Introduction

Primary gastric lymphoma (PGL) comprises only a minority of all gastric malignancies. The description of MALT lymphoma and the “discovery” of Helicobacter pylori in 1983 are landmarks in the history of gastric lymphoma.1,2 In 1991, the relationship between H. pylori and gastric malignancies, both carcinoma and lymphoma, was described for the first time.3,4 PGL is defined clinically as a dominant lesion within the stomach.5 In the recently formalized WHO classification, gastric lymphoma is considered as the “disease entity” of marginal zone lymphoma, MALT-type with a characteristic morphologic spectrum, immunologic marker pattern and discriminative chromosomal aberrations.6 The new insights in the role of chronic H. pylori infection in the pathogenesis of gastric MALT lymphoma have resulted in a disease-adapted therapy with the substitution of traditional lymphoma therapies, such as surgery, radiotherapy and chemotherapy, with simple H. pylori eradication using antibiotics. However, rates of about 7–15% H. pylori-negative gastric MALT lymphoma patients have been reported.7–9 In those patients, H. pylori eradication therapy seems to be irrelevant, and other therapeutic modalities are required.

We present a case of gastric MALT lymphoma in an H. pylori-negative patient, in whom partial gastric resection was performed. We review the literature and discuss the possible therapeutic options.

Helicobacter pylori-negative Low-grade Extranodal B-cell Primary Gastric Mucosa-associated Lymphoid Tissue Lymphoma

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Case Report

This patient was a 77-year-old man with a history of bleeding gastric ulcers in the past 1 year. In March 2005, he visited our outpatient department (OPD) due to intermittent epigastralgia, postprandial fullness and poor digestion for 2 months. Upper gastrointestinal (UGI) endoscopy revealed many irregular ulcers (0.9–1.2 cm in size) with erosive and hard surrounding mucosa over the antrum. Due to its wide extension and nodular appearance associated with the poor distention of the stomach, Bormann type IV gastric cancer (linitis plastica) was suspected. However, the pathologic findings from the biopsy specimens of the ulcers only showed intestinal metaplasia without \textit{H. pylori} infection or malignancy. Abdominal sonography done at the same time showed mild fatty liver and right renal cyst. The 2\textsuperscript{nd} UGI endoscopy done in April showed a submucosal tumor over the anterior wall, lesser curvature side (LCS) of the antrum and extension to the LCS of the low body with several irregular nonbleeding ulcers. However, the pathologic examinations revealed the same results as obtained in March. However, the 3\textsuperscript{rd} UGI endoscopy done in August, after 3 months of proton pump inhibitor treatment, showed lack of ulcers healing or regression of the submucosal tumor. Thus, malignancy was still highly suspected, but the pathologic findings of the biopsy specimen only showed chronic inflammation and intestinal metaplasia without \textit{H. pylori} infection. Abdominal computed tomography (CT) showed irregular eccentric nodular wall thickening over the LCS extending from the lower body to the prepyloric region. Meanwhile, several para-gastric lymph nodes (LNs, <0.5 cm) over the left gastric wall were also suspected by abdominal CT.

Due to the bizarre pattern of the mass and suspected regional LNs noted on CT, a 4\textsuperscript{th} UGI endoscopy was done. The pathologic examinations of specimen by multiple (8 fragments) deep biopsies of these lesions showed only atypical lymphoid infiltration (prominent lymphoid aggregates in the lamina propria) without lymphoepithelial lesion or \textit{H. pylori}. The immunohistochemistry (IHC) study of those specimens showed that they were follicular center cells positive for leukocyte common antigen, CD20, CD10 and bcl-6 but negative for CD3, CD5 and bcl-2. The pathologist reported that although extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue (MALToma) was suspected by histology, IHC study could not support the impression. Additionally, nested polymerase chain reaction (PCR) monoclonality studies for B cell IgH of the biopsy specimen showed smearing (polyclonal pattern), which did not support the diagnosis of MALToma. We consulted the surgeon for evaluation of the necessity of operation. Before operation, a 5\textsuperscript{th} UGI endoscopy was done in September, which found a nodular mass with discrete irregular ulcers over the LCS and posterior wall of the low body and antrum, which was highly suggestive of gastric lymphoma (Figure 1). Finally, the pathologic examinations of the biopsy specimen confirmed the diagnosis of extranodal marginal zone B-cell MALToma negative for \textit{H. pylori} infection (Figure 2).

A fasting serum gastrin level of 141 pg/mL (normal, <90 pg/mL) was noted from the general blood routine and biochemical tests, tumor markers such as \textalpha-\textit{fetoprotein}, carcinogen antigen-199 and carcinoembryonic antigen were within reference limits. Chest and abdominal X-rays and EKG were also normal. Finally, radical subtotal gastrectomy with Billroth II gastrojejunostomy was done in October. The operative findings included 2 adjacent mass lesions (5 × 3.5 cm and 2 × 1.8 cm) with ulceration over its surface at the LCS of the antrum and mid-body of the stomach (Figure 3). The pathologic findings of surgical specimens suggested diffuse large B-cell low-grade lymphoma with mucosa and submucosa involved. In addition, the surgical margins of the resected gastric lesion were negative for tumor involvements, as well as regional LNs and omentum. No evidence of \textit{H. pylori} was found in the specimen examined. Finally, the patient was discharged 2 weeks after operation, and has received regular OPD follow-up for 20 months.
Discussion

