

[CASE REPORT]

A Rare Combination of Gastric Mucosa-associated Lymphoid Tissue Lymphoma, Autoimmune Gastritis, Thyroiditis, Hemolysis, and Systemic Lupus Erythematosus

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Abstract:

We herein report a case with the rare combination of mucosa-associated lymphoid tissue lymphoma (MALT lymphoma) of the stomach, autoimmune gastritis (AIG), autoimmune thyroiditis, autoimmune hemolytic anemia (AIHA), and systemic lupus erythematosus. A 68-year-old woman was diagnosed with gastric MALT lymphoma associated with *Helicobacter pylori* (*H. pylori*) infection and AIG. Complete remission of the MALT lymphoma was achieved by *H. pylori* eradication and radiotherapy. Three years after the diagnosis of MALT lymphoma, the patient developed AIHA and anti-nuclear and anti-Smith autoantibody-positive lupus serositis, which were successfully managed with prednisolone administration.

Key words: mucosa-associated lymphoid tissue lymphoma, autoimmune gastritis, systemic lupus erythematosus

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Introduction

Autoimmune gastritis (AIG) is a type of chronic atrophic gastritis that results from autoimmune-mediated destruction of gastric parietal cells by cytotoxic T-cells and autoantibodies. The resulting severe gastric atrophy leads to iron- or vitamin B12-deficient anemia and creates a background for the development of gastric neoplasia, such as adenocarcinoma and carcinoid (1). While AIG and *Helicobacter pylori* (*H. pylori*) infection frequently overlap, the role of *H. pylori* remains elusive. A majority of extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) of the stomach develop in association with another type of chronic atrophic gastritis with persistent infection of *H. pylori* (2).

The association of autoimmune thyroiditis with other autoimmune diseases is known as type 3 autoimmune poly-

endocrine syndrome (APS), and the association with AIG has long been known as type 3B (3).

We herein report a case of gastric MALT lymphoma associated with AIG and followed by the development of autoimmune thyroiditis, autoimmune hemolytic anemia (AIHA), and systemic lupus erythematosus (SLE).

Case Report

In April 2015, a 68-year-old woman visited the department of gastroenterology at our hospital to undergo esophagogastroduodenoscopy (EGD). In addition to gastric atrophy, a discolored lesion with reddish erosion was observed at the greater curvature of the upper gastric body (Fig. 1a). A positive rapid urease test indicated *H. pylori* infection. Hematoxylin and Eosin (HE) staining of the biopsy specimens obtained from the lesion revealed lymphoid follicles and dense infiltration of lymphoid cells, as well as

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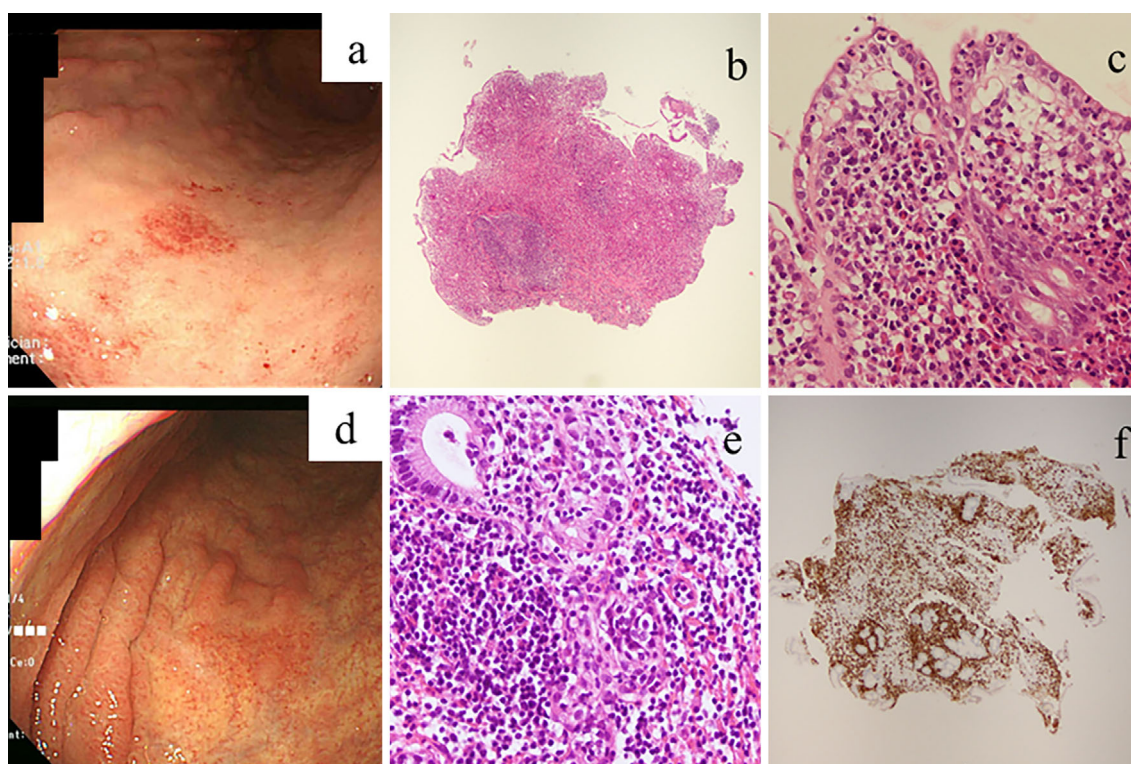


