

Original Article

CT features and pathologic characteristics of lymphoepithelial carcinoma of salivary glands

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Abstract: Objective: To investigate and analyze the typical CT findings of salivary gland lymphoepithelial carcinoma. Methods: CT findings in 8 patients with lymphoepithelial carcinoma (LEC) in salivary gland were studied retrospectively. Surgical resection was performed in all cases. Results: 8 cases were subdivided to primary tumor and secondary tumor. In primary tumor group, 5 were localized in the parotid gland, 2 were found in the submandibular glands; 6 lesions had with homogeneous density, 1 was associated with cystic degeneration and 1 with calcification; the margins of lesions in 5 cases were poorly defined, while well-defined in 2. On enhanced CT: obvious enhancement was achieved in all of the 7 solitary lesions, among which 4 were homogeneously enhanced while the other 3 had heterogeneous enhancement. In the 2 cases of nodules in deep lobe, retromandibular vein was affected; 7 patients had positive Epstein-Barr virus (EBV) test, with Ki-67 measurements ranged from 40% to 80%. 1 patient had LEC secondary to Benign Lymphoepithelial Lesion (BLEL), with involvement of bilateral parotid glands; the lesion was manifested as multiple differently-sized nodules, with partial cystic change, all of the nodules had clear margins, and obvious ring-shape enhancement was seen in the nodules with cystic change; the patient with secondary LEC had negative EBV test and a Ki-67 value of 20%. Conclusion: In most cases, LEC was primary and occurred in the parotid glands. The probable diagnosis could be made based upon Dual-phase contrast-enhanced CT scan findings combined with positive expression of EBV.

Keywords: Lymphoepithelial carcinoma, salivary tumor, X-ray computed, tomography

Introduction

Lymphoepithelial carcinoma (LEC) of salivary glands is a rare and specific malignant salivary gland tumor associated with undifferentiated carcinoma featuring interstitial infiltrations by lymphocytes and plasma cells [1-3]. Epidemiologically, LEC demonstrates evidently regional and racial predisposition; and the episode of this disorder is highly related to infection of Epstein-Barr virus (EBV) [1]. The detailed typical radiographic findings of LEC have not been described, probably due to its low incidence. In the present study, based on their individual radiographic presentations and pathological findings, the clinical data of 8 patients who were pathologically diagnosed with LEC between June 2004 and June 2011 were reviewed respectively, and the classification, CT manifestation and pathological features of

the disease were also discussed, aiming to provide an improved recognition of the disease.

Materials and methods

Patients

The clinical data of 8 patients who were pathologically diagnosed with salivary gland LEC and in whom malignant tumors originated from nasopharynx and other regions were excluded between June 2004 and June 2011 in our hospital were collected. These enrolled patients (3 males and 5 females) aged between 24 and 72 years, with a mean age of 42.5 years and a median of 51 years. Clinically, all of the patients presented parotid nodules or enlarged bilateral parotid glands and local discomfort on admission. 1 of the 8 patients had LEC secondary to benign lymphoepithelial lesions (BLEL), which manifested as Sjogren's syndrome

