

Case Report

Non-Epstein-Barr virus-associated double primary lymphoepithelioma-like carcinoma of the esophagus and stomach: a case report and literature review

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Abstract: A 55-year-old Chinese male was admitted to the hospital for epigastralgia and dysphagia with a two month history, and hematemesis and melena with a two-day history. Two lesions were found in the esophagus and stomach by esophago-gastroduodenoscopy and computed tomography. The patient underwent subtotal esophagectomy and gastrectomy, esophagogastric anastomosis above the aortic arch, and thoracic-abdominal two-field lymph node dissection. Pathological and immunohistochemical studies showed that both lesions had the same form of poorly differentiated carcinoma with dense lymphoid stroma, which was diagnosed as lymphoepithelioma-like carcinoma (LELC). No metastatic relationship was found between the two tumors. Therefore, the case was double primary lymphoepithelioma-like carcinoma of the esophagus and stomach. Epstein-Barr virus (EBV) in the two tumors were negative by EBV-encoded small RNA1 (EBER-1) in situ hybridization. No adjuvant therapy was performed due to his poor physical condition post-operatively, and no evidence of tumor recurrence or metastasis was found during the next 14 months of follow-up. Esophageal and gastric LELC are rare, especially the former, which has a specific geographical distribution. Literature reported cases showed upper gastrointestinal LELC were highly malignant with good prognosis, and EBV was detected less in esophageal LELC cases but more commonly in gastric LELC cases. Upper gastrointestinal LELC lesions are usually singular, and no synchronous lesions were reported in the literature. Our case is the first LELC to present as double primary lymphoepithelioma-like carcinoma of both esophagus and stomach simultaneously, which demonstrates that LELC can be multifocal in the upper gastrointestinal tract.

Keywords: Esophagus, stomach, lymphoepithelioma-like carcinoma, double primary, diagnosis

Introduction

Lymphoepithelioma carcinoma (LEC) was first reported by Regaud and Reverchon, and Schminke in 1921 [1, 2]. LEC is a form of undifferentiated carcinoma, characterized by prominent lymphoid stroma, which was originally described in the nasopharynx [3]. LEC occurring outside the nasopharynx are rare and have been termed lymphoepithelioma-like carcinoma (LELC), including that of the salivary gland, thymus, thyroid, breast, lung, stomach, esophagus, uterine cervix, urinary bladder and the skin [4-7]. Epstein-Barr virus (EBV) has been frequently detected in LELC cells in several organs

in Oriental populations and appears to be related to tumorigenesis [8, 9]. Although LELC is a type of undifferentiated carcinoma with dense lymphoid stroma that is characterized by high malignancy, the prognosis of which is more favorable as compared to other undifferentiated carcinomas when diagnosed early and managed correctly [10-13].

Recently, the authors experienced a rare case of LELC presenting as two giant ulcers in the esophagus and stomach, wherein pathological examination and immunohistochemical staining revealed that the two lesions displayed the same form of poorly differentiated carcinoma