Figure 1. Endoscopic views and histopathology. a, d: Endoscopic views of the lesion at the first (a) and second EGD session (d). b, c: Hematoxylin and Eosin (H&E) staining reveals lymphoid follicles and the dense infiltration of lymphoid cells, plasma cells in the lamina propria, and neutrophils in the surface layer [original magnification $\times 40$ (b), $\times 200$ (c)]. e: H&E staining reveals the dense infiltration of lymphoid cells as well as plasma cells in the lamina propria and LELs (original magnification $\times 200$). f: Immunohistochemical staining for the B-cell surface marker CD79a (original magnification $\times 40$).

plasma cells in the lamina propria and neutrophils in the surface layer, suggesting chronic active gastritis with *H. pylori* infection (Fig. 1b and c). Although the possibility of gastric MALT lymphoma was also considered, immunohistochemical staining for Ig κ and Ig λ did not indicate clonality. Eradication therapy for *H. pylori* was performed successfully, as confirmed by a negative urea breath test.

A second EGD session, four months after the eradication of *H. pylori*, revealed the unchanged lesion (Fig. 1d). The second biopsy specimens showed lymphoepithelial lesions (LELs) in addition to the dense infiltration of lymphoid cells and plasma cells (Fig. 1e). Unlike the first biopsy, neither lymphoid follicles nor neutrophil infiltration were observed. An immunohistochemical analysis showed that the infiltrating cells were positive for the B-cell surface marker CD79a (Fig. 1f) and positive for Ig κ light chain. These findings confirmed the diagnosis of gastric MALT lymphoma and implied its resistance to *H. pylori* eradication.

The patient was referred to the department of hematology of another hospital for a further examination and treatment. Positron emission tomography/computed tomography (PET/CT), colonoscopy, and bone marrow aspiration revealed no involvement of organs other than the stomach. The patient was offered the option of undergoing either follow-up EGD in another three months or radiotherapy to treat the MALT

lesion. Choosing the latter, she was given a radiation dose of 30 Gy in 20 fractions to the stomach and perigastric nodes. Follow-up EGD and biopsies at 6 and 12 months after the radiation therapy confirmed the disappearance of the lesion.

