

LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE UTERINE CERVIX SHOWING NEGATIVE EPSTEIN-BARR VIRUS AND POSITIVE HUMAN PAPILLOMA VIRUS PROPERTIES

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ABSTRACT

Lymphoepithelioma-like carcinoma (LELC) of the uterine cervix is a rarely seen variant of squamous cell carcinoma. It differs from the usual squamous cell carcinoma with its better prognosis, and different clinical behavior and morphology. Different association rates have been reported between LELC and Epstein-Barr virus and human papilloma virus in the Asian and Western countries; however, the relationship remains

controversial. In order to make a contribution to the further studies on the etiopathogenesis of LELC, we, herein, present a 62-year-old Turkish female with LELC of the uterine cervix, which is negative for Epstein-Barr virus but positive for human papillomavirus virus.

Key Words: Lymphoepithelioma-like carcinoma, cervical carcinoma, epstein-barr virus, human papilloma virus. *Nobel Med 2014; 10(2): 84-87*

EPSTEİN-BARR VİRÜS NEGATİFLİĞİ VE HUMAN PAPİLLOMA VİRÜS POZİTİFLİĞİ GÖSTEREN SERVİKSİN LENFOEPİTELİOMA BENZERİ KARSİNOMU

ÖZET

Serviksın lenfoepitelioma benzeri karsinoması (LELC) daha iyi prognoz göstermesi, farklı klinik davranışı ve morfolojisi ile squamöz hücreli karsinomanın nadir bir varyantıdır. Epstein-Barr virus ve human papilloma vi-

rus ile ilişkisi Asyada ve Batı ülkelerinde değişik oranlarda gösterilmiş ancak hala tartışmalı olarak kalmıştır. Biz 62 yaşında bir Türk kadınında Epstein-Barr virus negatifliği ve Human papilloma virus pozitifliği gösteren uterin serviksın lenfoepitelioma benzeri karsinomu etyopatogeneze yönelik gelecekteki çalışmalara katkıda bulunmak amacıyla sunuyoruz.

Anahtar Kelimeler: Lenfoepitelioma benzeri karsinom, servikal karsinom, epstein-barr virus, human papilloma virus. *Nobel Med 2014; 10(2): 84-87*

INTRODUCTION

Lymphoepithelioma, which is characterized by undifferentiated malignant cells with vesicular nuclei that shows prominent stromal lymphocytic infiltration and syncytial growth pattern, has been primarily identified in nasopharynx. Later on, similar histological characteristics have been shown in salivary gland, lungs, thymus, and stomach.¹⁻³ Lymphoepithelioma-like carcinoma (LELC) of the uterine cervix has been reported as a variant of the conventional squamous cell carcinoma; and it has also been reported in the vulva, vagina, and endometrium.^{3,4}

The etiopathogenesis of LELC has been questioned in terms of Epstein-Barr virus (EBV), which has strong association with the tumors of the nasopharynx and tumors at other anatomical locations, and human papillomavirus virus (HPV), which has been considered responsible for the carcinogenesis of squamous cell carcinoma. Nonetheless, studies conducted in the Western countries and in Asia have shown no clear results, and the relationship remains controversial.^{3,5-12}

Herein, we present pathological and immunohistochemical findings of a 62-year-old Turkish female with LELC of the uterine cervix, which is negative for EBV but positive for HPV.

CASE REPORT

A 62-year-old female patient, who had been menopausal for seven years, was admitted to the Gynecology Outpatient Clinic with complaints of vaginal bleeding and vaginal discharge for 3 months. She had no previous history of a gynecological problem or malignancy. General physical examination and laboratory findings were unremarkable. On her pelvic examination, the cervix was multiparous, seemed to be retroposed, and there was an infected, fragile and polypoid lesion that slightly protruded from the cervical os. The lesion was bleeding on touch. Neither the parametrium nor the pelvic wall was involved, and other pelvic organs were normal [International Federation of Gynecology and Obstetrics (FIGO) Stage I]. The patient underwent dilatation & fractional curettage. The patient, who was diagnosed with LELC of the uterine cervix on histopathological evaluation, underwent radiotherapy following intracavitary brachytherapy. At the end of the follow-up visits performed at 3-month intervals, she was disease-free at 20 months.

