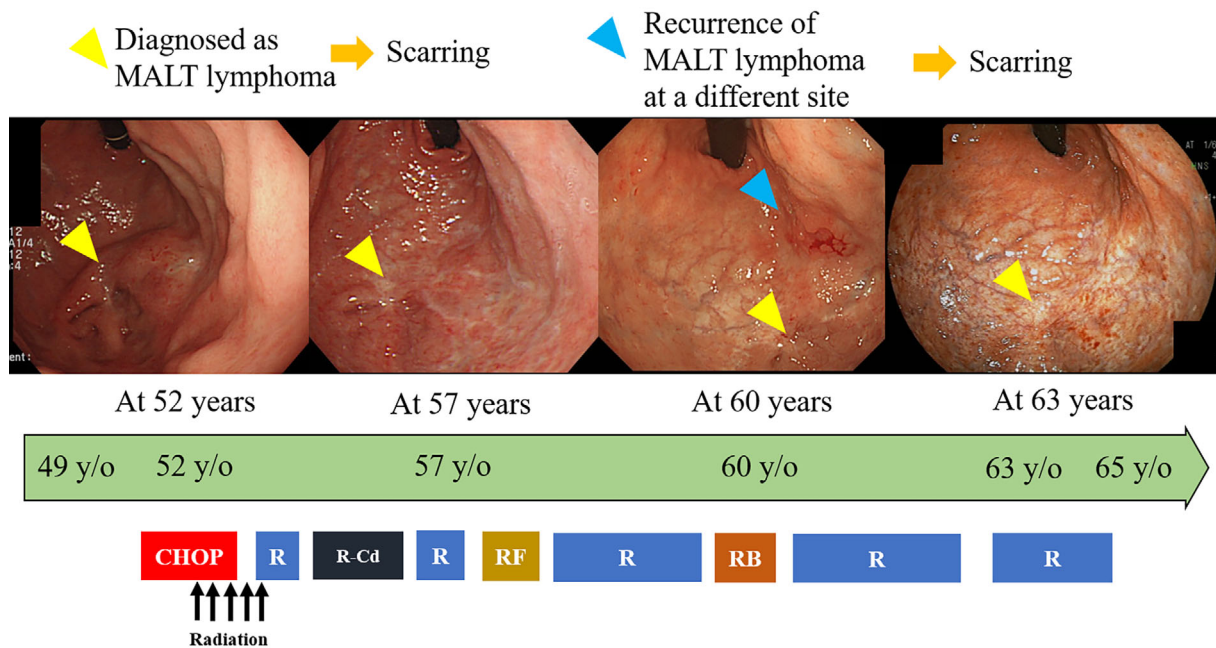


Figure 1. Changes in the endoscopic image of gastric mucosa-associated lymphoid tissue (MALT) and course of treatment during long observation periods. The yellow arrowheads indicate the sites corresponding to each endoscopy. Biopsy tests indicated repeated relapse and remission of MALT lymphoma. The blue arrowheads indicate areas of MALT lymphoma relapse from other biopsy sites. CHOP: cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone, R: rituximab, R-Cd: rituximab, cladribine, RF: rituximab, fludarabine, RB: rituximab, bendamustine

scribed the endoscopic findings when both types of tumors are mixed.

We herein report a case of collision tumors of gastric adenocarcinoma and MALT lymphoma in which both findings were detected with IEE.

Case Report

The patient was a 65-year-old woman. She was referred to our hospital at 49 years old for a detailed examination of splenomegaly and anemia. As a result of the detailed examination, she was diagnosed with splenic marginal zone B-cell lymphoma. Since lymphoma lesions were found in multiple organs, including the stomach, rectum, and bone marrow, the stage of this lymphoma was IVB (Lugano classification). Splenectomy was performed to improve the anemia, and t (11;18)(q21;q21) translocation was detected by a chromosome analysis.

The patient underwent chemotherapy and radiotherapy for endotracheal lesions and submandibular lymphadenopathy, but pulmonary lesions appeared, and the lymphadenopathy relapsed every few years, being treated with chemotherapy.

