FREQUENCY OF EPSTEIN BARR VIRUS POSITIVITY IN GASTRIC CANCER AND ADJACENT NON-TUMORAL EPITHELIUM

Mide Kanseri ve Komşu Non-Tümoral Epitelde Epstein Barr Virüsü Pozitifliğinin Sıklığı

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ABSTRACT

Objective: Epstein-Barr virüs (EBV) -associated gastric cancer is one of four molecular subtypes defined by the Cancer Genome Atlas Program. Epstein-Barr virus -associated gastric cancer incidence has ethnic and geographical differences. The aims of the present study were to investigate the frequency of EBV in gastric cancer tissues and adjacent non-tumoral epithelium.

Material and Methods: EBV positivity was assessed by chromogenic EBER-ISH in tumor tissues of 101 patients who were diagnosed with gastric carcinoma and underwent gastrectomy in our center between January 2008 and August 2023. The link between EBV incidence in gastric cancer, survival and clinicopathological prognostic factors was statistically assessed.

Results: EBV was positive in tumor tissue in 6 of 101 (5.9%) cases. In addition, positive staining was detected in intestinal metaplasia areas adjacent to the tumor in 10 cases (9.9%) and in normal gastric mucosa adjacent to the tumor in 13 cases (12.9%). All 6 cases with EBV- associated gastric cancer were male, 4 had diffuse histological type and 3 were histological grade 3, 4 had lymph node metastases and 2 had distant metastases. No statistically significant correlation was found between EBER positivity and clinicopathological prognostic factors, except for male gender (p=0.021). There was no statistical correlation between EBV positivity and survival.

Conclusion: The frequency of EBV- associated gastric cancer was 5.9% in our center. EBV positivity is also present in inflammatory cells, intestinal metaplasia and normal tissues adjacent to gastric carcinoma tissue.

Keywords: *Gastric Carcinoma; EBV; EBER-ISH; Survey*

ÖZET

Amaç: Epstein-Barr virüsüyle (EBV) ilişkili mide kanseri, Kanser Genom Atlası Programı tarafından tanımlanan dört moleküler alt tipten biridir. Epstein-Barr virüsüyle ilişkili mide kanseri insidansı etnik ve coğrafi farklılıklar gösterir. Bu çalışmanın amacı mide kanseri dokularında ve bitişik tümör dışı epitelde EBV sıklığını araştırmaktır.

Gereç ve Yöntemler: EBV pozitifliği, Ocak 2008 ile Ağustos 2023 arasında merkezimizde mide karsinomu tanısı konulan ve gastrektomi geçiren 101 hastanın tümör dokularında kromojenik EBER-ISH ile değerlendirildi. Mide kanserinde EBV insidansı, sağ kalım ve klinikopatolojik prognostik faktörler arasındaki bağlantı istatistiksel olarak değerlendirildi.

Bulgular: EBV, 101 vakanın 6'sında (%5,9) tümör dokusunda pozitifti. Ek olarak, 10 vakada (%9,9) tümöre bitişik intestinal metaplazi alanlarında ve 13 vakada (%12,9) tümöre bitişik normal gastrik mukozada pozitif boyanma tespit edildi. EBV ile ilişkili gastrik kanserli 6 vakanın hepsi erkekti, 4'ü diffüz histolojik tipteydi ve 3'ü histolojik derece 3'tü, 4'ünde lenf nodu metastazı ve 2'sinde uzak metastaz vardı. Erkek cinsiyeti dışında (p= 0,021), EBER pozitifliği ile klinikopatolojik prognostik faktörler arasında istatistiksel olarak anlamlı korelasyon bulunmadı. EBV pozitifliği ile sağkalım arasında istatistiksel olarak anlamlı korelasyon bulunamadı.

Sonuç: Merkezimizde EBV ile ilişkili gastrik kanser sıklığı %5,9'dur. EBV pozitifliği ayrıca inflamatuar hücrelerde, intestinal metaplazide ve gastrik karsinom dokusuna bitişik normal dokularda da mevcuttur.

