

# CT findings and clinical features of Epstein–Barr virus-associated lymphoepithelioma-like gastric carcinoma

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## Abstract

Epstein–Barr virus (EBV)-associated lymphoepithelioma-like gastric carcinoma (LELGC) is a rare primary stomach tumor, which has overlapping imaging features with mass forming gastric carcinoma (GC). The aim of our study was to present the computed tomography (CT) findings and clinical features of EBV-associated LELGC to increase awareness of this entity.

The CT findings and clinical features of 4 patients with pathologically documented EBV-associated LELGC were retrospectively analyzed.

Among the 4 patients, 3 were male, and 1 was female. The medium age was 51 years old. All cases were single lesions including 1 was in the gastric cardia, 1 was in the gastric body, and 2 were in the gastric antrum. A focal thickening of the gastric wall was conducted, with a large thickness-to-length ratio. The low-density stripe of the normal gastric wall abruptly terminated at the edge of the lesion. The CT images of 4 cases showed inhomogeneous density with the radiodensity values ranging from 25 to 48 HU. In addition, an ulcer was demonstrated with an irregular base and slightly raised borders in all cases. Enhancement after injection of contrast material was heterogeneous enhancement (n=3) or homogeneous (n=1). After enhancement, obvious enhancement was seen in 1 case, moderate enhancement was seen in 3 cases, with the peak value of the tumor in the portal phase. No evidence of lymph node involvement and distant invasion was observed.

Although LELGC is quite rare, it should be considered in differential diagnosis of early GC, advanced GC, and lymphoma. The relatively typical CT appearance, combined the age and sex of patients, can suggest the diagnosis of LELGC.

**Abbreviations:** CT = computed tomography, EBER-1 = EBV-encoded RNA-1, EBV = Epstein–Barr virus, ESD = endoscopic submucosal dissection, GC = gastric carcinoma, i.v. = intravenous, LELCs = lymphoepithelioma-like carcinomas, LELGC = lymphoepithelioma-like gastric carcinoma.

**Keywords:** Epstein–Barr virus infections, lymphoepithelioma-like gastric carcinoma, stomach neoplasms, tomography, X-ray computed

## 1. Introduction

Lymphoepithelioma-like gastric carcinoma (LELGC) is an extremely rare subtype of gastric carcinoma (GC), characterized

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This study was approved by the institutional review board, and the requirement for written informed consent was waived in this retrospective study.

Images are entirely unidentifiable and there are no details on individuals reported within the manuscript.

The authors have no conflicts of interest to disclose.

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by morphological features similar to undifferentiated nasopharyngeal carcinoma, and this was first described in 1976 by Watanabe et al<sup>[1]</sup> About 60% of the lymphoepithelioma-like carcinomas (LELCs) cases occur in the nasopharynx, while a wide variety of sites may also be affected, including the lungs, tonsils, esophagus, salivary glands, thymus, cervix, and skin.<sup>[2]</sup>

Fewer than 200 cases of LELGC have currently been reported in the English medical literature. However, to the best of our knowledge, the majority of them have focused on the pathology and clinical manifestation; previous reports have not systemically described the radiological appearance of this tumor. From January 2010 to May 2018, 4 cases of LELGC were identified from a series of 7631 patients with GC who underwent surgical resection at the First Affiliated Hospital of Zhengzhou University. The purpose of the present study was to analyze the computed tomography (CT) findings and clinical features of LELGC.

## 2. Methods

### 2.1. Patients

This study was approved by the institutional review board, and the requirement for written informed consent was waived in this retrospective study. From January 2010 to May 2018, we searched pathology records and the picture archiving and communication systems using the following search terms: “lymphoepithelioma-like gastric carcinoma,” “lymphoepithelioma-like carcinoma,” and “EBV-associated gastric carcinoma.”

All the cases were reviewed by a single pathologist (K.S.C.), who is an expert in diagnosing LELC. LELC was defined<sup>[3]</sup> by well-defined tumor margin, dense lymphocytic infiltration of a degree whereby the number of tumor-infiltrating lymphocytes was greater than the number of tumor cells throughout the tumor, indistinct cytoplasmic borders and a syncytial growth pattern with poorly formed glandular structures, and no desmoplasia. A total of 4 cases were identified as having LELGC and enrolled in the present study. All patients had undergone radical gastrectomy. Clinical data, including age, sex, symptoms, and treatment outcome, were obtained by the review of medical records.

