

# Lymphoepithelioma-like carcinoma of the uterine cervix: correlation with Epstein-Barr virus and human papillomavirus infection. A single-center experience

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## Summary

**Background and objectives:** Lymphoepithelioma-like carcinoma of the uterine cervix (LELC) is a rare subtype of the squamous cell carcinoma with unclear viral carcinogenesis and prognosis. **Aim:** We aimed to investigate the status of HPV and EBV infection in a cohort of Caucasian women with LELC of the uterine cervix and to compare the results on prevalence, association with both viruses and methods of detection in this disease with the results of other studies. **Materials and methods:** We retrospectively evaluated all patients with LELC, diagnosed and treated at Department of Gynaecologic Oncology, Medical University Pleven, Bulgaria between 2008 and 2015. The status of infection with HPV and EBV was investigated on tumor tissue by polymerase chain reaction (PCR) and in situ hybridization (ISH). We compare the results with the results from a systematic search of the literature on this topic. **Results:** LELCs represented 3.03% (16 patients) of all stage I cervical carcinoma cases. Infection with HPV and EBV was investigated in 50% (8) of them. ISH and PCR testing detected HPV in 37.5% (3) and 50% (4) of the patients; EBV in 12.5% (1) and 75% (6). No cases of co-infection were found with ISH and 4 with PCR. In the literature are reported 98 cases of this disease and infection with EBV is found in 25.7% of the tested patients. **Conclusion:** HPV and EBV strains and a co-infection of the two viruses are possible factors in genesis of LELC of the uterine cervix. Our data suggests that infection with EBV could be more common in Caucasians women with LELC, than previously reported.

**Key words:** Cervical cancer; Lymphoepithelioma-like carcinoma; Epstein-Barr virus; Human papillomavirus; In situ hybridization; Polymerase chain reaction.

## Introduction

Cervical carcinoma is the fourth most frequent cancer disease in women worldwide with over half a million new cases each year [1]. Human papillomavirus (HPV), human herpesvirus II, and cytomegalovirus are proven as factors in cancerogenesis of cervical carcinoma [2]. HPV is considered to be of greatest significance in the etiopathology of the disease [3]. This has opened a new pathway for cancer prevention [4]. Increasingly more researchers focus also on Epstein-Barr virus (EBV) as it may also have a poten-

tial role in the oncogenesis of this carcinoma [5, 6]. In the last few years two meta-analyses were published describing EBV as co-factor in the genesis and/or progression of cervical cancer [7, 8] but it's role is still unclear because more than 90% of people worldwide are affected [9]. The pooled prevalence of EBV in cervical cancer has been found to be 43.63%, which is two times higher compared to healthy controls (19%) [7].

Histologically, cervical carcinomas are subdivided into squamous cell carcinoma (SCC), adenocarcinomas and adenosquamous carcinomas, with SCC being the most fre-

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Table 1. — Search strategy and key words.

Key words	Pubmed	Science Direct	Scopus	
Lymphoepithelioma-like cervical cancer	80	139	268	
Lymphoepithelioma-like carcinoma, uterine cervix	39	46	230	
Total	119	185	498	802

quent histological type, diagnosed in 90 to 95% of all cervical cancer cases [10]. Each of these cancer types is further subclassified to subtypes [11]. Lymphoepithelioma-like carcinoma (LELC) is an unusual variant of SCC, first described by Hamazaki *et al.* in 1968 [12]. It belongs to the squamous cell carcinoma with variants of cervix uteri, which are rare cancers. This makes difficult the investigation of the tumor behavior and the prognosis reported by other authors [13] is different from our experience. There is data that LELC is related to co-infection of HPV and EBV in Asian women, whereas in Caucasian females with LELC HPV is the only established viral pathogen [14, 15]. Additional problems are the different sensitivity and positivity rates of EBV demonstrated when different diagnostic assays are applied – PCR, *in situ* hybridization and immunohistochemistry [6]. Thus, the role of EBV in the carcinogenesis of the LELC of the uterine cervix is not known.

We first aimed to investigate the prevalence of HPV and EBV infection among our cohort of Caucasian women with LELC of the uterine cervix. Secondly, we aimed to perform a systematic review on studies reporting the prevalence of LELC of the uterine cervix, its association with HPV and EBV and the methods of detection of these viruses.

## Materials and Methods

We retrospectively evaluated the medical records of all patients with cervical carcinoma diagnosed and treated at the Gynaecologic Oncology Clinic, University Hospital, Pleven, Bulgaria, between January 1st, 2008, and December 31st, 2015. We identified a group of 16 Caucasian women, diagnosed with LELC. All histological slides were reviewed by dedicated experts in order to reconfirm the histological diagnosis of this rare entity. All cases were subsequently tested for HPV and EBV infection via ISH and PCR. Eight cases were excluded of the study due to material exhaustion and inability to conduct further tests. Pathological and clinical staging was done as per TNM classification or FIGO staging.