Pathological Findings

On pathological examination, tumor tissue, which was differentiated with its loose fibrillary stroma, and

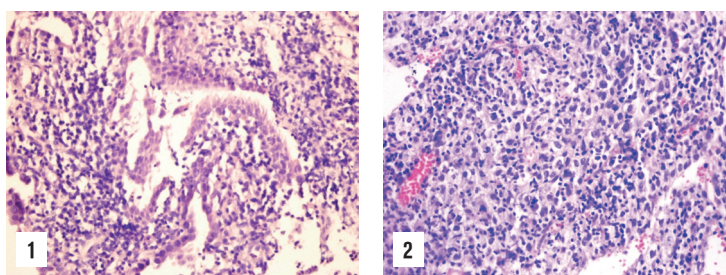


Figure 1: Histological features of the tumor. Low power view. This photomicrograph showing a typical syncytial growth pattern of undifferentiated malignant cells with prominent lymphocytic infiltration (HE;x200).

Figure 2: High power view. The atypical cells show hyperchromatic nuclei, increased nucleocytoplasmic ratio, distinct nucleoli and mitosis. Some atypical cells have clear cytoplasm. Distinction between carcinoma and lymphoma is unclear. (HE;x400)

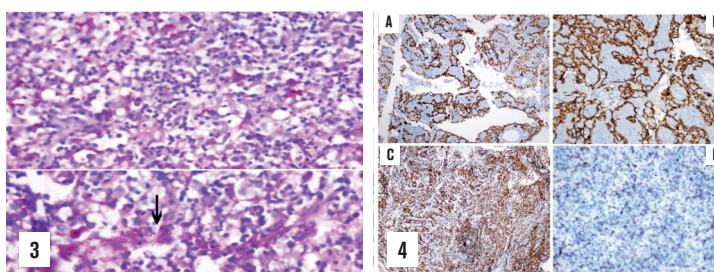


Figure 3: PAS positive cytoplasmic granules in tumor cells (PAS staining, arrow showing PAS+granules.x400)

Figure 4: Immunohistochemical findings: (A,x100); positive Pan CK staining in syncytial tumor cells while negative in lymphocytes. (B,x200); positive staining for EMA in syncytial tumor cells and negative staining in lymphoid cells. (C,x100); positive immunoreactivity for CD 45 in mature lymphoid cells and negative immunoreactivity in tumor cells. (D,x400); positive immunoreactivity for HPV in tumor cells.

which made anastomosis and showed cellular-dense mature lymphocytic infiltration as cords and masses, was observed in all tissue samples taken from the endometrium and cervix (Figure 1). Histologically, the tumor was composed of malignant epithelioid cells and mature lymphoid cells. The epithelioid cells showed cellular atypia including polygonal cells with large, oval-round and irregular hyperchromatic nuclei, increased nucleus-cytoplasmic ratio, mitotic figures, and prominent nucleoli (Figure 2). The cytoplasm appeared to be fine granular, slightly eosinophilic, and clear in patches. Periodic acid-Schiff positive granules were observed in tumor cells with clear cytoplasm (Figure 3). The number of mitotic figures was 1-2 mitoses per high-power field. These features are highly suggestive of malignant nature. The malignant epithelioid cells showed immunoreactive epithelial markers such as pan-Cytokeratin (1:50-AE1/AE3, Thermo, UK) and EMA (1:400-800, Epithelial Membran Antigen, E29 clone, Thermo, UK). From these overall findings, it is concluded that the epithelioid cells are carcinoma cells. The carcinoma cells did not show any differentiations histologically.

The lymphoid cells consisted of mature lymphoplasmacyte, and showed no atypia.→

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Immunohistochemically, the lymphocytes were composed of various types of lymphocytes, and showed no pan-Cytokeratin (AE1/AE3) expression and EMA. Also CD5 (1:20-40, 4C7 clone, Thermo, UK), CD15 (BY87 clone, Leica, UK), and CD30 (1:40-80Ber H2 clone, Thermo, UK) stains were negative to rule out lymphoma. However lymphoid cells were positive for CD45RO (1:200-400, UCHL1 clone, Thermo, UK). From these overall examination, it can be concluded that the lymphocytes are not tumor cells but are reactive non-neoplastic lymphocytes.

While staining with EBV associated molecule latent membrane protein 1 (1:50, LMP-1, clone, Thermo, UK) showed no immunoreactivity, a strong HPV (1:20, K1H8 clone, Thermo, UK) positivity was observed (Figure 4A-D). Testing for HPV used genotypes including type 6, 11,16,18,31,33,42,51,52,56,58. Positive staining was identified as brown cytoplasmic dots.

