

**Case Report****Epstein-Barr virus negative lymphoepithelial carcinoma of parotid gland - a case report with review of literature**Mary Yang<sup>1\*</sup>

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**Abstract**

**Background:** Primary lymphoepithelial carcinoma (LEC) of salivary gland is a rare tumor with strong racial and geographical predilection among Eskimos and Orientals in Greenland and Asia, and with strong association with Epstein-Barr virus (EBV). So far, only about 4 cases of EBV negative LEC of salivary gland were reported in the non-endemic area in non-predilected ethnic groups in the English literature. **Case report:** A 41 year old Hispanic female presented with right parotid mass. Fine needle aspiration of mass showed only lymphoid cells. Incisional biopsy showed anaplastic carcinoma cells with dense stromal lymphoplasmacytic infiltration, consistent with lymphoepithelial carcinoma. In-situ-hybridization (ISH) for EBV-encoded small RNAs (EBER) was negative. **Discussion:** The author reported a case of EBV negative LEC of salivary gland in a non-endemic area. The observation suggested that EBV may be an important contributing factor, but not a necessary factor in the pathogenesis of LEC of parotid gland. Other factors such as environmental and genetic predisposition may have a contributing role in the pathogenesis of the tumor. Additional studies in non-endemic areas will be necessary to clarify the pathogenesis.

**Key words:** lymphoepithelial carcinoma; parotid gland; Epstein-Barr virus (EBV); parotid tumor

**Introduction**

Primary lymphoepithelial carcinoma (LEC) of salivary gland is a rare tumor characterized by islands of anaplastic carcinoma cells with dense benign stromal lymphoplasmacytic infiltration. The tumor mainly involves parotid gland with rare reported cases of submandibular gland involvement. About 90% of all parotid tumors are benign. LEC accounts for about 0.4% of all malignant salivary gland tumors and about 1.4% of malignant major salivary gland tumors [1]. Its prevalence has a strong racial and geographical predilection among Eskimos and Orientals in Greenland and Asia. Previous reports showed a strong

association of the tumor with EBV [2, 3]. Only a limited number of cases are reported outside the endemic areas or predilect ethnic groups. The author reports a case of EBV negative LEC of parotid gland in a Hispanic female patient.

**Case Presentation**

A 41 years old Hispanic female presented with a progressively enlarging right parotid mass for 8 months with development of right facial weakness, difficulty in opening her mouth and chewing, and significant pain. Physical examination revealed right facial paralysis and right parotid mass. Magnetic resonance imaging of

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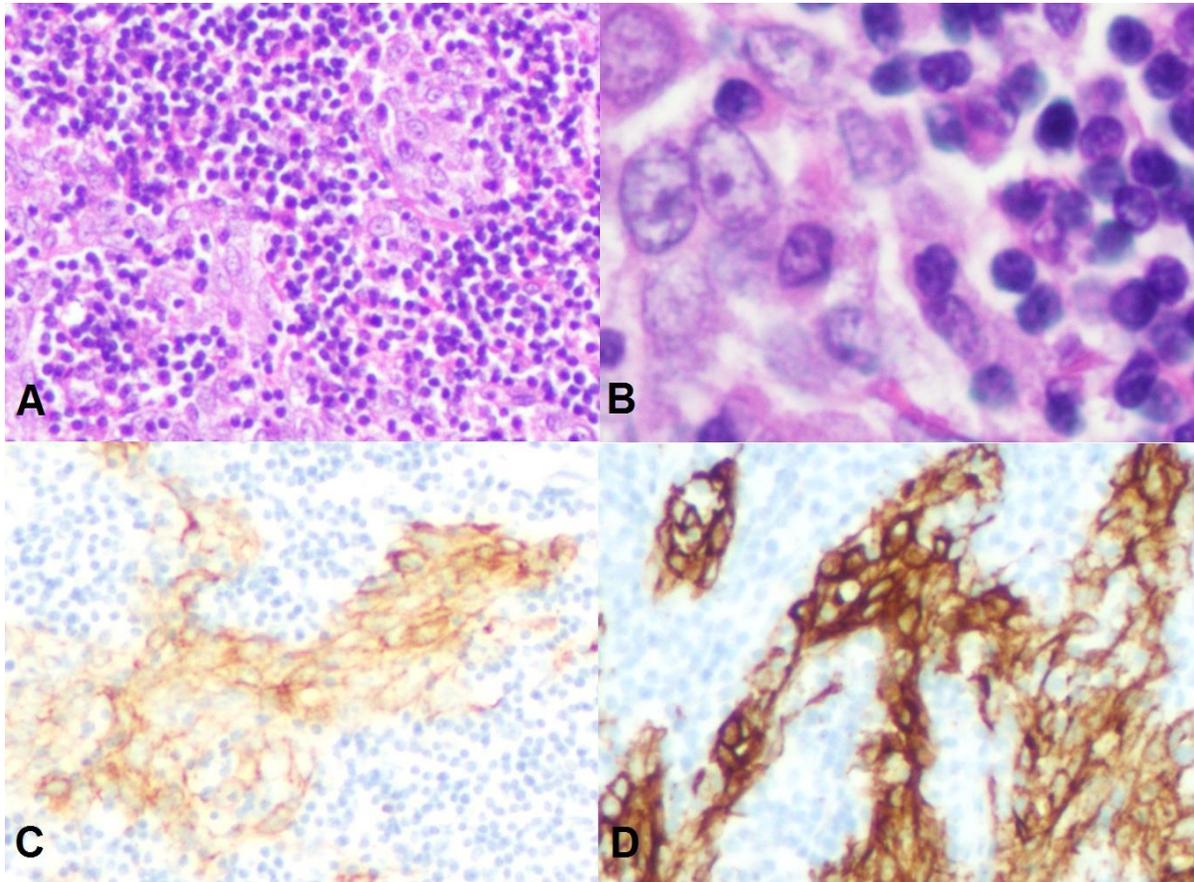
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**Figure 1.** A: Islands of anaplastic carcinoma cells surrounded by dense lymphoplasmacytic infiltrate (H&E x100); B: The anaplastic carcinoma cells showed prominent nucleoli (H&E x400); C: The carcinoma cells were positive for pancytokeratin on immunohistochemical study (pancytokeratin x100); The carcinoma cells were positive for CK5/6 on immunohistochemical study (CK5/6 x100).

