



Expanding Horizons: Unveiling the Clinical Features of Early Gastric Lymphoepithelioma-Like Carcinoma and the Potential of Endoscopic Resection as Curative Therapy

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See “Clinicopathological Characteristics and Lymph Node Metastasis Rates in Early Gastric Lymphoepithelioma-Like Carcinoma: Implications for Endoscopic Resection” by Tae-Se Kim, et al. on page 807, Vol. 18, No. 5, 2024

Gastric lymphoepithelioma-like carcinoma (LELC) is a rare form of gastric cancer with distinct clinicopathological features, first systematically reported by Watanabe *et al.* in 1976.¹ Gastric LELC is also referred to as gastric carcinoma with lymphoid stroma, which is characterized by gastric carcinoma composed of small nests of cancer cells with abundant, diffuse lymphocyte infiltration in the stroma that resembles nasopharyngeal carcinoma.² They are known to be strongly associated with either Epstein-Barr virus (EBV) infection and microsatellite instability, which are mutually exclusive features.³ The prognosis of LELC is considered favorable compared to other types of gastric cancer,¹ but due to its rarity and the limited data available, its clinical features and optimal treatment strategies are not well understood.

In the current issue of *Gut and Liver*, Kim *et al.*⁴ provide valuable insights into the unique features of early gastric LELC by comparing it to differentiated-type early gastric cancer (EGC). This rare subtype of gastric cancer was analyzed in terms of clinicopathological characteristics and lymph node metastasis (LNM) rates, particularly to assess the feasibility of endoscopic submucosal dissection (ESD) as a curative approach.

Notably, LELC patients tended to be younger and more frequently had tumors located in the proximal stomach. Among the LELC patients assessed for EBV status, 94.6% (107/113) were EBV positive. Despite a higher prevalence of deep submucosal invasion (SM 2 and 3) in LELC compared to differentiated-type EGC (86.2% vs 29.8%), the overall rate of lymphatic invasion was lower in LELC (6.0% vs 16.2%). Particularly in the cases with deep submuco-

sal invasion, LELC exhibited a lower frequency of both lymphatic invasion (6.0% vs 40.2%) and LNM (10.0% vs 19.4%) compared to differentiated-type EGCs. Furthermore, it is notable that the rate of LNM in mucosal or shallow submucosal invasive LELC was 0% (0/16).

In a previous Korean case-control study involving 70 patients with early gastric LELC, with EBV positivity confirmed in 81.4% of cases, similar results were observed.⁵ While submucosal invasion was more frequent in the early LELC group (77.1% vs 44.4%, $p < 0.001$), this group exhibited a lower LNM rate (4.0% vs 19.4%, $p = 0.007$) compared to the early non-LELC group, even among patients with SM3 invasion (5.3% vs 24.5%, $p = 0.007$). These findings collectively suggest that early gastric LELC behaves differently from other forms of gastric cancer, potentially due to its association with EBV infection, which was present in most of the evaluated LELC cases.

Notably, in Asia, over 80% of gastric LELCs are associated with EBV infection, highlighting its close association to the carcinogenesis process.⁵ On the other hand, EBV positive cases are less frequent in Western countries (7% to 39%).³ It is believed that EBV is involved in the early stage of cancer development through various molecular pathways. Abnormal mutations and amplification of the host genome, along with interactions between the EBV genome and the host genome, promote carcinogenesis. The molecular profile of EBV-associated gastric cancer is characterized by EBV-induced DNA hypermethylation, frequent mutations in key signaling pathways, and the overexpression of specific oncogenic proteins.⁶ Clinically,



EBV-associated gastric cancer exhibits a lower frequency of LNM and a more favorable prognosis compared to EBV-negative gastric cancer.^{7,8} The low incidence of lymphovascular invasion and LNM might be linked to the strong immune response associated with EBV positivity in many cases, suggesting that LELC may be less aggressive in spreading via lymphatic pathways. However, this has not been definitively proven.