Anahtar Kelimeler: *Gastrik Karsinom; EBV; EBER-ISH; Sağkalım*

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INTRODUCTION

Gastric cancer is the fifth most common cancer globally and is in fifth place for cancer-linked deaths (1). The Epstein-Barr virus (EBV) is an oncovirus with a role in the etiology of some lymphomas and nasopharynx carcinoma clearly revealed, led by Hodgkin lymphoma and Burkitt lymphoma (1). EBV is defined as a subgroup in patients with gastric cancer. This subgroup was shown to have different pathological features and its own specific genomic disorder compared to other gastric cancers (2,3). Additionally, it is associated with good prognosis. The mean survival in EBV-positive gastric cancers is 8.5 years, while it is reported to be 5.3 years in EBV-negative gastric cancers (4). Significant correlation were reported from EBV-positivity with PD-L1+ expression and increased tumor infiltrating lymphocyte (5). Currently EBV-associated gastric cancers are accepted as a specific molecular subtype of gastric cancers (6). The Cancer Genome Atlas Program divides gastric cancers into 4 molecular subgroups of EBV-positive (9%), microsatellite unstable (22%), genomic stable (20%) and chromosomal unstable (50%) (1). In gastric cancer patients, generally observed to have short survival and high mortality, detection of EBV-positive and microsatellite unstable groups is very important as these groups have the ability to respond to immunotherapy. The gold standard diagnostic method for determination of EBV positivity in gastric cancers is the EBV-encoded small RNA-in situ hybridization (EBER-ISH) method in tumor tissue (7). EBER-ISH is superior to PCR in ensuring differentiation of EBV-positive tumor cells and in-tumor EBV-positive inflammatory cells. The incidence of EBV-positive gastric cancer displays geographical differences. The goal of our study is to determine the EBV- associated gastric cancer rate in our center and to evaluate EBV positivity in inflammatory cells, intestinal metaplasia and normal cells adjacent to gastric cancer.

MATERIAL AND METHOD

The study included 101 cases diagnosed at Kahramanmaraş Sütçü İmam University (KSÜ) Health Implementation and Research Hospital from February 2012 to August 2023 who underwent gastrectomy. The electronic and printed files of all cases were screened and data were obtained about age, sex, tumor histological type, histological grade, World Health Organization (WHO) TNM classification, tumor stage, date of diagnosis, mortality status, and date of death. Preparates belonging to cases were reassessed after being taken from the pathology archive and histopathological data were updated. Paraffin blocks representing tumor tissue were chosen and sections with 3.5 micron thickness were prepared. These sections had chromogenic EBER-ISH (INFORM EBER probe, Ventana) test applied with a Ventana Benchmark XT autostainer device. Preparates stained with EBER were evaluated for positive staining in tumor tissue, in normal tissue surrounding the tumor and in inflammatory cells around the tumor with a light microscope. Any nuclear staining was considered positive.

As control group, non-neoplastic gastric biopsies (50 minimal chronic gastritis and 50 intestinal metaplasia cases) were chosen and stained with chromogenic EBER-ISH.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study was permitted by KSÜ University non-interventional clinical research ethics committee (date: 09.11.2021, session no: 2021/36, decision no: 2).

This retrospective study used anonymized information and did not obtain informed consent.

Correlations between data with normal distribution were researched with the Pearson chi-square test and Fisher exact test, while correlations between categoric data without normal distribution were researched with the Mann-Whitney U test. Statistically, p value <0.05 was accepted as significant. Survival was calculated as the duration between date of diagnosis and date of death. Kaplan-Meier was preferred for univariated analysis of overall survival. Data were analyzed statistically with SPSS version 20 (IBM, Chicago, USA).

RESULTS

The study included 35 women (34.7%) and 66 men (65.3%) with mean age 69.13 years (range: 30-96).

