Features of Gastric Carcinoma With Lymphoid Stroma Associated With Epstein-Barr Virus

Hyun Lim,[*,a] Young Soo Park,[‡,a] Jeong Hoon Lee,[*] Da Hye Son,[‡] Ji Yong Ahn,[*] Kwi-Sook Choi,[*] Do Hoon Kim,[*] Kee Don Choi,[*] Ho June Song,[*] Gin Hyug Lee,[*] Hwoon-Yong Jung,[*] Jin-Ho Kim,[*] Jeong Hwan Yook,[§] and Byung Sik Kim[§]

*Department of Gastroenterology, ‡Department of Pathology, §Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

BACKGROUND & AIMS: **Gastric carcinoma with lymphoid stroma (GCLS) is a distinct histologic subtype of gastric cancer that is characterized by undifferentiated carcinoma mixed with prominent lymphoid infiltration. More than 80% of GCLS cases are associated with Epstein–Barr virus (EBV) infection, but it is unclear if the virus affects disease progression. We investigated how EBV infection affects the clinical and pathologic features of GCLS, as well as patients' outcomes.**

METHODS: **We performed a retrospective analysis of 274 patients (mean age, 56.8 y; 85.4% male) diagnosed with GCLS, based on pathology findings, from March 1998 through December 2012 at the Asan Medical Center in Seoul, South Korea. Their data were compared with those from 822 age- and sex-matched patients who underwent resection for gastric adenocarcinoma. EBV was detected in tumor samples by in situ hybridization.**

RESULTS: **Of the 274 patients with GCLS, 236 had EBV-positive tumors (86.1%) and 38 had EBV-negative tumors (13.9%). EBV-positive GCLS was more prevalent than EBV-negative GCLS in younger patients, tended to be located proximally, and was more frequently of an early stage macroscopic type. The 10-year, disease-specific rates of survival were 89.1% for patients with EBV-positive GCLS and 66.9% for patients with EBV-negative GCLS ($P = .009$). Patients with EBV-negative GCLS had clinical and pathologic features and survival times similar to those of patients with conventional adenocarcinoma. By multivariate analysis, longer survival time was associated with EBV-positive tumors ($P = .007$), younger patient age ($P = .002$), smaller tumor size ($P = .046$), lower stage (based on American Joint Committee on Cancer classification; $P < .001$), and lack of lymphovascular invasion ($P = .012$). The proportion of undifferentiated tumor cells was not associated significantly with patient survival time.**

CONCLUSIONS: **Clinical and pathologic features of GCLS differ based on EBV infection status. EBV-negative GCLS is similar to conventional adenocarcinoma, and patients have similar survival times. EBV status may be more important than the proportion of undifferentiated tumor cells in the diagnosis of GCLS and management of patients.**

Keywords: Stomach Cancer; Prognostic Factors; Viral Infection; Carcinogenesis.

See editorial on page 1745.

Despite its decreasing incidence throughout the 20th century, gastric cancer remains the fourth most commonly diagnosed cancer and the third-leading cause of cancer-related mortality worldwide.[1,2] Although chronic *Helicobacter pylori* infection is the primary cause of gastric cancer, a number of other environmental and lifestyle factors also play important roles in gastric carcinogenesis.[3]

Epstein–Barr virus (EBV) is a ubiquitous human herpes virus with oncogenic activity and is present in the tumor cells of approximately 9% of gastric cancer patients.[4,5] EBV-associated gastric cancer is more predominant in men, tends to be located proximally, is often a diffuse histologic subtype, and shows a lower frequency of lymph node metastasis than conventional adenocarcinoma,

[a]Authors share co-first authorship.

Abbreviations used in this paper: AJCC, American Joint Committee on Cancer; EBV, Epstein–Barr virus; GCLS, gastric carcinoma with lymphoid stroma; HR, hazard ratio.

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although some controversies remain.[4,5] Gastric carcinoma with lymphoid stroma (GCLS), which also is known as *gastric lymphoepithelioma–like carcinoma* and is distinguished by undifferentiated carcinoma mixed with prominent lymphoid infiltration, constitutes the core of EBV-associated gastric cancer.[6,7] The incidence of GCLS is 1% to 4% of all gastric cancer cases, and more than 80% of GCLS cases are associated with EBV infection.[8–10] It now widely is accepted that GCLS shows a significantly better prognosis than conventional adenocarcinoma.[11] However, data on GCLS have been reported in only a limited number of small series to date, and the histologic diagnosis of GCLS has not been defined clearly. Furthermore, there have been few studies on the clinicopathologic features and prognosis of GCLS according to EBV infection.[8,12]

In our current study, we evaluated the role of EBV infection in GCLS from both a pathologic and clinical perspective, the distribution of EBV infection in tumoral and stromal areas, and the differences in clinical features in accordance with EBV infection status. In addition, we compared these results with those of conventional gastric adenocarcinomas (with no GCLS morphology) and identified the prognostic factors related to survival outcomes in GCLS patients.

