

# Gastric Carcinoma With Lymphoid Stroma (Gastric Medullary Carcinoma): A Rare Case Report

## Lenfoid Stroma İlişkili Gastrik Karsinom (Gastrik Medüller Karsinom): Nadir Bir Olgu Sunumu

Sumeyye EKMEKCI<sup>1</sup>, Yelda DERE<sup>2</sup>, Mustafa DEGIRMENCI<sup>3</sup>,  
Bulent CALIK<sup>4</sup>, Ozgul SAGOL<sup>5</sup>, Sulen SARIOGLU<sup>5</sup>

<sup>1</sup>Tepecik Training and Research Hospital, Department of Pathology, Izmir  
<sup>2</sup>Muğla Sıtkı Koçman University, School of Medicine, Department of Pathology, Muğla  
<sup>3</sup>Tepecik Training and Research Hospital, Department of Medical Oncology, Izmir  
<sup>4</sup>Tepecik Training and Research Hospital, Department of General Surgery, Izmir  
<sup>5</sup>Dokuz Eylül University, School of Medicine, Department of Pathology, Izmir

### Abstract

Gastric carcinoma associated with lymphoid stroma (GCLS), also known as gastric medullary carcinoma is a rare neoplasia of the stomach which is characterized with poorly developed tubular structures admixed within a lymphocyte-rich stroma. Most of the GCLS are found to be associated with Epstein-Barr virus (EBV) infection. Herein we present a case of GCLS in a 76-year-old patient. Gastroscopic examination revealed an ulcerated mass located at the cardia and the biopsy was diagnosed as poorly differentiated adenocarcinoma. After gastrectomy, the microscopic examination revealed an ulcerated tumor limited to the subserosa with pushing borders and dense lymphocytic infiltrate. The tumor diffusely consisted of sheets of pleomorphic tumor cells showing vesicular nuclei. In-situ hybridization analysis of EBV encoded RNA (EBER) was positive lymphoid cells. The disease was staged as T3N0M0. He had no relapse until now and he is under follow-up for 36 months treated with adjuvant systemic treatment.

**Keywords:** EBV Related Cancers, Gastric Cancers, Gastric Medullary Carcinoma

### Öz

Mide medüller karsinomu olarak da bilinen lenfoid stroma ilişkili mide karsinomu (GCLS), lenfositlerden zengin bir stroma içerisinde kötü düzenlenmiş tübül yapıları ile karakterize midenin nadir görülen bir neoplazisidir. Çoğu GCLS Epstein-Barr virüsü (EBV) ile ilişkilidir. Burada 76 yaşında erkek GCLS olgusu sunulmaktadır. Gastroskopik muayenede kardiyada ülser kitle saptanan olgu, endoskopik biyopsisinden kötü diferansiyeli adenokarsinom tanısı aldı. Gastrektomi sonrası mikroskopik incelemede subserozal alanda sınırlanmış, lenfositlerden zengin stromada, solid paternde gelişim göstermiş büyük ve pleomorfik, veziküler nükleuslu hücrelerden oluşan, itici sınırlara sahip tümör izlendi. In-situ hibridizasyonda EBV encoded RNA (EBER) lenfoid hücrelerde pozitifliği. Hastalık evre T3N0M0'dı. Hasta sistemik adjuvan tedavi almıştır. 36 aylık takibinde, şu ana kadar nüks saptanmamıştır.

**Anahtar Kelimeler:** EBV İlişki Kanserler, Gastrik Kanserler, Gastrik Medüller Karsinom

### Introduction

Gastric carcinoma with lymphoid stroma (GCLS); also known as medullary carcinoma, is a rare gastric tumor characterized by poorly developed tubular structures in a background of dense lymphocytic infiltration (1,2). GCLS is more common in the sixth decade and in male patients (1,3). Epstein-Barr virus (EBV) has been associated with several malignancies including Burkitt's Lymphoma, Hodgkin Lymphoma, post-transplant lymphoproliferative disease, and nasopharyngeal carcinoma (4,5). More than 80% of GCLSs are found to be associated with EBV infection (6). Latent EBV infection or microsatellite instability (MSI) is blamed for the cause of GCLS and it has been

reported that GCLS has a more favorable outcome when compared to classic gastric adenocarcinomas (1-4). Herein; we report a case of GCLS with EBV positivity in lymphoid cells.

