***Systematic Review***

**Lymphoepithelial Carcinoma of Oral cavity: A systematic review**

**Abstract**

**Introduction-** Lymphoepithelial Carcinoma is a subtype of Oral Squamous Cell Carcinoma, morphologically similar to non-keratinizing Nasopharyngeal Carcinoma, un-differentiated subtype. Oral Lymphoepithelial Carcinoma is extremely rare and its characteristics differs from those at other sites of head and neck region. Awareness of the occurence of this lesion in oral cavity is important to promote differentiation from other oral neoplasms. **Objectives-** To explore the demographics, clinical and histopathological features, differential diagnosis, treatment and patient outcomes in Lymphoepithelial Carcinoma of oral cavity. **Methods-** Case reports and case series of Lymphoepithelial Carcinoma of Oral cavity were searched from the year 2002- 2024 by a systematic search of scientific databases, including PubMed Central (National Library of Medicine), Google Scholar (Google, Mountain View, USA), COCHRANE CENTRAL. **Results-** Total of 14 Case reports and 2 Case series that is 16 articles which were satisfying our inclusion-exclusion criteria were considered in the review. The mean age of the study participants across the studies were 50.23 in the middle-aged population with most common affected site was tongue and oral mucosa of the posterior teeth. Histopathological features showing nests and cohesive sheets of undifferentiated carcinoma mixed with a lymphoid stroma. IHC for cytokeratin AE1/AE3, p40, and p53 are positive. **Conclusion-** Oral lymphoepithelial-like carcinoma (LELC) is a rare variant of head and neck squamous cell carcinoma, histologically resembling nasopharyngeal carcinoma (NPC). While NPC is strongly associated with Epstein-Barr Virus (EBV), oral LELC typically lacks EBV involvement. Some oropharyngeal cases may be linked to high-risk HPV, highlighting the need for p16 and HPV testing. **Keywords-** Lymphoepithelial Carcinoma, Oral Squamous Cell Carcinoma Oral cavity

**Introduction**

Oral squamous cell carcinoma (OSCC) is a malignant neoplasm characterized by squamous differentiation arising from the mucosal epithelium. It is one of the most common malignancies affecting oral cavity1. OSCC typically arises in the setting of chronic exposure to carcinogens such as tobacco and alcohol, which induce a high mutational burden in the affected tissues2. A distinct subset of carcinomas, termed virus-associated carcinomas, has been identified, with a pathogenesis linked to viral infections such as Epstein-Barr virus (EBV) and human papillomavirus (HPV)3.

Lymphoepithelial-like carcinoma (LEC) is a well-recognized undifferentiated carcinoma subtype, initially described in the nasopharynx, where it shows strong association with EBV infection4. Nasopharyngeal carcinoma, particularly the undifferentiated subtype, demonstrate a consistent association with EBV through serologic and immunologic studies, as well as through the identification of viral DNA, RNA, and protein expression within tumor cells5. EBV infection establishes a latent phase in epithelial cells of the oropharynx, salivary glands, and B-lymphocytes, where it may persists as a low-grade chronic infection6.

LEC of the nasopharynx was first described by Schminke in 19214. The World Health Organization (WHO) defines LEC as “a poorly differentiated squamous cell carcinoma (SCC) or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma”3. Over time, LEC has been identified in several non-nasopharyngeal sites, including the skin, salivary glands, and oral cavity7,8. Within the salivary glands, LEC most commonly affects the parotid gland, accounting for approximately 80% of cases. Involvement of the minor salivary glands is rare9. Intraorally, LEC has been documented in the regions such as tonsils and base of tongue (Waldeyer’s ring), palate, floor of the mouth, buccal mucosa, retromolar region, tongue and lips10,11. Epidemiologically, LEC has shown a marked racial predilection for populations such as Southeastern Chinese and Eskimos. It typically affects individuals between 40 to 70 years of age, with a slight male predominance3.

Histologically, LEC is characterized as a nonkeratinizing, undifferentiated squamous-cell carcinoma composed of atypical epithelial-derived cells with pale cytoplasm, large vesicular nuclei, and prominent nucleoli. These malignant cells are interspersed with a dense lymphoplasmacytic infiltrate which gives the tumor its characteristic histological appearance12. Unlike conventional SCC, LEC lacks keratinization, necrosis, and mucus production making it histologically similar to nasopharyngeal carcinoma13. The differential diagnosis of LEC includes squamous carcinoma with a lymphoid stroma, malignant lymphoma, malignant melanoma, and lymphoepithelial sialadenitis. Immunohistochemical staining for epithelial markers such as cytokeratins is crucial in distinguishing LEC from these histologically similar malignancies14.

Oral LEC is an exceedingly rare entity, accounting for only 0.2-2% of all oral and nasopharyngeal malignancies. Notably, not all cases of oral LEC are EBV-positive, suggesting that alternative pathogenic mechanisms may be involved in EBV-negative cases15. The presence of EBV in LECs is typically assessed using in situ hybridization for Epstein-Barr encoding region (EBER), while polymerase chain reaction (PCR) may be used for viral DNA detection15. However the biological role of EBV in the initiation and progression of oral LEC remains poorly understood, necessiating further investigations16.

In addition to EBV, recent studies have demonstrated a possible link between LEC and HPV17. HPV-related head and neck squamous cell carcinomas (HPV-HNSCCs) with lymphoepithelial features are misdiagnosed as metastatic nasopharyngeal carcinomas due to histologic similarities. Unlike conventional SCC, HPV-HNSCC tends to occur in patients (below 60 years) often with no history of smoking, exhibits a low risk of distant metastasis, and is associated with a favorable clinical prognosis17. The immunohistochemical profile of HPV-associated LECs includes strong nuclear and cytoplasmic expression of p16 in over 70% of tumor cells, while EBER staining is typically negative. Molecular analyses using PCR or in situ hybridization confirm the presence of transcriptionally active HPV in most cases18. In some cases, overexpression of p53 has been observed, suggesting a possible role of TP53 mutations in the pathogenesis of HPV-associated LECs16.The etiology of LEC remains unclear, some studies suggest a genetic or environmental component based on case clustering. Cervical lymph node involvement is observed in approximately 70% of cases. LECs of the oropharynx, particularly those associated with HPV, may present as occult primary tumors with nodal metastasis. Due to clinical and histopathological overlap with nasopharyngeal carcinoma, a thorough evaluation of the nasopharynx is necessary to exclude a primary nasopharyngeal tumor before diagnosing intraoral LEC13.