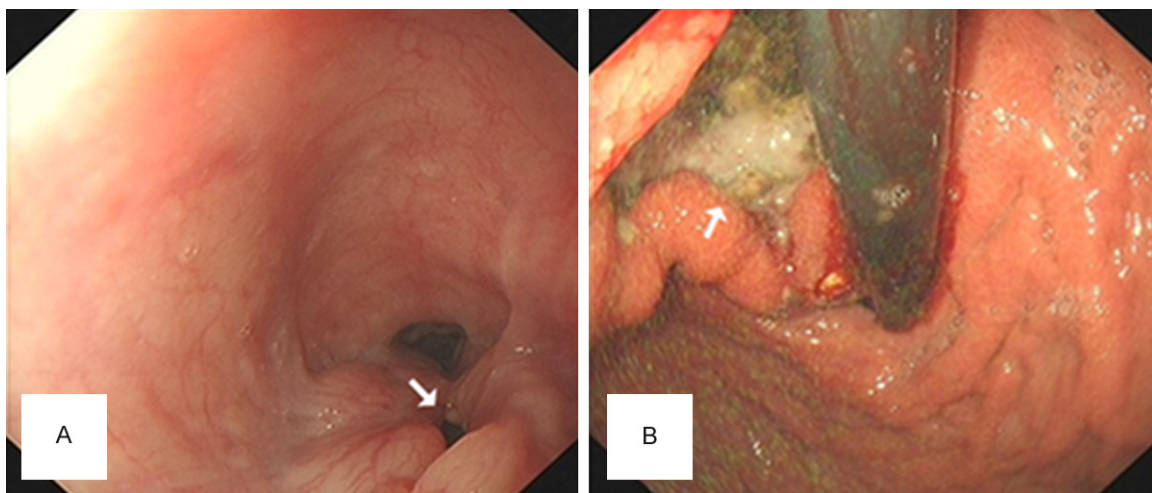


Figure 1. Esophago-gastroduodenoscopy revealed an elevated lesion in the left posterior esophagus with a central ulcer 30-35 cm from the upper incisors (A) and an ulcerative lesion in the cardia, fundus and anterior and posterior lesser curvature of the stomach with a soiled and purulent surface (B).

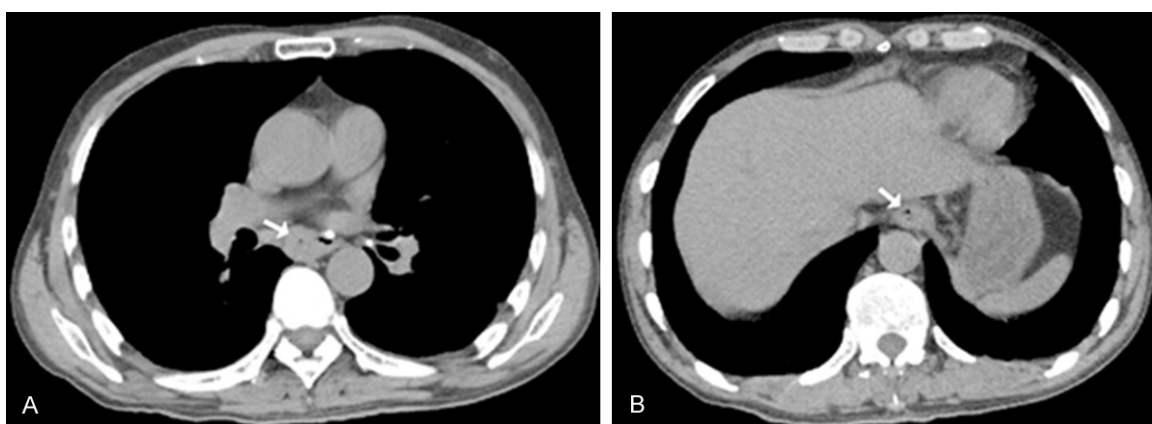


Figure 2. Computed tomography of the chest and abdomen revealed a thickened wall and almost occluded lumen that was located at the middle and lower thoracic portion of the esophagus (A) and a thickened cardiac wall demonstrating protrusion into the gastric cavity (B), no enlarged lymph nodes were found around them (120 KV, 200 mA, WW: 350, WL: 40).

with a dense lymphoid stroma and diagnosed as LELC. Moreover, no metastatic relationship was found between either of the two tumors. Thus, the case was diagnosed as double primary lymphoepithelioma-like carcinoma of the esophagus and stomach.

In the current article, we have described the clinical and pathological characteristics of upper gastrointestinal LELC, and we review the relevant literature. To exclude the metastatic relationship between the two LELCs and to confirm the diagnosis of double primary LELC, we also reviewed the pertinent literature with regard metastatic esophageal carcinoma of the

stomach. Our case was typical in that it displayed important referenced significance to the diagnosis of upper gastrointestinal LELC and double primary carcinoma.

Case report

A 55-year-old Chinese gentleman was admitted for epigastralgia and dysphagia with a two month history, and hematemesis and melena with a two day history in December 2013. His epigastralgia aggravated progressively without any obvious exacerbation and remission regularly, accompanied by progressive dysphagia. He had massive hematemesis four times within

