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CASE REPORT

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

Sheng-Nian Lu, Cheng Huang, Ling-Li Li, Lian-Jun Di, Jin Yao, Bi-Guang Tuo, Rui Xie

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Sheng-Nian Lu, Cheng Huang, Ling-Li Li, Lian-Jun Di, Bi-Guang Tuo, Rui Xie, Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi 563003, Guizhou Province, China

Jin Yao, Pathology Department, Affiliated Hospital of Zunyi Medical University, Zunyi 563003, Guizhou Province, China

Corresponding author: Rui Xie, PhD, Full Professor, Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, No. 149 Dalian Road, Zunyi 563003, Guizhou Province, China. xr19841029@aliyun.com

Abstract

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* (*H. 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.

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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 diagnose 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

Esophagogastroduodenoscopy 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 musculature 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 colonoscopy (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

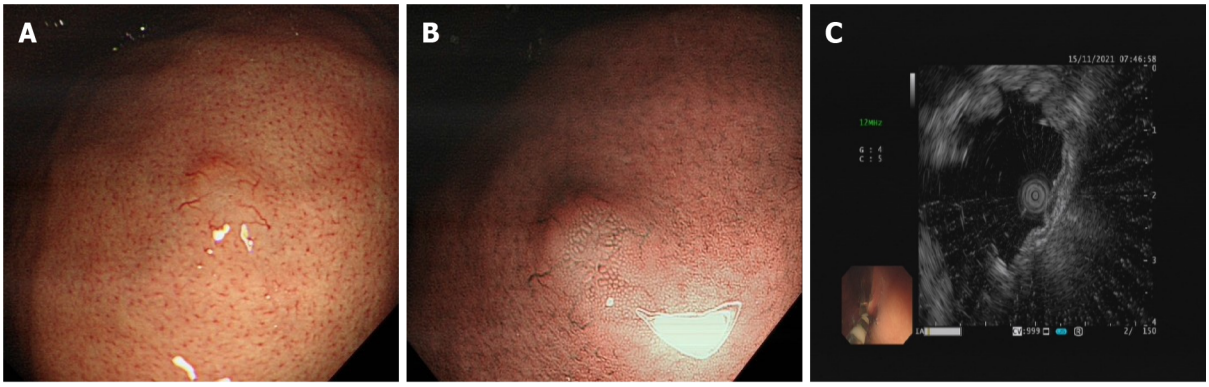

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Figure 1 Endoscopic images of the gastric lesion. A: A solitary submucosal eminence was observed; B: Narrow-band imaging appearance of gastric pit pattern elongates and expands, with appearance of irregular abnormal vessels; C: Endoscopic ultrasonography showed thickening of muscularis mucosa with a hypoechoic lesion 2 mm × 5 mm in size.

