

A Case of Epstein-Barr Virus (EBV) Associated Remnant Gastric Cancer Diagnosed 2 Years After the Distal Gastrectomy for Primary EBV-Associated Gastric Cancer Secondary to Polymyositis

Kenji MATSUMOTO¹⁾, Kazuo MIZUMOTO²⁾ and Riruke MARUYAMA³⁾

¹⁾Department of Internal Medicine, Ohda Municipal Hospital, 1428-3 Ohda-cho, Ohda, Shimane 694-0063, Japan

²⁾Department of Surgery, Ohda General Medicine Education Center, 1428-3 Ohda-cho, Ohda, Shimane 694-0063, Japan

³⁾Department of Pathology (Organ Pathology Sec.), Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan

(Received October 15, 2014; Accepted December 2, 2014)

A 54-year-old woman was admitted to our hospital with elevated creatine phosphokinase (3537U/L) and muscle weakness of the lower limbs without any cutaneous lesions. Therefore, we diagnosed polymyositis. Upper gastrointestinal endoscopy and computed tomographic scan revealed a Borrmann type III tumor on the lower body of the stomach. We performed laparoscopic distal gastrectomy. Two years after the distal gastrectomy, early remnant gastric cancer was found and we performed total remnant gastrectomy. *In situ hybridization* against EBV-encoded small RNA 1 revealed that most of the cancer cells of both tumors were Epstein-Barr virus positive.

Key words: Epstein-Barr Virus associated gastric cancer, remnant gastric cancer, dermatomyositis, polymyositis

INTRODUCTION

Dermatomyositis/polymyositis (DM/PM) is a rare disease with an incidence less than 0.001%. However, about 20-30% of patients with DM/PM develop malignancies. Although many types of malignancies have been reported in these patients, gastric cancer,

one of the most common neoplasms in Japan, is the most prevalent in Japan. In many cases, gastric cancer associated with DM/PM is already advanced at the time of diagnosis. Therefore, research on DM/PM is focused not only on the incidence of the disease but also on the poor prognosis [1].

In 1990, Burke *et al* detected Epstein-Barr virus (EBV) DNA by polymerase chain reaction in a paraffin-embedded block of undifferentiated lymphoepithelial gastric carcinoma [2]. Since that time, because of the popularization of *in situ* hybridization (ISH) with digoxigenin-labeled probe against EBV-encoded small RNA 1 (EBER) 1, EBV has been detected in approximately 10% of gastric cancers worldwide. Gastric cancer associated with EBV are known to differ from EBV-negative gastric cancers. Here, we report a patient who was diagnosed as having EBV-associated remnant gastric cancer 2 years after a distal gastrectomy for primary EBV-associated gastric cancer secondary to polymyositis.

CASE PRESENTATION

In January 2012, a 54-year-old woman was admitted to our hospital with elevated creatine phosphokinase (3537U/L) and muscle weakness of the lower limbs without any cutaneous lesions. Her younger brother had been diagnosed with esophageal, pharyngeal, gastric, and colon cancers, and two cousins had died from gastric cancer at 31 and 47 years of age. Magnetic resonance imaging showed high signal intensity in the proximal muscles of the lower limbs. Therefore, we diagnosed polymyositis and initiated treatment with prednisolone at 60mg/

Address for correspondence and reprint requests: Kazuo Mizumoto, M.D., Ph.D.

Department of Surgery, Ohda General Medicine Education Center, 1428-3 Ohda-cho, Ohda, Shimane 694-0063, Japan

Tel: +81-854-82-0330

Fax: +81-854-84-7449

E-mail: k.mizumoto@ohda-hp.ohda.shimane.jp

day. Upper gastrointestinal endoscopy and computed tomographic scan revealed a Borrmann type III tumor on the lower body of the stomach. Colonoscopy revealed no abnormal findings. In February 2012, we performed laparoscopic distal gastrectomy with the dissection of regional lymph nodes and Roux-en-Y reconstruction. A 35 × 30-mm type III tumor was located on the greater omentum side in the middle part of the stomach (Fig. 1). Microscopi-

cally, most of the cancer cells appeared as poorly differentiated adenocarcinoma and the tumor had a medullary stroma with severe lymphocytic infiltration (Fig. 2). The cancer cells had invaded the muscularis propria and had metastasized to 2 of 27 regional lymph nodes.

