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EBV-negative lymphoepithelial-like carcinoma of the lower lip

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ABSTRACT

Lymphoepithelial-like carcinoma (LEC) is a rare malignant neoplasm, which can be associated with Epstein-Barr virus (EBV) infection. Histologically, LEC is an undifferentiated carcinoma with an intermixed reactive lymphoplasmacytic infiltrate. LEC appears to be an uncommon tumor type of lip carcinoma. An 82-year-old white woman presented a lesion on her lower lip that developed over the last year. The lesion was characterized by ulceration with flat edges, hardened base, painful, and absence of regional lymphadenopathy. Microscopical analysis evidenced an intense inflammatory infiltrate, composed of lymphoplasmacytic cells, associated with scarce pleomorphic epithelial cells. Immunohistochemistry highlighted the LEC cells with strong expression of pan-CK AE1/AE3, EMA, p63, and p53. CD138 was also faintly positive. Ki-67 was >85%. In situ hybridization analysis did not show evidence of EBV. A diagnostic of EBV-negative LEC was made. We present an uncommon type of lip carcinoma, which can represent a diagnostic challenge for clinicians and pathologists.

Keywords
Immunohistochemistry; In Situ Hybridization; Lip diseases; Squamous Cell Carcinoma of Head and Neck.

INTRODUCTION

Lymphoepithelial-like carcinoma (LEC) is a well-recognized undifferentiated carcinoma subtype in the nasopharynx quite often related to Epstein-Barr virus (EBV) infection.[1-3] The World Health Organization (WHO) has defined it as "a poorly differentiated squamous cell carcinoma (SCC) or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma".[1,4] LEC is commonly diagnosed in patients between 40 and 70 years old.[1] Histologically, LEC consists of atypical epithelial-derived cells that have pale cytoplasm, prominent stroma, large-round vesicular nuclei, and prominent nucleoli. The tumor cells are surrounded by an extensive number of lymphocytes and plasma cells.[5] There is no keratinization, necrosis, or mucus production.[5] Thus, syncytial sheets of large undifferentiated cells with vesicular nuclei intermingled with numerous nonneoplastic small lymphocytes and plasma cells characterize LEC histologically.[2,3]

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The EBV had been detected in 87.5% of all LEC cases.[1,6] The role of EBV in the pathogenesis of LEC appears to be anatomical site-dependent.[2,6] Tumors showing a similar histologic appearance have been described at different sites outside the nasopharynx. The EBV association has only been found in the salivary gland, lung, stomach, and thymus.[2,6] Among the salivary glands, the parotid gland is most often affected. Moreover, in the head and neck region, LEC may also occur in the skin, oral cavity and nasopharynx.[2] In the nasopharyngeal location, LEC frequently affects the tonsillar region and the base of the tongue. The palate, floor of the mouth, retromolar region, and buccal mucosa are among the affected oral sites.[2,3,7] A systematic review gathered 30 LEC cases in the oral cavity and oropharynx (13 males and 17 females). Thus, a slight male predominance (1.3:1) was observed, being the median age of 62 years (age range 11-80 years).[1,2] To date, only two LEC cases affecting the lips have been reported.[2,5]

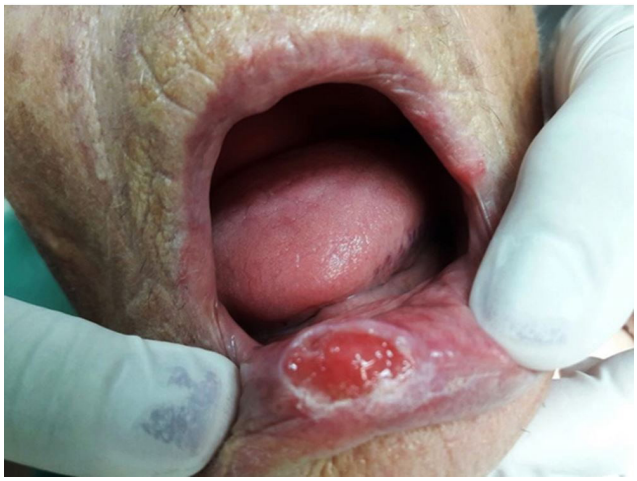

Figure 1. Clinical view of the ulcerated lesion on the right side of the lower lip.

