Pathogenesis of gastric lymphoma: The enigma in Hong Kong

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Summary

Background: Helicobacter pylori (H. pylori) infection has been postulated to be a pathogenetic factor in gastric lymphoma. However, the etiological factors for gastric lymphoma could vary in different populations.

Materials and methods: We looked for histological evidence of H. pylori infection in 53 gastric resection specimens from Hong Kong Chinese patients with primary gastric B-lymphoma. We also screened for Epstein-Barr virus (EBV) in these cases using in situ hybridization with oligonucleotide probes for EBV-encoded small RNA1 and 2.

Results: H. pylori was found in 29 of 53 (55%), including 8 of 13 (62%) cases of low-grade lymphoma of mucosa-associated lymphoid tissue (MALT) type. These infection rates in gastric lymphoma are lower than those reported in Western populations (80%-100%) and comparable to that found in healthy Chinese blood donors (55%) or in non-ulcer dyspeptic patients (52%-57%). EBV was found in tumor cells only in one case of high-grade gastric lymphoma with low-grade MALT component which was H. pylori-negative, and in occasional nontumor lymphoid cells in 7 other cases.

Conclusions: These results suggest that (1) the role of H. pylori in pathogenesis of gastric lymphoma may vary in different populations; (2) very few gastric lymphomas are associated with EBV; (3) not all low-grade gastric MALT lymphomas are H. pylori-dependent.

Key words: Epstein-Barr virus, gastric lymphoma, Helicobacter pylori, mucosa-associated lymphoid tissue

Introduction

Helicobacter pylori (H. pylori) is a well-known pathogenic factor for gastroduodenal diseases, and in primary gastric non-Hodgkin's B-cell lymphomas (B-NHL) arising from mucosa-associated lymphoid tissue (MALT) type. These infection rates in gastric lymphoma have not been well understood. We therefore carried out a retrospective study to investigate the prevalence of H. pylori and EBV infections in 53 cases of primary gastric B-NHL of Hong Kong Chinese patients.

Materials and methods

Fifty-three gastrectomy specimens with histologically diagnosed B-NHL were collected from the archival material of the Department of Pathology, University of Hong Kong, Queen Mary Hospital, over the period 1981 to 1994. The mean age of the patients was 51.4 years with a range of 23-92 years. The male to female ratio was 1.3:1. The cases were classified into low-grade MALT lymphoma (LG-MALT), high-grade lymphoma with low-grade MALT lymphoma component (HG-LG), and high-grade lymphoma without features of low-grade MALT lymphoma (HGL), including centroblastic or immunoblastic lymphomas. The criteria used for diagnosis of LG-MALT included the essential findings of (1) a predominance of centrocyte-like cells and (2) the presence of lymphoepithelial lesions, with supportive features being (1) a superficial spreading pattern of the lymphomatous infiltrate hugging both sides of the muscularis mucosae, (2) a perifollicular pattern of involvement, and (3) presence of plasma cell differentiation in the tumor population. HGL referred to those cases showing features of LG-MALT with at least focal areas harboring clusters or sheets of centroblastic or immunoblastic cells. There were 13 cases of LG-MALT, 27 cases of HG-LG, and 13 cases of HGL (12 centroblastic, 1 immunoblastic). Two blocks of lymphoma with adjacent mucosa and 2 blocks with mucosa distant to lymphoma (one from the antrum and one from the body of the stomach) were examined whenever such tissue was available (30 of 53 cases). A minimum of 2 blocks were examined in every case. Preoperative endoscopic biopsy specimens were available in 17 of these cases, and these...
were also examined. All sections were from paraffin-embedded tissue and Warthin-Starry silver staining was used for detection of *H. pylori*. In situ hybridization (ISH) for EBV-encoded small RNA1 and 2 (EBER1 and 2), was performed on all 53 cases using a cocktail of fluorescein-conjugated oligonucleotide probes (DAKO A/S, Denmark) and ISH detection kit (DAKO A/S, Denmark) according to the supplier's protocol.

**Results**

*H. pylori* colonization (Figure 1) was found in 8 of 13 (62%) LG-MALTs, 14 of 27 (52%) HG-LGs, and 7 of 13 (54%) HGLs (Table 1). The overall positivity was 55% (29/53). There was only one case of HG-LG whose gastrectomy was negative but biopsy was positive; the biopsy was taken five years before gastrectomy and diagnosed as gastric ulcer. For the other 16 cases with endoscopic biopsy, biopsies were taken either in the same year, or from one to two years before gastrectomy, and *H. pylori* colonization status in the biopsy was the same as in the gastrectomy specimens.

EBV was found in tumor cells in only one case of high-grade lymphoma (centroblastic) with remnant areas of low-grade component, which was negative for *H. pylori*. EBER signal was seen in virtually all tumor cells (Figure 2). EBV was detected in occasional nontumor lymphoid cells in 7 other cases (< 0.1% of total cells present).

**Discussion**

In this study, the positivity of *H. pylori* infection in gastric lymphoma specimens of Hong Kong Chinese patients was found to be surprisingly low (55%). This figure is in contrast to the findings of Muller et al. [4] and Wother- spoon et al. [1] in the United Kingdom and Eidt et al. in Germany [2], where *H. pylori* was found in 80%, 92%, and 100% of gastric lymphoma specimens, respectively. Eidt et al. only examined biopsy specimens for *H. pylori* colonization in only 5 of 12 (41.7%) cases of gastric MALT lymphoma, either in the gastrectomy specimens or in previous gastric biopsy samples [11]. Even using three methods, urease test on biopsy material, histological analysis and serological assay, Karat et al. in the United Kingdom only found *H. pylori* infection in 6 of 12 (50%) primary gastric lymphoma cases [13]. In Finland, Miettinen et al. also reported a low positivity, 13 of 22 (59%) [12].

