Lymphoepithelial carcinoma of the salivary glands

Yeun J. Kim, MD\textsuperscript{a}, Hyun S. Hong, MD, PhD\textsuperscript{a,}\textsuperscript{*}, Sun H. Jeong, MD\textsuperscript{a}, Eun H. Lee, MD, PhD\textsuperscript{b}, Min J. Jung, MD\textsuperscript{c}

Abstract

Rationale: Lymphoepithelial carcinoma (LEC) is a rare malignancy with the histopathological feature of undifferentiated carcinoma and an intermixed reactive lymphoplasmacytic infiltration. Although clinically significant because of its malignant nature, it is difficult to make a differential diagnosis by preoperative imaging. Here, we report 3 cases of primary LEC arising in the major salivary glands, which showed unusual imaging features unlike other malignant tumors.

Patient concerns: Our first case is a 44-year-old man with LEC in the right parotid gland, the second case is a 71-year-old woman with LEC in the right submandibular gland, and the third case is a 35-year-old woman with LEC in the right parotid gland. All of the patients presented with a palpable mass of variable duration.

Diagnoses: Computed tomography (CT) scans revealed a relatively well-defined, slightly hyperattenuated exophytic solid mass that had homogeneous well-enhanced regions. Ultrasonography (US) in the first 2 cases showed well-defined, hypoechoic solid masses with posterior enhancement. The CT findings seem to be benign tumors, but US features are compatible with highly cellular and hypervascular tumors.

Interventions: The resection of the involved salivary gland with postoperative radiation therapy was performed.

Outcomes: There was no evidence of recurrence or metastasis after 5 years in all 3 patients.

Lessons: Understanding these unusual imaging findings may be helpful in detecting LEC, and may also help clinicians provide adequate management to patients, such as surgery with adjuvant radiotherapy, because of its malignant entity.

Abbreviations: ADC = apparent diffusion coefficient, CT = computed tomography, DWI = diffusion-weighted imaging, EBER = Epstein-Barr virus-encoded small RNA, EBV = Epstein-Barr virus, FNA = fine-needle aspiration, LEC = lymphoepithelial carcinoma, MR = magnetic resonance, PET-CT = positron emission tomography-computed tomography, RT = radiotherapy, T1W = T1-weighted, T2W = T2-weighted, US = ultrasonography.

Keywords: computed tomography, lymphoepithelial carcinoma, salivary gland, ultrasonography

1. Introduction

Lymphoepithelial carcinoma (LEC) is an uncommon malignant tumor composed of undifferentiated malignant epithelial cells with characteristic lymphoid stroma.\textsuperscript{[1-2]} The most common location of LEC is the nasopharynx. However, it can also occur in other organs including the salivary glands, particularly the parotid and submandibular glands. However, LEC in these glands is very rare, only accounting for 0.4% of the malignant tumors.\textsuperscript{[1]} LEC has a unique ethnic predilection for the Eskimo, Chinese, and Japanese populations,\textsuperscript{[3]} with a significant association with Epstein-Barr virus (EBV).\textsuperscript{[4]} These tumors mainly affect females in the fifth decade of life.\textsuperscript{[1]} Although it is clinically significant because of its malignant entity, it is difficult to make a differential diagnosis by preoperative imaging of a salivary gland mass.

Here, we report 3 rare cases of confirmed LEC originating from the salivary glands and discuss the radiologic features of LEC and several considerations of salivary gland tumors.

