Simultaneous Occurrence of Gastric Adenocarcinoma and Low-Grade Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue

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Gastric adenocarcinoma developing concomitantly with a gastric lymphoma of the mucosa-associated lymphoid tissue (MALT) type is rare. Herein, we report a case with a synchronous primary gastric MALT lymphoma and an early adenocarcinoma of the stomach. A 72-year-old patient with initial presentation of weight loss was found with endoscopy to have a large tumor mass in the gastric body. Pathologic examination of biopsies revealed a low-grade MALT lymphoma for which chemotherapy with cyclophosphamide, vincristine, and prednisolone was administered. A gastric adenocarcinoma was found at a different site in the of stomach 3 months after cessation of chemotherapy when there was still residual MALT lymphoma in the stomach. The presence of double neoplasms was established preoperatively. The patient underwent a proximal gastrectomy. Infection with *Helicobacter pylori* (*H. pylori*) was detected once in the repeated endoscopic gastric biopsies. The occurrence of both gastric MALT lymphoma and gastric adenocarcinoma was reviewed and the association of *H. pylori* infection with both malignancies is discussed. (Chang Gung Med J 2002;25:115-21)

**Kew words:** gastric mucosa-associated lymphoid tissue (MALT) lymphoma, gastric adenocarcinoma, *Helicobacter pylori*

Low-grade B-cell non-Hodgkin's lymphoma (NHL) arising from mucosa-associated lymphoid tissue (MALT) is a special type of extranodal marginal zone lymphoma related to chronic antigen stimulation, with characteristic clinical behavior, histological features, and cytogenetic abnormalities. The overall incidence of MALT lymphomas is approximately 7.6% of all NHLs in Western countries, and the gastric MALT lymphoma is the most common and best-studied site. Low-grade gastric MALT lymphomas are usually characterized by an indolent course with prolonged confinement to the stomach. A close association has been suggested between gastric MALT lymphoma and chronic *Helicobacter pylori* (*H. pylori*) infection; also, *H. pylori* infection is now considered to be a cause of gastric cancer.

A gastric MALT lymphoma in patients can progress into a high-grade lymphoma or second cancers. On rare occasions, a gastric lymphoma might occur concomitantly with or after therapy for a gastric MALT lymphoma. To the best of our knowledge from a review of the English literature, less than 10 cases were found to have simultaneously coexisting separate gastric cancer and a gastric MALT lymphoma. No case has been reported in...
Taiwan. Herein, we report on a patient who was found to have gastric adenocarcinoma 3 months after cessation of chemotherapy for a gastric MALT lymphoma when the residual tumor was still present.

CASE REPORT

A 72-year-old male patient presented with body weight loss of 5 kg in one year. There was no history of epigastralgia or dysphagia. He had diabetes mellitus and hypertension which were under good medical control. In a general health examination at a local hospital on January 14, 1999, an upper gastrointestinal endoscopy disclosed a mass in the stomach. He was referred to Chang Gung Memorial Hospital on January 27, 1999 for further management. Physical examination revealed the patient to be in good general condition, with no lymphadenopathy or hepatosplenomegaly. The remaining examinations were unremarkable. An endoscopic examination showed a large polypoid mass in the gastric body with extension to the cardiac region; the Campylobacter-like organism (CLO) test which detects the urease enzyme of *H. pylori* was negative.

Pathological examination of the gastric biopsy revealed ordered gastric mucosa with diffuse infiltration of centrocytelike cells and the presence of lymphoepithelial lesions, which indicated a MALT lymphoma, but no Helicobacter-like bacteria. Laboratory tests including complete blood counts, liver and renal function tests, and bone marrow examination were all within normal limits. The chest X-ray, both upper and lower gastrointestinal series of radiological barium studies, and abdominal computed tomography showed that the tumor was limited to the stomach. Chemotherapy with a regimen of 750 mg/m² cyclophosphamide, 2 mg vincristine, and 60 mg prednisolone (COP) every 3 weeks was initiated on February 23, 1999. A follow-up endoscopic examination on May 18, 1999, after 4 cycles of COP treatment, showed diffuse gastritis, an irregularly elevated submucosal lesion in the posterior wall of the gastric body, and a much smaller mass. In addition, a 1.2-cm polyp on the posterior wall of the antrum was also found; the biopsy of the submucosal lesion revealed features of a MALT lymphoma, while a biopsy of the polyp revealed it to be a hyperplastic polyp with severe dysplasia. The patient then received an additional 3 cycles of COP chemotherapy. On July 13, 1999, the previous lesions of MALT lymphoma had disappeared in follow-up endoscopy of the stomach, but diffuse erythematous mucosae and 2 small polyps on the posterior wall of the low and high body were noted. Biopsies of the gastric polyps revealed them to be on adenomatous polyp (low body) and hyperplastic polyp (high body), but with no evidence of lymphoma or *H. pylori* infection. Chemotherapy was stopped on July 20, 1999. Three months later, an infiltrative tumor with ulceration in the high gastric body as well as 2 polyps at the low and high body were again found on endoscopic examination. Pathology of the tumor showed it to be a MALT lymphoma, and biopsy of the gastric polyp at the high body showed it to be a well-differentiated adenocarcinoma. Some Helicobacter-like organisms were first seen in the biopsy specimen. The patient underwent a proximal gastrectomy with lymph node dissection and liver biopsy on November 26, 1999. The histopathological examination revealed 2 distinct malignancies: a well-differentiated adenocarcinoma of the intestinal type confined within the mucosa (Fig. 1), which arose from the previously existing hyperplastic polyp at the high body (Fig. 2); and a low-grade MALT lymphoma with submucosa invasion which was also taken from the high body (Figs. 3, 4). Of the 2 hyperplastic