At 60 years old, esophagogastroduodenoscopy (EGD) revealed an ulcerative lesion in the fundus of the stomach that was diagnosed as MALT lymphoma via a biopsy. The gastric MALT lymphoma and splenic marginal zone B-cell lymphoma were considered pathologically separate tumors. A microscopic examination of the biopsy specimen and a

serological test showed negative results for *H. pylori*. Because bone marrow involvement, parotid gland, and cervical lymphadenopathy associated with splenic marginal zone B-cell lymphoma were also detected, the patient was treated with bendamustine and rituximab.

At 63 years old, after these treatments, a biopsy of the scar on the fundus of the stomach revealed residual MALT lymphoma cells. However, no additional therapy was administered because the other lesions showed no residual lymphoma (Fig. 1). She declined to undergo EGD for about two years because she had no symptoms.

At 65 years old, the patient experienced stomach discomfort. EGD revealed a reddish elevated lesion with an irregular surface that corresponded to the area of scarring on the fundus (Fig. 2A, B). The surrounding mucosa was discolored, emphasizing the redness of the lesion compared with the surrounding mucosa. Indigo carmine dye spraying revealed more distinct borders than conventional endoscopy (Fig. 2C). The lesion appeared bright red with LCI and was well contrasted with the surrounding gastric mucosa, creating a distinct boundary (Fig. 2D). Magnifying narrow-band imaging (NBI) endoscopy revealed several findings, including glandular structures of varying sizes, pruned blood vessels, and dilated blood vessels in the deeper mucosa (Fig. 3).

A biopsy revealed the proliferation of cells with enlarged atypical nuclei and increased chromatin forming ductal structures, and she was diagnosed with well-differentiated