orbit, face and neck showed a 2.2 cm anterior-posterior x 3.9 cm transverse x 2.9 cm craniocaudal enhancing mass with ill-defined borders spanning the deep and superficial lobes of the right parotid gland, spreading along the facial nerve up to the stylomastoid foramen and appearing to infiltrate the greater petrosal nerve. Right cervical lymphadenopathy was also identified. Fine needle aspiration of right parotid mass was performed twice with smears showing only lymphoid cells. The possibility of lymphoproliferative disorder was raised although flow cytometry failed to reveal evidence of non-Hodgkin lymphoma. Incisional biopsy was performed for a definitive diagnosis. The biopsy showed islands of anaplastic carcinoma cells with dense lymphoplasmacytic infiltration in the background (Figure 1). The carcinoma cells were positive for pancytokeratin, CK5/6, p63, negative for

HPV, p16, EBV on immunohistochemical study and negative for EBER on ISH. A diagnosis of LEC was rendered on the biopsy. Examination of the nasopharynx and Waldeyer's ring found no lesions. Subsequent right radical parotidectomy, right neck dissection and right mastoidectomy were performed. Gross examination revealed almost total replacement of the parotid gland by a 4.5 x 3.2 x 2.3 cm mass with areas of necrosis. Microscopic examination showed LEC with extraparenchymal extension and perineural invasion. Metastatic carcinoma was identified in two lymph nodes. Surgical resection margins are clear. Patient received post-surgery concurrent chemotherapy and radiotherapy (6 cycles of weekly Cisplatin 40 g/m<sup>2</sup> IV and a total of 6,360 Gy in 30 fractions). Metastatic carcinoma to right proximal humerus was detected about 15 months after surgery and was treated with 6

**Table 1. LEC of the parotid gland in non-endemic area and non-predilected ethnic group with EBV study described in the English literature**

Author	Reference	Ethnic group	Sex	Age	EBV study
Hamilton-Dutoit et al (1991)	#13	Faroese	M	74	ISH-DNA -
Hamilton-Dutoit et al (1991)	#13	Dane	F	32	ISH-DNA -
Kountakis et al (1995)	#14	Hispanic	F	68	ISH-EBER -
Kountakis et al (1995)	#14	Hispanic	F	57	ISH-EBER -
Kotsianti et al (1996)	#15	White	M	64	ISH-EBER +
Squillaci et al (2000)	#16	Italian	F	54	ISH-EBER +
Wu et al (2001)	#17	Italian American	F	54	ISH-EBER +
Bialas et al (2002)	#18	Polish	F	74	ISH-EBER +
Squillaci et al (2006)	#19	Italian	F	72	ISH-EBEB +
Saqui-Salces et al (2006)	#20	Mexican Mestizo	F	56	ISH-EBER +
Saqui-Salces et al (2006)	#20	Mexican Mestizo	F	26	ISH-EBER +
Abdelkrim et al (2009)	#21	North African	F	70	ISH-EBER +
Ambrosio et al (2013)	#22	Italian	F	45	ISH-EBER +

cycles of carbo/taxotere (carboplatin AUC5 IV on day 1 plus docetaxel 65 mg/m<sup>2</sup> IV on day 1 every 3 weeks). Stereotactic body radiation therapy (SBRT) consisted of 3 fractions of 3000 cGy was administered to the right humeral lesion. Size of humeral lesion remained unchanged and appeared less solid on MRI eight months post treatment.

### Discussion

LEC characterized by islands of anaplastic carcinoma cells with dense benign stromal lymphoplasmacytic infiltration was first described in the nasopharynx by Schminke in 1921 [4]. Although LEC rarely occurred outside nasopharynx, involvement of various organs, such as lung [5], breast [6], bladder [7], oropharynx [8], maxillary sinus [9] had been described. Primary LEC of salivary gland is rare. The first case of LEC of parotid gland was described in 1962 by Hildermann et al [10].