Treatment strategies of LEC typically involve surgical excision often in combination with adjuvant radiotherapy and/or chemoradiation. While local invasion and nodal metastases are frequently observed at the time of diagnosis, the prognosis of adequately treated LEC patients remains relatively favorable compared to other forms of SCC9. This systematic review has been registered in the International prospective register of systematic review.

**AIM**

To conduct a systematic review to asses Lymphoepithelial Carcinoma of Oral cavity

**OBJECTIVES**

To explore the demographics, clinical and histopathological features, differential diagnosis, treatment and patient outcomes in Lymphoepithelial Carcinoma of oral cavity.

**MATERIALS AND METHOD**

Case reports and case series of Lymphoepithelial Carcinoma of Oral cavity were retrieved by a systematic search of scientific databases, including PubMed Central (National Library of Medicine), Google Scholar (Google, Mountain View, USA), COCHRANE CENTRAL with the keywords ‘Lymphoepithelial Carcinoma’ AND ‘oral cavity’. Retrieved literature was scanned to identify any cases reported with a name differing from Case reports before the year 2000. An independent researcher searched the databases and identified relevant reports.

Reference checks of the cases identified were also made to help snowballing or networking of the cases. A table was framed regarding author, year of publication, demographic data as age, gender, clinical features, microscopic histopathological features, immunohistochemistry, and differential diagnosis treatment opted for each of the case reports included.

**PROTOCOL**

The search protocol is designed based on the PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analysis-Protocols) guidelines 2015.

**SEARCH STRATEGY**

To find pertinent studies on the Demographics, clinical and histopathological features, differential diagnosis, treatment and patient outcomes in Lymphoepithelial Carcinoma of oral cavity, a thorough search was undertaken in the Google scholar, PubMed, Cochrane and DOAJ database. The filters were fixed at article type (prospective, retrospective, cross-sectional studies), publication date (January 2000 till December 2024), and the best match option. Controlled vocabulary (MeSH terms in PubMed) and free-text terms in the titles and/or abstracts were used to define the search strategy in the database.

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| **Primary keywords** | **Secondary keywords** |
| * Patients with Lymphoepithelial   carcinoma of the oral cavity (P) | * Patients diagnosed histopathologically   with Lymphoepithelioma  of oral cavity |
| * Lymphoepithelial carcinoma   oral cavity(E) | * Lymphoepithelioma-like carcinoma * Squamous cell thymic carcinoma |
| * Demographics, clinical   and histopathological features,  differential diagnosis, treatment  and patient outcomes in  Lymphoepithelial Carcinoma  of oral cavity.(O) | * Clinical outcomes of   lymphoepithelial carcinoma   * Oral involvement of   lymphoepithelial carcinoma   * Oral Soft tissue involvement of lymphoepithelial carcinoma |

**List 1 : keywords for the study**

**ELIGIBILITY CRITERIA**

**Inclusion Criteria**

Following articles are included

1.Case reports, case series and case reports and series with reviews on patients with Lymphoepithelial Carcinoma of Oral cavity.

2. Articles published in English

3. Case reports and case series reports between 2000-2024

**Exclusion Criteria**

Following articles are excluded:

1. Case reports and case series on patients with Lymphoepithelial Carcinoma of other sites of head and neck region.
2. Articles published in other languages.
3. Abstracts
4. Randomized and nonrandomized clinical trials
5. All studies
6. Articles with incomplete data.

**FOCUSED QUESTION:**

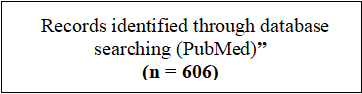
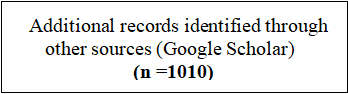
The review aims to answer the following deterministic question in PICOT format.

* To know the demographics, clinical and histopathological features, differential diagnosis, treatment and patient outcomes in Lymphoepithelial Carcinoma of oral cavity.

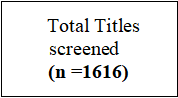
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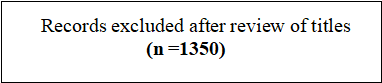
The study selection was done in three steps. All the titles were reviewed and based on the inclusion and exclusion criteria; appropriate studies were selected. For all the selected titles, abstracts were obtained and reviewed, from which appropriate abstracts were selected based on the criteria. Full-text articles were obtained and analyzed, and the final set was obtained keeping in mind the selection criteria.The initial search strategy yielded 1616 references. After removing duplications and non-relevant articles, the number of references reduced to 68. This number was further reduced to 17 based on abstracts and titles. The main reason for exclusion were review articles without new cases, (n=198 ), studies *related to title (n=1350 ), abstracts only (n=40) and abstracts not mentioning the outcome* (n=5)

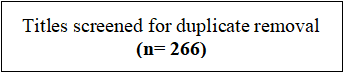
**Figure 1: PRISMA Flow chart presenting the screening process**

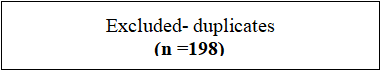
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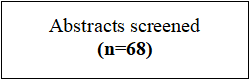
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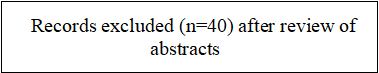
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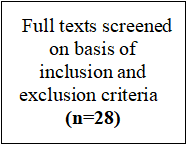
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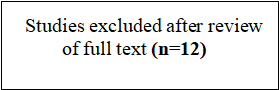
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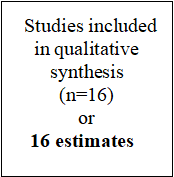