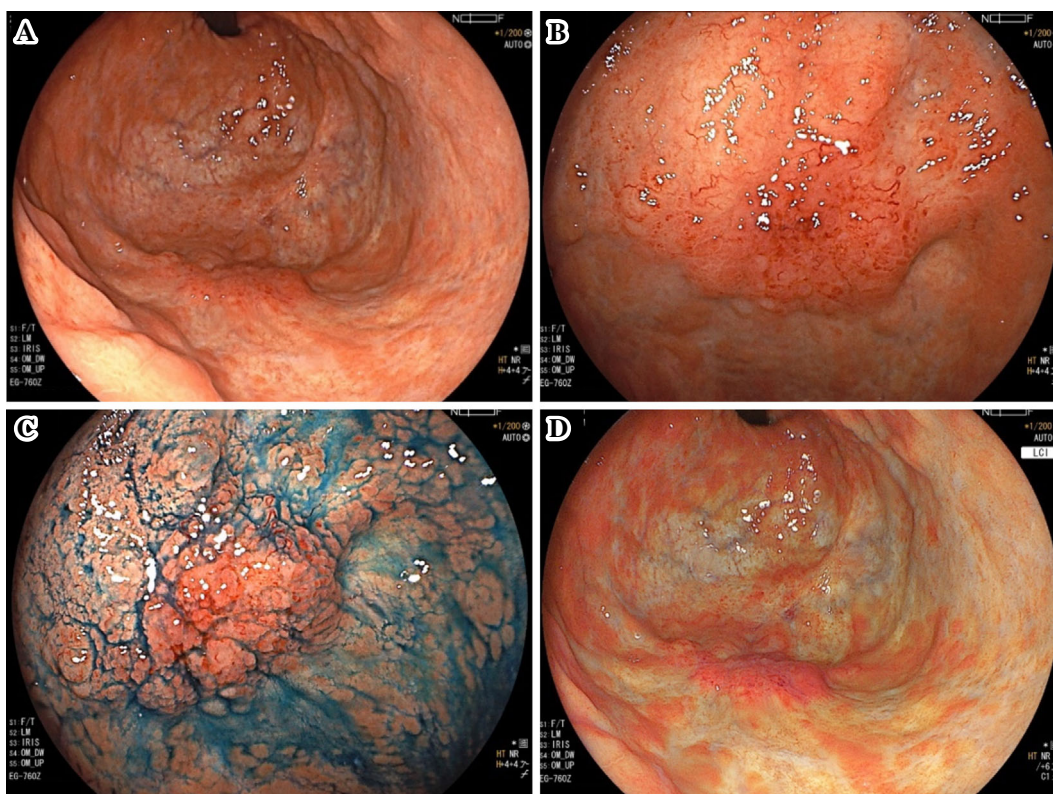


Figure 2. A: Endoscopic image far from the lesion with white light. Neither atrophy nor intestinal metaplasia was observed. B: Endoscopic image close to the lesion. C: The area became clearer with indigo carmine dye spraying. D: The redness of the tumor, when observed with linked-color imaging, became clearer due to the greater contrast with the surrounding non-cancerous area.

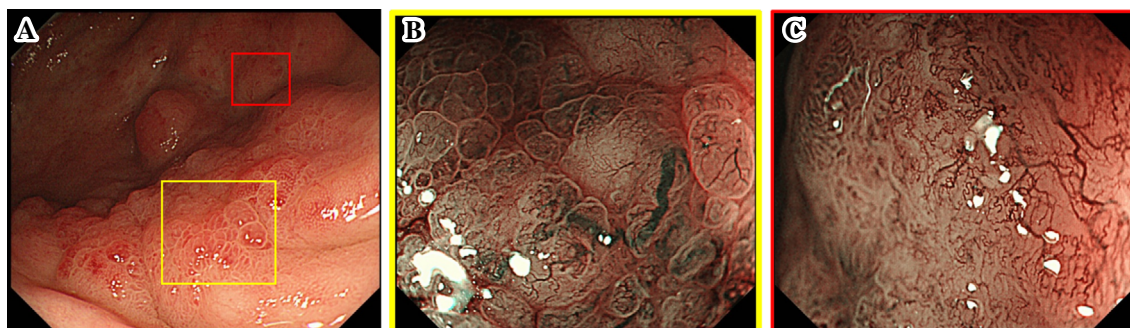


Figure 3. A: Endoscopic image close to the lesion with white light. B: The different-sized glandular structures were confirmed with magnifying narrow-band imaging (NBI). The dilated blood vessels were also visible. C: A tree-like appearance was observed with magnifying NBI at a different site.

adenocarcinoma. In addition to adenocarcinoma, diffuse lymphoid infiltration of small to medium cells was observed in the lamina propria. Immunophenotypically, the tumor cells were positive for CD20 but negative for CD3, CD5, CD10, and Cyclin D1, resulting in a diagnosis of MALT lymphoma. No apparent distant metastases were found on computed tomography (CT). Given these findings, she was diagnosed with double tumors of gastric adenocarcinoma and MALT lymphoma.

Although total gastrectomy was an option, the preoperative diagnosis was early gastric cancer, and the patient's quality of life was prioritized, so she underwent laparo-

scopic fundectomy and D-1+ dissection. The final pathological diagnosis was well-differentiated adenocarcinoma, pT3, pN2, cM0, pStage IIIb, and MALT lymphoma, Stage II. Although oral S-1 was administered as postoperative adjuvant chemotherapy, 15 months later, enlargement of the left subphrenic, paraaortic, and hepatoduodenal ligament lymph nodes and liver metastasis were found on CT, and she was diagnosed with recurrence of gastric adenocarcinoma. There was no relapse of MALT lymphoma. Her general condition gradually deteriorated, and she died approximately two years after the operation.