## 2.2. CT evaluation

The CT examinations were obtained using a 64 multidetector (Discovery CT750HD, GE Healthcare, Waukesha, WI). A conventional axial scan (120kV, 350mA, field of view 500 mm, matrix 512 × 512, and section thicknesses 0.75 mm) was performed before and after intravenous (i.v.) injection of nonionic iohexol (iopromide, 370 mg/mL, GE Medical Systems, 1.5 mL/kg and 3 mL/s) by a dual-head pump injector (Medrad, Warrendale, PA). Finally, 20-mL saline flush was injected at a rate of 3 mL/s. Contrast-enhanced CT scans were performed with a scanning delay of 30 s (arterial phase) and 70 s (portal venous phase) after start of i.v. injection of iopromide. CT dose index volume for the 3 phases was 15 mSv.

## 2.3. Image analyzes

The CT images were retrospectively reviewed by 2 experienced radiologists with 14 and 30 years' experience in abdominal CT. All analyses were performed at AW4.6 work-station (GE Healthcare) and radiologists were blinded to the clinical information of patients. The images were specifically evaluated for the tumor location (gastric cardia, gastric fundus, gastric body, gastric angle, and gastric antrum), lesion size, shape, attenuation, and characteristics of enhancement. The characteristics include enhancement pattern and degree of enhancement. The enhancement pattern of the tumor was classified as homogeneous or heterogeneous based on arterial phase. The degree of enhancement of the tumor was based on dynamic CT imaging using HU attenuation, where "obvious enhancement" if >40 HU, "moderate enhancement" if >20 HU and "mildly enhancement" if <20 HU.

## 3. Results

### 3.1. Patient characteristics

The patients included 3 men and 1 woman ranging in age from 42 to 64 years with a median age of 51 years (Table 1). The clinical

and CT features of these patients are summarized in Table 1. All patients had nonspecific symptoms, including abdominal discomfort, epigastric discomfort, discontinuous black stool, and intermittent vomiting. All patients underwent radical resection surgery.

On immunohistochemical examination, the tumor cells showed positive reactions for pan-cytokeratin (Fig. 1B). Immunohistochemical analysis for Ki-67 revealed a high proliferation index (Fig. 1D), but the results were negative for chromogranin, synaptophysin, and neuron-specific enolase. The presence of Epstein-Barr virus (EBV)-encoded RNA-1 in gastric tumor cells was revealed by strong nuclear staining, while the background lymphocytes were negative for the same (Fig. 1C). The stromal lymphocytes were predominantly positive for CD3-positive T-cells with diffuse arrangement (Fig. 1E).

### 3.2. CT findings

Of the 4 cases of LELGC, 1 was gastric cardia, 1 was in the gastric body, and 2 were in the antrum. A focal thickening of the gastric wall was noted, with the maximum thickness ranging from 0.7 to 2.7 cm. The lesions had a large thickness-to-length ratio (see arrows on Fig. 2), with the low-density stripe of the normal gastric wall abruptly terminated at the edge of the lesion (see arrows on Fig. 2). Three of the tumors had invaded the gastric serosa, consistent with the pathological diagnosis, while 1 case originated from the muscular layer. CT findings were originally interpreted as gastric adenocarcinoma in 3 cases and gastric lymphoma in 1.

All the 4 tumors showed inhomogeneous density on CT, with radiodensity values ranging from 25 to 48 HU (Fig. 2). An ulcerative lesion with an irregular base and slightly raised borders was observed in all 4 cases. Three cases demonstrated heterogeneous enhancement due to the necrotic or cystic areas, the fourth showed homogeneous enhancement with the radiodensity values ranging from 50 to 100 HU in the arterial phase and from 76 to 124 HU in the venous phase. One case showed obvious enhancement with contrast enhancement, the other 3 showed moderate enhancement; the peak value for the tumor was observed in the portal phase. None of the cases showed evidence of lymph node involvement and distant invasion.

