Review

PRESENCE OF EBV AND HPV INFECTION IN LYMPHOEPITHELIOMA-LIKE CARCINOMA IN THE UTERINE CERVIX

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Summary

Squamous cell carcinoma is the cause in most cases of cervical cancer. A very unusual subtype of squamous cell carcinoma is lymphoepithelioma-like carcinoma, found in less than 1% of the neoplasm processes in the uterine cervix. Histologically it looks like a large nest of big-sized tumor cells with large vascular nuclei. Immunohistochemical markers used for LELC are p63, p16, human leukocyte antigen-D related (HLA-DR), and B-cell lymphoma 2. Even though it has aggressive morphological features, it has a better prognosis than most carcinoma cases of the uterine cervix. The condition is treatable, with a hysterectomy and bilateral salpingo-oophorectomy as the most common method. There are rare cases of pelvic lymph node dissection reported in the literature.

There is data that lymphoepithelioma-like carcinoma is associated with the Ebstein-Barr virus and human papillomavirus. According to a survey by Tseng et al. and Chao et al., EBV is associated with LELC in Asian women, while HPV is associated with Caucasian women.

Due to the small number of studies found in the literature, no conclusion can be drawn concerning the said viruses' involvement in Asian and Caucasian patients.

Keywords: Ebstein-Barr virus, human papillomavirus, lymphoepithelioma-like carcinoma

Introduction

Lymphoepithelioma-like carcinoma (LELC) is a rare subtype of squamous cell carcinoma (SCC). It is a malignant tumor arising from rapid uncontrolled mitosis of transformed epithelial cells [1]. Morphologically, it is similar to undifferentiated nasopharyngeal carcinoma. Commonly, it presents as poorly differentiated epithelial cells in the nasopharynx. LELC is also detected in the lungs, skin, breast, thymus, stomach, esophagus, urinary bladder, and the uterine cervix [1,2,3].

LELC in the uterine cervix (UC) has a better prognosis, partially because it does not involve lymph nodes and is seen in younger women. The involvement of EBV and HPV in LELC of the UC in Asian and Caucasian patients has been proven multiple times by case reports and systematic reviews [1,4-6]. However, the data in the literature is inconsistent.

Epidemiology

The UC carcinomas are divided into three groups: SCC, adenosquamous carcinoma, and adenocarcinoma in most cases, being SCC (90-95%) [7]. LELC is an unusual variant of SCC in the UC. According to Tseng et al., 0.7 of the UC neoplasms are caused by LELC [5]. It is described by Hamazaki and al. in 1968 [9]. Yun H. (2017) claimed that it is associated with 5.5% of primary cervical cancer (PCC) in the Western world and 0.63% of the PCC in Japan. According to the literature, LELC has a frequency of 5.5% in Asia, of 0.7% in Western Europe, and 3.03% in Eastern Europe. These data come to prove that location has a significant impact on the spread of LELC. Age is another contributing factor. In 1977 Hasumi et al. published a study, reporting that 41% of the patients with LELC were under 40 years [9]. Another study has shown that only 37.5% of the patients involved are over 40, 12.5% of these are over 45. According to Tseng et al., the median age is 56 (range 37-72) [5].

Prognosis

Even though LELC of the UC seems to have aggressive morphological features, it has a better prognosis than SCC. It is characterized by fewer regional lymph node metastases. According to Tseng et al., LELC tumors in other organs are also less aggressive and are associated with good outcomes. Hasumi et al. explain that tumors may induce both humoral and cell-mediated immunologic reactions. The infiltrated lymphocytes found in the tumor stroma reflect the humoral and cell-mediated immune response to tumors. The response seems to reduce lymph node metastases and increase survival rate [9]. Yun et al. and Saroha et al., and other authors point out that their patients have no metastatic sites, namely lymph nodes [10,11]. However, Yordanov et al. have reported a case with metastatic pelvic lymph nodes [12].

Histology

Morphologically, LELC is defined by large anastomosing islands or nests of tumor cells growing in syncytial sheets (Figure 1). The cells are large and polygonal in shape, with large vesicular nuclei. Lymphocytic infiltration, marked by CD8+, is often present [13, 1].

Immunohistochemistry

Pinto et al. examined immunohistochemical markers used to diagnose LELC of the UC (Figure 2). Immunohistochemistry for p16 (Figure 3), p63, B-cell lymphoma 2 (BCL-2) (Figure 4), and human leukocyte antigen-D related (HLA-DR) were used. All 8 cases were p16, p63, and HLA-DR positive. BCL-2 samples were negative in 6 of the cases (75%), and there was weak positive staining in the remaining 2. BCL-2 results are slightly controversial, as BCL-2 is a protein that confers a selective growth enhancement to the EBV-infected B cells [4].

