



Lymphoepithelioma-like carcinoma in the cervix with human papilloma virus infection: A case report and review of literature

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ABSTRACT

Lymphoepithelioma-like carcinoma (LELC) in the uterine cervix is a very rare variant of squamous cell carcinoma and accounts for 0.7% of all primary malignant neoplasms. The pathogenesis of LELC in the uterine cervix is unclear but some studies have reported association with human papilloma virus (HPV) in Western women and Epstein-Barr virus (EBV) in Asian women.

Here we have summarized the literature available on LELC in the uterine cervix. As a result, HPV and EBV were associated with LELC at the same rate in Asian women but that was not the case in Western women. Until now, only one case has been reported on LELC with HPV infection in a Korean woman and we report a case of a 57-year-old Korean woman with LELC in the uterine cervix (FIGO stage IB1) with HPV infection.

Key words: lymphoepithelioma-like carcinoma, cervical cancer, uterine neoplasm

SOMMARIO

Il carcinoma simil-linfoepitelioma (LELC) nella cervice uterina è una variante molto rara di carcinoma delle cellule squamose e rappresenta lo 0,7% di tutte le neoplasie primarie maligne. La patogenesi del LELC nella cervice uterina non è chiara, ma alcuni studi hanno segnalato l'associazione con il virus del papilloma umano (HPV) nelle donne occidentali e il virus di Epstein-Barr (EBV) nelle donne asiatiche.

Qui abbiamo riassunto la letteratura disponibile sul LELC nella cervice uterina. Di conseguenza, HPV e EBV sono stati associati con LELC con la stessa frequenza nelle donne asiatiche, ma nelle donne occidentali non era così. A tutt'oggi è stato segnalato un solo caso di LELC con infezione da HPV in una donna coreana, e riportiamo il caso di una donna coreana di 57 anni con LELC nella cervice uterina (stadio FIGO IB1) con infezione da HPV.

Parole chiave: carcinoma simil-linfoepitelioma, cancro cervicale

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) commonly occurs in the nasopharynx and is seen in the stomach, salivary glands, lungs, and thymus⁽¹⁾. LELC in the uterine cervix is an uncommon variant of squamous cell carcinoma (SCC)⁽²⁾.

It is difficult to distinguish LELC in the uterine

cervix from lymphoproliferative diseases and other types of poorly differentiated SCC because of its very low incidence and their similar growth pattern^(2,3). Until now, the pathogenesis of LELC in the uterine cervix has been unclear; some studies have reported that the Epstein-Barr virus (EBV) and human papilloma virus (HPV) might be involved⁽⁴⁾. Here we present a case of LELC in the uterine cervix of a menopausal woman and review the existing literature on LELC in the uterine cervix⁽¹⁻¹⁶⁾.

CASE REPORT

A 57-year-old Korean menopausal woman (gravida 4, para 4) visited her local physician because of a history of vaginal bleeding for the previous 5 days. Her other medical history was non-specific. Her cervical cytology revealed atypical squamous cells, which did not exclude high-grade squamous intraepithelial lesions and was positive for HPV 16. A punch biopsy of the cervix was performed, which revealed SCC and she was transferred to our hospital for further evaluation and treatment. On pelvic examination, the cervix was eroded, bled on touch, and a mass confined to the cervix was found, but the parametrium was intact.

Her serum hemoglobin level was 11 g/dL (normal range, 11 - 15 g/dL) and serum SCC antigen was slightly elevated at 2.5 ng/mL (normal range, 0 - 2 ng/mL). Magnetic resonance imaging revealed a 30 mm mass lesion in the posterior portion of the uterine cervix; the uterine body and both adnexa were intact, and no distant metastases were observed (**Fig. 1**).

