Human Pathology (2005) **36**, 82–90

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Cervical adenoid basal tumors comprised of adenoid basal epithelioma associated with various types of invasive carcinoma: Clinicopathologic features, human papillomavirus DNA detection, and P16 expression

Anil V. Parwani MD, PhD[a], Ann E. Smith Sehdev MD[a,1], Robert J. Kurman MD[a,b], Brigitte M. Ronnett MD[a,b,*]

[a]*Department of Pathology, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD 21231, USA*
[b]*Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD 21231, USA*

Received 28 June 2004; accepted 25 August 2004

Keywords:
Adenoid basal tumor;
Adenoid basal carcinoma;
Cervical carcinoma;
Human papillomavirus DNA;
p16 immunohistochemistry

Summary Adenoid basal tumors are uncommon cervical lesions that some pathologists consider invasive carcinomas but others consider "epitheliomas" due to their low-grade histological appearance and rarely documented malignant behavior. We report the clinicopathologic features of 10 tumors comprised of both typical low-grade adenoid basal tumors (epitheliomas) intimately associated with invasive carcinomas having infiltrative growth, increased cytological atypia and mitotic activity, and various types of differentiation, including adenoid basal/squamous, pure squamous, adenoid cystic, and small cell neuroendocrine. Tumors were evaluated for the presence of human papillomavirus (HPV) DNA and immunohistochemical p16 expression. The patients in the study group ranged in age from 45 to 81 years (mean, 65 years). Most of the patients presented with abnormal cervicovaginal smears. The initial diagnosis was made on specimens obtained by cervical biopsy, laser electrocautery excision procedure (LEEP), or cone biopsy in 8 patients. Two 2 patients were incidentally diagnosed in hysterectomy specimens. All 10 patients had squamous intraepithelial lesions (9 high-grade, 1 low-grade). In all cases diagnosed in LEEP or cone biopsy specimens, the invasive carcinoma component was present in the excisional specimen and extended to the margins. Seven patients diagnosed on excisional or biopsy specimens who underwent hysterectomy had residual tumor in the cervix, ranging from microscopic foci to deeply invasive. No lymph node metastases were identified in 4 patients who were staged. Seven patients with follow-up were alive without evidence of disease after follow-up intervals of 8 to 84 months (mean, 45 months; median, 29 months). One patient with a component of small cell carcinoma died of other causes without evidence of disease at 18 months. HPV 16 DNA was detected in both the adenoid basal epithelioma and invasive carcinoma components in 9 tumors by in

Abbreviations: HPV, human papillomavirus; LEEP, laser electrocautery excision procedure; PCR, polymerase chain reaction.

* Corresponding author. Department of Pathology, Johns Hopkins Hospital, Weinberg Bldg., Room 2242, 401 N. Broadway, Baltimore, MD 21231.
E-mail address: bronnett@jhmi.edu (B.M. Ronnett).
[1] Currently at Department of Pathology, Good Samaritan Hospital, Portland, OR.

doi:10.1016/j.humpath.2004.08.015

situ hybridization, and HPV 33 was detected by polymerase chain reaction in 1 tumor. All tumors expressed p16 diffusely. Adenoid basal tumors are high-risk HPV-related tumors that can be comprised of both a low-grade adenoid basal tumor, which can be designated as epithelioma, and invasive carcinomas of various types. The invasive component is usually evident in the excisional biopsy specimen, allowing for recognition of a tumor that needs further management.

1. Introduction

Adenoid basal tumors of the cervix have been designated as "adenoid basal carcinomas" since their initial recognition, even though malignant behavior has rarely been observed [1-8]. They are unusual cervical tumors composed of nests of uniform cells displaying basaloid, squamous, and glandular differentiation. The tumors are usually associated with squamous intraepithelial lesions, most often high-grade. Most affected patients are asymptomatic postmenopausal women who are diagnosed during follow-up of an abnormal cervicovaginal smear. Pure, typical tumors appear to behave in a benign fashion, leading the authors of one study to recommend the term "adenoid basal epithelioma" rather than adenoid basal carcinoma [9]. Although the cases described in that report were not associated with other types of invasive carcinomas (except for 1 case of a microinvasive squamous carcinoma), some other reports have described adenoid basal tumors associated with invasive carcinomas and carcinosarcomas [3,4,10-12]. In the present study we describe the clinicopathologic features of a series of adenoid basal tumors composed of a typical low-grade adenoid basal component ("epithelioma") intimately associated with invasive carcinomas displaying one or more types of differentiation. We investigate the relationship between the adenoid basal epitheliomas and invasive carcinomas by assessing for the presence of HPV DNA and p16 expression in both tumor components. We then present a proposal to subclassify these tumors into adenoid basal epitheliomas and carcinomas.

2. Materials and methods

This study was approved by the Johns Hopkins Institutional Review Board. The files of the Gynecologic Pathology Consultation Service and Surgical Pathology Division, The Johns Hopkins Hospital were searched for cases designated as adenoid basal carcinoma, adenoid basal tumor, adenoid basal and squamous carcinoma, or adenoid basal epithelioma for the period 1984 to 2004. Of 14 potential cases of low-grade adenoid basal tumor associated with additional types of invasive carcinoma, 10 retrievable cases (9 consultation cases and 1 routine case) were identified. Typical low-grade adenoid basal tumors (n = 19) were excluded from the study.

2.1. Immunohistochemistry for p16

Formalin-fixed, paraffin-embedded tissue sections were used. Immunoperoxidase labeling was done with an automated BioTek-Tech Mate 1000 Staining System (Ventana/Biotek Solutions, Tucson, AZ) at room temperature with anti-p16(INK4a) (MTM Laboratories AG, Heidelberg, Germany) at a dilution of 1:500.

2.2. Human papillomavirus DNA detection by in situ hybridization

Formalin-fixed, paraffin-embedded tissue sections were used. Biotin-labeled HPV probe solutions (Dako, Carpinteria, CA) were applied to individual sections. These included a wide spectrum probe (cocktail of HPV 6, 11, 16, 18, 31, 33, 45, and 51) and separate type-specific probes for HPV 16 and HPV 18. Detection of hybridized probe was done by tyramide-catalyzed signal amplification using the Genpoint kit (Dako). Chromogenic detection was performed with diaminobenzidine/H_2O_2. Controls included tissue sections positive for HPV wide spectrum, the HeLa cell line for HPV 18, and the SiHa cell line for HPV 16. Biotin-labeled plasmid probes served as negative controls in each case. Cases with a discrete punctate reaction product specifically in tumor cell nuclei were interpreted as positive.

2.3. HPV DNA detection by polymerase chain reaction

To further analyze the tumors for the presence of HPV, polymerase chain reaction (PCR) for HPV DNA was performed on those specimens that were negative by in situ hybridization. Tissue sections were deparaffinized with xylene and resuspended and digested with buffer containing proteinase K. Amplifications were performed for betaglobin and for HPVs by the Roche line blot method [13]. This method uses biotinylated pooled primers for HPV and for betaglobin amplification. The amplified products are screened against more than 35 HPV probes and betaglobin probes immobilized on an extended filter strip. Specimens that are negative for betaglobin and HPV are considered unsatisfactory.

3. Results

3.1. Clinicopathologic features

The clinicopathologic features of the 10 cases are summarized in Table 1. The patients ranged in age from 45 to 81 years (mean, 65 years). Most of the patients presented with abnormal cervicovaginal smears. The initial