

Case Report

Integrative Gastroenterology and Hepatology

Case Report: Epstein-Barr virus Positive Gastric Carcinoma

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Abstract

In 2014, The Cancer Genome Atlas provided a molecular classification defining Epstein-Barr virus (EBV)-positive gastric cancer as a separate subtype. While its prognostic role is still debatable, emerging potential biomarker role for personalized treatment strategies is already recognized by international guidelines. We report a case with successful combined therapy of a 64-year-old EBV-positive gastric cancer male patient. Patient initially presented with locally advanced gastric cancer, which was treated surgically; three years later patient developed recurrence within the remnant stomach and was treated surgically. Two years after operation patient developed distant metastases and was enrolled in a clinical trials' (NCT01630083) arm 2: receiving chemotherapy and monoclonal antibody claudiximab. This treatment induced durable disease stabilisation for 34 months. After progression, second line chemotherapy with docetaxel and cisplatin provided additional disease stabilisation and symptom control for 8 months. Patient's overall survival reached 9.1 years. Presented report shows EBV-positive gastric cancer case with better overall survival compared to reported average, which contributes to the meaningfulness of its distinction as a separate subtype, evidence that targeted therapy is more effective in selected patient groups, and EBV as an emerging biomarker.

Keywords: Gastric cancer, Epstein-Barr virus (EBV)-positive gastric cancer, Epstein-Barr virus, Case report

Abbreviations: BMI: Body Mass Index; CT: Computer Tomography; EBV: Epstein-Barr virus; EBVaGC: Epstein-Barr virus associated Gastric Cancer; ECOG: patients performance status; GC: Gastric Cancer; Her-2: Human epidermal growth factor receptor 2; MSI: Microsatellite Instable; NCCN: National Comprehensive Cancer Network guidelines; PD-L1: Programmed death-ligand 1; PET: Positron Emission Tomography

Introduction

Epstein-Barr virus (EBV)-positive gastric cancer (GC) or EBV-associated GC-(EBVaGC) has been proposed to be a distinct condition [1,2]. In 2014, The Cancer Genome Atlas provided a molecular classification defining EBV-positive GC as a separate GC subtype [2]. In a systematic review of observational studies published in 2008 by Sousa et al., the worldwide prevalence of EBVaGC among gastric

adenocarcinomas was reported for 8.29% of cases [3].

The majority of GC is diagnosed at an advanced stage, and prognosis remains poor. Cytotoxic chemotherapy provides only modest benefit, with median overall survival (OS) reported in the range of 9-11 months. Until recently, only two targeted treatment options were available: first-line setting: Trastuzumab (for Her-2 positive GC) and second-line setting: Ramucirumab [4,5].

In the era of the rise of the immunotherapy in cancer management, two subtypes of GC-EBVaGC and microsatellite instable (MSI) GC - are considered to be most potentially responsive to immunotherapy. Programmed death-ligand 1 (PD-L1) gene amplification is frequently detected in EBVaGC, which suggests higher immunogenicity and might therefore be more likely to respond to immune checkpoint inhibition. It is known that PD-L1 is highly predictive in lung cancer, but clinical implications of the existence of PD-L1 in GC are still controversial. Both MSI and EBVaGC have a high somatic mutational burden which is also a feature that has been associated with response to immunotherapy [6-8]. For example, very high response rates to pembrolizumab (anti PD-L1 antibody, immunotherapy drug) were observed in two subtypes GC patients: overall response rate of 85.7% in MSI-high metastatic GC and 100% in EBV-positive metastatic GC [9]. Pembrolizumab has been incorporated in the *National Comprehensive Cancer Network* guidelines (NCCN) for second or subsequent line MSI-high and third or subsequent line PD-L1-positive gastric adenocarcinoma [10].

Despite these advances, treatment options remain limited, and there is still a dire need for more effective treatment for GC patients. The presented case report aims to show the meaningfulness of incorporation. The Cancer Genome Atlas subtype analysis in clinical trials.