Two years after the distal gastrectomy, early remnant gastric cancer was found on follow-up upper gastrointestinal endoscopy. In February 2014, the

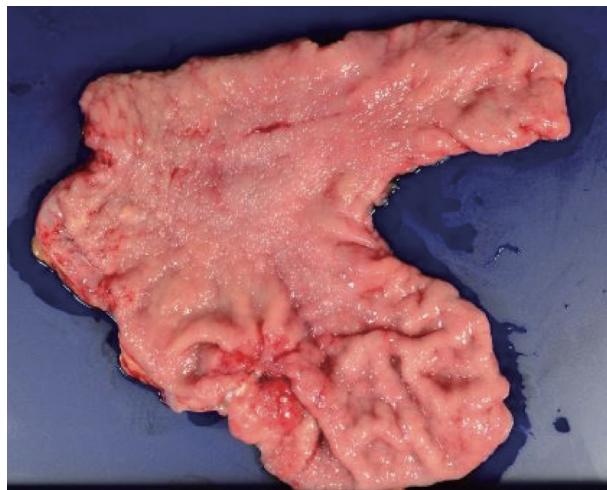


Fig. 1. Macroscopic findings of the resected specimen showed a 35 × 30-mm type III tumor was located on the greater omentum side in the middle part of the stomach.

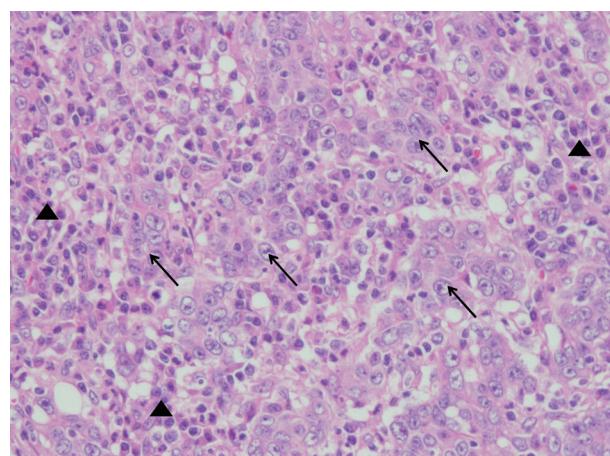


Fig. 2. Microscopically, most of the cancer cells appeared as poorly differentiated adenocarcinoma (arrow) and severe lymphocytic infiltration (arrow head) was found (hematoxylin-eosin, original magnification × 400).

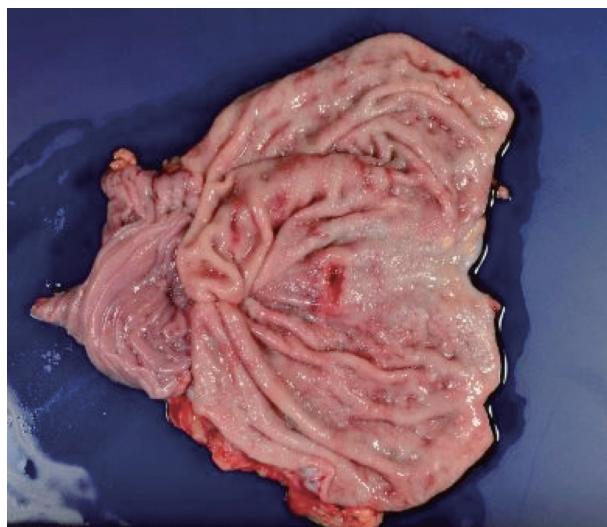


Fig. 3. Macroscopic findings of the resected specimen showed a 18 × 11-mm type IIc+III tumor was located on the lesser omentum side of the middle part of the remnant stomach.