### Case

A 76-year-old man applied with fatigue, loss of weight for three months. Physical examination, laboratory results and tumor markers were normal. An upper endoscopy showed an ulcerated mass located in the cardia and the biopsy taken from the lesion was diagnosed as poorly differentiated adenocarcinoma. Total gastrectomy was performed to the patient. Macroscopically the ulcerated tumoral lesion was in the cardia with a size of 4x3.5 cm. In the microscopic examination, the tumor which was densely associated with lymphocytic infiltration was limited to the subserosa but had pushing margins (Figure 1). The tumor diffusely consisted of sheets of pleomorphic tumor cells with vesicular nuclei (Figure 2). Immunohistochemically, cytokeratin was positive in the carcinomatous cells but negative in the lymphocytic infiltration (Figure 3). Tumor cells were negative with synaptophysin, chromogranin A and CD56. Immunohistochemically, there was no nuclear protein expression loss in MLH-1, MSH-2,

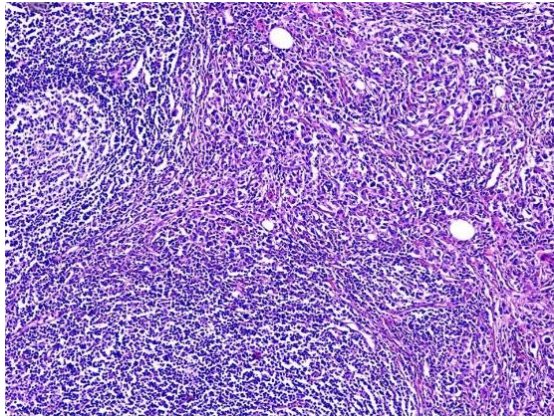
	ORCID No
Sumeyye EKMEKCI	0000-0003-1607-500X
Yelda DERE	0000-0003-0238-2236
Mustafa DEGIRMENCI	0000 0001 6988 9205
Bulent CALIK	0000-0002-9054-1446
Ozgul SAGOL	0000-0001-9136-5635
Sulen SARIOGLU	0000-0003-4877-3064

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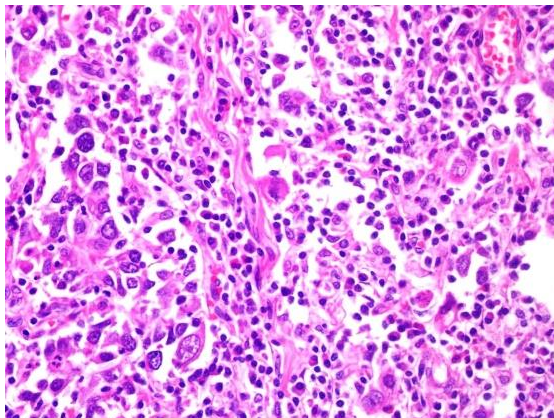
Adres / Correspondence : Sumeyye EKMEKCI  
Tepecik Training and Research Hospital, Department of Pathology,  
Izmir  
e-posta / e-mail : ekmekcisumeyye@gmail.com

MSH-6, PMS-2 in tumor cells. In situ hybridization analysis of EBV encoded RNA (EBER) showed positivity in the lymphoid cells (Figure 4).

No metastasis was detected in the regional lymph nodes. By all these results, the case was diagnosed as GCLS showing EBV association and the stage of the disease was T3N0M0. The patient was given six cycles of adjuvant (capecitabine 2000 mg/m<sup>2</sup> per day, on days 1 to 14 and cisplatin 75 mg/m<sup>2</sup> on day 1, repeated every 3 weeks) chemotherapy. He had no relapse until now with 36 months of follow-up.



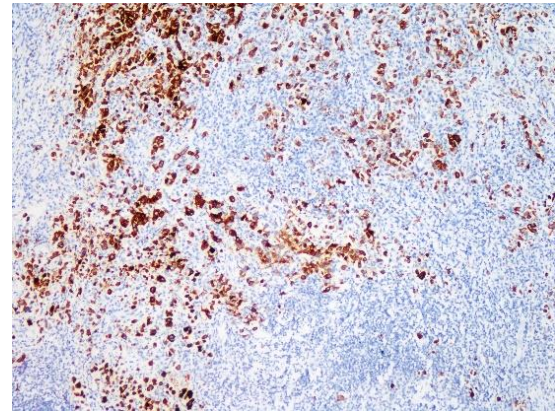
**Figure 1.** Microscopic view of tumor with dense lymphocytic infiltrate (H&E, x100).



