

# Lymphoepithelial carcinoma of the larynx: An unusual response to EXTREME regimen therapy. A new option for treatment?

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## Abstract

Lymphoepithelial Carcinoma (LEC), an aggressive variant of Squamous Cell Carcinoma (SCC), is an undifferentiated carcinoma with an intermixed reactive lymphoplasmacytic infiltrate. Most cases of LEC occur in the nasopharynx, while it rarely involves other sites. LEC of larynx and hypopharynx is an extremely rare and aggressive neoplasm, characterized by a high propensity to loco-regional dissemination and a poor prognosis; it represents the 0,2% of all tumours of the larynx. Since it is such a rare tumor, the current literature provides only recommendations and there are no treatment guidelines available. A 70-year-old man with laryngeal LEC and both distant and nodal metastases was treated with chemotherapy, following EXTREME regimen therapy. It was classified as a cT3 N3b M1 glottic cancer (Stage IVC, AJCC 8th Ed.), stage IVC. As the response on metastases was unexpectedly encouraging, surgical treatment on T could be performed. Patient underwent to total laryngectomy and bilateral neck dissection. To date, eight

months after surgery, the patient is disease free. The unusual clinical course is reported.

## Introduction

Lymphoepithelial Carcinoma (LEC) is a rare malignant tumor composed by undifferentiated and non-keratinizing epithelial cells that possesses a characteristic non-neoplastic lymphoplasmacytic infiltrated stroma.<sup>1,2</sup>

LEC is significantly associated with Epstein-Barr Virus (EBV);<sup>3-6</sup> it shows an endemic distribution, reaching the greatest incidence in Southeast Asia. LEC most commonly affects the nasopharynx and very rarely involves anatomical sites other than Waldeyer's tonsillar ring.<sup>7-9</sup> LEC of the larynx and hypopharynx represents 0.2% of all cancers of the larynx and is very aggressive,<sup>7,10</sup> with loco-regional dissemination and lymph nodes metastases, that occur in 75% of cases. The prognosis is poor: five-year survival is estimated to be around 60% and patients show a median Overall Survival (OS) of less than 1 year.<sup>11-14</sup> Alcohol and tobacco consumption do not seem to be risk factors for the development of LEC. Mean patient age is 62-years-old and male are more often affected than women (3:1 ratio is reported).<sup>14-16</sup>

As far as non-nasopharyngeal LEC is an extremely rare tumor, no treatment protocol is available nowadays: only small series or anecdotal cases can be found in English literature.<sup>17,18</sup>

LEC can hide in submucosal sites, which can delay and make diagnosis difficult.<sup>10,19,20</sup> The biopsy must take a representative specimen in order to allow performing immunohistochemistry on the tissues, which is helpful in discovering the diagnosis, especially when the tumor is undifferentiated.<sup>21,22</sup>

From the histologic point of view, LEC presents non-neoplastic lymphocytes and plasma cells along with islands of malignant epithelial cells.<sup>23,24</sup>

Possible differential diagnoses include neuroendocrine carcinoma, alveolar and embryonal rhabdomyosarcoma, the most common types of non-Hodgkin's lymphoma, mucosal melanoma and laryngeal large cell neuroendocrine carcinoma.<sup>23,25,26</sup>

Radiotherapy appears to be the most appropriate conservative treatment for LEC,<sup>27-29</sup> therefore, surgery is considered for locally advanced tumours. Ibrahimov *et al.* have recommended adjuvant chemotherapy for cases where surgery cannot be performed, but the effectiveness of chemotherapy on this tumor has yet to be demonstrated.<sup>30</sup>

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## Case Report

We report a case of a 70-years-old man first presented in August 2019, with a history of hoarseness and increasing neck lump. At flexible fiberoptic laryngoscopy, a submucous lesion involving the anterior third of both the vocal folds and the anterior commissure was identified. Mobility of the right vocal fold was affected. Respiratory space was preserved. The lesion did not involve the hypo glottis or dislocate the trachea. The remaining physical examination was negative.

MRI and PET were performed to stage the disease and to plan treatment. MRI showed the presence of a glottic neof ormation extending to the anterior commissure

and to both vocal cords anteriorly. Bilateral massive infiltration of the lower paraglottic space was reported, without infiltration of the thyroid cartilage. Several right lymph node levels in the neck appeared pathological.

A hypermetabolic neoplasm at the laryngeal level, lymph node metastases at the right laterocervical and mediastinal level, and also a hypermetabolic lytic alteration of the dorsal spine were found in PET images (Figure 1A).

In September 2019, incisional biopsy of the laryngeal lesion was performed under general anesthesia. Histopathologic study of all specimens demonstrated lymphoepithelioma of the larynx (Figure 2). Serological tests for antibodies specific for Epstein-Barr Virus (EBV) antigens were negative.