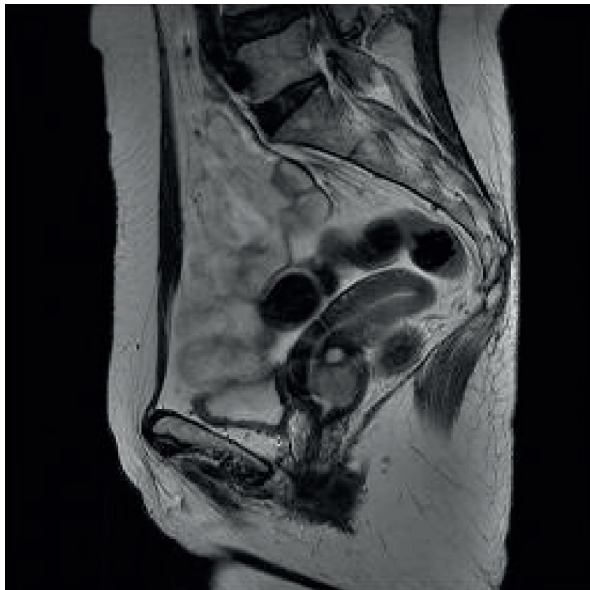


Figure 1.
Magnetic resonance imaging showing a 30 mm tumor in the posterior portion of the uterine cervix.

The tumor was staged clinically as cervix cancer IB1 according to the International Federation of Gynecology and Obstetrics (FIGO) classification. Therefore, we decided to perform radical hysterectomy type III with bilateral pelvic lymph node dissection.

Grossly, the cervical mass measured 30x 15 mm and it was a slightly elevated lesion with diffusely hemorrhagic appearance (**Fig. 2**).



Figure 2.
Grossly, the cervical mass measures 30x15 mm and the depth of invasion is 13 mm.

Microscopically, the depth of invasion was 13 mm and 5 mm apart from the parametrial resection margins and had a clear vaginal cuff. The size of the tumor cells was medium to large, with an eosinophilic cytoplasm and prominent lymphoid reaction. Some lesions were infiltrated by inflammatory cells, including lymphocytes, eosinophils, and plasma cells. These histological findings were consistent with the features of LELC in the uterine cervix. There was no evidence of lymphovascular space invasion and lymph node metastases. Regarding immunohistochemical staining, EBV-encoded small RNAs (EBER) in-situ hybridization was negative. The tumor cells were strongly positive for p16, p63, and cytokeratin-pan (**Fig. 3**).

Postoperatively, she received external radiation therapy of 5040 rad. She is being followed up every 3 months with serum level for SCC, Pap smear of

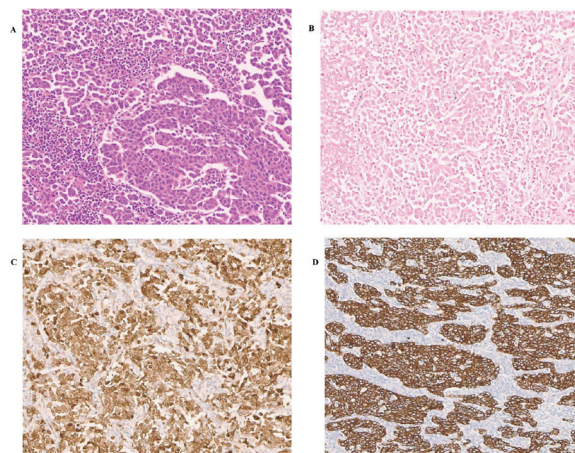


Figure 3.
(A) Poorly defined islands of undifferentiated cells are seen in a background of intense infiltration with lymphocytes, eosinophils, and plasma cells (H&E, x200).
(B) EBER in-situ hybridization was negative (x200).
(C,D) The tumor cells are strongly positive for p16 and p63 (both x200)

the cervix, and annual computed tomography of the abdomen, pelvis, and chest. She had no clinical evidence of tumor recurrence and metastasis at 18 months after surgery and is undergoing close follow-up.

DISCUSSION

LELC in the uterine cervix is also called medullary carcinoma of the cervix. This rare tumor constitutes only 0.7% of all primary cervical malignancies in Western countries, and its incidence is similar in Asia^a (2). Until now, only 83 cases have been reported and a review of previously published original articles and cases of LELC in the uterine cervix are listed in **Table I** (1-16).

Table I.

A review of previously published original articles and cases of LELC in the uterine cervix are listed (1-16).

