Am J Transl Res 2023;15(4):2561-2567
www.ajtr.org /ISSN:1943-8141/AJTR0147563

Original Article

Gastric lymphoepithelial-like carcinoma presenting as a sub-mucosal mass: a case report and literature review

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Received November 6, 2022; Accepted February 17, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: Background: Lymphoepithelioma-like carcinoma of the stomach (LELC), also known as carcinoma with lymphoid stroma of the stomach, is a rare type of gastric cancer, accounting for approximately 1-4% of all gastric cancers. It is mainly associated with Epstein-Barr virus (EBV) infection. Here, we report a case of gastric lymphoepithelial-like carcinoma presenting as a submucosal mass that tested negative for EBV. Case description: a 70-year-old patient was diagnosed with a gastric mass through routine endoscopy. There was no abdominal pain, fever, hematemesis, chills, or other discomfort, and the patient had a history of hypertension. The complete blood count, blood chemistry, and tumor indices were normal, and the results for EBV infection were also negative. According to EUS, it was diagnosed as a gastric stromal tumor. The patient underwent endoscopic submucosal dissection (ESD). Pathological exams suggested that it was a low-differentiated carcinoma, and surgical dissection was performed. Conclusion: Cases of gastric LELC are rare, and clinicians need to improve their understanding of the disease to avoid misdiagnosis. The etiology and pathogenesis of this disease need further investigation.

Keywords: Gastric mass, lymphoepithelial-like carcinoma, rare disease, case report

Introduction

Gastric cancer is the second leading cause of cancer-related deaths and the fourth most diagnosed cancer worldwide [1, 2]. Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma with prominent lymphoid stroma and was first reported in 1926. Initially, it was reported to be present in the nasopharynx. It is primarily associated with Epstein-Barr virus (EBV) infection and may be involved in tumorigenesis [3-6]. EBV was identified in human neoplastic cells, (Burkett's lymphoma cell line), in 1964. LELCs have been reported in the lungs, skin, salivary glands, thymus, larynx, uterine cervix, breast, and urinary bladder, and in gastroenterology, it has been reported in the esophagus, stomach, colon, and rectum [6-13]. According to the WHO's (2010) pathological classification, LELC is an independent subtype of gastric adenocarcinoma, also known as carcinoma with lymphoid stroma or medullary carcinoma of the stomach, which is a rare subtype of epithelial tumors [14]. It accounts for approximately 1-4% of all gastric cancers worldwide [15].

Here, we present a rare case of LELC that was diagnosed as a submucosal mass in the fundus of the stomach. Pathological and immunological results showed that LELC infiltrated the muscular layer. After a confirmed diagnosis of LELC, a gastrectomy was performed.

Case description

A 70-year-old patient was admitted to our hospital (Hangzhou First People's Hospital, Hangzhou, Zhejiang, China) with a "gastric tumor" found during routine physical examination

Table 1. Biochemical and Immunohistochemical results of the patient before and after ESD

Name	Status	Name	Status
Biochemical results			
Aspartate aminotransferase	54 U/L	Creatine kinase	392 U/L
Total bilirubin	49.6 umol/L	blood amylase	121 U/L
Conjugated bilirubin	15.5 umol/L	HBsAg	Weak positive
Indirect bilirubin	34.1 umol/L	HBeAb	Positive
β-hydroxybutyric acid	444 umol/L	HBcAb	Positive
Free fatty acid	1057 umol/L		
Immunohistochemical results			
EBV (EBER)	-	CK7	-
CK	+	CK20	-
Cam.53	+	Vim	+
EMA	+	LCA	-
Ki-67	+ 80-90%	CerbB2	0
Mismatch repair gene protein			
MSH6	++ >90%	MSH2	+ >1%
MLH1	++ >90%	PMS2	+ >1%

HbsAg, Hepatitis B surface Antigen; HbeAb, Hepatitis B Antigen and Antibody; HbcAb, Hepatitis B core Antibody; EBV, Epstein-Barr Virus; EBVR, Epstein-Barr encoding Region; CK7, Cytokeratin 7; CK20, Cytokeratin 20; MSI-H, Microsatellite Instability-High; EMA, Epithelial Membrane Antigen; LCA, Leukocyte Common Antigen; Ki-67, Proliferation marker, Human Epidermal growth factor Receptor 2, c-erbB2, MSH6, MutS Homolog 6; MSH2, MutS Homolog 2; MLH1, MutL Homolog 1; PMS2, PMS2 gene Lynch syndrome.