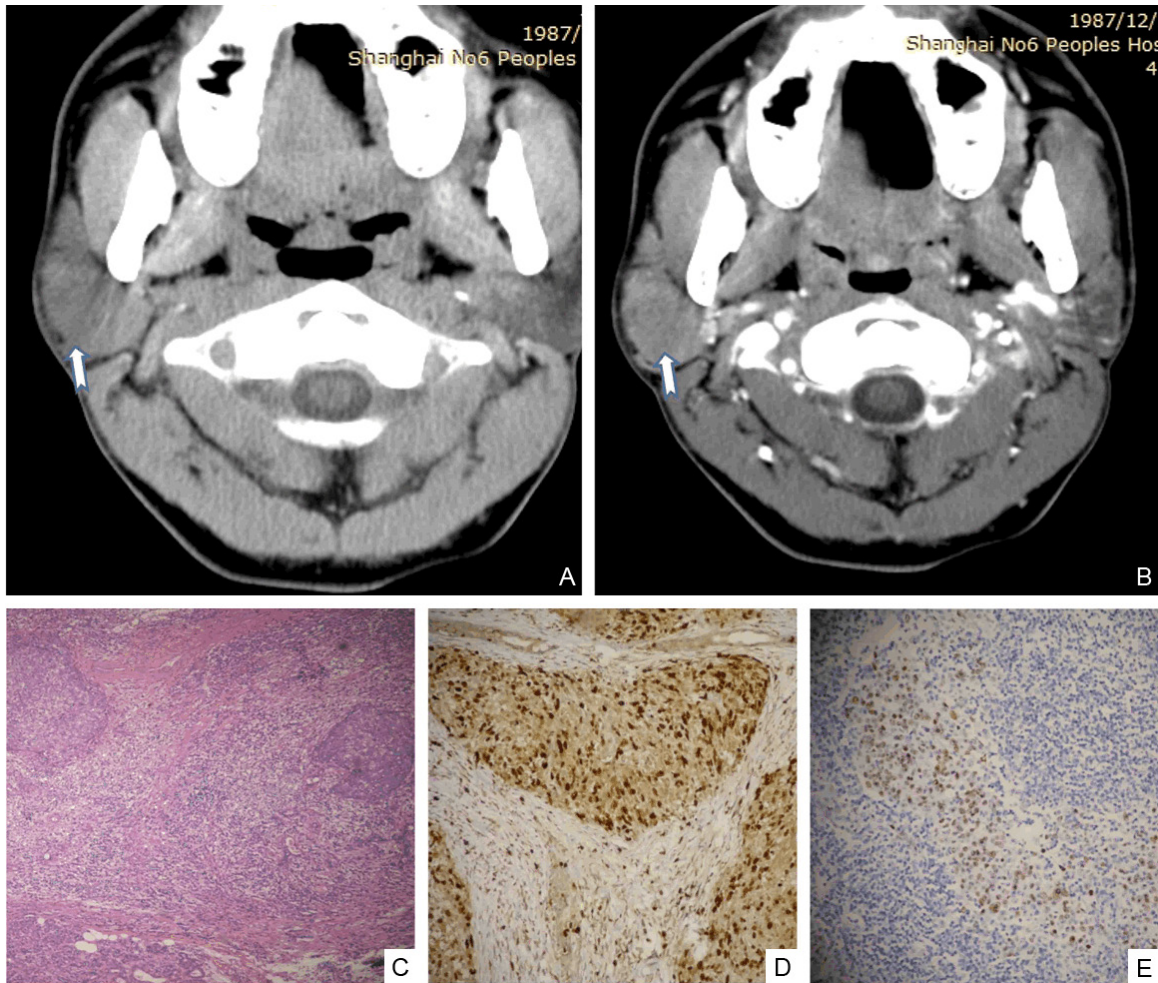


Figure 1. LEC of right parotid gland in a 24-year-old woman. A: An irregular nodule of soft-tissue density was seen in the right parotid gland on plain CT, poorly defined margins. B: On enhanced CT, the lesion was heterogeneously enhanced; submandibular vein was not visualized. C: (HE \times 100) neoplastic epithelium associated with interstitial infiltration by lymphocytes. D: (En Vision \times 100) Ki-67 (brownish particles) was highly expressed. E: EBV (brownish particles) positive.

and with the following serologic finding, anti-SS-A (+), anti-SS-B (+) and anti-Ro-52 (+); while the other 7 patients had solitary nodules, including 6 posterior to earlobe and 2 in the submandibular regions. Among these 7 patients, 6 of them had painless solid nodules, 2 felt palpatory tenderness on and 1 was complicated by facial paralysis. On palpation, most of the nodules were irregular and circular in shape; and 5 were mobile while 3 were relatively fixed.

