


# Epstein-Barr Virus–Associated With Lymphoepithelial Carcinoma: A Rare Tumor of the Larynx

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**ABSTRACT:** Lymphoepithelial carcinoma of the larynx is a rare tumor, as this histological entity is mostly diagnosed in nasopharynx. However, it may be present in other non-nasopharyngeal sites and it is extremely rare in the larynx. The authors present a case of a 59-year-old man who presented to the Otorhinolaryngology–Head and Neck Surgery Department complaining of a long-standing dysphonia, odynophagia, and dysphagia. The clinical examination revealed a laryngeal tumor involving the right epiglottis, right aryepiglottic fold, and ipsilateral false vocal fold. It presented with ipsilateral neck lymph node extension. Multiple biopsies of the laryngeal lesion were performed under local anesthesia and the histological examination showed a poorly differentiated squamous cell carcinoma. After discussing the case in a multidisciplinary tumor board, a total laryngectomy with a bilateral neck dissection was performed and the histological specimen showed a lymphoepithelial carcinoma. Although immunostaining with LMP-1 antibody was negative, in situ hybridization for Epstein-Barr virus was positive. He underwent adjuvant chemoradiation. He is now at 9-months follow-up period, with no evidence of disease. Lymphoepithelial carcinoma of the larynx is an extremely rare disease, with an aggressive pattern. Epstein-Barr virus–associated lymphoepithelial carcinoma has been exceptionally reported. A correct diagnosis and close collaboration with pathologist is crucial to achieve the best treatment strategy. We present this case to discuss the clinical and histology findings and the different therapeutic aspects of this uncommon histological subtype carcinoma.

**KEYWORDS:** Lymphoepithelial carcinoma, Epstein-Barr virus, larynx

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## Introduction

Lymphoepithelial carcinoma (LEC) of the larynx is a neoplasm that is located in most of the cases in the nasopharynx, where it represents 40% of all tumors.<sup>1,2</sup> In the nasopharynx, it is generally associated with the presence of Epstein-Barr virus (EBV).<sup>2</sup> However, even more rarely, this tumor can originate in other sites, such as the lungs, stomach, salivary glands, and thymus,<sup>3–5</sup> the larynx being an extremely rare location.<sup>6</sup> This type of tumor constitutes only 0.2% of all larynx malignant tumors.<sup>3,7,8</sup> Although a variety of nomenclatures, such as undifferentiated carcinoma of non-nasopharyngeal type, undifferentiated carcinoma with lymphoid stroma, lymphoepithelial-like carcinoma, lymphoepithelioma, and LEC,<sup>9,10</sup> have been used for non-nasopharyngeal LEC, the term lymphoepithelial carcinoma is the one approved by World Health Organization.<sup>11</sup>

The authors present this rare clinical case of EBV-associated LEC of the larynx to discuss clinical and histological findings and the different therapeutic aspects of this uncommon carcinoma subtype.

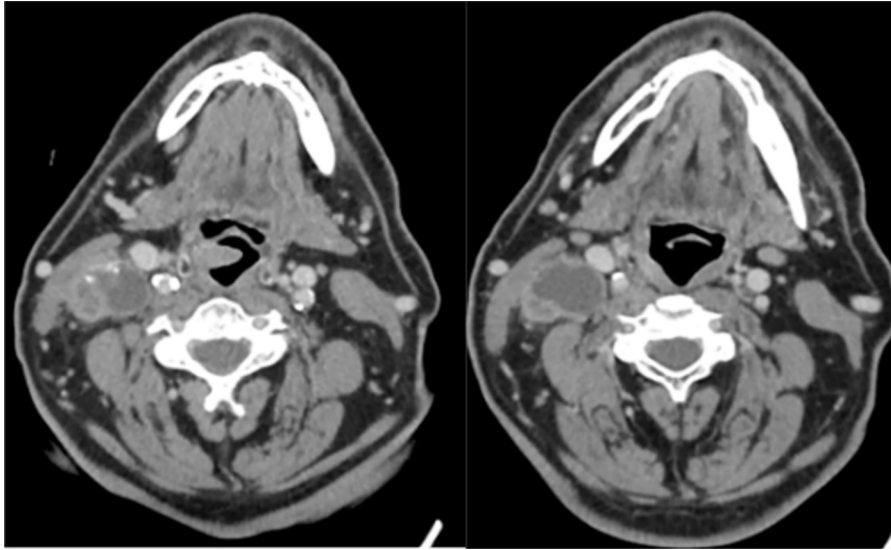
## Clinical Case Presentation

We present a case of a 59-year-old man, smoker (30 smoking pack-year), who presented to the Otorhinolaryngology–Head and Neck Surgery Department with a 8 months history of progressive dysphonia, odynophagia, and dysphagia. At nasopharyngeal and

