Lymphoepithelioma-like Carcinoma of the Uterine Cervix

A Case Report Studied by In Situ Hybridization and Polymerase Chain Reaction for Epstein-Barr Virus

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• Lymphoepithelioma-like carcinomas have been reported outside the nasopharynx in many sites, including the uterine cervix. The association with the Epstein-Barr virus in the latter site is still controversial. To date, Epstein-Barr virus genome has only been demonstrated in Asian patients. We report a case of lymphoepithelioma-like carcinoma of the uterine cervix in a white woman in whom the Epstein-Barr virus infection was tested for by in situ hybridization and polymerase chain reaction. The results of both techniques were negative. Our case and a review of the literature support the contention that cervical lymphoepithelioma-like carcinoma is not associated with Epstein-Barr virus infection in non-Asian patients.

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Lymphoepithelioma-like carcinomas (LELCs) have been reported outside the nasopharynx in many sites, including the uterine cervix.[1] Although this distinct neoplasm accounts for only 0.7% of all uterine cervix primary malignant neoplasms, it has become a well-known entity since the original report by Hamazaki et al in 1968.[2,3] It has been proposed that cervical LELC may be related to Epstein-Barr virus (EBV) infection, since it occurs in LELC arising at other locations.[2,4]

We report a case of LELC of the uterine cervix in which the EBV infection was tested by in situ hybridization and polymerase chain reaction.

REPORT OF A CASE

A 44-year-old white woman, gravida 3 para 3, had postcoital bleeding of 8 months' duration. Medical history was noncontributory (cervical cytologic test results were reported as negative 2 years before). At gynecologic examination, there was a fungating tumor, 3 cm in diameter, that occupied the posterior lip of the cervix. Laboratory findings were within normal limits. A biopsy was performed, and after histopathologic diagnosis, the patient underwent radical hysterectomy and pelvic lymph node dissection. Her postoperative course was uneventful, and she remains free of disease 12 months after diagnosis.

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PATHOLOGIC FINDINGS

Microscopic examination of the biopsy specimen disclosed a poorly differentiated nonkeratinizing carcinoma composed of cohesive nests surrounded by prominent lymphoplasmacytic infiltrate. Cells were large and had indistinct cell margins (syncytial-like pattern). Nuclei were vesicular and contained 1 or 2 prominent nucleoli and peripheral chromatin (Figure 1). There was no evidence of glandular differentiation, keratinization, or intercellular bridges. Microscopic sections from the posterior lip of the cervix only revealed residual tumor after step sections were examined. Small foci of nonkeratinizing carcinoma appeared in the stroma, surrounded by marked inflammatory reaction. The depth of invasion was 0.4 cm. No adjacent carcinoma in situ was identified. The rest of the surgical specimen and the regional lymph nodes showed no evidence of malignancy. On review, all available previous cervicovaginal smears were negative.

Immunoperoxidase studies were performed on paraffin-embedded sections. The tumor cells were strongly positive for cytokeratin 8 and high-molecular-weight cytokeratins (k-903). Neoplastic cells were negative for cytokeratin 20, synaptophysin, chromogranin, and several lymphoid markers (CD20, CD3, and leukocyte common antigen). The inflammatory background (Figure 2) contained many $CD3^+$ cells, but there were few $CD20^+$ cells. Immunohistochemical staining for EBV latent membrane probe 1 was also negative. Finally, neither in situ hybridization for EBV-encoded RNAs nor polymerase chain reaction yielded positive results. A known EBV-positive specimen and DNA from the RAJI cell line were used as positive controls.