CT scan techniques

Dual-phase scans were underwent by using multi-detector row CT scanner (LightSpeed VCT, GE Healthcar) in all patients, with the following

settings: collimation 64×0.625 mm; thickness 5 mm; preferred table speed 20 mm; scanning speed 0.5 s/r; CARE dose scan mode; intravenous injection of 300 mg I/ml non-ionic contrast agent (iohexol) at a dose of 1.5 ml/kg by using an automatic injector, with a injecting speed of 3 ml/s and a total injection volume of 80-100 ml; the arterial and venous phases were approximately 35 and 75 s, respectively, after the start of injection.

Image analysis

The 8 patients were divided into two groups, namely the primary group (without underlying lesions) and the secondary group (featured Sjogren's syndrome in salivary glands). All the

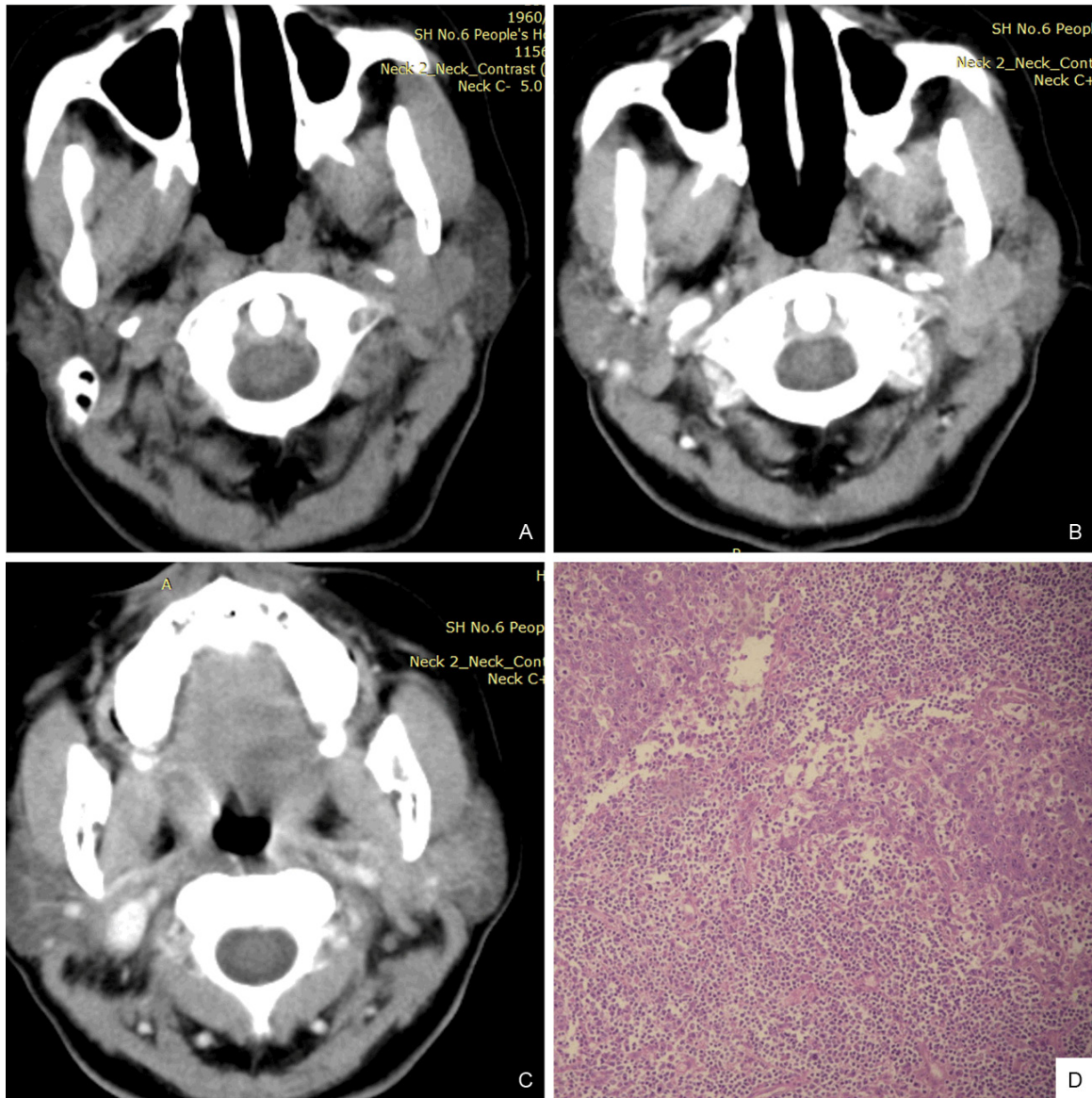


Figure 2. LEC of left parotid gland in a 51-year-old woman. A: An irregular masses of soft-tissue density was seen in the deep lobe of left parotid gland, the masses was lobulated and had poorly-defined margins. B: Markedly enhancement was seen on enhanced CT. C: Submandibular vein was affected and became thinner. D: (HE × 100) neoplastic epithelium associated with interstitial infiltration by lymphocytes.

images obtained were analyzed by two Head and Neck radiologists, in terms of the location, size, margin clarity, density, degree of calcification, cystic degeneration of the lesion, as well as mode and degree of CT enhancement, involvement to peripheral structures and periglandular lymphatic metastasis. The degree of enhancement was classified into 3 categories, namely mildly enhanced (post-enhancement increment in CT value <15 HU), moderately enhanced (15-30 HU) and significantly enhanced (>30 MU). All the recovered specimens were fixed in 4.0% neutral methanol, before being

prepared to paraffin-embedded sections used for H&E staining. S-P method was employed for immunohistochemical observation focused on two parameters EBV and Ki-67.

Results

Morphological features

There were 7 cases of primary LEC; 5 lesions were located at the parotid glands (3 cases in superficial lobe and 2 cases deep lobe in 2 case) (**Figures 1, 2**), while 2 lesion sited at

