

Correlation between Epstein Barr Virus and early gastric cancer

G.S. Kouklakis¹, S.M. Dokas¹, S.T. Stefanidis¹, G. Minopoulos²

SUMMARY

Objective: The aim of this study was to explore the possible oncogenic role of Epstein Barr virus in early gastric cancer.

Patients and methods: In eleven patients diagnosed with early gastric cancer, specific anti-EBV immunoglobulines were measured before and after their treatment. The possibility of Helicobacter Pylori infection was also considered and examined both with rapid urease test and haematoxylin – eosin staining.

Results: In nine patients the anti-EBV immunoglobulines tested out positive in very high titers before the treatment. In three of them the titers dropped to the usual titers detected in healthy individuals with past EBV infection, six months after the treatment. Helicobacter Pylori infection was detected in only three of the patients.

Conclusion: Epstein Barr virus is probably a direct oncogenic factor in early gastric cancer. It is also possible that a geographic allocation exists regarding it's prevalence in different populations which could be explained by variations in HLA expression.

Key words: Epstein Barr virus, early gastric cancer, Helicobacter pylori, oncogenesis

INTRODUCTION

Despite the fact that a marked decrease in the prevalence of gastric cancer is reported, it still remains as one of the most frequently diagnosed malignancies world-

wide. A lot of risk factors have been studied over the past years, including genetic diseases (familial adenomatous polyposis – hereditary nonpolyposis colorectal cancer), dietary habits and preferences (smoked and salted foods), ingested bacteria from poorly preserved food, decreased gastric acidity (post-gastrectomy, atrophic gastritis, pernicious anemia), Helicobacter pylori (Hp), intestinal metaplasia,^{1,2} while the role of Epstein Barr virus (EBV) is being studied by researchers throughout the world.

EBV is a well known oncogenic virus. The correlation between EBV and Burkitt's lymphoma (BL) as well as nasopharyngeal carcinoma (NPC) has been thoroughly investigated and generally accepted.⁴

The aim of this study was to elucidate the prevalence of EBV infection in Greek patients suffering from early gastric cancer (EGC).

PATIENTS AND METHODS

Eleven patients diagnosed and treated for EGC in 424 General Army Hospital during the period of 1993 to 1998 were included in this study. Specific antibodies against EBV were measured in these patients before and after treatment. The antibodies measured were: Anti-EBV VCA (viral capsid antigen) IgM, Anti-EBV VCA IgG, Anti-EBV NA (nucleic antigen) IgG and Anti-EBV EA (early antigen) IgM. The patients were also examined for the presence of Hp infection, both with rapid urease test and haematoxylin – eosin staining of six gastric biopsies (two from the cardia, two from the corpus and two from the antrum).

None of the patients had spreading of the tumor to the regional lymph nodes nor to distal organs, as the preoperative CT scan demonstrated and surgical scrutiny confirmed.

All the patients were followed up with physical ex-

¹424 General Army Hospital, Department of Gastroenterology,

²Democritus University of Thrace, Endoscopic Department

Author for correspondence:

Stefanos Dokas, 1 Hatziandreu str., 546 35 Thessaloniki, Greece,
Tel.: (+30-31) 204670, Fax: (+30-31) 241941

amination, ultrasonography of the abdomen and gastroscopy three months after the operation and even six months thereafter. The first postoperative CT scan was performed three months after the operation and was repeated once a year. The same antibodies against EBV were remeasured six months after treatment.

RESULTS

In all eleven patients the Anti EBV VCA IgM and Anti EBV EA IgM tested out negative since there was no recent infection, whereas in nine patients, the Anti EBV VCA IgG and Anti EBV NA IgG tested out positive in very high titers, 8-20 fold the normal titers found in healthy individuals with past EBV infection.

Hp infection was detected in only three patients both with rapid urease test and pathology examination, from which only one demonstrated high titers of Anti EBV VCA IgG and Anti EBV NA IgG (Table 1).