Martorell et al. published a study of 4 cases of LELC between 1990 and 2000. They discovered

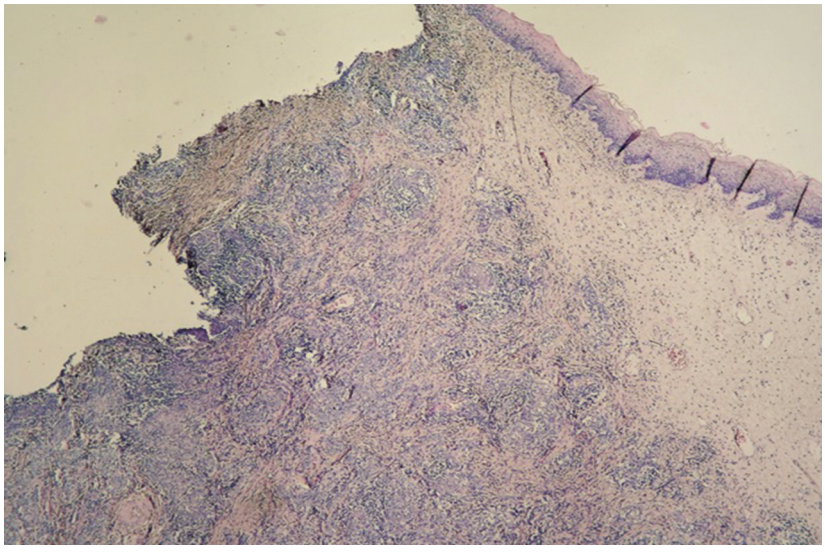

Figure 1. Histological image: Hematoxylin and eosin, x100

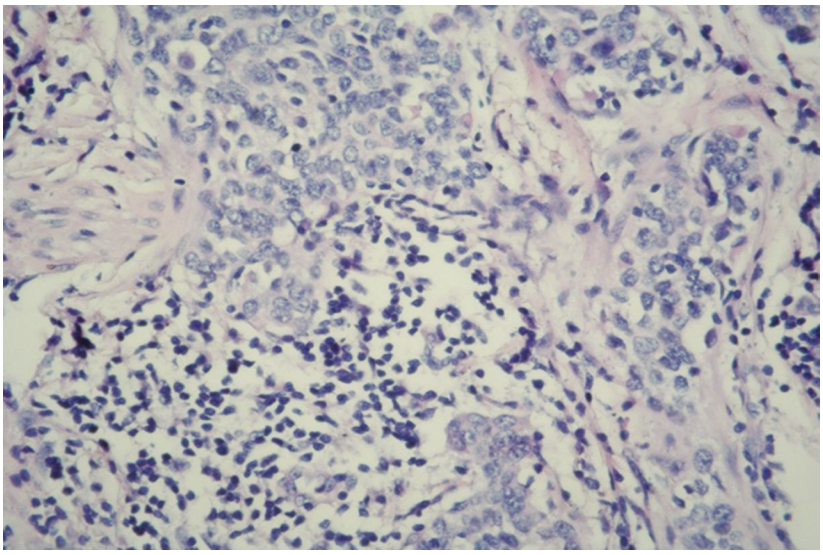

Figure 2. Hematoxylin and eosin, x400

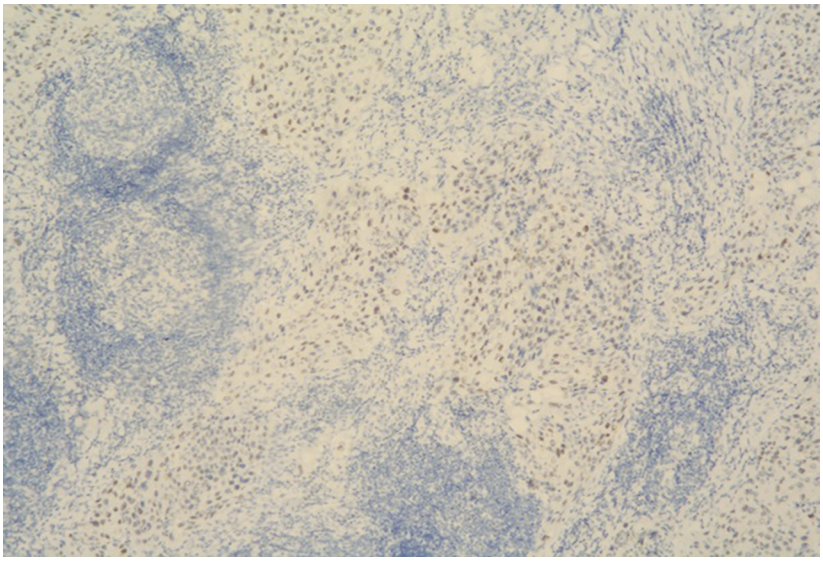

Figure 3. Immunohistochemistry: p16(+), x100

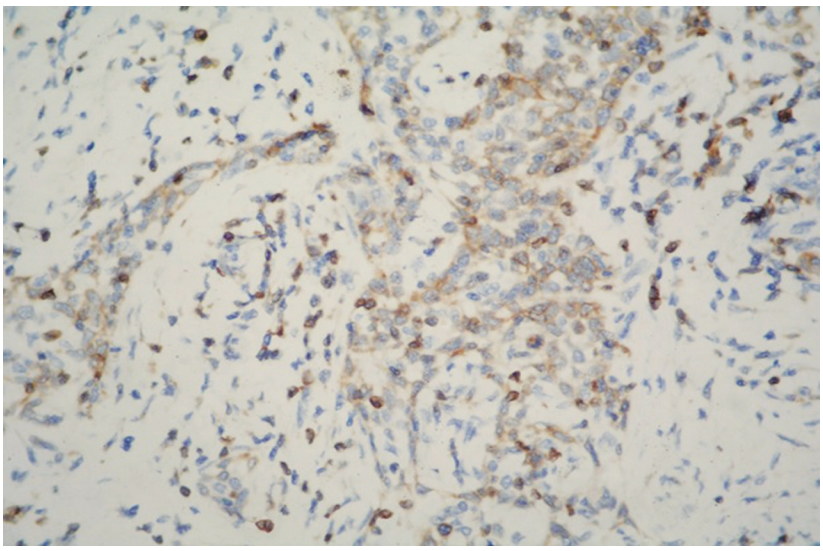

Figure 4. Immunohistochemistry: BCL-2(positive lymphocytes and singular tumor cells), x400

that tumor cells were positive for MIB-1, p53, and cytokeratins. BCL-2 and progesterone staining were negative. However, estrogen receptors were positive in one of the cases [14].

Treatment

Different surgical approaches have been reported in the literature. Sahora et al. have reported 2 cases, both of which were staged as Ib1 according to the FIGO classification. The first patient underwent a radical hysterectomy with ovarian conservation and pelvic and para-aortic lymph node dissection. The second patient had had a history of vaginal bleeding for seven months and underwent a radical hysterectomy with bilateral salpingo-oophorectomy with dissection of the pelvic and para-aortic lymph nodes [11].

Kaul et al. reported a case with FIGO stage 1 endometrial cancer. The patient underwent radical hysterectomy and pelvic lymph node dissection [15].

