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Case Report

Lymphepitheliomatoid Carcinoma of Maxillofacial Region: A Case Report and Literature Review

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Abstract

Lymphoepithelioma-like carcinoma (LELC) is a tumor that occurs outside the nasopharynx, and its morphological characteristics are similar to those of nasopharyngeal lymphoepithelioma. LELC in the maxillofacial region is a rare tumor with an unknown etiology and low malignant potential. This case of lymphoepithelioid carcinoma is clinically characterized by hard nodules in the facial subcutaneous tissue. Histologically, LELC shows infiltration of dense lymphoplasmacytic cells between the stroma and cancer cells. We report a case of maxillofacial LELC, and discuss the etiology, clinical histopathology, immunohistochemistry, and treatment of this rare skin tumor.

Keywords: Maxillofacial region; Lymphoepithelioma-like carcinoma; Immunohistochemistry.

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is a rare epithelial malignant tumor, and its main feature is the presence of a large number of tumor infiltrating lymphocytes (TILs) in the tumor background. LELC can occur in any organ of the body. However, due to its low incidence, there is a lack of large-scale clinical research on LELC, and its etiology, pathogenesis, clinicopathological, and molecular pathological characteristics remain unclear [1].

In this paper, we collected and analyzed the clinical data of a patient with maxillofacial LELC. We conducted a systematic search of the literature from the past 15 years, both domestically and internationally, to analyze their clinical characteristics, with the aim of improving the ability of clinicians in the diagnosis, treatment, and management of this disease.

The Case Data

The patient, a 37-year-old female, was admitted to the hospital for "finding a tumor on the left face for 3 months". Three months earlier, a tumor appeared on the left face, which gradually increased in size, without pain, bleeding, or angular deviation. Physical examination revealed a tumor of approximately 1.5cm*1cm under the skin on the left side, with a tough texture, poor mobility, no tenderness, and no ulceration on the surface skin. A color Doppler scan detected a cystic mass measuring about 15*11*7mm in the soft tissue approximately 5mm under the skin, with a clear boundary and poor internal transmission sound. CDFI showed that the blood flow signal was not pronounced. After admission, the left facial tumor was resected under local anesthesia, with the incision made along the tumor's long axis to separate the skin and subcutaneous tissue. The tumor, which adhered significantly to the surrounding tissues, was completely removed. It was generally pale yellow, soft, and enveloped (Figure 1).

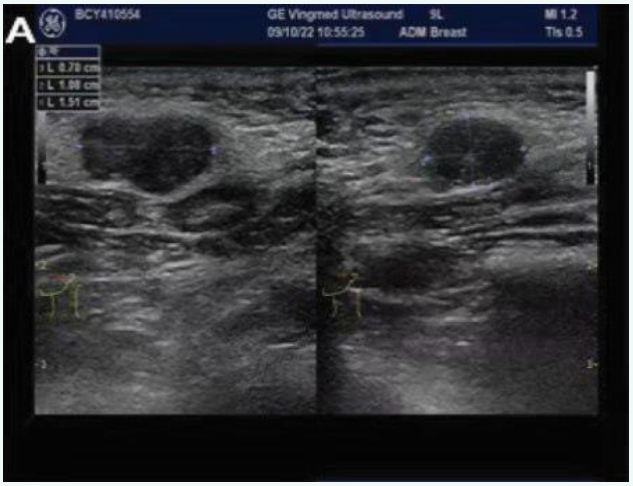

Figure 1A: Color Doppler ultrasound showing a cystic mass approximately 15*11*7mm in size in the soft tissue, about 5mm under the skin, with a clear boundary and poor internal transmission sound. CDFI indicates that the blood flow signal is not pronounced

Post-operation, the specimens were fixed in 10% neutral formaldehyde solution, dehydrated, embedded in paraffin, sectioned at 4μm thickness, and stained with hematoxylin-eosin (HE) for observation under a light microscope. Immunohistochemistry was conducted using the EnVision two-step method. The antibodies used included CK, CK7, nuclear antigen KI-67, P63, and p53. Conventional pathology showed tumor cells nested, with obvious nucleoli and abundant lymphocytes in the stroma. Immunohistochemistry results were CK (+), P63 (+), CK7 (-), KI-67 (80%+), p53 (plaque refutation +), and EBER(+). The diagnosis was lymphoepithelioid carcinoma.

