Collision of Lymphoepithelioma-like Carcinoma with Diffuse Large B-cell Lymphoma of the Stomach: A Case Report

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Abstract. Background/Aim: Collision of Epstein-Barr virus (EBV)-associated lymphoepithelioma-like carcinoma (LELC) with non-Hodgkin’s lymphoma of the stomach is extremely rare. Patients and Methods: Herein we report a case of LELC with primary diffuse large B-cell lymphoma (DLBCL) of the stomach in a 65-year-old patient. Results: Gastric endoscopy showed a poorly differentiated adenocarcinoma of the stomach. The patient underwent radical gastrectomy, and histopathological examinations revealed the collision of LELC and DLBCL of the stomach. In situ hybridization showed that most carcinoma cells of LELC were positive for EBV-encoded small RNA (EBER) suggesting that the virus infection happened in the early stage of tumorigenesis, while DLBCL was negative. Conclusion: This is the first report of collision of EBV-associated LELC with primary DLBCL of the stomach.

Gastric lymphoepithelioma-like carcinoma (LELC) is a rare type of gastric carcinoma (GC) that is characterized by diffuse infiltrating lymphoid nodule of undifferentiated carcinoma cells surrounded by the lymphoid stroma. It constitutes 1-4% of all GC, while more than 80% of LELC are related with Epstein Barr Virus (EBV) infections (1). Gastric lymphoma (GL) is uncommon, accounting for about 2-8% of all gastric malignancies (2). It has mainly two histological subtypes, including mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL). Collision of EBV-associated GC with non-Hodgkin’s lymphoma of the stomach is very rare. According to the previous reports, five cases of EBV-associated GC with GL have been reported (2-6) (Table I).

In this report, we displayed a case of a 65-year-old patient with two tumors of the stomach. After radical gastrectomy, histopathological examinations revealed the collision of LELC and primary DLBCL of the stomach. LELC was positive for EBER, while DLBCL was negative in in situ hybridization.

Case Report

A 65-year-old man presented with a two-month history of radioactive upper abdominal pain. The patient had been treated with drugs in a local hospital, but with no obvious symptoms improvement. For further evaluation, the patient was admitted to the Affiliated Hospital of Qingdao University (Qingdao, China) in March, 2015.

An endoscopic biopsy of the tumor showed a poorly differentiated adenocarcinoma (antrum and body of the stomach). A diagnosis of GC was rendered and the patient underwent radical gastrectomy. Macroscopic examination showed that there are two pieces of pathological tissues. One was a superficial ulcer (3.5×3 cm in size), which located at the lesser curvature of the body. It was brittle, and its surface was grey-white and had invaded the muscular layer of the gastric wall. The other one was an ulcer tumor (2.5×2 cm in size), which was located at the lesser curvature side of the antrum. It was brittle and grey-white and had invaded the submucosa and muscularis of the stomach.

Microscopically, the former was a gastric LELC. The tumor cells penetrated the submucosa and muscularis of the stomach. It consisted of many undifferentiated epithelial cells with dense lymphocytes and plasma cells infiltrating. The latter was a non-Hodgkin lymphoma, with diffuse B lymphocyte infiltrating. The tumor cells had penetrated the mucous layer, submucosa, and muscularis of the stomach (Figure 1). Immunohistochemical staining of the LELC
revealed marked immunoreactivity for pan-keratins protein (CK1/CK3), CD20, CD3, CD38; however, the tumor was found to be negative for CK7, CK20. 67% of the tumor cells expressed Ki-67 (Figure 2). Immunohistochemical staining of the gastric DLBCL revealed marked immunoreactivity for CD20, CD10, Bcl-6, Bcl-2, and LCA (CD45); however, the tumor was negative for Mum-1, CK1/CK3. 90% of tumor cells expressed Ki-67 (Figure 3). In in situ hybridization, LELC was basically positive for EBER (Figure 2), while DLBCL was negative (Figure 3). We did not detect components of MALT-type lymphoma.

On the basis of the clinical pathological characteristics, a diagnosis of collision of gastric LELC with primary DLBCL was rendered. The patient was treated with a standard ECF (epirubicin, cis-platinum and floxuridine) chemotherapy. After chemotherapy, no signs of recurrence were detected during the first 6 months of follow-up with the exception of diarrhea.

**Discussion**

EBV can cause many types of carcinoma, including GC. EBV-associated GC includes two subtypes, including gastric

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**Table I.** Collision of EBV-associated gastric carcinomas and gastrointestinal lymphomas in the literature.

