

# First Case Report of Bilateral Parotid Lymphoepithelial Carcinoma

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**Abstract.** *Background/Aim:* The parotid is the largest salivary gland and is located anteriorly to the sternocleidomastoid muscle and laterally to the ramus of the mandible. Neoplasms in this gland are relatively rare, with 80% being benign and 20% malignant, primarily represented by mucoepidermoid carcinoma. In the head and neck region, lymphoepithelial carcinoma (LEC) accounts for 0.4% of malignant salivary gland tumors. *Case Report:* A 35-year-old man with no previous comorbidities was admitted to a Head and Neck Surgery Specialty Service for a painless right cervical mass of uncertain growth. Extensive diagnostic investigation revealed involvement of the contralateral parotid, associated with systemic lymph node enlargement. Thus, adjuvant radiotherapy

was decided by the treating team. *Conclusion:* This case confirms the heterogeneous features and distinctive behavior that the disease can present, as seen with bilateral parotid LEC.

The salivary glands comprise three pairs of major glands and small other accessory glands scattered throughout the submucosa of the upper aerodigestive tract. Mostly located along the buccal, lingual, and palatal regions are the submandibular, sublingual, and the biggest gland, the parotid (1, 2). Salivary gland neoplasms represent a heterogeneous group of diseases with varied characteristics and distinct biological behaviors (3).

The parotid, the largest salivary gland, is located anteriorly to the sternocleidomastoid muscle and laterally to the ramus of the mandible. It is responsible for producing about 30% of the salivary secretion in the oral cavity, which is serous, aqueous, and enzyme-rich (4). Furthermore, 80% of the neoplasms that affect the parotid gland are benign, mostly corresponding to pleomorphic adenoma. Malignant neoplasms affect about 20%, most commonly represented by mucoepidermoid carcinoma (1, 3).

Lymphoepithelial carcinoma (LEC) is a rare, poorly differentiated tumor, accounting for less than 1% of salivary gland neoplasms. First described by Hilderman in 1962, LEC is a malignant tumor of the salivary glands that presents as an undifferentiated carcinoma, revealing a stroma infiltrated by plasma cells and lymphocytes (2, 4-6).

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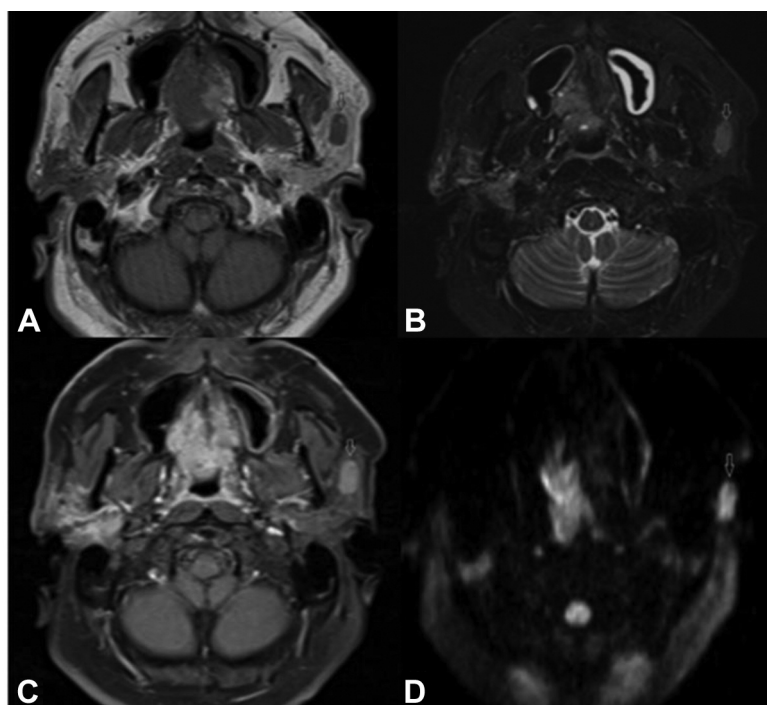


Figure 1. Circumscribed focal lesion within the left parotid gland, showing low signal on T1, high on T2, with contrast uptake and diffusion restriction suggesting aggressive solid neoplastic lesion (hollow arrow). A) T1 without contrast, B) T2 with fat suppression, C) T1 post contrast, D) Diffusion.