The patient returned to our hospital for a general health checkup in December 2017, two years after the radiotherapy. The physical examination was normal, and EGD showed body-predominant gastric atrophy but no evidence of lymphoma relapse. A retrospective review of the first and second EGD images (before and after *H. pylori* eradication) revealed that each had similar gastric atrophy with patchy spared areas and multiple pseudopolyps (Fig. 2), which were suggestive of AIG. Positive tests for the autoantibodies; anti-parietal cell antibody (PCA, 1:160) and anti-intrinsic factor antibody (IFA); and an elevated serum gastrin level (1,431 pg/mL), supported the diagnosis of AIG. Mild normocytic anemia [hemoglobin (Hb): 11.4 g/dL, mean corpuscular volume (MCV): 99.4 fL] was seen, while the serum levels of iron (95 μ g/dL) and vitamin B12 (450 pg/mL) were normal. Positive tests for both anti-thyroglobulin antibody (160.1 U/mL) and anti-peroxidase antibody (25.8 U/mL) suggested the coexistence of autoimmune thyroiditis. However, the serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were normal.

The follow-up laboratory data in January 2018 showed

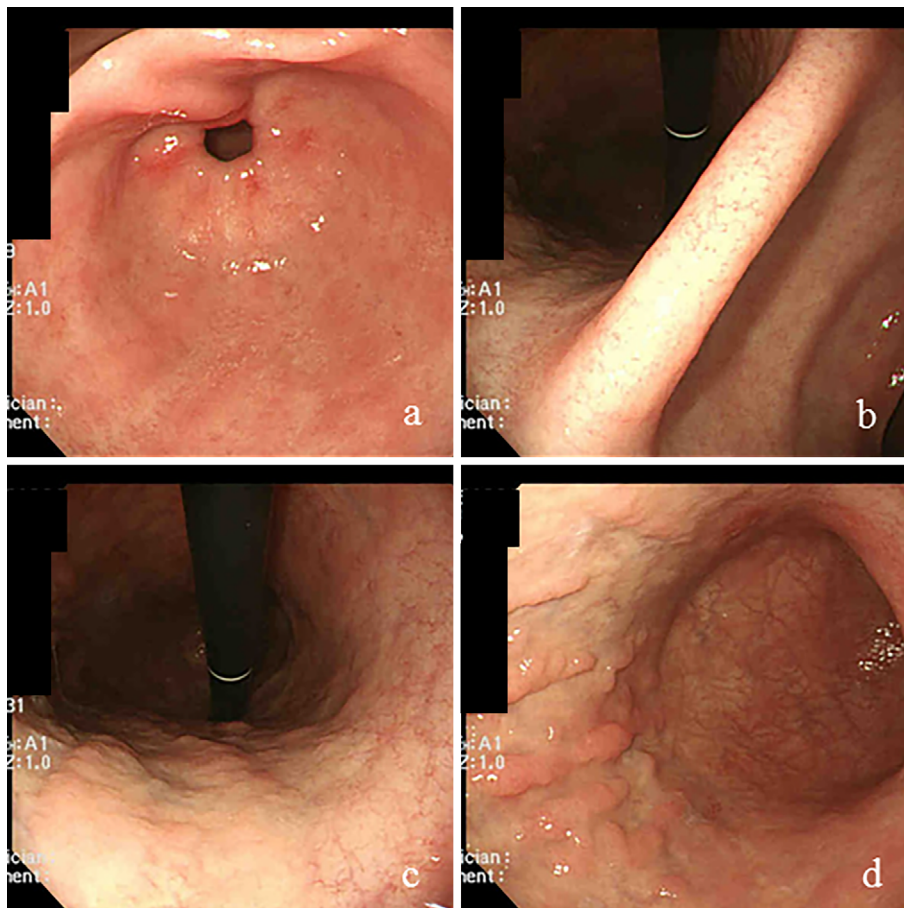


Figure 2. Body-predominant gastric atrophy at the first EGD session (before eradication of *H. pylori*). a: antrum, b: angle, c: lesser curvature of the gastric body, d: greater curvature of the gastric body