According to the WHO TNM classification, 11 cases were stage 1 (10.9%), 21 cases were stage 2 (20.8%). 52 cases were stage 3 (51.5%) and 17 cases were stage 4 (16.8%). In terms of lymph node metastasis, it was present in 79 cases (78.2%), while distant metastasis

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was present in 17 cases (16.8%). For type, 55 cases had intestinal type (54.5%), 30 cases had diffuse type (29.7%), 11 cases had mixed type (10.8%), and 5 cases had mucinous type (4.9%). Histological grade was, 1 for 22 (21.8%), 2 for 30 (29.7%) and 3 for 48 cases (47.5%).

Cases were monitored for mean 32.7 months (1-167 months,) and 89 cases were exitus during surveillance (88.1%). Statistically significant correlations were identified between lymph node metastasis (N) (p=0.005), tumor spread (T) (p=0.001), distant metastasis (M) (p=0.001) and TNM stage (p=0.001) with survival.

For EBER-ISH, only nuclear staining was scored as positive. Of the 101 cases, 6 (5.9%) were identified to have EBER-ISH positive tumor cells. Additionally, positive staining was detected in lymphocytes surrounding the tumor in 18 cases (17.8%), in intestinal metaplasia areas adjacent to the tumor in 10 cases (9.9%) and in normal gastric mucosa adjacent to the tumor in 13 cases (12.9%) (Figure 1). In 68 cases (67.3%), no positive staining was identified with EBER. The clinicopathological data for the 6 EBER-positive cases are summarized in Table 1. In 5 out of 6 cases, along with the tumor, surrounding lymphocytes, intestinal metaplasia or normal mucosa was observed to have positive EBER staining.

There was widespread (50%) and intense staining in tumor cells in all EBER-ISH-positive gastric cancer cases (Figure 1). There was no case present with focal (<50%) and weak staining in tumor cells. Staining in nontumoral normal mucosa and intestinal metaplasia fields adjacent to the tumor was observed in sparse isolated cells in the basal crypt, with 10-12 cells/40x objective field in most intense areas. Staining of inflammatory cells within and around the tumor was in the form of sparse, scattered cells.

Table 1. Clinicopathological features of EBV-associated gastric carcinoma cases

	Age	Sex	Histological grade	Tumor type	T	N	M	Stage	Tumor site	Survival	EBER positivity in tumor adjacent epithelium
Case 1	59	m	3	D	4	0	1	4	Corpus	Ex./13.6 months	In the lymphocytes and normal epithelium
Case 2	58	m	2	I	3	3	1	4	Corpus	Ex./15.31 months	In the normal epithelium
Case 3	72	m	3	D	3	1	0	2	Cardia	Ex./19.45 months	No Positivity
Case 4	82	m	3	D	2	0	0	1	Antrum	Ex/35.12 months	In the lymphocytes
Case 5	54	m	2	D	3	3	1	4	Corpus	Ex/15.31 months	In the lymphocytes and normal epithelium
Case 6	59	m	2	I	3	2	0	3	Corpus	Surviving/167 months	In the intestinal metaplasia

m: Male, D: Diffuse type, I: Intestinal type, T: Tumor spread, N: Lymph node metastasis, M: Distant metastasis

A statistically significant correlation was identified between EBER positivity of cancer cells with only the clinicopathological parameter of sex (p=0.021). Significant correlations were not identified between the other clinicopathological parameters and survival with EBV positivity.