It was first cited in 1991 as "undifferentiated carcinoma with lymphocyte in its stroma" by the World Health Organization (WHO) histological classification, without a distinguishing feature. However, it was only in 2017, in the fourth edition of the WHO, that the new distinct and different description of this pathology was recorded (3, 5, 7, 8).

LEC has a certain histological similarity with undifferentiated nasopharyngeal carcinoma (NPC) and can also affect other organs, such as the lung, stomach, ovary, uterus, renal pelvis, bladder, and skin (2, 5, 7). In the head and neck region, LEC is primarily found in the nasopharynx, and then in the salivary glands, tonsil, thymus, larynx, and soft palate (3). LEC accounts for 0.4% of malignant salivary gland tumors, preferentially affecting the parotid and then the submandibular gland (4, 7).

Patients with LEC usually present with a unilateral parotid nodule of uncertain duration. Pain may be associated. 20% of cases present with facial nerve palsy and 40% with cervical lymphadenopathy and also, 20% of patients may develop distant metastases, approximately after three years of treatment. The main sites affected are the lungs, brain, bone, and liver (4).

The physical examination of the head and neck should be thorough. Complementary imaging exams, such as computed tomography (CT) and magnetic resonance imaging (MRI) characterize the nodule in size and appearance. Cytological sampling by fine needle aspiration (FNA) can be performed to better elucidate the diagnosis (2, 4, 6).

Evaluation of the upper respiratory tract and digestive tract should be performed: Nasopharyngoscopy with biopsy targets the primary site in the nasopharynx. FNA of the cervical nodule can differentiate between primary parotid LEC or metastasis of NPC (4, 6). Furthermore, immunohistochemistry is used to diagnose LEC, the panel being positive for pancytokeratin, CK5/6, P63, P43; negative for melanoma and lymphoma tumor markers (5).

In the present paper, we present a case of LEC characterized by bilateral parotid nodulation and systemic reactive lymph nodes.

### Case Report

A 35-year-old man with no previous comorbidities was admitted to a Head and Neck Surgery Specialty Service for a painless right cervical mass of uncertain growth. Physical examination revealed a mass on the right parotid topography, without palpable cervical lymph nodes. Ultrasonography (US) of the parotid revealed two expansive lesions within the right parotid, measuring about (2.6×1.5 cm) and (1.9×0.7 cm). In addition, a biopsy of the nodular lesion of the right parotid was performed, which showed a dense proliferation of small lymphoid cells, with lymphoepithelial lesions permeated by squamous cell blocks with moderate nuclear pleomorphism, as well as the presence of focal necrosis and

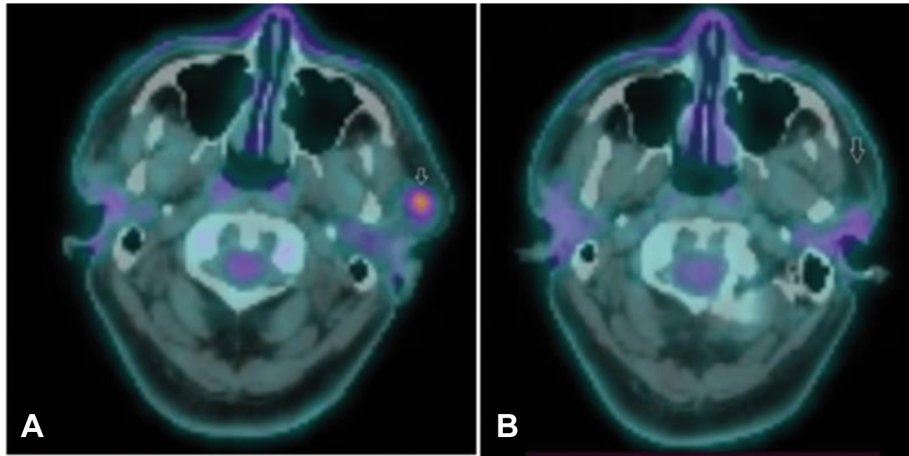


Figure 2. Left parotid lesion with significant radiopharmaceutical uptake on PET-CT performed before surgical intervention (A) and after parotidectomy (B).

