

Lymphoepithelioma-like esophageal carcinoma with macroscopic reduction

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Abstract

Esophageal lymphoepithelioma-like carcinoma (LELC) is extremely rare. We report the first case of esophageal LELC showing macroscopic reduction. A 67-year-old male presented with dysphagia and, by endoscopic examination, was found to have a significantly raised tumor of 10 mm in diameter in the thoracic esophagus. The biopsied material showed esophageal cancer. We performed endoscopic submucosal dissection. However, the tumor became flattened, similar to a scar, in only 2 mo. Histologically, the carcinoma cells had infiltrated the submucosal layer. Prominent infiltration of T lymphoid cells that stained positive for CD8 was observed around

the carcinoma cells. Therefore, this lesion was considered to be an LELC with poorly differentiated squamous cells. Because the margin was positive, an esophagectomy was performed. Carcinoma cells were detected in the neck in one lymph node. The staging was T1N0M1b. However, the patient has been well, without adjuvant therapy or recurrence, for more than 5 years.

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Key words: Esophageal cancer; Lymphoepithelioma-like carcinoma; Lymphoid stroma; Tumor-infiltrating lymphocyte; Cytotoxic T lymphocyte; Reduction

Core tip: The first case of esophageal lymphoepithelioma-like carcinoma showing macroscopic reduction is reported. In only 2 mo, the appearance of the esophageal tumor changed from a protruding lesion to a flat scar-like entity. After esophagectomy, one lymph node was diagnosed with metastasis. Prominent infiltration of T lymphoid cells that stained positive for CD8 was observed around the carcinoma cells. Strong expression of human leukocyte antigen-DR was evident in the cell membrane. The immune responses against the main tumor and the denatured carcinoma cells in the metastatic lymph node developed at the same time. Therefore, systemic immune responses against the carcinoma might have been occurring.

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INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is defined as a tumor with histological similarity to undifferentiated nasopharyngeal carcinoma, with lymphoid stroma (lymphoepithelioma) that occurs outside the nasopharynx. Although LELC has been detected in the salivary gland^[1], stomach^[2], thymic gland^[3], breast^[4], and lungs^[5], it is extremely rare in the esophagus^[6]. The prognosis of patients suffering from this type of cancer has been reported to be favorable^[7]. However, there have been no reports of a tumor being reduced macroscopically.

We herein describe the treatment of a patient suffering from an esophageal LELC that spontaneously became small macroscopically and also discuss the results of a pathological analysis of the tumor.

CASE REPORT

A 67-year-old Japanese male with a seven-month history of intermittent dysphagia underwent an upper endoscopic examination at another clinic in May 2008 (Figure 1A) and was diagnosed as having squamous cell carcinoma of the esophagus, with prominent infiltration of lymphoid cells, based on biopsied material (Figure 2). He was admitted to our hospital for treatment in June 2008. No familial disease and no history of previous gastrointestinal disorders were documented. The patient was a heavy drinker and a non-smoker. A physical examination and laboratory data on admission did not reveal any abnormalities.

A barium esophagogram demonstrated a protruding lesion of 10 mm in diameter on the left and posterior wall of the middle thoracic esophagus. An endoscopic examination in June 2008 revealed a raised tumor with a central dip 33 cm from the upper incisors (Figure 1B). Moreover, the tumor had a smooth surface, similar to a submucosal tumor. Endoscopic ultrasonography in July 2008 demonstrated a well-circumscribed, hypoechoic mass originating in the mucosa, without involvement of the submucosal layer. A computed tomography (CT) scan revealed no metastasis. Therefore, we believed that endoscopic submucosal dissection of the tumor was possible and performed the procedure in July 2008.

However, the tumor became flattened, similar to a scar (Figure 1C), and there was a superficial smooth tumor measuring 6 mm × 3 mm in the resected mucosa (Figure 3A). Histologically, the large-sized carcinoma cells formed small focal nests and infiltrated into the submucosal layer, 400 μm from the muscularis mucosae (Figure 3B). Prominent infiltration of T lymphoid cells, which stained positive for CD8, was observed between and around the carcinoma cells (Figure 4A and B). Based on these histopathological features, this lesion was considered to be an LELC with poorly differentiated squamous cells. The other pathological findings included human leukocyte antigen-DR (HLA-DR), strongly positive (Figure 4C); p53, strongly positive; Ki67, moderately