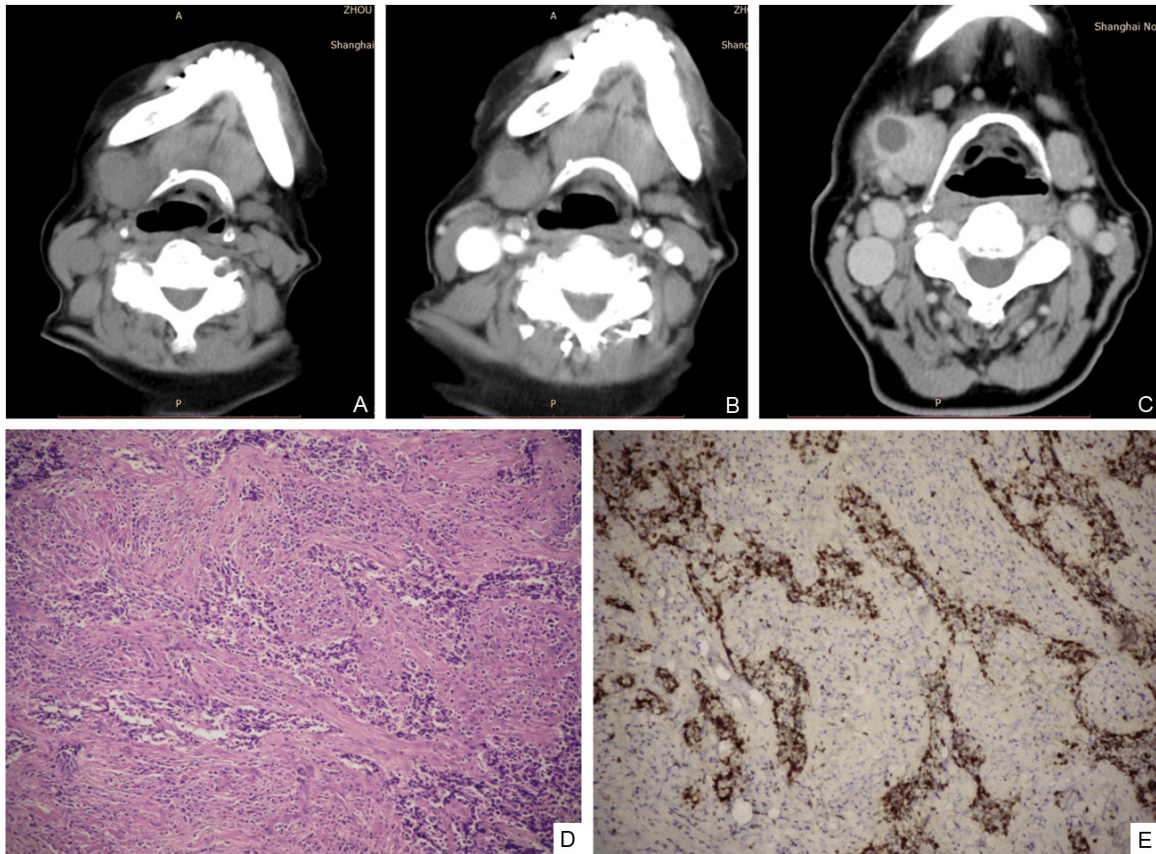


Figure 3. LEC of right submandibular gland in a 72-year-old woman. A: Heterogeneous masses of soft-tissue were seen in the right submandibular gland, with poorly defined margins. B: Markedly enhancement was seen on enhanced CT. C: Cystic degeneration was visualized on thin-layer CT (thickness 3 mm), smooth margins. D: (HE × 100) neoplastic epithelium associated with interstitial infiltration by lymphocytes. E: Ki-67 (brownish particles) was highly expressed.

submandibular glands (**Figure 3**). Morphology and density analysis showed that all of the lesions manifested as solitary solid nodules with irregular morphologies, sized 1-3.5 cm. 6 of these nodules showed homogenous density; slight cystic degeneration and calcification were seen in 1 case each, respectively. Of the 7 nodules, 5 had poorly-defined margins while 2 had clearly-defined margins.

Secondary LEC occurred in 1 patient, in whom bilateral parotid glands were affected (**Figure 4**). Multiple nodules with varied sizes were visualized within the gland body. All of the nodules had clearly-defined margins, but some of them showed cystic degeneration.

Density of LEC on CT and the degree of CT enhancement

The 7 cases of patients with primary LEC all presented solitary nodule, which depicted

morphologically irregular nodule of soft-tissue density on plain CT. 6 of these 7 lesions demonstrated homogenous density (24.5 Hu-51.1 Hu), higher than parotid glands (**Figures 1A** and **2A**). Calcification and cystic degeneration were seen in 1 case each, respectively (**Figure 3C**). On contrast-enhanced CT, significant enhancement was achieved in the 7 cases of solitary solid nodule, among which 4-exhibited homogenous enhancement (**Figure 2B**) while 3 were heterogeneously enhanced (**Figure 1B**). The post-enhancement CT value ranged between 68.2 and 101.4 Hu, i.e. increment of 33.8-73.4 HU. In the 2 cases of deep-lobe nodule, both patients' retromandibular veins were affected, resulting in distorted and stenosis images (**Figures 1B, 2C**). In 2 cases, multiple enlarged lymph nodes with homogenous enhancement were visualized.

