Epstein-Barr Virus Associated Lymphoepithelioma-like Carcinoma of the Esophagogastric Junction and Stomach: A Case Report and Review of the Literature

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Abstract

A 63-year-old man was admitted to our hospital with 2 months history of dysphagia. Endoscopic examination revealed an ulcerative tumor starting from distal esophagus and extending to the cardia. Pathological examination of the biopsy revealed an epithelial malignant tumor without further classification. The patient underwent a surgery following neo-adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX) regimen. Postoperative pathological analyses showed high grade EBV-associated lymphoepithelioma-like carcinoma of the gastroesophageal junction and stomach. After surgery, we planned to administered 6 cycles of FOLFOX regimen as an adjuvant treatment. Lymphoepithelioma-like gastric carcinoma is a rare type of gastric carcinoma and has distinct clinic-pathologic characteristics, including male predominance, preferential location in the gastric cardia, lymphocytic infiltration, a lower frequency of lymph node metastases and more favorable prognosis. Surgical resection is the most effective treatment modality. Chemotherapy may be considered for patients who have high risk factors.

Keywords

Lymphoepithelioma-like carcinoma; Gastric cancer; EBV associated cancers

Introduction

Epstein-Barr virus (EBV) has been associated with the pathogenesis of a variety of lymphoproliferative disorders and several epithelial cancers, including undifferentiated nasopharyngeal carcinoma (UNPC, lymphoepithelioma). Lymphoepithelioma-like carcinomas (LELC) are tumors with morphologic features identical to UNPC that occur outside the nasopharynx [1]. These tumors have been reported in the salivary glands, tonsils, thymus, lungs, uterine cervix, skin, stomach, and liver [1], but rarely in the esophagus [2-5]. Lymphoepithelioma-like gastric carcinoma (LELGC) is also a rare type of gastric carcinoma and it was demonstrated that 1-4% of total gastric carcinomas were LELCs [6]. In this report we present an EBV-associated LELC of the esophagogastric junction and stomach and discuss this rare tumor with clinical and pathological features.

Case Report

A 63-year-old man with no co-morbid disease was admitted to our hospital with 2 months history of dysphagia. He visited emergency room with hematemesis one month ago and underwent endoscopic biopsy that showed squamous cell carcinoma at another hospital. His physical examination was unremarkable except his pale. Laboratory results revealed decreased hemoglobin (8.4 g/dl), hemotocrit (25.8%) and hypoalbuminemia (3.1 g/dl). Endoscopic examination revealed an ulcerative tumor starting from distal esophagus and extending to the cardia, fundus and proximal corpus of the stomach. The histopathological consultation of the previous biopsy at our hospital, revealed a malignant tumor made up of cells with eosinophilic nuclei and vesicular nucleus with distinct cytoplasm; forming sheets, without gland formation or keratinisation. (Figure 1) and the tumor cells were positive for pankeratin and negative for K5/6 (-), CK7 (-), CK20 (-) actin(-), pankeratin(+) and vimentin(-). p40(-), p63 (-), napsin-A (-), CD56 (-), chromogranin-A (-), synaptophysin (-). Also mucicarmine was negative. Pathological examination of the biopsy revealed an epithelial malignant tumor without further classification. The histopathological diagnosis was the same in repeated biopsy (Figure 1).