Considering the clinical staging of the tumour (Stage IVC: T3 N3b M1, AJCC 8<sup>th</sup> Ed.), after multidisciplinary Disease Management Team (DMT) evaluation, the patient underwent systemic chemotherapy.

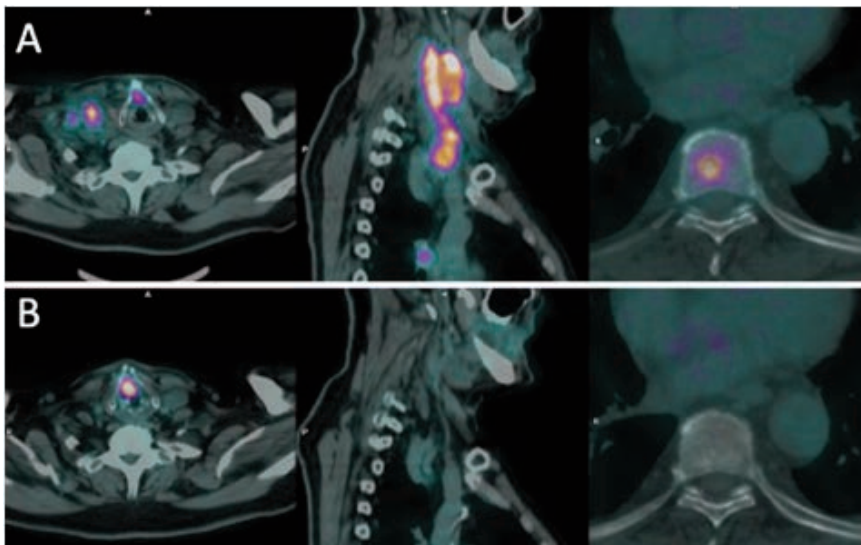
Consequently, patient was addressed to EXTREME regimen therapy (cisplatin, cetuximab and fluorouracil),<sup>31</sup> recommended as the standard care for recurrent/metastatic head and neck cancer not eligible for surgery or chemotherapy with curative intent, accordingly to NCCN guidelines (2018).<sup>32</sup> Vermoken *et al.* in 2008 demonstrated that survival can be significantly increased from 7.4 to 10.4 months by adding Cetuximab to 5-fluorouracil and cisplatin/carboplatin (the EXTREME regimen).<sup>33</sup>

In line with scheduled follow-up, 6 months from the first cycle of chemotherapy administration, PET-CT scan was performed: the patient was still alive with disease and showed an optimal response in terms of distant disease and lymph nodes while being stable in terms of the T stage of tumor cT3N0M0 (AJCC 8<sup>th</sup> Ed) (Figure 1B).

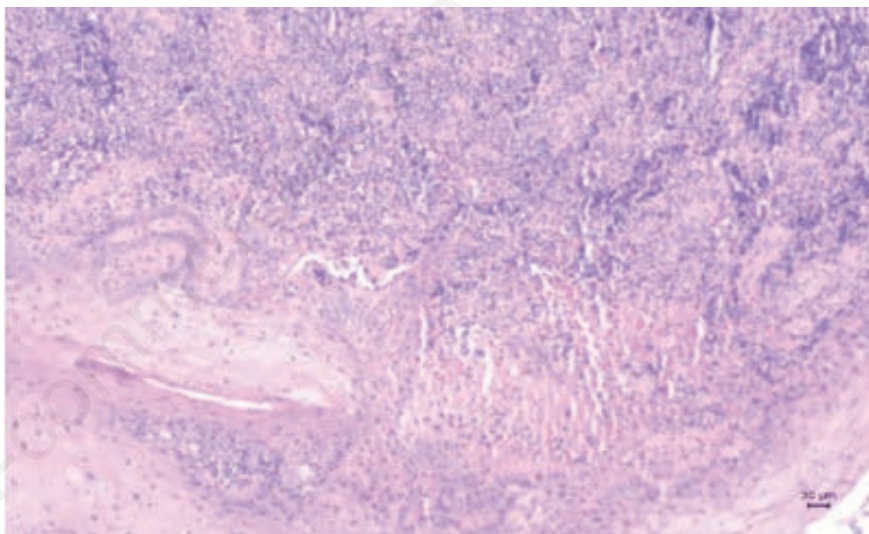
Our patient showed a complete response of M and became eligible for surgery on T and N, remaining disease-free at mid-term follow up.

Considering the improvement in the clinical picture, it was possible to perform a total laryngectomy with bilateral selective dissection of the neck.

