

Original Article

Adenoid basal carcinoma of the cervix: report of 10 cases with reference to the expression of 3 basal cell antibodies

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Abstract: Adenoid basal carcinoma (ABC) of the uterine cervix is a rare neoplasm and its cell origin is still controversial. The clinicopathologic features was analyzed in a series of 10 pure ABCs. The immunohistochemistry expression of 3 basal markers including CK5/6, p63 and CAM5.2 was further investigated to explore the cell origin of ABC. The ages of the patients ranged from 56 to 73 years with a mean of 61 years. The majority of all patients were asymptomatic. None had a gross cervical tumor. All tumors had typical histologic features of adenoid basal carcinoma. All three basal cell markers were diffusely positive in the basaloid cells area; while for squamous differentiation areas, both CK5/6 and p63 showed diffuse staining, contrasted with the peripheral staining in the squamous foci for CAM5.2. In conclusion, cervical ABC has unique clinical and pathological features. The immunohistochemical evidence suggests that ABC may be originated from cervical reserve cells.

Keywords: Cervix, adenoid basal carcinoma, immunohistochemical features

Introduction

Adenoid basal carcinoma (ABC) is a rare uterine cervical malignant tumor. This tumor closely resembles adenoid cystic carcinoma (ACC). In fact, it has been reported as the same entity in some early reports [1]. It is until the first description by Baggish and Woodruff [2] in 1966, the indolent clinical course unique to ABC is well recognized. Until now, less than 100 cases of adenoid basal carcinoma have been reported [3]. ABC is characterized by specific histological appearance and excellent prognosis. Patients are usually asymptomatic, without grossly detectable masses. Further more, there is no metastatic or recurrent cases have been reported irrespective of the modality of treatment. In contrast, ACC and basaloid squamous cell carcinoma, which morphologically closely resemble ABC, have an aggressive clinical course and often associated with recurrence or metastasis [4] ABC was reported to mainly occur in postmenopausal black women, usually in their 60 s and 70 s. However, a few cases

have indicated that the neoplasm can occur in Asian women recently [5, 6].

As an uncommon lesion, the cell origin of ABC is still controversial. In this study, we described the clinicopathologic features of 10 pure ABCs. What's more, a series of immunohistochemical markers for basal reserve cells were also investigated to further investigate their putative cell origin.

Materials and methods

Case selection

Ten cases of pure ABC were retrieved from the files of the affiliated hospital school of medicine Zhejiang University from January 2005 to December 2009. Associated clinical data were extracted from the patients' medical records. In all of these cases, hematoxylin and eosin-stained slides were reviewed to confirm the original pathologic diagnosis, and formalin-fixed, paraffin-embedded tissues were avail-

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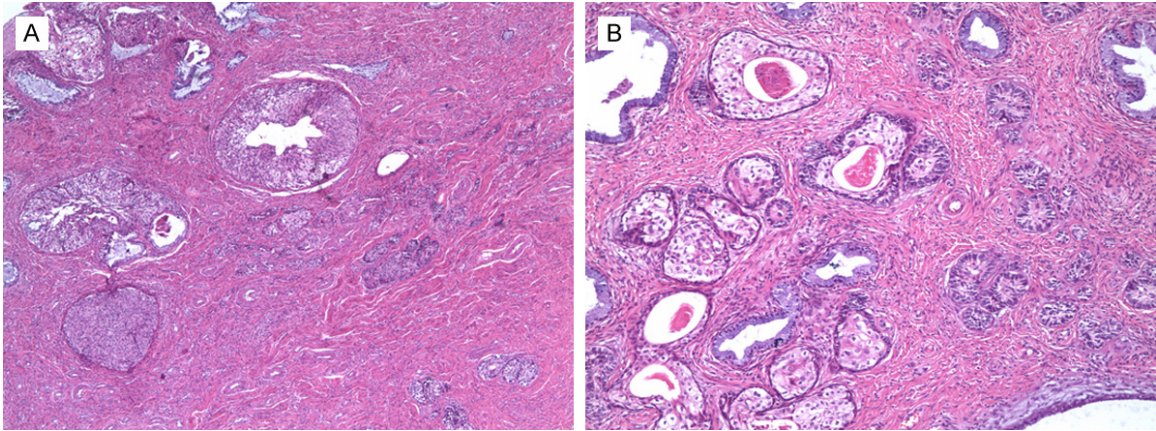


Figure 1. Adenoid basal carcinoma of the uterine cervix, hematoxylin and eosin. A. Scanning magnification view of adenoid basal carcinoma. The tumor cells are arranged in small nests with associated high-grade squamous intraepithelial lesion lying ahead. B. Intermediate power view, showing a transition from squamous differentiation foci to typical adenoid basal cell nests.

