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CASE REPORT | ESOPHAGUS

Difficult Preoperative Diagnosis of Lymphoepithelioma-Like Carcinoma of the Esophagus

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ABSTRACT

A 60-year-old man with a medical history of diabetes, liver cirrhosis, and distal gastrectomy was referred for further examination of a 10-mm pale-colored submucosal tumor around 40 cm from the incisors. Narrow band imaging–magnifying endoscopy revealed the lesion covered by smooth epithelium with irregular microvascular architecture in a sparse distribution. Endosonography showed an irregular-shaped hypoechoic lesion in the submucosa. With no evidence of metastases, we performed en bloc endoscopic submucosal dissection, whose specimen revealed esophageal lymphoepithelioma-like carcinoma invading up to 500 μm in the submucosa, a rare disease entity. Despite no additional treatment, he was alive without recurrence for longer than 88 months.

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC), first reported in the lung, is defined as a tumor with histologic similarity to undifferentiated nasopharyngeal carcinoma with lymphoid stroma.[1] Esophageal LELC is very rare among gastrointestinal LELCs.[2] Most of the superficial LELCs of the esophagus were observed as submucosal tumors (SMTs) covered with normal-appearing epithelium by conventional esophagogastroduodenoscopy (EGD) or endosonography (EUS). Histologic diagnosis of LELC using biopsy specimens is difficult and often diagnosed as squamous cell carcinoma (SCC) or no malignancy.[2–5] We report a case of esophageal LELC, whose diagnosis was made using en bloc specimens obtained by endoscopic submucosal dissection (ESD), and suggest that the finding of narrow band imaging (NBI)-magnifying endoscopy (NBI-ME) of a small SMT-like lesion might be useful to suspect esophageal LELC.

CASE REPORT

A 60-year-old Japanese man with a medical history of diabetes, alcoholic liver cirrhosis, distal gastrectomy for duodenal ulcer, and partial pancreatectomy for pancreatic cyst presented for an annual screening examination. He had a history of alcohol abuse and was a heavy smoker. A physical examination revealed multiple operation scars on his abdomen, and laboratory data showed no abnormalities. A conventional EGD depicted a pale-colored SMT around 40 cm from the incisor, and histologic diagnosis of endoscopic biopsy was suspicious for poorly differentiated SCC (Figure 1). Under histopathologic examination, cancer cells were observed mainly in lamina propria with an infiltration of CD8-positive T-lymphocyte in tumor nests. Thereafter, he was referred to our hospital for further examination. EGD demonstrated a 10-mm SMT-like lesion with a depression. NBI-ME (H260Z; Olympus, Tokyo, Japan) demonstrated that it was covered by normal-appearing epithelium with irregular microvascular architecture in a sparse distribution (Figure 2). With no demarcation line, the pattern of intrapapillary capillary loops (IPCLs) in the mucosa were mixed with regular patterns, as type A, dilated and irregular shapes, as type B1, and plexiform patterns, as type R, all of which were on the extended microvascular in the submucosa.[6] A chromoendoscopy

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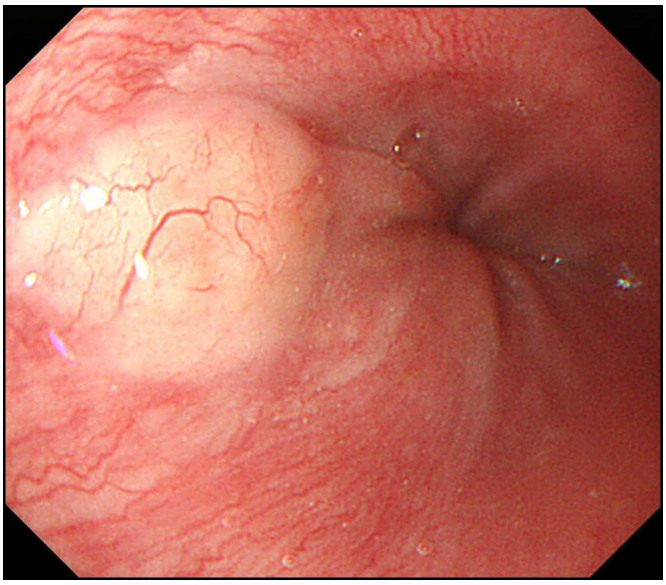