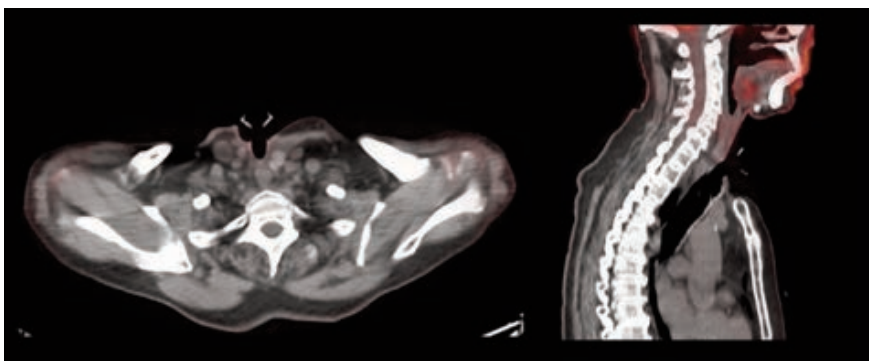
Histopathological analysis confirmed laryngeal LEC, describing solid sheets or irregular islands of malignant epithelial cells with indistinct cell borders, round to oval vesicular nuclei, and a single and large central nucleoli. Solid pattern was intimately intermingled with prominent component of non-neoplastic lymphocytes and plasma cells.



**Figure 1.** PET-CT scan: A) pre-treatment imaging; B) scan imaging post EXTREME therapy. The metabolic activity showed on bone and laterocervical lymph node, is absent after the EXTREME regimen. FDG is seen on Larynx.



**Figure 2.** Hystologic specimen: hematoxylin and eosin staining, original magnification. Solid sheets or irregular islands of malignant epithelial cells with prominent component of non-neoplastic lymphocytes and plasma cells.



**Figure 3.** PET-CT at eight months follow up after surgical treatment. No evidence of disease (NED).

The staging after histological examination was found to be pT3 pN0 (AJCC 8<sup>th</sup> Ed) with negative margins. According to NCCN 2020.1 guidelines, no adjuvant radiotherapy was performed. To date, eight months after surgery, the patient performed a PET-CT (October 2020), which was negative for persistence or recurrence of disease (Figure 3).

According to the EXTREME scheme, our patient received indication to continue treatment with Cetuximab as maintenance.

## Discussion

At the present day, standardized chemotherapy protocols are not available for LEC treatment, a rare but aggressive neoplasm.<sup>34</sup> Some studies suggest that LEC could be considered an “adverse feature”: prognosis for LEC patients is poor compared to neoplasm equal for T and N, in so far as five-year survival is estimated to be around 60% and the median overall survival is less than 1 year.<sup>11-13</sup>

It has been estimated that almost 87% of patients receive diagnosis of LEC already with local or lymph nodes metastases, so that are eligible for EXTREME regimen.<sup>35</sup>

The standard regimen is administered in line with the following therapeutic scheme: i) Cetuximab 400 mg/mEq on first administration and then 250 mg/mEq on days 1, 8 and 15 and then repeat on day 21; ii) Cisplatin 100 mg/mEq in single administration and then repeat on day 21 (an alternative may be 20 mg/mEq for 5 consecutive days and then repeat on day 21); iii) Fluorouracil (5-FU) 200 mg/mEq on days 1, 2, 3, 4, 5 and then repeat after 21 days.

Cisplatin dosage is modifiable, in consideration of the age, clinical condition and renal function of the patient. Another variant is the use of carboplatin instead of cisplatin, which has shown less renal toxicity and similar efficacy.<sup>33</sup>

On the other hand, for nasopharynx lymphoepithelial-like tumours, the EBV-related cytotype, chemotherapy is indicated in addition to radiotherapy.<sup>36</sup>

As regard EBV theme, the EBV-LEC relationship have been proposed being crucial in lymphoepithelioma by virtue of an established association between EBV and nasopharyngeal carcinomas. However, the relationship between LEC that occur outside of the nasopharynx and EBV infection remains controversial.

Even though many question marks still remain, several researches are underway to improve the clinical outcomes of this kind

of patient, looking for less toxic and equally effective treatment protocols.

## Conclusions

In our institution we have recently treated an extremely rare case of lymphoepithelial carcinoma of the larynx.<sup>37-39</sup> The patient had come to our attention at an advanced stage (stage IVC, AJCC 8<sup>th</sup> Ed) so we opted for a chemotherapy-only treatment with EXTREME regimen, as suggested by the poor recommendations in the literature on lymphoepithelial carcinoma.

The unexpected effectiveness of this treatment on distant metastases allowed surgical treatment on the primary neoplasm and, after eight months, the patient is still alive free from disease.

To our knowledge, this is the first case of metastatic LEC to achieve such excellent results with chemotherapy treatment followed by surgery.<sup>40</sup>

In light of the surprising and remarkable response of metastases in our case to EXTREME treatment, we suggest considering it as induction chemotherapy and we recommend it in similar cases.

Further studies are needed to validate chemotherapy-regimen as a neoadjuvant therapy and assess its efficacy also in the management of LEC-like EBV-related nasopharynx tumours,<sup>41</sup> even though the rarity of cases makes it harder to produce strong evidence. It still remains an interesting conundrum for research.

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