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**RESULTS**

Comprehensive findings after a detailed review of all the cases are collectively tabulated in master chart in the following Table no. 1. Total of 14 Case reports and 2 Case series that is 16 articles which were satisfying our inclusion-exclusion criteria were considered in the review. All the search was limited to articles in English language and those published from the year 2002- 2024 were included. Lymphoepithelial carcinoma of oral cavity presents widely over an age range of 30-80 years; the youngest case patient being 30 years old and oldest being 82 years. The mean age of the study participants across the studies varied 50.23 (3.45) in the middle-aged population. Out of 16 studied included, there were 19 cases reported across all case reports and case series. About 13 (68.42%) cases were found in males. Whereas 6 (31.58%) were found in females. Common Clinical presentations of lymphoepithelial carcinoma showed a nodular lesion with an ulcerated surface, with flat edges, hardened base, and were painful in most of the cases. In some cases, it was exophytic, haemorrhagic mass with an indurated surface.The most common affected site of lymphoepithelial carcinoma was tongue and oral mucosa of the posterior teeth followed by upper and lower lip. The tumours ranged from 2-2.5 cm to 1.0 cm in the smallest dimension whilst the greatest dimension reported was 6 x 4 cm. In some cases, this clinical information was limited. Duration of presence of lesion varied from 1 week to over 1 year. In almost 14 cases, the inset of lesion was from 1 month to 6 months; whereas the longest duration of presence of lesion was 1 and half year in a case. The lymph node involvement was noted in some of the cases included in the review. It was noted that majority of the cases showed upper/lower cervical lymph node involvement (4 cases) whereas, sub-mandibular (2 cases) and bilateral involvement of the lymph nodes (2 cases) was also noted. The histopathological features across the cases were noted. A classical picture of the tumour was made-up of nests and cohesive sheets of undifferentiated carcinoma mixed with a lymphoid stroma. The carcinomatous cells were undifferentiated large cells forming syncytial sheets, with large nuclei and prominent nucleoli. Mitotic figures and individual tumor cell necrosis were also identified. The immunohistochemistry showed positive or negative EBV antigen with positive for cytokeratin AE1/AE3, p40, and p53. Differential diagnoses were not reported in majority of the case reports; whereas a few reported squamous carcinoma (with a lymphoid stroma) or other local tumors such as adenoma. From the total included studies (16 studies) in this present systematic review, a total of 19 cases were reported (including the case series). From the 19 cases reported, 12 cases (63.15%) were negative for EBV and 7 cases (36.85%) were EBV positive and HPV negative. All the EBV negative cases showed a positive AE1/AE3, p40, and p53 cytokeratin. The differential diagnosis for Lymphoepithelial carcinoma was squamous carcinoma (with a lymphoid stroma) or other local tumors such as adenoma, unusual morphologic variant of SCC, Hodgkin lymphoma etc. The treatment given was surgical excision and in metastases cases, radical neck dissection or mandibulectomy or ipsilateral neck dissection was performed in most of the cases. In this present review out of 19 cases of lymphoepithelial carcinoma, all the cases were followed up over a period of 1-3 years. Almost all the cases showed no recurrence of disease or relapse after treatment; whereas only 2 cases succumbed to death due to denying the advised treatment at a critical stage of this disease.

**ASSESSMENT OF RISK OF BIAS**

Risk of bias assessment of all the included studies was performed. From the 16 included studies, about 14 were case reports and about 2 studies were case series. For the risk of bias assessment of included case reports and case series, JBI’s appraisal tool was used.

