Int J Clin Exp Pathol 2020;13(7):1902-1908
www.ijcep.com /ISSN:1936-2625/IJCEP0111341

Case Report

Superficial esophageal lymphoepithelioma-like carcinoma treated with endoscopic submucosal dissection: a case report

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Received March 24, 2020; Accepted April 28, 2020; Epub July 1, 2020; Published July 15, 2020

Abstract: Lymphoepithelioma-like carcinoma (LELC) of esophagus is an extremely rare tumor only a few cases were successfully treated with endoscopic submucosal dissection (ESD). We herein report one case of superficial esophageal LELC with adjacent squamous intraepithelial neoplasia successfully treated by ESD, and the status of Epstein-Barr virus (EBV) infection and microsatellite instability (MSI) were detected simultaneously. A 71-year-old woman presented with complaints of substernal discomfort. Under endoscopy, a dome-shaped bulge of 1.2 cm × 0.8 cm was located at the mucosal lamina propria in the left lateral wall of the middle esophagus, and the mucosa covering the bulge was smooth and normal-appearing. A brownish lesion was found adjacent to the bulge. Microscopically, the tumor was well demarcated, and nests of syncytial epithelioid cells were identified in the lamina propria of the mucosa, with a large number of inflammatory cells. The squamous epithelium covering the surface of the infiltrating tumor and the second brownish lesion demonstrated low grade squamous intraepithelial neoplasia. Tumor tissue showed CK5/6, p63, and p40 positive staining, was EBV negative, and had microsatellite stability. After treatment with ESD, this patient received no further treatment, and had no recurrence or metastasis at 25-month follow-up.

Keywords: Esophagus, lymphoepithelioma-like carcinoma, endoscopic submucosal dissection, Epstein-Barr virus, microsatellite instability

Introduction

Lymphoepithelioma-like carcinoma (LELC) of esophagus is considered a unique subtype of undifferentiated carcinoma, and is characterized by poorly differentiated tumor cell nests lacking definite microscopic features of squamous, glandular, or neuroendocrine differentiation, but with dense infiltrate of lymphocytes. Most LELC occur in the head and neck region, especially in the nasopharyngeal region [1], but they may occur in the digestive tract, such as stomach or colon [2]. LELC of the esophagus is an extremely rare neoplasm, that was first reported by a Japanese author Amano [3] in 1988, and most reported cases were in Asia [4].

LELC of esophagus usually presents as a protuberant or ulcerative mass, that may infiltrate deep into the esophageal wall. Radical esophagectomy combined with chemotherapy or molecular targeted therapy is preferred to treat LELC of esophagus. With the development of endoscopic technology, endoscopic submucosal dissection (ESD) is recommended for treating superficial esophageal cancer (only in the lamina propria or superficial submucosa) without risk factors for LNM, such as lymphovascular invasion. To date, 5 cases of superficial esophageal LELCs have been reported (**Table 1**) [5-9], and only two cases were successfully treated with ESD without additional treatment [5, 6]. Epstein-Barr virus (EBV) infection and microsatellite instability (MSI) have been considered pathogenic factors for gastric LELC [10]. In general, the association between EBV and LELC was strong in head and neck including nasopharyngeal carcinoma, but relatively weak in other areas. However, the molecular mechanism of esophageal LELC remains unclear. There was only a postulated correla-

Table 1. Reported cases of superficial esophageal lymphoepithelioma-like carcinoma

Case	Gender	Age (year)	Esophageal Localization	Symptom	Size (cm)	Immunohistochemical Features	EBV Status	Depth of invasion	Treatment	Reference
1	Male	60	Distal	No	1.0	34βE12, p63+	Negative	Submucosa (SM1)	ESD	[5]
2	Female	69	Proximal	No	Not described	P16, p63, AE1/AE3+	Negative	Mucosa	ESD	[6]
3	Male	79	Middle	No	1.0	Not described	Negative	Submucosa (SM3)	ESD+Chemoradiation	[7]
4	Male	67	Middle	Dysphagia	0.6	P53, human leukocyte antigen-DR+	Negative	Submucosa (SM1)	ESD+gastrectomy	[8]
5	Male	70	Distal	Stomach ache, nausea	1.0	AE1/AE3+; Ki-67: 76%+	Negative	Mucosa	Gastrectomy	[9]
6	Female	71	Middle	Substernal discomfort	1.2	CK5/6, p40, p63+; Ki-67: 80%+	Negative	Mucosa	ESD	Our report

