

Lymphoepithelioma-like carcinoma of the uterine cervix: a case report

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Summary

Lymphoepithelioma-like carcinoma (LELC) is a rare variant of carcinoma of the uterine cervix, of which Epstein-Barr virus (EBV) and/or human papilloma virus (HPV) may play an important role in the pathogenesis. The authors report a case of a patient with cervical LELC who was also examined for the presence of EBV and HPV. A 31-year-old Japanese female presented with irregular genital bleeding. The biopsy showed an invasive squamous cell carcinoma. Based on the clinical data, the patient was diagnosed as having squamous cervical carcinoma, and radical hysterectomy with ovarian conservation was performed. A diagnosis of cervical LELC was then made by histological methods. An additional examination revealed that the patient was infected with HPV types 16 and 71, but not infected with EBV.

Key words: Lymphoepithelioma-like carcinoma; Cervix; Epstein-Barr virus; Human papilloma virus; Cervix.

Introduction

Lymphoepithelioma-like carcinoma (LELC) usually occurs in the nasopharynx, salivary glands, lung, thymus, stomach, and liver. Histopathologically, it is characterized by a diffused growth of undifferentiated malignant cells in a background of inflammatory cells with prominent lymphocytes, plasma cells, and eosinophilic infiltration [1]. LELCs of the uterine cervix are less common, accounting in 0.7-5.5% of all carcinomas of the uterine cervix [2]. Despite the poorly differentiated pathomorphosis, LELC of the uterine cervix appears to have a better prognosis than that of squamous cell carcinoma (SCC). A relationship with the Epstein-Barr virus (EBV) infection is strongly suggested by the appearance of LELC in the nasopharynx and other locations [3]. Noel *et al.* reported that EBV infection may play a role in the pathogenesis of cervical LELC in Asian women [4]. While high-risk human papilloma virus (HPV) infection usually involves the onset of conventional squamous cervical carcinoma [5], the relationship between cervical LELC and HPV infection remains unclear. The authors herein describe a case of a Japanese woman with LELC of the uterine cervix who was investigated for the presence of EBV and HPV.

Case Report

A 31-year old Japanese female, para 2, presented with irregular genital bleeding occurring over the previous five months. On clinical examination, there was a bulky cervical mass about 4×5

cm in size, and a cervicovaginal smear revealed various sizes of neoplastic cells with increased cytoplasm and vesicular nuclei with nucleoli well-stained in light green and orange, of which background consisted in small amount of lymphocytes and no necrotic cells. A further biopsy showed an invasive SCC. Serum SCC antigen level was increased to 23.9 ng/ml. Magnetic resonance imaging showed a mass localized in the uterine cervix. Based on these data, the patient was diagnosed with SCC and categorized as Stage IB2 according to the current FIGO (2008) staging system. A radical hysterectomy with ovarian conservation was therefore performed. The tumor margin was well-circumscribed and measured 4×4×5 cm (Figure 1). The vagina, corpus uteri, and parametrium were free of dissemination.

Microscopically, LELC were composed of nests of undifferentiated epithelial cells surrounded by intense lymphocytes, eosinophil granulocytes, and plasma cell infiltration (Figure 2). The epithelial cells had abundant cytoplasm and vesicular nuclei with prominent nucleoli, but the boundary between these cells was unclear. No tumor was found in the lymph node, vagina, corpus uteri, or parametrium.

Immunohistochemistry was performed using anti-CD3 and anti-CD20 antibodies to confirm the distribution of infiltrating T lymphocytes and B lymphocytes into the cervical carcinoma in a paraffin-embedded tissue section. Most lymphoid cell membranes were positive for anti-CD3 around the cords of carcinoma (CD3 [+] cells > CD20 [+] cells) (Figures 3A, B). The carcinoma cells were diffusely positive for cytokeratin (AE1/AE3) (Figure 3C). After histological examination, a diagnosis of cervical LELC was confirmed. After surgery, the patient underwent whole pelvic radiation with 50 Gy. No recurrence or metastasis was found during the first-year follow-up examination by systematic CT, vaginal stump smear, and tumor marker.

The presence of EBV was investigated by using a digoxigenin-labelled EBV-encoded small nuclear RNA (EBER-1) antisense probe. All tests were negative for both the malignant epithelial

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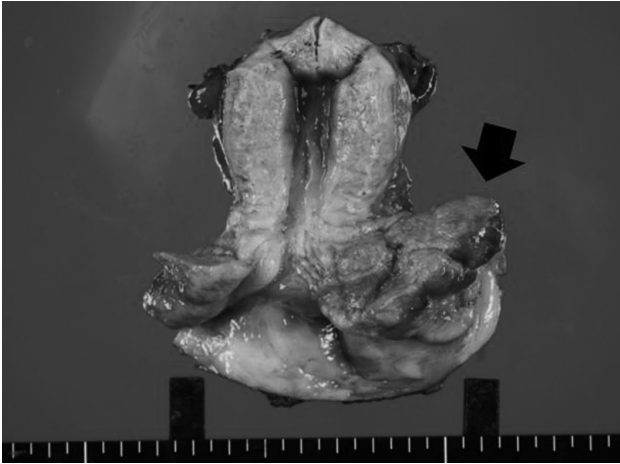


Figure 1. — The tumor margin is well circumscribed and measures 4×4×5 cm (arrow).