![Fig. 1](image-url)
polyps, one was located on the posterior wall of the antrum with gross invasion of the submucosa (2.5 × 1.5 cm) and the other was near the distal section margin (1 × 1.5 cm). A shallow 15-mm shallow ulcer located at the high body was also noted. One regional lymph node at the greater curvature was positive for lymphoma involvement. The surrounding mucosae showed severe chronic atrophic gastritis with intestinal metaplasia. The resectional margin and the omentum were negative for malignancy. There were tumor-free mucosae between the carcinoma and lymphoma. No Helicobacter infection was seen. Biopsy of the liver was normal. Adjuvant radiotherapy was suggested, but the patient was reluctant to receive gastric irradiation. Neither follow-up endoscopic examinations, on March 11, 2000 and July 22, 2000, showed evidence of tumor recurrence or H. pylori infection by endoscopic biopsy.

**DISCUSSION**

Extranodal marginal zone B-cell lymphoma is a discrete clinicopathological entity arising in mucosa-associated lymphoid tissue. The histologic appearance of a low-grade gastric lymphoma of MALT is characterized by prominent and often multifocal lymphoepithelial lesions showing dense infiltrates of centrocyte-like cells within the lamina propria in associated with plasma cell differentiation and with the presence of reactive lymphoid follicles. Treatment of a gastric MALT lymphoma includes surgery, radiation therapy, and chemotherapy. Because gastric MALT lymphomas are highly associated with H. pylori infection, eradication of H. pylori with antibiotics is very important.

An unexpectedly high incidence of other cancers was observed in patients with low-grade gastric MALT lymphomas by some investigators. In contrast, Au et al. found that patients with MALT lymphomas did not have a statistically significantly increased incidence of other malignancies when compared to an age-matched population. The occurrence of both gastric MALT lymphomas and gastric adenocarcinoma in the same patients has been very rare. Cogliatti et al. reported that 14 of 145 patients (9.6%) with gastric MALT lymphomas had another cancer, but only one of them had a gastric carcinoma. Zucca et al. found that 17 of 83
patients (20%) with low grade gastric MALT lymphomas had one or more additional cancers of 23 types; however, no patient developed another cancer in the stomach.\(^{(19)}\) Au et al. reported that 32 of 147 patients (21.8%) with low-grade MALT lymphomas had other cancers, but only one patient had gastric adenocarcinoma which developed 5 months after a total gastrectomy for treating the gastric MALT lymphoma. In the series of Montalban et al., other cancers were detected in 16 of 136 patients (11.8%); only 3 patients had gastric adenocarcinoma either concomitantly or after diagnosis of the gastric MALT lymphoma.\(^{(7)}\) Nakamura et al. disclosed that 10 of 9392 consecutive gastric resection specimens of primary gastric lymphoma or gastric carcinoma had the occurrence of both lymphoma and adenocarcinoma in the same patients in Japan.\(^{(8)}\)

It was interesting to note that among the reported cases with double malignancies, gastric carcinoma occurred either synchronously or metachronously after treatment of the MALT lymphoma, but not before the diagnosis of gastric MALT lymphoma. In our case, the adenocarcinoma and lymphoma coexisted but were separated macroscopically and microscopically by areas of tumor-free gastric mucosa. The simultaneous occurrence of 2 different tumors in the same stomach may be a case of either synchronous collision tumors in which 1 tumor grows into the other\(^{(12-15)}\) or synchronous independent tumors in which there is tumor-free mucosa between both malignancies as in the present case.\(^{(8,12,14)}\) In a reviews of the published data, less than 10 documented patients reported in the English literature were found to have separate coexisting separate tumors (Table 1). The 2 histologically different tumors were precisely diagnosed preoperatively in the current case. Among the reported cases for which detailed information is available, a diagnosis of the coexistence of 2 malignancies was not established prior to surgery except in one case.\(^{(19)}\) Frequent endoscopic examination with multiple biopsies from various sites of the lesions is important in achieving a correct diagnosis early.