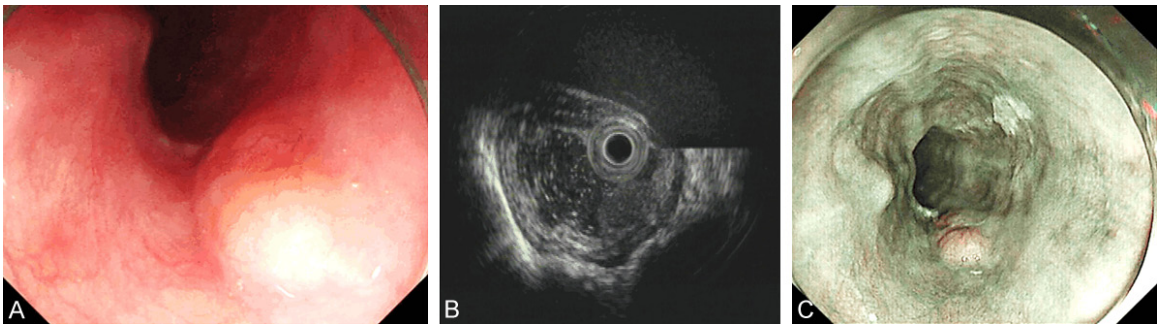

Figure 1. Upper gastrointestinal endoscopy findings. A. White light endoscopy showed a dome-shaped bulge with a normal surface. B. Endoscopic ultrasonography showed that the lesion was located in the mucosal lamina propria. C. Lugol's iodine staining demonstrated another brown lesion with irregular border.

tion between the incidence of esophageal LELC and EBV infection, as esophageal LELC was occasionally positive for EBV [11, 12].

We herein report one case of superficial esophageal LELC with adjacent squamous intraepithelial neoplasia successfully treated with ESD, and the status of EBV infection and MSI were detected simultaneously.

Case report

A 71-year-old woman was evaluated because of substernal discomfort including heartburn and fullness. She did not have a history of gastrointestinal disease, alcohol abuse, or smoking. Before admission to our hospital, the patient was evaluated in a local hospital. Gastroscopy revealed chronic gastritis with mucosal erosion and esophageal mucosa protrusion. The patient was transferred to our hospital for further treatment on esophageal lesion.

The serum tumor markers, including AFP, CEA, Ferritin, CA125, CA153 and CA199, were within normal ranges. Under white light endoscopy, a dome-shaped bulge of 1.2 cm × 0.8 cm in the left lateral wall of the middle esophagus, about 32 cm from the incisor, was detected. The mucosa covering the bulge was smooth and normal-appearing (**Figure 1A**). Endoscopic ultrasonography demonstrated that the bulge was uniformly hypoechoic, well-demarcated, located at the mucosal lamina propria, and did not involve the submucosa (**Figure 1B**). Meanwhile, a brownish lesion was found in the anterior wall adjacent to the bulge under white light endoscopy. After Lugol's iodine staining, the lesion showed a clearer irregular border (**Figure 1C**). ESD was performed to remove these two lesions successfully.

Two excised specimens were fully expanded on a foam board with needles, and fixed overnight with 10% buffered formalin. The specimens were cut with parallel sections at a 2 mm interval. All tissues were routinely embedded, sectioned and stained with hematoxylin and eosin. Immunohistochemical staining for cytokeratin (CK) 5/6 (1:150 dilution, clone D5/16B4, Dako, Santa Clara, CA), p40 (1:150 dilution, clone 2R8, Maixin Bio, Fuzhou, China), p63 (1:200 dilution, clone DAK-p63, Dako, Santa Clara, CA), Ki-67 (1:200 dilution, clone MIB-1, Dako, Santa Clara, CA), desmin (1:200, clone D33, Dako, Santa Clara, CA) were performed on Dako automatic immunostainer (Link 48, Carpinteria, CA), and p16 (predilute antibody, clone MX007, Maixin Bio, Fuzhou, China) was performed on Roche automatic immunostainer (Ventana, Tuscon, AZ). Epstein-Barr virus encoded RNAs (EBER) were detected using in-situ hybridization technique (ZSGB-BIO, ISH-7001, Beijing, China). Microsatellite instability evaluation was performed using multiplex PCR for five quasimonomorphic mononucleotide repeat markers (BAT25, BAT26, D2S123, D5S346 and D17S250) both in tumor and corresponding blood samples on ABI Genetic Analyzer 3500 (Applied Biosystems, Foster City, CA).