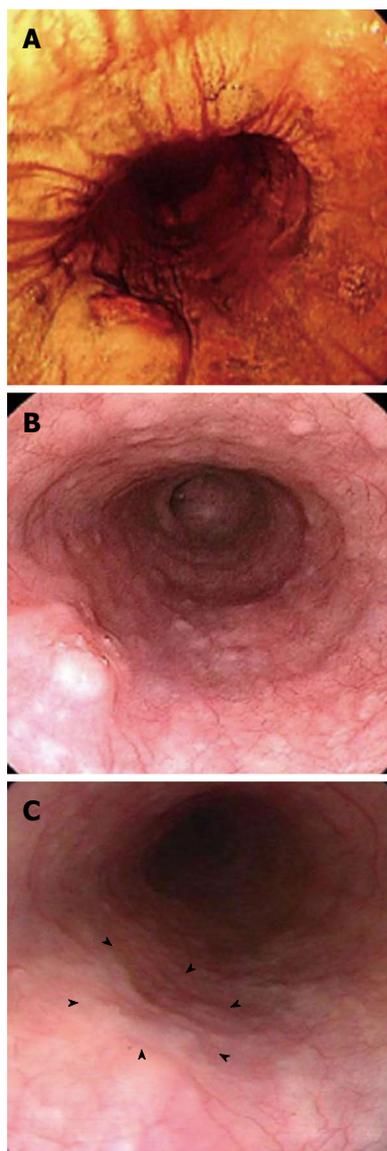


Figure 1 The endoscopic findings. A: The first endoscopy (at the previous clinic) showed a submucosal-like tumor of approximately 10 mm in diameter. The lesion, except for the erosion at the top, was stained with Lugol's solution; B: The second endoscopy (performed two weeks after the first endoscopy) showed a raised tumor with a central dip. The height of the tumor had decreased; C: The third endoscopy (performed during the endoscopic operation, two months after the first endoscopy) showed that the tumor had become flattened, similar to a scar (arrowhead).

positive; and Epstein-Barr virus (EBV)-encoded small RNA1 (EBER-1), negative. Because the vertical margin was positive, a subtotal esophagectomy and dissection of the lymph nodes were performed in October 2008. No remnant tumor was found. However, carcinoma cells were detected in the neck area in one of the 53 dissected lymph nodes (Figure 5).

According to the tumor node metastasis (TNM) classification of esophageal cancer, the tumor was diagnosed to be stage IVB (T1, N0, M1b). However, many denatured carcinoma cells were observed in the metastatic lymph node (Figure 5B). The patient's postoperative course was uneventful, and he was discharged two weeks

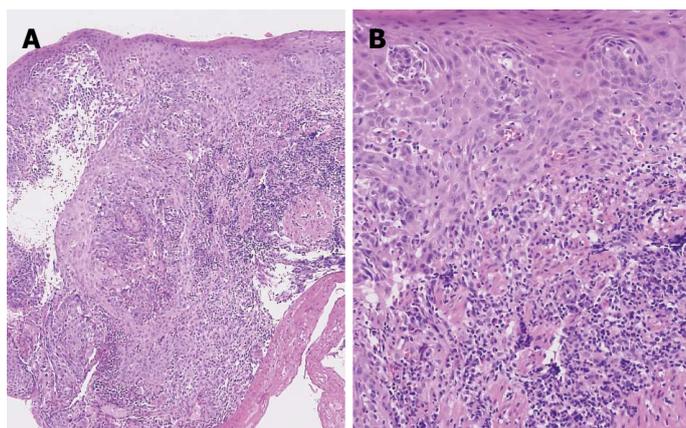


Figure 2 The endoscopically-biopsied material. A: The inflammatory cell infiltration in the mucosa was remarkable (HE staining, original magnification $\times 40$); B: Squamous cell carcinoma with prominent infiltration of lymphoid cells was revealed (HE staining, original magnification $\times 100$).

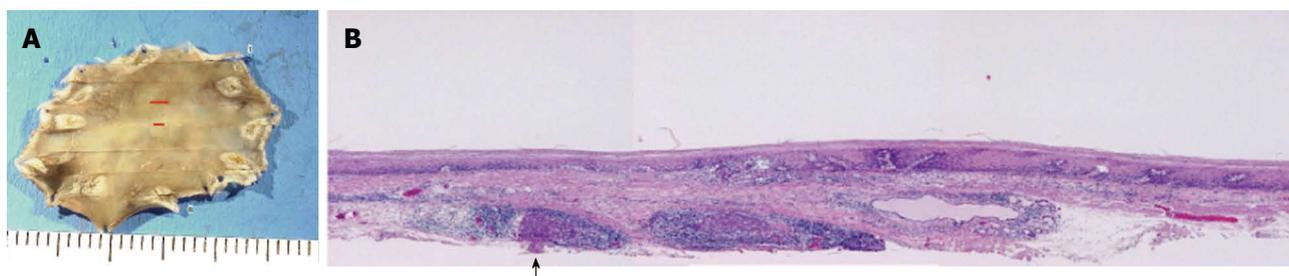


Figure 3 The endoscopically-resected material. A: The gross appearance of the resected esophageal mucosa is shown. There was a superficial smooth tumor measuring 6 mm \times 3 mm in the resected mucosa (line), and it was difficult to find the tumor macroscopically; B: The tumor, with prominent lymphoid cell infiltration, was mainly visible in the submucosal layer (HE staining, original magnification $\times 10$). The vertical margin was positive (arrow).