**Table 2- Details of the study participants, intervention, and comparator of the studies included in**

**the systematic review**

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| **Sr**  **No.** | **Author Name** | **Demographic Data** | | | | | **Histopathological features** | | **Differ**  **ential**  **Diagno**  **sis** | **Treatment** | **Patient Outcome** |
|  |  | **Age/**  **Sex** | **Site** | **Size & Features** | **Duration** | **TNM**  **Staging** | **Microscopic** | **IHC** |  |  |  |
| **1** | Sheng-Yun Lu, Chao-Cheng Huang, Ching-Yeh Hsiung, Hock-Liew Eng, Hsuan-Ying Huang (8) | 50/  F | Right buccal mucosa | 2.0x 1.6x 1.0 cm, multinodular | 1 year | NR | Residual lobules of minor salivary glands juxtaposing with several separated, various-sized tumor nodules. beneath an intact nondysplastic stratified squamous epithelium. Tumor composed of large, polygonal, undifferentiated tumor cells with vesicular nuclei & prominent nucleoli that were arranged in cohesive nests within abundant lymphoplasmacytic infiltrates, focally forming germinal centers.The cell borders between adjacent cells were indistinct, creating a syncytial cytoplasmic appearance. Mitotic figures averaged one to two per high-power field. Necrosis, keratinization, and benign lymphoepithelial lesions were all absent | Positive for epithelial membrane antigen (EMA), AE1/AE3 cocktail, and CD117. Negative for cytokeratin 7, cytokeratin 20, and latent membrane protein-1 (LMP-1). Ki-67 & p53 were approximately 10% and 25%.ISH of EBV by use of EBER1-specific antisense oligoprobe disclosed abundant EBER1 in undifferentiated carcinoma but not in the surrounding lymphoid stroma. | **NR** | wide local excision followed by adjuvant radiotherapy with a total  dose of 6520 cGy | no evidence of disease after 120 months of long-term follow-up. |
| **2** | Farzana Mahomed, and Wayne Grayson  (21) | 73/  M | Lower  lip | 1 x 1 cm, an ulcerated lesion filled with yellowish slough and marginated by irregular, raised, and indurated edges. | 4 month | **NR** | a malignant infiltrate with ill-defined cords of large pale-staining undifferentiated cells & dense lymphoid stroma. Numerous small lymphocytes and occasional plasma cells were intermingled with the large cells that were dissociated by the reactive lymphoplasmacytic infiltrate. The tumor cells had ill defined cell borders with markedly pleomorphic vesicular nuclei and prominent nucleoli. Binucleated tumor cells that resembled ReedSternberg cells were frequently identified. | CD45 expressed by lymphocytes but not by neoplastic cells. Strong staining for A1/ AE3 and EMA but not for CK 7 and CK 20, supporting their squamous epithelial nature. IHC for EBV antigen LMP-1 was negative, and no EBV DNA could be detected after PCR amplification | unusual morphologic variant of SCC | Excision | No evidence of recurrence after 20 month follow-up |
| **3** | H. Merz, S. Marnitz, A. Erbersdobler, O. Goektas (29) | 73  F | Base of tongue | Induration on right side of base of tongue | 8 weeks | 3 suspicious lymph nodes of level II on right side & 1 on left side,1 of level III/IV on left side | a lymphoepithelial mucosa of the base of the tongue with a subepithelial infiltration of medium-sized, atypical, blastary cells with vesicular cores | Pan-Cytokeratin positive. Negative for CD 40 & CD 2. PCR showed virus genome of EBV. | NR | Partial doses of 2 Gy up to an entire dose of 30 Gy. chemotherapy including cisplatin and 5-fluorouracil | NR |
| **4** | Dardo Menditti, Luigi Laino, Massimiliano Milano, Cristian Caputo, Mariarosaria Boccellino, Alfredo D'avino And Alfonso Baldi (30) | 56/M | Mucosa of upper lip | 2.5x1.0cm, hyperemic overlying mucosa without ulceration. hemispherical, well-circumscribed, elastic and indolent  tumor | 2 months | NR | Nests and cohesive sheets of undifferentiated carcinoma mixed with a lymphoid stroma. The carcinomatous cells were undifferentiated large cells forming syncytial sheets, with large nuclei and prominent nucleoli. Mitotic figures and individual tumor cell necrosis were also identified. | EBV antigen (LMP-1) was negative | squamous carcinoma (with  a lymphoid stroma)  & Adenoma | Complete excision with a margin free region of 3-5 mm | Patient remains tumor-free after 2 years. |
| **5** | Enrico Pegolo, Piercamillo Parodi,y Michela Francescon,z and Carla Di Loreto (31) | 73/M | Lower  lip | 4 cm, Ulcererated lesion | 3 month | T3N0, Sentinel lymph node was reactive and free of tumor | An ulcerated malignant neoplasm of the lip vermilion mucosa infiltrating the striated muscle. Tumor was composed of isolated and ill-defined sheets of atypical large undifferentiated cells associated with a dense lymphoid stroma. Numerous small lymphocytes, plasma cells, and some eosinophils were intermingled with the large cells. Tumor cells had ill-defined borders, marked pleomorphic vesicular nuclei, and prominent nucleoli. Several mitotic figures present. Lymphovascular and perineural invasions by  tumor cells were not identified | Positive for AE1/AE3 cytokeratin and epithelial membrane antigen (EMA), the neoplastic cells diffusely expressed p63),lymphocytes within tumor expressed CD45. IHC & ISH for EBV negative, real-time PCR(RT-PCR)detected 102/mL DNA copies of EBNA-1 EBV in the tumor sample. | NR | surgery for radical removal  of the lesion and for a sentinel lymph node  procedure. | No evidence of recurrence after 12 month follow-up |
| **6** | Ming Zeng, Shuangjiang Li, Jinhua Fu, Hanjiang Wu And Yijun Gao  (33) | 38/  F | Left side of hard palate | well‑defined, nodular mass , 26 x 24 x 17 mm in size, non‑tender  and soft to palpation,  with areas of fluctuance. Surface mucosa red  in color with no erosion, bleeding or ulceration. MRI-invasion into the nasal cavity | 1 month | NR | Irregular tumor nests of undifferentiated epithelial cells intimately intermingled with lymphocytes and plasma cells. The tumor cells exhibited a syncytial pattern with indistinct cell borders, vesicular nuclei, and large central nucleoli | IHC-positive for cytokeratin AE1/AE3  ISH-r EBV-encoded RNA was diffusely positive in undifferentiated carcinoma, however, it was negative in the surrounding lymphoid stroma and adjacent salivary gland tissues | NR | a partial maxillectomy | No evidence of recurrence after 12 month follow-up |
| **7** | Shota Shimizua, Akihiro Miyazaki, Kenji Nakamori, Hiromi Nakai , Kazuhiro Ogi, Tadashi Hasegawa, Hiroyoshi Hiratsuka (33) | 82/M | Floor of the mouth that had invaded the tongue and mandible | ulcerative  60 × 45 mm indurative swelling | 3 months | T4aN2cMx, bilateral regional lymph node metastases | Tumor cells were characterized by nests and islands of undifferentiated polygonal cells with indistinct borders and eosinophilic cytoplasm, large vesicular nuclei, and single to multiple prominent nucleoli. Several mitotic figures were present with ulcerative changes. Tumor nests were surrounded and invaded by a lymphoid infiltrate comprised predominantly of small lymphocytes. | ISH- negative for EBV-encoded RNAs (EBERs) . AE1/AE3 & CK34E12 are positive | NR | Radiotherapy, n HLA-A24- restricted survivin 2B peptide vaccine with interferon-a | Poor, he died after 12 months |
| **8** | Sawako Ono, Hidenori Marunaka, Hiroyuki Yanai, Hotaka Kawai , Kiyofumi Takabatake, Kenji Nishida, Tomohiro Toji, Keisuke Nakano, Hitoshi Nagatsuka and Tadashi Yoshin  (16) | 82/M | Posterior Left edge of tongue | 2 × 1 cm2, a hard, slightly bulging mass with a smooth surface, | NR | NR | Tumor cells showed proliferation of pale staining, cohesive epithelial cells with prominent surrounding and infiltrating lymphocytes. The tumor cells are polygonal and contained large round vesicular nuclei with prominent nucleoli. No keratinization was found in the tumor. | Positive for cytokeratin AE1/AE3, p40, and p53. ISH the epithelial cells were negative for EBV-encoded small RNA | NR | Surgical excision | no recurrence was observed at the 7-month follow-up visit. |
