The Clinical Feature of Epstein-Barr Virus-Associated Gastric Carcinoma

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Introduction

The Epstein-Barr virus (EBV) is a ubiquitous human herpes virus. The association of EBV with human malignancies was originally found in African Burkitt's lymphoma and nasopharyngeal carcinoma, and is often found in B-cell lymphomas in immunocompromised individuals\(^1-3\). The presence of EBV DNA in gastric carcinoma was documented in 1990 using the polymerase chain reaction\(^4\). Recently, the use of in situ hybridization (ISH) for EBV-encoded small RNA1 (EBER-1), which is present in about ten million copies per EBV-infected cell, indicated that almost 10% of gastric carcinomas are EBER-1 positive\(^5-7\). EBV was clonally and specifically presented in an even distribution within EBV-associated gastric carcinoma cells, and a causal role in gastric carcinogenesis was suspected\(^8\). This review focuses on the clinical feature of EBV-associated gastric carcinoma and its carcinogenic background.

Endoscopic and Endosonographic Feature of EBV-Associated Gastric Carcinoma

In our study, EBER-1 was detected in 9.7% (12 of 124) of the gastric carcinoma lesions, and 10.3% (12 of 105) of the patients\(^9\). EBER-1 signals were specifically present within the gastric carcinoma cells and were absent in the surrounding lymphocytes. There were no significant differences in age or gender between the EBV-associated lesions and the EBV-negative lesions. The location and the histologic type of the lesions significantly differed between EBER-1-positive and EBER-1-negative lesions. Approximately 83% of the EBV-associated lesions were located in upper part of the stomach. Seventy-five percent (9 of 12) of the lesions of EBV-associated gastric carcinomas were of the diffuse type. And five of 8 (62.5%) of the gastric carcinoma with lymphoid stroma were EBER-1-positive.

From a clinical perspective, endoscopy is the most useful modality for the diagnosis of gastric carcinoma, and endoscopic ultrasonography and endoscopic treatment for early gastric carcinoma have been developed\(^10,11\). Endoscopically, EBV-associated early gastric carcinomas were mainly of the superficial depressed type. Furthermore, almost a half of the early EBV-associated lesions were accompanied by the formation of submucosal nodules of carcinoma with lymphoid stroma, resulting in characteristic submucosal tumor-like findings. Endoscopic ultrasonography revealed a hypo-echoic mass in the third layer (corresponding to submucosal layer), which reflected submucosal nodules\(^12\). These findings indicated that endoscopy and endoscopic ultrasonography are of great use for determination of EBV association with early gastric carcinoma.
EBV-Associated Gastric Carcinoma and Atrophic Gastritis

It is currently believed that, chronic atrophic gastritis and subsequent intestinal metaplasia are the lesions most closely linked to intestinal-type gastric carcinoma\(^{13}\). We have already reported EBV infection in non-carcinomatous gastric epithelium\(^{14}\). A study about histologic details of the background gastric mucosa surrounding EBV-associated gastric carcinoma was needed.

EBV-associated gastric carcinomas are mainly of the diffuse type in the gastric body. Ordinarily, these are believed to arise from the nonatrophic gastric body mucosa and barely related to chronic atrophic gastritis. However, in grading the background gastritis using the histologic variables of The Updated Sydney System, we found that EBER-1-positive carcinoma lesions were accompanied with mucosal atrophic changes as EBER-1-negative lesions\(^{15}\). Many lesions of both groups had normal to moderate neutrophil infiltration and mild to moderate mononuclear cell infiltration. Mild to moderate atrophy was common in both groups. Moderate to marked intestinal metaplasia was found in the background of many of EBER-1-positive lesions. EBV-associated lesions were mainly located in the gastric body. However, in many cases, the atrophic border had shifted from the antrum to the upper gastric body in the lesser curvature, and the gastric body mucosa had changed from the fundic gland to mucous or intestinal type glands, especially in the lesser curvature\(^{16}\). EBER-1-positive lesions were located in the atrophy side near the mucosal atrophic border.

The gastric mucosal atrophic border is at the front of the area in which the glandular structure changes, where the regular epithelial cell kinetics of the generative zone can be disrupted. This stagnation of epithelial cell kinetics may result in some condition allowing for survival of EBV-immortalized gastric epithelial cells.

EBV and Malignant Phenotypes of Gastric Epithelial Cells

EBV immortalizes B-lymphocytes in vitro. However, in vitro, in comparison to B-lymphocytes, infection of epithelial cells is more difficult. Recently, Yoshiyama, et al. developed direct EBV infection system for gastric carcinoma cell lines using recombinant EBV\(^{17}\). Their results indicate that EBV infects epithelial cells through a receptor other than CD21. Furthermore, Nishikawa, et al. attempted to infect non-carcinomatous gastric primary culture cells with EBV. The EBV-infected clones had higher proliferation rates and at least twice the cell saturation density in 10% serum of non-infected clones, and the malignant phenotype was confirmed by colony formation in soft agar\(^{18}\).

Conclusions

Clinically, the endoscopic images of EBV-associated gastric carcinomas reflect the histologic characteristics of diffuse-type carcinoma with lymphoid infiltration. Superficial depressed-type with submucosal wall thickening, early gastric carcinoma, and ulcerated without definite limits, advanced gastric carcinomas, of diffuse-type histology with lymphoid infiltration in the upper part of the stomach are suspicious for EBV-associated lesions.

EBV-associated gastric carcinomas had arisen in the chronic atrophic gastritis background. Many EBER-1 positive lesions were located near the mucosal atrophic border. In many of EBV-associated malignancies, co-factors such as malaria in Burkitt's lymphoma are important in the oncogenic process\(^{19}\). Accordingly, chronic atrophic gastritis may be considered to be a co-factor in EBV-associated gastric carcinogenesis. Helicobacter pylori (H. pylori) is believed to cause atrophic gastritis. Further study for possible interaction between EBV and H. pylori is appears to be warranted.

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