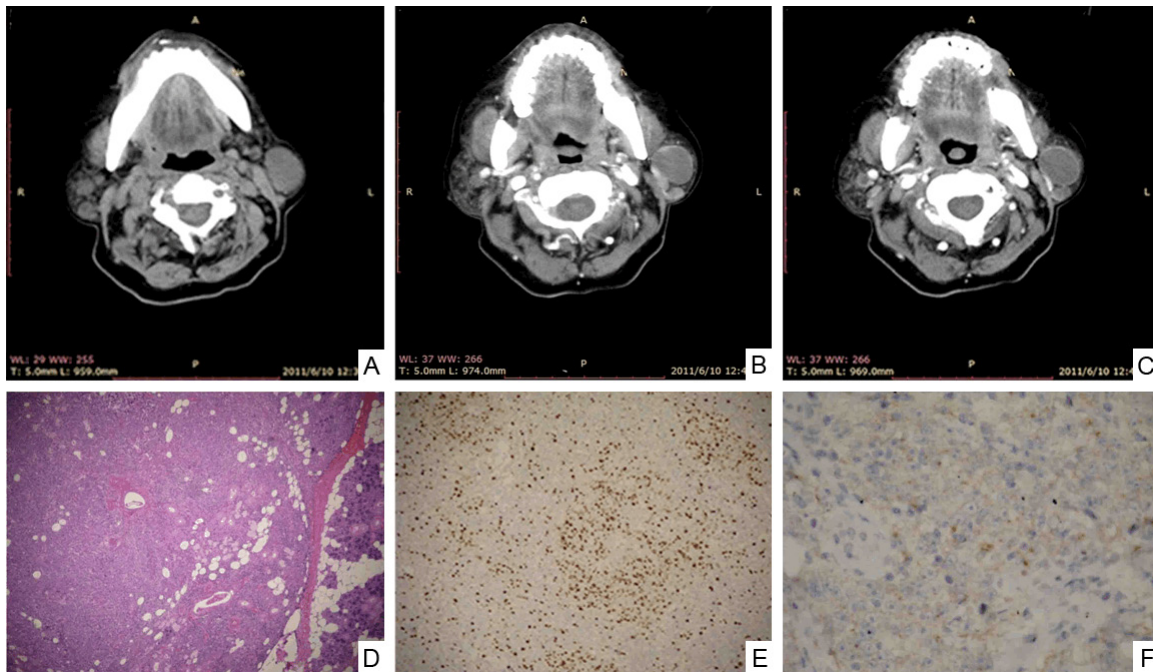


Figure 4. Multiple LECs in bilateral parotid glands associated with BLEL in a 55-year-old woman. A: On plain CT, enlarged bilateral parotid glands were revealed, within which there were several nodules with smooth margins. B: On enhanced CT, the margins of cystic-degenerated nodules were enhanced; solid nodules were markedly enhanced. C: Displacement of left submandibular vein due to compression was seen. D: (HE \times 100) neoplastic epithelium associated with interstitial infiltration by lymphocyte; the nodules had smooth margins. E: Ki-67 (brownish particles) was moderately expressed. F: EBV (brownish particles) examination did not produce definite results.

The only patient with secondary LEC had multiple nodules (**Figure 4A**), of which the solid part had a density of 24.0 HU, presenting ring enhancement on enhanced CT scan (**Figure 4B**). The CT value was 68.8 HU, implying an increment of 44.8 HU. The central region was unenhanced, and the enhanced ring was heterogeneous in thickness. Those solid non-cystic-degenerated nodules demonstrated to be markedly enhanced (**Figure 4B**). Compressed displacement and mild stenosis of retromandibular vein occurred (**Figure 4C**).

Pathological manifestation

Sections of primary tumor were greyish yellow or grey in color; 5 lesions had incomplete capsules while 2 had no capsule. In 1 case, infiltration of facial nerve by tumor was seen. Regional nodal metastasis presented in 2 cases. In this group of patients, Ki-67 ranged from 40% to 80% (a mean of 70%) (**Figures 1D, 3D**), and all had a positive serologic test for EBV (**Figure 1E**).

The only patient with secondary tumor had multiple grayish-red cyst-like malignant nodules,

of which the sections were liquefied and coffee in color; the cyst wall had a thickness of 0.1-0.2 mm, smooth in nature. Ki-67 value was 20% (**Figure 4E**), EBV test negative (**Figure 4F**).

Microscopic observations (H&E staining) (**Figures 1C, 2-4D**): lymphocytes-rich and plasma cells infiltration were visualized, and usually associated with reactive lymphoid follicles. The boundaries of tumor cells were clear, within which filled by eosinophilic cytoplasm and an oval, bubble-like nucleus with empty chromatin and prominent nucleoli. The tumor was infiltrative and sheeted, insular or streak in shape.