	Ref.	No. of case	Age (year)	HPV	EBV	Neither EBV nor HPV	FIGO	F/U*(month)
Asia	1	3	41	0	0	1	IB	100
			44	0	0	1	IIA	75
			69	0	0	1	IB	15
	2	39	30-61	X*	X	X	IB	3-60
			40	X	X	X	IB	14
	3	2	43	X	X	X	IB	12
			37-72	3	11	1	IB(9) II(6)	20-63
	7	9	40-67	8	0	0	IB	63-134
	8	1	45	X	0	X	IB	4
	9	1	57	0	0	1	IB	26
	10	1	63	1	1	0	IB	34
	11	1	42	X	X	X	IB	12
	12	1	55	X	X	X	1B	34
13	1	45	0	0	1	IB	8	
Western	4	2	56	1	0	0	IB	X
			53	1	0	0	IB	24
	5	1	44	1	1	0	IB	15
			74	0	0	1	IB	84
	14	4	58	0	0	1	IB	60
			77	0	0	1	II	24
			67	0	0	1	IB	Recur at 24
	15	1	44	X	1	X	IB	12
	16	1	72	1	X	X	IB	X
	Total	1-16	83	49.5(median)	16	14	10	IB

* F/U : follow up status (no recurrence), *X : not described in case

According to this table, the most prevalent age group was 40 - 49 years (62%) and the mean age was 49.5 years. The mean follow-up duration was 56 months and only one patient experienced recurrence at 24 months.

Table II shows a comparison of two groups, Asian and Western women, in terms of the age and pathogen involved. We did not include cases in which both HPV and EBV infections were not evaluated (1-16).

Some studies have reported that the EBV and HPV may be involved in its pathogenesis. Tseng et al. reported that 73% of Asian female patients with cervical LELC were positive for EBV antibody; however, EBV appears less likely to have a role in cervical LELC in Western women (4).

Table II.

Comparison of two groups of women, Asian and Western, in terms of the age and pathogen at the time of diagnosis. The pathocases in which both HPV and EBV were not examined have not been included (1-16).

Age*	Asia		Western		Total case 83	
	Total	case 74	Total	case 9		
40-49	46		2		48	
50-59	26		3		29	
60 ≤ age	2		4		6	
Pathology [#]	Asia		Asia		Total case 37	
	Total	case 30	Total	case 7		
	HPV	11	2			13
	EBV	11	0			11
	Both HPV and EBV	1	1			2
Neither HPV nor EBV	7		4		11	

* : References 1,3,4 were made to mean age because the exact age did not appear[1-16], # : They are not include cases in which test for either EBV or HPV were not performed [1,4-7,9,10,13,14].

A possible role of HPV infection in the pathogenesis of LELC in the uterine cervix has been reported in Western women (4,5). After reviewing all the cases reported so far, we found that HPV and EBV are equally associated with LELC in the uterine cervix in Asian women. On the other hand, in Western women, HPV and EBV does not seem to be related to disease. In this case, no EBV infection was detected, but HPV 16 infection was noted. The precise pathogenesis of the disease is yet to be known, and further research is needed in this regard.

In this cancer, the most common presenting symptom is abnormal vaginal bleeding and on pelvic examination, the mass is usually in the endocervical canal and accompanied by superficial ulceration (5). This patient also experienced vaginal bleeding and had an extruding cervical mass that bled on touch.

Microscopically, the major characteristic of this cancer is that it is well-circumscribed and is composed of undifferentiated cells with prominent nucleoli, usually growing in syncytial sheets. These cells are surrounded by an inflammatory infiltrate including plasma cells, lymphocytes, and eosinophils (1,3,6). LELC in the uterine cervix can be misdiagnosed as other forms of the cervical cancer because of its very low incidence and the epithelioid appearance of the tumor cells. Saroha et al. reported that because the diagnosis is very difficult, immune-histochemical staining for cytokeratin or epithelial membrane antigen is necessary (3). Tseng et al. suggested that a biopsy alone is not sufficient and hysterectomy must be performed because of highly inflammatory lesions or obscure tumor cells (6).

The prognosis, including the 5-year survival rate, of LELC in the cervix is better than that of SCC or adenocarcinoma because LELC in the cervix has a lower frequency of lymphocytic metastasis and tumor recurrence (2,5).

In this case, we did not detect microscopic lymphovascular invasion or metastasis to lymph nodes and the patient is disease-free at 18 months after the surgery. Furthermore, older age, higher parity, lower FIGO stage, and predominant exophytic growth have been shown to be associated with a better prognosis, as seen in our patient⁽⁸⁾. However, the exact pathogenesis is still unclear^(4,5).

In conclusion, we have reported a rare case of LELC in the uterine cervix and summarized the

literature on LELC in the uterine cervix reported to date.

Further studies are needed to better understand the accurate diagnostic methods, pathogenesis, and treatment of this rare cervical cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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