The computer tomography showed that wall thickness of the distal thoracic esophagus and cardio-esophageal junction was increased and no distant metastases or obvious enlarged lymph nodes (Figure 2). The patient was evaluated by a multidisciplinary oncology team and on the basis of these findings; a surgery following neoadjuvant chemotherapy was planned. He received 6 cycles of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX) regimen, and then radical total gastrectomy was performed with distal esophageal resection and D2 lymph node dissection. Postoperative pathological analyses showed high grade EBV-associated lymphoepithelioma-like carcinoma of the gastroesophageal junction and stomach. The in situ hybridization for EBV-encoded small RNAs (EBR) showed intensive positivity. No lymph node metastasis was found on the regional lymph node and surgical margins were clear. Tumor invaded the...
It is generally accepted that multimodality therapy, including surgical resection, is most effective for these tumors regardless of location. There is no data or recommendation on literature about which patients should receive adjuvant or neoadjuvant chemotherapy. Huang et al. [10] compared 52 EBV-associated GC cases with 968 EBV-negative cases in their study and they reported that EBV-associated GC cases with a tumor size >5 cm, non-LELC, or lymph node ratio >0.15 had a worse overall survival. These prognostic factors; tumor size, LELC classification and lymph node ratio may be considered when selecting high-risk patients for adjuvant treatment. In our case, we did not know accurate histological subtype of gastric cancer before surgery and administered neoadjuvant chemotherapy with FOLFOX regimen because of clinical T3N0 stage. After surgery, pathological analyses revealed a large of tumor which is bigger than 5 cm (9×9×2.5 cm) and pathological T3N0. Response to neoadjuvant chemotherapy was reported as minimal by pathologist. In the light of current literature we consider that the patient has a high-risk and decided to continue perioperative chemotherapy. In this manner, the disease did not progress during neoadjuvant chemotherapy and we probably treated the micro metastases.

Conclusion

We present a case of Epstein-Barr virus associated LELC of the esophagogastric junction and stomach which has high risk factors. This type of tumors is seen very rarely. LELGCs have distinct clinic-pathologic characteristics, including male predominance, preferential location in the gastric cardia or postsurgical gastric stump, lymphocytic infiltration, a lower frequency of lymph node metastases, perhaps a more favorable prognosis. The diagnosis of the LELC in biopsy specimen is difficult due to the stromal lymphocytic infiltration. Biopsy forming the malignant tumor (H&EX400).

EBV-associated gastric carcinoma (EBVaGC) is a subtype of gastric cancers that is defined by monoclonal proliferation of tumor cells with latent EBV infection. Approximately 10% of all gastric cancers have EBV infection. Recent studies showed that EBV causes some genetic and epigenetic changes in cells and these contribute to EBVaGC carcinogenesis [7]. There are 3 histological subtypes of EBVaGC; typical LELC, Crohn’s disease-like lymphocytic reaction (CLR), and conventional adenocarcinoma. Song et al. [8] reported 123 EBV-associated GCs and 43.1% were LELC.

The clinical presentations of LELGC are not different than other gastric cancers. Endoscopic and radiologic features are also similar. Pathological and immunohistochemical findings provide the diagnosis but it is hard to recognize LELGC with biopsy specimens because of the stromal lymphocyte infiltration. This infiltration may obscure the neoplastic epithelial component. In our case, two biopsies were performed and both were reported as epithelial malignant tumor by two different pathologists. Finally, postoperative pathological analyses showed the accurate diagnosis. Similarly, Wang et al. [9] reported a LELGC and their patient’s first biopsy was reported as inflammatory changes, the second one was adenocarcinoma and surgical specimen showed LELGC. LELC should be kept in mind during biopsy evaluation and EBER in situ hybridization should be part of the diagnostic protocol, especially if there are problems with the classification of the tumor histology and immune profile.

EBV-aGCs have distinct clinic-pathologic characteristics, including male predominance, preferential location in the gastric cardia or postsurgical gastric stump, lymphocytic infiltration, a lower frequency of lymph node metastases, perhaps a more favorable prognosis, and a diffuse type of histology in most but not all series [7,8,10]. Song et al. [8] compared 123 EBV-associated gastric cancers (GC) with 405 EBV-negative GCs. This study showed that patients with EBV-associated GC had longer survival times than controls (p<0.004) upon univariate analysis; this difference was not significant in a multivariate analysis. They investigated in this study whether the survival advantage of LELC is related to the EBV infection itself or to associated inflammatory immune responses. They found that prognosis of EBV-associated GCs depends on the patient’s inflammatory response. The rate of 12-year disease free survival in patient with LELGC was reported to be approximately 95% in this study.
infiltration. Surgical resection is the most effective treatment modality. The type of treatment should be evaluated case by case basis. The risk factors should be considered in the identification of high-risk patients. Chemotherapy may be considered for patients with high risk factors.

References