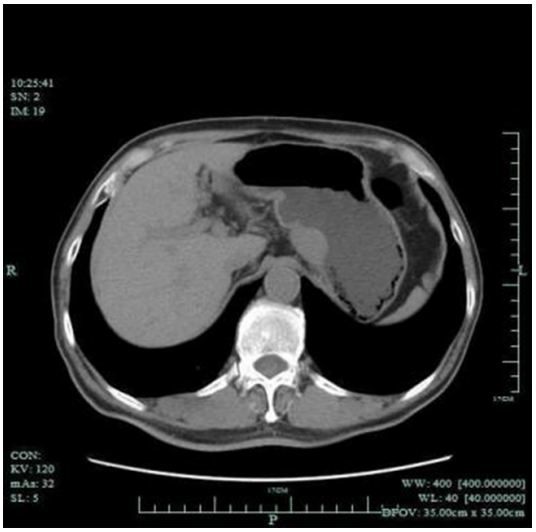

Figure 1. CT images shows space-occupying lesion of gastric lesser curvature at the fundus of stomach, benign lesion of sub mucosal origin, and schwannoma or stromal tumor.

endoscopy. The patient did not complain of nausea, vomiting, or fever. There was no abdominal pain and no obvious aggravating or relieving factors. There was no hematemesis, melena, acid regurgitation, belching, chills, or any other discomforts. The patient had a ten years history of hypertension, had been taking anti-hypertensive drugs showing effective blood pressure control, and had no any family history of such diseases. After admission to our hospital, the complete blood count, blood chemistry, and tumor indices were normal. The Biochemical tests results are presented (**Table 1**). Contrast-enhanced abdominal computed tomography (CT) showed: "Space-occupying lesions of gastric lesser curvature at the fundus of stomach, benign lesions of submucosal origin, and schwannoma or stromal tumors can be considered" (**Figure 1**). Gastroscopy examination image showed; "A 2.0 cm × 2.0 cm hemispherical submucosal eminence at the fundus of the stomach with regular borders, a smooth surface, and a shallow central ulcer, can be seen" (**Figure 2**). Endoscopic ultrasonography showed "a hypoechoic mass originating from the muscularis propria of the gastric wall, which was 2.4 cm × 1.5 cm in size, round and protruding into the gastric cavity, with clear boundary, uniform internal echo, complete mucosal, submucosal, and serosal layers, and no surrounding swollen lymph nodes" (**Figure 3**). Based on all the examination results, the tumor was suspected to be a gastric stromal tumor.

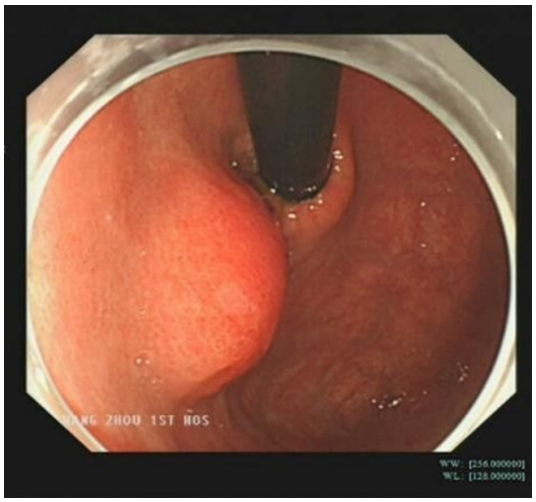

Figure 2. Gastroscopy examination showed a 2.0 cm × 2.0 cm hemispherical submucosal eminence at the fundus of the stomach with regular borders, smooth surface and a shallow central ulcer.

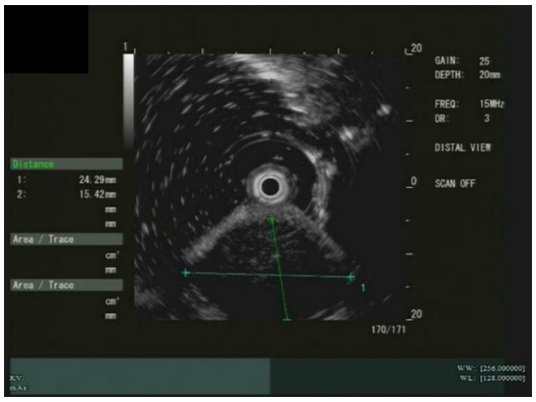

Figure 3. Endoscopic ultrasonography examination; a hypoechoic mass originating from the muscularis propria of the gastric wall was observed at the lesion, which was 2.4 cm × 1.5 cm in size.