Lymphoepithelioma-like carcinoma

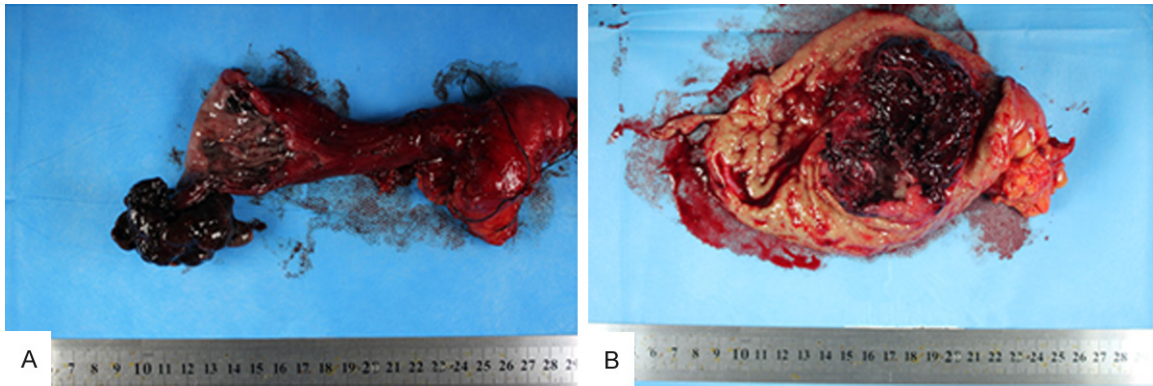


Figure 3. (A) 4 × 2.5 × 1.2 cm ulcerative and infiltrative type of tumor was observed in the resected esophageal specimen (A) and another 7 × 5 × 2.5 cm ulcerative and infiltrative type of tumor was observed in the resected gastric specimen (B).

two days and the total volume was about 200 ml. He had no chronic peptic ulcer history, but had a history of heavy smoking and drinking for 20 years.

Physical examination revealed no positive signs, and routine laboratory tests presented no remarkable abnormality, with the exception of slight anemia and positive fecal occult blood analysis. An emergency esophagogastroduodenoscopy was performed that identified two ulcerative lesions in the esophagus (**Figure 1A**) and stomach (**Figure 1B**). The cardiac dentate line was 42 cm from the incisor, and the esophageal lesion was located 30-35 cm from the incisor. The gastric lesion was located in the cardia, fundus and lesser curvature of the stomach. The two lesions were bleeding when the esophago-gastroduodenoscope was retreated; thus, the biopsy was not conducted. Computed tomography of the chest and abdomen revealed two lesions in the esophagus (**Figure 2A**) and stomach (**Figure 2B**), no obvious enlarged lymph nodes were found around them.

According to the case medical history, clinical presentation, and the findings of endoscopy and imaging, this case might represent two tumors of the esophagus and stomach. The patient underwent subtotal esophagectomy and gastrectomy, esophagogastric anastomosis above the aortic arch, and thoracic-abdominal two-field lymph node dissection on the third day after admission.

Macroscopically, an ulcerative lesion was located in the lower esophagus (**Figure 3A**), the

lesion was about 4 × 2.5 × 1.2 cm in size. The other ulcerative lesion was located in the cardia, fundus and lesser curvature of the stomach (**Figure 3B**), and the lesion was about 7 × 5 × 2.5 cm in size. Both lesions had invaded the whole layer including the serosa. In addition, the grey white sections were well-defined.

Microscopically both lesions had similar forms, and both were sub-mucosal carcinoma that had invaded the whole layer including the serosa. The carcinoma cells were poorly differentiated, displayed a sparse nest-like distribution, with a small palisading arrangement. Massive mature lymphocytes were seen around the carcinoma nests, including small lymphocytes and plasmacytes (**Figure 4A, 4B, 4D and 4E**). The carcinoma cells were enlarged, with very large and atypical oval nuclei with vesicular chromatin and prominent nucleoli (**Figure 4C and 4F**). No carcinoma cells were seen in the proximal and distal incisal margins of the esophagus and stomach and no lymph nodes were found to have evidence of metastasis.

Immunohistochemical staining of both lesions had the same result. The carcinoma cells were positive for CK, P63, EMA, Ki67 (labeling c =c70%), and negative for Desmin, Vim, NSE, Syn, S-100, P53, CD3, CD45RO, CD20, and CD79α. Various lymphocytes were positive for CD3, CD45RO, CD20, and CD79α. EBV in both lesions was negative by EBV-encoded small RNA1 (EBER-1) in situ hybridization.

