

## Case Report

# Primary lymphoepithelial carcinoma of the parotid gland with mild enhancement degree on CT scan and low Ki-67 value in northern China: a case report

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**Abstract:** Lymphoepithelial carcinoma (LEC) of the parotid gland is a rare malignant tumor of salivary gland. Previous reports have described a higher prevalence of this clinicopathological entity in southern Chinese, Japanese and Eskimo population. We report a 37-year-old man from northern China who presented with a parotid gland neoplasm. On computed tomography (CT), the largest cross section of the mass was 2.2 × 3.5 cm. Plain CT scan value was 24 HU-44 HU, and enhanced CT scan value was 36 HU-60 HU. Surgical resection of the right parotid gland tumor along with some peritumoral normal gland was performed. Histological examination showed an invasive growth pattern and an ill-defined tumor boundary. Tumor cells were of irregular shape and arranged in island pattern and funicular distribution. Tumor cell boundary was inconspicuous, mildly eosinophilic cytoplasm vesicular oval nuclei, empty chromatin bodies, and well-defined nucleoli. Extensive lymphocytic and plasma-cell infiltrate was observed in the fibrosclerotic tumor stroma accompanied by lymphoid follicle formation. Immunohistochemical examination showed positivity for CK5/6 (+), p63 (+) and Ki-67 (+ 15%); *in situ* hybridization showed positive EBER. Based on the characteristic histopathology a diagnosis of primary parotid LEC was made. The patient belonged to a non-endemic area and showed some distinctly different characteristics from those reported earlier. These include EBV positivity, a mild degree of CT enhancement, and low expression of Ki-67 (15%). This disease is relatively rare and is liable to be misdiagnosed. Further research is required to characterize this entity.

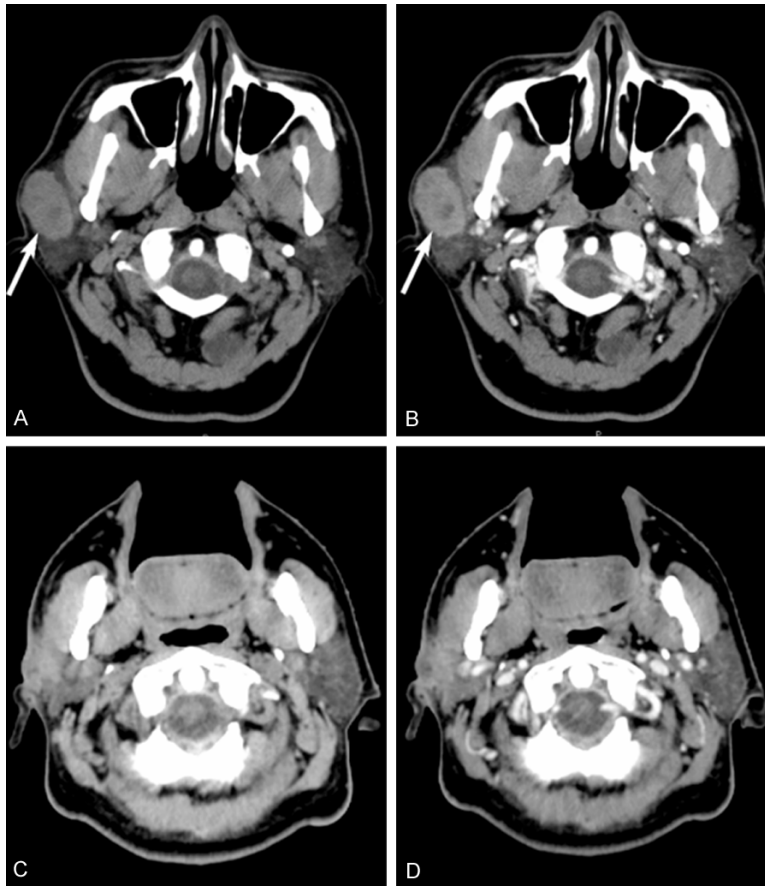
**Keywords:** Lymphoepithelial carcinoma of the parotid gland, mild enhancement degree on CT scan, low Ki-67 value, northern China, Epstein-Barr virus positive

## Introduction

Lymphoepithelial carcinoma (LEC) is a rare form of malignant tumor marked by extensive stromal infiltration of lymphocytes and plasma cells. Its histological characteristics are similar to those of undifferentiated nasopharyngeal carcinoma. LEC has been reported in the stomach [1], lungs [2], esophagus [3], liver [4], urinary bladder [5], skin [6], uterine cervix [7], endometrium [8], salivary gland [9] and thymus [10]. LEC of the salivary gland accounts for approximately 0.4% of all malignant tumors of the salivary gland, of which 80% occur in the parotid gland [11]. LEC of the parotid gland was shown to occur mainly in southern Chinese,

Japanese and Eskimo populations; cases from northern China have not yet been reported. In endemic areas, a vast majority of cases of LEC of the salivary gland are associated with Epstein-Barr virus (EBV) infection [12], while no such association has been reported in the non-endemic areas [13].