absence of lymphovascular invasion. The patient underwent right parotidectomy and the contents were evaluated by immunohistochemistry, confirming LEC. After about two months, post-surgical control was performed with a contrast-enhanced MRI of the face, which showed two nodular lesions compromising the left parotid gland, with enhancement, measuring approximately (1.6×0.9×0.9 cm) and the other (0.9×1.5×0.7 cm) (Figure 1). Also, an ultrasound showed hypoechoic lesions, one measuring (1.5×0.7 cm) with lobulated contours and with internal flow on Doppler, and another measuring (1.0×0.8 cm) with regular contours and with peripheral flow on Doppler, inside the left parotid.

To complement the diagnosis, the patient was submitted to video pharyngolaryngoscopy, which showed a hypertrophic image of inferior concha suggestive of lymphoid tissue, partially occluding the tubal torus; biopsy revealed a chronic inflammatory process with absence of neoplasia. A positron emission tomography-CT (PET-CT) scan was subsequently ordered, and the results showed the following: elevated glycolytic metabolism in hypodense nodular lesions in the left parotid, infracentimetric level II cervical lymph nodes on the right, in axillary lymph nodes on the right (1.5×1.0 cm) and left (1, 2 cm×0.8 cm), in inguinal lymph nodes on the right (1.2 cm) and left (1.0 cm), with nodular densification subcutaneous of the right iliac region and left gluteal region, and in the gastric chamber diffusely (Figure 2), given the suspicion of the disease's systemic behavior. Subsequently, FNA of the nodule in left parotid was performed, with the inconclusive result of paucicellular cellularity, composed of rare epithelial cells. In this context, the patient underwent a subtotal parotidectomy with preservation of the facial nerve, without complications.

The anatomopathological study showed an atypical epithelioid proliferation permeated by a dense lymphoid

infiltrate. The immunohistochemical study showed that the atypical epithelioid cells were positive for CK AE1/AE3, CK34BE12, and p40, confirming squamous differentiation. Evaluation of the lymphoid infiltrate for the markers CD3, CD20, Bcl-2, Bcl-6, CD5, CD23, and CD43 showed its polyclonal character. There was no labeling for CK7, SOX-10, and anti-EBV LMP (Figure 3).

After three months, a video pharyngolaryngoscopy was again performed, which showed granulation on the posterior wall of the left nasopharynx with no signs of tumor lesion. In addition, a PET-CT with FDG-18F was performed, showing little radiopharmaceutical enhancement in the level II cervical lymph nodes bilaterally (short axis 0.8 cm), bilateral axillary lymph nodes (short axis up to 1.1 cm), bilateral inguinal lymph nodes (short axis up to 1.3 cm), and densification subcutaneous of the right inguinal region. Thus, adjuvant radiotherapy was decided upon.

## Discussion

Salivary gland tumors (SGTs) affect around 2-6% of all HN cancers and 59% are located at the parotid gland, followed by minor (32%) and submandibular (8%) salivary glands. There was a peak of SGTs involvement being observed in people between the fourth and seventh decade of life (approximately 69% of the cases analyzed) (9). According to the WHO, LEC is a rare tumor with cellular features similar to non-keratinized NPC, with an undifferentiated subtype. Common positive immunohistochemical markers include pancytokeratin, CK5/6, P63, and P40 (10).