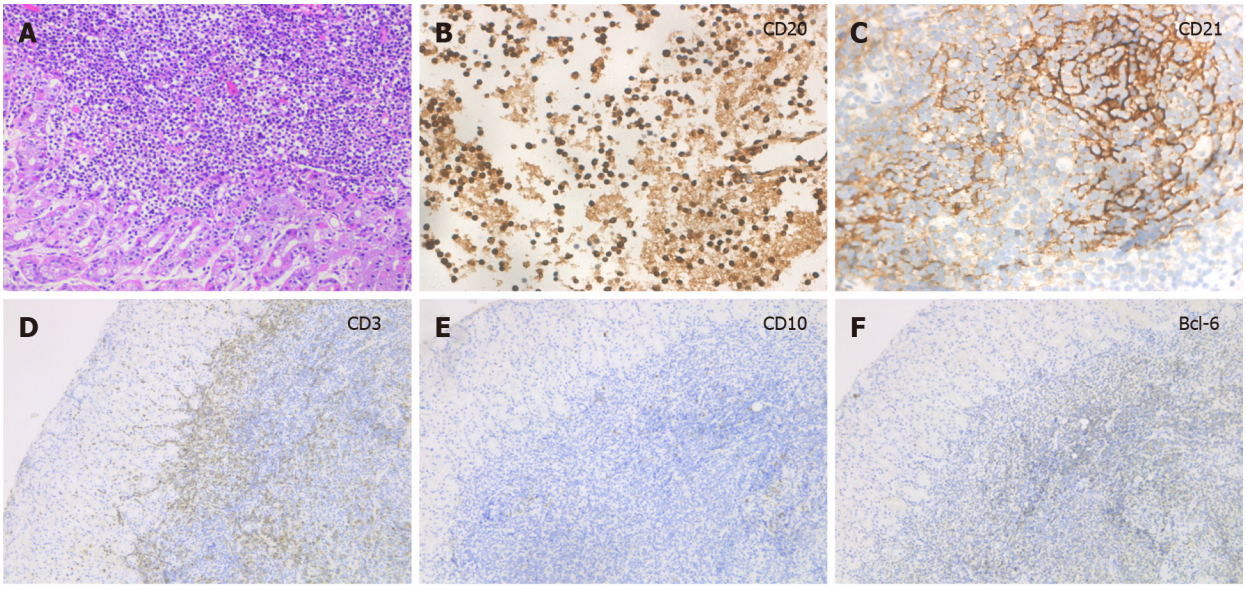

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Figure 2 Immunohistochemical results of the gastric mucosa-associated lymphoid tissue lymphoma. A: Hematoxylin-eosin staining of extensive lymphocytic infiltration (200×); B: Immunohistochemistry showed that the lymphoid cells were diffusely positive for CD20 (400×); C: CD21 showed expansion and destruction of follicular dendritic cells (400×); D: Immunohistochemical stains showed CD3 negative (100×); E: CD10 was negative (100×); F: Bcl-6 was negative (100×).

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

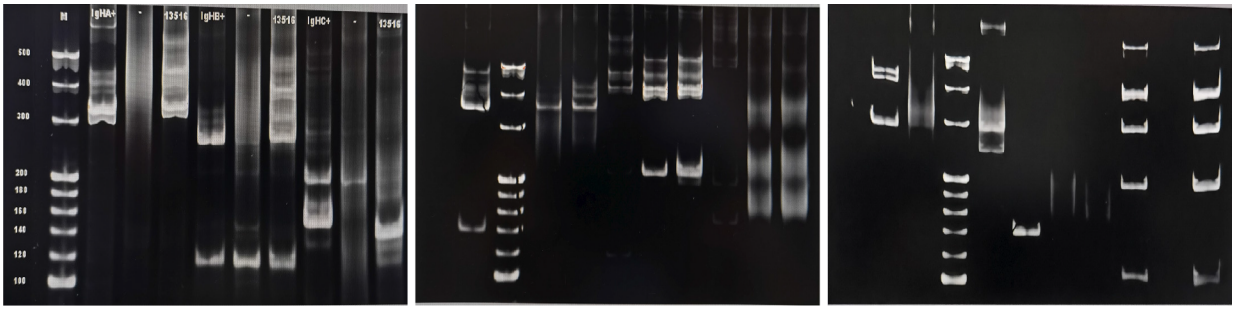

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Figure 3 Gene detection revealed clonal rearrangement of the *IgH* gene in B cells.