## 4. Discussion

LELGC is a type of EBV-associated GC, characterized by the presence of a lymphoid stroma with cells arranged primarily in microalveolar, thin trabecular and primitive tubular patterns, or isolated cells. LELGC can present as 2 histomorphological forms of a EBV-positive carcinoma and a microsatellite instability-high carcinoma.<sup>[2]</sup> It has been demonstrated that over 80% of the tumor have been proven to be associated with EBV infection,

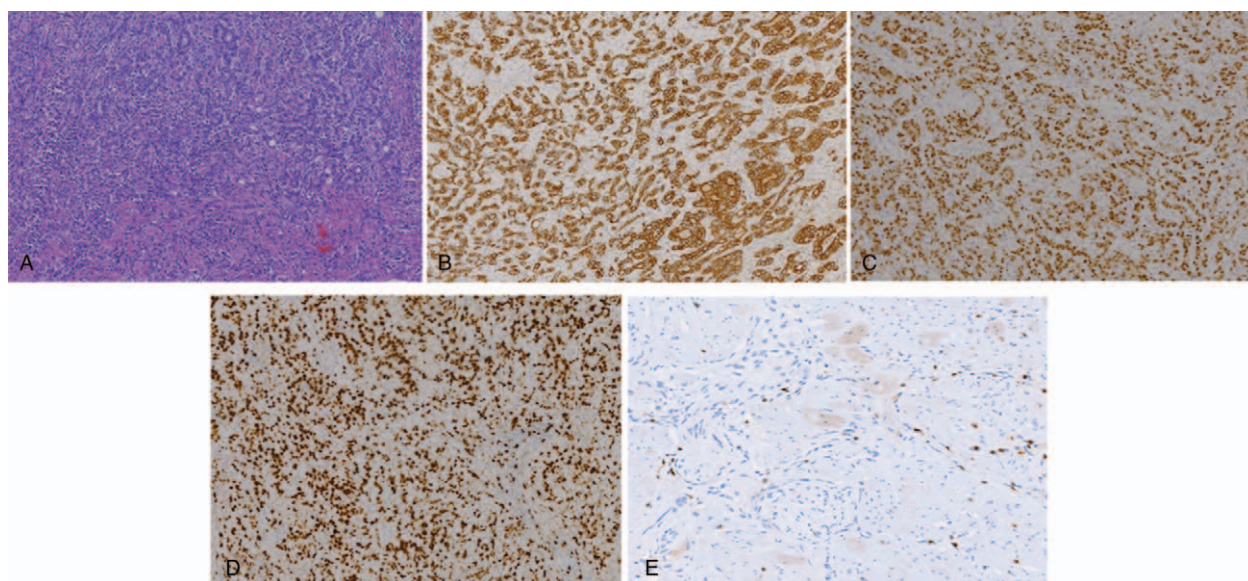
**Table 1**  
Clinical and computed tomography features in 4 cases of lymphoepithelioma-like gastric carcinoma.

Case	Sex	Age	Complaint	Location	Thickness-to-width ratio	Ulcers	EBV*	Stage (TNM)	Therapy
1	F	50	Abdominal discomfort	Gastric body	0.23	+	+	IIA(T3 NO M0)	Resection
2	M	49	Epigastric discomfort	Gastric antrum	0.35	+	+	IIB (T4a NO M0)	Resection
3	M	42	Intermittent vomiting	Gastric antrum	0.44	+	+	IIIA (T4a NO M0)	Resection
4	M	64	Discontinuous black stool	Gastric cardia	0.41	+	+	IIIA (T4a NO M0)	Resection

F=female, M=male, age in years; follow-up in months.

EBV=Epstein-Barr virus; TNM=tumor node metastasis.

\* Detected by EBER-1 in situ hybridization.



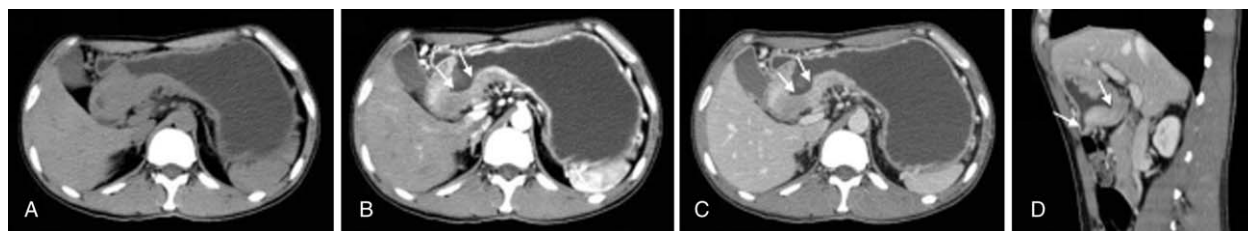
**Figure 1.** (A) Small nests of cancer cells were noted with no glandular structures. Marked infiltration of lymphocytes was noted in the tumor stroma (hematoxylin-eosin stain). (B) Strongly positive for Ckpan was noted in the tumor cells (immunohistochemical stain). (C) Strong nuclear staining was noted in the nuclei of the cancer cells (Epstein-Barr virus-encoded RNA-1 1; in situ hybridization). (D) Greater than 90% of the expression of Ki67 was noted in tumor cells (immunohistochemical stain). (E) Lymphocytic infiltrate predominantly consisted of CD3-positive T-cells with diffuse arrangement.

