EBV Positive Gastric Carcinomas and Their Clinicopathological Characteristics

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Abstract

BACKGROUND: The understanding of the etiopathogenesis of gastric carcinoma (GC) can be a base for development of new therapeutic methods to reduce mortality and to increase survival in patients with GC. The percentage of Epstein-Barr virus (EBV) positive gastric carcinomas is uncertain, and the etiologic importance of EBV in the pathogenesis of GC has not been elucidated.

AIM: This study aimed to determine the percentage of EBV associated GC as well as to determine their clinicopathological characteristics.

MATERIAL AND METHODS: The study included 80 patients with GC who were analysed for ethnicity, local growth of a tumour (T status), the presence of nodal metastases (N), the presence of distant metastases (M), stage of the disease and degree of carcinoma differentiation. For detection of EBV, immunostainings were performed on tumour tissue and the peripheral non-tumour gastric mucosa.

RESULTS: Positive immunostaining with an antibody against EBV was found in 19 (23.75%) of the 80 patients with gastric carcinomas. EBV immunostainings were significantly different in patients with or without metastasis and between patients of Macedonian and Albanian ethnicity (p < 0.0001, p < 0.009, respectively). EBV immunoeexpression was significantly associated with the presence of distant metastases and with patients of Albanian ethnicity.

CONCLUSION: Association of EBV immunostainings with distant metastasis in patients with GC suggests the influence of EBV infection on the progression of gastric carcinoma. Due to scarce and doubtful literature data on EBV associated GC, further studies are necessary to determine the role of EBV regarding aetiology, treatment and prognosis in patients with EBV associated gastric carcinoma.
believed to play a role in the carcinogenesis of this neoplasm. The percentage of EBV positive gastric carcinoma is uncertain, and the etiological importance has still not been elucidated [5] [6]. The conducted meta-analysis of 70 studies that included a total of 15,952 cases of GC revealed that EBV positive gastric carcinomas differed from the other gastric carcinoma by gender distribution, anatomic localisation and surgically different anatomy, indicating that EBV-associated gastric carcinoma is a particular etiological entity [5]. Epidemiological studies from different regions and studies that contribute to defining the role of EBV in the carcinogenesis and progression of GC are useful for the development of new therapeutic modalities [6].

This study aimed to determine the association of EBV with gastric carcinoma as well as to correlate it with different clinicopathological parameters.

**Material and Methods**

This study included 80 patients with gastric carcinoma surgically treated at the University Clinic for Abdominal Surgery in Skopje, whose operative material was analysed at the Institute of Pathology, Medical Faculty in Skopje.

The following parameters were analysed in the study: ethnicity of patients, local tumour growth (T status), the presence of nodal metastasis (N), the presence of distant metastasis (M), stage of the disease and degree of carcinoma differentiation.

The data for the parameters of the TNM classification (AJCC Cancer Staging 2017) were obtained from the archival histopathological reports of the Institute of Pathology in Skopje, and for the clinical stage we used patient’s files from the University Clinic for Abdominal Surgery in Skopje, including ultrasound and computed tomography files.

For detection of EBV, immunostainings were performed on tumour tissue and the peripheral non-tumour gastric mucosa.

A standard commercial control was used for immunostaining control.

Immunohistochemical stainings for EBV were made with a standard procedure using Immunoperoxidase LSAB + system and specific primary monoclonal EBV-antibody (DAKO – Monoclonal Mouse. Anti-Epstein Barr Virus, LMP. Clones CS. 1-4. Code IR753).

EBV expression was defined in 2 histological patterns, nuclear and cytoplasmic (Figure 1).

Descriptive statistical methods were used for statistical analysis of the data. Categorical variables are presented with absolute and relative numbers (%). Fisher’s exact test, Student’s t-test and Chi-square test were used for comparison of categorical variables. Spearman’s correlation coefficient was used to determine the degree of correlation between analysed parameters. The statistical program SPSS for Windows, version 19.0 was used.

**Results**

Expression of EBV in cells was nuclear and cytoplasmic. Nuclear expression was found in 15 (18.75%) cases and cytoplasmic in 4 (5%) cases. In 10 (66.67%) of positively stained cases, nuclear EBV expression showed the patchy distribution in clusters of cells and the other 5 (33.33%) cases EBV positivity was diffuse in the tumour cells. The expression of EBV in the peri-tumour gastric mucosa showed patchy distribution.

Positive expression of EBV protein was also detected in plasma cells present in the tumour stroma, or gastric submucosa of the patients with GC (Figure 1).

Positive immunostaining with the antibody against EBV was found in 19 (23.75%) of the total of 80 gastric carcinomas.

