Synchronous early gastric and intestinal mucosa-associated lymphoid tissue lymphoma in a *Helicobacter pylori*-negative patient: A case report

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**CASE REPORT**

**BACKGROUND**
Mucosa-associated lymphoid tissue (MALT) lymphoma occurs largely in the digestive tract, with the stomach being the most commonly affected organ, followed by the small intestine, large intestine, and esophagus. It is rarely found in both the stomach and colon. *Helicobacter pylori* infection is strongly associated with gastric MALT lymphoma, although there is a small number of *H. pylori*-negative gastric MALT lymphomas. Diagnosis of MALT lymphoma is challenging because of nonspecific symptoms and diverse presentations of endoscopic findings.

**CASE SUMMARY**
We report a case of an asymptomatic patient who during screening endoscopy and was found to have stromal tumor-like submucosal uplift lesions in the stomach body and polypoid lesions in the rectum. After endoscopic resection, the patient was diagnosed with multiple early simultaneous gastrointestinal MALT lymphomas.

**CONCLUSION**
This study may help improve our understanding of MALT lymphomas and multifocal lesions treated using early endoscopy.

**Key Words:** Mucosa-associated lymphoid tissue lymphoma; Endoscopy; Synchronous; *Helicobacter pylori*; Negative; Case report
Core Tip: Mucosa-associated lymphoid tissue (MALT) lymphoma is a subtype of non-Hodgkin’s lymphoma that is rarely found in both the stomach and colon. Diagnosis of MALT lymphoma is challenging because of nonspecific symptoms and diverse presentations of endoscopic findings. Helicobacter pylori (H. pylori) infection is the initial event in gastric MALT lymphoma. We report a case of H. pylori-negative gastric MALT lymphoma mimicking a gastric stromal tumor, together with a rectal presentation of intestinal MALT with a polyp-like appearance, which were treated endoscopically with complete remission.

INTRODUCTION
Mucosa-associated lymphoid tissue (MALT) lymphoma is a subtype of non-Hodgkin’s lymphoma classified by the World Health Organization as an extranodal marginal zone B-cell lymphoma, which accounts for approximately 5% of non-Hodgkin’s lymphomas and has a good long-term prognosis with a 10-year survival rate > 90%. MALT lymphoma can occur at many sites, including the salivary glands, thyroid, orbits, lungs, breast, kidneys, skin, liver, and prostate, and most often involves the gastrointestinal tract. The lack of specificity in the endoscopic presentation of MALT lymphoma of the gastrointestinal tract, especially in its early stages, presents a significant risk of underdiagnosis and misdiagnosis, posing a clinical diagnostic challenge.

Helicobacter pylori (H. pylori) infection is the initial event in gastric MALT lymphoma. There are a variety of clinical approaches for diagnosing H. pylori infection, usually combining noninvasive and invasive methods as well as the need to exclude false-negative results caused by antacids[1]. Most gastric MALT lymphomas are H. pylori positive and sensitive to eradication therapy. However, recent studies have found that the pathogenesis of H. pylori-negative gastric MALT lymphoma is increasing annually and may be related to genetics, autoimmunity, or other microorganisms. The clinical features and endoscopic presentation lack specificity, and the occurrence of simultaneous MALT lymphoma in the stomach and intestine in an H. pylori-negative background has rarely been reported[2].

Here, we report a case of H. pylori-negative gastric MALT lymphoma mimicking a gastric stromal tumor, together with a rectal presentation of intestinal MALT with a polyp-like appearance, which were treated endoscopically with complete remission.

CASE PRESENTATION
Chief complaints
A 46-year-old woman presented with a gastric submucosal uplift by screening endoscopy. She was admitted to our hospital for a further diagnosis without any symptoms.

History of present illness
One week ago, the patient presented to the hospital for a screening endoscopy and gastroscopy revealed a submucosal bulge in the upper anterior wall of the gastric body. The possibility of a stromal tumor was considered, and rectal polyps were found by colonoscopy; therefore, the patient was admitted for further endoscopic treatment. The patient was lack of bowel habits change and other alarm symptoms.

History of past illness
The patient had no history of H. pylori infection or chronic infection.

Personal and family history
The patient denied any family history of malignant tumor.
**Physical examination**
There were no obvious abnormalities during physical examination.

**Laboratory examinations**
Carbon-14 breath test results were negative, and antibodies against *H. pylori* types I and II were negative, indicating that the patient had no history of *H. pylori* infection. Routine blood examination showed normal white blood cells, lymphocytes, hemoglobin and platelets, normal liver and renal functions and electrolytes, and a negative fecal occult blood test.