| **9** | Luciana Yamamoto Almeida, Heitor Albergoni Silveira, Evânio Vilela Silva, Camila de Oliveira Barbeiro, Joaquim Augusto de Paula , Andreia Bufalino, Alfredo Ribeiro-Silva, Jorge Esquiche León  (34) | 82/M | Lower lip | nodular lesion presented an ulcerated surface, with flat edges, hardened base, painful | 1 year | NR | An intense inflammatory infiltrate, composed of lymphoplasmacytic cells, associated with scarce pleomorphic epithelial cells. | 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  ISH nalysis did not show evidence of EBV infection | NR | Surgical excision | After 2-year of follow-up, the patient is well, without recurrences. |
| **10** | Jevtic M et al  (35) | 81/M | Palatine tonsil and lymph node involvement | 33x31x38 mm heterodense  mass in right palatine tonsil, | 2 months | 37x30  mm and 21x20 mm lymph nodes on the right side of the neck | sheets and islands of polymorphic and polygonal cells, vesicular nuclei, dispersed chromatin,  noticeable pathological mitosis and areas of geographic necrosis | expression  of p63 and Epstein-Barr virus (EBV) | NR | Surgery, radiotherapy  and chemotherapy. | NR |
| **11** | Daisuke Takeda, Manabu Shigeoka, Tenyu Sugano, Nanae Yatagai, Takumi Hasegawa and Masaya Akashi (36) | 72/M | Left tongue | Unilateral, non-detachable white patch. After 11 months monitoring, a mass with induration. | 5 months | T1N0M0 | Incisional biopsy- atypical epithelium that does not rule out neoplastic change  Excisional biopsy Invasive cancer was detected in resected specimens. The depth of invasion was 4.6. Observation of the cancer nests was difficult due to lymphoplasmacytic infiltration. Both keratinization and desmoplastic stromal reaction were absent. The tumor cells have enlarged vesicular nuclei with prominent nucleoli. Nuclear pleomorphism is also increased. | Tumor cells were negative for EBER-ISH. Positive for CK AE1/AE3. The monoclonal reactivities for both a B-cell (CD20) and a T-cell (CD3) marker in infiltrating lymphocytes could not be detected | NR | Partial glossectomy with 10-mm tumor-free margins. | no evidence of disease at the 1-year follow-up |
| **12** | Sally Nguyen Timothy Kong Eric Berthelet · Tony Ng· Eitan Prisman(37) | 78/M | Left lingual tonsil | slightly larger left lingual tonsil (1.5 × 1 cm) | 4 weeks | both lymph nodes were palpable and located in level 5A. | a non-keratinizing squamous cell carcinoma with no overlying in-situ component | EBV-positive, HPV negative non keratinizing squamous cell carcinoma. positive for CK5/6, p63, EBV ISH and and negative for CK20, CK7, TTF1 and p16. | NR | external radiotherapy. 6 fractions per week (twice daily 6 h apart, once a week). Treatment was delivered using 6 megavoltage (MV) photons and VMAT technique | No evidence of recurrence after 8 months |
| **13** | Rodopi Emfietzoglou, Efstathios Pettas, Maria Georgaki, Erofili Papadopoulou,Vasileios Ionas Theofilou, Nikolaos Papadogeorgakis, Evangelia Piperi, Marcio Ajudarte Lopes and Nikolaos G. Nikitakis (22) | 51/M | Buccal and lingual gingiva of the right mandibular premolarsedentulous alveolar mucosa posteriorly to the second premolar & left posterior maxillary palatal giniva | 3 cm in dia, exophytic, hemorrhagic, ulcerated mass | 1 week | T2N2bM0  painful and fixed lymph node in the right submandibular. | Diffuse infiltration of the underlying connective tissue by neoplastic cells arising from a partially ulcerated and non-keratinized stratified squamous epithelium, diffuse dense lymphoplasmacytic cell infiltrate surrounding the neoplastic epithelial cells and obscuring the tumor islands, focal keratin pearl formation, and , focal areas of tissue necrosis | Positive to cytokeratin AE1/AE3,p63,CK5/6 & p40 confirming their squamous epithelial phenotype. P16 IHC negative, LMP-1 IHC & ISH for EBER negative | Lymphoma, sarcomas, SCC, diffuse gingival enlargement due to calcium channel blockers, peripheral giant cell granuloma or even brown tumor of secondary hyperparathyroidism induced by renal failure | wide surgical resection with segmental mandibulectomy and ipsilateral neck dissection. adjuvant chemotherapy and radiation therapy | at 28 months post-treatment, he remains free of disease. |
| **14** | Diksha Karki, Meenakshi Kamboj, Sunil Pasricha, Ghanashyam Manda, Vishal Yadav, Vikas Arora (27) | 36/M | left lateral border of tongue | 3 × 3 cm, e ulceroproliferative lesion | NR | Cervical I and II lymph nodes palpable | an infiltrative nodular patterned lesion lying in the submucosal tissue; the overlying squamous mucosa showed focal ulceration without any dysplasia. The tumor nodules predominantly comprised of lymphocytes, plasma cells, and eosinophils. A minor component of large, atypical cells having conspicuous nucleoli, and few binucleate and multinucleate cells were seen which resembled Reed‑Sternberg (R‑S) cells. Mitotic figures were frequently seen in these large cells. | Large cells were positive for Pan‑cytokeratin (CK), CK5/6 and P40 confirming an epithelial malignancy of squamous origin. IHC for CD20, CD3, CD5, CD10, and CD1a was negative, excluding the diagnosis of lymphoid neoplasm. S‑100 highlighted the follicular dendritic cells. IHC for p16 and EBER by FISH were negative in the tumor cells | Hodgkin lymphoma | left sided hemiglossectomy with modified neck dissection (MND) of level I‑V lymph nodes. concurrent radiotherapy and chemotherapy (RT/CT) | After a regular follow up of 22 months, no residual disease has been detected clinically and radiologically |
| CASE SERIES | | | | | | | | | | | |
| **15** | T. L. Chow, T. K. Chow, Y. H. Lui, W. M. Sze, N. W. F. Yuen, S. P. Y. Kwok  (10) | 58/M | Junction of the soft and hard palate in the midline | 2 cm ulcer | 1&half  year | upper cervical lymph nodes were palpable, three other smaller lymph nodes at the left and right sides of the neck | oral mucosa was infiltrated by irregular islands of undifferentiated tumour cells with vesicular nuclei and prominent nucleoli. Florid infiltration of lymphoid cells was present | IHC-Cytokeratin +  The tumour cells were positive for EBV-encoded RNAs (EBERs) | NR | External radiotherapy | no sign of tumour recurrence after a follow up of 2 1/2 years |
|  |  | 56/  F | Soft Palate | submucosal lump about  1.5 cm in diameter | 1 year | NR | Oral mucosa was infiltrated by irregular islands of undifferentiated tumour cells with vesicular nuclei and prominent nucleoli. Florid infiltration of lymphoid cells was present | ISH-positive for EBV-encoded RNAs (EBERs) | NR | 66 Gy of radiation in 33 fractions over 40 days, while the neck received 50 Gy in 25 fractions over 29 days, simultaneously. | no tumour relapse 1 year after the diagnosis |
|  |  | 80/  F | right retro-molar region | ulcerative mass | 1 month | enlarged right submandibular lymph node | Oral mucosa was infiltrated by irregular islands of undifferentiated tumour cells with vesicular nuclei and prominent nucleoli. Florid infiltration of lymphoid cells was present | ISH-positive for EBV-encoded RNAs (EBERs) | NR | patient refused treatment at that time | succumbed 2 years and 10 months later due to tumour progression. |
| **16** | Aleksi E. Rytko ¨nen • Pasi P. Hirvikoski • Tuula A. Salo  (23) | 49/  M | Uvula | a solid tumor mass, approxi mately 2 cm in diameter | 6 months | enlarged cervical lymph nodes and nodal metas tases | syncytial islands of epithelial cells with large, vesicular nuclei, and prominent surrounding lymphocytic stroma. The squamous epithelium above the tumor was intact | IHC for AE1/AE3 was positive on tumor cells. EBV IHC and ISH (EBERs) were negative. IHC for p16 expressed focal positivity in the surface epithelium while tumor cells were negative | NR | Adjuvant therapy  included chemoradiation with a dose of 2.0 Gray (Gy) five  times a week up for a total dose of 70 Gy, and Cisplatin  (80 mg) once a week for 6 weeks. | 11 months after  treatment, the patient was without any evidence of LEC  recurrence |