Following this diagnosis, the patient was suggested to receive endoscopic submucosal dissection (ESD). After informed consent was obtained, the patient underwent ESD. A transparent cap at the front end of the endoscope was established, and the mucosal tunnel entrance was at the lower segment of the esophagus, approximately 5 cm away from the side of the mouth of the lesion. After the endoscope entered the tunnel, it was separated from the submucosal layer to the anal side of the gastric mucosa by using with a gold knife (Micro-Tech Nanjing). A white tumor body measuring approximately 2.5 cm was found at the

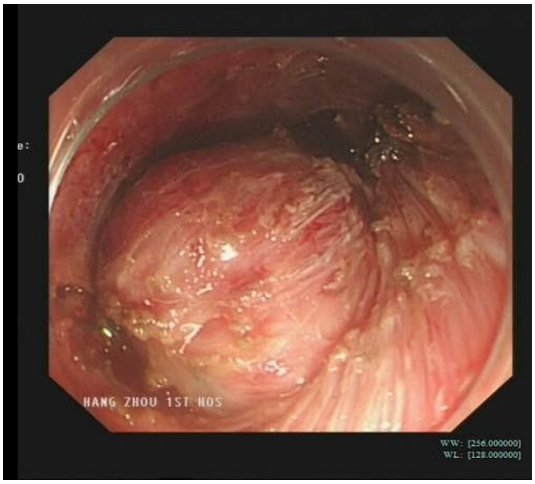

Figure 4. Tumor resection through endoscopic submucosal dissection surgery and a round tumor mass was discovered.

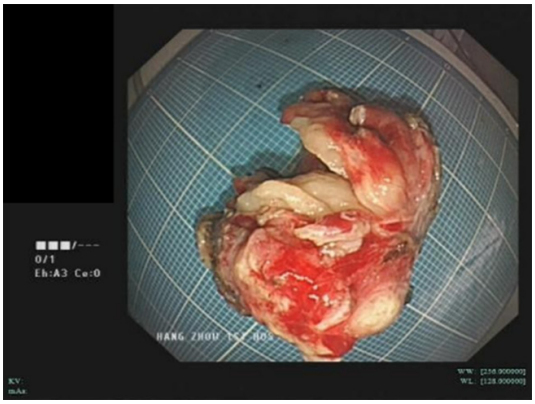

Figure 5. After the resection the mass of 2.8 cm × 1.5 cm × 0.8 cm was sent for pathological examination (One small box in white shows length of 1 cm).

cardia and the gastric bottom (**Figures 4**, **5**). The tumor body was closely connected to the muscularis propria, which was separated entirely from the muscles layer by using a gold knife. The tumor body was too large, and could not be removed from the tunnel. Therefore, ESD was performed under gastroscopy, and the lesion was entirely excised. No obvious bleeding was observed on the wound surface. A purse-string suture was used, and the surgical procedure was smooth.

Postoperative pathological results: The tumor size was 2.8 cm × 1.5 cm; low-differentiated carcinoma (**Figures 6**, **7**). Immunohistochemical results: lymphoepithelial carcinoma, infil-

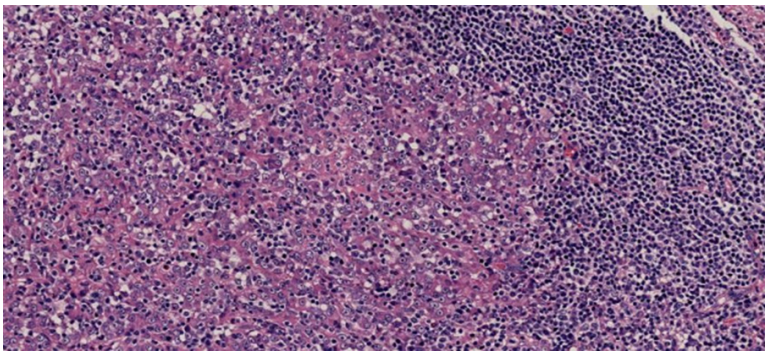

Figure 6. Postoperative pathological results shows that the tumor size was 2.8 cm × 1.5 cm Low-differentiated carcinoma (HE staining ×200 magnification).