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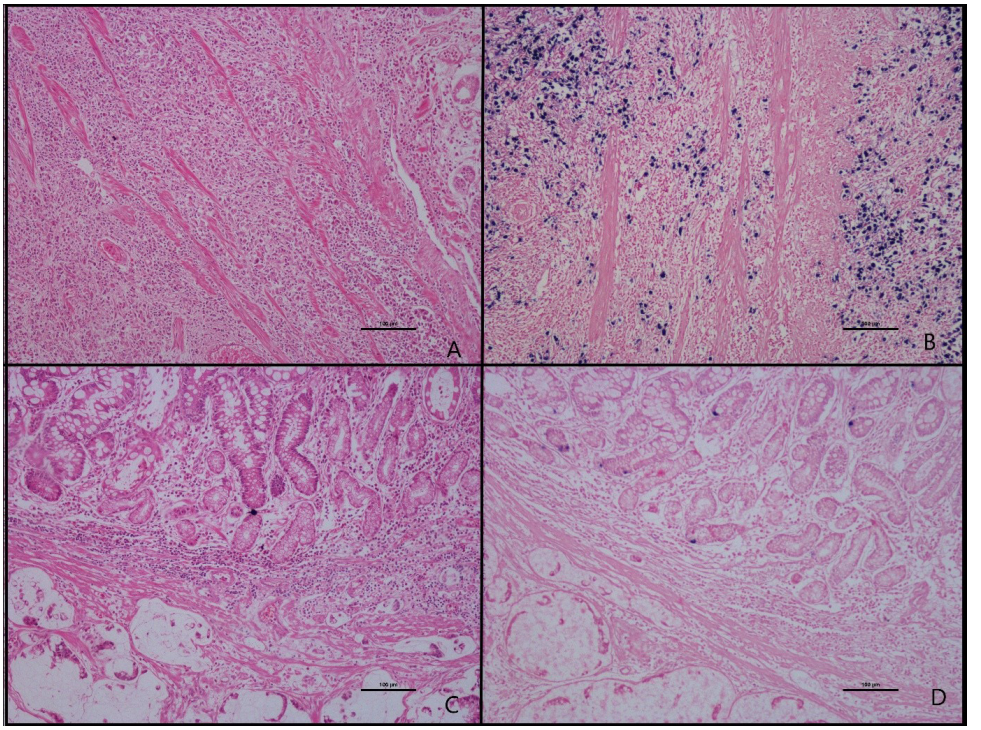

Figure 1. A) Diffuse type gastric carcinoma muscular infiltration area (H&E stain, 10x), B) Positive staining with EBER-ISH in tumor cells in the same field (EBER-ISH, 10x), C) Carcinoma creating mucin ponds in the lower half of the picture, intestinal metaplasia observed in the upper half (H&E stain, 10x), D) Tumor cells in the same area EBER-ISH negative, while EBER-SIH positive cells are present in the metaplasia field (EBER-ISH, 10x)

In the control group (tumor-free dyspepsia patients), EBER positivity was observed in 2 cases in basal crypt cells and in 2 cases in lymphocytes (4/100).

When cases are grouped into those with >1% positive staining with EBER in cancer cells or any epitelial cell and cases without staining of any epitelial cells and the correlations of clinicopathological parameters with these groups are assessed, there was a statistically significant difference identified for perineural invasion between the groups (p=0.003). Perineural invasion as observed in 22/24 (92%) of cases in the EBER positivity in any cell group and 35/69 (50 %) of the all cells EBER negative group. No significant correlation was identified with the other parameters and survival.

When cases are grouped into those with >1% positive EBER staining in cancer cells or normal or metaplastic epithelial cells (not including staining of lymphocytes) and those without staining of any cell and the correlations with clinicopathological parameters are assessed, statistically significant differences were identified between the groups in terms of lymph node metastasis (p=0.009) and perineural invasion (p=0.044). Lymph node metastasis was observed in 12/21 (57%) of the group with positive tumoral or non-tumoral epithelial cells and 67/80 (83%) of the other group. Perineural invasion was present in 11/12 (92%) of the group with positive tumoral or non-tumoral epithelial cells and 45/69 (65%) of the other group. No significant correlations were identified with other parameters or survival.

DISCUSSION

Definition of EBV-associated epithelial cancer involves neoplasm where the EBV genome is detected into the tumor and this is observed in nasopharynx carcinoma (89%) most frequently, followed by gastric carcinoma (10%) (8). The presence of EBV is believed to indicate infection

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with the virus in the early stages of the tumorigenic process, more than induction of the tumor by EBV alone. EBV infection may ensure clonal proliferation and avoidance of the immune system by causing p16 inactivation and programmed death-ligand (PDL1/2) overexpression in tumor cells (9,10).