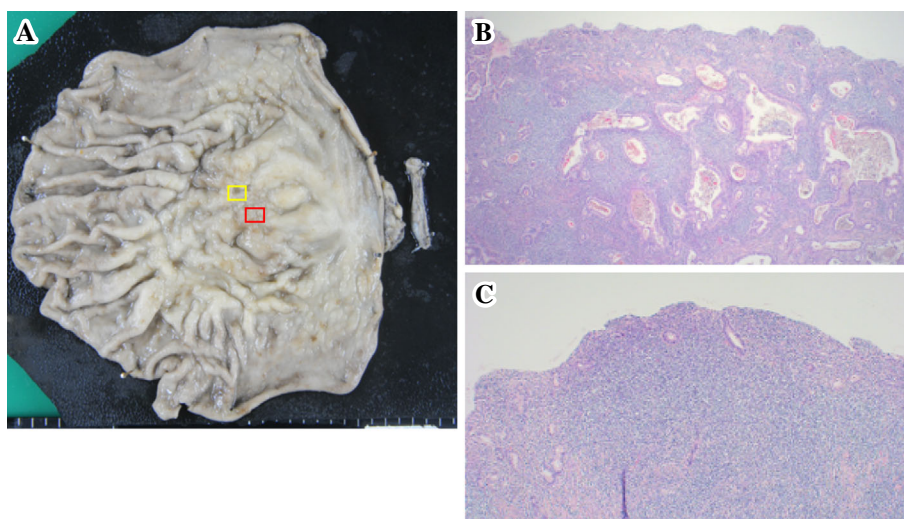


Figure 4. A: Macroscopic findings of resected specimen. The yellow frame corresponds to the endoscopic image in B, and the red frame corresponds to C. B: Histological findings corresponding to Figure 3 B; 50× magnification with Hematoxylin and Eosin (H&E) staining. C: Histological findings corresponding to Figure 3 C; 50× magnification with H&E staining.

Histopathological findings from the surgical specimen (Fig. 4, 5)

The histopathological features of gastric cancer were well-differentiated adenocarcinoma invading the subserosa. Aside from gastric cancer, histology also revealed invasion by the MALT lymphoma, which was primarily limited to the submucosa (Fig. 5B, C). There was no normal tissue between the two lesions. Small to medium-sized cells with pale cytoplasm and a slightly irregular nucleus, also called centrocyte-like cells, had diffusely infiltrated, and plasmacytic differentiation was observed in some areas. The lymphoid cells were positive for CD20 but negative for CD3, CD5, CD10, and Cyclin D1. In addition, kappa light chain restriction by immunohistochemistry and IgH rearrangement by polymerase chain reaction were detected. It was difficult to determine the t(11;18)(q21;q21) translocation of MALT1 through a chromosomal analysis with fluorescence in situ hybridization (FISH). Well-differentiated adenocarcinoma and metastasis of MALT lymphoma were found in the regional lymph nodes.

Discussion

In this case, gastric MALT lymphoma was observed during treatment of stage IV splenic marginal zone B-cell lymphoma, which had infiltrated multiple organs, and after five years, double tumors of the gastric adenocarcinoma and gastric MALT lymphoma developed. The association between gastric MALT lymphoma and splenic marginal zone B-cell lymphoma was difficult to determine because further investigations, including additional immunostaining, could not be performed due to insufficient specimens; pathologically, however, the gastric lesion was diagnosed as MALT lymphoma.

Double tumors refer to the presence of histologically distinct malignant tumors, and Meyer has classified them into three subtypes (12). Two neoplastic components that develop separately and collide or intersect with each other are defined as collision tumors, two neoplastic components that simultaneously develop from a common stem cell and grow mixed together are defined as contiguous tumors, and two neoplastic components that develop simultaneously but exist independently of each other are defined as independent tumors. The most common of these types is independent tumors, followed by collision tumors and contiguous tumors. Isosaka et al. reported that independent tumors account for approximately 62% of double tumors, followed by collision tumors, which account for approximately 24% (19). In the present case, gastric adenocarcinoma developed after follow-up of a patient with MALT lymphoma, and the histopathological evaluation of the resected specimen revealed that gastric adenocarcinoma was located at the same place where MALT lymphoma was located. As a result, the patient was diagnosed with collision tumors based on the findings (Fig. 5).

Magnifying IEE is useful for differentiating malignant gastric tumors. Yao et al. reported the VS classification in 2002 for magnifying NBI observation of gastric adenocarcinoma, which markedly improved the ability to diagnose gastric cancer endoscopically (4). Diagnosing the surface structure, vascular structure, and demarcation line makes it possible to differentiate between cancerous and non-cancerous areas as well as between differentiated and undifferentiated adenocarcinoma (5, 6). However, abnormal blood vessels with a tree-like appearance (TLA) is a characteristic finding of gastric MALT lymphoma, and this finding is useful for differentiating MALT lymphoma from gastric adenocarcinoma (20-22). Gastric adenocarcinoma is characterized by findings such as microvasculature with notable irregular di-