Following the definitive diagnosis, further resection of the left facial

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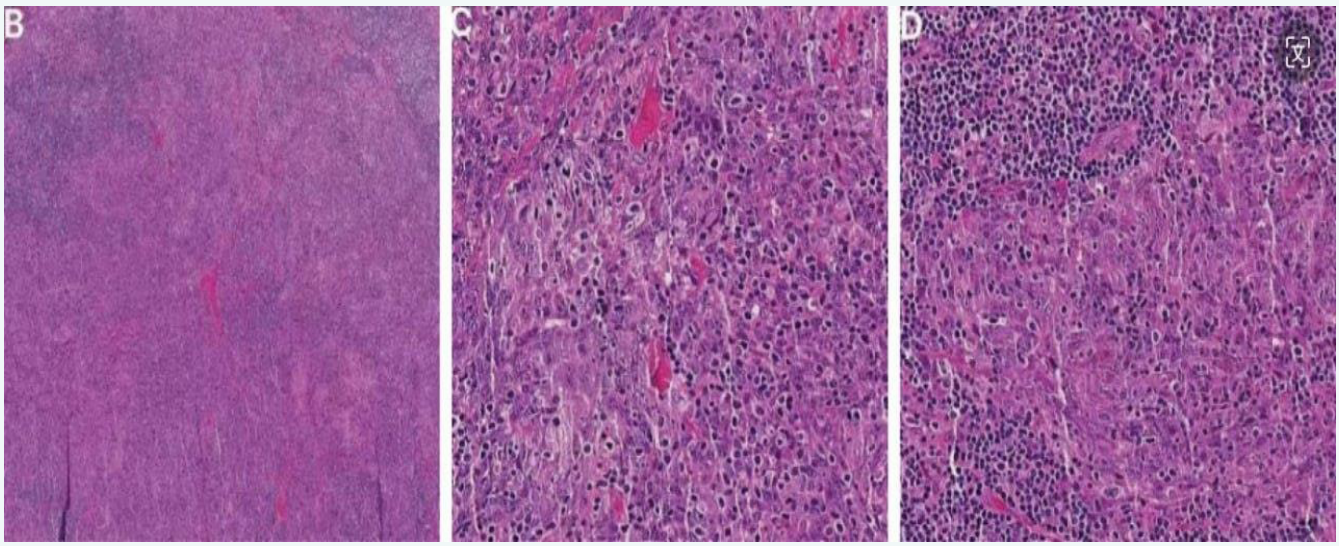

Figure 2B: Microscopic image (HE staining 100x) displaying cancer cells nested with numerous lymphocytes; Figures 2C and 2D: Microscopic images (HE staining 400x) depict the cytoplasm of cancer cells as eosinophilic, with the nucleus being round, oval, vacuolar, and nucleolar.

malignant tumor was performed. Additionally, nasal endoscopy revealed thickened nasopharyngeal mucosa, prompting a nasopharyngeal biopsy. Routine pathology of the nasopharynx indicated chronic mucosal inflammation with lymphoid tissue hyperplasia. The patient was followed up for 6 months with no recurrence observed (Figure 2).

Literature Review

Using "lymphoepithelioma-like carcinoma" as the keyword, related articles published in the past 30 years were searched in the PubMed and China HowNet databases, yielding 271 domestic and 842 foreign documents. The search results indicate that most domestic and foreign documents are case reports, and there is still a lack of research involving large samples. In 1921, Schminke first reported lymphoepithelioma in the nasopharynx, and in 1934, Cappell first reported lymphoepithelioma in the tonsil. Later, lymphoepithelioma in the nasopharynx was renamed as nasopharyngeal undifferentiated carcinoma, while cancers in other parts similar in morphology to the former were termed lymphoepithelioid carcinoma.