compared with ~6% of diffuse and 7% of intestinal gastric adenocarcinomas, suggesting that EBV infection is a possible factor in the etiology of LELGC.<sup>[4]</sup> The possible mechanism of carcinogenesis by EBV is currently unclear but may be linked to that orally excreted EBV infects a small number of gastric epithelial cells to express latent membrane protein 1 and EBV determined nuclear antigen 1.<sup>[5]</sup> Some of the EBV infected cells evade immune surveillance proliferating monoclonally to develop EBV-positive LELGC.<sup>[5]</sup>

Due to EBV infection is a risk factor of a wide variety of tumor, several cases of concurrent EBV-positive LELGC with other tumors have been reported in the literature. Vasef et al<sup>[6]</sup> reported a patient with LELGC and jejunal low grade B-cell lymphoma of mucosa-associated lymphoid tissue with histologic transformation to large cell lymphoma. In their study, polymerase chain reaction studies confirmed that the same viral strain infected both the stomach and jejunal tumors, suggesting that EBV may have played a role in large cell transformation. Lee et al<sup>[7]</sup> found an EBV-associated nasopharyngeal undifferentiated carcinoma case of simultaneous LELGC, demonstrated that EBV infection was closely correlated with the 2 kinds of malignant tumors.

Therefore, Lee et al<sup>[7]</sup> suggested that the mechanism of occurrence and progress in both the 2 tumors was similar. Patients with HIV have weakened immune systems. This puts them at increased risk for viral infections, such as EBV infections, and causes viral infections-related diseases. Kim et al<sup>[8]</sup> reported EBV-associated LELGC in a patient with HIV.

Tumors rarely occur in the stomach with an incidence of 1% to 4% of all GC. The findings of the present study were consistent with those in the literature. From January 2010 to May 2018, 7631 GC cases were surgically treated at the First Affiliated Hospital of Zhengzhou University. Of these cases, only 4 were of these LELCs occurred in the stomach (0.05%). According to the published study, Cheng et al<sup>[9]</sup> only found 10 cases of gastric LELC in 702 GC cases, in which 8 cases were EBV-positive. The mean age of the reported cases of the primary LELCs was 56.1 years,<sup>[10]</sup> which is consistent with the age of the patient in the present study (51 years). It is considered to have an obvious male predominance, with a ratio of man to female approximately 2:1, which is consistent with the general trend of the present study. However, this obvious male predominance was not reported in some studies.<sup>[5,11,12]</sup>



**Figure 2.** Lymphoepithelioma-like gastric carcinoma in 42-year-old man. (A) Unenhanced CT image of stomach reveals a well-circumscribed mass in the gastric antrum with a large thickness-to-width ratio (arrows). (B and C) Contrast-enhanced CT image shows heterogeneous enhancement of mass, with the peak value of the tumor on the portal phase. An ulcer was demonstrated with an irregular base and slightly raised borders of the gastric wall. (D) Sagittal reformatted images showed the low-density stripe of the normal gastric wall abruptly terminated at the edge of the lesion (arrows). (B) Arterial phase of contrast enhancement image; (C) portal phase of contrast enhancement image.



Due to the occurrence of LELC in stomach has seldom been reported, most radiologists and clinicians are not familiar with these tumors. The clinical symptoms of LELGC are varied and similar to GC including no obvious early symptoms and occasional/aggravated abdominal pain, loss of appetite, fatigue, weight loss, etc. Epigastric discomfort is common because of the increased thickening of the upper gastric wall. Two patients in the study presented with stomach discomfort were consistent with those reported in prior studies. In addition, patient of LELGC without any clinical symptoms has also been reported.<sup>[13]</sup> Tumors generally located in the upper gastric region, such as gastric cardia, gastric fundus, and the gastric body. It typically presents with gastric protuberant lesion, characterized by an ulcerating tumor with well-delineated margins and pushing borders.<sup>[14]</sup> While part of lesions had ulcer only, some of the edge were intumescent and a little depression in the middle.

