Lymphoepithelioma-Like Carcinoma of the Stomach with Epithelioid Granulomas

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Abstract
An 83-year-old Japanese man was admitted to our hospital for gastric adenocarcinoma mimicking a submucosal tumor in the gastric body. Considering his general condition, partial resection of the stomach and dissection of regional lymph nodes were performed; a dome-shaped tumor that was largely covered by normal mucosa and having a shallow central stellate ulcer was removed. Histopathologically, the carcinoma cell nests were surrounded by prominent lymphoid stroma. Sarcoid-like epithelioid granulomas were noted both in the tumor stroma and in the regional lymph node with metastasis. Epstein-Barr virus (EBV)-encoded RNA (EBER) in situ hybridization showed an intense and diffuse positive reaction in the carcinoma cells and no reaction in the surrounding gastric and lymphoid tissues. While the presence of lymphoid stroma is a characteristic finding in EBV-associated lymphoepithelioma-like carcinoma, sarcoid-like epithelioid granulomas might be associated with latent EBV infection.

Introduction
Lymphoepithelioma-like carcinoma (LLC) is a rare and peculiar type of gastric carcinoma that is reported to be associated with latent Epstein-Barr virus (EBV) infection. On the other hand, the development of epithelioid granuloma similar to that seen in systemic sarcoïdosis is termed as a sarcoïd-like reaction and may be observed in tumors themselves or in the regional lymph nodes draining the malignant tumors. Although this...
reaction is rarely observed in conventional gastric carcinoma, epithelioid granulomas have been reported to occur in LLCs of the stomach [1]. We describe a case of LLC of the stomach accompanied by many epithelioid granulomas both in the tumor tissue and in the metastatic regional lymph node.

Case Report

An 83-year-old Japanese man was admitted to the neighborhood hospital for epigastric pain. The initial endoscopic biopsy revealed no malignancy. An endoscopic biopsy performed 2 months later revealed the presence of gastric cancer, and he was referred to our hospital for further examination and surgical treatment.

The physical examination and laboratory data first performed at our hospital yielded no abnormal findings; superficial lymphadenopathy was not detected, and no abnormalities were apparent in the eyes, joints, or respiratory and circulatory systems. Gastroduodenal endoscopy revealed a submucosal tumor (SMT)-like mass covering the anterior and lower walls of the gastric body, with a small ulcer on the top of the lesion (fig. 1). Biopsy of the specimen thus obtained revealed solid proliferation of the carcinoma cells, but the histological type of the lesion could not be established. Upper gastrointestinal barium contrast study showed an elevated tumor, with an irregularly shaped depression on its surface, located on the anterior wall of the lower gastric body (fig. 2). The findings of computed tomography were negative for tumor, enlargement of the hilar nor intraabdominal lymph nodes, and liver metastasis. On the basis of these findings, the clinical diagnosis of gastric cancer was established.

Considering the patient’s age, general condition, and quality of life after the operation, partial resection of the stomach was performed. During laparotomy, lymph nodes along the right gastroepiploic vessels were found to be enlarged and were dissected.

Macroscopic findings of the resected specimen revealed a dome-shaped tumor measuring about 2 cm in diameter, largely covered by normal-appearing gastric mucosa and having a shallow, central, stellate depression (fig. 3). Panoramic view of the hematoxylin and eosin (H&E) section showed that this SMT-like mass was clearly demarcated and composed of nodular growths, which extended into the deepest part of the submucosa (fig. 4). H&E sections showed round-to-short spindle carcinoma cells that were arranged in sheets and surrounded by dense infiltration of lymphocytes and plasma cells throughout the tumor stroma. One of the dissected lymph nodes revealed tumor metastasis. Epithelioid granuloma was observed both in the tumor stroma and in the lymph node with metastasis (fig. 5).

Immunohistochemical staining for expression of cytokeratin (CAM5.2) and epithelial membrane antigen and carbohydrate antigen 19-9 were positive. On the other hand, EBV-encoded nuclear antigen 2 (EBNA-2) and latent membrane protein 1 were negative. In situ hybridization for EBV-encoded small RNA 1 (EBER-1) was performed for the lesion, and an intensive nuclear hybridization signal was seen in areas corresponding to the cancer cell and nest (fig. 6). Furthermore, immunological examination was performed after surgery. The levels of serum EBV-specific antibodies were elevated (VCA-IgG 1:160; EBNA 1:80). Finally, EBV-associated LLC of the stomach was diagnosed and staged as T1, N1, M0, and stage IB according to the WHO Classification of Tumours, Pathology and Genetics of Tumours of the Digestive System, 2000.

The postoperative course was uneventful, and there were no complications. The patient was followed up for 24 months and was found to have recovered well, with no recurrence.