The diagnostic criteria for PGL include: (1) no palpable superficial lymphadenopathy; (2) no obvious enlargement of mediastinal nodes on chest X-ray; (3) normal peripheral blood counts and uninvolved bone marrow; and (4) absence of liver, spleen, or distant lymph node involvement. In this case, the patient fulfilled all the above criteria. The majority of PGLs are B cell non-Hodgkin’s lymphomas. The pathogenesis of H. pylori infection in PGL begins with an immunologic response, leading to chronic gastritis with formation of lymphoid follicles within the stomach. These lymphoid follicles resemble nodal tissues found throughout the body and are composed of reactive T, plasma and B cells. The B cells are responsible for initiating a clonal expansion of centrocyte-like cells that form the basic histology of MALT lymphoma. In some H. pylori-negative PGL, association with autoimmune diseases or infections has been described. There is a possibility that an unknown bacterium or virus which behaves like H. pylori may stimulate lymphoid proliferation in the stomach. Another possibility in H. pylori-negative PGL patients is that low bacterial counts may escape detection by the currently available tests. Till now, there has been no consensus on whether or not these cases should receive triple therapy.

The main histologic feature of low-grade PGL is the presence of lymphoepithelial lesions. High-grade PGL is characterized by malignant infiltrate of large lymphoid blasts without lymphoepithelial lesions. Monoclonality, a positive rate of 67–80%, can be used to confirm the diagnosis of low-grade PGL cases in doubt. From the patient’s 4th UGI endoscopy, the gastric biopsy specimen was also studied for monoclonality by nested PCR.

Most cases diagnosed as PGL are elderly persons who are older than 50 years. Clinically, the challenge with PGL is to make the diagnosis early enough to prevent tumor progression from low to high grade. However, this is not easy as patients may be asymptomatic or have nonspecific symptoms that overlap with those of peptic ulcer disease. Compatible with these observations, the patient in this case presented with nonspecific epigastric pain and abdominal fullness. Endoscopic findings of PGL include ulceration, polypoid mass or diffuse infiltration, which is most commonly located over the antrum and low body of the stomach. Tumors with bulky disease greater than 5 cm are more likely to represent high-grade PGL, and the majority of low-grade PGLs behave as diffuse.
submucosal tumor infiltration.\textsuperscript{16} Repeat UGI endoscopy in our case displayed diffuse submucosal tumor with ulceration on the surface of the antrum, low and high body of the stomach.

Only 41.9\% of cases have a correct histologic diagnosis at the 1\textsuperscript{st} endoscopy.\textsuperscript{17} Submucosal growth of neoplasm, necrotic material taken during biopsy and inadequate amount of specimen are conditions that might render the examination nondiagnostic. Thus, repeat endoscopies and more aggressive tissue sampling, with multiple and submucosal biopsies of endoscopically abnormal and normal mucosa, should be performed to confirm the diagnosis. This is particularly important in view of the possible multifocal distribution of the tumor and potential foci of high-grade lymphoma.\textsuperscript{17} Our patient received a total of 5 endoscopic examinations with repeat multiple biopsies to confirm the diagnosis.

The Musshoff modification of the Ann Arbor staging system is most widely used to evaluate the extent of PGL by both medical oncologists and gastroenterologists. With careful examination by repeat UGI endoscopies, whole abdominal sonography, abdominal CT and surgical specimen, our patient was diagnosed to have low-grade PGL. In this case, UGI series was not done due to a complete study by repeating UGI endoscopies and abdominal CT scan.

Previous studies reported that eradication of \textit{H. pylori} accompanied complete regression of low-grade PGL in 50–100\% of cases, with a disease-free survival time of greater than 6 years post-therapy.\textsuperscript{20,21} However, no consensus exists for further treatment after failure of \textit{H. pylori} eradication in low-grade PGL and for \textit{H. pylori}-negative cases. Thus, these cases can be treated with surgery, radiotherapy (RT), or chemotherapy (C/T). Due to good condition and patient willingness, our case received radical subtotal gastrectomy with Billroth II for his \textit{H. pylori}-negative low-grade PGL. It was reported that radical gastrectomy in patients with low-grade PGL had 5- and 10-year survival rates of 90\% and 70\%, respectively.\textsuperscript{21} Actually, the role of C/T in cases of low-grade PGL was also discussed in Aviles et al’s series. The relapse-free and overall survival were equivalent in both groups with C/T alone or combined C/T and surgery (75\% in 24–28 cases). Cumulative evidence suggested that surgery might not be necessary for patients with low-grade PGL with no complications such as bleeding or perforation.\textsuperscript{22}

Rosin et al reported a 49-year-old woman who received radical gastrectomy for her low-grade \textit{H. pylori}-negative PGL. Postoperatively, she was treated with RT directed to the tumor bed, with a total dose of 3 Gy. Despite the absence of \textit{H. pylori}, antibiotic triple therapy was administered after the operation. Repeat endoscopy of that patient 1 year after operation was negative for tumor recurrence.\textsuperscript{9} In a series reported by Taal et al, the 5-year survival rates were 71\% (46 cases) and 82\% (73 cases), respectively, in patients with low-grade PGL with RT alone or combined RT and surgery.\textsuperscript{22–24} However, complete remission and complication rates were not reported in that series. Thus, the role of combined RT and surgery remains unclear.

References