Slow Progression of Poorly Differentiated Gastric Carcinoma Associated with Epstein-Barr Virus Infection: 12-year Follow-up

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Abstract

Epstein-Barr virus (EBV)-associated gastric carcinoma accounts for nearly 10% of all gastric carcinomas and has distinct demographic, clinical and pathological features compared with EBV-negative gastric carcinoma. We herein report the case of a patient with EBV-associated gastric carcinoma followed up for 12 years during the natural course of the disease. The appearance of the tumor on gastroscopy and computed tomography gradually changed, and the size of the lesion increased very slowly during the 12 years, without metastasis. The present case indicates that some EBV-associated gastric carcinomas progress very slowly.

Key words: Epstein-Barr virus, gastric carcinoma, natural history


Introduction

Epstein-Barr virus (EBV) is a well-known cause of gastric carcinoma. EBV-associated gastric carcinoma accounts for nearly 10% of all gastric carcinomas and is characterized by the monoclonal growth of EBV-infected gastric epithelial cells (1, 2). Patients with EBV-associated gastric carcinoma have distinct demographic, clinical and pathological features compared to that observed in subjects with EBV-negative gastric carcinoma. Major features of EBV-associated gastric carcinoma include a male predominance, young age, tumor location in the gastric cardia or body, high incidence of tumor presentation in the remnant stomach, presence of multiple carcinomas, lymphoepithelioma-like histology and presentation as either moderate or poorly differentiated adenocarcinoma (3-5). Moreover, global CpG island DNA methylation in the promoter region of many cancer-related genes is a striking molecular characteristic of this type of carcinoma (6, 7). Recently, an international pooled analysis revealed that patients with EBV-associated gastric carcinoma have a better prognosis than those with EBV-negative gastric carcinoma (8). However, most patients in that analysis received treatment for the carcinoma, and no previous studies have reported the natural course of EBV-associated gastric carcinoma. In this report, we describe the case of a patient with EBV-associated gastric carcinoma who was observed over the course of 12 years.

Case Report

A 58-year-old man first presented to our hospital to undergo treatment for hepatocellular carcinoma and liver cirrhosis due to hepatitis C virus 12 years before his most recent admission. At that time, upper gastrointestinal endoscopy revealed an ulcerated saucer-like tumor in the upper gastric body of the remnant stomach after subtotal gastrectomy for a duodenal ulcer at 24 years of age (Fig. 1A). As he was under treatment for hepatocellular carcinoma, he was scheduled for periodic follow-up for the gastric lesion without intensive examinations. No remarkable changes were observed on gastroscopy two or four years later (data not shown, Fig. 1B); however, a biopsy of the lesion showed diffuse-type poorly differentiated carcinoma with tubular...
formed every two years.

During the current admission, and the biopsy disclosed the coexistence of poorly differentiated and tubular adenocarcinoma with diffuse-type poorly differentiated carcinoma with weak lymphocytic infiltration (Fig. 2A, B). EBV-encoded small RNA (EBER) in situ hybridization (ISH) revealed an even distribution of EBER-positive cancer cells, although no EBER-positive cells were noted in the surrounding non-tumor tissue (Fig. 2C, D). The cancer cells were positive for CAM5.2 and p53 immunostaining, but negative for leukocyte common antigen and p16 (data not shown). The patient was therefore diagnosed with EBV-associated gastric carcinoma. We again performed a histopathological examination of the biopsy samples obtained 10 and 8 years before the current admission, and the biopsy disclosed the coexistence of poorly differentiated and tubular adenocarcinoma with EBER-positive carcinoma cells on ISH (Fig. 2E, F).

In summary, we were able to observe the 12-year natural course of a case of EBV-associated gastric carcinoma on gastroscopy (Fig. 1A-D) and CT (Fig. 1E-H). A CT scan showed a well-circumscribed mass in the lesser curvature of the upper body of the stomach; however, no metastasis in the lymph nodes or other organs was observed. In addition, the tumor appearance gradually changed on both gastroscopy and CT, and the size of the lesion increased very slowly during the course of 12 years.
This report describes a case of very slow progression of an EBV-associated gastric carcinoma over the course of 12 years. The patient exhibited the typical clinical features of EBV-associated gastric carcinoma, including a male sex, tumor location in the gastric body and presentation in the
remnant stomach (3-5). The endoscopic and CT findings in this case were also typical for EBV-associated gastric carcinoma, including an ulcerated saucer-like tumor accompanied by marked thickening of the gastric wall (10). These characteristic features were already present 12 years previously. Thereafter, these findings gradually changed, although the rate of tumor progression was extremely slow. Ten years earlier, histology revealed poorly differentiated diffuse-type adenocarcinoma without a lymphoepithelioma-like histology.ISH demonstrated that almost all of the neoplastic cells were EBER-positive and remained so on the biopsy sample obtained eight years before the most recent admission.

A relatively favorable prognosis of EBV-associated gastric carcinoma compared with EBV-negative gastric carcinoma has been proposed in earlier studies. EBV-associated gastric carcinoma shows a lower rate of lymph node involvement, especially within the submucosa during the early stage (11). A recent international pooled analysis demonstrated that this type of carcinoma tends to have a lower tumor-node-metastasis (TNM) stage and is associated with a relative survival advantage, even when adjusted for the TNM stage and other prognostic indicators (8). Although the reason for the superior prognosis of EBV-associated gastric carcinoma is unclear, we speculate that the rate of progression of EBV-associated gastric carcinoma is slower than that of EBV-negative gastric carcinoma. However, the nature of progression during the natural course of the lesion has remained unknown until now. The case described in this report indicates that some EBV-associated gastric carcinomas progress very slowly.

In the present case, the treatment for hepatocellular carcinoma may have affected the natural course of the gastric carcinoma. The patient received three sessions of transcatheter arterial chemoembolization (TACE) with an emulsion of epirubicin hydrochloride and lipiodol, followed by the injection of gelatin sponge particles into the feeding artery at seven, nine and 12 years and partial hepatectomy at both seven, nine and 12 years and partial hepatectomy at both seven and nine years before the most recent admission; he achieved complete remission after receiving these therapies. Epirubicin hydrochloride, an anthracycline cytotoxic agent, may have had an effect on the rate of progression of the gastric carcinoma. However, the gastric carcinoma findings observed on gastroscopy, CT and histology did not change after TACE, and the speed of progression of the gastric carcinoma continued to be slow for seven years after the termination of therapy for the hepatocellular carcinoma. Therefore, we suggest that the natural course of progression of the EBV-associated gastric carcinoma was slow in this case.

In conclusion, we herein reported a case of EBV-associated gastric carcinoma exhibiting very slow progression during its natural course. Although further studies with larger numbers of patients are required to clarify the natural course of EBV-associated gastric carcinoma, this case implies the need for a distinct treatment strategy for EBV-associated gastric carcinoma.

The authors state that they have no Conflict of Interest (COI).

References


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