Although LELGC is defined as the malignant tumor of the gastric epithelium mucosa, it usually invaded the submucosa with the formation of the submucosal mass induced by the lymphocytic reaction.<sup>[15]</sup> With the raised margin surrounding the depression, it was superficially covered with a normal mucosal layer and thus formed an unrecognizable border between the cancerous and noncancerous areas like submucosal tumors.<sup>[15]</sup> Therefore, the differential diagnosis for LELGC usually includes gastrointestinal stromal tumor, lymphoma, leiomyoma, carcinoid, and glomus tumor. Gastroscopy and multipoint biopsy could greatly aid in the diagnosis of LELGC. It is worth mentioning that mostly tumor located in the submucosal layer, with the distribution characteristics of the sheet and the nests of the tumor cells, the inappropriate pathologic examination frequently lead to misdiagnosed or underdiagnosed. In our series, 2 patients were considered chronic severe superficial gastritis, undergoing gastroscopy biopsy for 2 times, and frozen section during surgery suggested a clinical diagnosis of gastric malignant lymphoma.

The CT appearance diagnosed as LELCs in the stomach has not been systematic reported previously. In the present study, the lesions were described as a mass that has a large thickness-to-length ratio, with the low-density stripe of the normal gastric wall abruptly terminated. It has been reported that the majority of the lesion was located in the submucosa by pathological investigation. Kim et al<sup>[16]</sup> reported a case of an EBV-associated LELGC that presented as a submucosal mass on CT. Larger thickness-to-length ratio is a characteristic presentation of EBV-associated GC. The formation of the submucosal mass may be attributed to various factors, including epithelioid granulomas and lymphocytic induction (4). Maeda et al<sup>[17]</sup> reported that EBV-associated GC had various appearances on CT including focal mucosal thickening, marked wall thickening with contrast enhancement, and bulky mass formation. Therefore, it is difficult to differentiate LELGC with cases of early GC, advanced GC, and lymphoma. It has been reported that both EBV-associated GCs and submucosal tumors can present with mucosal ulceration, the ulcerated shape of the advanced EBV-associated lesions is associated with superficial depressed shape of the early lesions.<sup>[16]</sup> In addition, in a CT study including a LELC of the stomach, the authors reported that the tumor tissue with epithelioid granulomas exhibited a bulging mass and formed a nodule after invading the submucosa.<sup>[4]</sup> The preoperative CT features may suggest a submucosal tumor and the biopsy results of the adenocarcinoma. When the presence of LELCs is suspected, detection of EBV using gastroscopy biopsy specimens may suggest the diagnosis of LELGC.

The present predominant management for LELGC remains unknown. Since the tumor is a relatively rare cancer, there are no specific National Comprehensive Cancer Network guidelines for its treatment alone. Therefore, most of the confirmed cases are usually treated as gastric adenocarcinoma, including radical surgery, chemotherapeutic agents, targeted therapies, and radiotherapy. In recent years, endoscopic submucosal dissection (ESD) has been useful in the diagnosis and treatment of LELGC.<sup>[13]</sup> Moon et al<sup>[13]</sup> reported a LELGC with 19 × 14 mm in size that presented as a flat depressed lesion, treated by complete en bloc resection using ESD.

Because the tumor frequently involved mucous layer and the submucosa, abundant lymphocytic and granulomatous reactions prevented the spread of the tumors through the gastric wall,<sup>[18]</sup> which is consistent with the present study that no lymph node or distant organ metastasis was detected. As mentioned, LELGC has been reported to have a favorable prognosis compared with other forms of EBV-associated GCs and conventional GCs. Even compared with the GCs invaded the whole gastric lay, the 3-year survival rate (96.5%) and the 5-year survival rate (77.5%) of the LELGC group was better.<sup>[1]</sup> These findings seem to suggest that the strong immune response based on the arrangement of the lymphocytic infiltrate.<sup>[19]</sup> This, to some extent, might be piece of evidence supporting that the favorable prognosis is the result of the combination between strong cellular and humoral immunities.<sup>[19]</sup>

## 5. Conclusions

In conclusion, although rare, LELGC was associated with EBV infection. It should be considered this tumor when a mass that has a large thickness-to-length ratio, with the low-density stripe of the normal gastric wall abruptly terminated in the stomach. This tumor generally has a better prognosis than other forms of EBV-associated GCs and conventional GCs. LELGC is difficult to identify by CT features, diagnosis is based on pathologists and clinicians.

## Author contributions

P.L. is the primary author. J.B.G. and K.S.C. critically reviewed the paper and revised it. P.L. and X.C.R. performed the database search and literary review. K.S.C. did the pathology review and analysis. All authors read and approved the final manuscript.

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