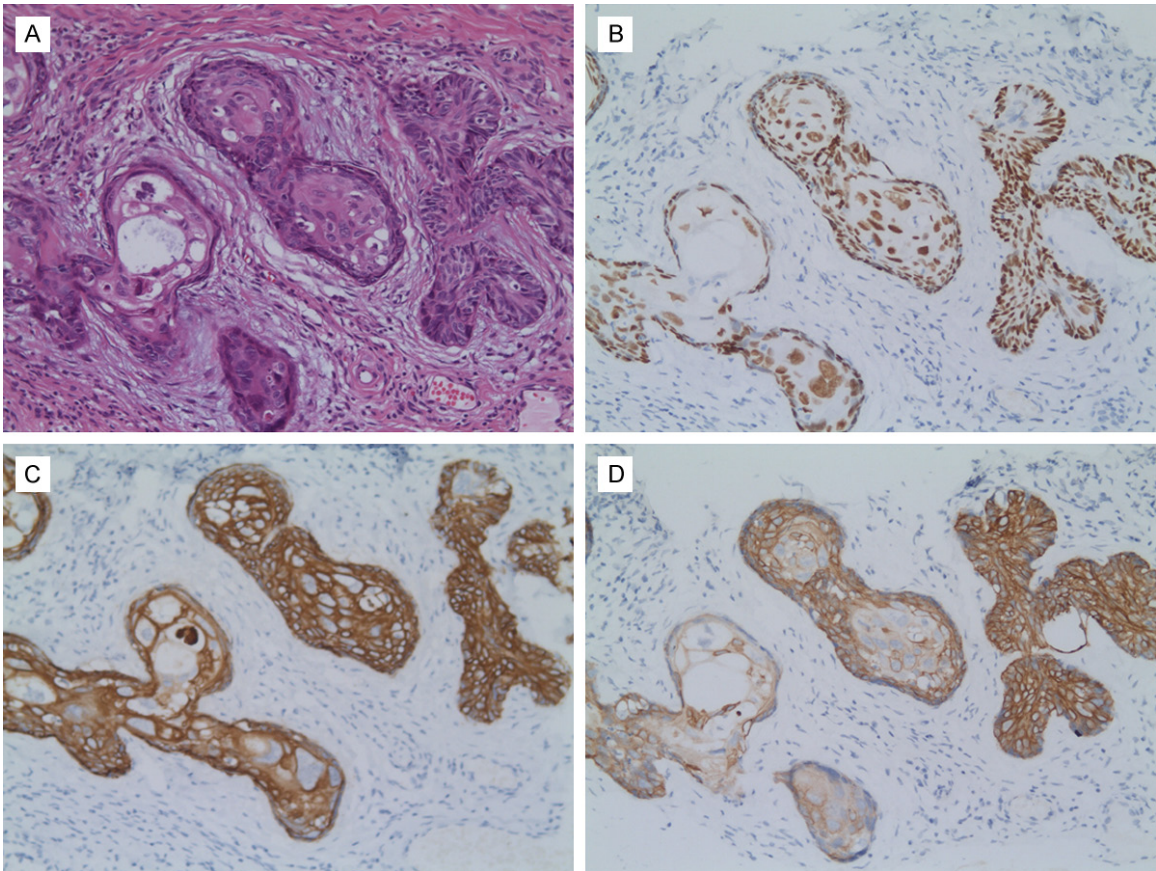


Figure 2. The expression of 3 basal reserve cell in adenoid basal carcinoma. (A) A case of adenoid basal carcinoma with squamous differentiation, hematoxylin and eosin (B) p63 is diffusely positive in both basaloid cells area and squamous differentiation areas, (C) CK5/6 is positive diffusely positive in both basaloid cells area and squamous differentiation areas. (D) CAM5.2 is positive in adenoid cells, while in squamous areas, the obvious staining was shown only at the periphery of the nests.

able for the immunohistochemical studies. All cervical ABCs fulfilled the criteria of the current

World Health Organization Classification (WHO) of Tumors in female genital organs [7].