### Methods for detection of HPV and EBV

#### Chromogenic in situ hybridization

All cases were tested via manual in situ hybridization (CISH) using the ZytoFast EBV Probe (ZytoVision) for EBV-RNA detection in paraffin-embedded tissues, and the ZytoFast Plus CISH Kit HRP-DAB (ZytoVision). Specimen pretreatment (e.g., dewaxing, proteolysis) and further processing was carried in compliance with the instructions for use of the ZytoFast PLUS CISH Implementation

Kits (ZytoVision). Enzyme reaction with chromogenic substrates led to formation of coloured precipitates. Hybridized probe fragments were visualized by light microscopy after nuclei dye counterstaining.

Patients were tested for high-risk HPV DNA-ISH employing a Ventana Benchmark Autostainer with a commercial kit (Inform HPV III family 16 trials (B), recognizing the following HPV subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66 and ISH iVIEW Blue Plus Detection Kit.

### Detection of EBV and HPV DNA by real-time PCR

EBV and HPV DNA detection in all extracted DNA samples was performed using AmpliSens EBV-screen/monitor-FRT PCR kit and the AmpliSens HPV HCR genotype-FRT PCR kit (HR HVP 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), respectively (Ecoli s.r.o., Slovak republic). Preparation of the PCR reaction mixture and PCR cycling parameters were as specified by manufacturer's instructions. The  $\beta$ -globin gene served as an internal endogenous control. The PikoReal 96 Real-Time PCR System (Thermo Scientific, USA) was applied for DNA amplification and detection of fluorescent dyes. Reactions were considered valid only if no PCR products are detected in the negative control.

### Systematic review

In order to compare our results with the results on prevalence and methods of detection of the viral infections in LELC of the uterine cervix in patients from other published studies we performed a search in PubMed, Scopus and ScienceDirect with the following terms: "lymphoepithelioma-like cervical cancer" and "lymphoepithelioma-like carcinoma, uterine cervix". We searched among total of 802 articles in the three databases, published before May 2020. Two reviewers independently evaluated the manuscripts and excluded all studies for other cancer localizations and duplicate articles. Further analysis is performed following the PRISMA guidelines. The search strategy and key words are presented in Table 1.

## Results

### Results from our retrospective cohort

Five hundred and twenty eight patients with cervical carcinoma were diagnosed and surgically treated at the Gynaecologic Oncology Clinic, University Hospital, Pleven, Bulgaria, during the study period. Sixteen patients (or 3.03 % of all cases of stage I cervical carcinoma) were diagnosed with LELC carcinoma and were further investigated in the current study. All patients with LELC were referred di-

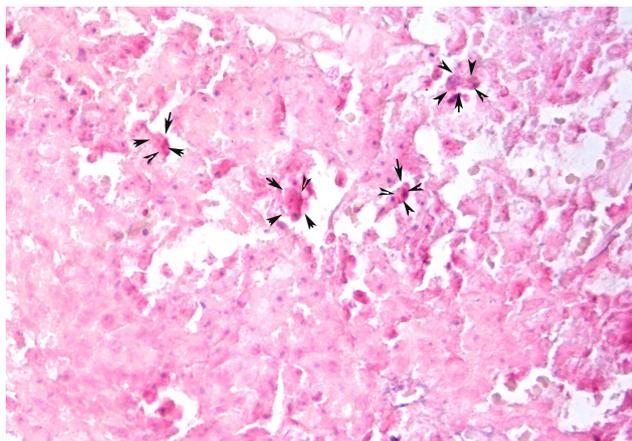


Figure 1. — Signals, produced by HPV probe in nuclei in a LELC case. ISH 400 $\times$ .

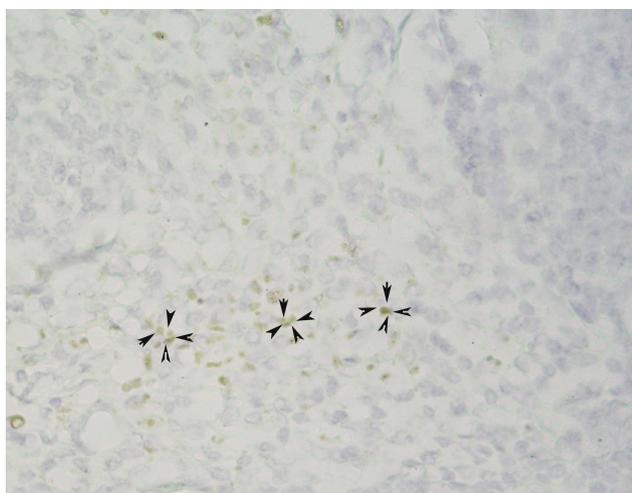


Figure 2. — Signals, produced by EBV probe in nuclei in a LELC case. ISH 400 $\times$ .

rectly to surgery, without neoadjuvant treatment to be applied. The diagnosis was histologically confirmed with cervical biopsy prior surgery.

