

Primary Buccal Lymphoepithelial Carcinoma: Report of a Case

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Cases Journal TAOMFR 2010; 2:4

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Keywords: lymphoepithelial carcinoma, buccal

Received: 1 August 2010; Accepted: 20 August, 2010

Lymphoepithelial carcinoma (LEC) is a well-recognized but uncommon clinical and histological entity, usually affecting the head and neck region with the highest frequency involving the nasopharynx [1]. It is characterized histologically by non-keratinizing, undifferentiated squamous cell carcinoma with various degrees of non-neoplastic (reactive) lymphocytic infiltration and is always related to Epstein-Barr virus (EBV) [1]. Non-nasopharyngeal LEC of the head and neck may occur in salivary gland [2], skin [3] and oral cavity [4]. LEC of salivary glands is considered as the malignant counterpart of benign lymphoepithelial lesion; parotid gland is most commonly affected, less commonly, the submandibular gland [2] and minor salivary gland are even rarely involved [5,6]. For cutaneous counterpart, the face and scalp are usually affected [3]. Reviewing English-language literature, most cases of oral LEC have been reported in the tonsil and tongue base of Waldeyer's ring, less frequently with the palate, mouth floor, retromolar area as well as the labial and buccal mucosa [4-7]. In this report, we present a case of primary buccal LEC in a Taiwanese patient with immunohistochemical and EBV examinations.

CASE PRESENTATION

A 50-year-old female was referred to our dental clinic by her family dentist for evaluation of a painless, non-tender, firm mass about 2cm in diameter beneath the left buccal mucosa for 3 months without a history of cigarette smoking, alcohol drinking, or betel-quid chewing or relevant systemic diseases. The overlying mucosa of the tumor was

unremarkable without surface ulceration. No local fever was noted. Furthermore, there were no palpable cervical lymph nodes. An incisional biopsy was subsequently performed with a clinical impression of submucosal tumor of origin to be determined.

Histopathologic examination revealed that pale-staining malignant cells were

predominantly composed of large, polygonal, undifferentiated tumor cells with vesicular nuclei and prominent nucleoli intermingled with abundant lymphoid infiltrate (Figure 1A & B). The cell borders between adjacent cells were indistinct, creating a syncytial cytoplasmic appearance with bizarre appearance (Figure 1B). Immunohistochemically, leukocyte common antigen (LCA) was expressed by the lymphocytes within the stroma but not by the tumor cells (Figure 2A). The tumor cells were positive for pancytokeratin (AE1/AE3) (Figure 2B), epithelial membrane antigen (Figure 2C), and cyclin D1 (Figure 2D) but negative for low-molecular-weight cytokeratins (CK7 and CK20). In situ hybridization (ISH) for detection of EBV by use of EBER1-specific antisense oligoprobe disclosed EBER1 in undifferentiated carcinoma but not in the surrounding lymphoid stroma (Figure 3A). Moreover, EBV serology was positive. Therefore, a histological diagnosis of LEC was rendered for this buccal lesion; however, a metastatic nasopharyngeal LEC should also be

considered. The subsequent biopsy of the left nasopharynx revealed lymphoid hyperplasia (Figure 3B). Computerized tomography (CT) revealed a well defined soft tissue mass over the left buccal space (Figure 4A); neither enlarged neck lymph nodes nor abnormality of the nasopharynx, providing further support for the primary nature of this tumor. Furthermore, Ga-67 whole body scan revealed focal radiotracer accumulation over the left cheek; normal uptake in nasopharynx, bilateral lacrimal glands, breast, liver, spleen, bone marrow, and gastrointestinal organ.

After discussion with the patient for different treatment modalities, she preferred to receive chemotherapy concurrent with radiotherapy (CCRT): cisplatin (20mg/ml) and 35 fractions RT with a total dose of 7000 cGy. The patient tolerated the treatment without major side effects. Most of the tumor was regressed, but residual tumor appeared to be noted by CT soon after CCRT treatment (Figure 4B). The patient was still under regular follow-up.