2. Case report 1

A 44-year-old man presented with a painless, slowly growing palpable mass in the right preauricular region for 1 year. Upon physical examination, an approximately 3-cm, well-defined mobile mass was found in the right parotid area. Facial nerve function was intact, and there were no palpable enlarged cervical lymph nodes. Otherwise, he had no notable medical history. Contrast-enhanced computed tomography (CT) scans revealed an oval-shaped, well-defined, hyperattenuated exophytic solid mass compared to the parotid gland, which had homogeneous enhancement in the lower portion of the right parotid gland (1.9 × 1.7 × 1.9 cm, 3.1 mL). Color Doppler images revealed focal increased vascularity in the hypoechoic mass (Fig. 1C). A US-guided fine-needle aspiration (FNA) biopsy was performed, and the histopathological report showed metastatic squamous cell carcinoma. The patient underwent magnetic resonance (MR) imaging; the mass lesion was...
isointense relative to muscle with homogeneous and strong enhancement in T1-weighted (T1W) images, and was hyperintense relative to the parotid gland in T2-weighted (T2W) images. It also showed diffusion restriction in diffusion-weighted imaging (DWI). Because the FNA biopsy revealed metastatic squamous cell carcinoma, a positron emission tomography-computed tomography (PET-CT) scan was performed to evaluate the primary malignancy. There was no evidence of hypermetabolic lesions except for a biopsy-confirmed salivary mass (Fig. 1D). The patient underwent a total right parotidectomy, and the resected parotid gland showed a 2.0 × 1.7-cm sized well-circumscribed gray-white, round, solid mass. Histologic findings revealed sheets of cohesive tumor nests with dense lymphoid proliferation (Fig. 2A). The tumor cells had enlarged vesicular nuclei with prominent nucleoli and indistinct cell borders. In situ hybridization for EBV, Epstein-Barr virus-encoded small RNA (EBER), was positive in tumor cells (Fig. 2B). The patient was discharged without complication and postoperative radiation therapy was performed. There was no evidence of recurrence or metastasis after 5 years.

3. Case report 2
A 71-year-old woman was admitted with a painful, recently growing palpable mass in the right submandibular region for 1 week. According to the patient, the mass was first detected 3 months ago, and she had not experienced any discomfort associated with the mass at the time. Upon physical examination, an approximate 2-cm, firm, and movable mass was found in the right submandibular area. Examination of the oral cavity, oropharynx, and laryngopharynx found no lesions. The patient had a medical history of insulin-dependent diabetes and hypertension, which had occurred about 4 years before. Contrast-enhanced CT scans showed a lobulated, marginated, well-enhanced exophytic solid mass with an internal cystic change, abutting to the right submandibular gland (Fig. 3A). There were no enlarged lymph nodes. US revealed an approximate 2-cm, well-defined, lobulated hypoechoic solid mass with posterior enhancement, which was abutting to the right submandibular gland. Color Doppler images showed increased vascularity in the hypoechoic mass (Fig. 3B). The patient underwent excision and biopsy with right neck dissection, which was confirmed as LEC on pathology. The patient had no evidence of recurrence or metastasis after 5 years.

4. Case report 3
A 35-year-old healthy woman complained of a palpable and slowly growing mass in the left periauricular region for 3 years. At the time, the patient had no pain and her facial nerve was intact. Physical examination revealed a 2-cm, nontender, and movable mass in the left parotid area. Contrast-enhanced CT scans showed a round, well-defined, hyperdense solid mass with homogeneous enhancement in the superficial lobe of the left parotid gland. There

Figure 1. (A) A 44-year-old man presented with a palpable preauricular mass for 1 year. A precontrast computed tomography scan shows a hyperdense homogeneous solid mass compared to the surrounding parotid gland. (B) The mass shows well-defined homogeneous enhancement on a postcontrast scan. (C) Color Doppler ultrasonography shows a well-defined hypoechoic solid mass with posterior enhancement and focal increased vascularity in the hypoechoic mass in the lower portion of the right parotid gland. (D) The mass shows hypermetabolism on a positron emission tomography-computed tomography scan; the maximal SUV was 6.5.
was no evidence of cystic change or calcification in the mass, and no enlarged lymph nodes (Fig. 4). The patient underwent a left superficial parotidectomy, which confirmed LEC. The patient was discharged without complication. The patient had no evidence of recurrence or metastasis after 5 years.

5. Discussion

Salivary gland tumors are uncommon neoplasms, accounting for <3% of all head and neck tumors. They comprise a diverse group of benign and malignant histologies with a variety of differential diagnoses with different treatments and prognoses. However, FNA cytology can be inconclusive in cases of improper sampling or inaccessible tumor location. Therefore, preoperative imaging plays an important role in the management of salivary gland tumors.