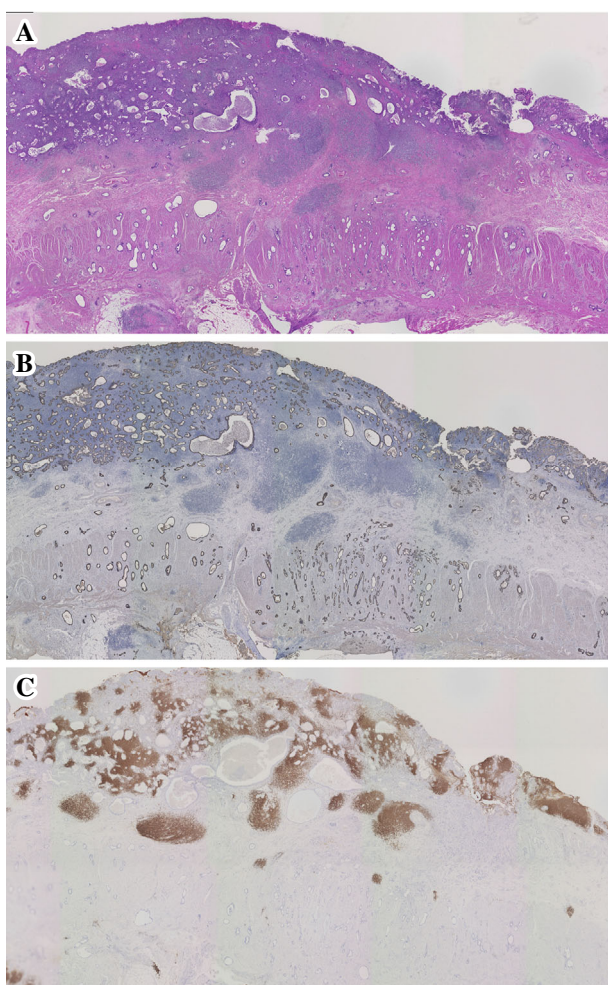


Figure 5. A: Histology of the collision tumors of well-differentiated tubular adenocarcinoma and MALT lymphoma. 20× magnification with Hematoxylin and Eosin staining. B: Histology of the collision tumors of well-differentiated tubular adenocarcinoma and MALT lymphoma. 20× magnification with AE1/AE3 staining. C: Histology of the collision tumors of well-differentiated tubular adenocarcinoma and MALT lymphoma. 20× magnification with CD20 staining.

ameters and an uneven shape; however, there are few abnormal blood vessels with irregular diameters in MALT lymphoma, and the blood vessels tend to diverge like branches from the trunk of a tree. The glandular structures in the present patient varied in size, and the vascular structure was irregular, and although there were endoscopic findings characteristic of adenocarcinoma, the demarcation line was unclear, suggesting the possibility of the coexistence of another disease in addition to typical adenocarcinoma. Furthermore, TLA and dilated vasculature were also found, suggesting the coexistence of MALT lymphoma.

Histopathologically, adenocarcinoma dominated the superficial layer of the mucosa, but the MALT lymphoma had also invaded the superficial and deep layers (Fig. 5). Well-differentiated adenocarcinoma and MALT lymphoma coexisted on the tumor surface, with both a fine network pattern characteristic of differentiated adenocarcinoma and TLA-like

blood vessels characteristic of MALT lymphoma, which were considered to reflect the histological findings (23-26).

LCI, an image-enhancement technique, has been reported to improve the visibility of gastric adenocarcinoma (7-9). LCI uses short-wavelength light to emphasize the microvasculature and surface structures on the mucosal surface, which highlights slight differences in reddish areas. Reports have shown that the red color tone in LCI correlates with vessel density (9). In the present patient, LCI not only emphasized the redness of the lesion area but also differentiated the red color tone from the redness due to gastritis in the surrounding mucosa, thereby improving visibility. Non-magnifying observation with LCI was considered useful for lesion detection in this patient.