Case Report

The 64 years old patient, Caucasian, male, presented to his primary care physician with a heartburn. Symptoms increased over the last six months. There was no weight loss (patients' height 173cm, weight 90 kg, BMI 30), results of a complete blood count showed grade 2 anaemia (erythrocytes $4.33 \times 10^{12}/L$ reference interval 4.5-5.9, haemoglobin 99 g/L reference interval 131-175 g/L); plasma levels of electrolytes and tests of kidney and liver function, tumour markers CEA, CA 19-9 and electrocardiogram were normal. He was an ex-smoker - had smoked for twenty years 20 cigarettes a day, drinking occasionally in moderation, had no personal or family history of cancer. Serologically *H. Pylori* (HP) IgG was negative: 22.8 enzyme immunoassay units (*BIOHIT HealthCare, Helsinki, Finland*). Patient's past medical history was notable for periodic lower back pain (symptomatic treatment with nonsteroidal anti-inflammatory drugs), arterial hypertension grade 2 (treated with *T. Enalapril maleas* 20mg once a day), and impaired glucose tolerance (regulated with a diet).

An upper endoscopy was performed and revealed five centimetres large exophytic tumour with an ulceration and sangvination in the middle 1/3 of the stomach body (Figure 1).

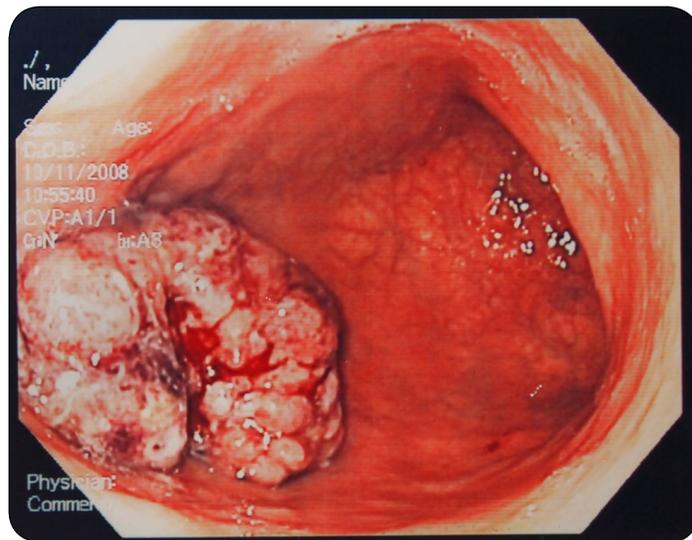


Figure 1: Upper endoscopy macroscopic appearance of the tumour.

Pathological examination of biopsy specimens showed moderately differentiated adenocarcinoma. Staging computer tomography (CT) scans of the chest and abdomen showed no evidence spread in the adjacent lymph nodes or metastatic disease. Given that the disease appeared localized, surgery was planned. Distal subtotal gastrectomy and D1 lymphadenectomy was performed during the December 2008, it complicated with internal bleeding, and patient was re-operated. Later convalescence period went without any complications. Post-operative histological report showed moderately differentiated (Grade II) tubular adenocarcinoma, Lauren classification - mixed type, Bormann III with lymphovascular invasion, penetrating serosa (visceral peritoneum) but without invasion of adjacent structures. Three out of eight regional lymph nodes had moderately differentiated adenocarcinoma metastases, no metastases were found in biopsy from the peritoneum or intraoperative peritoneal washings - pT₃N₁M_xR₀ (according to TNM classification 6th ed.). Her-2 testing was not performed. Final clinical stage of the gastric cancer was determined: T₃N₁M₀ IIIA, no additional treatment was offered, patient underwent regular CT and upper endoscopy examinations.