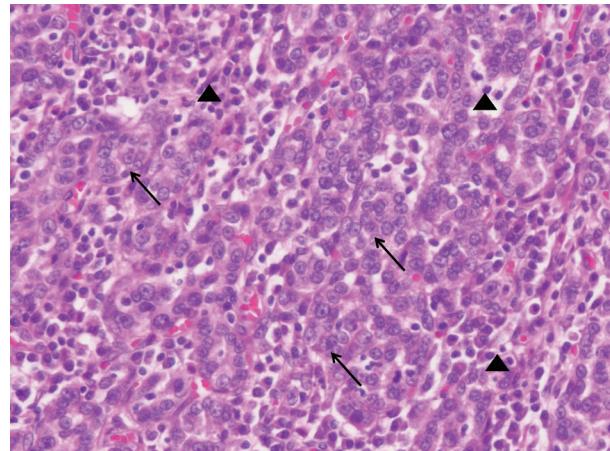


Fig. 4. Microscopically, most of the cancer cells appeared as poorly differentiated adenocarcinoma (arrow) and severe lymphocytic infiltration (arrow head) was found (hematoxylin-eosin, original magnification × 400).

patient was readmitted for further surgery. We performed total remnant gastrectomy with the dissection of regional lymph nodes and Roux-en-Y reconstruction. An 18×11 -mm type IIc + III tumor was located on the lesser omentum side of the middle part of the remnant stomach (Fig. 3). Microscopically, most of cancer cells appeared as poorly differentiated adenocarcinoma with severe lymphocytic infiltration (Fig. 4). The cancer cells had invaded the submucosa but had not metastasized to regional lymph nodes. ISH against EBER 1 revealed that most of the cancer cells in both tumors were EBV positive (Fig. 5a-b). Furthermore, adequate care was taken to protect the privacy of the patient in this case. She was informed of the present report's intent and we did not use the clinical data study for any purpose other than for present study.

DISCUSSION

EBV is a gamma-herpes-virus containing a double-stranded DNA genome of approximately 170 kbp. The virus may cause infectious mononucleosis during initial infection and can be maintained asymptotically in a latent form in memory B lymphocytes. More than 90% of infected adults become carriers, because EBV can asymptotically

in a latent form in memory B lymphocytes. However, EBV is an oncogenic virus and is associated with several malignancies such as naso-pharyngeal carcinoma, Hodgkin lymphoma, and gastric cancer [3]. Gastric cancer associated with EBV show distinct clinicopathological features. ISH for EBERs demonstrated EBV infection in all neoplastic cells in gastric cancers. Histopathologically gastric cancer associated with EBV are characterized by poorly differentiated adenocarcinoma with marked lymphocytic infiltration into the stromal tissue, classified as gastric cancer with lymphoid stroma (GCLS) [4]. The clinical features of EBV positive gastric cancer also differ from EBV-negative gastric cancer with higher incidence in male, a more proximal location, and relatively more favorable prognosis reported for EBV-positive gastric cancer [5].

Kaizaki *et al* reported that, in patients whose primary gastric cancers were EBV-positive, 55% of remnant gastric cancers were also EBV-positive. However, in patients whose primary gastric cancers were EBV-negative, only 2.9% of remnant gastric cancers were EBV-positive [6]. Kaizaki *et al* also reported that the interval between the first and second operation for EBV positive gastric cancer (3.5 ± 2.4 years) was shorter than that for EBV-negative gastric cancer (6.9 ± 4.7 years). Therefore, they