Correlation analysis of CT findings and pathological manifestation

In 7 cases of primary LEC, the sections of nodule were parenchymal, which was in consistent with the CT findings of solid nodule. Most capsules were incomplete and demonstrated as poorly defined margins on CT scan. Infiltration of facial nerve by tumor was seen in 1 patient, but such infiltration was not revealed

by CT. Ki-67 values were all higher than 40% (with a mean of 70%), suggesting highly proliferative nature of LEC cells. The tumors were generally lobulated; and this finding was in consistent with the morphologies observed on CT. All nodules recovered from the 7 primary LEC cases showed positive and characteristic expression of EBV. The only secondary LEC lesion exhibited as bilateral multiple cyst-like nodules with smooth nodule wall and grayish red in color. The sections of this lesion had negative EBV test, with a Ki-67 value of 20%; both findings were different from those obtained from primary tumor.

Discussion

Lymphoepithelial carcinoma (LEC) of salivary glands, a rare malignancy only accounted for 0.4% of salivary gland tumor [1-3], was first described by Hilderman in 1962; LEC was a subtype of undifferentiated salivary gland carcinoma associated with lymphoid stroma [2, 3]. Histologically, LEC consists of differently sized infiltrative-growth neoplastic epithelium and varying amount of lymphoid interstitial. The diagnosis of LEC should exclude metastasis of extraglandular cancer, especially the metastasis of nasopharyngeal carcinoma metastasis or lowly differentiated extraglandular cancer. Epidemiologically, LEC showed obvious geographic and racial predisposition; its incidence in Eskimos, Greenlandic Inuit, people in the southern coastal region of China and Japanese were relatively higher than the other populations [1, 4]. LEC was highly associated with EBV infection; almost 100% of endemic LEC cases had a positive serologic test for EBVs [1, 5], and a majority of the non-endemic LEC patients were EBV positive, only a minority were EBV negative [6, 7]. LEC was clinically more common in major salivary gland and parotid gland (82%), followed by submandibular gland and minor salivary glands; most cases had unilateral episodes and manifested as slow-growth painless masses [1, 5]. 20% cases were associated with facial paralysis, while 40% with enlarged cervical lymph node [1]. The subjects enrolled in the present study were all patients from East China; all of the 7 patients in the primary salivary gland LEC group were EBV positive and showed solitary intra-glandular lesion on CT scan, with Ki-67 >40%.

LEC secondary to benign lymphoepithelial lesions (BLEL) rarely occurred [1]; most BLEL

patients had Sjogren's syndrome (more prevalently secondary to non-Hodgkin lymphoma) as its clinical presentation. BLEL, which could affect salivary glands on either a singular or a diffuse manner, was typically characterized by bilateral involvement and more prevalent in females [8]; diffusely spread multiple sacculiform BLELs has been reported [9]. LEC secondary to BLEL has seldom been reported [1]; in the present study, LEC secondary to BLEL only occurred in 1 case, who were EBV negative and showed multiple parotid gland lesions distributed bilaterally; the patient's Ki-67 value was 20%. The enrolled subjects were divided into two groups, namely the primary and the secondary groups, which showed significant difference in CT manifestation and histochemical expressions. However, the present study was limited by small number of patients with secondary LEC, and thus further studies were required to confirm its variations from primary LEC.

For diagnosis of salivary gland tumor, the most critical concern was to determine it was benign or malignant [10]. Diagnosis of salivary gland tumor could hardly be made clinically, but mainly depended on imaging findings. Therefore, preoperative imaging has an important role in surgical planning [10]. Being a rare neoplasm, imaging findings of LEC has not been defined. Therefore, in the present study, the conclusion on typical CT findings of LEC was speculative, based on data obtained from the 8 cases enrolled in combination with the observations of previous literatures: 1) Sites of lesions: salivary gland LEC was most commonly seen in the parotid glands. Among the 8 lesions studied, 6 were in the parotid glands while 2 were in the submandibular glands and no minor salivary gland involvement was seen. The 6 lesions in the parotid glands were distributed in the superficial lobe (3 cases), deep lobe (2 cases) or with a diffuse pattern (1 case), indicating no evidence of predisposition to superficial/deep lobular distribution. The statement of "tumors in minor salivary glands were more likely to be malignant", a diagnostic evidence of malignant salivary gland tumor, was not applicable to LEC case [11]. Most LEC affected the parotid glands, while both submandibular and minor salivary gland involvements were less common. 2) Morphology and density: Most salivary gland LEC was