Yun et al. reported the case of a 43-year-old female with persistent vaginal bleeding for one month. The patient was diagnosed with FIGO stage Ib1 endometrial cancer. Radical hysterectomy with bilateral pelvic lymph node dissection and transposition of both ovaries was performed [10].

In all the cases, there was no evidence for metastases and complications during the follow-up.

EBV and HPV

The pathogenesis is unclear. It has been stated that EBV infection may have a role in Asian patients, and HPV - in Caucasian females. However, the results are not definitive.

The presence of EBV in LELC was first proved in 1997 by Tseng et al. in a study on 15 women. According to their study from 1997, 11 (73.3%) of the patients diagnosed with LELC had traces of EBV gene sequence. In 3 of them (20%), traces of HPV were found. In all of the samples, a PCR method was utilized. The study of Tseng et al. was conducted in Taiwan. Based on this study, the literature concludes on EBV's role in Asian women [5].

In 2009 Chao et al. conducted similar research again in Taiwan, addressing EBV and HPV's role. They used the data of 9 patients collected for four years with their respective clinicopathologic findings and follow-up data. After conducting an SPF1/GP6+ PCR for HPV and type-specific E6 PCR of the 18 most common HPV genotypes in Taiwan and PCR for EBV and ISH, it was estimated that 88.9% of the patients had HPV traces. HPV-16 was found in 3 cases, HPV-18, HPV-31, HPV-35, and HPV-58 in 1 case each. One of the cases displayed positivity for HPV-16 and HPV-58 both [6].