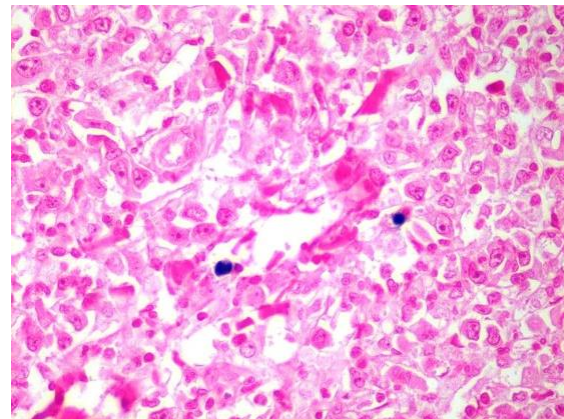
**Figure 2.** Sheets of polygonal cells with vesicular nuclei and prominent lymphocytic response (H&E, x200).

## Discussion

GCLS forms 1-4% of all gastric carcinomas (6). GCLS is a rare tumor having similarities with poorly differentiated carcinomas except the behavior of the tumor (7). The major histopathological feature of this type of tumor is the presence of the tumoral cells in an intense lymphoid infiltration (2,3). This lymphoid infiltration usually consists of T and B lymphocytes, macrophages, plasma cells (3). The tumor is generally localized in cardia or corpus (90%) as in our case (3). Mitosis and necrosis are also common in these tumors (2). As endoscopic biopsies were small sized and includes only mucosa and submucosa the lymphoid stroma, which are the diagnostic criteria of tumor, cannot be generally



**Figure 3.** Cytokeratin positivity in tumor cells (DAB, x100).



**Figure 4.** EBER-ISH positivity in lymphoid cells (AEC, x400).

assessed in these biopsies. Differentiating lymphoid stroma with host response in endoscopic biopsies is another difficulty. The endoscopic biopsy can be interpreted as suspicious of the lymphoid stroma if a significant lymphocytic response accompanies a high grade tumor. However, the exact diagnosis should be made in the resection material.

The new classification which was based on molecular profiling and proposed by The Cancer Genome Atlas project, has pointed out the importance of EBV-infected tumors and MSI tumors in gastric carcinomas (2,3). It is almost always pointed out that only tumoral cells show EBV positivity in GCLSs in the literature; however in our case, EBV positivity was detected in lymphoid stromal cells (5,6,8). Ribeiro et al. found EBER expression in more than 90% of the tumor cells in their study, and no expression was observed in non-malignant and stromal cells (5).

DNA mismatch repair (MMR) deficiency is an important molecular mechanism of genetic instability in gastric cancer. The higher instability at microsatellites is reported to be associated with more favorable prognosis (9).

There are several methods for detecting MSI status. There is no consensus on the best, most competent method. The most widely used and inexpensive method is the immunoistochemistry (IHC) method. IHC staining always indicates the

presence of detectable protein for MMR protein. IHC cannot differentiate the functionality or abnormality of these proteins. Thus, protein expression is not always sufficient to exclude MSI. It has been reported in the literature that the sensitivity and specificity of IHC vary due to tumor heterogeneity, interpretation differences, staining techniques. In general, there are studies in the literature that report that IHC has a high specificity to detect a mutation in the MMR gene. (10, 11).

Ramos et al. reported EBER positivity in only tumoral cells in GCLS. In addition to that they mentioned negativity in non-neoplastic gastric mucosa, areas with intestinal metaplasia, stromal cells and infiltrating inflammatory cells within the tumoral sections (1). Only one EBV negative case showed mismatch repair protein loss (MLH1 and PMS2) in the areas of mucinous differentiation (1). Cho et al. analyzed EBV positivity in tumor infiltrating lymphocytes (TIL) of various tumor types such as gastric, colorectal and ampullar tumors. EBV positivity in TIL was reported as 10% in EBV (-) gastric carcinomas. They stated that they were unable to estimate EBV positivity in lymphocytes of EBV (+) gastric carcinomas because of the similarity of scattered tumor cells. Therefore, they did not clearly explain the importance of EBV positive TILs (12).

It is reported that there are differences in the pathogenesis of lymphocyte-rich gastric cancers (13) and a negative relation between EBV and MSI in the literature (14,15). None of the tumors that were EBV positive were MSI high (14,15).

Many different studies report about the EBV positivity in cancerous cells, but only few studies report the EBV positivity in the surrounding lymphoid cells, especially B lymphocytes. These studies did not focus on the real mechanism and the prognostic role of the infected lymphocytes.

In our case we detected the EBV positivity also in the surrounding lymphocytes and we think that further studies are needed to enlighten this enigma (16).

In conclusion, the importance of EBV positivity in such cases remains unclear. Should these cases be accepted as EBV positive regarding the lymphoid cells are the component of the tumor or not? We also aimed to take attention to this point with this case which may be the starting point of various new studies.

**Informed Consent:** Written informed consent was obtained from patient who participated in this case (20.01.2015).

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