Most salivary gland tumors are benign and 80% occur in the parotid gland. The general rule about salivary gland neoplasms is that the smaller the salivary gland involved, the higher the malignancy rate. Thus, the malignancy rate increases from 20% to 25% in the parotid gland to 40% to 50% in the submandibular gland and to 50% to 81% in the sublingual and minor salivary glands. The most common tumors of the salivary gland are pleomorphic adenomas, and the most frequent malignancy of the parotid gland is mucoepidermoid carcinoma.

In the submandibular, sublingual, and minor salivary glands, adenoid cystic carcinoma is the most common malignancy. Tumors in these glands are either primary salivary tumors, which arise in lymphatic tissue, or metastases; they rarely originate from other tissues such as blood vessels, nerves, and fat.

Pleomorphic adenoma is the most common salivary gland tumor and represents 70% to 80% of all benign tumors of the major salivary glands. These tumors show typical imaging features of a benign-appearing tumor. Pleomorphic adenomas are typically solitary, ovoid, and well-defined masses that have high attenuation compared to the surrounding parotid parenchyma. In contrast-enhanced CT scans, all of these tumors have variable enhancement. The smaller masses have homogeneous enhancement, and the large masses often have a heterogeneous appearance with internal necrosis, old hemorrhage, cystic changes, and dystrophic calcifications. There are several
Clinical and imaging features of patients with lymphoepithelial carcinoma of salivary glands.

Table 1

Clinical and imaging features of patients with lymphoepithelial carcinoma of salivary glands.

| Case 1          | Case 2          | Case 3          |
|-----------------|-----------------|-----------------|
| Sex/age         | M/44            | F/71            | F/35            |
| Chief complaints| Palpable mass   | Palpable mass   | Palpable mass   |
| Symptom duration| 1 y             | 3 mo            | 3 y             |
| Epstein-Barr virus on pathology | +              | +               | +               |
| Imaging characteristics | compared to salivary gland | Hyperdense      | Hyperdense      |
| Tumor location  | Right parotid   | Right submandibular | Left parotid  |
| Tumor size, cm  | 1.9 × 1.7 × 1.9 | 2.2 × 1.9 × 2.2 | 1.7 × 1.5 × 1.8 |
| Tumor margin    | Well defined, oval | Frank invasion to extraglandular soft tissue | Well defined, round |
| Inner necrosis  | Hyperdense      | +               | Hyperdense      |
| CT scan         | Hyperdense      | Hyperdense      | Hyperdense      |
| Enhancement pattern | Hypoechoic solid mass with posterior enhancement | Well, inner cystic change | Homogeneous, well |
| Ultrasonography | Hypoechoic solid mass with posterior enhancement | Hypoechoic solid mass with posterior enhancement | Not performed |
| Color Doppler image | Focal increased vascularity | Focal increased vascularity | Not performed |
| MRI imaging     | Isointense on T1WI, hyperintense on T2WI | Not performed   | Not performed   |
| PET-CT scan     | Hypermetabolic  | –               | –               |
| Pathologic lymph nodes | Homogeneous, well | –               | –               |

= present, — = not present, CT = computed tomography, MR = magnetic resonance, PET-CT = positron emission tomography-computed tomography, T1WI = T1-weighted image, T2WI = T2-weighted image.
have low signal intensity on T2W images with moderate enhancement on MR images. However, these imaging findings are nonspecific, making it difficult to definitively differentiate from other benign and malignant tumors of the salivary glands. Unlike other malignant salivary tumors, such as mucoepidermoid carcinoma and adenoid cystic carcinoma, cystic degeneration and calcification are rare in LEC and typically show homogeneous attenuation or signal intensity.

In our cases, CT showed well-defined, enhancing, exophytic, homogeneous masses in the salivary glands with internal necrosis in only 1 case. US revealed a hypoechoic solid mass with posterior enhancement and increased vascularity on Color Doppler images in 2 cases. On MR imaging of case 1, the mass lesion was isointense relative to muscle in T1W image, hyperintense relative to fat in T2W image, and well-defined margin on post contrast T1W image (Table 1). These CT and MR findings seem to be benign tumors, but US features are compatible with highly cellular and hypervascular tumors. When these atypical findings are encountered, an LEC diagnosis should be considered.