When primary LEC involves the salivary gland, about 80% of tumor involves the parotid gland [11]. It accounts for about 0.4% of all malignant salivary gland tumors. However, the rare prevalence is relative since LEC of salivary gland has a unique ethnical and geographical predilection, affecting mainly Eskimos and Orientals in Greenland, Southeast Asia and Japan. The Eskimos have the highest incidence of malignant salivary gland tumor, of which most are LEC [12]. So far, about 19 cases of LEC of salivary gland, all of which affecting the parotid gland, occurred in non-endemic areas and non-predilected ethnic groups had been reported in the English literature [13-22]. Patients usually presented with parotid mass. Facial nerve involvement and cervical lymph node metastasis occurred in about 20% and 40% of cases at presentation, respectively [21].

LEC of parotid gland can be diagnosed cytologically on fine needle aspiration when the smears

showed undifferentiated malignant epithelial cells surrounded by lymphocytes in the background [20]. The mere presence of lymphoid cells with no or minimal epithelial cells in the fine needle aspiration smears, as in the present case, posed diagnosis challenges. However, its possibility should be suspected when the clinical presentation is not typical of lymphoproliferative disorder. Histologically, LEC of parotid gland is indistinguishable from metastatic LEC of nasopharynx. The diagnosis of primary LEC of parotid gland should be established only after thorough examination and exclusion of primary tumor involving nasopharynx and mucosa over Waldeyer's ring.

An association of EBV with LEC of nasopharynx was first reported by Zur Hausen et al in 1970 [23], and the association was consistent irrespectively of ethnic group [24]. A similar strong association was observed in LEC of salivary gland in the endemic areas and predilected ethnic groups [13, 24]. Salivary gland is a known reservoir for EBV replication. The strong association in the endemic areas suggested a possible role of EBV in the pathogenesis of the tumor. It was postulated that EBV latency might have associated with neoplastic transformation of keratinocytes and tumorigenesis of lymphoepithelial carcinoma of the salivary gland [25]. Cases associated with chronic autoimmune disease suggesting an altered immune response in containing EBV infection had been reported [20]. The lymphoid elements were considered to be a reactive response to antigens induced by the virus on the tumor cells [14].

The association with EBV was less consistent with LEC of parotid gland in non-endemic areas. Review of English literature identified 13 cases of LEC of parotid gland in non-endemic areas and non-predilected ethnic groups with EBV study by in-situ hybridization (ISH) for DNA or ISH for EBV-encoded small RNAs (EBER). Including the present case, 38% (5 cases) are negative for EBV (Table 1). The observation suggested that EBV may be an important contributing factor, but not a necessary factor in the pathogenesis of LEC of parotid gland. Human papilloma virus (HPV) association with benign lymphoepithelial lesion in salivary gland [26] and association with LEC in oropharynx and breast [27, 28, 29] has been described, but study for HPV in LEC of salivary gland has not been reported. Although immunostains for HPV and p16, a surrogate marker for HPV, were both negative in the present case, study for possible association with HPV might be worthwhile particularly in EBV negative

cases. Close association with benign lymphoepithelial lesions has been reported in EBV negative LEC of parotid gland [14]. The possibility of malignant transformation of an epimyoeplithelial island in the lymphoepithelial lesions has been suggested.

The main treatment modality for LCA of parotid gland is combination of complete surgical excision with clear margins and radiotherapy [30]. The five-year survival rate for patients underwent surgery and radiotherapy was 85.6% [31]. Therapy modality with radiotherapy alone to avoid poor functional and cosmetic outcomes of radical surgery had been reported in the literature [32, 33]. Systemic chemotherapy was recommended for patients who presented with regional lymphadenopathy [32]. In the present case, the patient was treated with post-surgery combined chemotherapy and radiotherapy due to the presence of regional lymph node metastasis. Patient remained disease free for 15 months. The size of the humeral metastatic lesion remained unchanged and appeared less solid on MRI after subsequent chemotherapy and SBRT, compatible with favorable response to therapy. Due to the rarity of LEC of the parotid gland, the optimal treatment options and prognosis have not been extensively studied. With the relatively limited data, the prognostic implications of the presence or absence of EBV in LEC are uncertain.

So far, the pathogenesis of LEC remains unclear and its high association with EBV in endemic areas with certain ethnic group is still unexplainable. This case demonstrated a rare EBV-negative LEC of parotid in a patient of non-predilected ethnic group in a non-endemic area, suggesting factors other than EBV, such as environmental and genetic predisposition, may have a contributing role in the pathogenesis of the tumor [34]. Additional studies in non-endemic areas will be necessary to clarify the pathogenesis.

#### Abbreviations list

LEC, lymphoepithelial carcinoma;  
EBV, Epstein-Barr virus;  
ISH, in-situ-hybridization  
RNA, ribonucleic acid;  
EBER, EBV-encoded small RNAs;  
HPV, human papilloma virus;  
IV, intravenous;  
Gy, Gray;  
SBRT, Stereotactic body radiation therapy;  
MRI, magnetic resonance imaging;

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