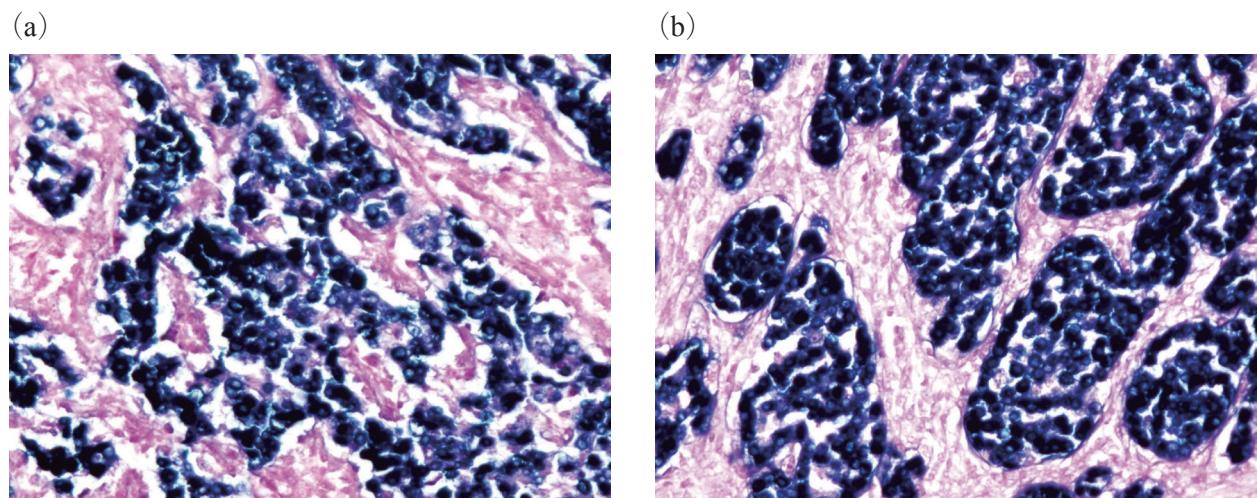


Fig. 5. a) primary gastric cancer. b) remnant gastric cancer.

Paraffin-embedded sections were deparaffinized with xylene, hydrated with ethanol, and predigested with proteinase K. EBV-ISH was performed using Fluorescein-Conjugated INFORM EBER Probe and VENTANA ISH NEW BLUE Detection Kit (VENTANA, Tucson, USA) according to the manufacturer's instructions just before color development. The fluorescein labeled probe was then visualized with 5-Bromo-4-chloro-3-indolyl phosphate (BCIP) and nitro blue tetrazolium (NBT) chromogen, which produced a blue precipitate that is readily detected by light microscopy. (original magnification $\times 400$).

suggested the presence of synchronized multiple cancers [6]. In addition, Hosokawa *et al* reported that the frequency of EBV-positive gastric cancer in metachronous gastric cancer was 47.4% for primary lesions and 31.1% for secondary lesions. Therefore, they suggested that determining the presence or absence of EBV in cancer tissues was useful for identifying high-risk patients with metachronous cancer [7]. In the present case, using ISH for EBERs we retrospectively confirmed that both primary and remnant gastric cancers were associated with EBV. We propose that, for improved risk management, ISH for EBERs should be performed at the time of diagnosis if the primary lesion shows histopathological features of EBV-positive gastric cancer. It remains unclear whether the present case was synchronized or metachronous gastric cancer. However, if the primary lesion is EBV-positive, close clinical follow-up is indicated because of the incident of remnant gastric cancer and short interval between first and second operation.

In general, endoscopic submucosal dissection (ESD) for remnant gastric cancer is difficult because of fibrosis and the presence of staples at the anastomotic site. Tasaki *et al* reported that the vertical margins of early remnant EBV-associated gastric cancer, excised using ESD, were unclear [8]. Total remnant gastrectomy may therefore be an appropriate treatment option for remnant EBV-associated gastric cancers, because of the multiple carcinogenesis of EBV-associated gastric cancer and the difficulties involved with ESD in the remnant stomach.