Our patient originally developed gastric adenocarcinoma during the course of MALT lymphoma. The development of gastric adenocarcinoma during follow-up of MALT lymphoma has been previously reported, and some of these cases are assumed to be due to chronic irritation of the gastric mucosa by MALT lymphoma (27-29). However, a report of 12 patients with double primary gastric lymphoma and adenocarcinoma showed that all patients were positive for *H. pylori*, and the authors concluded that *H. pylori* infection was associated with the development of these double malignancies (15). The present patient had no general *H. pylori* infection as the cause of gastric adenocarcinoma. Therefore, it is suspected that this case was preceded by MALT lymphoma, which induced local immunodeficiency and gland duct cell production while damaging the mucosal microvasculature, and thereby triggering adenocarcinoma; however, this is mere speculation (19, 30-32). Another report indicated that the survival rate of synchronous gastric adenocarcinoma and gastric MALT lymphoma was the same as that of gastric adenocarcinoma alone, and the progression of gastric adenocarcinoma has been shown to often determine the prognosis (15). A previous study also showed that gastric adenocarcinoma tended to be early cancer restricted to the mucosa and submucosa, with gastric lymphomas invading more deeply than adenocarcinoma (15). Despite the long duration of MALT lymphoma, our patient died approximately two years after the diagnosis of gastric adenocarcinoma. If patients with disseminated MALT lymphoma have involvement of the stomach, periodic EGD is recommended over the long term, bearing in mind the possibility of gastric adenocarcinoma.

In summary, we encountered a case of collision tumors of gastric adenocarcinoma and gastric MALT lymphoma. The features of both tumors were able to be observed simultaneously with image-enhanced endoscopy.