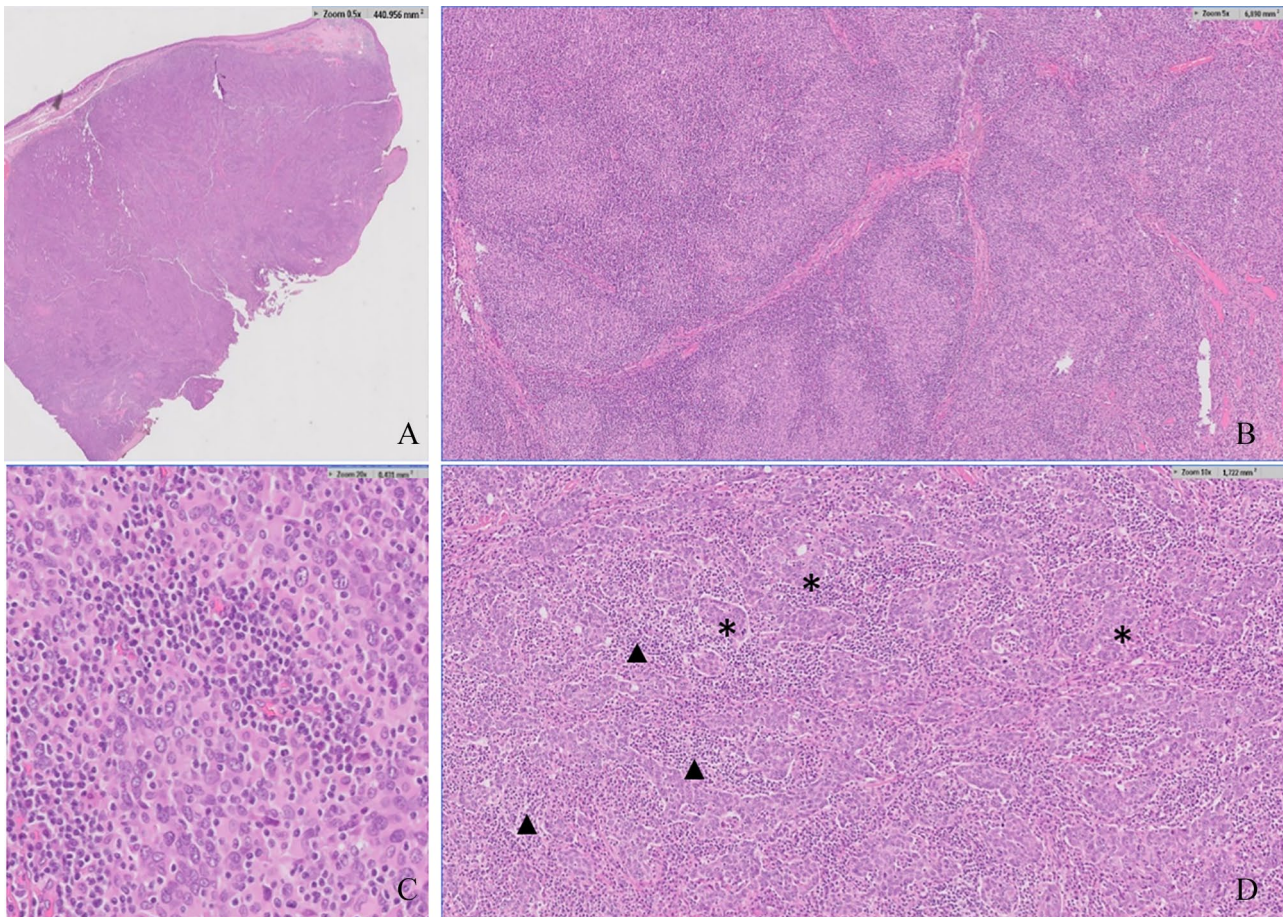
laryngeal endoscopy, a nonulcerated supraglottic neof ormation that extended from laryngeal part of right epiglottis to ipsilateral arytenoid epiglottic fold (both medial and lateral parts), false vocal fold, and ventricle were noticed. Neck examination revealed firm enlarged lymph nodes on ipsilateral side at levels II to III. Computed tomographic (CT) scan of the neck showed a right laryngeal tumor (24 mm × 21 mm dimensions) with necrotic lymphadenopathy (35 mm × 27 mm dimensions; Figure 1). The thorax CT scan excluded distant metastasis. The positron emission tomographic scan only revealed an increased fluorodeoxyglucose uptake in the right larynx and in lymph nodes located in the right II and III areas of the neck. Multiple biopsies of the laryngeal lesion were performed under local anesthesia and the histological examination showed a poorly differentiated squamous cell carcinoma (cT2N2bM0). After discussing the case in a multidisciplinary tumor board, a total laryngectomy with a bilateral neck dissection was performed. On the left side, 41 lymph nodes were isolated, none of them with metastases. On the right side, 2 in 21 lymph nodes were metastatic, with extracapsular spread. The histopathologic study of the surgical specimen revealed a poorly differentiated carcinoma (pT2N3bM0) exhibiting an expansive growth pattern B and epithelial nests in a dense lymphoid stroma (Figure 2).