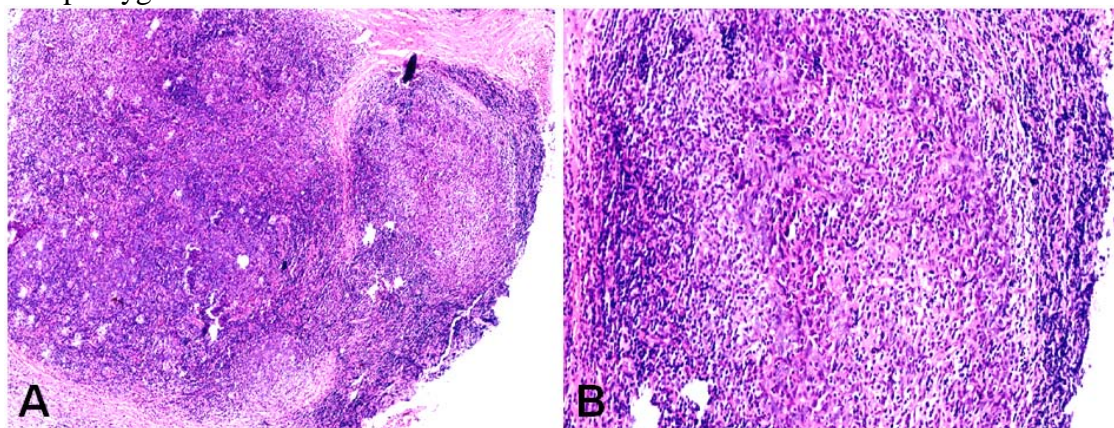


Figure 1 (A) The undifferentiated tumor cells were intermingled with lymphoid infiltrate (H&E, $\times 40$). (B) The tumor cells had indistinct cell border, pale eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli (H&E, $\times 200$). (C) Bizarre appearance of the tumor cells (H&E, $\times 400$)

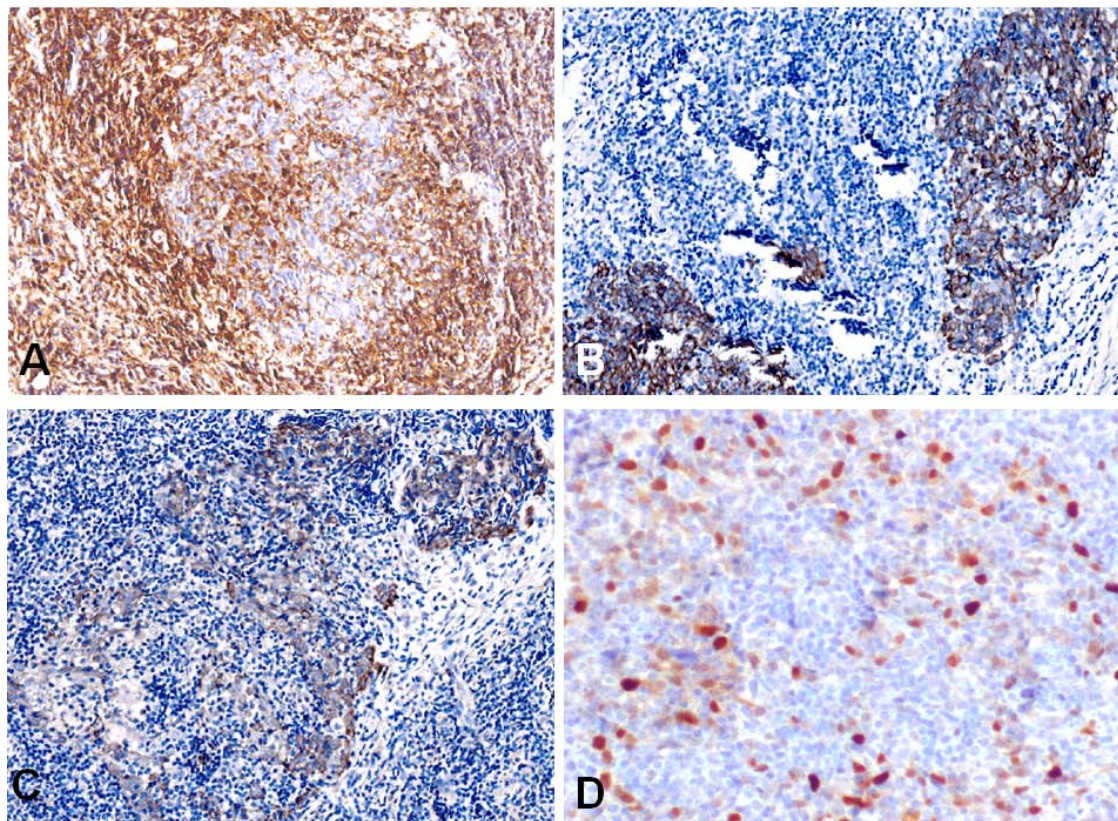


Figure 2 Immunohistochemical stainings. (A) Leukocyte common antigen was expressed by the lymphocytes within the stroma but not by the tumor cells ($\times 100$). The tumor cells were positive for pancytokeratin (B, $\times 100$), epithelial membrane antigen (C, $\times 100$) and cyclin D1 (D, $\times 200$)