Macroscopically, lesion #1, a piece of esophageal mucosa measuring 1.6 cm × 1.1 cm with a protrusion measuring 1.1 cm × 0.7 cm covered with normal mucosa. A solid gray-red well-demarcated mass was found right below the epithelium in cut section. Lesion #2, a piece of esophageal mucosa measuring 1.6 cm × 1.1

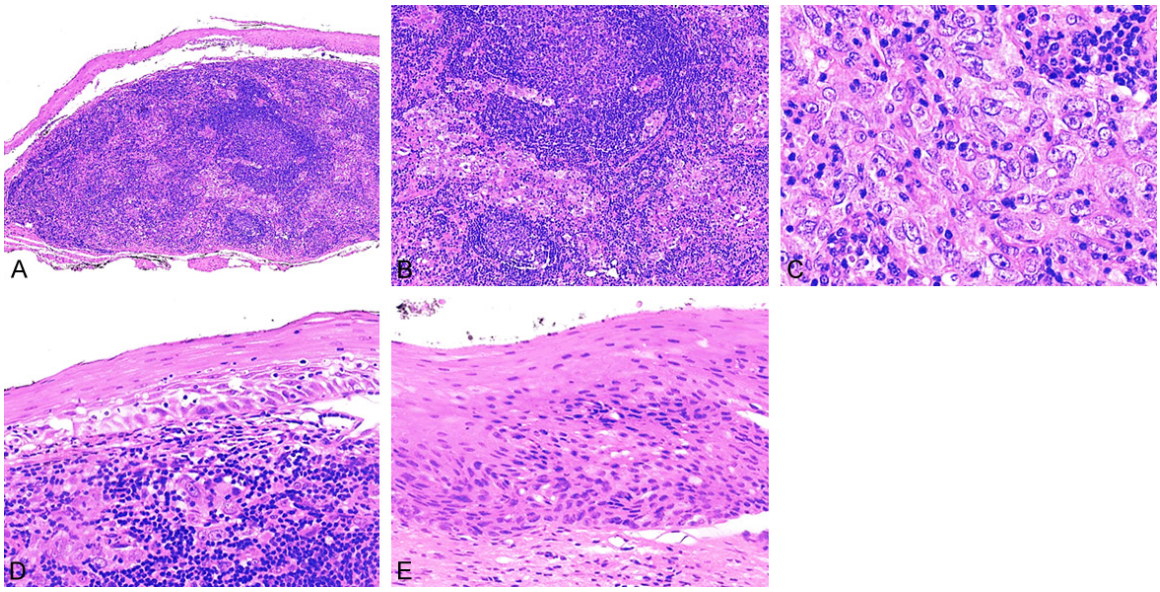

Figure 2. Histologic features. (A) Low-power magnification showing well-demarcated tumor (hematoxylin and eosin, original magnification × 40). (B) Nests of epithelioid cells in the lamina propria with inflammatory cells and lymphoid follicles (hematoxylin and eosin, original magnification × 100). (C) High-power magnification showing syncytial tumor cells with amphophilic cytoplasm, indistinct cell boundary, vesicular nuclei, and prominent nucleoli (hematoxylin and eosin, original magnification × 400). (D, E) High-power magnification showing low grade squamous intraepithelial neoplasia on the tumor surface (D) and the second brownish lesion (E) (hematoxylin and eosin, original magnification × 200).

cm, showed slightly roughened surface without apparent erosion.

Microscopically, lesion #1, on low power, showed a well demarcated lesion with pushing border into the surrounding stroma (**Figure 2A**). Nests of epithelioid cells were identified in the lamina propria of the mucosa, with a large number of inflammatory cells infiltrating in the nests (**Figure 2B**). On high power, epithelioid cells showed amphophilic cytoplasm, indistinct cell boundary, vesicular nuclei, and prominent nucleoli (**Figure 2C**). Mitoses were found easily. Inflammatory cells were composed mainly of lymphocytes and plasma cells with lymph follicles forming. The squamous epithelium covering the surface of the infiltrating tumor and the second brownish lesion (lesion #2) demonstrated low grade squamous intraepithelial neoplasia (**Figure 2D**, **2E**). The tumor did not invade into submucosa unequivocally, with clearly demonstrated muscularis mucosae by desmin immunostaining (**Figure 3A**). CK 5/6, p63, and p40 (**Figure 3B**) immunostaining clearly revealed the invasive cancer cells hidden in the lymphoid tissue. The Ki-67 proliferation index of tumor cells was about 80%. P16 was immunopositive in the low grade squamous intraepithelial neoplasia area, while immunonegative in the invasive cancer cells (**Figure 3C**). By in situ hybridization EBER was negative in invasive cancer cells (**Figure 3D**) and low grade squamous intraepithelial neoplasia area. Microsatellite fragment analysis displayed microsatellite stability (MSS) of tumor tissue (**Figure 4**).