We present a 37-year-old man with LEC of the parotid gland, who resides in north China and had a parotid gland neoplasm for six years. The patient is from a non-endemic area and was EBV (+). A mild degree of CT enhancement and low expression level of Ki-67 (15%) observed in this case are also in contrast to previous reports.



**Figure 1.** CT radiographs of a 37-year-old man with LEC in the right parotid gland. A. An oval, well-defined and heterogeneous density with a low-density shadow inside the mass in the right parotid gland on plain CT scan (24 HU-44 HU; 2.2 × 3.5 cm; white arrow); B. On enhanced CT scan (36 HU-60 HU), an increment of 12 HU-16 HU (2.2 × 3.5 cm; white arrow) from plain CT is seen; C, D. No recurrence two months after the operation in plain and enhanced CT respectively. LEC, Lymphoepithelial carcinoma; CT, computed tomography; HU, Hounsfield unit.

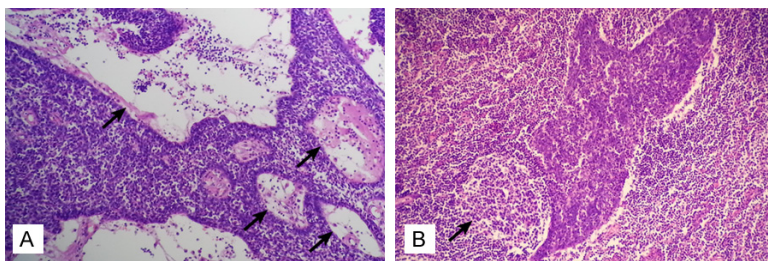
### Case report

A 37-year-old northern Chinese man was referred to us for evaluation of a painless right parotid mass. The patient volunteered that the mass was about the size of a thumb tip in 2009. As the mass was asymptomatic, he did not consent to undergo surgery. Although the mass grew slowly initially, a sudden growth was observed from December 2014 onwards. By April 2015, the mass had grown to the approximate size of a chicken egg. The patient's facial nerve function was intact. CT examination revealed an oval, well-defined right parotid gland with a heterogeneous density; a low-density shadow was observed inside the mass. The surrounding lymph nodes were not enlarged.

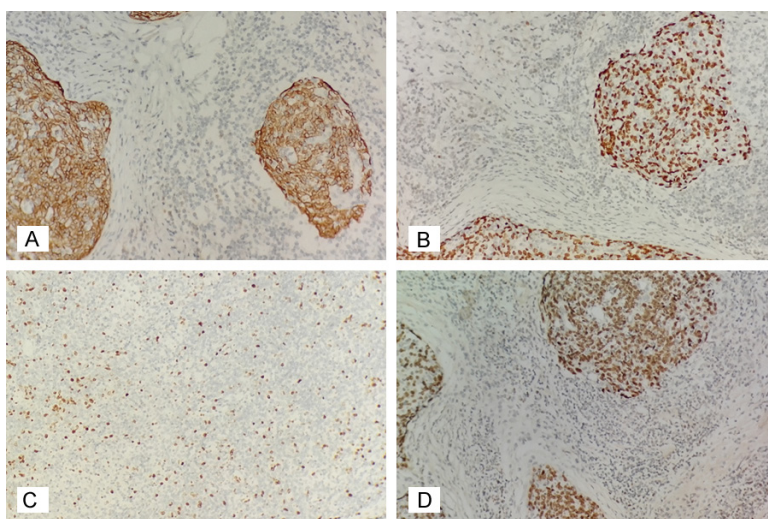
The largest cross section of the tumor was 2.2 × 3.5 cm. The plain CT scan value was 24 HU-44 HU (**Figure 1A**), and the enhanced CT value was 36 HU-60 HU (**Figure 1B**). Based on imaging findings, the mass was first considered to be a pleomorphic adenoma.

