Abstract. The present case report presents a rare case of Epstein-Barr virus (EBV)-associated early gastric carcinoma with lymphoid stroma, accompanied by lymph node metastasis. A 61-year-old woman was referred to our hospital following observation of a gastric mass lesion that was initially diagnosed at a medical check-up. Endoscopic ultrasonography revealed a well-circumscribed hypoechoic mass located predominantly within the submucosa and the mucosa. Biopsy specimens of the lesion indicated the possibility of carcinoma with lymphoid stroma with a lymphoepithelial lesion. Abdominal contrast-enhanced computed tomography (CT) revealed a well-defined mass with homogeneous enhancement approximately 1.2 cm in diameter in the middle part of the stomach, demonstrating lymphadenopathy in the perigastric area at a maximum size of 1.4 cm in diameter. The patient underwent laparoscopic distal gastrectomy with regional lymphadenectomy due to suspicion of a gastric carcinoma with lymphoid stroma. Histopathological and immunohistochemical findings verified the diagnosis of carcinoma with lymphoid stroma. The present case is informative of the pathological characteristics of this condition, and clinicians should recognize the features of this disease to make an accurate diagnosis and select the appropriate treatment.

Introduction

Epstein-Barr virus (EBV) is an established cause of various types of lymphoma including Burkitt lymphoma and Hodgkin's lymphoma, and nasopharyngeal carcinoma. Similar to Helicobacter pylori, EBV is accepted as an infective agent that plays an important pathogenic role in gastric cancer. Gastric carcinoma with lymphoid stroma (GCLS) is a rare histological subgroup of gastric cancers, constituting approximately 1-4% of all gastric carcinomas. Approximately 80% of the reported GCLS cases are associated with an EBV infection. To diagnose GCLS accurately, the immunohistochemical approach of the tumor was important in addition to sophisticated observation of the endoscopic findings, while standardized diagnostic criteria are lacking. Early gastric cancer has favorable outcomes with curative resection including gastrectomy and endoscopic submucosal resection. The current prognosis for GCLS is favorable due to its lower lymph node metastatic rate and a higher survival rate despite deep submucosal invasion of tumor cells.

Case report

A 61-year-old woman was referred to Kochi Medical School Hospital as a result of an evaluation of a gastric mass lesion that was initially diagnosed by a local medical doctor. Endoscopic ultrasonography, including serum carcinoembryonic antigen and cancer antigen 19-9 screening showed no significant abnormalities. Esophagogastroduodenoscopy (EGD) revealed an elevated lesion with a central irregularly depressed area in the posterior wall of the middle third of the stomach (Fig. 1A). The elevated lesion descended in a gradual slope to the surrounding mucosa when indigo carmine dye was used in chromoendoscopy (Fig. 1B).
well-circumscribed hypoechoic mass located predominantly within the submucosa and the mucosa (Fig. 2, arrow). Biopsy specimens of the lesion showed prominent lymphocyte infiltration with a lymphoepithelial lesion, suspected of being carcinoma with lymphoid stroma.

Abdominal contrast-enhanced computed tomography (CT) revealed a well-defined mass with homogeneous enhancement approximately 1.2 cm in diameter in the middle part of the stomach. The CT analysis also revealed lymphadenopathy in the perigastric area with a maximum size of 1.4 cm in diameter (Fig. 3, arrow). Double-contrast upper gastrointestinal imaging shows a round filling defect with central collection of Barium measuring 1.2 cm with a clear margin in the middle part of the stomach (Fig. 4, arrow).

As a result of these investigations we suspected that the patient had a gastric carcinoma with lymphoid stroma accompanying lymph node metastases. The patient underwent laparoscopic distal gastrectomy with regional lymphadenectomy followed by Billroth I reconstruction. Macroscopic examination of the resected specimen showed a slightly elevated lesion-like submucosal tumor with a central depression measuring 1.2x1.2 cm (Fig. 5, arrow).