Three years and two months later (January 2012), patient developed signs of fatigue. Recurrence within the remnant stomach was diagnosed during upper endoscopy;

patient did not have any other complaints. CT scans of the chest and abdomen showed no evidence spread in the adjacent lymph nodes or metastatic disease, therefore, a repeated surgery was planned. During the February 2012, resection of the remnant stomach, D1 lymphadenectomy and oesophago-jejuno-jejuno-jejunoanastomosis was performed. Post-operative histological report showed low differentiated (Grade III) tubular adenocarcinoma, Lauren classification - mixed type, Bormann III with lymphovascular invasion, penetrating serosa (visceral peritoneum) but without invasion of adjacent structures. None of the twelve examined regional lymph nodes had metastases; no metastases were found in biopsy from the peritoneum or intraoperative peritoneal washings- $pT_{4a}N_0M_xR_0$ (according to TNM classification 7th ed.). No additional treatment was offered, patient underwent regular CT and upper endoscopy examinations for the period of a year and a half after the last operation.

In May 2013, patient developed symptoms of an acute ileus, after prompt examination and failure of the conservative treatment diagnosis of small bowel obstruction was posed and patient underwent an urgent operation during which small bowel conglomerate due to adhesions was diagnosed and partly resected creating new jejuno-jejunoanastomosis. There were no signs of the metastatic disease and post-operative histological report did not find malignant cells in the resected tissues or peritoneal washings. CT scans performed in the January of 2014 showed disease progression with peritoneal dissemination and metastases in the retroperitoneal lymph nodes (Figure 2).

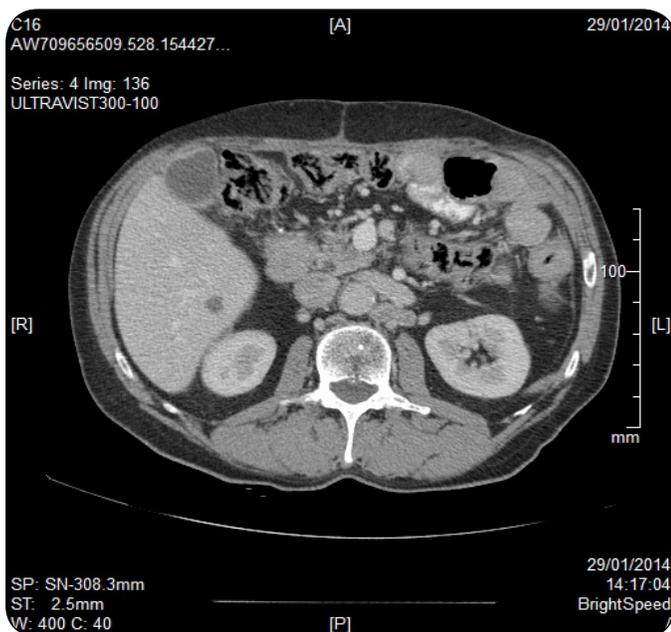


Figure 2: Metastases in the retroperitoneal lymph nodes

Patient's performance status was ECOG 1. To plan the further therapy, tumour Her-2 testing was performed, and results were negative.

Patient was enrolled in the international, multicentre, randomized, phase II clinical trial (NCT01630083) Arm 2. Eligible patients had a CLDN18.2 expression of $\geq 2+$ in $\geq 40\%$ tumor cells, an ECOG PS of 0-1 and were not eligible for trastuzumab. Patients were randomized 1:1 to first-line EOX (epirubicin 50 mg/m² and oxaliplatin 130 mg/m² d1, and capecitabine 625 mg/m² bid, d1-21; qd22, Arm 1) with or without IMAB362 (loading dose 800 mg/m², then 600 mg/m² d1, qd21 Arm 2). The study was extended by an exploratory Arm3 to investigate a high dose IMAB362 (1000 mg/m²) plus EOX [11,12]. Patient had a stable disease from February 2014 until December 2016 (34 months). In December 2016 CT scans showed large pathological mass in the area of jejuno-jejuno anastomosis and retroperitoneal lymph nodes.

In January 2017, therapy was changed to docetaxel 75 mg/m² and cisplatin 75 mg/m² every 3 weeks, tegafur 400mg orally bid on a 28-day schedule. After the first course patient developed prostatitis with urethral stricture and under the supervision of the urologist received antibiotic treatment which prolonged interval between the chemotherapy courses up to eight weeks. CT scan performed after three and six courses of chemotherapy showed stable disease (Figure 3).