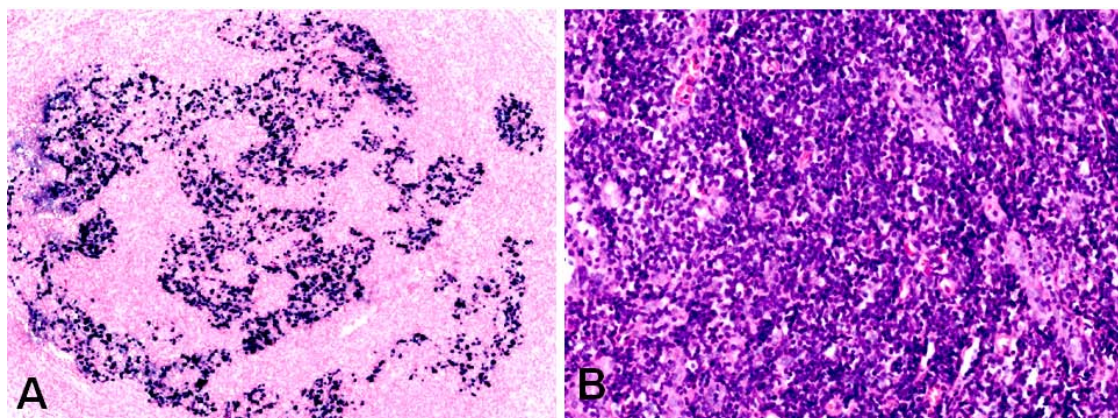


Figure 3 (A) The tumor cells were positive for EBER1 with in situ hybridization technique ($\times 40$). (B) Biopsy of the left nasopharynx revealed lymphoid hyperplasia (H&E, $\times 100$)

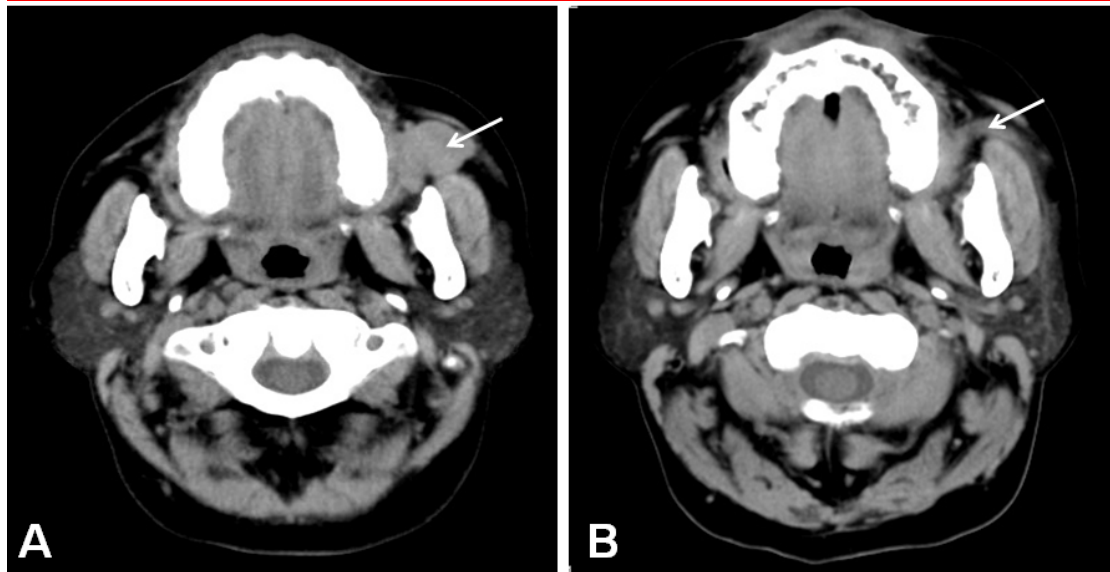


Figure 4 (A) Computer tomography (CT) revealed a well-defined soft tissue mass over the left buccal space. (B) A large portion of the tumor was regressed with some residual tumor appeared to be noted by CT after treatment

COMMENTS

LEC occurred in the oral cavity is defined by the World Health Organization as a poorly differentiated squamous cell carcinoma or undifferentiated carcinoma infiltrated by a prominent reactive lymphoid stroma [8] sharing a microscopic resemblance to its nasopharyngeal counterpart. Therefore, the possibility of oral LEC is being a metastatic lesion from nasopharyngeal LEC should be considered. For the present case, both the findings of CT and Ga-67 whole body scan as well as the nasopharyngeal biopsy do not support a metastatic lesion from nasopharynx. Therefore, the current case would be regarded as a primary LEC occurred in the cheek of the oral cavity.