With the aim of directing clinical approaches and treatment strategies for gastric cancer, the Cancer Genome Atlas (TCGA) published a comprehensive molecular classification in 2014 (10). This classification suggest as a candidate of the use of phosphatidylinositol-3-kinase (PI3K) inhibitors, janus kinase-2 inhibitors and immune checkpoint antagonists for EBV-positive gastric cancers (10).

The prevalence of EBV-positive gastric cancers displays geographical variations, and it is reported most frequently in Poland (43%) and least frequently in the United Kingdom (1.7%) (7). In our country, there are 7 studies related to the prevalence of EBV in gastric cancers. Özmen et al. evaluated EBV frequency in gastric cancer with EBER-ISH and reported rates of 2.3% (2/85 cases) (11). Irkkan et al. reported the EBV frequency was 7.6% (8/105) with EBER-ISH (12). Güner et al. assessed EBV frequency with EBER-ISH and reported the rate was 1.8% (2/109) (13). Uner et al. reported the EBV frequency was 25% (10/40) with EBER-ISH in the group with advanced gastric carcinoma without rich glandular differentiation from the lymphoid stroma (14). Uprak et al. reported the EBV frequency in the gastric medullar carcinoma group was 32% (6.19) with EBER-ISH (15). Gareayaghi et al. reported the EBV freuqency was 35.2% (12/34) with PCR (16). Durmaz et al. reported the EBV frequency was 56.9% (37/65) with PCR (17). In our study, we identified the EBV-positive gastric carcinoma rate was 5.9% in our region. Our findings are close to the results found by Irkkan et al. (12).

Tumors in the gastric cardia or corpus were reported to have two-times higher EBV positivity than those in the antrum and a reducing trend was reported for non-cardia tumors in recent years (18). In light of this information, it may be predicted there will be an increase, albeit relative, in the EBV-positive gastric cancer rates. In our study, investigating cases from 2012 to 2021, 4 EBV-positive cases had upper gastric localization, and their diagnosis being given after 2017 may be consistent with this trend.

The male sex is reported to have 2-fold EBV positivity compared to the female sex (18). In a study researching gastric cancer molecular subtypes and association with mortality, Eskuri et al. reported the EBV positive subtype rate was 7.3% (37/503) and the male patient rate was 30/37 (81%) in a broad series (19). All of our EBV-positive cases were men, consistent with the literature.

EBV-positive gastric cancer is associated with best prognosis among the molecular groups (10). However, the molecular classification of the Asian Cancer Research Group included EBV-positive gastric cancers within the MSS/TP53+ group and defined this group as having intermediate prognosis (20). Irkkan et al. identified the mean survival with EBV-positive gastric cancer was 11.5 months, and did not report significant correlations with clinicopathological prognostic parameters (12). Eskuri et al. did not report a significant difference in terms of mean survival between the molecular subtypes, though they did report the mean survival duration was longer in the EBV-positive group (19). In this study, cases with intestinal type (78%) and early stage (67%) had high rates in the EBV-positive group (19). In our study, we could not create a statistically significant correlation between EBV positivity and survival. The mean survival duration for our EBV-positive cases was shorter compared to the EBV-negative group; however, diffuse type (4/6) and advanced stage (4/6) being dominant in the EBV-positive group may have affected the outcomes.

In most EBV-associated gastric cancer studies, it was not stated whether or not there was staining in non-neoplastic tissues adjacent to tumor while focusing on EBV positivity of cancer cells. Zhang et al. reported intestinal metaplasia was observed more frequently in EBV-negative gastric carcinoma (21). In this study, intestinal metaplasia tissue was not studied with EBER. In our literature scan, there were similar findings to this study, with very few studies reporting the EBV positivity rate in intestinal metaplasia and inflammatory cells adjacent to the tumor, as in our study. In a 19-case gastric carcinoma series, Shousha et al. identified positivity with EBER-ISH in 1