In Western populations, the infection rates of *H. pylori* in primary gastric lymphoma in some series are substantially higher than that in their general populations (50%–60%) [1]. Although we do not have matched controls, there is a similar rate of infection in the general population of Hong Kong as detected by serological assay on healthy Chinese blood donors (55%) [17], or in endoscopic

**Table 1. H. pylori positivity rates in different types of primary gastric lymphoma in Hong Kong Chinese.**

<table>
<thead>
<tr>
<th>Histological type</th>
<th>LG-MALT</th>
<th>HG-LG</th>
<th>HGL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>13</td>
<td>27</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td>Positive cases</td>
<td>8 (62%)</td>
<td>14 (52%)</td>
<td>7 (54%)</td>
<td>29 (55%)</td>
</tr>
</tbody>
</table>

Abreviations: LG-MALT - low-grade MALT lymphoma; HG-LG - high-grade lymphoma with low-grade MALT component; HGL - high-grade lymphoma without low-grade MALT component.

However, we did not find a significant difference in positivity rate between gastrectomy and biopsy specimens in the detection of *H. pylori*. In this regard, in the study of Wotherspoon et al., most of their cases were also gastrectomy materials (73/110) [1]. Furthermore, Stolte et al. found *H. pylori* colonization in 175 of 178 (98%) of surgical specimens with primary gastric B-NHL [3]. The difference cannot be explained, therefore, simply by use of different tissue samples (biopsy or gastrectomy).

Recently, some Western studies have also described low positivity of *H. pylori* infection in gastric lymphoma specimens although they were all small series. Calvert et al. in the United Kingdom found *H. pylori* colonization in only 5 of 12 (41.7%) cases of gastric MALT lymphoma, either in the gastrectomy specimens or in previous gastric biopsy samples [11]. Even using three methods, urease test on biopsy material, histological analysis and serological assay, Karat et al. in the United Kingdom only found *H. pylori* infection in 6 of 12 (50%) primary gastric lymphoma cases [13]. In Finland, Miettinen et al. also reported a low positivity, 13 of 22 (59%) [12].

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biopsies from non-ulcer dyspeptic patients (52%–57%) [17, 18]. The absence of an observed higher infection rate in our gastric lymphoma patients could be due to two possibilities. First, the infection status could change during the long-term development and progression of gastric lymphoma. In one of our cases, \( H. pylori \) cannot be detected in the gastrectomy specimen while it was seen in the endoscopic biopsy taken five years before the presentation of gastric lymphoma. If this situation also holds true for some of the other negative cases, then the low positivity would not necessarily undermine the role of \( H. pylori \) in the early stage of development of gastric lymphoma. However, this cannot explain the difference between low and high positivity rates in different reports.

Alternatively, the low positivity results in some studies may suggest that the role played by \( H. pylori \) may be of varied importance in different populations and be consistent with the view that etiologic factors other than \( H. pylori \) may also play an important role in the pathogenesis of gastric lymphoma. EBV has been described in gastric lymphoma by several studies. Ott et al. in Germany found EBV DNA in 2 of 24 (8%) gastric centroblastic and immunoblastic lymphomas with ISH and blotting techniques [14]. Liu et al. in Japan also found EBV in a small proportion (4 of 49, 8%) of gastric B-NHL with ISH [15]. EBV has been found in a significant proportion (9 of 59, 15%) of gastric high-grade B-NHL without MALT features in Hong Kong by Hui et al. with EBER1 ISH [16]. However, EBV was detected in tumor cells only in one case of HG-LG in our series. We do not know the reason for this discrepancy and this should be studied further. Based on our results and those from other countries, we are of the view that in general few gastric lymphomas are associated with EBV. Besides \( H. pylori \) and EBV, Fagioli et al. in Italy proposed that occupational exposure to solvents and pesticides could play a pathogenic role in a proportion of their cases [19]. Although none of the other factors has been as well established as \( H. pylori \), given the fact that the incidence of gastric lymphoma is generally uncommon despite the high prevalence of \( H. pylori \) infection worldwide [20–22], \( H. pylori \) infection alone cannot induce gastric lymphoma. Studies on a wider range of factors would likely further our understanding of the pathogenesis of gastric lymphoma. An appropriate consideration may be that both \( H. pylori \) and other factors contribute to the development of gastric lymphoma, although to varying degrees.

The most important suggestion from the lack of evident \( H. pylori \) infection in a certain number of low-grade gastric MALT lymphoma cases in both of our series and in the other studies [11–13] is that \( H. pylori \) may not be necessary for the maintenance of proliferation of all low-grade gastric MALT lymphomas whether they are \( H. pylori \)-associated in their early development or not. Besides, presence of \( H. pylori \) in the lymphoma specimen should not automatically be equated with dependence on \( H. pylori \) for tumor growth. The high-grade gastric lymphoma of MALT is generally accepted to be independent of \( H. pylori \) [7, 9, 23]. Although hitherto, clinical anti-biotic therapy trials and experimental evidence for the dependence of some low-grade gastric MALT lymphoma on \( H. pylori \) stimulation is convincing, not all cases have demonstrated this relationship [7–10]. This situation has also been recently reported by Savio et al.; one case of gastric low-grade MALT lymphoma in their series failed to regress even 16 months after eradication of \( H. pylori \) [24]. Further experimental and clinicopathological studies are therefore necessary to investigate the factors in operation in cases of low-grade gastric MALT lymphoma that appear to be independent of \( H. pylori \).

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References


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