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Immunohistochemistry

Immunohistochemical studies were performed on 5- μ m-thick sections of formalin-fixed, paraffin-embedded tissue, using standard techniques, heat-induced epitope retrieval buffer, and primary antibodies against CK5/6 (clones E3, 1:50 dilution; Dako, Denmark), p63 (clones E3, 1:50 dilution; Dako, Denmark) and CAM5.2 (clones E3, 1:50 dilution; Dako, Denmark). CK5/6 and CAM5.2 were cytoplasmic staining, while p63 was positive in nucleus.

Results

Clinical data

The age of patients with ABC ranged from 56 to 71 years of age, with a mean of 63 years. Cervical smears were abnormal in 9 of 10 patients, most often for a high-grade squamous intraepithelial lesion. This was the only reason for further evaluation in eight otherwise asymptomatic patients. Of the other two patients, one had abnormal vaginal bleeding and the other had dysuria urodynia. None of the patients had an observed abnormality of the cervix at pelvic examination. In subsequent colposcopy, acetowhite lesion was shown in 7 cases. Gross evaluation of conization and hysterectomy specimens did not reveal a cervical tumor in any case. The diagnosis of ABC was made by biopsy for 3 patients and by cervical conization or hysterectomy samples for 7 patients.

Pathological findings

Microscopically, all cases of ABC were associated with overlying high grade cervical intraepithelial neoplasia (CIN). The tumor nests usually had a lobule like arrangement the epithelial nests and they were composed of uniform small epithelial cells with basaloid features that were often palisaded at the periphery (**Figure 1A**). The basaloid cells were cuboidal, oval or spindle, and generally had uniform bland nuclei. There were no areas of necrosis in the basaloid nests. Mitotic activity generally was low in the basaloid cells, with 0 MF/10 HPF to 5 MF/10 HPF (median, 2 MF/10 HPF). Squamous differentiation in the central portions of the nests was present to a variable extent (**Figures 1B, 2A**). Typically, the squamous cells had bland nuclei. Two tumors that contained multi-

ple expanded nests with markedly dysplastic squamous cells closely simulated invasive squamous cell carcinoma. Edematous stromal reactions with predominantly lymphocytic infiltrate were observed in more than half of the cases, although some of these were considerably focal. The depth of stromal invasion ranged from 2.5 mm to 8.5 mm (mean, 4.5 mm). According to the International Federation of Gynecology and Obstetrics (FIGO), six tumors were classified as Stage IA1 and four were Stage IA2.

Immunohistochemistry

In ABC cases, keratin 5/6 stained strongly the cytoplasm of the cervical intraepithelial neoplasia (CIN) as well as the ABC nests of basaloid cells and squamous differentiation areas (**Figure 2C**). P63 displayed a diffuse nuclear staining in full layer of CINs. P63 also stained intensely in the basaloid cells as well as in the squamous foci (**Figure 2B**). CAM5.2 was positive in 7/10 CINs. All nests of basaloid cells showed diffuse CAM5.2 staining, In the squamous differentiation foci, the obvious staining at the periphery of the nests was seen contrasting with the faint staining in the squamous areas (**Figure 2D**). As the internal controls, keratin 5/6 and p63 were expressed in the overlying normal squamous cells, while CAM5.2 was positive in normal columnar cells.

Clinical follow-up data

Six patients treated with conization and four patients underwent hysterectomy. Follow-up information was available for all 10 patients. Nine patients were alive without evidence of disease from 12 to 74 months after diagnosis, with a mean follow-up period of 42 months. One patient died of hypertension without evidence of disease after 27 months. None had recurrent or metastatic tumor.