The mean age of patients with negative EBV expression was 66.05 ± 10.6 years, and of those with positive EBV expression was 63.2 ± 9.5 years (p > 0.05).
The immunoexpression of EBV about the analysed clinicopathologic parameters is shown in Table 1.

Table 1: Immunoexpression of EBV about the analysed clinicopathologic parameters

| Parameter                  | EBV expression | P-value      |
|----------------------------|----------------|--------------|
| Gender                     |                |              |
| Male                       | 25             | 4 (16)       |
| Female                     | 55             | 10 (21.84%)  |
| Intragastric localisation  |                |              |
| Cardia                     | 31             | 8 (25.81)    |
| Body                       | 20             | 8 (30)       |
| Pylorus                    | 29             | 5 (17.24)    |
| T                          |                |              |
| T1                         | 4              | 0.25 ns      |
| T2                         | 13             | P (Fisher exact test) |
| T3                         | 14             | 6 (42.86)    |
| T4                         | 49             | 11 (22.45)   |
| Lymph node metastasis      |                |              |
| No                         | 16             | 1 (0.625)    |
| Yes                        | 64             | 10 (15.62%)  |
| Stage                      |                |              |
| I                          | 7              | 0.076 ns     |
| II                         | 17             | 6 (35.29)    |
| III                        | 47             | 13 (27.66)   |
| IV                         | 9              | 1 (100)      |
| Grade                      |                |              |
| G1                         | 1              | 0.12 ns      |
| G2                         | 36             | 16 (44.44%)  |
| G3                         | 43             | 12 (27.91)   |
| Ethnicity                  |                |              |
| Macedonian                 | 62             | 10 (16.13)   |
| Albanian                   | 18             | 9 (50)       |

The results obtained in this study regarding positivity of EBV between patients with gastric carcinoma with different N stage showed no significant difference (p > 0.05).

A significant difference regarding immunoexpression of EBV was found in GC patients with or without distant metastases (p < 0.0001). In patients with gastric carcinoma, the presence of infection along with EBV was significantly associated with distant metastases.

Infection with Epstein-Bar virus was significantly more common among patients of Albanian nationality than in Macedonian patients (p = 0.009). EBV immunoexpression was detected in 50% (9) of Albanian patients against 16.13% (10) of Macedonian patients.

Discussion

EBV is a herpes virus that is widely spread among the human population. The infection with EBV is commonly acquired during early childhood by salivary transmission [7]. The virus causes long-term infection of B lymphocytes in about 90% of adults, who are asymptomatic. A small percentage of infected people develop hematopoietic, epithelial and mesenchymal tumours. The EBV infection is a cause for the development of Burkitt lymphoma, lymphoma associated with immunosuppression, Hodgkin’s lymphoma, sinonasal angioinvasive T lymphoma, nasopharyngeal carcinoma and leiomysarcoma in immunocompromised patients [5] [7]. It is believed that the oncogenic effect of the virus is carried out by expression of an EBV nuclear antigen and latent membranous proteins that interact with some suppressor genes and signal pathways [7].

According to literature data, the EBV infection is associated with 2-16% of gastric carcinoma, but the published data, in general, refer to the role of EBV in carcinogenesis. Few data on the association of EBV with gastric carcinoma and its characteristics are available in the literature [7] [8] [9] [10]. The prevalence of gastric carcinoma associated with EBV infection shows geographic variations [11] and is related to the lifestyle of patients. Thus, studies about EBV associated gastric carcinomas are necessary and very actual [5] [6].

Gastric carcinomas of the antrum show a low percentage of EBV-associated infection compared to the carcinoma of the cardia [5], and it is found in the highest percentage (90.5%) in lymphoepithelioma-like gastric carcinoma [12].

Some studies have demonstrated the association of EBV gastric carcinoma with the age of patients [13].

The meta-analysis conducted by Lee JH et al, of 48 studies on EBV-associated gastric carcinoma (EBVaGC) showed a significant association with the nationality. The analysis also found that EBVaGC was more frequent in men, young individuals, Caucasians and Latin Americans, in cardia as a localisation of the carcinoma, and in the diffuse histological type [14].

In our study, we detected EBV presence in 23.75% (19) of our patients, which is a high percentage of EBV-associated GC in comparison with the results in the literature [11] [13]. EBV immunoexpression was significantly different in patients with or without metastasis and patients of Macedonian and Albanian nationality.

EBV immunosuppression was significantly associated with the presence of distant metastases and with Albanian ethnicity.

The significant correlation of EBV immunosuppression with distant metastasis in GC patients suggests the influence of EBV infection on the progression of gastric carcinoma.

Due to relatively limited and doubtful literature data about EBV-associated gastric carcinoma, further studies are necessary to determine the role of EBV regarding the aetiology, treatment and prognosis in patients with EBV-associated carcinoma.
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