Figure 1. Endoscopy showing a pale-colored 10-mm submucosal tumor-like lesion around 40 cm from the incisors, with no demarcation line, a smooth surface, and covered by normal-appearing epithelium.

depicted a tiny iodine-voiding lesion on the tumor. A 20-MHz miniature probe of EUS (UM-3R; Olympus, Tokyo, Japan) showed an irregular-shaped hypoechoic lesion in the submucosa, whose layer was intact (Figure 3). Computed tomography revealed no metastasis. An en bloc ESD was performed with a well-documented informed consent. Based on the microscopic findings of the ESD specimens, irregular-shaped cancer cells with eosinophilic cytoplasm existed with prominent lymphoid stroma invading up to 500 μm in the submucosa, although they were fully covered with non-neoplastic squamous epithelium. Immunohistochemically, the cancer cells were positive for cytokeratin 34βE12 and p63, but negative for in situ hybridization for the Epstein-Barr virus encoded small RNA (EBER-1) transcript, and tumor nests were observed in a scattered manner with infiltration of CD3-positive T-lymphocytes (Figure 4). Accordingly, the histologic diagnosis was esophageal LELC,

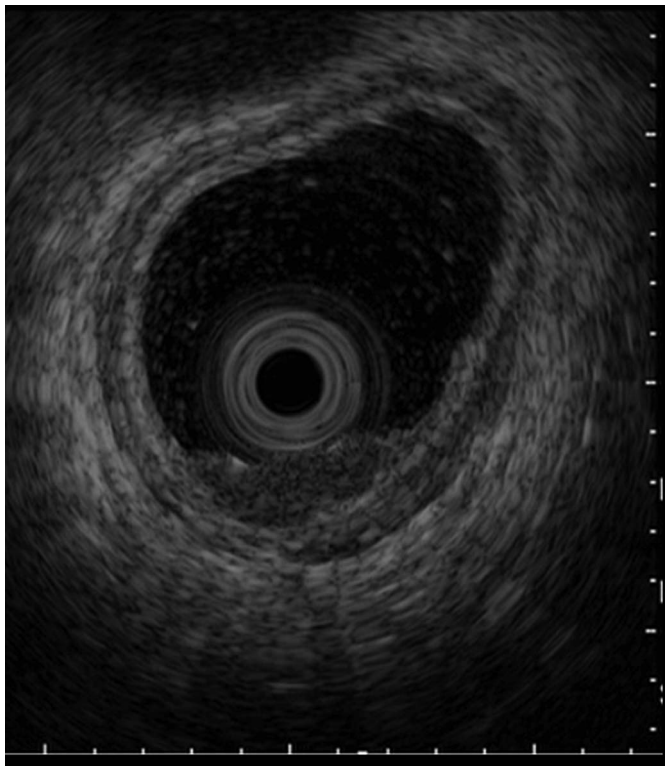

Figure 3. 20-MHz miniprobe endoscopic ultrasound showing a hypoechoic 10 × 4 mm lesion with an irregular shape in the submucosa, but an intact submucosal layer.

whose horizontal and vertical margins were negative for cancer invasion. Although surgical resection was recommended based on the pathological stage I; pT1b, N0, M0, he did not request additional treatment. He was alive without recurrence for longer than 88 months after ESD.

DISCUSSION

We report a rare case of esophageal LELC. Our case fulfilled the criteria of primary LELC of the esophagus, which is pathologically defined as undifferentiated carcinoma or poorly

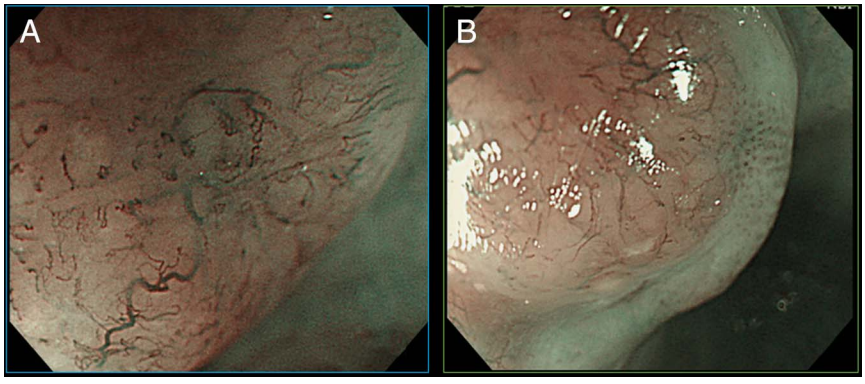

Figure 2. Narrow band imaging–magnifying endoscopy showing irregular microvascular architecture in a sparse distribution. At a prominent area of the oral side, irregular microvascular architecture of (A) type B1 and (B) type R in the mucosa were observed on a background of extended microvessels in submucosa.