macrocytic anemia (Hb: 10.0 g/dL, MCV: 106.5 fL) and a slight increase in lactate dehydrogenase (LDH) and reticulocytes. Considering the possibility of vitamin B12-related anemia, we started the patient on daily oral mecobalamin (1,000 µg). Despite this treatment, in July 2018 she began to experience palpitation and general fatigue. Chest X-ray showed no abnormality (Fig. 3a). The laboratory data indicated the further development of macrocytic anemia (Hb: 8.4 g/dL, MCV: 117.3 fL) with an increase in total bilirubin, glutamic oxaloacetic transaminase (GOT), LDH, and reticulocytes, suggesting hemolysis. Based on a positive direct antiglobulin test and decreased haptoglobin, we confirmed the diagnosis of AIHA. The sudden elevation of thyroid hormone levels (FT3, FT4) and a drop in the TSH level were observed concurrently with this hemolysis. A test for TSH receptor antibody was negative, which implied that this hyperthyroidism was due to painless thyroiditis rather than Graves' disease. The hyperthyroidism resolved within a month without any treatment. The Hb level also returned to 9.5 g/dL in 2 months.

However, a low-grade fever and dyspnea on effort arose at the end of September 2018. The patient had a history of Raynaud's phenomenon, although neither malar rash nor arthralgia was observed. Chest X-ray (Fig. 3b), chest CT, and

echocardiography revealed pleural and pericardial effusion without left ventricular failure. The presence of AIHA and Raynaud's phenomenon suggested the effusion to be of autoimmune origin. Anti-nuclear antibody (ANA, 1:5,120, speckled pattern), anti-U1 ribonucleoprotein (RNP) antibody (>200 U/mL), anti-single strand DNA antibody (33.0 U/mL), and anti-Smith (Sm) antibody (192.7 U/mL) were positive. Anti-double strand DNA and anti-SSA/SSB antibodies were negative. Proteinuria was not seen. The pleural effusion was of exudative type according to Light's criteria (pleural fluid protein/serum protein ratio: 0.59; pleural fluid LDH/serum LDH ratio: 1.037) (4). The pleural effusion was also positive for ANA (1:5,120, speckled pattern) and had an adenosine deaminase level of 15.6 U/L. The results of a cytological analysis and bacterial cultures of the pleural effusion, including for tuberculosis, were negative. The positive findings for serum ANA and anti-Sm antibody and on tests for AIHA and serositis (pleuritis and pericarditis) met the American College of Rheumatology-endorsed criteria for SLE (5, 6). We therefore diagnosed the patient with lupus serositis and started oral steroid therapy.

A dose of 30 mg (0.7 mg/kg body weight) oral prednisolone was administered daily for 2 weeks and then tapered gradually. The symptoms soon improved, and the pleural ef-