In the UK and USA, regions not endemic for Epstein-Barr Virus (EBV), the prevalence of this type of tumor corresponds to 0.3-0.7% of malignant salivary gland tumors (6). In Brazil, there are no reports on the incidence of this

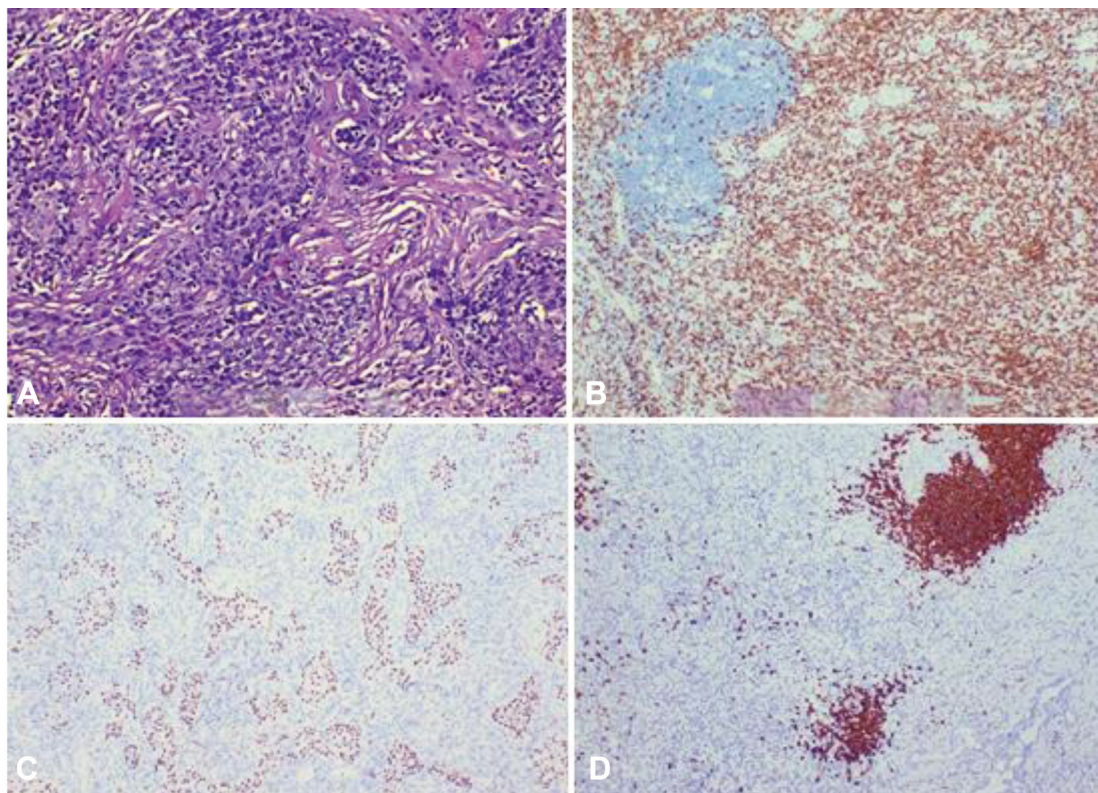


Figure 3. The anatomopathological study of parotid nodule. A) Infiltrates with a predominance of mature lymphocytes, amidst large epithelioid cells. B) Immunohistochemistry for CD3 showing predominance in the lymphoid infiltrate. C) Immunohistochemistry for p40 in tumor cells shows positive nuclear staining in p40 single-staining. D) Immunohistochemistry for CD20 showing nodular aggregates of B cells.

type of tumor. The patient in the present report does not have oriental ancestry or originates from EBV endemic regions.

EBV infection has a strong association with the development of LEC. As reported in the series of studies by Whaley *et al.* (2020), whites and blacks are part of a small proportion of affected patients, with no correlation with EBV infection. In this way, a complex genetic interaction is noted focusing on ethnic, environmental, and geographic factors (4, 11-13).

The aforementioned patient was a 35-year-old male without EBV infection. Patients from non-endemic regions for EBV infection are generally older, with a mean age of 59.3 years, and show no predilection for sex (13). Kim *et al.* (11) reported a greater association in women aged 40 years, which differs from the present report.

The most common presentation is the appearance of nodulation in unilateral parotid, with variable duration, and no metastatic lymph node presented (11). Lymph node metastasis is infrequently present in patient presentation (involvement present in 10-50% of cases), corroborating with the report by Topal and Erinanc (12).