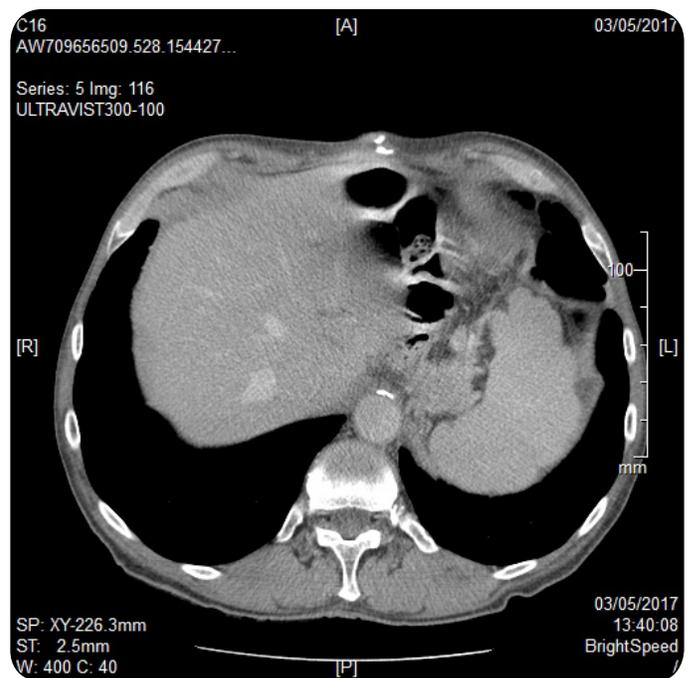


Figure 3: Pathological metastatic mass with pancreatic and diaphragm involvement, stable disease.

Follow-up CT scan scheduled in October 2017 showed disease progression with new metastases in the peritoneal lymph nodes and bone metastasis (Figure 4).

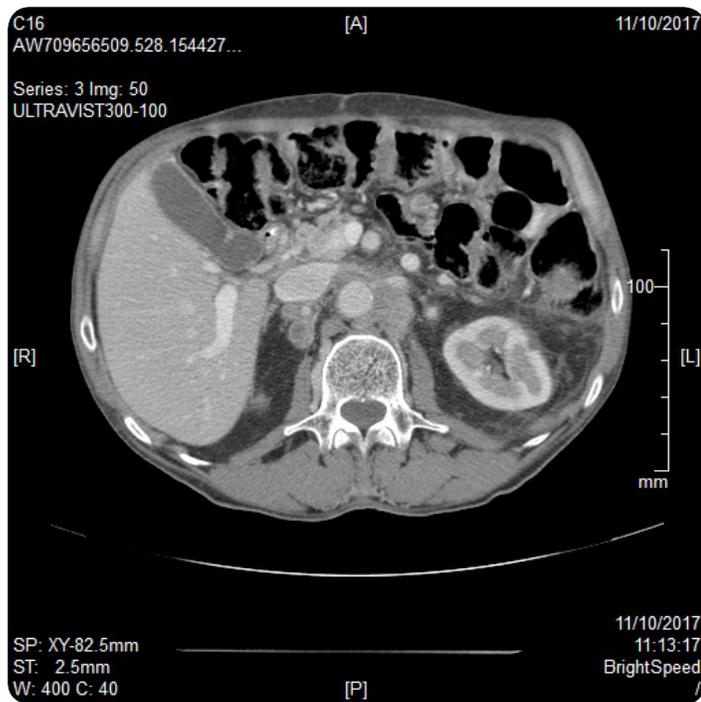


Figure 4: Large retroperitoneal metastatic lymph conglomerate, disease progression.

Clinically performance status had deteriorated to ECOG 2-3 and patient was offered best supportive care. He died in January 2018.

Patient's overall survival was 109 months (9 years and 1 month), time to the local recurrence 38 months (3 years and 2 months), time from the diagnosis to the development of distant metastases 61 month (5 years and 1 month), time from the development of distant metastases to death 48 months (4 years). Timeline of the disease and treatment shown in figure 5.