The etiology of DM/PM is still unknown, but various causative factors have been proposed, including autoantibodies, toxins, drugs, and viral infection. RNA fragments of coxsackie B virus have been found in the muscles of patients with DM/PM [9]. It was suggested that anti-Jo-1 antibodies could arise as a result of immunization against picornaviruses [10]. Infection with EBV may also be triggered in some patients with DM/PM. Kamel *et al* found that 6 of 18 lymphoproliferative disorders that developed in patients with rheumatoid arthritis or DM were EBER 1 positive [11]. Yamashita *et al* hypothesized that EBV was associated with the development of both gastric cancer and DM/PM or that EBV-associated gastric cancer caused DM as a

paraneoplastic syndrome [12].

We performed a literature search using PubMed with the following terms: Epstein Barr virus-associated remnant gastric cancer, dermatomyositis, and polymyositis. We found no result; therefore, we believe that this is the first report of EBV-associated remnant gastric cancer in a patient with PM. However, in view of the frequency of EBV-associated gastric cancers, it is likely that many similar unreported cases exist. We hope that future large-scale studies may provide new information on the etiology of DM/PM and EBV-associated gastric cancer.

REFERENCES

- 1) Kaneko K, Kikuchi R, Arai Y and Hidano M (1985) Dermatomyositis and malignancy. *Hifu Rinsyo* 27: 499-505.
- 2) Burke AP, Yen TSB, Shekitka KM and Sabin LH (1990) Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. *Mod Pathol* 3: 377-380.
- 3) Niedobitek G, Agathanggelou A, Steven N and Young LS (2000) Epstein-Barr virus (EBV) in infectious mononucleosis: detection of the virus in tonsillar B lymphocytes but not in desquamated oropharyngeal epithelial cells. *Mol Pathol* 53: 37-42.
- 4) Tokunaga M, Uemura Y, Tokudome T, Ishidate T, Masuda H, Okazaki E, Kaneko K, Naue S, Ito M and Okamura A (1993) Epstein-Barr virus related gastric cancer in Japan: a molecular patho-epidemiological study. *Acta Pathol Jpn* 43: 574-58.
- 5) Murphy G, Pfeiffer R, Camargo MC and Rabkin CS (2009) Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differ based on sex and anatomic location. *Gastroenterology* 137: 824-833.
- 6) Kaizaki Y, Hosokawa O, Hattori M, Hayashi H and Dohden K (2004) Clinicopathological feature and development process of metachronous gastric remnant carcinoma: from the standpoint of Epstein-Barr virus-associated gastric carcinoma. *Stomach and Intestine* 39: 1009-1019.
- 7) Hosokawa O, Tsuda J, Watanabe K, Tanigawa Y, Shirasaki S and Hayashi H (1995) The detection of the assesory lesions in synchronous multiple gastric cancer and the early detection of meta-

- chronous gastric cancer. *Jpn Gastroenterol Surg* 28: 2107-2110.
- 8) Tasaki T, Nagai T, Nakashima H, Nakagawa Y, Hisamatsu A, Hashinaga M, Okawara H, Yokoyama S, Kikuchi T and Kagawa K (2011) A case of Epstein-Barr (EBV)-associated cancer of the gastric remnant 2 year after a distal gastrectomy for primary gastric cancer which was also associated with EBV. *Gastroenterological Endoscopy* 53: 270-274.
- 9) Bowles NE, Dubowitz V, Sewry CA and Archard LC (1987) Dermatomyositis, polymyositis and Coxsackie B-virus infection. *Lancet* 1: 1004-1007.
- 10) Mathews MB and Bernstein RM (1983) Myositis autoantibody inhibits histidyl tRNA synthetase: a model for autoimmunity. *Nature* 304: 177-179.
- 11) Kamel OW, van de Rijn M, LeBrun DP, Weiss LM, Warnke RA and Dorfman RF (1994) Lymphoid neoplasms in patients with rheumatoid arthritis and dermatomyositis: frequency of Epstein-Barr virus and other features associated with immunosuppression. *Hun Pathol* 25: 638-643.
- 12) Yamashita K, Hosokawa M, Hirohashi S, Arimura Y, Endo T, Denno R, Ikeda T and Imai K (2001) Epstein-Barr virus-associated gastric cancer in a patient with dermatomyositis. *Internal Medicine* 40: 96-99.