Discussion

LLC is a type of gastric carcinoma with characteristic clinicopathologic features [1, 2]; it is also called gastric carcinoma with lymphoid stroma [3]. LLC is also known as EBV-associated gastric carcinoma because LLC lesions have been found to be infected with EBV [4, 5]. After the publication of the report by Moore and Foote indicating that medullary carcinoma of the breast with lymphoid infiltration is associated with EBV
infection [6], similar findings were reported regarding carcinomas of the stomach [3]. It has been reported that worldwide crude EBV-positive prevalence was 8.29% for gastric adenocarcinoma, with 7.08% for intestinal type and 9.82% for diffuse type [7]. According to the WHO method for the classification of tumors of the digestive system, LLC of the stomach is a type of tubular carcinoma [8].

LLC of the stomach is known to have a favorable prognosis despite the fact that tumor cells are often of the poorly differentiated type [9]. Watanabe et al. reported that the prognosis of LLC of the stomach was better than that of ordinary gastric carcinoma and also suggested that lymphocytic infiltration in LLC was a host defense reaction against the cancer and that a greater extent of lymphocytic infiltration was indicative of better prognosis [3].

Macroscopically, LLCs of the stomach often mimic SMTs [1, 10]; therefore, accurate diagnosis may be difficult before the operation, even if endoscopic biopsy is performed [11, 12]. In fact, even in our case, a definitive diagnosis of LLC could not be established using the sample obtained by endoscopic biopsy. Takahashi et al. showed the strategy for the diagnosis and treatment of gastric SMTs by laparoscopic surgery based on tumor measuring, and recommended that this procedure is very useful, since it helps accurate diagnosis and can be followed by curative surgery [13]. In our case, we could not arrive at a definite diagnosis, despite performing endoscopic biopsy thrice, because the tumor mimicked SMT. We performed laparotomy for local resection and were finally able to establish the diagnosis of LLC on the basis of the histological characteristics of the surgical biopsy specimen. This strategy, which was proposed by Takahashi et al., will be helpful because for the diagnosis of LLC, it is necessary to evaluate the tumor as a whole, using the molecular biological method in order to diagnose LLC definitely [13].

On the other hand, since the initial report by Herxheimer [14], many cases of epithelioid granulomas associated with malignant tumors have been documented. Although several hypotheses have been proposed, the mechanism of this reaction is still unknown. Bhatia et al. reported that granulomatous reaction within neoplastic tissue was believed to be the result of immune T cell-dependent reaction to degrade tumor particles and similarly, granuloma formation takes place in regional lymph nodes draining the tumor in characteristic location in the sinus [15]. With regard to gastric cancer, some reports have shown that the incidence of epithelioid granulomas in the regional lymph nodes decreased with the progress of the cancer [16] and that gastric cancer with epithelioid granulomas did not recur, suggesting that the prognosis of such lesions is better than that of gastric cancers without epithelioid granulomas [17]. These reports support the hypothesis that the development of epithelioid granulomas may be a type of immunological response and can be recognized as a favorable prognostic factor with regard to immune response to the tumor.

It is indeed a fact that granuloma formation is quite common in the regional lymph node of the tumor tissue but rarely in the tumor tissue, particularly of LLC. Granulomatous reaction so-called sarcoid reaction is frequently encountered in the regional lymph node. We considered that as one of the tumor drainage lymphadenopathies. In the tumor tissue, however, many epithelioid granulomas with multinucleated giant cells are extremely rare in the tumor tissue. To the best of our knowledge, only two reports have been published on epithelioid granulomas occurring in LLC of the stomach [1, 18]. Iwashita et al. [1] reported that epithelioid granulomas were
found in the stroma of the tumor in 13 (16.6%) of the subjects included in their study and in both the stroma and in the regional lymph nodes in 5 (10.3%) of the 78 lesions in 77 patients with medullary carcinoma of the stomach with lymphoid infiltration; similar to the reports by previous studies, their report also indicated that the presence of epithelioid granulomas in the stroma with prominent lymphocyte infiltration supports the theory that stromal reaction in LLC represents the host response to the carcinoma.

Although the dissected lymph nodes revealed tumor metastasis in our case, epithelioid granulomas were found both in the stroma and in the regional lymph node with metastasis. The patient is being followed up even 2 years after the operation, and there has been no recurrence until now. Considering the immune response seen in this interesting case, it can be inferred that the presence of epithelioid granuloma with prominent lymphocyte infiltration is associated with a favorable prognosis.

![Fig. 1](image_url)

**Fig. 1.** Endoscopic finding. An elevated lesion mimicking a SMT with a small, central ulcer is seen on the anterior wall of the lower part of the gastric body.
Fig. 2. Gastroduodenal barium study. Double-contrast barium study shows a SMT-like nodule, with an irregularly shaped depression on its surface, on the anterior wall of the lower part of the gastric body.