The patient also had cirrhosis of the liver ostensibly caused by hepatitis B virus infection and hypersplenism. Laboratory examination showed low white blood cell (WBC) and platelet counts ( $1.71 \times 10^9/L$  and  $31.00 \times 10^9/L$ , respectively). The patient was treated with subcutaneous injections of recombinant human granulocyte colony stimulating factor, platelet transfusions and splenectomy. As a result, his WBCs and platelet counts increased ( $6.87 \times 10^9/L$  and  $205.00 \times 10^9/L$ , respectively). The patient subsequently consented to undergo surgical resection of the right parotid gland tumor along with some peritumoral normal gland. Surgery was performed in August 2015. The size of the surgically resected specimen was 4 × 4

× 2.5 cm; the tumor size was 3 × 2.8 × 1.5 cm. The tumor mass was gray-colored, of a medium consistency and had focal areas of necrosis within the tumor. The boundary between the tumor and the parotid gland was not well-delineated. On light microscopy, the tumor cells were variably arranged as sheets, islands and funicular nests. The tumor cells were polygonal, spindle or irregular shape. Tumor cells were of a similar size with ill-defined cell boundary. The nuclei were oval or spindle shaped, vacuolated, showed prominent nucleoli and signs of nuclear fission. Signs of differentiation, intercellular bridges, adenoid structure and keratinization were not observed. Also seen were scattered tumor cell nests in an inflammatory infiltrate comprising predominantly of lymphocytes and



**Figure 2.** Histological examination of HE-stained section of surgical specimen. A. Tumor cell nests, extensive stromal infiltration of lymphocytes and plasma cells and formation of edematous cyst-like structures (black arrows; magnification  $\times 200$ ); B. Extensive lymphocytic and plasma-cell infiltration in the tumor stroma accompanied by lymphoid follicle formation (black arrow; magnification  $\times 200$ ). HE, hematoxylin-eosin.



**Figure 3.** Immunohistochemical examination of the carcinomatous component of the lesion. A. CK5/6 positive; B. p63 positive; C. Low-level expression of Ki-67 (15%); D. *In situ* hybridization for detection of EBV using Epstein-Barr encoded RNA (EBER) stain shows EBV positivity. (magnification A  $\times 200$ ; B  $\times 200$ ; C  $\times 100$ ; D  $\times 200$ ). EBV, Epstein-Barr virus.

plasma cells, interspersed with mildly edematous microcyst-like structures (**Figure 2A**). In addition, extensive stromal infiltrates comprising of lymphocytes and plasma cells were observed accompanied by lymphoid follicle formation (**Figure 2B**). Immunohistochemical examination showed: CK5/6 (+) (**Figure 3A**), p63 (+) (**Figure 3B**), Ki-67 (+15%) (**Figure 3C**), CD117 (-), CD5 (-), CK7 (-) and CK20 (-), EBV in situ hybridization (EBER) showed EBV (+) (**Figure 3D**). Based on histological characteristics and immunohistochemical staining, the patient was diagnosed as a case of primary LEC of the parotid gland. The patient accepted postoperative radiotherapy. Plain and enhanced CT exam-

ination performed in October 2015 showed no signs of recurrence (**Figure 1C, 1D**).

The present study was approved by the Ethics Committee at the First Affiliated Hospital of Dalian Medical University. Written informed consent was obtained from the patient for the publication of the case report along with the accompanying images.

## Discussion

The earliest description of a “malignant lymphoepithelial lesion” was published by Schminke in 1921 [14]. He described a nasopharyngeal neoplasm which comprised of anaplastic cells surrounded by lymphoid stroma. Subsequently, lesions with similar histological characteristics were identified in other organs, such as the stomach and lungs. Similar findings in the salivary gland were first reported in 1962 [15]. Malignant lymphoepithelial lesions of the salivary gland have been variably referred to as “lymphoepithelioma-like carcinoma”, “malignant lymphoepithelial lesion”, and “undifferentiated carcinoma with lymphoid stroma”. In

2005, the WHO [16] proposed a standard nomenclature, i.e., “lymphoepithelial carcinoma (LEC)” for this pathological entity. The diagnosis of LEC of the salivary gland is primarily histopathological, as clinical and imaging findings tend to be non-specific.