Reviewing English-language literature, only two cases of LEC of presumed minor salivary gland origin of buccal region of the oral cavity have been reported [6,8]. Hilderman et al [8] were the first to report this malignancy affecting a 69-year-old white woman with concurrent benign lymphoepithelial

lesion (BLE) and cervical lymph node metastasis at first diagnosis. Lu et al [6] have described the second LEC of the minor salivary gland of buccal area of the oral cavity affecting a 50-year-old Taiwan woman without association with BLE but related to EBV. The possibility of minor salivary gland origin cannot be identified for the present buccal lesion because residual glandular tissues could not be found for histological examination. It may be due to the fact total excision has not been performed for this lesion; only a portion of tumor obtained from incisional biopsy has been submitted for microscopic examination precluding the finding of salivary gland tissues. Nonetheless, it is interested to note that our case is quite similar to the case reported by Lu et al [6] from our nearby hospital of the same city regarding to the age, gender, race as well as the EBV association. Does this lend further support to the fact that the incidence of LEC of salivary gland of Taiwan is much higher than in the Western population [9]?

Oral LEC is a rare epithelial malignancy accounting for 0.8%–2% of all oral and oropharyngeal carcinomas [6]. A slight male preponderance (1.5:1) and an average age of 55 years (16–78 years) has been noted for oral LEC [4]. The exact etiology for LEC of the oral cavity remains doubtful. Studies of EBV have been performed for some cases of oral LECs with nearly 50% of these cases serology was employed as the technique of examination [10,11]. Due to the high prevalence of worldwide EBV infection, serology alone has not been considered as a consistent marker to demonstrate association of EBV with neoplasia. Therefore, the preferred modalities to detect EBV comprise ISH, Southern blot hybridization, or polymerase chain reaction. The association of EBV with the current case has not only been established with positive EBV serology but also by ISH technique which has a further merit to demonstrate the presence of EBV inside the tumor cells. Significantly, for those oral lesions detected for EBV using ISH, including the present case, tumors affecting Chinese patients were positive [6], whilst those affecting Caucasians were negative. These interesting results may imply [7,12] a potential ethnic impact on the association of EBV with oral LEC. Moreover, a similar association of EBV to LEC has been suggested for other types of non-nasopharyngeal LEC such as salivary gland and lung [13].

Two microscopic types of nasopharyngeal LEC were designated by Regaud & Reverchon [14] and Schmincke [15] respectively. Regaud & Reverchon [14] described the LEC as well delineated clusters of neoplastic epithelial cells bordered by a fibrous lymphoid stroma. Alternatively, the neoplastic epithelial cells intermingled with inflammatory cells were described by Schmincke [15]. The histological

picture of the present case is largely compatible to the type described by Schmincke [15]. The histologic diagnosis of this type of LEC relies heavily on immunohistochemical stainings. The neoplastic epithelial cells are detected by cytokeratin staining whilst admixed lymphoid cells are demonstrated by LCA staining. On the other hand, cyclin D1 is a protein coded by *CCND1* gene located in chromosome 11q13. This protein acts on the cell cycle, accelerating G1 phase and has been described as an oncogene [16]. Overexpression of cyclin D1 has been reported in oral squamous cell carcinoma [16]; however, to our knowledge, this protein has not been demonstrated in oral LEC. Nuclear staining of cyclin D1 of the malignant epithelial cells has been noted for the current case.

Due to a high radiosensitivity for LEC, RT is considered as the first choice for loco-regional treatment of this disease. Surgery combined with RT as well as CCRT are other options of treatments. Galliozione et al [17] reported on two cases of tonsil LEC treated with CCRT with complete response for both cases after follow-up for 31 and 43 months respectively whilst most of the tumor has been regressed upon CCRT for the present case.

The biologic behavior of LEC of the oral cavity and salivary gland is similar to the nasopharyngeal counterpart, with a high frequency of metastasis to neck lymph nodes and significant radiosensitivity [18,19]. On the other hand, LEC of skin is a slow-growing lesion and rarely metastasize [3]. In the current case, although a large portion of the tumor has been regressed, residual tumor is still noted after CCRT for 18 months' follow-up, suggesting that CCRT alone is inadequate for complete eradication of the disease. Surgery is considered as a salvage procedure.

CONCLUSION

An uncommon case of primary buccal LEC in a 50-year-old Taiwanese woman is reported with EBV expressed in the tumor cells by ISH, indicating that this virus may involve in the pathogenesis of oral LEC in Asian patients. Moreover, the expression of cyclin D1, an oncogene accelerating G1 phase of the cell cycle, has been first demonstrated for oral LEC. □

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This article has been peer reviewed

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