In conclusion, LEC represents a rare malignant tumor of the salivary gland, and may be diagnosed when a well-defined, homogeneously attenuated, and relatively significant enhancing tumor is seen in the salivary gland with an exophytic growth pattern, particularly in the parotid gland. Furthermore, US can be helpful for discriminating between highly cellular and hypervascular tumors such as LECs. Additional information including the correlation with different ethnic groups and EBV should be considered. Understanding these unusual imaging findings may be helpful in detecting LEC, and may also help clinicians provide adequate management to patients, such as surgery with adjuvant RT, because of its malignant entity.

Acknowledgement

The authors are not associated with the funding.

References

[1] Schneider M, Rizzardi C. Lymphoepithelial carcinoma of the parotid glands and its relationship with benign lymphoepithelial lesions. Arch Pathol Lab Med 2008;132:278–82.

[2] Wang CP, Chang YL, Ko JY, et al. Lymphoepithelial carcinoma versus large cell undifferentiated carcinoma of the major salivary glands. Cancer 2004;101:2020–7.

[3] Sheen TS, Tsai CC, Ko JY, et al. Undifferentiated carcinoma of the major salivary glands. Cancer 1997;80:357–63.

[4] Hilderman WC, Gordon JS, Large HL, Jr, et al. Malignant lymphoepithelial lesion with carcinomatous component apparently arising in parotid gland. A malignant counterpart of benign lymphoepithelial lesion? Cancer 1962;15:606–10.

[5] Manganaris A, Patalkioura F, Xiropo P, et al. Lymphoepithelial carcinoma of the parotid gland: Is an association with Epstein-Barr virus possible in nonendemic areas? Int J Oral Maxillofac Surg 2007;36:556–9.

[6] Boring CC, Squires TS, Tong T. Cancer statistics 1993. CA Cancer J Clin 1993;43:18–9.

[7] Batsakis JG. Tumors of the Head and Neck: Clinical and Pathological Considerations. 2nd ed1979;Williams & Wilkins, Baltimore, Maryland:1–120.

[8] Freling NJ, Molenaar WM, Vermeij A, et al. Malignant parotid tumors: clinical use of MR imaging and histologic correlation. Radiology 1992;185:691–6.

[9] Weber RS, Byers RM, Petit B, et al. Submandibular gland tumors. Adverse histologic factors and therapeutic implications. Arch Otolar-yngol Head Neck Surg 1990;116:1055–106.

[10] Shah JP, Head and Neck Surgery. 2nd ed1996;Mosby-Wolfe, London, United Kingdom:431–460.

[11] Som PM, Brandwein-Gensler MS, Curtin DC. Anatomy and pathology of the salivary glands. Head and Neck Imaging 5th edMosby, St Louis:2011;2449–609.

[12] Kuo T, Hsueh C. Lymphoepithelial-like salivary gland carcinoma in Taiwan: a clinicopathological study of nine cases demonstrating a strong association with Epstein-Barr virus. Histopathology 1997;31:75–82.

[13] Christie A, Waldherr C, Hallett R, et al. MR imaging of parotid tumors: typical lesion characteristics in MR imaging improve discrimination between benign and malignant disease. Am J Neuroradio 2011;32:1202–7.

[14] Balcić Č, Akan H, Incešu L. Evaluating of parotid gland tumours according to diffusion weighted MRI. Eur J Gen Med 2014;11:77–84.

[15] Dong Y, Lei GW, Wang SW, et al. Diagnostic value of CT perfusion imaging for parotid neoplasms. Dentomaxillofac Radiol 2013;43:20130237.

[16] Zhan KY, Nicolli EA, Khaja SF, et al. Lymphoepithelial carcinoma of the major salivary glands: predictors of survival in a non-endemic region. Oral Oncol 2016;52:24–9.

[17] Abdulla AK, Mian MY. Lymphoepithelial carcinoma of salivary glands. Head Neck 1996;18:577–81.

[18] Zhang G, Tang J, Pan Y, et al. CT features and pathologic characteristics of lymphoepithelial carcinoma of salivary glands. Int J Clin Exp Pathol 2014;7:1004–11.