lymphoepithelial-like carcinoma case, while 11 of the other 18 cases were reported to have sparse positive cells in the normal gastric and duodenal epithelium (22). Herrera-Goepfert et al. reported EBER-ISH positivity in regenerative epithelium adjacent to the tumor in a case with EBV-negative gastric carcinoma (23). Contrarily, in a 235-case series, Truong et al. reported the EBV-positive gastric carcinoma rate was 5.4% (n=12) (24). They evaluated EBV positivity of non-neoplastic cells surrounding the tumor tissue in 72 cases and did not report positivity in any case (24). In some studies, there was staining in adjacent dysplastic epithelium in cases with EBV-positive gastric cancer; however, staining was not reported in lymphoid cells, stromal cells and normal mucosa (25). Some studies reported positivity of isolated lymphoid cells surrounding the tumor; however, there was no staining of normal epithelium (26).

Vanvimonsuk et al. analyzed the amplification increase in EBV LMP-1 protein with PCR and reported amplification increase rates of 42% in normal mucosa, 22% in intestinal metaplasia, 13% in gastric dysplasia and 33% in gastric carcinoma. In gastric dysplasia and gastric cancer patients with amplification increase identified with PCR, staining with EBER-ISH was not identified in gastric dysplasia cases, while 12% positivity was reported for tumor tissue (27). The reduction in the rate of gastric carcinoma patients with EBV LMP1 amplification increase identified with PCR (33%) when detected with EBER-ISH (12%) may be explained by inflammatory cells surrounding the tumor, normal mucosa and intestinal metaplasia tissues being positive for EBV. Dursun et al. researched the EBV frequency with EBER-ISH in Helicobacter pylori-negative gastritis and reported EBER positivity in both normal epithelium and inflammatory cells (28). In our study, sparse positive staining was observed with EBER-ISH in normal mucosal epithelium of patients with gastritis and intestinal metaplasia with endoscopic biopsy taken due to non-cancer dyspepsia complaints.

In our study, different to other studies in the literature, we reported the rates of EBER-ISH adjacent to gastric cancer. When we grouped gastric cancer patients into those with EBER positivity in any cell (tumor cells, lymphocytes, intestinal metaplasia and normal epithelial cells) (n=33/101) and without EBER positivity, we observed the perineural invasion rate was significantly high in the positive group. A similar relationship was observed when staining of lymphocytes was not included. In the literature, no direct correlation is reported between perineural invasion with EBV in gastric cancer. However, a study by Li Xunjun et al. evaluating the correlation of tumor microenvironment and perineural invasion reported PDL-1, a molecular characteristic of the EBV subtype in the TCGA classification, was high in neuroinflammatory inflammation, indicating high correlation with perineural invasion (29).

We observed less lymph node metastasis in the group with any epithelial cell positive for EBER-ISH compared to the other group. There are many studies available reporting lymph node metastasis is less in EBV-associated gastric carcinoma (19,26). While a significant correlation was not observed with lymph node metastasis in the group positive for only tumor cells/EBV-associated gastric carcinoma, the lack of correlation in the group positive in any epithelial cell with EBER-ISH may be explained by the small size of our sample.

CONCLUSION

In our study, we analyzed EBER-ISH positivity in tumor cells in gastric carcinoma and lymphocyte and epithelial cells surrounding the tumor and correlation with some clinicopathological parameters. While statistically significant correlations were observed between positive staining of non-tumoral cells with perineural invasion and lymph node metastasis, the importance of these findings is open for discussion as there is no study with which we can compare our results in the literature. Our findings may guide other studies to be performed in the future by contributing to better understanding of the gastric cancer microenvironment and cancer-EBV relationship. Additionally, our findings emphasize that EBER-ISH is a more accurate tool than other tests for detecting EBV positivity in carcinoma, as also suggested in a recent review article (30).

The main limitations of our study are that it was completed in a single center and includes a relatively small sample. As a result, it appears that marginal values may have affected statistical results, led by

mean survival. Another important limitation is the lack of assessment of non-surgical treatments administered to cases.

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