Fig. 3. Macroscopic view of the resected specimen. An elevated tumor measuring about 2 cm in diameter with a central stellate depression is apparent.
**Fig. 4.** Panoramic view of the H&E section. A SMT-like mass is clearly demarcated and composed of lobulated nodules. Tumor invasion is up to the lamina submucosa.

**Fig. 5.** H&E sections of the tumor. Diffuse proliferation of the tumor cells is seen with no glandular structures (a). Marked infiltration of lymphocytes and plasma cells is observed in the tumor stroma (b). Epithelioid granulomas with Langhans type giant cells are noted in the lymphoid stroma (c).
**Fig. 6.** EBER-1 in situ hybridization. Diffuse and intense signals are observed in the nuclei of the cancer cells. The positive reaction indicates the presence of nodules of carcinoma cells, with abundant stroma.

**References**

1. Iwashita A, Ueyama T, Yamada Y, et al: Clinicopathological study on medullary carcinoma with lymphoid stroma of the stomach. I to Cho (Stomach and Intestine) 1991;10:1159–1166 [Japanese with English abstract].
2. Minamoto T, Mai M, Watanabe K, et al: Medullary carcinoma with lymphocytic infiltration of the stomach. Clinicopathologic study of the subpopulations of infiltrating lymphocytes in the tumor. Cancer 1990;66:945–952.
3. Watanabe H, Enjoji M, Imai T: Gastric carcinoma with lymphoid stroma. Its morphologic characteristics and prognostic correlations. Cancer 1976;38:232–243.
4. Burke AP, Yen TSB, Shekitka KM, et al: Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. Mod Pathol 1990;3:377–380.
5. Tokunaga M, Uemura Y, Tokudome T, et al: Epstein-Barr virus related gastric cancer in Japan: a molecular patho-epidemiological study. Acta Pathol Jpn 1993;3:574–581.
6. Moore OS, Foote FW: The relatively favorable prognosis of medullary carcinoma of the breast. Cancer 1949;2:635–642.
7. Sousa H, Pinto-Correia AL, Medeiros R, et al: Epstein-Barr virus is associated with gastric carcinoma: the question is what is the significance? World J Gastroenterol 2008;14:4347–4351.
8. Fenoglio-Preiser C, Carneiro F, Correa P, Guilford P, Lambert R, Megraud F: Gastric carcinoma. WHO classification of tumours; in Hamilton SR, Aaltonen LA (eds): Pathology and Genetics of Tumours of the Digestive System. Lyon, IARC Press, 2000, pp 37–52.
9. MacCarty WC, Mahle AE: Relation of differentiation and lymphocytic infiltration to postoperative longevity in gastric carcinoma. J Lab Clin Med 1921;6:473–480.
10. Minamoto T, Mai M, Ohta T, et al: Medullary carcinoma with lymphocytic infiltration of the stomach with attention to characteristic gross appearance. I to Cho (Stomach and Intestine) 1995;6:799–806 [Japanese with English abstract].
11 Tominaga J, Kawase S, Yoshida M, et al: An early gastric cancer resembling a submucosal tumor followed-up for over three years – A case report and a review of the literature. Gann no Rinsyo (Jpn J Cancer Clin) 1992;38:69–74 [Japanese with English abstract].

12 Ishihara Y, Ikegami M, Yokoyama T, et al: A case of early lymphocytic infiltrating medullary carcinoma of the stomach with a morphology of a submucosal tumor demanded 3 years for making definite diagnosis. Nippon Rinshogeka Gakkai Zasshi (Jpn J Clin Surg) 2003;64:347–351 [Japanese with English abstract].

13 Takahashi T, Otani Y, Yoshida M, et al: Gastric cancer mimicking a submucosal tumor diagnosed by laparoscopic excision biopsy. J Laparoendosc Adv Surg Tech A 2005;15:51–56.

14 Herxheimer G: Über Karzinom und Tuberkulose. Z Tuberk 1917;27:251–258.

15 Bhatia A, Kumar Y, Kathpalia AS: Granulomatous inflammation in lymph nodes draining cancer: A coincidence or a significant association? Int J Med Sci 2009;2:13–16.

16 Takeuchi H, Suchi T, Suzuki R, et al: Histological study of immune parameters of regional lymph nodes of gastric cancer patients. Gann (Jpn J Cancer Res) 1982;73:420–428.

17 Yamamoto T, Tateishi H, Nishimura Y, et al: A study of gastric cancer with sarcoid reaction as observed in the regional lymph node. Nippon Shyoukakibyo Gakkai Zasshi (Jpn J Gastroenterol) 1980;77:1555–1561.

18 Chaturika H, Runjan C: Epstein-Barr virus-associated lymphoepithelioma-like gastric carcinoma. Arch Pathol Lab Med 2008;132:706–709.