**DISCUSSION**

The World Health Organization (WHO) classification system for histologic subtypes of head and neck squamous cell carcinoma (HNSCC) includes eight distinct histopathological variants: basaloid, spindle cell, adenosquamous, carcinoma cuniculatum, verrucous, lymphoepithelial, papillary, and acantholytic subtypes19. Lymphoepithelial carcinoma (LEC), as defined by the World Health Organization (WHO), is a poorly differentiated squamous cell carcinoma or an undifferentiated carcinoma characterized by a prominent reactive lymphoplasmacytic infiltrate. Histologically, it closely resembles the undifferentiated carcinoma of nasopharyngeal type. Histologic subtypes of nasopharyngeal carcinoma include keratinizing squamous cell carcinoma (SCC), nonkeratinizing carcinoma, and basaloid SCC. The nonkeratinizing subtype is further classified into differentiated and undifferentiated variants. The undifferentiated subtype, also referred to as lymphoepithelial carcinoma (LEC), being the most commonly encountered form of nasopharyngeal carcinoma. Histologically, it is characterized by a dense lymphoid stromal infiltration, which can obscure the identification of malignant epithelial cells in routine hematoxylin and eosin (H&E)–stained sections.20 Non-nasopharyngeal lymphoepithelial carcinoma (LEC) has been described using various terminologies such as *undifferentiated carcinoma of nasopharyngeal type, undifferentiated carcinoma with lymphoid stroma, carcinoma ex lymphoepithelial lesion, malignant lymphoepithelial lesion, lymphoepithelioma, and lymphoepithelioma-like carcinoma*—each emphasizing the histological resemblance to nasopharyngeal LEC21. Lymphoepithelioma-like carcinoma (LELC) is defined as an undifferentiated carcinoma that arises outside the nasopharynx, with or without an associated non-neoplastic lymphoplasmacytic infiltrate. Histologically, it closely resembles the nonkeratinizing undifferentiated subtype of nasopharyngeal carcinoma (NPC).