Based on the clinico-pathological features and immunohistochemical staining, lymphoma and neuroendocrine tumors were excluded, and both lesions were non-EBV virus-associated

Lymphoepithelioma-like carcinoma

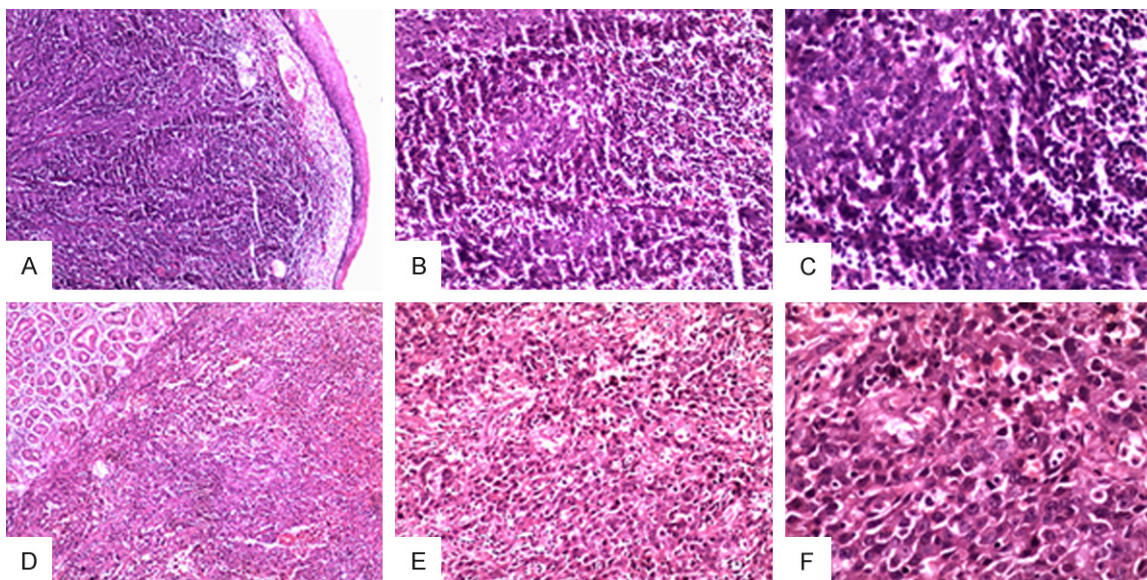


Figure 4. Microscopy revealed the esophageal lesion (A-C) and the gastric lesion (D-F) had similar form, and that they were both sub-mucosal carcinoma that had invaded full layer, including the serosa. Low power view (seen in panels A and D above): The carcinoma cells were poorly differentiated, with a sparse nest-like distribution, and a small palisading arrangement. HE staining; $\times 40$ magnification. Medium power view (seen in panels B and E above): Massive mature lymphocytes were seen around the carcinoma nests, including small lymphocytes and plasmocytes. HE staining; $\times 100$ magnification. High power view (C and F): The carcinoma cells were enlarged, with very large and atypical oval nuclei with vesicular chromatin and prominent nucleoli. HE staining; $\times 200$ magnification.

lymphoepithelioma-like carcinoma. Considered that both tumors were separated from each other and no carcinoma cells were seen in the margins between the esophagus and stomach, the histogenesis of both tumors tended to originate independently. Therefore, the case was considered as double primary lymphoepithelioma-like carcinoma of both the esophagus and stomach. Both tumor stages were T3N0M0 according to the 7th AJCC staging system.

The patient recovered well post-operatively and was discharged 12 days after the operation. His epigastralgia and dysphagia had completely regressed, and the hematemesis and melena were no longer evident post-operatively. He ate a normal diet at one month after the operation. After the diagnosis of the cancer, he refrained completely from habitual smoking or drinking alcoholic beverages. No adjuvant therapy was performed post-operatively, and no evidence of tumor recurrence or metastasis was found during the 14 months of follow-up examination.

Discussion

Upper gastrointestinal LELC is a rare disease, especially esophageal LELC. Previous reports

of these conditions are sporadic; while gastric LELC is seen a little more frequently, and constitutes about 4% of all gastric carcinomas [14, 15]. Primary lymphoepithelioma-like esophageal carcinoma was first reported by Amano et al [11] in 1988. From then on, cases that presented with the pathological characters of LELC continued to be reported mainly in Japan. A total of 49 cases were published around the world by summarizing the literature from 1988 to today, and along with our case, makes a total of 50 cases at the time of writing. Among them, 36 cases were reported in Japan (72.0%), 4 cases were reported in Occident (8.00%, one of them was an Arab American), 9 cases were reported in China (18.0%, including our current case reported herein, and one was a Taiwanese case), and 1 case was reported in South Korea (2.0%). Asian countries accounted for 92.00% of total cases and the geographical distribution was mainly in East and South Asia, especially in Japan (72.0%).