There was an interesting study that analyzed the clinicopathological features and prognoses of EBV-associated gastric cancer based on the pattern and degree of host cellular immune response, classifying the cancers into three histologic subtypes: LELC, Crohn's disease-like lymphocytic reaction, and moderate-poorly differentiated conventional adenocarcinoma.⁸ Notably, patients with LELC demonstrated significantly better prognosis, with longer overall survival and disease-free survival compared to the other subtypes. Moreover, EBV infection seems to serve as an independent predictor of survival in patients with LELC, and reports indicate that EBV-negative LELC cases tend to have relatively poor prognosis.⁹ However, data on EBV-negative LELC are very limited, emphasizing the need for further research on the role of EBV in LNM rates and prognosis of LELC. Overall, these findings suggest that the host's inflammatory response to EBV may be a factor influencing the clinical characteristics and prognosis of gastric LELC.

The low LNM rate in mucosal or shallow submucosal invasive LELC supports the consideration of ESD as a curative treatment option for these patients. This is particularly relevant given the less invasive nature and reduced recovery time associated with ESD compared to traditional surgical methods. There are several guidelines covering ESD indications, and as long-term data accumulates, the indications are gradually expanding.¹⁰ In this context, the present study, which presents the clinical characteristics and potential applicability of ESD for the rare entity of early LELC, is of significant value.

This study has some limitations that must be acknowledged, and the results should be cautiously interpreted. The exclusion of patients who underwent ESD introduces potential selection bias, limiting the generalizability of the findings. Despite being one of the largest studies on early LELC, the sample size, particularly for superficial cases, remains too small (only 16 patients) to draw definitive conclusions. Additionally, this study does not include data on the clinical efficacy or long-term follow-up of early LELC patients undergoing ESD.

In summary, the study's conclusions advocate for the consideration of ESD as a curative approach for early LELC confined to the mucosa or shallow submucosa, given the

negligible LNM rate in these cases. This recommendation could significantly impact clinical practice, offering a less invasive alternative to traditional gastrectomy, with the potential for improved patient outcomes and reduced healthcare costs. The potential for ESD to become a standard treatment for early LELC may depend on future studies investigating long-term outcomes, which will hopefully address the current gaps and solidify its role in managing this rare and distinct subtype of gastric cancer.

CONFLICTS OF INTEREST

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

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REFERENCES

1. Watanabe H, Enjoji M, Imai T. Gastric carcinoma with lymphoid stroma: its morphologic characteristics and prognostic correlations. *Cancer* 1976;38:232-243.
2. Nakamura S, Ueki T, Yao T, Ueyama T, Tsuneyoshi M. Epstein-Barr virus in gastric carcinoma with lymphoid stroma. Special reference to its detection by the polymerase chain reaction and in situ hybridization in 99 tumors, including a morphologic analysis. *Cancer* 1994;73:2239-2249.
3. Hissong E, Ramrattan G, Zhang P, et al. Gastric carcinomas with lymphoid stroma: an evaluation of the histopathologic and molecular features. *Am J Surg Pathol* 2018;42:453-462.
4. Kim TS, An JY, Choi MG, et al. Clinicopathological characteristics and lymph node metastasis rates in early gastric lymphoepithelioma-like carcinoma: implications for endoscopic resection. *Gut Liver* 2024;18:807-813.
5. Shin DH, Kim GH, Lee BE, et al. Clinicopathologic features of early gastric carcinoma with lymphoid stroma and feasibility of endoscopic submucosal dissection. *Surg Endosc* 2017;31:4156-4164.
6. Yang J, Liu Z, Zeng B, Hu G, Gan R. Epstein-Barr virus-associated gastric cancer: a distinct subtype. *Cancer Lett* 2020;495:191-199.
7. Ramos MFKP, Pereira MA, Dias AR, et al. Lymphoepithelioma-like gastric carcinoma: clinicopathological characteristics and infection status. *J Surg Res* 2017;210:159-168.
8. Song HJ, Srivastava A, Lee J, et al. Host inflammatory response predicts survival of patients with Epstein-Barr virus-

- associated gastric carcinoma. *Gastroenterology* 2010;139:84-92.
9. Min BH, Tae CH, Ahn SM, et al. Epstein-Barr virus infection serves as an independent predictor of survival in patients with lymphoepithelioma-like gastric carcinoma. *Gastric Cancer* 2016;19:852-859.
 10. Park CH, Yang DH, Kim JW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. *Clin Endosc* 2020;53:142-166.