<table>
<thead>
<tr>
<th>Case (Ref.)</th>
<th>Gastric carcinoma</th>
<th>Gastrointestinal lymphoma</th>
<th>Patient’s chronic gastric</th>
<th>Relationship between multiple tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histologic type</td>
<td>EBER</td>
<td>Histologic type</td>
<td>EBER</td>
</tr>
<tr>
<td>1(2)</td>
<td>G-LELC</td>
<td>+</td>
<td>G-MALT</td>
<td>-</td>
</tr>
<tr>
<td>2(3)</td>
<td>G-LELC</td>
<td>+</td>
<td>RG-MALT</td>
<td>-</td>
</tr>
<tr>
<td>3(4)</td>
<td>G-LELC</td>
<td>+</td>
<td>J-MALT*</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>J-DLBCL</td>
<td>+</td>
</tr>
<tr>
<td>4(5)</td>
<td>GA</td>
<td>+</td>
<td>G- DLBCL</td>
<td>+</td>
</tr>
<tr>
<td>5(6)</td>
<td>GA</td>
<td>+</td>
<td>T-cell lymphoma</td>
<td>+</td>
</tr>
</tbody>
</table>

Ref: Reference list number; +: positive; -: negative; G: gastric; GA: gastric adenocarcinoma; J: jejuna; RG: remnant gastric; *MALT transform to DLBCL; #Reported two cases.

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![Figure 1. Hematoxylin-eosin staining showing gastric LELC with primary DLBCL. The tumor features of LELC (A) x100 and (B) x200 are shown. Features of DLBCL (C) x100 and (D) x200 can be seen.](image-url)
Figure 2. Micrographs demonstrating gastric LELC positive immunohistochemical staining for (A) CK1/CK3, (B) CD20, (C) CD3 and (D) CD38; (E) approximately 67% of the tumor cells were positive for Ki67; and (F) in situ hybridization for EBER was positive.

Figure 3. Micrographs demonstrating gastric primary DLBCL positive immunohistochemical staining for (A) CD20, (B) LCA/CD45, (E)CD10, (F) Bcl-6 and negative for (C) CD3, (D) Bcl-2, (G) Mum-1; (H) approximately 90% of the tumor cells were positive for Ki67; and (I) in situ hybridization for EBER was negative.
LELC and ordinary gastric adenocarcinoma (1). Non-Hodgkin lymphoma mainly includes B cell lymphoma (DLBCL and MALT) and very few T-cell lymphomas. Collision of EBV-associated GC with gastric non-Hodgkin lymphoma is extremely rare. According to the previous reports, five cases of EBV-associated GC with GL have been reported (2-6).

This report described a rare case of a patient suffering from two different tumors. One was in the proximal stomach, which consisted of many poorly differentiated carcinomas with a dense lymphocytes and plasma cells infiltrating. The second tumor was an ulcer type, which was located at the distal stomach. Tumor cells had formed many lymphoepithelial lesions and had invaded the submucosa and muscularis of the stomach. As these tumor cells were positive for CD10 and Bcl-6 but negative for Mum-1, it was identified as a primary DLBCL (7). As 90% of the tumor cells expressed Ki-67, it suggests that the cells were fast growing and so was diagnosed as a high-degree malignant lymphoma.

Most of the carcinoma cells of gastric LELC were positive for EBER, suggesting that the virus infection happened in the early stages of tumorigenesis. The infected, malignantly transformed cells formed the tumor after monoclonal proliferation. The lymphoma cells were negative for EBER, suggesting that the pathogenesis of DLBCL was independent from LELC. We could not however, exclude a relationship between the two tumors. Firstly, the two tumors were present simultaneously in the stomach and the infiltrating lymphocytes of LELC can continuously stimulate other tumors and lead to deteriorating (3). Secondly, infection by Helicobacter pylori (H. pylori) can cause GC and GL. H. pylori infection can cause chronic active gastritis, intestinal metaplasia, ulcers, GC, MALT and DLBCL (8). However, in this case, H. pylori was not detected, so we speculated that the infection of H. pylori had nothing to do with the emergence of the two malignancies. Thirdly, in the pathogenesis of gastric LELC, chronic persistent inflammation plays an important role (1, 4). Wong et al., reported that an environment with an active inflammation and immunosuppression contributed to the occurrence of EBV positive lymphomas which were promoted by an inflammatory or immunosuppressive microenvironment (9). In this report, the gastric mucosa of the patient also had chronic gastritis.

So far, the pathogenesis of the collision of multiple tumors is not clear. There may be many factors involved in its pathogenesis. Besides the infection of pathogenic microorganisms (EBV and H. pylori), many other risk factor may also be involved, such as genetic susceptibility and environmental factors. Genetic susceptibility may play an important role. For example, loss of chromosomes, gene insertion or mutation of chromosome are related with DLBCL (10) and human epidermal growth factor receptor 2 (EGFR2) abnormalities are associated with gastric cancer, breast cancer and other tumors (11, 12). Previous case reports have not shown any special genetic aberration accounting for the multiple malignancies. For future work, we would like to examine molecular genetic abnormalities existing in multiple malignancies and to study their detailed roles. Environmental factors, such as smoking, eating habits and drinking, may be involved in the pathogenic process (12, 13). Age may also play a role in the process of tumorigenesis, whilst most of the cases of multiple malignancies reported have happened in elderly people (14). This is consistent with our case which happened in a 65-year-old patient.

In conclusion, we report a rare case of collision of gastric LELC and DLBCL in one patient. It is unknown if infection by pathogenic microorganisms, population age, environmental pollution has contributed to the coexistence of multiple tumors in one patient, though it may happen more frequently than before. The pathogenesis of DLBCL was independent from LELC, but it may be triggered by the immune response caused by infection.

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References