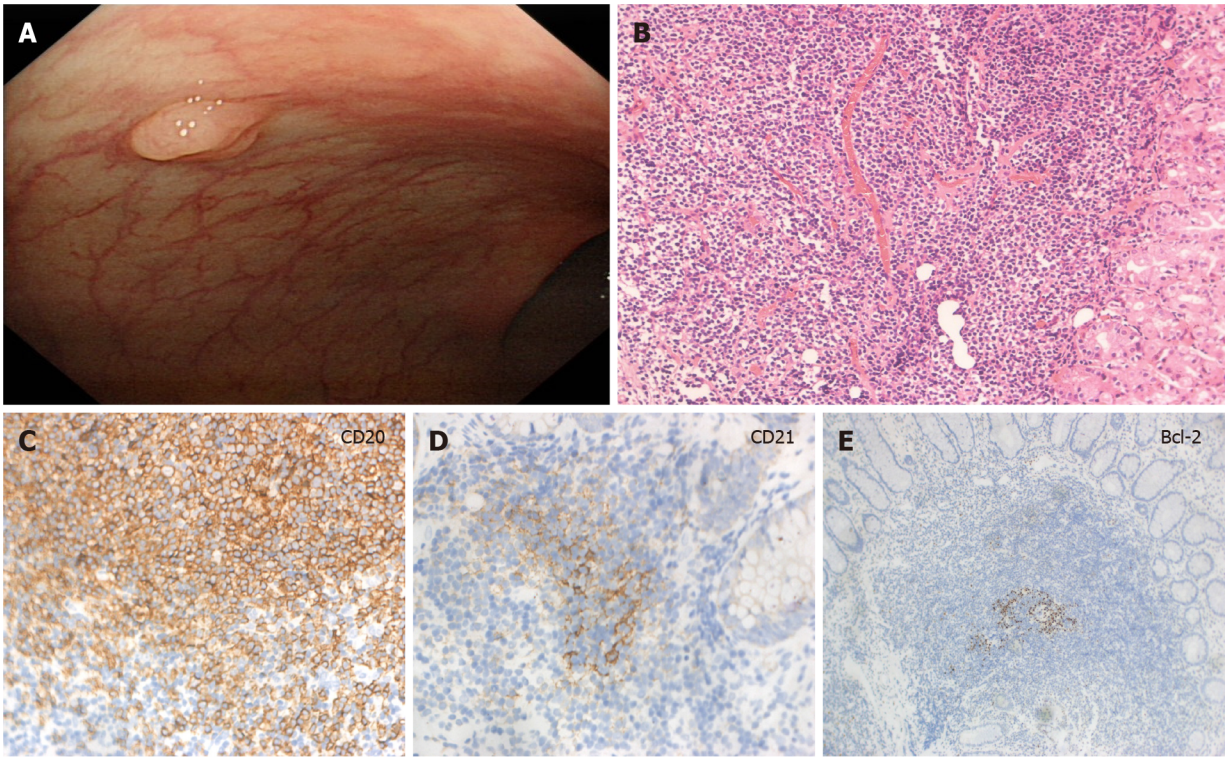

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Figure 4 Endoscopic images and immunohistochemical results of colon mucosa-associated lymphoid tissue lymphoma. A: Endoscopic images showing a single 5mm polypoid lesion; B: Hematoxylin-eosin staining of lymphocytic infiltration (200×); C: Immunohistochemistry 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*[2]	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 polypoid 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 thicken	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-descried; *H. pylori: Helicobacter pylori*; HPE: *Helicobacter pylori* eradication.

may be accompanied by lymphoma at other sites. Only one of the nine cases reported a relationship with t(11;18)(q21;q21) API2 MALT1 chimeric gene associated with translocation[12]. Therefore, it may not be representative and should be explored further. In the present case, the patient had no *H. pylori* infection, other bacterial infection, or underlying disease, and the examination was good. No lymphoma was found in other parts of the stomach or large intestine, suggesting an early stage of the tumor. Endoscopic biopsy is the gold standard method for the diagnosis of lymphoma. The endoscopic manifestations of lymphoma are diverse, ranging from normal gastric mucosa to ulceration or masses. Studies have shown that superficial lesions are more common[15,17], similar to erosion, multifocal gastritis, and other malignant tumors, and are often indistinguishable from gastric cancer or gastritis. Nakamura *et al*[18] found that *H. pylori*-negative cases were more often located proximal to the stomach, invading the submucosa but rarely presenting with the common superficial type, and *H. pylori*-negative gastric MALT lymphomas were often clinically advanced. The endoscopic appearance of NBI magnifying glasses is characterized by a tree-like appearance[19]. This is helpful for the endoscopist's judgment in guiding the biopsy. In our case, the gastric lesion appeared in the upper third of the gastric body, was confined to the submucosa, and appeared as a small submucosal bulge. No typical dendritic vascular manifestations were observed under NBI, which was different from the endoscopic features of gastric MALT lymphoma reported in the past, and may provide a reference to endoscopists when similar cases are encountered in future. Colorectal MALT lymphoma is rare, and there is no consensus regarding colonic MALT lymphoma. A flat, raised, polypoid, or semi-pedicled appearance can be observed during endoscopy. In the rectum, polypoid lesions are more common, the tumors vary in size, with a median diameter of 20 mm[20]. In our case, since the diameter of the lesion was only 5 mm, it was difficult to recognize that it was lymphoma before pathology.

This case was found incidentally in an *H. pylori*-negative setting, confined to the site that had been endoscopically resected, with no other organ metastases; therefore, we did not opt for further treatment, and no recurrence or progression of the lesion was detected during follow-up. There is no consensus or recommendation for *H. pylori*-negative gastric MALT lymphoma or intestinal MALT lymphoma. However, because of the low malignancy and slow progression of MALT lymphoma, endoscopic resection as a local treatment method has achieved ideal results.

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.

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ORCID number: Sheng-Nian Lu 0000-0002-3893-551X; Cheng Huang 0000-0003-1882-828X; Ling-Li Li 0000-0002-0208-1364; Lian-Jun Di 0000-0002-8937-4679; Jin Yao 0000-0002-9589-3555; Bi-Guang Tuo 0000-0003-3147-3487; Rui Xie 0000-0001-7970-5916.

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