**Imaging examinations**
Esophagastroduodenoscopy revealed an isolated submucosal protrusion in the upper anterior wall of the gastric body, about 4 mm × 5 mm in size, and the surface was slightly faded. The blood vessels were slightly dilated, elongated, and thickened (Figure 1A). Narrow-band imaging (NBI) revealed elongated and dilated marginal crypt epithelium and widened intervening space, similar to the pyloric gland structure, elongated and thickened blood vessels, and slightly thickened radial vessels around the area (Figure 1B). The possibility of gastric fundus gland cancer could not be ruled out using endoscopy. To further characterize this suspicious lesion, endoscopic ultrasonography was performed, which showed thickening of the muscularis of the mucosa and homogeneous hypoechoic changes in the lesion of the gastric body (Figure 1C), and leiomyoma was suspected. At this point, the nature of the lesion examined by endoscopy and endoscopic ultrasonography remained controversial. Therefore, diagnostic endoscopic submucosal dissection was performed after communicating with the patient, but no intact tumor was found during the dissection. Therefore, the lesion was removed via endoscopic mucosal resection and sent for pathological examination. Results of hematoxylin and eosin staining showed massive lymphocytic infiltration (Figure 2A). Immunohistochemistry was positive for CD20 (Figure 2B) and MUM1. CD21 (Figure 2C) showed expansion and destruction of follicular dendritic cells. Immunohistochemistry was negative for (Figure 2D-F) CD3, CD10, Bcl-6, CK, cyclin-D and P53. The Ki-67 proliferation index was < 10%. Gene detection revealed clonal rearrangement of the IgH gene in B cells (Figure 3), and Giemsa staining confirmed the absence of *H. pylori* infection. Therefore, *H. pylori*-negative gastric MALT lymphoma was diagnosed. Rectal polypoid lesions were observed by colonscopy (Figure 4A), and electrosurgical treatment was performed. Lymphocyte sheet infiltration was observed on hematoxylin and eosin staining (Figure 4B). Immunohistochemistry was positive for CD20 (Figure 4C). CD21 (Figure 4D) showed expansion and destruction of follicular dendritic cells. It was negative for Bcl-2 (Figure 4E), Bcl-6 and MUM1. Therefore, rectal MALT lymphoma was considered. Systemic positron emission tomography/computed tomography showed no abnormal uptake in the stomach and other areas of the body.

**FINAL DIAGNOSIS**
The patient was diagnosed with synchronous gastrointestinal MALT lymphoma (stage I).

**TREATMENT**
The patient was referred to the Department of Hematology because of multiple simultaneous MALT lymphomas in the gastrointestinal tract. After a multidisciplinary discussion, the clinical manifestations of MALT lymphoma were considered to be indolent and *H. pylori* negative, and complete endoscopic resection was performed. Close follow-up monitoring was then performed.

**OUTCOME AND FOLLOW-UP**
Five months later, gastroenteroscopy showed no residual or recurrent MALT lymphoma. Currently, the patient is undergoing regular follow-up.

**DISCUSSION**
MALT lymphoma can occur anywhere in the gastrointestinal tract, but most cases occur in the stomach. Colorectal MALT lymphomas are rare, accounting for < 1% of malignant tumors of the large intestine. The clinical presentation of gastrointestinal lymphoma varies and lacks specificity. Common symptoms include abdominal pain, bloating, nausea, vomiting, loss of appetite, and diarrhea. A few patients present with acute abdomen, such as gastrointestinal perforation, intestinal obstruction, or...
gastrointestinal bleeding, but approximately one third of patients have no alarming symptoms; therefore, the diagnosis is often incidental, especially in the early stages. Histologically, the disease is characterized by a heterogeneous small B-cell infiltrate that usually shows lymphoepithelial lesions or follicular colonization and a typical immunophenotype of CD20(+), CD5(-), CD10(-) and cyclin D1(-), in marginal zone B cells. Restriction molecular techniques have revealed immunoglobulin light chain restriction or clonal IgH rearrangement.

In this case, the patient was diagnosed with *H. pylori*-negative, early MALT lymphoma with gastrointestinal co-occurrence. We conducted a literature review based on the characteristics of this case. Recent studies have confirmed that the occurrence and development of most gastric MALT lymphomas are associated with *H. pylori* infection[3], and the main pathogenic mechanism may be that *H. pylori* leads to chronic inflammation and proliferation of T and B cells in the gastric mucosa. Long-term inflammation causes gastric mucosa without lymphoid tissue to produce MALT, which can lead to genetic abnormalities and malignant transformation, namely MALT lymphoma. However, recent studies have found that *H. pylori*-negative gastric MALT lymphoma is on the rise, and it is believed to be closely related to genes, autoimmunity, or other bacterial and viral infections. In a recent study of genetic alterations and somatic mutations in 57 patients with *H. pylori*-negative gastric MALT lymphoma, Kiesewetter et al[4] reported t(11;18)(q21;q21)/BIRC3-MALT1 mutations in 22 patients and nuclear factor-kappa B signaling molecule mutations in 14 patients. Autoimmune diseases such as
Synchronous early gastrointestinal MALT lymphomas

Figure 3 Gene detection revealed clonal rearrangement of the IgH gene in B cells.