In the current report, the appearance of nodules in the parotid topography occurred bilaterally, without involvement of lymph node metastasis. This presentation, however, is uncommon, with no clear reports in the literature. Topal and Erinanc (12) reported a patient from a non-endemic region for EBV with concomitant lesions in salivary gland structures: LEC in the parotid and a pleomorphic adenoma in the contralateral submandibular gland.

The diagnosis of LEC was made by a complementary study with immunohistochemistry. FNA of the parotid nodule only revealed paucicellular cytology without atypia. In the present case, only after the first surgical approach was the exact diagnosis made. Immunohistochemistry showed carcinoma with squamous differentiation and associated dense lymphoid infiltrate, corroborative of LEC, measuring 1.5×1.0 cm. Histological presentation was compatible with several studies in the literature (4, 6, 8, 12, 13).

The therapeutic management of salivary gland cancer depends mainly on the staging and degree of aggressiveness of the disease. In an analysis of 47 patients with SGTs who underwent adjuvant radiotherapy compared to adjuvant chemotherapy, it was observed that staging is the most

important factor in indicating the prognosis of the disease (14). However, other factors, such as the possibility of development and dissemination of the tumor, as well as the general health status of the patient, may also be important in defining the management to be practiced.

When it comes to malignant lymphoepithelial lesions of the major salivary glands, surgical treatment associated with postoperative radiotherapy is the main treatment employed (2). Chemotherapy is not consensual (10, 12, 13, 15). Nakano and collaborators (2022) retrospectively identified 19 patients through a study who were treated with the EXTREME chemotherapy regimen (cisplatin/carboplatin, 5-fluorouracil plus cetuximab) for advanced-stage salivary gland cancer, where the best responses observed in this study were only partial responses observed in 2 cases (mucoepidermoid carcinoma and one of LEC), but even with this fact all cases had treatment discontinuation due to adverse effects (16).

Postoperative radiotherapy of the tumor bed and ipsilateral neck was recommended in this case, in order to eradicate the disease in the tumor bed and microscopic residual (2, 8, 13). In other conditions, radiotherapy may also be a sole treatment option when surgery is contraindicated or the patient refuses. However, it is not clear whether radiotherapy alone is as likely to eradicate the disease (15).

The prognosis of these patients differs. Barnes *et al.* (2005) cite a 5-year disease-free survival rate of 50% in localized disease, in those up to 60 years of age and of Caucasian ethnicity. Topal and Erinanc (12) cite that approximately 20% of patients develop distant metastasis within three years of treatment. The same analysis reports a 5-year survival rate of approximately 50-90%, which is consistent with the published literature, where a survival rate of 56% in Europe, 63% in Japan, and 77% in Taiwan has been demonstrated in patients with SGTs (specifically those located in the parotid gland) (17). The Wang *et al.* (2021) retrospective study of 12 Chinese patients reported a 5-year survival rate of approximately 39.4%. Despite this, LEC is presented as a tumor with better prognosis than other forms of undifferentiated malignant neoplasm of the salivary gland (8).

Topal and Erinanc (12) also reported some worse prognostic factors, such as: advanced stage of disease, mitosis rate, presence of anaplasia, and necrosis. According to the study by Soffer and collaborators (2021), surgery-radiation-chemotherapy, intraparenchymal extension, and tumor size >40 mm were prognostic factors (17). None of these criteria were present in the patient here presented.

## Conclusion

In conclusion, this case affirms the heterogeneous feature and distinctive behavior that the disease can present, as seen with bilateral parotid LEC.

## Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

## Authors' Contributions

Research Concept and design: WM, PR, AT, PA, JS, FM; Collection and/or assembly of data: WM, PR, HP, DA, AT, PP, MS; Data analysis and interpretation: VJ, HP, DA, PA; Writing the article: WM, PA, PP, JS, MS, GF; Critical revision of the article: WM, VJ, JS, GF; Final approval of article: WM, PA, JS, GF.

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