Another case series of Takai et al. from 2009 examined the correlation between HPV, EBV, and LELC, using ISH. The authors claimed that all 3 of the patients had no trace of either of the viruses. Thus, they concluded that in their Japanese series, there was no connection between this carcinoma, and HPV and EBV. However, the investigations revealed a large number of CD3(+) and CD8(+) cells and a low number of CD4(+), CD20(+), and CD79(+) cells [17]. These findings confirmed the hypothesis of Hasumi et al. from his publication from 1977 [9].

Pinto et al. conducted similar research in 2019. They tested eight women from the USA for HPV and EBV in LELC samples, using ISH and PCR. Seven of these (87.5%) were HPV positive. Of the ISH samples, six were positive. There were six positive PCR samples, as well. However, one of the PCR (+) was ISH (-). Of the HPV genotypes, one was positive for HPV 33, three were positive for HPV 16, and two samples were positive samples for HPV 18. This study's results should be taken with caution because of the USA's heterogenic population and the possibility for these patients to have Asian, Black, or Caucasian background [4].

A study by Yordanov et al. was published in 2019. It collected the data of all 17 females diagnosed with LELC between 2007 and 2016. Fourteen (82%) patients were tested for the presence of EBV or HPV via IHC. Of them, eight (57.1%) were positive, and six were negative. The remaining three patients were not tested due to a lack of paraffin blocks [1].

Another study of Yordanov et al., again from 2019, presented 16 women diagnosed with LELC. Thirteen of these patients were tested via IHC, and histological means for the presence of EBV or HPV. Of the patients tested, two were EBV positive, three were HPV positive, and two had a co-infection. No infection was detected in 6 patients [17].

Table 1. Cases of LELC involving EBV and KPV infections

	N	EBV-positive n (%)		HPV- positive n (%)	
		ISH	PCR	ISH	PCR
Tseng et al.	15	Not done	11 (73.33%)	Not done	3 (20%)
Chao et al.	9	0 (0%)	0 (0%)	Not done	8 (88.8%)
Pinto et al.	8	0 (0%)	0 (0%)	6 (75%)	6 (75%)
Takai et al.	3	0 (0%)	Not done	0 (0%)	Not done
Yordanov et al.	14	8 (57.1%)			
Hachisuga et al.	1	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Bais et al.	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Takebayashi et al.	1	Not done	Not done	1 (100%) (according to author)	
Ram et al	2	0 (0%)		2 (100%)	
Yordanov et al.*	13	2		3	
Yordanov et al.**	3	1 (33.3%)	Not done	2 (66.6%)	Not done
Noel et al.	2	Not done	0 (0%)	Not done	2 (100%)

A third study of Yordanov et al. described 3 cases of LELC – aged 40, 47, and 67. They were tested for the presence of EBV and HPV via IHC. Of the three cases, only one was EBV positive [12].

In 1992 Hachisuga et al. published a case report on a 60-year old female diagnosed with LELC. The ISH test proved that she was EBV(+), but she was not examined for HPV [18]. In contrast, a report on two cases of LELC was published in 2001 by Noel et al. They performed PCR for EBV. Both samples were negative. In contrast, the PCR results for HPV were positive for HPV-16 or HPV-18 [19].

Takebayashi et al. presented a case of a 45-year old female with LELC and SCC. She was not tested for EBV, but the authors claimed that because the lesions of SCC and LELC were mixed, an HPV infection was strongly suspected [20].

In 2017 Ram et al. reported LELC in two females, aged 42 and 70, respectively. Both women were positive for HPV and negative for EBV [21].

Bais et al. published a case report of a 44-year old female with vaginal bleeding. She was diagnosed with LELC. PCR was performed to determine the presence of HPV and was found positive for HPV types 16 and 45 [22].

From the data gathered, we can conclude that there is a higher number of patients diagnosed with LELC, in whose samples traces from HPV than EBV were found (Table 1). Also, the data is inconsistent due to the small number of cases and low awareness. In some studies, the patients were tested for EBV or HPV only or not tested at all [23].

Conclusion

LELC is classified as a subtype of SCC. It is very rarely found in the uterine cervix. However, it should be considered a different entity. It has a better prognosis and, in some cases, affects younger women. Also, EBV is in no way a predisposition to LELC for Asian women, just as HPV is not for Caucasian women. Due to the small number of cases examined, claims should be considered speculations.

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