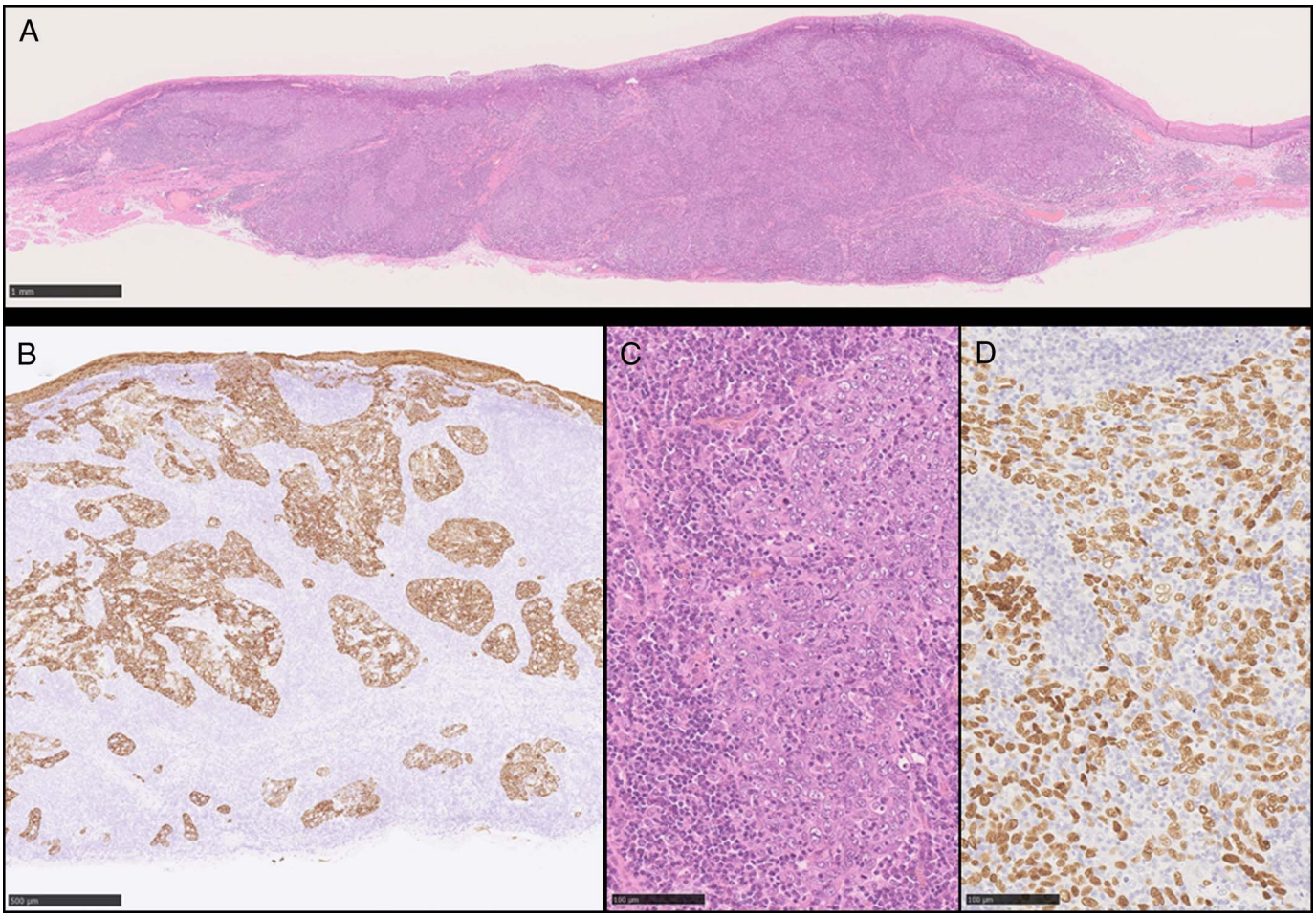

Figure 4. Microscopic findings of esophageal lymphoepithelioma-like carcinoma. (A) Hematoxylin and eosin (H&E) staining showing non-neoplastic squamous epithelium covering of the tumor. (B) Cancer cells were positive for cytokeratin 34βE12. (C) H&E staining showing irregular-shaped cancer cells with eosinophilic cytoplasm with prominent lymphoid stroma invading up to 500 μm in the submucosa. (D) Tumor nests were observed in a scattered manner with the infiltration of CD3-positive T-lymphocytes.

differentiated SCC accompanied by prominent non-neoplastic reactive lymphoplasmacytic infiltration.[2–5] Based on a search of the PubMed database using the keywords "lymphoepithelioma-like carcinoma" and "esophagus," only 5 cases of superficial LELC of the esophagus were reported, mainly from Asia. None were reported to have Epstein-Barr virus (EBV) infection, despite a close association between EBV infection and nasopharyngeal or gastric LELC.[2,3] The typical EGD findings were SMT covered with normal-appearing mucosa, and histologic diagnosis of the primary biopsy tended to be poorly differentiated SCC or no malignancy.[2–5] This is not surprising because the histologic characteristics are observed mainly in the submucosa, where undifferentiated cancer cells exist in the stroma, while nondysplastic epithelium is overlaid. A previous report revealed that after histologic diagnoses of biopsies taken by standard forceps, there was no malignancy twice, but boring biopsy yielded esophageal LELC at the third trial.[7] Accordingly, it is difficult preoperatively distinguish esophageal LELC from popular SMTs without malignant potential.

EUS can provide preoperative diagnoses on SMTs with detection of the original layer, size, and border, but its accuracy is still controversial. A multicenter prospective study revealed that its sensitivity and specificity for predicting malignancy were 64% and 80%, respectively.