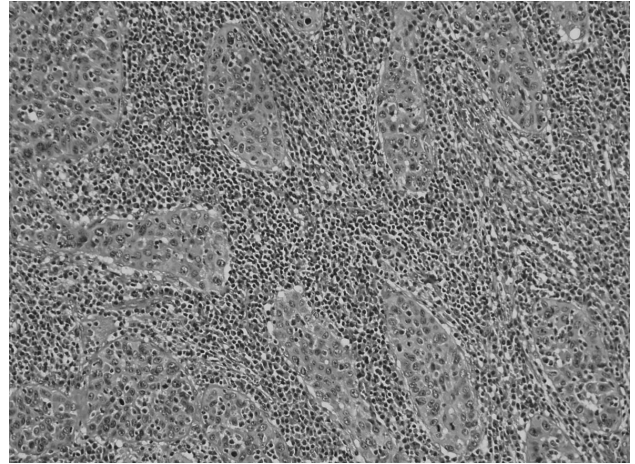


Figure 2. — Histological features of LELC. It is composed of nests of undifferentiated epithelial cells surrounded by intense lymphocytes (H and E, original magnification ×200).

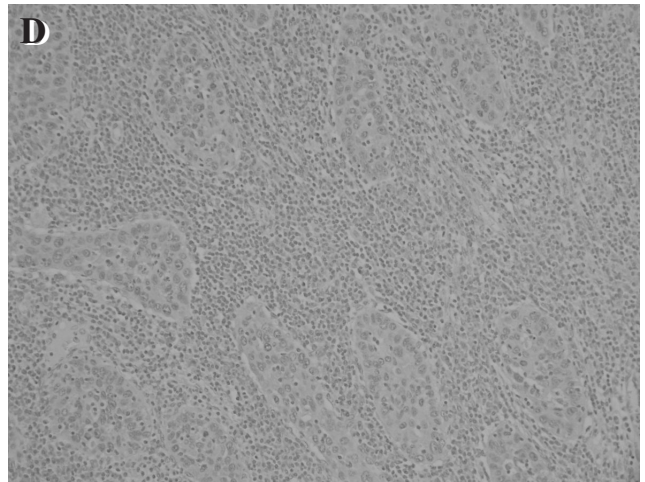
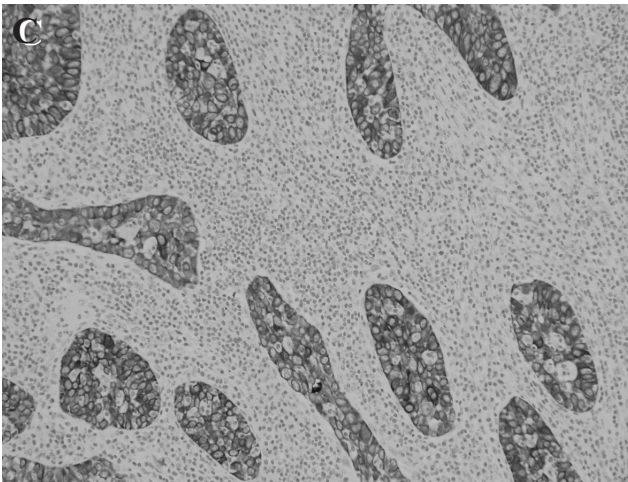
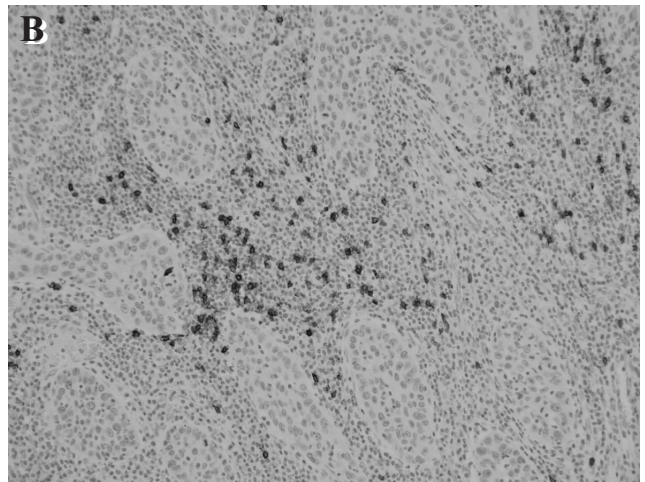
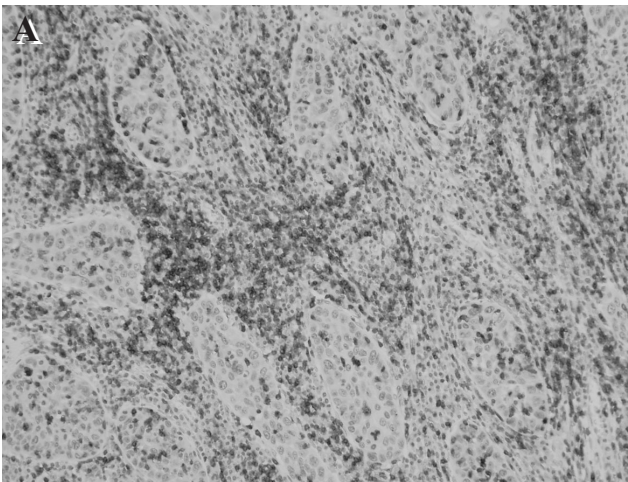