COMMENT

Lymphoepithelioma-like carcinoma of the uterine cervix is an uncommon neoplasm that usually occurs in Asian patients. The outcome has been better than the usual squamous cell carcinoma of the cervix.[2] Therefore, it is essential to only consider as such those poorly differentiated tumors that fulfill strict morphologic criteria: negative lymphoid markers, indistinct cytoplasmic margins, vesicular nuclei with prominent nucleoli, and, in the opinion of most authors, *absence* of glandular or squamous differentiation.[5,6]

To the best of our knowledge, only 20 previously well-

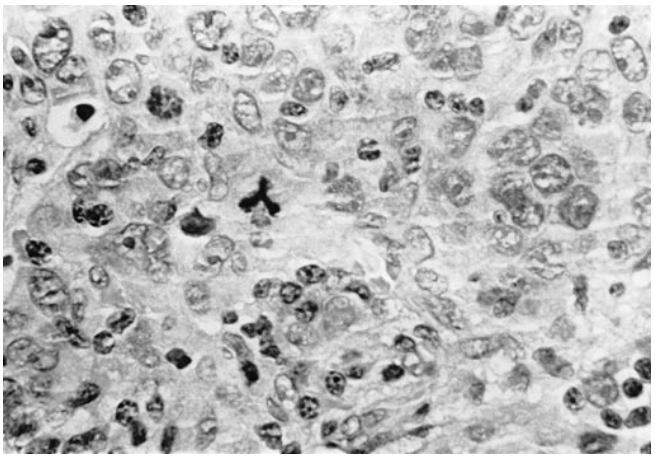

Figure 1. *High-power view of lymphoepithelioma-like carcinoma. Note syncitial arrangement and prominent nucleoli (hematoxylin-eosin, original magnification ×400).*

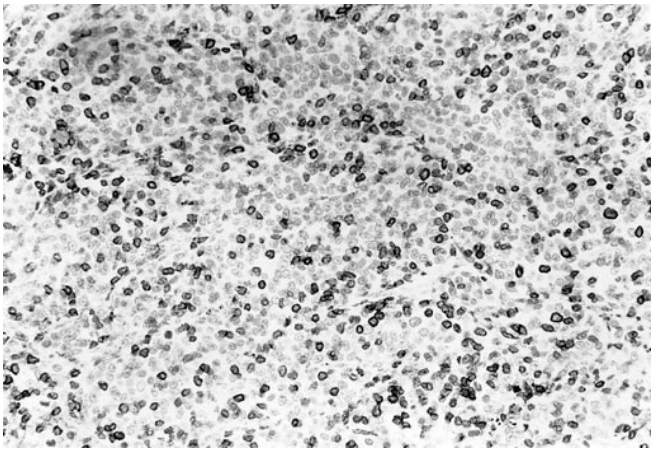

Figure 2. *Immunohistochemical stain for leucocyte common antigen: darker cells represent dense lymphoplasmacytic reaction (original magnification ×200).*

documented cases of cervical LELC have been tested for the EBV genome.[2,4,7–10] All 5 cases in Western patients were negative,[4,7–10] whereas 73% of the Taiwanese women studied by Tseng et al[2] harbored EBV in the neoplastic cells. Our case and a review of the literature support the contention that cervical LELC is not associated with EBV infection in non-Asian patients.[2] Additional studies, particularly in Western patients, are needed to verify whether this relation has a definitive geographic or racial influence, similar to that of Burkitt lymphoma.[1,2]

In the anatomic sites studied to date, the prognostic role of EBV remains unclear.[1] For example, Chen et al[11] have studied the presence of EBV-encoded RNA transcript in non–small cell lung carcinomas. All the LELCs (5/5) and 6 squamous cell carcinomas (6/43) tested positive, but this finding showed no correlation with the 2-year survival rate of overall cases. The heterogeneity in prognosis and EBV status of LELC has supported the idea that this neoplasm ''probably represents a morphologic pattern rather than a distinct clinicopathologic entity.''[12]

Finally, the role and mechanism of EBV in epithelial tumorigenesis are not fully understood. In lung LELCs, up-regulation of bcl-2 has been suggested.[11] In gastric salivary gland and nasopharyngeal LELCs, nonmutational up-regulation of p53 has been found.[13,14] However, the precise interaction between the virus and the cell is still unknown.

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