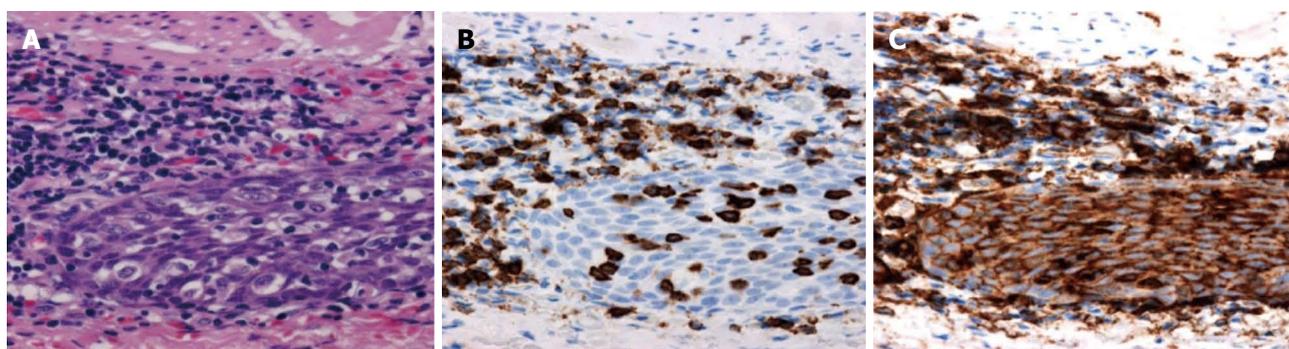


Figure 4 The histopathological findings. A: Poorly differentiated squamous cells and lymphocytes that had infiltrated into the carcinoma cell nests were observed (HE staining, original magnification $\times 400$); B: Prominent infiltration of cytotoxic T lymphoid cells that stained positive for CD8 was observed between and around the carcinoma cells ($\times 400$); C: Strong expression of human leukocyte antigen-DR was evident in the cell membrane in nearly all carcinoma cells and in the lymphocytes around the tumor ($\times 400$).

later. He has been well, without adjuvant therapy or any evidence of recurrence, for more than five years after the surgery. After the diagnosis of the esophageal cancer, he did not smoke or drink alcohol. Furthermore, he did not take any special medicines or examinations.

DISCUSSION

LELC was first reported by Bégin *et al.*^[8] in 1987. LELC is defined as a tumor with histological similarity to undifferentiated nasopharyngeal carcinoma with lymphoid stroma, and this condition has been described in various organs^[1-5]. However, an esophageal LELC is extremely

rare. According to the PubMed database, there have been only 21 cases, including the present case, reported in the English-language literature to date^[6,9-21]. Our report presents the first case of esophageal LELC that was macroscopically reduced in size.

Burke^[22] first detected EBV DNA in gastric cancer that histologically resembled nasopharyngeal lymphoepithelioma, and after that, several reports also demonstrated a close relationship between that type of gastric cancer and EBV. However, there does not appear to be a relationship between esophageal cancer and EBV. In the current case, no relationship between the cancer and EBV was revealed by EBER-1 staining. In addition, we

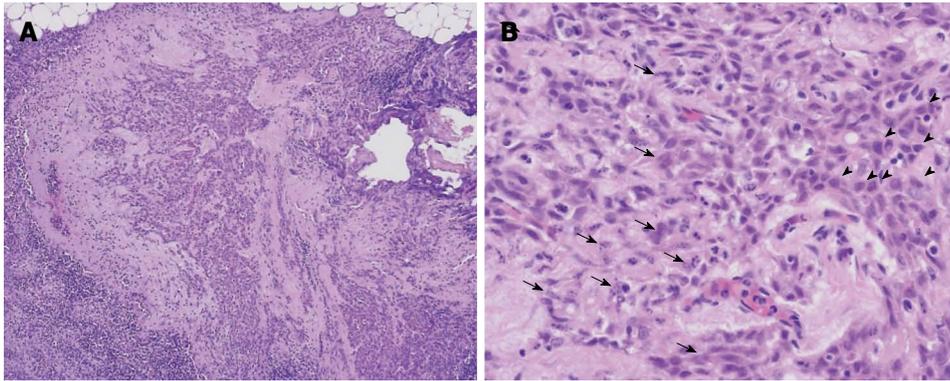


Figure 5 The surgically dissected lymph node from the neck area. A: In the lymph node, which was 5 mm in diameter, a metastasis that was 2 mm in diameter was found (HE staining, original magnification $\times 40$); B: Histological evaluation showed that lymphocytes had infiltrated around the carcinoma cells (HE staining, original magnification $\times 200$). Many denatured carcinoma cells, which had karyorrhexis, an indistinct cell membrane, or karyotheca in the lymph node, were observed (arrow). Many viable carcinoma cells were observed (arrowhead).