During the postoperative period all of the patients remained asymptomatic and gastroscopy, ultrasonography of the abdomen and CT scan were negative for metastasis.

In three patients the Anti EBV VCA IgG and Anti EBV NA IgG dropped to the usual titers found in healthy individuals with past EBV infection, 6 months after the operation.

DISCUSSION

EBV is a herpesvirus with well established oncogenic capacity. Its target cell is the B lymphocyte, which, after infection is transformed and becomes immortal, both in vitro and in vivo.^{4,5} There is a direct association between EBV and the African BL as well as the NPC.³⁻⁷ In fact EBV was first isolated from BL cell cultures in 1964.⁴ In many studies, mainly from Japan, EBV proteins and genetic material were present in approximately 7-15% of gastric carcinomas;⁸⁻¹⁵ but the question regarding the exact association between EBV and EGC still remains. Can EBV directly infect the epithelial gastric cells? Is EGC triggered by EBV-carrying lymphocytes, or is the detection of EBV genes and proteins a random event?

In our study we measured very high titers of anti-EBV immunoglobulines in patients diagnosed with EGC. These same antibodies are detected in very high titers in patients suffering from BL and NPC even years before the diagnosis is made and it is considered as a bad prognostic sign.⁴

In a recent study recombinant EBV, carrying a selective marker gene only, successfully infected human epithelial cells, so it might be possible that direct epithelial infection actually occurs in vivo.¹⁶

The results from our study, regarding the prevalence of EBV associated EGC, differ considerably from con-

Table 1. Anti EBV immunoglobulines and Hp detection in our patients

Patient	Age	Gender	Tumor Location	Anti EBV VCA IgG	Anti EBV VCA IgM	Anti EBV NA IgG	Anti EBV EA IgM	Hp
1	23	Female	Gr. Curv ¹	1/320	N ³	1/160	N ³	N ³
2	25	Female	Antrum	1/640	N	1/80	N	N
3	32	Female	Gr. Curv.	1/160	N	1/40	N	N
4	38	Female	Gr. Curv.	1/2560	N	1/320	N	N
5	42	Male	Antrum	1/320	N	1/40	N	N
6	46	Male	Gr. Curv.	1/1280	N	1/40	N	N
7	54	Male	Antrum	1/160	N	1/80	N	N
8	56	Female	Gr. Curv.	N	N	N ³	N	N
9	57	Male	Gr. Curv.	1/320	N	1/40	N	P ⁴
10	61	Male	Gr. Curv.	N	N	N	N	P
11	78	Male	Antrum ²	N	N	N	N	P

¹Gr. Curv.: Creater Curvature, ²In this patient 3 sites of EGC were detected in the antrum, ³N: Negative, ⁴P: Positive

clusions reported by other researchers. This fact, if not random due to the limited number of our patients, could be explained by different HLA expression in the Greek population.

EBV-associated tumors (BL and NPC) demonstrate geographic allocation, a fact attributed by authors to diseases causing immunosuppression of varying degrees (Malaria – AIDS), or to differences in HLA expression. In the case of African BL, its 100% association with EBV is attributed to the very high prevalence of malaria in the African continent. Malaria is responsible for defective T leukocyte cytotoxic response, resulting in inadequate suppression of EBV-infected B leukocytes, leading to BL.⁴ In the case of NPC its higher prevalence in the Orient and the Mediterranean is probably due to differences in HLA expression, but it still remains to be proven.⁴

In AIDS patients 100% of CNS lymphomas are EBV associated.⁷ It is possible that the same pattern exists in the EBV associated EGC. In three of our patients the Anti-EBV titers dropped to the usual titers found in healthy adults with past EBV infection. The test was repeated three months later and confirmed the decrease. The exact reason for this rapid and intense decrease is unclear to us.

We have not found any study with such results regarding EBV and EGC nor EBV and BL or NPC.

Several hypotheses can be made; but certainly this event deserves serious attention, as it could be established that Anti-EBV titers are tumor markers, useful not only in making the diagnosis but also in the follow up of the patients as a prognostic indicator.

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