Treatment of LECs consists of surgery combined with radiotherapy and/or chemoradiation. Although local spread or nodal metastases are reasonably common at the time of diagnosis, the mortality rate of adequately treated LEC patients is low.[1]

Herein, we report the clinicopathological features of an EBV-negative LEC case affecting the lower lip of an old patient, with immunohistochemical and *in situ* hybridization analyses.

CASE REPORT

An 82-year-old white woman was referred to the Dental School, presenting an ulcerative lesion on her lower lip that has been developing over the last year. The nodular lesion presented an ulcerated surface, with flat edges, hardened base, painful, and absence of regional lymphadenopathy (Figure 1).

An incisional biopsy was performed. The microscopical analysis evidenced an intense inflammatory infiltrate, composed of lymphoplasmacytic cells, associated with scarce pleomorphic epithelial cells. Immunohistochemistry highlighted the malignant cells, which showed strong expression of pan-cytokeratin (pan-CK) AE1/AE3, EMA, p63 and p53. CD138 was also faintly positive. Ki-67 labeling index was >85%. EBER oligonucleotide RNA *in situ* hybridization analysis did not show evidence of EBV infection (Figures 2, 3, and 4). The patient was submitted to

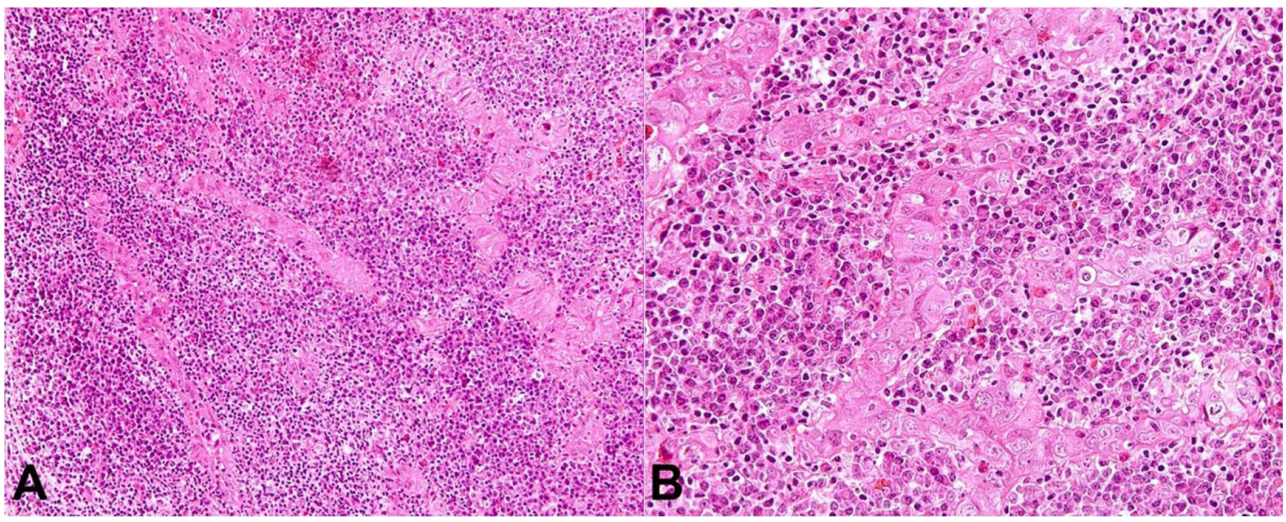

Figure 2. Photomicrographs of the lip biopsy showing: **A –** Tumor cells arranged in cords with a ribbon-like appearance admixed with intense lymphoplasmacytic inflammatory infiltrate; **B –** High magnification showing malignant epithelioid cells. (H&E stain, original magnification [A] x 20; [B] x40).