DISCUSSION

LELC of the uterine cervix is a rare variant that has a better prognosis than squamous cell carcinoma.⁴ These rare tumors are commonly seen in stomach, salivary glands and lungs, and are generally associated with EBV infection. EBV seems to be associated with the tumors of the foregut-derived organs.¹ It accounts for 0.7% of all primary cervix cancers in the Western society, whereas it has such a high incidence as 5.5% in Asia. The disease is seen between 21 and 58 years of age in the West and between 58 and 77 years of age in the East.²

Macroscopic (gross) appearance of LELC, which typically affects the young population, may range from a cervical lesion that cannot be seen with the naked eye to a large exophytic mass. If lymphoid reaction is prominent in scanty biopsy specimens obtained from a woman presenting with vaginal bleeding, generally, malignant cells might be overlooked and misdiagnosed as an inflammatory reaction. Biopsy should be repeated in such a case with no doubt. Non-keratinized squamous cell carcinoma, glassy cell carcinoma, Lennert's lymphoma in particular, and metastatic Schmincke-Regaud tumor should be considered in the differential diagnosis due to the presence of cells with vesicular nuclei and marked nucleoli on microscopic examination because, LELC of the uterine cervix, which is a variant of squamous cell carcinoma, has a better clinical prognosis than the usual squamous cell carcinoma, as was shown in the Hasumi's study.^{2,4,8} The carcinoma cells of the present LELC showed no squamous differentiation. The negative reactions of CD5, CD15, CD30 definitely indicate that the tumor was not malignant lymphoma. In glassy cell carcinoma

tumor cells have moderate amount of cytoplasm with a ground glass or finely granular appearance, a prominent eosinophilic and PAS positive cell wall. PAS staining showed a small amount of glycogen in the cytoplasm of tumor cells not in cell wall. Glassy cell morphology was not observed. PAS showed glycogen in the cytoplasm of tumor cells. Therefore, the clearness of the cytoplasm of some tumor cells is thought to be due to glycogen. These findings also indicate that the tumor cells are not poorly cohesive signet-ring cell carcinoma-like cells seen in various organs.

Treatment options include radical hysterectomy plus bilateral pelvic lymphadenectomy or radiotherapy following intracavitary brachytherapy.

By considering all the above-mentioned features of LELC, the present case was diagnosed with LELC of the uterine cervix based on punch biopsy and subsequent examination with light microscope and with immunohistochemical staining. EBV has been suggested as a potential causative agent and has been detected in 75% of cervical LELC cases in Asian women. The latent membrane protein 1 (LMP1) is a viral protein that regulates its own expression and the expression of human genes. LMP1 has a molecular weight of approximately 63 kDa, and its expression induces many of the changes associated with EBV infections and activation of primary B cells.² Therefore the presence of EBV and HPV, which might be associated with the etiology as is in the nasopharyngeal and cervical carcinomas, was investigated. At this point, we confronted different results about each virus reported from the Western countries and from Asia.^{3,5-12}

Tseng et al. identified the presence of EBV gene sequence by using polymerase chain reaction (PCR) in 11 (73.3%) out of 15 Asian women with LELC of the uterine cervix, whereas the presence of HPV 16-18 gene sequence was identified in only three (20%) patients.² On the other hand, Chao et al. examined nine women with LELC of the uterine cervix via in situ hybridization method and reported positive rates for EBV and HPV in 0% and 88.9% (n=8) in LELC of the cervix, respectively.¹⁰ The authors concluded that the EBV sequences might exist in a florid inflammatory stromal component but not in the carcinogenesis of LELC of the uterine cervix. LELC, which may occur in the other organs, may stimulate cellular and humoral immunity by means of dense lymphocytic inflammatory cell infiltration as a response of the host against the tumor, and shows better clinical prognosis.²

EBV could not be detected in any of the women with LELC of the uterine cervix reported until today →

in the Western society.^{3,6-12} On the other hand, the presence of HPV shows variations in the studies ranging from the absence of HPV to the presence of several (HPV type;16-18) or multiple types.^{2,6-12} These discrepancies suggest that different pathways might be involved in the etiopathogenesis of LELC of the uterine cervix in the Asian and Western countries. Moreover, two specific EBV variants, Taiwan and CAO strains isolated from patients with lymphoepitheliomas in Taiwan and the Republic of China have strengthened the above-mentioned hypothesis; the HLA-A2 and HLA-BW histocompatibility loci have been identified after cytogenetic analysis of tumor tissues among the Chinese population.²

In conclusion, LELC of the uterine cervix, which is a rarely seen tumor, is an intriguing and different clinicopathological entity that attracts attention of the pathologists and clinicians.

We think that, further molecular genetic studies that would be performed on a large number of cases with LELC of the uterine cervix in Asia and in the Western countries will play a significant role in both elucidating the etiology and exhibiting the geographical differences.

* The authors declare that there are no conflicts of interest.



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