In the head and neck region, lymphoepithelioma-like carcinoma (LELC) most commonly arises in the salivary glands, oral cavity, oropharynx (including the palate, tonsils, and base of tongue), nasal cavity, paranasal sinuses, and larynx. Among these, the salivary glands—particularly the parotid gland—are the most frequent non-nasopharyngeal sites of origin. The parotid gland accounts for approximately 80% of salivary gland LELC cases, followed by the submandibular gland. Involvement of the sublingual gland is rare. LELCs have also been documented in minor salivary glands throughout the upper aerodigestive tract, including the oral cavity. Oral LEC may originate either from the surface mucosal epithelium or from adjacent minor salivary glands (MSGs).22 Rodopi Emfietzoglou et al. (2022) described two cases of lymphoepithelial carcinoma with intrabony involvement—one in the maxilla and one in the mandible—raising the possibility of an origin from odontogenic epithelial rests or entrapped minor salivary glands (MSGs) within the jaws. In the present systematic review cases from oral cavity (i.e the anterior border at the lip vermillion and includes the soft palate and posterior border as base of tongue, uvula and lingual and palatine tonsil) were considered. Lesions involving the major salivary glands and bone of maxilla and mandible were excluded. Melis Gultekin et al. (2014) noted that lymphoepithelial carcinoma (LEC) of the lip closely resembles lymphoepithelioma-like carcinoma (LELC) of the skin, which is believed to originate from the cutaneous epithelium and consistently tests negative for Epstein–Barr virus (EBV). This contrasts with LECs arising in other regions of the oral cavity, where EBV association may still be observed. Farzana Mahomed et al. (2008) reported a case of LEC arising in the setting of actinic cheilitis, which exhibited squamous differentiation and continuity with the surface keratinocytes, suggesting that it represent an uncommon morphological variant of squamous cell carcinoma (SCC).

Oral LEC is commonly diagnosed in patients between 30 and 82 years with mean age of 50 years. In our review, we observed a male predominance in Oral LEC cases (13 male and 6 female) which contrasts with findings by Aleksi E et al (2011) and Sawako Ono et al (2021) that reported equal gender distribution23. The most common affected site were the tongue and oral mucosa of the posterior teeth followed by upper and lower lip.

Epidemiologic studies have shown a strong association between lymphoepithelial carcinomas (LECs) and Epstein-Barr Virus (EBV) primarily in Southeast Asia, where both LEC and nasopharyngeal carcinoma (NPC) show a strong correlation with EBV infection24. The EBV genome is detected exclusively within epithelial cells, rather than lymphocytes. This suggests that tumorigenesis likely involves the clonal proliferation of EBV-infected epithelial cells10. However, there is evidence for the absence of EBV in LEC. In our review, 12 cases tested negative for EBV using IHC and in situ hybridization (EBERs- EBV-encoded small RNA) or more rarely PCR. Although EBER in situ hybridization has been regarded as the ‘‘gold standard’’ for the identification of EBV in neoplasm. It has been suggested that immunohistochemistry (IHC) may offer limited relevance for therapeutic or prognostic value. However, EBV status has proven to be more valuable in diagnosing distant tumors that are suspected to be metastases of nasopharyngeal carcinoma (NPC)23. Leung et al.(1995) reported the presence of Epstein-Barr virus (EBV) in a clonal episomal form, along with the expression of the viral oncoprotein, Latent Membrane Protein -1 (LMP-1), supporting a causative role of EBV in the oncogenesis of lymphoepithelial carcinoma (LEC)30.

However, in our cases, only EBER-1 expression was detected, while LMP-1 protein expression was absent. No association has been demonstrated between oral cavity lymphoepithelial-like carcinoma (LELC) and EBV. This contrasts with nasopharyngeal lymphoepithelioma, which shows a strong association with EBV. According to Menditti et al;(2012) the development of EBV-associated tumors is largely attributed to the activity of specific viral proteins. Among them, EBNA-1 has been shown to induce malignant transformation of lymphoepithelioma cells in vitro. Latent Membrane Protein 1 (LMP-1), expressed during the latent phase of EBV infection, plays a key role in immune evasion by suppressing T-cell activity. It also promotes epidermal hyperplasia and inhibits squamous differentiation. The ZEBRA protein (also known as BZLF1) is crucial for reactivating the viral genome and initiating the lytic cycle. Meanwhile, LMP2A contributes to the switch from latency to lytic replication and enhances epithelial cell migration, invasion, and metastatic potential. Although serological tests confirm that EBV infection is widespread globally, these tests are not considered reliable indicators for identifying EBV-associated tumors.

Recently, human papillomavirus (HPV) has also been proposed as a potential etiological factor for squamous cell carcinomas (SCCs) that exhibit morphological similarities to EBV-related lymphoepithelial carcinomas17. In the oropharynx, among the various histologic subtypes of SCC, the lymphoepithelial pattern is rare and typically associated with p16-positive tumors25. A study by Singhi et al. [26], reported thar all 22 cases of oropharyngeal lymphoepithelial-like carcinoma (LELC) were p16-positive, with 86% also showing HPV positivity by in situ hybridization (ISH), while EBV was not detected in any of the cases.

These findings suggest that head and neck LELCs—particularly those presenting as cervical lymph node metastases—should be evaluated for HPV status, in addition to EBV, as they may originate from an HPV-positive lymphoepithelial SCC of oropharyngeal origin. The most reliable method for HPV detection involves p16 immunohistochemistry (IHC) followed by ISH targeting high-risk HPV subtypes, most commonly HPV-16 and HPV-1827. In our review, one case tested positive for p16. Oropharyngeal LELCs with an HPV-related etiology may represent a clinically less aggressive subset of this malignancy 26.

Among the cases with sufficient clinical details, most patients presented with an ulcerated mass exhibiting an indurated border, while others showed either nodular or multinodular growth patterns. Lymph node involvement was observed in 8 cases, primarily affecting unilateral or bilateral submandibular nodes, as well as cervical lymph nodes extending up to Level VA. Out of 8 cases that showed nodal involvement 5 were EBV positive. Diksha Karki et al (2022) showed that EBV positive has increased incidence of lymph node metastasis as compared to EBV negative cases. Daisuke Takeda et al. (2021) reported that, despite the tendency of lymphoepithelial carcinomas (LECs) to metastasize or exhibit local invasion, the overall prognosis appears relatively favorable when compared to other poorly differentiated epithelial tumors. Their findings also suggest that patients with EBV-positive malignancies tend to have better survival outcomes than those with EBV-negative tumors, similar to the improved prognosis seen in HPV-positive oropharyngeal cancers.