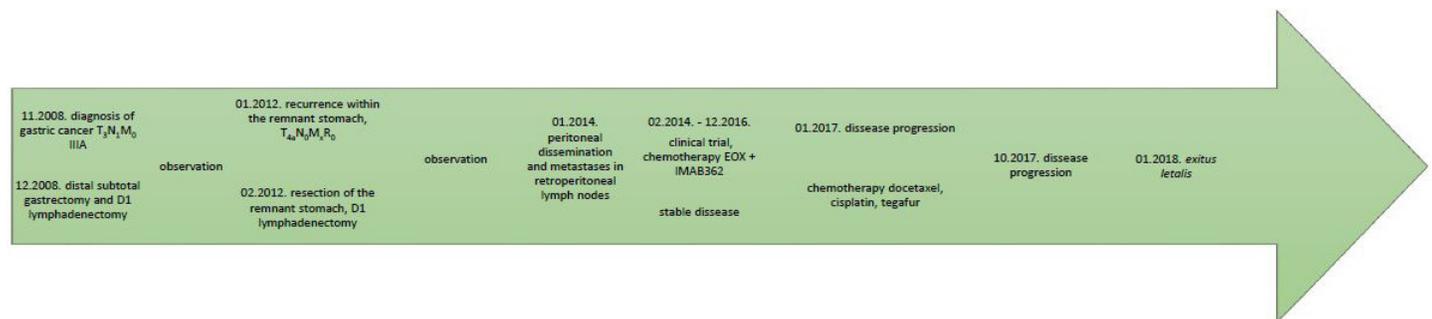


Figure 5: Timeline of the disease and treatment.

Tumour EBV status was determined by *in situ* hybridization for EBV-encoded RNA (EBER, Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina, USA, 2017) as a part of the retrospective study data yet to be published.

Discussion

Stage IIIA GC has a poor prognosis with one-year survival rate 65%, two years - 39%, three years - 27%, four years - 22% and five years - 20% (according to the AJCC Cancer Staging Manual 6th Edition, which was used at the time of the diagnosis) [13]. Prognosis is described as a favourable for distal lesions, but worse for Bormann III type of tumours (ulcerating and infiltrating). EBVaGC patients have been described to have lower mortality (HR, 0.72; 95% CI 0.61 to 0.86, multicentre case series study with 4599 GC patients) [14]. The results were consistent with meta-analysis of 8336 GC patients, HR: 0.62, 95 % CI: 0.48-0.75; $P < 0.001$) where an association between EBV infection and better survival in Asian patients was found [15]. At the same time, several studies have showed no survival differences in EBV positive and negative GC patients [16,17]. For example, Huang S.C. et al. retrospectively analysing 1 020 GC patients' survival revealed no difference in survival between the EBVaGC cases and the EBV-negative cases ($p = 0.977$) [16].

Patient described in our clinical case reached five-year survival bar and exceeded it; his overall survival was 9 years and 1 month, even though he had prognostically unfavourable Bormann III type of tumour.

EBVaGC is described to predominantly localize in the middle or upper stomach and appear as superficially depressed or ulcerated lesion [18,19] that corresponds to presented case of ulcerated tumour in the middle 1/3 of the stomach body. A high prevalence of EBV involvement (25 to 41.2%) in gastric remnant carcinoma has been

reported [20,21]. In our case, tumour EBV status was determined only in the histological samples from the primary operation and not remnant carcinoma, which would have been interesting to compare.