Figure 4 Endoscopic images and immunohistochemical results of colon mucosa-associated lymphoid tissue lymphoma. A: Endoscopic images showing a single 5mm polypoid lesion; B: Hematoxylin-eosin staining of lymphocytic infiltration (200×); C: Immunohistochemistry showed that the lymphoid cells were diffusely positive for B cell marker CD20 (400×); D: CD21 showed expansion and destruction of follicular dendritic cells (400×); E: Immunohistochemical stains showed Bcl-2 negative (100×).

Sjogren’s syndrome, IgG4-related diseases, and obesity also increase the risk of primary MALT lymphoma[5]. Another possibility is infection with bacteria other than *H. pylori*, which could explain why the eradication of *H. pylori* can treat some *H. pylori*-negative MALT lymphomas[6].

Currently, there is no unified conclusion regarding the etiology of simultaneous gastrointestinal or multisite lymphomas. Clinical reports of simultaneous gastrointestinal MALT lymphoma are rare. We reviewed nine cases of simultaneous gastrointestinal MALT lymphoma reported in the literature (*Table 1*), and the analysis of the clinical characteristics of these cases showed that the incidence in males was higher than in females, which was consistent with the overall sex characteristics of MALT lymphoma. The median age of onset was 70 years (57-85 years), which is higher than that of single-site lymphoma (50-60 years)[15]. *H. pylori* infection was present in seven of the nine cases, but six failed to eradicate *H. pylori* infection, which was lower than the previously reported effective eradication rate of 70%-80%[16]. Most patients (5/9) presented with large tumor-like lesions associated with ulceration with lymphoma other than in the stomach and colon, and 3/9 patients had underlying diseases, including diabetes mellitus, celiac disease, and early gastric cancer. Analysis of the above clinical characteristics suggests that the therapeutic effect of *H. pylori* eradication in patients with homologous gastrointestinal lymphoma may be less than that in patients with a single site tumor, and most cases
**Table 1 Summary of co-occurring gastric and colon mucosa-associated lymphoid tissue lymphoma case reports**

| Ref.          | Sex | Age (yr) | Gastric                  | Colon                      | *H. pylori* | HPE | Other                                      |
|---------------|-----|----------|--------------------------|----------------------------|-------------|-----|--------------------------------------------|
| Nakagawara et al.\(^7\) | M   | 50       | Enlarged folds           | A polypoid tumor           | Negative    | ND  | No                                         |
| Isomoto et al.\(^7\)       | F   | 67       | Multiple ulcer           | Ulcer                      | Positive    | Invalid | Duodenum MALT                            |
| Arakura et al.\(^8\)       | M   | 65       | Red and swollen          | Submucosal tumor (> 50mm)  | Positive    | Invalid | Small intestine MALT                      |
| Fares et al.\(^9\)         | M   | 70       | An ulcer on top of a polyploid mass | Multiple polyps            | Positive    | Invalid | Lungs MALT                                |
| Tursi et al.\(^10\)        | M   | 57       | Ulcer                    | Irregular area             | ND          | ND   | Coeliac disease                           |
| Venizelos et al.\(^11\)    | F   | 70       | Nodular pattern          | Mucosal thickening         | Positive    | Invalid | Small intestine MALT                      |
| Sahara et al.\(^12\)       | M   | 85       | Petechial                | Low protuberant lesion (> 20 mm) | Positive    | Invalid | Early gastric cancer/small intestine MALT |
| McFarlane et al.\(^13\)    | M   | 73       | Spherical mass (> 30 mm) with ulceration | Polypoidal sigmoid (> 50 mm) | Positive    | Invalid | Diabetes mellitus                         |
| Singh et al.\(^14\)        | M   | 60       | Erythematous areas       | Diffusely friable, nodular and erythematous mucosa | Positive    | Effective | Strongyloides stercoralis                  |

ND: Non-described; *H. pylori*: *Helicobacter pylori*; HPE: *Helicobacter pylori* eradication.

**CONCLUSION**

In this case report, we have described the endoscopic presentation of early gastrointestinal MALT lymphoma in the asymptomatic stage, where endoscopic presentation is rare and easily misdiagnosed. The patient in this case was treated using endoscopic resection.
FOOTNOTES

Author contributions: Lu SN wrote the manuscript; Huang C, Di LJ and Li LL diagnosed the patient and contributed to the endoscopic; Yao J contributed to pathological diagnosis and provided the pathological images; Tuo BG and Xie R performed the treatment and revised the manuscript; and all authors have read and approve the final manuscript.

Supported by: Master’s Start-up Fund of the Affiliated Hospital of Zunyi Medical College, No. [2015]34; Basic Research Projects of Science and Technology Department of Guizhou Province, No. Qian Ke He-zk[2022]-646; and Collaborative Innovation Center of Chinese Ministry of Education, No. 2020-39.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

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