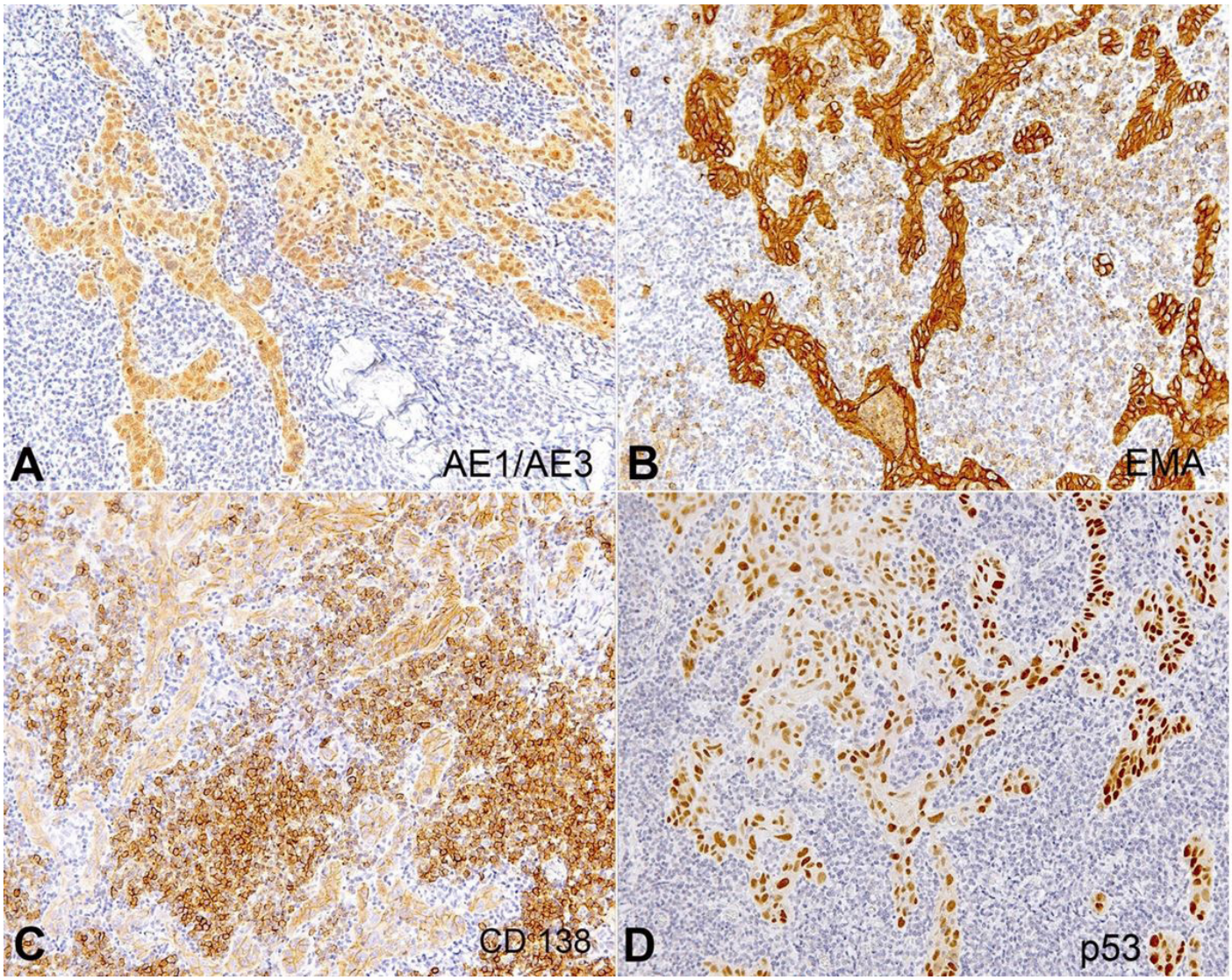

Figure 3. Photomicrographs of the lip biopsy showing: **A –** pan-CK AE1/AE3 positivity highlighting the malignant cells; **B –** Malignant epithelial cells positive for EMA. Notice the positivity on plasma cells; **C –** Tumor cells exhibiting faint cell membrane staining positivity for CD138. Observe that the plasma cells are more strongly stained; **D –** Uniform positivity for p53 in LEC cells (A-D, immunohistochemistry, original magnification x20).