investigated 17 of the 21 described patients to determine whether they had an EBV infection. Only three (17.6%) of the 17 described patients were revealed to have an EBV infection. However, Nakasono^[20] reported that esophageal LELC may not always be linked with EBV, but that the sensitivity of the detection methods may also be problematic, leading to false-negative findings. Therefore, further investigations are needed to clarify the role of EBV infection in esophageal LELC.

Endoscopically, most cases of LELC have been documented as submucosal tumors covered with normal-appearing esophageal epithelium and with a depression or ulcer in the center of the lesion^[6,16,20], as in the present case. However, there has been no previous report of the diagnosis of LELC by endoscopy or biopsy. Because esophageal LELC may be confused with a benign tumor, a biopsy of deeper tissue is required. Moreover, regarding the clinical course, there was a previous report that one year after the first endoscopic examination, the size of the lesion remained unchanged, despite no treatment^[20]. However, in our case, the tumor was gradually reduced in size macroscopically and fully disappeared in only 2 mo. It may help the diagnosis of LELC if these endoscopic courses could be followed more closely.

The prominent lymphocytic infiltration in LELC is associated with HLA-DR expression in the deeper carcinoma cells^[16]. The T cell infiltration is significantly increased at the sites of HLA-DR expression^[23]. In our case, T lymphocytes were found around the lymphoid follicles or within the tumor cell nests, and most of these T cells were positive for CD8, which supports their classification as cytotoxic T lymphocytes.

The role of diffuse infiltrating lymphocytes, consisting of a large number of T lymphocytes and a small number of B lymphocytes, has not yet been clarified in LELC. Two hypotheses have been proposed^[13]. In one, the presence of diffuse lymphocytes is explained by the immune response of the host against the carcinoma. In the other, the diffuse lymphocytes are explained in terms of a cell reaction caused by the cytokines produced by the carcinoma cells. In our case, the immune responses

against the main tumor and the denatured carcinoma cells in the metastatic lymph node developed at the same time. Therefore, systemic immune responses against the carcinoma might have been occurring. Furthermore, we suppose that the systemic immune response against carcinoma becomes more significant over time and that the tumor becomes smaller when there is increased expression of HLA-DR, as was observed in our case.

Generally, the prognosis of patients suffering from poorly differentiated esophageal squamous cell carcinoma is extremely poor. However, esophageal LELC seems to have a relatively good prognosis^[6]. The prognosis is indicated by the survival curves and recurrence rates after treatments. It was fortunate that we could endoscopically follow an LELC lesion that did not receive any treatment for two months because this study helped to demonstrate the natural course of the disease. During this short time, the tumor was gradually reduced in size macroscopically. Histologically, prominent lymphocytic infiltration was revealed in the main tumor and the metastatic lymph node. The patient has remained in good health for the 5 years since the surgery. The immune responses in this case seem to have had nothing to do with his lifestyle. This unique observation was not described in any previous cases.

In conclusion, esophageal LELC has unique clinical and pathological features. In particular, the strength or weakness of the expression of HLA-DR in esophageal LELC may lead to differences in the patient's clinical course. Furthermore, LELC should be treated differently than other esophageal cancers based on its unique features.

COMMENTS

Case characteristics

A 67-year-old male with a 7-mo history of intermittent dysphagia.

Clinical diagnosis

A protruding lesion of 10 mm in diameter was observed on the left and posterior wall of the middle thoracic esophagus.

Differential diagnosis

Malignant lymphoma, gastrointestinal stromal tumor, endocrine cell tumor.

Imaging diagnosis

In only 2 mo, an endoscopic examination revealed that the appearance of the esophageal tumor had changed from a protruding lesion to a flat, scar-like lesion.

Pathological diagnosis

This lesion was considered to be an esophageal lymphoepithelioma-like carcinoma with poorly differentiated squamous cells.

Treatment

After the endoscopic submucosal dissection, a subtotal esophagectomy and dissection of the lymph nodes were performed.

Experiences and lessons

The esophageal lymphoepithelioma-like carcinoma that was macroscopically reduced in size might have occurred due to systemic immune responses against the carcinoma.

Peer review

This is a very interesting case report. Esophageal cancers are quite common in some parts of the world and this report highlights the fact that not all are associated with a dismal prognosis. The report is well written and adequate references. The photographs are very good and illustrative.

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