Discussion

There are no studies that have systematically investigated the incidence of ABL. However, retrospective analyses by most authors suggest that pure ABL constitute less than 1% of all cervical malignancies and nearly 100 cases of pure ABCs have been reported so far [3]. Although most cases were occurred in western countries, some reports have indicated that the

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neoplasm can occur in Asian women recently. In Japan, Teramoto et al. [6] identified 1 pure ABL out of 2600 “resected cervical malignancies” with an incidence less than 0.1% at the Shikoku Cancer Center. Chen et al. [5] found 12 pure ABC of the cervix among 7694 cervical carcinomas in Taiwan area with a 0.2% incidence. In our series, ten cases of ABC were identified among 3000 cases of cervical cancers with a 0.33% incidence which was slightly higher than other reports in Asian but significantly lower than Western countries. ABC, ACC and BSCC are believed to be part of a morphological and biological spectrum of basaloid cervical neoplasms, and a putative reserve cell origin has been suggested in World Health Organization classification of cervical tumors [7].

It is necessary to distinguish this tumor from its morphological counterparts due to the different prognosis. ACC as a rare basaloid cell tumor is also reported mainly in black female patients. In Asia the incidence is unknown. In Chen’s report, only 1 case of ACC was found in more than 7600 cervical carcinoma [5]. While Teramoto et al. [6] found non ACC case at all in 2600 cases of cervical neoplasm. We also didn’t found any ACC case in our pathology archive. Together with those literatures before, we believed the incidence of ACC is much lower in Asia than in Western countries, As such, the difference between ABC and squamous cell carcinoma (SCC) with basaloid features is more practical and necessary in Asian area. In our ABC series, two cases had greatly expensive squamous differentiation nests and the lesion deceptively resembled a purely squamous cell tumor. However, the obvious staining of CAM5.2 was seen at the periphery of the nests, while staining in the squamous areas was faint. This unique staining pattern is helpful in the differential diagnosis from SCC.

There is no definite histogenesis of ABC but several lines of evidence support the hypothesis of the reserve cell origin. Hiroi et al. [8] found sparse organelles and scattered intracytoplasmic filaments, a resemblance to normal cervical reserve cells in the cells of ABC through electron microscopy. Cviko et al. [9] bolstered the reserve cell origin by evaluating the p63 expression in ABC and cervical cancers. The anti-apoptosis gene product, bcl-2 which is

expressed in the basal layer of cervix show strong immunostains in ABC [10]. However, many such researches were based on limited immunohistochemical stains or single case reports [9, 11]. In this study, we used a well-defined set of immunohistochemical markers that enabled us to support the histogenesis of reserve cell origin. Reserve cells are pivotal in the metaplastic transition zone of the uterine cervix. During this process reserve cell can progress to immature squamous metaplastic epithelium, resulting in the formation of mature squamous epithelium. As the progenitor for squamous and columnar epithelium, reserve cells express some high-molecular weight and low-molecular weight keratin profiles including keratins 5 and 8. P63 immunostaining also has a strong association with immature squamous epithelium and reserve cells [12]. In our experiment, keratin 8 was detected by CAM5.2, which has frequently been suggested to be reactive to both keratins 7 and 8. However, the reactivity of CAM5.2 to keratins 7 is very weak on 2-D gel electrophoresis, and CAM5.2 does not detect keratins 7 immunohistochemically [13]. We found the immunoprofile expression of the 3 basal reserve cell antibodies (CK5/6, p63, CAM5.2) is similar to that of basal hyperplasia, which has been shown to be keratins 5,8-positive, and p63 positive [14]. These results support the hypothesis of the reserve cell origin. What’s more, the special expression pattern of CAM5.2 in squamous areas of ABC also highlights the unique squamous differentiation. Brainard et al. [15] also show similar CAM5.2 expression pattern in squamous areas of ABC in his experiment.

In conclusion, we described the clinicopathologic features of a series of ABC, with emphasis on the expression of an immunohistochemical panel composed of CK5/6, CAM5.2 and p63. Our findings, coupled with those in the literature, cast considerable lights regarding the reserve cell origin of adenoid basal carcinoma. However, further investigations including a large series of ABC are needed to prove the biological nature of ABC.

Disclosure of conflict of interest

None.

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