Some predisposing factors have been considered to be associated with these double malignancies. It is well recognized that a carcinoma arising from the gastric remnant is a late complication of gastrectomy,\(^{(8,9)}\) which has been attributed to bile salt reflux, a high pH level, atrophic gastritis, intestinal metaplasia, or adenomatous polyps. The metachronous development of cancer of gastric remnants in patients treated initially with surgery for lymphoma of the stomach has also been reported.\(^{(10,16)}\) Since there was no prior gastrectomy in our patient, gastric resection did not play a role in the carcinogenesis of the stomach. Chemotherapy has been implicated as a predisposing factor for subsequent carcinogenesis. The potential role of gastric carcinogenesis associated with alkylating agents has been suggested. The interval from the cessation of chemotherapy to the diagnosis of gastric carcinoma is usually longer than 4 years.\(^{(19)}\) In view of the time lapse from chemotherapy to the occurrence of cancer in this case being very short, it is less likely to have been a factor inducing the occurrence of the gastric cancer. Gastric irradiation is also considered to be a cause of gastric cancer,\(^{(10)}\) but the present case received no radiotherapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of case</th>
<th>Histology</th>
<th>Dx of double malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane, et al.</td>
<td>1982</td>
<td>1</td>
<td>lymphocytic lymphoma</td>
<td>postoperatively</td>
</tr>
<tr>
<td>Czerniai, et al.</td>
<td>1985</td>
<td>1</td>
<td>mixed type</td>
<td>postoperatively</td>
</tr>
<tr>
<td>Kelly, et al.</td>
<td>1994</td>
<td>1</td>
<td>low-grade MALT</td>
<td>preoperatively</td>
</tr>
<tr>
<td>von Herbay, et al.</td>
<td>1995</td>
<td>1</td>
<td>MALT with both low-grade and high-grade components</td>
<td>postoperatively</td>
</tr>
<tr>
<td>Nakamura, et al.</td>
<td>1997</td>
<td>5</td>
<td>4 low-grade and 1 high-grade lymphomas of MALT</td>
<td>postoperatively</td>
</tr>
<tr>
<td>Present case</td>
<td>2001</td>
<td>1</td>
<td>low-grade MALT</td>
<td>preoperatively</td>
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</tbody>
</table>

**Abbreviations:** MALT: mucosa-associated lymphoid tissue; Dx: diagnosis.
Helicobacter was detected on 1 occasion in the present case. Only 2 of the published cases with both gastric carcinoma and lymphoma were reported to be associated with *H. pylori* infection.\(^{(20)}\) Epidemiological studies have demonstrated a link between *H. pylori* infection and gastric tumors of both carcinomas and lymphomas. A likely cause of both malignancies is atrophic gastritis induced by *H. pylori* infection. *Helicobacter pylori* infection was found in more than 90% of cases of gastric MALT lymphoma, and eradication of *H. pylori* can bring regression of a gastric MALT lymphoma. *Helicobacter pylori* has also been designated as a carcinogen in humans. *Helicobacter pylori* infection induces multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and then carcinoma. The surgical resected specimen of our patient showed the presence of diffuse atrophic gastritis. The loss of gastric acidity in atrophic gastritis contributes to a gastric bacterial flora which promotes the endogenous formation of N-nitroso compounds, which play a role in gastric carcinogenesis. In this case, *H. pylori* infection may have played a major role in the development of the MALT lymphoma and gastric adenocarcinoma, so anti-*H. pylori* treatment was necessary for this patient. Of particular note, features of atrophic gastritis, intestinal metaplasia, a polyp with dysplasia, and carcinoma were all present in the gastric resection specimen of our patient. These findings are consistent with the concept of progression from metaplasia through dysplasia to carcinoma induced by *H. pylori* infection.

### REFERENCES


胃黏膜相關性淋巴瘤合併胃腺癌之發生

湯崇志 施麗雲 陳邦基^1 陳澤卿^2

胃腺癌同時合併胃黏膜相關性淋巴瘤發生是非常罕見的。我們報告一位72歲男性病人，因體重減輕，經內視鏡切片檢查發現胃黏膜相關性淋巴瘤，之後病人接受化學治療，結束化療3個月後，病人接受內視鏡切片檢查發現同時有胃腺癌及殘存之胃黏膜瘤，病人之後接受近端胃切除術。這位病人在整個治療過程中，曾在一次胃切除檢查發現幽門螺旋桿菌。因此，我們針對胃腺癌及胃黏膜相關性淋巴瘤的發生及相關性，以及幽門螺旋桿菌感染對於這兩種腫瘤的相關性進一步探討。(長庚醫誌 2002;25:115-21)

關鍵字：胃黏膜相關性淋巴瘤，胃腺癌，幽門螺旋桿菌。