[8] Therefore, histologic evidence, rather than endoscopic images alone, is essential to determine treatment strategy. Recently, ESD has been performed to remove SMTs less invasively, but its feasibility remains uncertain. In a prospective study to elucidate its feasibility for upper gastrointestinal SMTs whose mean size was 13.6 ± 9.5 mm, the rates of en bloc resection and critical complications were 92.9% and 1.8%, respectively, and the coincidence between EUS findings and histologic diagnosis of ESD specimens was 82.6%.[9] In our case, based on the EUS findings, an en bloc ESD was performed under direct vision of both the bottom of the lesion and the surface of the muscularis propria. As a result, negative residual cancer was confirmed histologically, and the patient is alive with no recurrence.

We demonstrated the NBI-ME findings of esophageal LELC for the first time. NBI-ME depicted irregular microvascular architectures in a sparse distribution. The IPCL pattern of this case was intermixed with type A, type B1, and type R on the extended

microvessels in the submucosa, but the poor density of irregular IPCLs and the absence of evident demarcation line were quite different from SCC. In agreement with the NBI-ME findings, tiny microvessels and the infiltration of stromal cells were histologically observed underneath the nondysplastic epithelium. Moreover, we could refer to IPCLs of other esophageal SMTs. Mucosal IPCLs of non-neoplastic SMTs are classified as type A, which has 3 or fewer factors of irregularity, for example, tortuosity, dilatation, irregular caliber, and different shape.[6] Those of esophageal carcinoid tumor were reported to resemble subepithelial reticular vessels on a shiny reddish surface.[10] Obviously, further studies are required to establish the utility of NBI-ME for preoperative diagnosis of esophageal LELC, and further accumulation of the cases might unmask its unique clinical features, such as prognosis.

DISCLOSURES

Author contributions: K. Uno, F. Fujishima, M. Saito, X. Jin, W. Hatta, K. Asanuma, N. Asano, T. Koike, and A. Imatani acquired and interpreted the data. T. Okata, K. Uno, and T. Koike wrote the manuscript. T. Koike and A. Masamune edited the manuscript. K. Uno is the article guarantor.

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Informed consent was obtained for this case report.

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