In the present case, the patient had a mass of the size of a “thumb tip” in the right parotid gland with no other symptoms. CT scan showed no remarkable characteristics and somewhat mimicked those of a pleomorphic adenoma. Further CT scans showed an enhanced CT value of 12-16 HU (an average of 14 HU). Zhang [17] conducted a quantitative analysis of CT



scan values in patients with LEC of the salivary gland; based on the degree of enhancement, they classified the CT values into three ranks: (i) mildly enhanced (post-enhancement increment in CT value <15 HU); (ii) moderately enhanced (15-30 HU); (iii) significantly enhanced (>30 HU). All seven cases of primary LEC of the salivary gland studied by Zhang showed significant enhancement. In contrast, the present case showed only mild enhancement. Histopathological findings for this case were typical of LEC of the salivary gland. Extensive stromal infiltration of lymphocytes and plasma cells, accompanied by formation of lymphoid follicles was observed. Immunohistochemical examination showed positivity for CK5/6 and p63 (+). These findings are consistent with the diagnosis of LEC of the salivary gland. We also carried out a Ki-67 immunohistochemical analysis in this patient. Ki-67, a substance found in the macromolecular protein in the cell nucleus, is highly sensitive to protease, and is a sensitive index of cell proliferation. In previous reports, Ki-67 levels in primary LEC of the salivary gland tended to be higher (40% to 80%) than those in secondary LEC of salivary gland (20%) [17, 18]. Although our patient had a primary LEC of the salivary gland and had no other salivary gland disease such as Sjögren syndrome, the Ki-67 level was low (15%). Indeed, it was lower than that of a secondary LEC (20%). Another distinct characteristic of this case was EBV positivity. Earlier reports of LEC of the salivary gland associated with EBV infection were confined to endemic areas [12], while no association with EBV infection was observed in non-endemic areas [13]. The present patient was a resident of northern China (non-endemic area) but was EBV (+). Further, appearance of microcysts in the tumor stroma is also a rare characteristic of this pathological entity.

In clinical settings, LEC of the salivary gland has been identified with the following diseases. (i) Metastases of nasopharyngeal carcinoma (NPC)-NPC has marked tendency to metastasize and invade [19], however, NPC rarely metastasizes to the parotid gland, but when this does occur, metastatic NPC and LEC of the salivary gland are difficult to distinguish on imaging and histopathology. In this case, the possibility of nasopharyngeal carcinoma metastasis was excluded by an otolaryngological specialist. (ii) Mucoepidermoid carcinoma:

This is the most common primary malignant tumor of the salivary gland. Histological characteristics include highly-differentiated mucous cells, epidermoid cells and intermediate cells, while poorly differentiated mucous cells are not obvious. Tumor cells were arranged in solid epithelial nests by squamous epithelium and intermediate cells. The findings of cellular heterotypic and nuclear fission are similar to that seen in squamous cell carcinoma; however, interstitial lymphocytic and plasma cell infiltrates and the presence of EBV infection is not consistent with mucoepidermoid carcinoma. (iii) Necrotizing sialometaplasia: Also referred to as salivary gland infarction, this is a benign condition with a tendency to self-heal. Histology shows salivary gland duct squamous metaplasia and the condition is liable to be misdiagnosed as squamous cell carcinoma. However, there is no cellular atypia and nuclear fission is rare. (iv) Benign lymphoepithelial lesion (BLEL) may cause unilateral or bilateral parotid enlargement; histology shows preservation of floccular gland structure, acinar atrophy, intralobular ductal hyperplasia and formation of solid clumps of epithelial cells; however, there is no cellular atypia and nuclear fission is not obvious. The lesion may show intra- and inter-lobular lymphocytic and plasma-cell infiltrate.

We report a case of LEC of the salivary gland which occurred in a non-endemic area. Compared with previously reported cases, this case showed certain differences. CT scan showed mild enhancement, expression of Ki-67 was low, EBV (+) and tumor cells formed cystic nests. Although LEC of the salivary gland has a low incidence, it is a clinically diverse and complex disease. Therefore, it is particularly liable to be overlooked and misdiagnosed. The pathology of this clinical entity requires more comprehensive characterization. Furthermore, hepatitis B virus (HBV) can be found in parotid gland tissue-HBsAg (+) and HBcAg (+) rates are as high as 45.5% and 45.5%, respectively [20]. Our patient had severe liver cirrhosis following hepatitis B infection, and the disease had progressed to hypersplenism. Hence, it is entirely conceivable that infiltration of HBV in the parotid gland tissue may have been responsible for the differences discussed above.

### Disclosure of conflict of interest

None.

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