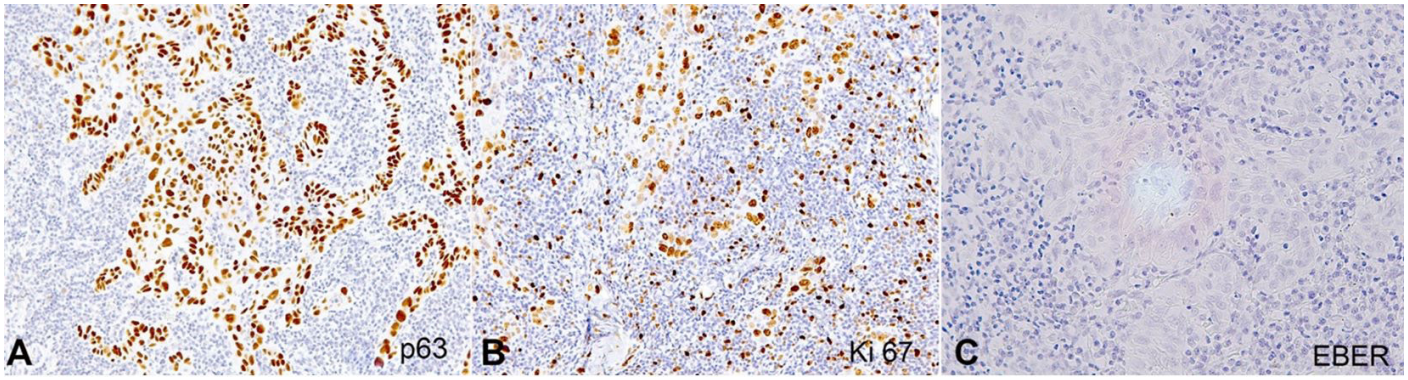

Figure 4. Photomicrographs of the lip biopsy showing: **A –** Strong p63 positivity highlighting the LEC cells; **B –** Most LEC cells positive for Ki-67 (>85%) (A-B, immunohistochemistry, original magnification x20). **C –** EBER oligonucleotide RNA in situ hybridization with uniform negativity (original magnification x40).

W-plasty surgery, which also provided good functional and aesthetic results. The surgical specimen showed similar microscopical features, with negative surgical margins. After 2-year of follow-up, the patient is well, without recurrences.

DISCUSSION

The LEC is a distinctive subtype of poorly differentiated SCC or undifferentiated carcinoma that shares morphologic features with undifferentiated nasopharyngeal carcinoma, which often shows association with EBV infection.[1-3] A similar association with EBV is emerging for LEC of the oral cavity, which appears to be strongly influenced by the patient's ethnia.[2] Noteworthy, LEC is rarely reported among the lip cancers.[2,4,5] To the best of our knowledge, only two cases of EBV-negative LEC of the lower lip have been reported.[2,5] The first case affected a 73-year-old man,[2] and the second case a 41-year-old man.[5] In the first case, there were no palpable cervical lymph nodes, and an elliptical excision was performed. At 20 months' follow-up, no signs of tumor recurrence were detected.[2] In the second case, surgical resection and bilateral selective neck dissection (level I-II) were performed. TNM classification was T1N1M0 (stage III); therefore, chemoradiotherapy was indicated. At 3 years' follow-up, the patient does not show evidence of disease.[5] Taking into account this scarce sample, we dare conclude the LEC of the lips has a good prognosis.

A review of the literature, from 1980 to 2018, on the MEDLINE database, manual searches of bibliographic references, and cross-referencing was performed. Case reports and clinical series of oral, oropharyngeal, nasal, and paranasal sinus LECs were reviewed, gathering a total of 110 cases. Differently from LEC affecting the lips, the oral and oropharyngeal LECs have a greater tendency to metastasize (70%), and 16.6% spread locally, while the nasal and paranasal LECs rarely metastasize, but 60% spread locally.[1]

By microscopy, LEC exhibits syncytial sheets of large undifferentiated cells with vesicular nuclei and prominent nucleoli admixed with numerous reactive small lymphocytes and plasma cells.[2,3] Sometimes, the neoplastic cells are challenging to visualize on microscopic examination, as observed in the current case. By immunohistochemistry, LEC shows strong positivity for CK in the epithelial component and CD45 in the lymphoplasmacytic infiltrate. Moreover, we observe positivity for EMA, p63, p53, and CD138, highlighting the malignant cells, whereas EMA and CD138 also evidenced the plasma cells.

The CD138 expression seems to correlate significantly with the histological differentiation grade, exhibiting weak and patchy immunostaining in poorly differentiated neoplasms.[8,9] It is known that the cells from the deep invasive front are highly aggressive and less differentiated. In this context, reduced CD138 expression was observed at the deep invasive front in oral SCC.[8] Moreover, it seems to be that the CD138 expression is reduced as lip carcinogenesis progresses.[9] Similarly, in the current case, different from CK and EMA, CD138 was faintly expressed.