Microscopic examination of the patient specimens showed a bulging mass consists of poorly differentiated adenocarcinoma. There was expansive growth into the submucosa that formed tubular structures and cancer nests with a submucosal depth of invasion of 4,000 µm (Fig. 6A and B). The tumor cells were positive for EBV-encoded RNA by in situ hybridization (EBER-ISH; Fig. 6C and D), and the expression of Ki-67 in cancer cells was 25%. In addition, there was one lymph node metastasis in 13 dissected lymph nodes, which was detected as lymphadenopathy in the CT imaging but there was no lymphovascular infiltration. The lymph node station number with metastasis was 3 according to anatomical definition of Japanese classification of gastric carcinoma (6), which was 2.0 cm in diameter, consisting of diffuse spreading of adenocarcinoma in the lymph node (Fig. 7A and B). The results of the other immunohistochemical investigations of the primary gastric cancer and metastatic lymph node showed positive immunostaining for cytokeratin (AE1/AE3) and negative for CDX-2. Marked infiltration of lymphoid cells was observed in the tumor stroma and these were negative for EBER-ISH. The postoperative course was uneventful and the patient has been well without evidence of recurrence for two months following the operation.

Discussion

GCLS has distinct clinical characteristics that occur in old age and predominantly in males. These tumors arise in the cardia or middle portion of the stomach and have prominent lymphocyte infiltration, particularly in the submucosa (7,8). EBER-ISH is the gold standard for determining EBV infection in histological sections. Carcinoma cells and dysplastic epithelial cells are positive for EBV, but not the normal epithelium or lymphoid stroma in EBV-associated GCLS. The estimate of EBV positivity in gastric cancer is 8.7% overall according to a meta-analysis, and the frequencies are not statistically different among different anatomical locations (1). Although EBV is considered to be the main cause of the lymphocytic response, the mechanism by which EBV contributes to the carcinogenesis of gastric mucosa has not been elucidated (9).
The rate of metastasis to the lymph node in submucosal cancers with GCLS is significantly lower than in conventional early gastric cancer, especially those involving an EBV infection (2,8). The spread of tumors through the gastric wall may be prevented by abundant lymphocytic reactions, which regulate the anti-tumor effect of immunity, resulting in a more favorable prognosis as a result of the immune response to the tumor (8,9). An investigation of 41 GCLS in early gastric cancer reported that there was no lymph node metastasis if the submucosal depth of invasion was ≤2,000 µm from the muscularis mucosa, while the incidence rate of lymph node metastasis was 28.6% if the SM depth of invasion was >2,000 µm (8).

Regarding the association between the sizes of gastric carcinoma and lymph node metastasis, Kim et al reported that there was no lymph node metastasis in the tumors with sizes <1.0 cm, and 2-dimensional tumor size was the only significant risk factor for lymph node metastasis in the analysis for 574 patients with differentiated minute submucosal cancer (10). Shin et al reported that tumor size was smaller in GCLS, 2.1 cm, than in no-GCLS, 3.1 cm, and only two patients with GCLS (3.4%) showed lymph node metastasis in the analysis of 1696 patients with early gastric cancer (11). Therefore, the lymph node metastasis of small size GCLS as the present case seems to be extremely rare.

In the present case, it was difficult to detect the submucosal invasion during EGD without EUS, because the majority of the lesion was a bulging mass with abundant lymphoid stroma that was located in the submucosa by pathological investigation. Standard radical gastrectomy with regional lymphadenectomy is important, recommending in cases with submucosal invasion of tumor cells to a depth of more than 2,000 µm, regardless of tumor size. EUS seems to be an essential modality to estimate the depth of tumor invasion in the diagnostic and therapeutic management of GCLS.
Since GCLS is a rare disease, clinicians should recognize the features of this entity to make an accurate diagnosis and select the appropriate treatment. Further studies and assessments of additional cases are required to establish standardized recommendation criteria and management for this entity.

References