EPIDEMIOLOGY

LELC has been identified in various anatomical parts of the body, including the salivary glands, tonsils, tongue, lungs and bronchi, bladder, female reproductive system, digestive system, and skin. The most common sites are the head and neck, followed by the lungs and digestive system. Other sites are less frequent [2-5]. Based on SEER data analysis, Wei Xiangqi et al., showed that the most common site for diagnosing primary tumors is nasopharyngeal LELC (56.22%), followed by non-nasopharyngeal head and neck LELC (21.32%) and the respiratory system (7.83%). Their research results are largely consistent with other literature.

Patients with LELC present a wide range of onset ages, from 9 to 89 years old. The median age for LELC in the upper digestive tract, head and neck, and respiratory system is around 50 years old [1]. Bladder LELC and digestive system LELC are primarily found in elderly patients [6]. With increasing age, the incidence of LELC steadily rises, peaking at 75-79 years old. The poor cancer-specific survival rate of LELC is significantly associated with age over 50 years, distant staging, and more than three occurrences of lymph node positivity. The primary site is an independent prognostic factor for LELC. Head and neck LELC has the best prognosis [7], while the prognosis for non-nasopharyngeal head and neck LELC is notably better than that for nasopharyngeal LELC [8].

Etiology and Pathogenesis

The occurrence of LELC is linked to virus infection, with the most common being the Epstein-Barr virus (EBV). However, the association between LELC and EBV varies geographically, racially, and by affected organ. The association of EBV is strong in LELC of the head and neck, but relatively weak in LELC of other parts [9]. LELC in the head and neck, salivary glands, and lungs is particularly closely related to EBV infection [10-13]. EBV infection is an independent predictor of survival in patients with esophageal and gastric LELC [9,14]. Besides EBV, some cases of LELC in the liver may be closely related to hepatitis virus infection [15]. Additionally, research indicates that LELC in the genitourinary system may have a strong correlation with human papillomavirus (HPV) [16,17].

CLINICOPATHOLOGICAL FEATURES

General Manifestations

LELC typically presents as a single, well-defined nodule with a relatively clear boundary from surrounding normal tissues. In the 18 cases of parotid LELC studied by Xiao Ping, all were unilateral with clear tumor boundaries, and advanced tumors could adhere to deep tissues or skin. About two-thirds of patients may experience local pain or tenderness, and the tumor tends to expand. Most capsules are incomplete, and skin involvement is less common. Regional lymph node metastasis is frequent, while distant metastasis is rare [13]. Under endoscopy, gastric LELC primarily presents as swelling or ulcerative masses, which are brittle [18]. Lung masses often appear as well-defined circular or elliptical single nodules [12]. The cut surface of the mass is gray and red, often with a capsule, and the boundary with surrounding tissues is unclear; the mass is of medium consistency [18,19]. In this case, the cut surface of the tumor is grayish-yellow, capped, soft, and well-demarcated.

Histopathology

The histopathological characteristics of LELC resemble those of low undifferentiated nasopharyngeal carcinoma, marked by TILs infiltration. Pathological examination reveals undifferentiated or poorly differentiated malignant epithelial cells accompanied by extensive mature lymphoid interstitial infiltration, including lymphocytes, plasma cells, and histiocytes, occasionally forming lymph follicular nodules. Proliferating epithelial cancer cells are arranged in strips, nests, or sheets. The cancer cells are oval or polygonal, large, with vacuoles, pronounced nucleoli, rich cytoplasm, and various mitotic figures [1,11,18,19]. In head and neck LELC, the tumor components are mainly poorly differentiated squamous cell carcinoma with abundant interstitial TILs. Some tumors primarily comprise infiltrating lymphocytes, with few neoplastic epithelial components [1,18]. In this case, the tumor cells are nested, with pronounced nucleoli and abundant lymphocytes in the stroma.