Oral and oropharyngeal LECs have a high tendency to metastasize, mainly to regional lymph nodes, which substantially alter the prognosis.[1,5,7] However, fortunately, these tumors are highly radiosensitive, with high rates of locoregional control.[4] Accordingly, radiotherapy can be used as the primary treatment in head and neck LEC.[5,7] However, a multimodality approach is generally recommended, where surgery must be the first choice, if possible, regardless of the localization, considering the clinical stage of the tumor.[5] The higher survival rate for LEC of the oral cavity is documented. In this setting, it was reported a 94% local control rate in LEC of the head and neck region with radiotherapy. The 5-year overall survival and disease-specific survival were found as 39% and 59%, respectively.[5,7] Despite this, literature data support the use of a combined modality approach. Adjuvant chemotherapy and/or radiotherapy should be considered when risk factors for recurrence are detected, including perineural invasion, lymphovascular invasion, positive lymph nodes, and positive surgical margins. Moreover, elective neck radiotherapy is recommended for patients with head and neck LEC.[5]

The lower lip LEC is a rare malignant neoplasm that should be included in the differential diagnosis of nodular ulcerative lesions affecting the lips. Immunohistochemistry and *in situ* hybridization analysis for EBV infection are important to establish the correct diagnosis. The treatment of choice for LEC is surgery, which can be associated with radiotherapy and/or chemotherapy. To the best of our knowledge,

we report the third EBV-negative LEC affecting the lower lip. These cases appear to present favorable prognosis; however, report of further cases is necessary to understand its clinicopathological features better.

REFERENCES

1. Rytkonen AE, Hirvikoski PP, Salo TA. Lymphoepithelial carcinoma: two case reports and a systematic review of oral and sinonasal cases. Head Neck Pathol. 2011;5(4):327-34. http://dx.doi.org/10.1007/s12105-011-0278-7. PMid:21698444.
2. Mahomed F, Grayson W. A rare case of lymphoepithelial carcinoma of the lip. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(5):e49-52. http://dx.doi.org/10.1016/j.tripleo.2008.01.016. PMid:18442735.
3. Chow TL, Chow TK, Lui YH, Sze WM, Yuen NW, Kwok SP. Lymphoepithelioma-like carcinoma of oral cavity: report of three cases and literature review. Int J Oral Maxillofac Surg. 2002;31(2):212-8. http://dx.doi.org/10.1054/ijom.2001.0148. PMid:12102423.
4. Bishop JA, Gaulard P, Gillison M. Lymphoepithelial carcinoma. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. editors. WHO classification of Head and Neck Tumours. Lyon: IARC Press; 2017; p. 18.
5. Gultekin M, Sari SY, Gunhan O, et al. Lymphoepithelial carcinoma of the lower lip: report of a case. UHOD. 2014;24(1):70-2. http://dx.doi.org/10.4999/uhod.12037.
6. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol. 1995;103(3):308-15. http://dx.doi.org/10.1093/ajcp/103.3.308. PMid:7872253.
7. Dubey P, Ha CS, Ang KK, et al. Nonnasopharyngeal lymphoepithelioma of the head and neck. Cancer. 1998;82(8):1556-62. http://dx.doi.org/10.1002/(SICI)1097-0142(19980415)82:8<1556::AID-CNCR18>3.0.CO;2-3. PMid:9554534.
8. Kurokawa H, Zhang M, Matsumoto S, et al. Reduced syndecan-1 expression is correlated with the histological grade of malignancy at the deep invasive front in oral squamous cell carcinoma. J Oral Pathol Med. 2006;35(5):301-6. http://dx.doi.org/10.1111/j.1600-0714.2006.00412.x. PMid:16630294.
9. Martínez A, Spencer ML, Brethauer U, Grez P, Marchesani FJ, Rojas IG. Reduction of syndecan-1 expression during lip carcinogenesis. J Oral Pathol Med. 2009;38(7):580-3. http://dx.doi.org/10.1111/j.1600-0714.2009.00761.x. PMid:19473447.

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The authors retain informed consent and the manuscript is by the Institutional Ethics Committee.

Conflict of interest: None

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