Figure 3. — An immunohistochemistry is performed. (A) Most lymphoid cell membranes are positive for anti-CD3. (B) Lymphoid cell membranes are also stained for anti-CD20 (CD3+cells > CD20+cells). (C) The tumor cells are strongly positive for cytokeratin (AE1/AE3). (D) EBER1 *in situ* hybridization shows no presence of EBV genome in tumor cells.

component and lymphocytic infiltrate (Figure 3D). However, serologic tests for an antibody against the EBV antigen revealed a previous EBV infection.

DNA was extracted from frozen samples cut into small pieces and amplified using standard polymerase chain reaction, which can identify all HPV types. HPV testing was positive for HPV types 16 and 71.

Discussion

LELC has been described as a neoplasm of the nasopharynx that also occurs in other anatomic sites, such as the salivary glands, stomach, lung, and thymus. LELC of the uterine cervix was first reported by Hamazaki *et al.* in 1968 [6]. It is an uncommon neoplasm histologically characterized by nests of undifferentiated epithelial cells with a syncytial growth pattern and intense lymphocytic infiltrate. The present case was diffusely positive for anti-CD3, suggesting that T lymphocytes around carcinoma cells were activated. The inflammatory infiltrates in the stroma may reflect immune responses of the patients against the tumor [7]. Actually, when compared with conventional SCC of the cervix, cervical LELC has a good prognosis with a low frequency of regional lymph node metastasis, as in the present case [8]. Therefore, differentiation from other cervical carcinomas of the uterus, including SCC with prominent stromal inflammation, glassy cell carcinoma, and malignant lymphoma, might be important in terms of prognosis.

There are regional differences in the prevalence of LELC. This rare variant of SCC in the uterine cervix occurs in less than 1% of all primary cervical malignancies in Western countries. However this type tumor is more frequent in Asia, which accounts for more than 5.5% of cervical carcinomas [4].

EBV has been suggested as a causative factor of cervical LELC, and racial and/or geographic factors may be associated with EBV infection in LELC, particularly in the cervix [3]. Tseng *et al.* reported that in a study comprising 15 Asian women with cervical LELC, EBV was detected in 73% (11 of 15) [7]. In contrast, the role of EBV in the pathogenesis of cervical LELC in Western countries appears to be less likely [9]. In the present Japanese case, the authors could not histologically detect an existing an EBV infection.

It has been recognized that cervical HPV infections are strongly associated with conventional SCC. However, for cervical LELC, the relationship with HPV infection remains unclear. For example, Tseng *et al.* reported that three out of 15 Asian women with cervical LELC were positive for HPV 16 [7], while Saylam *et al.* reported an HPV 18 positive case of cervical LELC [10]. Thus, the authors carried out a DNA test that could identify all types of HPV. Based on this test, they detected multiple HPV infections (HPV 16 and 71). HPV 16 is of a high-risk type for conventional SCC, how-

ever, HPV 71 is thought to be of a non-carcinogenic type [11].

To the present authors' knowledge, there have been no reports investigating the presence of all HPV types as well as EBV in LELC at the same time. Therefore, they examined for all types of HPV in LELC for the first time, and identified HPV types 16 and 71. The present case suggests that HPV type 16 and/or 71 may play a role in the pathogenesis of LELC of the uterine cervix. However, in order to establish the pathogenesis of LELC in association with EBV and with HPV, further accumulation of cases is necessary.

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