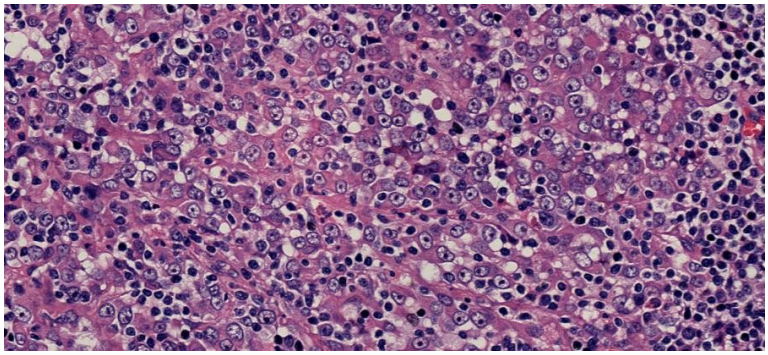

Figure 7. Immunohistochemical results showed lymphoepithelioid carcinoma, infiltrating into a muscular layer, without tumor thrombus and nerve invasion in vessels, and the lesion involved the lateral incisal margin (HE staining ×400 magnification).

trating the muscular layer, without tumor thrombus and nerve invasion in vessels, and the lesion involved the lateral incisal margin (**Table 1**). The patient was transferred to surgery for additional treatment and underwent radical gastrectomy plus lymph node dissection. Postoperative pathology revealed erosion near the cardia of the stomach bottom, granulation tissue formation, inflammatory cell infiltration, fibrous tissue hyperplasia, and residual lymphoepithelioma-like cancer. The largest diameter of the tumor was 0.9 cm, located in the submucosa and superficial muscle layers. The incisal margin was not involved, there was no tumor thrombus or nerve invasion in the vessels, and there was no cancer metastasis in the peripheral lymph nodes. The patient has kept healthy since the follow-up started two years ago.

Discussion

Lymphoepithelioma-like carcinoma (LELC) is a rare and unique carcinoma. The nasopharynx is the most common site for LELC, but it has also been reported to be the esophagus, stomach, colon, and rectum [6, 13]. A few cases have been reported at other sites, such as the lung, thymus, larynx, salivary gland, pancreas, breast, skin, and ureter. Epstein-Barr virus-associated (EBV) infection accounts for 4-10% of gastric carcinomas of total gastric cancer [16, 17]. LELC is mainly associated with EBV infection and varies from moderately differentiated tubular cancer to poorly differentiated adenocarcinoma. About 80% of LELC is related to Epstein-Barr virus infection, whereas approximately 6% are diffuse and 7% are intestinal-type adenocarcinomas [18-20]. Epstein-Barr virus-positive gastric LELC mainly occurs in men, with an onset age of 55-65. It is common in the proximal region of the stomach and sometimes in the antrum. Epstein-Barr virus-negative patients are relatively older in onset age, more common in women and have a smaller gastric antrum [21, 22]. EBV infection mainly occurs before the onset of the disease or in a latent state. It is regulated and activated by latent EBV genes (including LMP2A, EBER, BRLF1, BZLF1 and BLLF1, etc.), breaking the balance and inducing tumors [20, 23-26].

The clinical manifestations include abdominal discomfort, acid regurgitation, intermittent epigastric pain, hematemesis, or black stools. Most are characterized by a recent worsening of symptoms, but gastrointestinal symptoms have no apparent specificity. The typical endoscopic appearance is a bulge lesion, often accompanied by deep and shallow ulcers in the center with a clear boundary. As the tumor is located under the mucosa, it is difficult to

obtain tumor tissue using routine gastroscopic biopsy [27-29]. Endoscopic ultrasonography helps determine the nature, size, boundary, and origin of the tumors. However, it is difficult to distinguish them from other submucosal tumors, such as stromal tumors and lymphomas without pathological examinations [20]. Nevertheless, CT can assist in determining the nature and location of the lesion and presence of lymph node metastasis. However, it cannot be clearly diagnosed, with a particular guiding significance for subsequent treatment [30]. Diagnosis can be dependent only on the pathological and immunohistochemical diagnosis after lesion resection. If positive for EBV infection, the diagnosis can be confirmed as gastric LELC.