Mean age of the patients was 49.6 years (range 32-67). The main complaint that leads to diagnosis was abnormal genital bleeding. Patients underwent radical hysterectomy with total pelvic lymph node dissection and were consequently referred for adjuvant radiotherapy. Only 8 (50%) patients were tested for HPV and EBV infection via ISH and PCR.

HPV infection was diagnosed with ISH in 3 patients (37.5%), and EBV in 1 (12.5%); there was no co-infection reported with ISH (Figures 1 and 2). PCR diagnosed HPV infection in 4 patients (50%) and EBV infection in 6 (75%); co-infection was present in 4 cases (50%). It is noteworthy that the viral infection, detected in all four ISH positive cases was confirmed by PCR.

From all LELC patients 13 (81.25%) were in FIGO (2009) IB1 stage and 3 patients (18.75%) were in FIGO

(2009) IB2 stage. The size of the primary tumor was < 2 cm in 5 patients (31.25 %), 2-4 cm in 8 patients (50%) and > 4 cm in 3 patients (18.75 %). Lymph nodes had metastasis in 2 patients (12.5%), no metastasis in 13 patients (81.25%) and unknown in one patient. The clinicopathological characteristics such as tumor size and lymph node involvement as well as the results of ISH / PCR for the 8 investigated patients are shown in Table 2.

#### Systematic review

We found 37 reports in concordance with our review criteria. They include a total of 98 cases of LELC of the uterine cervix, reported in the literature.

From the 37 articles, 30 are case reports or are reporting a small patients' series up to 2 patients. Philippe *et al.* [13] reported 3 cases but they detected HPV and EBV only in 2 of them and this is the reason why we excluded them from larger series.

In total the case reports include 36 patients. In most of the case reports the HPV and EBV status are investigated with different methods. EBV is investigated in 7 case reports with ISH alone, in 3 of the reports with PCR, in 3 of the case reports both methods of detection of the viral infection is applied. In the remaining 15 cases the infection with EBV is investigated with immunohistochemistry or is not investigated at all. The results from the larger studies are summarized in Table 3.

From all identified studies and a total of 98 patients 66 were tested for HPV and 74 for EBV. Association with HPV and EBV, independent of the method of detection, is found in 31 (47%) and 19 (25.7%) of all tested patients with LELC of the uterine cervix, respectively, reported in the literature. PCR is used in 11 of the reports for detection of EBV and shows higher rate of detection of EBV compared to ISH.

#### Discussion

Lymphoepithelioma was first described as a nasopharyngeal neoplasm. Similar tumours were later reported in salivary glands [23], lung [24], stomach [25] and thymus [26] and were referred to lymphoepithelioma-like carcinoma (LELC). In the female genital tract LELC has been documented in the vulva, vagina, uterine cervix and endometrium [27]. The histological phenotype of this tumour consists of a syncytial growth pattern of undifferentiated tumor cells with significant lymphoplasmacytic infiltration in the stroma [13].

LELC of the uterine cervix has a low frequency of 5.5% in Asian [14] and 0.7% in Caucasian women. The incidence rate of LELC in our group of 3.03% of all uterine cervix carcinomas is considerably higher than the reported for Western women. A potential explanation of this fact is that in our cohort of patients only women, who underwent initial primary surgery, are included; patients who are referred for preoperative or definitive radiotherapy are not included. Other possibility is the high rate of EBV infection in Bulgarian population of reproductive age women

Table 2. — Clinicopathological characteristics and ISH / PCR results of the patients.

NO	age	Stage	Size of tumor	Lymph node metastasis	ISH		PCR	
					HPV	EBV	HPV	EBV
1	48	pT1b1pNoMo	2 – 4	negative	+	-	+	+
2	46	pT1b1pNoMo	2 – 4	negative	-	-	-	+
3	34	pT1b1pNoMo	2 – 4	negative	-	-	-	-
4	48	pT1b1pNoMo	< 2	negative	-	-	-	-
5	61	pT1b1pNoMo	2 – 4	negative	-	+	+	+
6	40	pT1b1pNoMo	< 2	negative	-	-	-	+
7	47	pT1b2pNoMo	> 4	negative	+	-	+	+
8	66	pT1b2pNoMo	> 4	negative	+	-	+	+
<b>Total n (%) mean 48.7</b>					<b>3 (37.5%) 1 (12.7%) 4 (50%) 6 (75%)</b>			

Table 3. — Studies reporting the prevalence of EBV and HPV infection and the methods of detection in LELC of the uterine cervix.