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solitary, solid, irregular, less lobulated nodule with homogenous density, complicated by small cystic degeneration and calcification. In contrast, Secondary LEC could multiple nodules associated with cystic degeneration. Of the 7 cases of patients with primary LEC studied in the present study, 6 had homogenous densities; and small cystic degeneration and calcification occurred in 1 case each, respectively. 3) Pattern of enhancement: All of the nodular lesions were significantly enhanced. Markedly enhancement was observed in the 7 patients with primary LEC, whereas the 1 patient with secondary LEC exhibited obvious ring enhancement, the increment of CT values ranged from 33.8 to 73.4 HU. Homogeneous enhancement was acquired in 4 patients, while heterogeneous enhancement in 3 patients. 4) Margins of nodule: Most lesions had poorly-defined margins, while only a minority of lesions had well-recognized margins. In the present study, 5 lesions of LEC nodules had blurred margins whereas 2 lesions had clear margins. 5) Peripheral infiltration. Involvements of sub-mandibular vein took place in 2 cases; on the other hand, enlarged peri-glandular lymph nodes and homogenous enhancement were visualized in 2 cases. 6) Well prognosis. On 3 years of follow-ups, no metastasis and recurrence occurred in 6 patients, while 1 patient had liver and retroperitoneal lymph node metastases occurred.

Nowadays, the morphology of lesion (in terms of margin and contour) still remained as a critical concern on the differential diagnosis of malignant salivary gland tumor. Benign tumor usually featured regular morphology and smooth margins, whereas malignant tumors were likely to be lobulated and irregular with poorly defined margins [11, 12]. Of the 7 patients with solitary nodules studied, 5 had poorly defined margins and 2 had easily recognized margins, suggesting that the general characteristics of LEC mimicked malignant tumors. However, it was difficult to differentiate LEC lesion with clear margins from the benign tumors, which may probable be explained by the formation of pseudocapsule attributed to the compression on gland by low-grade malignant tumor; thus the lesion appeared to be benign [12].

The 2 cases of LECs affecting deep salivary gland lobe studied herein was associated with stenosis and diminishment of submandibular

vein. Similarly, the 3 lesions found on superficial lobe and 1 secondary lesion all presented deformation and displacement of sub-mandibular vein, indicating a higher tendency of submandibular vein involvement by LEC occurred in deep salivary gland lobe and stenosis and diminishment of submandibular vein may be an evidence of malignant tumor.

CT findings of LEC nodules may reflect gross pathological morphology of the lesions: solid or cystic. Solid nodules were revealed on CT scan, which was in consistent with the typical finding of LEC, the incomplete capsules and poorly defined margin on CT scan were in consistent with the typical pathological findings. Infiltration of facial nerve was seen in 1 case, but the infiltration was not revealed on CT scan. The tumor cells of primary LEC were highly proliferative in nature, which could be reflected by lobulated distribution and blurred margins observed on CT image. Less degree of intra-nodular cystic degeneration and calcification, in combination with markedly CT enhancement, implied enriched nodular blood supply and less necrotic cystic degeneration. All the primary LEC lesions had a positive serologic test for EBV and high expression of Ki-67; whereas, the secondary LEC lesion was EBV negative and exhibited low expression of Ki-67; these were the two major differences observed between the two lesions. However, since the number of LEC cases enrolled in the present study was very limited, further studies were required for the confirmation of such differences.

In conclusion, LEC was more common in the parotid gland and could be divided into 2 types, namely the primary LEC and secondary LEC. There were differences in the distribution pattern and morphology of lesions, as well as the expression of EBV and levels of Ki-67 between these two types. Typical CT findings of salivary gland tumor combined with positive EBV expression are useful in predicting the diagnosis of LEC.

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