Diagnostic work-up recommends an *endoscopic ultrasound* for localization and determination of tumour depth and regional lymph node involvement. If disseminated disease is not identified on imaging, a staging laparoscopy with biopsies of suspicious areas and peritoneal washings should be performed. Cross-sectional imaging misses peritoneal carcinomatosis in 13-37% of cases. Laparoscopy has a sensitivity and specificity of 84% and 100%, respectively, for detecting occult metastases and can spare 20-30% of patients from an unnecessary laparotomy. Regarding positron emission tomography (PET) it is important to note that about 40% of GC is not FDG-avid, especially the non-intestinal and non-mucinous containing histologies [22]. F-18 FDG PET/CT may have roles in predicting biological aggressiveness and prognosis based on the metabolic activity of primary tumours. It has been reported that F-18 FDG PET or PET/CT has 21% to 100% of sensitivity and 78% to 100% of specificity for detecting primary tumors. The wide ranges of sensitivity are associated with technical and histopathological factors affecting the visibility of primary tumors on PET/CT [23]. In our case, *endoscopic ultrasound might have assisted in the determination of clinical stage or it might have showed* no regional lymph node metastases as CT scans probably because of the abundant lymphocyte infiltration. Tumour morphology of this case falls into the histological category where 40% of GC is not FDG-avid. Per NCCN guidelines [10], PET may be used as an option for greater specificity in characterizing suspected disease in gastric cancer; however, anatomic imaging remains the standard recommendation.

Management of the localized disease includes subtotal gastrectomy that may be carried out if a macroscopic proximal margin of five centimetres can be achieved between the tumour and the gastroesophageal junction [5], as in the described case. Regarding lymphadenectomy overtime, the standard surgical treatment for management of gastric cancer evolved with the available evidence. D2 lymph node dissection was adopted by the Japanese in 1981, followed by the Italian Research Group in 1992. Since then, the majority of European nations have followed suit. The NCCN guidelines are currently recommending a D1+ or a modified D2 lymph node dissection, with the latter performed by experienced surgeons in high-volume center [10,24]. In the presented

case D1 lymph node dissection was performed during first surgery with no additional therapy. Local recurrence occurred subsequently, which aligns with literature data: regional recurrence rates as high as 88% following surgery alone have been reported in patients following D1 lymphadenectomy [24]. Noticeably patient population with D2 lymphadenectomy had lower mortality and improved median OS in stage I and III patients [24-26].

ESMO guidelines suggest perioperative chemotherapy for patients with \geq stage IB resectable GC [5], while NCCN guidelines for GC cT2 or higher any N offer treatment options: surgery or perioperative chemotherapy or preoperative chemoradiation or systemic therapy in surgically unresectable cases [10]. Described case was managed surgically with no additional perioperative chemotherapy.

When disease progressed to metastatic enrolment in the clinical trial was offered. Clinical trial results showed claudiximabplus EOX improved OS (median 8.7 vs 12.5 months; HR 0.5, 95% CI 0.28-0.73) compared to EOX alone. In the subpopulation with very high CLDN18.2 expression ($\geq 2+$ intensity in $\geq 70\%$ tumor cells), efficacy was more pronounced (PFS, 6.1 vs 9.1 mon; HR 0.46; OS, 9.3 v 16.6 mon; HR 0.44) [11,12]. Treatment induced durable disease stabilisation for 34 months in the presented case contributes to the knowledge that it is a very promising targeted therapy in certain patient groups. After disease progression second line regimen was chosen in the context of performance status, medical comorbidities, toxicity profile and drug reimbursement system, providing disease stabilisation and symptom control for additional 7 to 8 months.

Tumour MSI and / or PD-L1 expression was not determined at the time of metastatic disease as U.S. Food and Drug Administration granted approval for pembrolizumab only on September 22, 2017 [27], when patients' performance status had worsened to ECOG II-III. NCCN guidelines state that tumour EBV status is emerging and potential biomarker for personalized treatment strategies in GC, but is not currently recommended in clinical care. Several studies have shown that EBVaGC show higher MSI and / or PD-L1 expression. Among new emerging biomarkers NCCN guidelines recommend MMR or MSI testing should be considered on locally advanced, recurrent or metastatic carcinoma. PD-L1 testing may be considered on locally advanced, recurrent or metastatic carcinoma in patients who are candidates for treatment with PD-L1 inhibitors [10].

Declarations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Competing interests

The authors declare that they have no competing interests. The data used and analysed during the case presentation are not publicly available (to maintain privacy) but can be available from the corresponding author on reasonable request.

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Author's contribution

All authors have contributed significantly and are in agreement with the content of the manuscript.

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