Although immunostaining with later membrane protein (LMP-1) antibody was negative, in situ hybridization for





**Figure 1.** Right supraglottic neof ormation with ipsilateral necrotic lymphadenopathy.

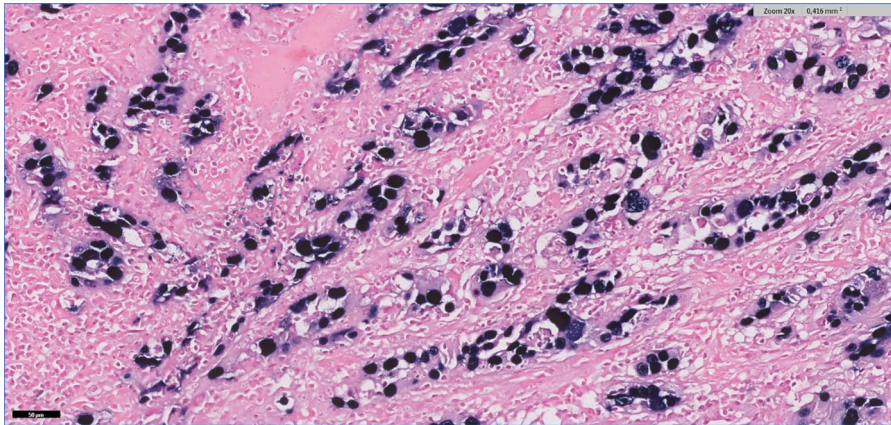


**Figure 2.** Lymphoepithelial carcinoma (hematoxylin-eosin): (A) poorly differentiated carcinoma exhibiting an expansive growth pattern (original magnification  $\times 0.5$ ), (B) epithelial nests in a dense lymphoid stroma (original magnification  $\times 5$ ), (C) large magnification showing epithelial cells with evident eosinophilic cytoplasm and irregular nuclei with prominent nucleoli—there is no evident keratinization (original magnification  $\times 20$ ), and (D) epithelial cells (asterisk) with a syncytial growth pattern and numerous lymphocytes (arrowhead) (original magnification  $\times 10$ ).

Epstein-Barr virus-encoded RNA (EBER) was positive (Figure 3). The patient underwent adjuvant chemoradiotherapy with

radiosensitizing cisplatin. He is currently on clinical surveillance, showing no signs of active disease (at 9 months of follow-up).