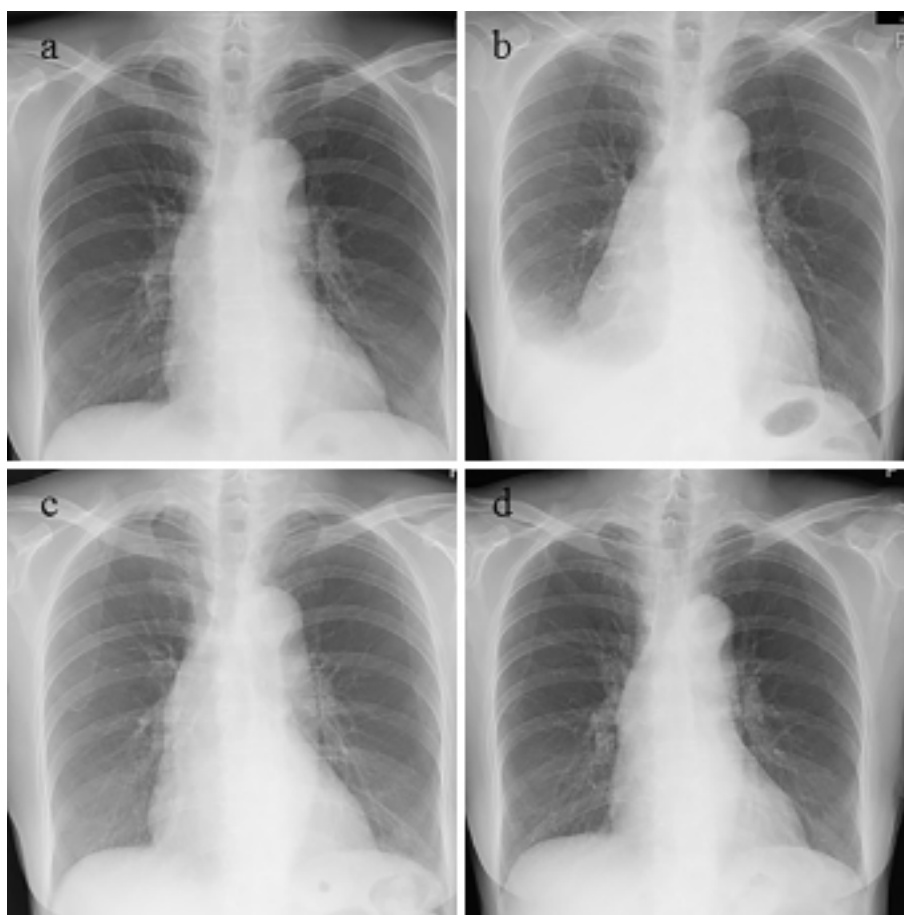


Figure 3. Chest X-ray findings. The chest X-ray findings were normal before the onset of SLE (a). Pleural effusion and mild cardiomegaly appeared at the onset of SLE (b) and disappeared after steroid therapy (c, d).

fusion had disappeared on chest X-ray at four weeks (Fig. 3c). Improvement has been maintained over a follow-up duration of more than two months (Fig. 3d).

Discussion

The diagnosis of *H. pylori* infection-related gastric MALT lymphoma and AIG was made in a 68-year old woman, who then developed AIHA and lupus serositis 3 years later. The AIG was discovered during the retrospective review of EGD images taken at the time of the MALT lymphoma diagnosis and was further confirmed by subsequent EGD and the presence of autoantibodies.

AIG is characterized by corpus-predominant gastric atrophy and the presence of the autoantibodies PCA and IFA. The demonstration of the histopathological features of AIG is also considered to be important for the diagnosis; however, as EGD was carried out as part of a checkup, we did not confirm the histopathology. Since the patient had thyrogastric syndrome, AIG associated with autoimmune thyroiditis, she was considered to be of APS type 3B (3).

AIG is also known to create a background for the development of gastric neoplasms, such as cancer and carcinoid, a type of neuroendocrine tumor. In our patient, AIG was ac-

companied by *H. pylori* infection and gastric MALT lymphoma, a combination that has been reported in only a few cases previously (7). Although *H. pylori* infection is one of the major causes of gastric MALT lymphoma, its association with the development of AIG remains controversial. Recent studies have proposed that *H. pylori* infection promotes T-cell dependent B-cell overgrowth, leading to gastric MALT lymphoma or else triggers the abnormal activation of cytotoxic T-cells, leading to AIG, depending on the type of host immune response made against *H. pylori* (8). However, the inhibitory effects of *H. pylori* infection against the development of AIG have been reported (9), implying that *H. pylori* eradication can hasten the development of not only AIG but also other autoimmune diseases related to AIG. In our case, three years after *H. pylori* eradication and the diagnosis of MALT lymphoma, the patient suffered an abrupt occurrence of hyperthyroidism, AIHA and lupus serositis. Recent studies have shown that cases of late-onset SLE (starting at >50 years old) represent a specific sub-group of the disease. Pulmonary manifestations, such as serositis and interstitial lung disease, are often observed in late-onset SLE, whereas, as with our patient, skin rash, photosensitivity, arthritis, and nephritis are rare (10, 11).

The association of AIG with autoimmune diseases other

than chronic thyroiditis has rarely been reported. A case of rheumatoid arthritis associated with AIG and cases of gastric carcinoid developing in patients with AIG and SLE have been reported (12-14). Therefore, our patient needs to receive ongoing endoscopic surveillance not only for relapse of gastric MALT lymphoma but also for the possible development of gastric carcinoid and adenocarcinoma.

In summary, in cases of MALT lymphoma in the stomach, the possible coexistence of *H. pylori* infection-related or AIG-type atrophic gastritis should always be considered. Patients with AIG may later develop autoimmune diseases, like thyroiditis, AIHA, and SLE.

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

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