Lymphoepithelioma (LE) was initially described in the nasopharynx independently by Regaud and Reverchon, and later by Schmincke. In the Schmincke type, the neoplastic epithelial cells exhibit a diffuse growth pattern and are intimately admixed with a dense infiltrate of inflammatory cells. In contrast, the Regaud type is characterized by well-circumscribed aggregates of neoplastic epithelial cells, surrounded by fibrous stroma and lymphoid infiltrates. Despite these histopathological distinctions, the classification into Regaud and Schmincke types does not significantly correlate with the biological behavior of the disease10. Tumors originating from the oral epithelium demonstrated diffuse infiltration of the underlying connective tissue by neoplastic cells emerging from the partially ulcerated oral mucosal surface. These tumor cells appear pleomorphic with large hyperchromatic or vesicular nuclei with prominent eosinophilic nucleoli. They are usually arranged in syncytial islands. Atypical mitotic figures and a high proliferative index were evident. A dense lymphoplasmacytic infiltrate intimately surrounds and often obscured the malignant epithelial islands. Additionally, scattered polymorphonuclear leukocytes and eosinophils were noted. Focal areas of keratin pearl formation and necrosis were also observed22.

In contrast, tumors arising from the intraoral minor salivary glands exhibited residual lobules of minor salivary tissue juxtaposed with or interspersed among multiple, variably sized tumor nodules, located beneath an intact, nondysplastic stratified squamous epithelium. This tumor was primarily composed of large, polygonal, undifferentiated cells with vesicular nuclei and prominent nucleoli, arranged in cohesive nests embedded within a dense lymphoplasmacytic infiltrate, which may occasionally form germinal centers. The tumor cell borders are indistinct, resulting in a characteristic syncytial cytoplasmic appearance. Mitotic figures typically range from one to two per high-power field. Notably, there was no evidence of necrosis, keratinization, or benign lymphoepithelial lesions28.

In 2 cases, few binucleate and multinucleate cells resembling Reed‑Sternberg (R‑S) cells were observed. The primary diagnostic challenge arises during incisional biopsy due to the presence of large tumor cells with prominent nucleoli set against a dense lymphoid background—and lacking desmoplastic stroma—features that may mimic non-epithelial malignancies such as lymphoma or melanoma. In several cases, the tumor appeared poorly differentiated, characterized by scattered large cells within a dense inflammatory infiltrate of lymphocytes and eosinophils, closely resembling a lymphoproliferative process, including Hodgkin lymphoma29. To establish a definitive diagnosis, immunohistochemistry (IHC) was performed in all cases.

Immunohistochemically, the tumor showd diffuse positivity for epithelial membrane antigen (EMA), AE1/AE3 cocktail, p63, CK5/6, p40, CD 138 and CD117 confirming its squamous epithelial origin. Almeida et al (2020) correlated CD138 expression significantly with the histological differentiation grade, exhibiting weak and patchy immunostaining in poorly differentiated neoplasms. Shota Shimizu et al. (2017) found that EBV-negative LECs showed a predominance of CD8⁺ and CD45RO⁺ TILs, which infiltrated tumor nests and likely contributed to an antitumor immune response. These tumors also had more PD-1⁺, FOXP3⁺, and CD8⁺ T cells compared to oral SCCs, suggesting a mixed cytotoxic and immunosuppressive microenvironment. CD45RO⁺ cells were more abundant and invasive than CD4⁺ cells, indicating a potential role in tumor immunity. IHC for CD20, CD3, CD5, CD10, and CD1a was negative, thereby excluding the diagnosis of lymphoid neoplasm. Some cases demonstrated overexpression of p53 and Ki-67, suggesting that mutations in the **TP53** gene may play a pivotal role in the tumor's carcinogenesis16. Given the microscopic resemblance between lymphoepithelial carcinoma (LEC) and nasopharyngeal carcinoma (NPC), exclusion of a nasopharyngeal primary considered essential. No evidence of a primary tumor was identified in any of these cases.

Surgical excision with modified neck dissection (MND) of level I‑V lymph nodes either alone or in combination with adjuvant radiotherapy—and occasionally chemotherapy—was the most commonly employed therapeutic approach. Non-nasopharyngeal lymphoepithelial carcinomas (LECs) of the head and neck, particularly those arising in the oral and oropharyngeal regions, are considered radiosensitive, often demonstrating high rates of locoregional control26,8. The potential for novel targeted therapies warrants further investigation. For instance, c-kit (CD117) overexpression observed in an oral LEC case suggests that tyrosine kinase inhibitors such as imatinib and gleevec 22,8. Sheng Yun Lu et al (2005) described two general mechanisms of c-kit activation in tumor cells, including acquisition of activating mutations and autocrine or paracrine stimulation loops. Follow-up data from 17 cases, revealed that nearly all patients remained tumor-free after two years. Only 2 patients succumbed to death due to denying the advised treatment at critical stage of their disease. According to Ming Zeng et al (2014) LECs appear to exhibit an improved prognosis compared with other undifferentiated carcinomas with the 5-year survival rate has been reported to range from 50-90%.

**Conclusion**

Oral lymphoepithelial-like carcinoma (LELC) is a rare variant of head and neck squamous cell carcinoma, histologically resembling nasopharyngeal carcinoma (NPC). While NPC is strongly associated with Epstein-Barr Virus (EBV), oral LELC typically lacks EBV involvement. Some oropharyngeal cases may be linked to high-risk HPV, highlighting the need for p16 and HPV testing.LELC may arise from mucosal epithelium or minor salivary glands and often mimics lymphoproliferative disorders, making immunohistochemistry essential for accurate diagnosis. Treatment usually involves surgical excision with neck dissection and radiotherapy, often achieving good locoregional control. Prognosis is generally favourable with timely and appropriate treatment. Additionally targeted therapies such as tyrosine kinase inhibitors may often benefit in selected cases.

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