After treatment with ESD, this patient did not receive any other treatment, such as radical surgery or adjuvant chemotherapy. The patient did not have any recurrence or metastasis after 25-month follow-up.

Discussion

LELC is an uncommon carcinoma with dense lymphoid stroma. LELC can be found in the digestive tract, mostly in the stomach, rarely in the esophagus, and can occur in both esophagus and stomach simultaneously [13]. We report herein a case of esophageal LELC with adjacent squamous intraepithelial neoplasia which was successfully treated with ESD.

Patients with esophageal LELC are usually 50 years to 80 years old, without gender differ-

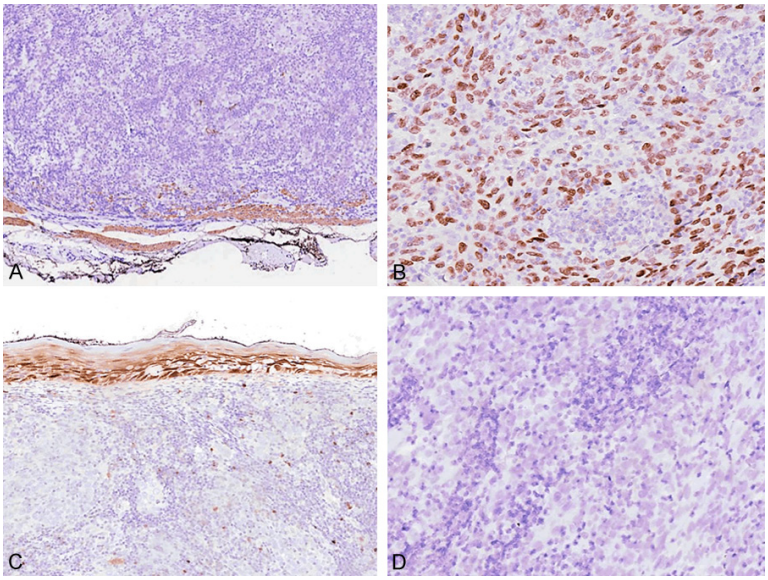

Figure 3. Immunohistochemical findings and EBER in situ hybridization. A. Desmin staining showed that the lesion was confined to the mucosal layer (original magnifications × 100). B. P40-positive staining in tumor cells (original magnifications × 200). C. P16-positive staining in the low grade neoplasia area of the tumor surface (original magnifications × 200). D. EBV-negative staining in tumor cells with in situ hybridization (original magnifications × 200).

ence. Clinical manifestations are nonspecific and may include retrosternal burning, dysphagia, and weight loss. The tumor is covered with normal smooth squamous epithelium. Depression or ulceration is rare. It can be misdiagnosed as leiomyoma under endoscopy, even under endoscopic ultrasonography. Moreover, an insufficient biopsy often fails to reveal the tumor parenchyma because the lesion often is located beneath the epithelium, which makes it get misdiagnosed as squamous cell carcinoma (SCC) or without malignancy.

The histopathologic features of esophageal LELC are similar to LELC of nasopharynx or other organs, which is characterized by nests of syncytial tumor cells with prominent vesicular nuclei and nucleoli, and a large number of non-neoplastic reactive lymphocytes and plasma cells infiltrating into the stroma of the tumor. Necessary immunohistochemical markers are also required to exclude melanoma, and neuroendocrine carcinoma if the morphology is not straightforward.

The etiology of esophageal LELC has not been determined. EBV is related to various hematopoietic tumors and epithelial malignancies, and closely to nasopharyngeal LELC. A spectrum of molecular changes of gastric carcinoma with lymphoid stroma including EBV and MSI were reported recently [14]. Studies had shown that EBV-positive gastric LELCs were rarely associated with MSI, but EBV-negative gastric LELCs were sometimes associated with MSI [10, 15]. However, the detection of EBV and MSI in this case did not show positive results. Instead of EBV and MSI [16], cervical LELC can be associated with human papilloma virus (HPV). In this case, although low grade squamous neoplasia was immunopositive for p16, the invasive cancer was negative. Immunohistochemical positive expression of p16 in esophageal LELC was reported, and in situ hybridization of HPV was negative [6], which suggested that p16 positivity in this case may not imply HPV infection. All the results suggested that EBV, MSI, or HPV might not be involved in the pathogenesis of this case. The difference in pathogenesis between LELC of the esophagus and LELC of other organs is still unclear. At present, no specific immunohistochemical antibodies can be used to distinguish between them.