According to the etiology and pathology of LELC. The tumor suppressor gene P16 is inactivated by the hypermethylation of the CpG islands. Inactivated P16 cannot inhibit the phosphorylation of the tumor suppressor protein retinoblastoma (Rb), which leads to uncontrolled cell growth and, eventually, malignant proliferation. The expression of mismatch repair proteins MLH1 and PMS2 is absent, which leads to an increase in microsatellite instability (MSI) and promotes tumorigenesis. In the tumor microenvironment, tumors EB virus-infection have up-regulated the expressions of various cytokines, which promote tumor growth. Programmed death molecule-1 (PD-1) immune checkpoints on T cells and programmed death molecule ligand-1 (PD-L1) with increased expression levels on tumor cells interact to provide inhibitory signals in T cell activation, leading to the downregulation of cellular and humoral immune responses and the promotion of malignant tumor progression. In addition, none of the 110 cases of LELC reported by Grogg et al., developed EBV-positive and MSI-H-positive simultaneously, which was consistent with the results reported in other cases, suggesting that EBV infection and MSI-H might be unrelated pathogenic factors involved in the different etiological pathways of LELC [31]. In contrast, our case was negative for EBV, but MLH1 and PMS2 were slightly positive, so it is hard to judge whether it is related to MSI-H.

The masses of the available LELC specimens were gray-white and grayish-red in many sections. Under a microscope, it is characterized by much more denser lymphocyte infiltration than cancer cells. The cytoplasmic boundary was unclear. Some masses fuse into syncytial cells and the glandular structure is poorly formed. Undifferentiated or poorly differentiated cancer cells are arranged into cords, nests, or a single scattered distribution. The cancer cells are oval or polygonal, with vacuolar nuclei, obvious nucleoli, and little mitosis [15].

There is no specific treatment plan for gastric LELC, and early surgical resection is the primary treatment option. Even after the lesion is resected by ESD and the diagnosis is confirmed, radical gastrectomy and peripheral lymph node dissection are still needed, and chemotherapy or radiotherapy should be supplemented according to the patient's condition after the surgery. Moreover, according to the microenvironmental characteristics of gastric LELC tumors, PD-1 or PD-L1 inhibitors may be essential for treating gastric LELC in the future. However, there are several case reports on the following treatment options [32]. Additionally, some studies have shown that demethylating agents can promote viral lytic infection in cells with latent EBV infection, which may lead to the dissolution of cancer cells. This scheme can also be considered for the treatment of gastric LELC in the future [33]. There are a few literatures on radiotherapy. Li H et al. suggested that low-dose γ-ray radiotherapy could be used for patients with EBV-positive stomach LELC. Therefore, surgery combined with radiotherapy can be considered and a better curative effect may be obtained [32].

The prognosis of gastric LELC is better than that of ordinary gastric cancer, which may be related to the body's immune response to a tumor, the limitation of tumor cell infiltration by lymphocytes, and the degree of lymphocyte infiltration, which is positively correlated with prognosis. In this case, the lesion was excised by ESD, and subsequently diagnosed as gastric LELC by pathology and immunohistochemistry, which reflected the diagnostic value of ESD. In the follow-up surgery, it was found that there was residual lesion after ESD surgery, but the postoperative pathological results showed no lymph node metastasis.

Conclusion

Cases of gastric LELC are rare, and clinicians need to improve their understanding of the dis-

ease to avoid misdiagnosis. The etiology and pathogenesis of this disease require further investigation. These results will be of great help in the study of the best treatment for gastric LELC.

Acknowledgements

This study was supported by grants from the Zhejiang health committee (2021441076), Hangzhou science and technology commission (202004A14) and The Construction Fund of Medical Key Disciplines of Hangzhou (0020190001).

Disclosure of conflict of interest

None.

Abbreviations

LELC, Lymphoepithelioma-Like Carcinoma of the Stomach; EBV, Epstein-Barr Virus; ESD, Endoscopic Sub-mucosal Dissection; MSI, Microsatellite Instability; Rb, Retinoblastoma; PD, Programmed Death molecule.

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