Methods

Study Population

Between March 1998 and December 2012, there were 16,398 patients with gastric cancer who underwent surgical resection at our institution. Of these patients, we retrospectively reviewed patients who met the following inclusion criteria: (1) pathologically confirmed GCLS; (2) complete clinical information available for further analysis, including treatment history and outcomes; and (3) gastric cancer tissue specimens available for EBV analysis. To compare these cases with conventional gastric adenocarcinomas (with no GCLS morphology), age- and sex-matched patients (patient:control ratio, 1:3; age-matching tolerance, $\pm$1 y) who underwent surgical resection for conventional gastric adenocarcinoma (with no GCLS morphology) during the same study period also were evaluated to serve as controls. This study was approved by the institutional review board of the Asan Medical Center (2013-1053).

Clinicopathologic Data

Clinical data, including age, sex, therapeutic modalities, and treatment outcomes, were obtained by medical chart review and telephone interview. Histopathologic data, including macroscopic type, tumor location, number of tumors, tumor size, tumor depth, lymph node metastasis, TNM stage (7th American Joint Committee on Cancer [AJCC]),[13] lymphovascular invasion, and perineural invasion, were collected after reviewing histology slides and pathology reports. For GCLS patients, the proportion of undifferentiated areas in the tumor and pushing border zones additionally were reviewed.

GCLS was defined according to the 2010 World Health Organization classification, as follows: poorly or undifferentiated tumor with prominent lymphoid infiltration.[14] Borrmann's classification was used to categorize the macroscopic tumor type: superficial (early gastric cancer); type 1 (polypoid tumor); type 2 (ulcerative tumor with sharp demarcated margins); type 3 (ulcerative tumor infiltrating into the surrounding gastric wall); or type 4 (diffuse infiltrated tumor).[15] Tumors demonstrating a smooth demarcation with a rounded infiltrative border was classified as having a pushing border configuration. Patients were staged according to the AJCC TNM staging system.[13] All histologic slides were reviewed by 2 gastrointestinal pathologists (Y.S.P. and D.H.S.).

Epstein–Barr Virus–Encoded RNA Chromogenic In Situ Hybridization

The presence of EBV in the cancer cells was assessed using EBV chromogenic in situ hybridization on an

Table 1. Comparison of Patient Characteristics Between GCLS and Control Group

	GCLS (n = 274)	Control (n = 822)	*P* value
Age, mean (range), *y*	56.8 (26–80)	56.8 (26–80)	-
Sex, male, n (%)	234 (85.4)	702 (85.4)	-
Macroscopic type, n (%)			<.001
Superficial type	113 (41.2)	456 (55.4)	
Borrmann type 1	6 (2.2)	7 (0.9)	
Borrmann type 2	55 (20.1)	81 (9.9)	
Borrmann type 3	98 (35.8)	262 (31.9)	
Borrmann type 4	2 (0.7)	16 (1.9)	
Location of tumor, n (%)			<.001
Upper third	52 (19.0)	67 (8.2)	
Middle third	171 (62.4)	307 (37.3)	
Lower third	51 (18.6)	448 (54.5)	
Lesions, n (%)			.001
Single	242 (88.3)	785 (95.5)	
Multiple	32 (11.7)	37 (4.5)	
Tumor size, mean (IQR), *cm*	3.6 (2.5–5.2)	3.8 (2.5–5.7)	.455
Pathologic T stage, n (%)			.029[a]
T1	113 (41.2)	444 (54.0)	
T2	64 (23.4)	96 (11.7)	
T3 + T4	97 (35.4)	282 (34.3)	
Pathologic N stage, n (%)			.174[a]
N0	180 (65.7)	524 (63.7)	
N1	46 (16.8)	119 (14.5)	
N2	30 (10.9)	98 (11.9)	
N3	18 (6.6)	81 (9.9)	
AJCC stage, n (%)			.477[a]
I	152 (55.5)	476 (57.9)	
II	83 (30.3)	177 (21.5)	
III + IV	39 (14.2)	169 (20.6)	
Lymphovascular invasion, n (%)	53 (19.3)	224 (27.3)	.009
Perineural invasion, n (%)	47 (17.2)	159 (19.3)	.422
Adjuvant chemotherapy, n (%)	102 (37.2)	325 (39.5)	.497

IQR, interquartile range.
[a]Linear-by-linear association chi-square test.