IMMUNOPHENOTYPE

Zheng Haihong conducted immunohistochemical analyses on 21 cases of LELC. The results revealed that LELC cancer cells highly expressed CKpan, p63, and p40, while interstitial lymphocytes prominently expressed CD8 and CD20. Furthermore, all 21 cases of LELC underwent EBER in situ hybridization staining, with 16 cases testing positive [18]. This underscores the strong correlation between LELC and EB virus infection. In the head and neck and respiratory system, most LELC express CK, EMA, CK5/6, P40, and p63, whereas gastric LELC typically expresses CK7 and low molecular weight keratin [1]. Mei Shiqi's immunohistochemical analysis of 43 lung LELC patients showed a 94.4% positive rate for EBER expression. Most patients expressed CK, CK5/6, and P63, a few expressed TIF-1, and all were negative for C7 [7]. In this case, cancer cells were EBER positive, but negative for CK, P63, Ki-67, p53, and CK7 [20, 21]. A study involving 66 lung LELC patients indicated that about 75.8% (50/66) of the tissues were PD-L1 positive, suggesting the potential of immunosuppressants in LELC treatment [22] (Figure 3).

IMAGING MANIFESTATIONS

Wu Jing et al., studied 28 cases of salivary gland LELC. CT features typically included solitary nodules or masses in the parotid region or submandibular area, with clear or unclear boundaries and various shapes. The density is often uniform, showing moderate to severe enhancement, and the mass is evenly or unevenly enhanced. It may be accompanied by lymph node metastasis in the ipsilateral drainage area, with pronounced enhancement of metastatic lymph nodes and adjacent bone destruction [23]. Gong Yan and others summarized the imaging features of 10 patients with pulmonary LELC, which were mainly peripheral solitary masses or nodules, mostly occurring in the middle and lower lobes of the lung field, close to or invading the mediastinum and pleura. The masses are round, quasi-round, or irregular, large in diameter, with smooth edges and no significant burr signs. Most lesions show shallow lobulation, and cavities and calcification are rare. CT scans reveal that mass density is uneven, with some cases exhibiting liquefied necrosis areas [24]. Ooi et al., summarized advanced pulmonary LELC imaging characteristics. Primary pulmonary LELC initially presents as small isolated subpleural nodules with clear boundaries, but in later stages may appear as tumors closely related to the mediastinum, accompanied by thickening and vascular wrapping around bronchial vessels [25]. Primary pulmonary LELC lesions are consistent in features, including lobulated and spiculate nodules located near the lung, in direct contact with the adjacent pleural surface. The lesion density is uniform, occasionally uneven, and sometimes accompanied by lymphadenopathy. In areas where EBV is endemic, isolated peripheral pulmonary nodules in direct contact with the pleural surface should prompt consideration of pulmonary LELC in differential diagnoses [26,27].

TREATMENT AND PROGNOSIS

Currently, the primary treatment for LELC is surgical resection of the tumor, with chemotherapy or radiotherapy as supplementary options based on varying conditions. The general treatment for head and neck LELC includes a combination of surgical resection, neck dissection, radiotherapy, and/or chemotherapy. Due to the favorable response to treatment, the prognosis for each site may differ but is generally positive [28,29]. The good prognosis of LELC may be attributed to the immune surveillance effect of diffuse infiltrating lymphocytes. Despite being low or undifferentiated, LELC has a better prognosis compared to other maxillofacial malignant tumors. Preoperative imaging diagnosis can be challenging but provides information on lesion shape, size, internal vascular structure, and growth characteristics, guiding surgical treatment and follow-up. However, metastasis from nasopharyngeal lymphoepithelial carcinoma should be excluded [18,19,30]. Lung LELC cases are typically operable, hence surgical resection is recommended. Han Anjia's analysis of 32 pulmonary LELC and 84 non-LELC cases revealed that pulmonary LELC patients had 2-year and 5-year survival