**Figure 3.** Hybridization *in situ* technique – EBER positive; Type of stain – EBER Roche ©, magnification 200x.

## Discussion

Lymphoepithelial carcinoma of the larynx is an extremely rare and aggressive tumor with a great propensity for cervical lymph node and distant metastasis.<sup>2</sup> Lymph node metastases at diagnosis are present in 75% and systemic metastases are present in 29% of cases.<sup>3</sup> It represents, nowadays, only 0.2% of all laryngeal cancers<sup>2</sup> and generally affects men in the fifth to sixth decades.<sup>3,8</sup> This type of cancer usually originates from supraglottic region, around the ventricles or involving epiglottis<sup>2,8,12</sup> and the patients frequently present with dysphagia and hoarseness as main symptoms.<sup>13</sup> In our case, the tumor was occupying the right supraglottis and the medial part of pyriform sinus and was accompanied by ipsilateral enlarged lymph nodes in II and III neck areas.

The diagnosis can sometimes be challenging as the tumor may grow from hidden submucosal sites.<sup>9</sup> Macroscopically, the LEC of the larynx is similar to that of the nasopharynx but it differs from the latter as it is less likely to harbor EBV.<sup>2</sup> In our case, immunostaining with LMP-1 antibody was negative but “*in situ*” hybridization for Epstein-Barr virus (EBER) was positive. Epstein-Barr virus serology was in favor of old EBV infection (negative anti-VCA IgM, positive anti-VCA IgG, positive anti-EBNA IgG). The expression of p16 was negative. The diagnosis considered was that of EBV-associated LEC of the larynx. At histological examination, lymphoepithelial carcinoma is similar to the nasopharyngeal primary, because it comprises solid sheets of malignant epithelial nest cells intimately intermingled with a prominent lymphoid stroma and plasma cells.<sup>2,9</sup> A component of epidermoid carcinoma corresponding to 10% to 75% can be seen in about half of the cases.<sup>9</sup> In our case, the histopathology identified a poorly differentiated carcinoma exhibiting an expansive growth pattern B with epithelial nests with a syncytial growth pattern in a dense lymphoid stroma. A component of squamous cell carcinoma was also identified. Nowadays, the pathogenesis of laryngeal LEC remains controversial and current results suggest that EBV plays a limited role in the etiology of laryngeal LEC.<sup>14</sup> The role of EBV, nowadays

largely associated with nasopharyngeal LEC, is much more controversial in extra-nasopharyngeal cases.<sup>13,15–17</sup> Only LEC of the salivary glands, thymus, lung, and stomach has been linked to EBV infection.<sup>5,13,16,18</sup> MacMillan et al<sup>8</sup> have studied and characterized 8 cases of laryngeal LEC and reported that none of them were associated with EBV infection and suggested that the association between the presence of EBV and laryngeal LEC is limited to individuals of non-Asian descent. After this, Marioni et al<sup>3</sup> showed that EBV plays a limited role in the etiology of laryngeal LEC. The association of smoking habits and LEC is different in laryngeal and nasopharyngeal sites. In the former, smoking may play a role; however, in the latter, it does not seem to represent a risk factor.<sup>1,9</sup>

Regarding the treatment, laryngeal LEC is a radiosensitive pathology and excellent control rates can be accomplished with radiotherapy.<sup>2,9</sup> Chemotherapy plays a role ensuring a better distant disease control when patients have metastatic neck disease at time of diagnosis.<sup>3,4,8</sup> It is, however, difficult to compare staging, survey, and adequate treatment modalities due to its rarity. In our clinical case, the patient was subject to a total laryngectomy and bilateral neck dissection and adjuvant chemoradiotherapy. At 9 months of follow-up, there is no evidence of local disease or distant metastasis. This can suggest that both surgery and chemoradiation can be useful in the treatment approach of locoregional disease. To our knowledge, we therefore report the sixth case of EBV-associated LEC of the larynx.

## Conclusions


Larynx lymphoepithelial carcinoma is a rare epithelial tumor with an aggressive pattern. The microscopic features are similar to those in nasopharyngeal location; however, the role of EBV cannot be determined yet due to the rarity of this tumor and also the absence of EBV in most of the cases. We report a very rare case of an EBV-associated LEC of the larynx. The diagnosis must be based on immunohistochemistry and “*in situ*” hybridization technique.

A correct diagnosis and a close collaboration with the pathologist is crucial to achieve the best treatment strategy.

### Author Contributions

FM wrote the manuscript and participated in the surgery. HB did the histological analysis and reviewed the manuscript. LR, Manuel Sousa, Edite Ferreira participated in the surgery and reviewed the article. PO, MGDA and AC have reviewed the article.

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