Lymphoepithelioma of the nasopharynx is considered to be closely associated with EBV. Some researchers have shown that EBV was a certain pathogenic factor and was related to primary lymphoepithelioma-like carcinoma of

Lymphoepithelioma-like carcinoma

the salivary gland, thymus, lung, and stomach [9]. About 80% of the gastric LEC cases are related to EBV [16]. However, the association of lymphoepithelioma-like carcinoma of the esophagus and EBV has not been confirmed to date, and EBV in more than half of the reported cases was negative.

Upper gastrointestinal LELC often presents as ulcerative or protuberant sub-mucosal neoplasm under esophagogastroduodenoscopy and the preoperative biopsy usually cannot provide clear results due to a limited collection of tissue and the impurity interference effects [17]. Because of the ulcers undergoing hemorrhage, the biopsy was not conducted on our patient pre-operatively. Post-operative histopathology and immunohistochemistry revealed that both lesions of the esophagus and stomach had similar results. Microscopically, the two lesions were poorly differentiated sub-mucosal carcinoma with massive lymphocytic infiltration. The tumor cells were positive for epithelial markers (CK, EMA), and negative for mesenchymal markers (Desmin, Vim), neuroendocrine markers (NSE, Syn, S-100), and lymphocyte markers (CD3, CD45RO, CD20, CD79 α) by immunohistochemical staining. These observations indicated that the tumor originated from the epithelial tissue, but not from tissues of mesenchymal, neuroendocrine or lymphoid origins. In addition, Ki67 was positive in 70% of tumor cells, which showed that the tumor proliferated actively and was highly aggressive. The lymphocytes were positive for CD3, CD45RO, CD20 and CD79 α , which revealed that the lymphocytes were expressed variously. In conclusion, the two lesions in the esophagus and stomach were diagnosed as lymphoepithelioma-like carcinoma.

At present, the diagnosis of gastrointestinal multiple primary carcinoma is done according to the Warren's criterion. The details are as follows: (1) each tumor was proven to be malignant by histocytology; (2) the histogenesis was different, in different positions or organs; (3) the metastatic relationship between the tumors must be excluded. The critical point is that the tumors are not continuous of one another. In addition, no metastatic tumor cells should be found in the junctional route of respective metastasis. In recent reports detailing esophageal carcinoma metastasis to the stomach [18-

21], almost all cases were found to have metastatic tumor cells in the submucosa between the esophagus and stomach. The mechanism of esophageal carcinoma metastasizing to the stomach is induced via submucosal lymphatic invasion [18]. In our case, both tumors separated from each other and no carcinoma cell was seen in the margins between the esophagus and stomach. Thus, the LELC of the esophagus and stomach was double primary, and both tumors had stages that were defined as T3N0M0 according to the 7th AJCC staging system.

As common esophageal or gastric carcinoma, surgery is preferred for upper gastrointestinal LELC treatment and radical resection is recommended. Upper gastrointestinal LELC is sensitive to radiotherapy and chemotherapy, and post-operative radiotherapy is usually used [22]. Although LELC is highly malignant and less differentiated than other upper gastrointestinal carcinomas, the prognosis is more favorable due to lymphocytic infiltration in the process of an anti-tumor immunologic reaction of the host [13]. Considering the favorable prognosis and poor physical condition of the patient, no adjuvant therapy was performed post-operatively. Endoscopy and imaging examination were used to evaluate tumor recurrence and metastasis. No emerging neoplasm was found in the remaining esophagus and stomach, and no metastatic lesion was found in the distant organs during the 14 months of follow-up examination.

Conclusion

Although upper gastrointestinal LELC is rare, it is still necessary to enhance the knowledge of the disease for practicing clinicians and examining pathologists. Acquiring the clinical and pathological features should assist in augmenting the capacity of physicians to diagnose these tumors correctly, and in guiding clinical therapy and continuous evaluation of the prognosis on a case-by-case basis. The association of esophageal LELC and EBV, racial/ethnic diversity and geographical distribution, and the function of LELC lymphoid stroma, all need to be further studied.

In addition, upper gastrointestinal LELC lesions are usually singular, and no synchronous lesions were reported in the previous literature.

Lymphoepithelioma-like carcinoma

Our case is the first case of LELC that presented as a double primary lymphoepithelioma-like carcinoma of both the esophagus and stomach simultaneously, which demonstrates that LELC can be multifocal in the upper gastrointestinal tract.

Disclosure of conflict of interest

None.

Abbreviations

LELC, Lymphoepithelioma-like carcinoma; CT, computed tomography; EBV, Epstein-Barr virus; EBEB-1, EBV-encoded small RNA-1.

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Lymphoepithelioma-like carcinoma

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