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

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality world-

- wide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**: 394-424, 2018.
2. Nashimoto A, Akazawa K, Isobe Y, et al. Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* **16**: 1-27, 2013.
 3. Peleteiro B, Bastos A, Ferro A, et al. Prevalence of helicobacter pylori infection worldwide: a systematic review of studies with national coverage. *Dig Dis Sci* **59**: 1698-1709, 2014.
 4. Yao K, Oishi T, Matsui T, Yao T, Iwashita A. Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer. *Gastrointest Endosc* **56**: 279-284, 2002.
 5. Kaise M, Kato M, Urashima M, et al. Magnifying endoscopy combined with narrow-band imaging for differential diagnosis of superficial depressed gastric lesions. *Endoscopy* **41**: 310-315, 2009.
 6. Uedo N, Fujishiro M, Goda K, et al. Role of narrow band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia-Pacific region. *Dig Endosc* **23** (Suppl): 58-71, 2011.
 7. Yoshifuku Y, Sanomura Y, Oka S, et al. Evaluation of the visibility of early gastric cancer using linked color imaging and blue laser imaging. *BMC Gastroenterol* **17**: 150, 2017.
 8. Kanzaki H, Takenaka R, Kawahara Y, et al. Linked color imaging (LCI), a novel image-enhanced endoscopy technology, emphasizes the color of early gastric cancer. *Endosc Int* **5**: E1005-E1013, 2017.
 9. Fujiyoshi T, Miyahara R, Funasaka K, et al. Utility of linked color imaging for endoscopic diagnosis of early gastric cancer. *World J Gastroenterol* **25**: 1248-1258, 2019.
 10. Nakamura S, Ponzoni M. Marginal zone B-cell lymphoma: lessons from Western and Eastern diagnostic approaches. *Pathology* **52**: 15-29, 2020.
 11. Ono S, Ono Y, Sakamoto N. Diagnosis and treatment of gastric malignant lymphoma. *Nippon Shokakibyō Gakkai Zasshi* **114**: 1948-1956, 2017 (in Japanese).
 12. Meyer R. Beitrag Zur Verständigung über die Namengebung in der Geschwulstlehre. *Zentralbl Allg Pathol* **30**: 291-296, 1919.
 13. Spagnolo DV, Heenan PJ, Frepa M. Collision carcinoma at the esophagogastric junction. *Cancer* **46**: 2702-2708, 1980.
 14. Plamker M, Fisher JT, Peters U, et al. Synchronous double primary malignant lymphoma of low grade malignancy and early cancer (collision tumor) of the stomach. *Hepatogastroenterology* **31**: 144-148, 1984.
 15. Nakamura S, Aoyagi K, Iwanaga S, et al. Synchronous and metachronous primary gastric lymphoma and adenocarcinoma: a clinicopathological study of 12 patients. *Cancer* **79**: 1077-1085, 1997.
 16. Suenaga M, Ohta K, Toguchi M, et al. Colliding gastric and intestinal phenotype well differentiated adenocarcinoma of the stomach developing in an area of MALT-type lymphoma. *Gastric Cancer* **6**: 270-276, 2003.
 17. Copie-Bergman C, Locher C, Levy M, et al. Metachronous gastric MALT lymphoma and early gastric cancer: is residual lymphoma a risk factor for the development of gastric carcinoma? *Ann Oncol* **16**: 1232-1236, 2005.
 18. Hamaloglu E, Topaloglu S, Ozdemir A, Ozenc A. Synchronous and metachronous occurrence of gastric adenocarcinoma and gastric lymphoma: a review of the literature. *World J Gastroenterol* **12**: 3564-3574, 2006.
 19. Isosaka M, Adachi T, Iida T, et al. A case of a collision tumor comprising mucosa-associated lymphoid tissue lymphoma and early gastric cancer. *Nippon Shokakibyō Gakkai Zasshi* **111**: 1391-1398, 2014 (in Japanese, Abstract in English).
 20. Ono S, Kato M, Ono Y, et al. Characteristics of magnified endoscopic images of gastric extra nodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue, including changes after treatment. *Gastrointest Endosc* **68**: 624-631, 2008.
 21. Nonaka K, Ishikawa K, Arai S, et al. A case of gastric mucosa-associated lymphoid tissue lymphoma in which magnified endoscopy with narrow band imaging was useful in the diagnosis. *World J Gastrointest Endosc* **4**: 151-156, 2012.
 22. Nonaka K, Ohata K, Matsushashi N, et al. Is narrow-band imaging useful for histological evaluation of gastric mucosa-associated lymphoid tissue lymphoma after treatment? *Dig Endosc* **26**: 358-364, 2014.
 23. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of *H pylori* in gastric MALT lymphoma. *Blood* **102**: 1012-1018, 2003.
 24. Liu H, Ye H, Ruskone-Fourmestreaux A, et al. T(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to *H. pylori* eradication. *Gastroenterology* **122**: 1286-1294, 2002.
 25. Inagaki H, Nakamura T, Li C, et al. Gastric MALT lymphoma are divided into three groups based on responsiveness to *Helicobacter pylori* eradication and detection of AP12 MALT fusion. *Am J Surg Pathol* **28**: 1560-1567, 2004.
 26. Isaka T, Nakamura T, Tajika M, et al. API2-MALT1 chimeric transcript-positive gastroduodenal MALT lymphoma with subsequent development of adenocarcinoma as a collision tumour over a clinical course of 7 years. *Histopathology* **51**: 119-122, 2007.
 27. Zucca E, Pinotti G, Roggero E, et al. High incidence of other neoplasms in patients with low-grade gastric MALT lymphoma. *Ann Oncol* **6**: 726-728, 1995.
 28. 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* **25**: 804-809, 2010.
 29. Tajika M, Matsuo K, Ito H, et al. Risk of second malignancies in patients with gastric marginal zone lymphomas of mucosa associated lymphoid tissue (MALT). *J Gastroenterol* **49**: 843-852, 2014.
 30. Tihan T, Filippa DA. Coexistence of renal cell carcinoma and malignant lymphoma. A causal relationship or coincidental occurrence? *Cancer* **77**: 2325-2331, 1996.
 31. Ikemura S, Moriyama M, Matsumoto K, et al. Lymph node collision tumor consisting of metastatic pulmonary adenocarcinoma and diffuse large B-cell lymphoma. *Intern Med* **57**: 1135-1139, 2018.
 32. Redman RA, Chesney J. Interesting collision between an indolent B-cell lymphoma and a microsatellite unstable adenocarcinoma of the colon. *J Hematol Thromb Dis* **1**: 110, 2013.

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