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Editorial

Clinical Relevance of *Helicobacter pylori* Coinfection in Ebstein-Barr Virus-Associated Gastric Carcinoma

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See "Clinical Significance of Epstein-Barr Virus and *Helicobacter pylori* Infection in Gastric Carcinoma" by Jin Hee Noh, et al. on page 69, Vol. 17, No. 1, 2023

Epstein-Barr virus (EBV), a ubiquitous human herpes virus with oncogenic activity, is a well-known risk factor for developing gastric carcinoma (GC). EBV infects over 90% of the adult population, mostly with a lifelong asymptomatic carrier state. Although how EBV infects gastric epithelial cells still remained unclear, cell-to-cell contact-mediated EBV transmission from virus-infected mucosal B lymphocytes with EBV reactivation is a convincing hypothesis.[1] EBV-associated GC (EBVaGC) is characterized by monoclonal proliferation of EBV-infected cells, indicating that EBV infection occurs in an early stage of carcinogenesis.[2] In 2014, The Cancer Genome Atlas Network defined EBVaGC as one of the four subtypes of GC, based on its quite different molecular profiles from those of conventional GC.[3] EBVaGCs exhibit a high frequency of DNA hypermethylation, and 80% have PIK3CA mutations, as well as amplifications of the JAK2, programmed death ligands 1 and 2 genes, while TP53 defects and microsatellite instability are unusual.[3] EBVaGCs thus show distinct clinical features with a male predominance, younger age, a high frequency in postsurgical gastric stump, proximal location, and a better prognosis.[4] Histologically, EBVaGC is particularly associated with GC with lymphoid stroma (GCLS), a rare histological variant, accounting for 1% to 4% of all GCs, and over 80% of GCLSs are associated with EBV infection as compared to 8.7% (range, 1.3% to 20.1%) of all GCs.[5] GCLS is characterized by poorly developed tubular structures associated with prominent lymphoid infiltrate in a non-desmoplastic stroma. Increased tumor-infiltrating lymphocytes, which reflects a host immune response to tumor cells, is thought to be associated with a better prognosis in GCLS.[5]

Chronic inflammation is known for a risk factor for EBVaGC as it sets the optimal conditions necessary for gastric carcinogenesis.[6] *Helicobacter pylori* (HP) is the greatest risk factor for GC, and HP-associated atrophic gastritis could serve as a lesion which enables cell-to-cell contact between infiltrated EBV-carrying lymphocytes and gastric epithelial cells.[6] A previous study demonstrated that EBV and HP coinfection synergistically induced severe inflammation in gastric tissue and this might increase the risk of developing GC.[7] However, it is unclear whether the carcinogenesis results from an additional inflammatory response with increased tissue damage by EBV and HP coinfection or is based on gene products interaction between EBV and HP.[8] Since there have been also some studies which do not show any association between the two pathogens, further research is necessary to determine the clinical importance of EBV and HP coinfection in GC.

In this issue of *Gut and Liver*, Noh *et al.*[9] retrospectively enrolled 956 patients who had undergone surgery for GC between September 2014 and August 2015, and they aimed to investigate the effect of EBV and HP coinfection on the clinicopathologic features and prognosis in GC, as well as to evaluate the role of EBV infection in non-GCLS. In results, EBV and HP coinfection was significantly associated with male sex, proximal location, GCLS morphology, and equivocal p53 expression, although it did not show differences in overall survival (OS). In multivariate analysis, EBV infection alone (hazard ratio, 0.362; 95% confidence

interval, 0.131 to 0.996; p=0.049) and lower third location (hazard ratio, 0.624; 95% confidence interval, 0.413 to 0.943; p=0.025) were independent factors correlated with a better OS. In non-GCLS patients, OS was not significantly different according to the infection status of EBV. The authors concluded that EBV infection, regardless of HP infection affected the clinicopathologic outcomes, while EBV positivity did not show significant survival difference in non-GCLS.

According to the present study, HP coinfection did not seem to determine the clinicopathologic characteristics in EBVaGC, since EBV+/HP+ GC followed the same features as EBVaGC. In Supplementary Table 1,[9] the clinicopathologic features of the EBV+/HP+ group were not different from EBV+/HP– group, while demonstrating a significant distinction between EBV+/HP+ and EBV– patients. This suggests that EBV regardless of HP infection is a key factor for determining the clinical phenotype in GC. EBVaGC can be divided into three histologic subtypes based on the host cellular immune response:[10] (1) lymphoepithelioma-like carcinoma (LELC); (2) carcinoma with Crohn's disease-like lymphoid reaction (CLR); and (3) conventional adenocarcinoma. As CLR demonstrates similar features to typical GCLS (LELC), it has been suggested as an expanded spectrum of GCLS.[10] Prognosis of EBVaGC depends on the patient's inflammatory response, which means LELC and CLR morphology has a better outcome compared with conventional adenocarcinoma.[10] Since EBVaGC and GCLS significantly overlap in clinical features, whether EBV infection itself is associated with an improved outcome is unclear. In the present study, GCLS morphology seems to be more important for improved OS than EBV infection, since the EBV infection status was not correlated with survival outcome in non-GCLS while EBV infection was a significant predictive factor for OS in all GCs. Regarding study limitations, authors only evaluated the current HP infection status in surgically resected gastric tissue. Since HP+ GC usually means HP-associated GC which includes past infection, the results would be more reliable if the study could assess both current and past infection for HP or evaluate atrophic gastritis/intestinal metaplasia with serum pepsinogen as an indirect indicator for HP status. Additionally, equivocal p53 expression was prevalent in EBVaGC, however, the interpretation for its clinical importance is unclear.

In summary, EBVaGC has specific tumorigenic profiles with distinct clinical features and prognoses. Although EBV and HP coinfection might synergistically increase the risk of developing GC, EBV infection seems to be an important factor for determining the clinical phenotype in EBV+/HP+ GC. Histologically, EBVaGC is highly associated with GCLS morphology, which is known to have better clinical outcomes. Recent advances in EBVaGC research improved the current knowledge for its unique molecular and clinical features, though we are in the early stages of understanding the pathogenesis of EBVaGC. EBV develops a distinct subtype of GC, and this means that EBV can serve as a biomarker for the management of GC. Further research and challenges in EBVaGC will play a vital role towards increased precision in the treatment of GC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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