The cell of origin of LELC is still unclear. Gastric LELC originates from glandular epithelium, and esophageal LELC can also be adenocarcinomas in rare cases [17]. Similarly, in a reported case of cutaneous LELC, a focus of adjacent squamous intraepithelial neoplasia was detected [18]. In this case, low grade intraepithelial neoplasia was observed in the squamous epithelium on the surface of the tumor and adjacent areas simultaneously, and CK 5/6, p63, p40 were expressed in tumor cells. Although the areas of intraepithelial neoplasia and invasive cancer cells were not continuous, LELC in this case was believed to originate from surface squamous epithelium, and to be a subtype of nonkeratinizing SCC.

Compared to other undifferentiated carcinomas, the prognosis of esophageal LELC is fa-

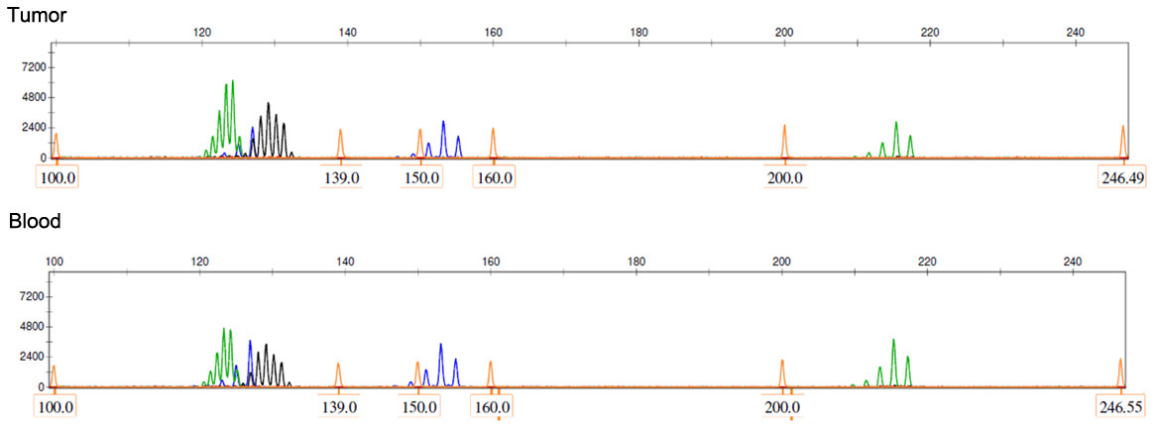

Figure 4. Microsatellite fragment analysis displayed microsatellite stability of the tumor.

vorable [4, 6], although it may be accompanied by extensive regional lymph node metastasis [11, 12]. A high Ki-67 index normally indicates an aggressive clinical course. Ki-67 index of this case (approximately 80%) and the reported case (76%) [9] were high, but the prognoses were excellent, which may be due to the antitumor immune response of dense stromal lymphocytes. Surprisingly, esophageal LELC with one lymph node metastasis in the neck spontaneously shrank in one patient, and the patient survived for a long time after esophagectomy [8]. Olmez reported a case of primary esophageal LELC who died 8 months after endoscopic resection exceptionally [19]. The status of EBV has also been reported to be associated with the prognosis of patients with gastric LELC. For example, the overall survival of EBV-negative gastric LELC patients was shorter than that of EBV-positive patients [15]. Fortunately, the case with esophageal LELC we reported was treated with ESD, and had met the standard of curative resection (superficial infiltration of the lesion with extremely low risk of LNM, and the incisor margin was negative) [20]. She did not need additional surgery or adjuvant chemotherapy or radiotherapy, and remained tumor-free after 25-month follow-up.

Conclusion

We present a tumor that was derived from the squamous epithelium, without relation to EBV or HPV infection. Preliminary study showed microsatellite stability, but further and detailed molecular analysis should be done in order to reveal molecular features of LELC. The prognosis of the case was favorable, and the management might be similar to other histologic subtypes of esophageal carcinomas according to the clinical stage, and risk factors of recurrence or metastasis. Although more cases need to be observed, early or superficial esophageal LECL may be successfully treated with ESD.

Acknowledgements

Consent was obtained from the patient for publication of this report and any accompanying images.

Disclosure of conflict of interest

None.

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