Author (year)	Country	N	HPV- positive n (%)		EBV-positive n (%)	
			ISH	PCR	ISH	PCR
Tseng <i>et al.</i> [11]	Taiwan	15	Not done	3 (20%)	Not done	11 (73.33%)
Chao <i>et al.</i> [17]	Taiwan	9	Not done	8 (88.8%)	0 (0%)	0 (0%)
Pinto <i>et al.</i> [18]	USA	8	6 (75%)	6 (75%)	0 (0%)	0 (0%)
Oliveira <i>et al.</i> [19]	Brazil	6*	Not done	Not done	0 (0%)	Not done
Takai <i>et al.</i> [20]	Japan	3	0 (0%)	Not done	0 (0%)	Not done
Martorell <i>et al.</i> [21]	Spain	4	Not done	0 (0%)	Not done	0 (0%)
Yordanov <i>et al.</i> [22]	Bulgaria	13**	3 (37.5%)	4 (50%)	1 (12.5%)	6 (75%)

\*Oliveira *et al.* [19] are not found during this systematic search. But since they report quite high number of patients, we included them.

\*\*We have previously reported the viral status in LELC of the cervix investigated by immunohistochemistry in 13 patients from our institution. Later on, the status of HPV and EBV is investigated in 8 of them with PCR and ISH.

[28]. In comparison to traditional carcinoma types of uterine cervix, LELC affects predominantly younger women, most frequently younger than 40 years [12]. Only 4 of our patients (25%) were under the age of 45 years and only 2 (12.5%) are under the age of 40.

There are large variations in the reported tumour size of LELC carcinomas of the uterine cervix - from a non-visible lesion to a large mass. Most studies are reporting early stage of diagnosis in this tumor type and better prognosis compared to the most common types of cervical carcinoma [14, 17]. The experience of our institution differs from those results, since the 5-year overall survival rate of our patients with LELC of uterine cervix as previously reported is 69.23% [29].

The pathogenesis of LELC of the uterine cervix is still not clear. It is presumed that viral oncogenesis may have a role as there is data about EBV infection in Asian women [14, 15] and HPV infection in Caucasians [14]. These findings are not definitive as reports have failed to confirm the results prospectively [30, 31] Tseng *et al.* reported that 73.3% (11/15) of their cohort of Asian women, diagnosed with LELC, are positive for EBV antibody [14]. In Caucasians, Noel *et al.* tested only for HPV [32]. Bais

*et al.* also report HPV infection in some of their patients [33]. Chao *et al.* publish the same results and hypothesise that racial and/or geographic factors may be relevant in the pathogenesis of LELC [17].

Consistent with our results are previously published studies suggesting that LELC is etiologically linked to high-risk HPV types of infections [34]. This is also in line with the results of our systematic review, where 47% of investigated patients were positive for HPV.

The detection rate of EBV among our samples is 12.5% by ISH, and 75% by PCR. This could indicate plausible involvement also of EBV virus in the etiopathogenesis of LELC of the uterine cervix, since the rate of EBV found in the tumors of our cohort of patients is higher compared to the rate of EBV in other types of cervical cancer [7] Co-infection of high-risk HPV types and EBV may also contribute to the pathogenesis of LELC of the uterine cervix.

Our systematic review shows that the detection of both HPV and EBV is mostly performed using PCR and ISH, not with immunohistochemistry. In our series the results of ISH were confirmed by PCR, which appears to be a more sensitive method.

From all identified studies patients positive for EBV are found in 2 reports [14, 35]. One of them [31] is a case report. Tseng *et al.* [11] reported a prevalence of EBV of 73.22% among his patients as detected by PCR.

The co-infection of EBV and HPV is not observed in other studies, except ours. Tseng [14] is the only author reporting the prevalence of both viruses among his patient population, but he is not reporting a co-infection. Since in 50% of our patients a co-infection is observed and this is a higher prevalence than observed in other cervical carcinoma histologic types [7], further studies with more patients are needed to confirm this possible association.

## Conclusions

In our patients, the incidence of LELC in Caucasian patients is higher than reported, affecting predominantly older women than previously documented. High-risk HPV and EBV strains, as well as a co-infection with the two viruses, are possible factors in its genesis. EBV is significantly more common for Caucasians than previously reported.

## Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Medical University Pleven (approval number: 414-КЕНИД/31/03/2016).

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## Conflict of Interest

The authors declare no competing interests.

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