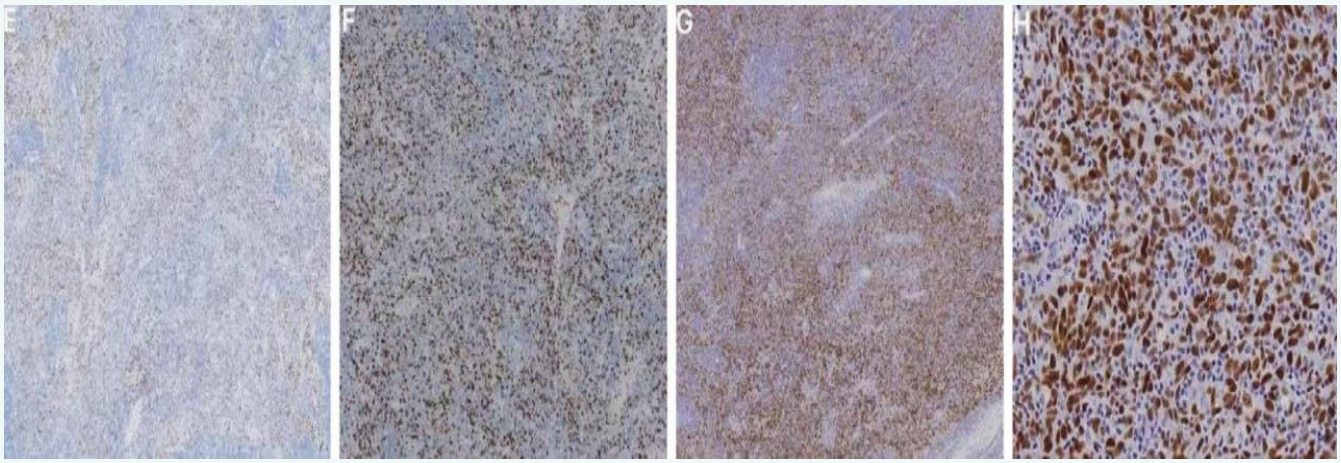

Figure 3E: Immunohistochemistry p63 positive; 3F: Immunohistochemistry Ki67 (EnVision method 200x); 3G: EBER in situ hybridization showing cancer cell positivity at low magnification; 3H: EBER in situ hybridization demonstrating cancer cell positivity at high magnification.

rates of 79.9% and 53.5%, respectively, compared to 59.5% and 39.1% for non-LELC patients [12]. Thus, the prognosis for lung LELC patients is significantly better than that for non-LELC patients. As a unique entity, lung LELC has a better prognosis than non-LELC. The 2-year and 5-year overall survival rates for LELC patients were 100% and 62.5% in stage II, and 80.8% and 60.6% in stages III and IV, respectively. In contrast, non-LELC patients had survival rates of 55.2% and 30.3% in stage II, and 50.0% and 21.4% in stages III and IV, respectively. These findings indicate significant differences in survival rates across stages II, III, and IV between LELC and non-LELC patients. Tumor recurrence and necrosis are associated with a poor prognosis [31,32]. Chung-Jen Huang and others conducted a retrospective analysis of 21 patients with pulmonary LELC, demonstrating that the prognosis for primary pulmonary LELC patients is better than for other types of non-small cell lung cancer, and the survival time is longer with multi-modal treatment, including surgery, chemotherapy, radiotherapy, and targeted therapy.

For advanced diseases, chemotherapy can be considered the first-line treatment along with radiotherapy, with the dosage dependent on the tumor location [33]. Studies also indicate that LELC tumor cells express PD-L1 at a high level, suggesting potential benefits from immunotherapy. Research by Cui Qian and others shows that gastric and parotid LELC express PD-L1 at a high level, enhancing the prospects of checkpoint immunotherapy in treating these forms of LELC [31,34]. In summary, LELC, although rare, has morphological similarities to nasopharyngeal carcinoma and is closely associated with EB virus infection. EBER detection is highly valuable in diagnosing this disease. Based on clinical experience, surgery combined with various comprehensive treatment plans remains the primary treatment approach. However, for better diagnosis and treatment strategies, further comprehensive analysis with a larger accumulation of cases is needed in the future.

AUTHOR'S CONTRIBUTIONS

JMMethodology, Data curation.SJInvestigation, Visualization. SZ: Conceptualization, Methodology. SZ, JK: Writing–original draft. SZ, JK, MX, XS: Data curation. All authors read and approved the final manuscript.

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