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Lymphoepithelioma-like carcinoma: A distinct type of gastric cancer

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ABSTRACT

Background: Lymphoepithelioma-like carcinoma (LELC) is a rare type of gastric carcinoma and has histologic features of intense lymphocytic infiltration. In this study, we attempted to analyze the clinicopathologic characteristics and survival outcome of patients with LELC compared with those with non-lymphoepithelioma-like carcinoma (NLELC).

Methods: We studied 4282 patients who underwent gastrectomies to treat gastric cancer at the Department of Surgery of the Samsung Medical Center in Seoul, between January 2008 and December 2010. The clinicopathologic features and clinical outcomes of patients with LELC ($n = 46$) were compared with those with NLELC ($n = 4236$). *In situ* hybridization for Epstein–Barr virus (EBV) positivity was performed on the tissue of patients with LELC ($n = 46$) and NLELC ($n = 1247$).

Results: The patients with LELC are male predominant and had more upper locations, more indeterminate Lauren classifications, lower T stages, less lymphatic invasion, and more positive EBV *in situ* hybridization compared with those of the NLELC group (80.4% versus 6.5%). Age, histologic type, Lauren type, the location of the tumor, the depth of the invasion, lymph node metastasis, and venous invasion were independent prognostic factors; however, the LELC type itself was not predictive of outcome. The 5-y survival rate of the LELC group (97.7%) was better than that of the NLELC group (89.4%); however, this difference was not statistically significant ($P = 0.127$).

Conclusions: The results of our study suggest that LELC is a less advanced disease than NLELC in terms of depth of invasion and lymphatic invasion at diagnosis. However, our study does not examine LELC as an independent prognostic factor of gastric cancer. Further studies are needed to explore its associations with EBV and a distinct pathway of carcinogenesis from NLELC.

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1. Introduction

Lymphoepithelioma-like carcinoma (LELC) of gastric cancer is a rare disease and has histologic features of intense lymphocytic infiltration. Watanabe *et al.* [1] described a specific type of lymphocyte-rich gastric cancer, termed gastric carcinoma with lymphoid stroma, which has a better prognosis than other gastric carcinomas. Burke *et al.* [2] first discussed the “lymphoepithelial carcinoma” of the stomach that was associated with Epstein–Barr virus (EBV). Then, in 1991, two studies from the same group described undifferentiated gastric carcinoma associated with EBV. [3,4]. In both articles, the authors clearly refer to the cancers as being “LELCs” because they resemble nasopharyngeal carcinomas, both histologically and virologically, in that they are associated with EBV. Gastric LELC constitutes approximately 1%–4% of all gastric carcinomas [5,6]. LELC of the stomach is known to be associated with better prognosis, and the previous results of clinicopathologic features of LELC in comparison with non-lymphoepithelioma-like carcinoma (NLELC) tumors are shown in Table 1 [1,7–9]. However, data on gastric LELC were rarely reported in small numbers, and standardized criteria for histologic diagnoses of LELC are lacking [10]. In this study, we attempted to clarify clinicopathologic characteristics and the survival outcome of LELC compared with NLELC to provide more sensible clinical guidance.

2. Patients and methods

2.1. Patients

We studied a consecutive series of 4282 patients who had undergone gastrectomy to cure gastric cancer at the Department of Surgery, Samsung Medical Center in Seoul, from January 2008–December 2010. There were 46 patients with LELC and 4236 with NLELC, and the mean follow-up period was 35.8 ± 13.8 mo and median follow-up period of LELC patients was 38.0 ± 12.27 mo. The inclusion criteria for patient selection was as follows: (1) be in pathologic stages IA–III, according to the 2010 American Joint Committee on Cancer staging system [11], (2) undergo curative resection with D2 lymph node dissection, according to the 2010 Japanese gastric cancer treatment guidelines [12], (3) complete clinical information

including treatment history and outcomes available for analysis; and (4) make available a gastric cancer tissue specimen for pathologic analysis. In the survival analysis, we excluded cases that did not receive curative resection. A diagnosis of LELC was determined by (1) a well-defined tumor margin, (2) dense lymphocytic infiltration of a degree whereby the number of tumors infiltrating the lymphocytes was greater than the tumor cells throughout the tumor, which means the presence of more lymphocytes than carcinoma cells in the deep level in infiltrating borders of the tumor. In addition, lymphocytic infiltration does not form a distinct or well-defined border, but an intermingled border with tumor cells, (3) indistinct cytoplasmic borders and a syncytial growth pattern with poorly formed glandular structures, and (4) no desmoplasia (Fig. 1) [7]. Patients were evaluated with respect to age, gender, multiplicity, tumor location, tumor size, Lauren type, histologic type, depth of invasion, lymph node metastasis, TNM stage (according to the seventh edition of American Joint Committee on Cancer), lymphatic invasion, venous invasion, perineural invasion, and EBV positivity. Tumor size refers to the maximal tumor diameter reported on the gross assessment of the tumor on the original pathology report. Surgical procedures are defined as curative when no grossly visible tumor tissue remains after resection, and resection margins were histologically normal (R0 resection). Any procedure that does not satisfy these conditions (R1 or R2 resection) was defined as non-curative. All patients received regular follow-up with physical examinations, laboratory tests, chest x-rays, computed tomography, ultrasonography, and endoscopy. Adjuvant chemotherapy was usually recommended, except for patients with stage T1N0 cancers after surgery. In LELC group, there were twelve patients with stage IA. Eight (seven with T2N0 and one with T1N1) of twenty three patients with stage IB, six of eight patients with stage II, and two of three patients with stage III have received adjuvant chemotherapy. Two patients with stage II and one patient with stage III refused adjuvant chemotherapy. Patient survival was evaluated according to the census register. The study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea.

2.2. EBV-encoded RNA in situ hybridization

Tissue microarray blocks were used for EBV-encoded RNA in situ hybridization. Three micrometer-thick sections were cut

Table 1 – Clinicopathologic features of LELC of the stomach in comparison with non-lymphoepithelioma-like carcinoma tumors.

Investigators	Reference number	Year of publication	Number of patients with LELC	Total number of patients	Country	Sex	Age	Tumor location	Depth of invasion	LN metastasis	Survival rate
Watanabe <i>et al.</i>	1	1976	42	1041	Japan	NS	NS	—	—	—	Higher
Song <i>et al.</i> *	7	2010	53	123	South Korea	NS	NS	NS	More in T2	Lower	Higher
Tak <i>et al.</i>	8	2013	17	36	South Korea	NS	NS	NS	NS	More in N1	NS
Cheng <i>et al.</i> †	9	2014	10	702	China	NS	NS	NS	NS	—	Higher

LN = lymph node; NS = not significant.

* In patients with EBV-associated gastric carcinoma and the survival outcome of LELC was compared with that of conventional adenocarcinoma.

† In patients with EBV-associated gastric carcinoma.

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