Case Report
Adenoid basal carcinoma of the uterine cervix: a case report with an immunohistochemical and ultrastructural study

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Abstract: A case of adenoid basal carcinoma (ABC) of the uterine cervix is reported. The patient was an 80-year-old woman who underwent hysterectomy for uterine prolapse, and ABC was incidentally found in the cervix. The tumor consisted of many cell nests of various sizes, which were composed of small basaloid cells and showed extensive invasion in the cervical wall. Both squamous and glandular differentiations were found in the center of some cell nests. Tumor cells showed the nuclear immunoreactivity for p40 and p63, and the diffuse cytoplasmic immunoreactivity for cytokeratin and p16. Although the deposition of hyaline material was not apparent around cell nests, the cell nests were surrounded by thin, membranous material immunoreactive for laminin, and the ultrastructural study demonstrated an accumulation of electron-dense lamellar material, which formed undulating or loop-forming, “seaweed-like” protrusions on the cell surface. These findings indicate that ABC produces redundant basal lamina material, although its amount is far less than that seen in adenoid cystic carcinoma, another neoplasm of the uterine cervix showing basaloid features.

Keywords: Adenoid basal carcinoma, uterine cervix, basal lamina material, immunohistochemistry, ultrastructure

Introduction
Adenoid basal carcinoma (ABC) of the uterine cervix is a rare neoplasm which predominantly affects postmenopausal women and consists of a proliferation of small basaloid cells forming solid cell nests with peripheral nuclear palisading [1-6]. It is commonly associated with intraepithelial neoplasm of the overlying squamous epithelium but usually follows an indolent clinical course, and tumor-related death seldom occurs after hysterectomy [1-6]. Since the first documentation by Baggish and Woodruff [7, 8], the distinction from adenoid cystic carcinoma (ACC), another rare cervical neoplasm showing a more aggressive biological behavior [1, 2, 4, 9], has been widely discussed [1, 2, 4, 5, 10-12]. The origin and pathogenesis of ABC are still unclear, but the “reserve cells” within the cervical epithelium are presumed to be the origin [1, 2, 4, 10-13], and human papillomavirus (HPV) (in particular type 16) infection plays an important role in its pathogenesis [6, 13-16].

We report a case of ABC which showed unusually extensive penetration in the cervical wall, and present some new ultrastructural findings which indicate the formation of redundant basal lamina material by neoplastic cells.

Clinical history
An 80-year-old woman, G6P2, who had been treated for microscopic polyangiitis from five years previously, presented with complaints of micturition disturbance and spotty vaginal bleeding. She was diagnosed with a cystocele and uterine prolapse and underwent vaginal hysterectomy. Because the pathological examination of the extirpated uterus demonstrated ABC of the cervix (International Federation of Gynecology and Obstetrics Stage IB1), computed tomography examination of the thoracic and abdominal cavities was performed, which yielded negative results. Her postoperative clinical course has been uneventful, and she is free from recurrence or metastasis for 12 months.
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Pathological findings

Gross appearance

The extirpated uterus showed age-matched, marked senile atrophy. The cervix appeared to be slightly enlarged as a whole in comparison with the corpus, but otherwise unremarkable. The ectocervical squamous epithelium was thickened and white in color.

Histopathological findings

Beneath the surface epithelium of the uterine cervix, a neoplasm consisting of many small, solid epithelial cell nests extensively spread and infiltrated the entire circumference of the cervix (Figure 1A). It deeply penetrated the cervical stroma until 10 mm in depth and spread horizontally up to 25 mm along the longitudinal axis. The cell nests were mostly of round or oval shape and had smooth contours, but irregularly shaped, fused nests were also found occasionally. Their sizes varied from 0.3 to 1.5 mm, basal lamina material is seen in the lower left corner. (scale bar: 5 μm), H: Electron-dense, small, round secretory granules were seen in the apical cytoplasm surrounding the glandular lumen. (scale bar: 2 μm), I: A localized accumulation of redundant basal lamina material protruded from the cell surface into the surrounding stroma. (scale bar: 5 μm), J: Redundant basal lamina material showed a “seaweed-like” appearance and was closely admixed with collagen fibrils. (scale bar: 2 μm).

Informed consent to use both clinical data and pathologic material was obtained in accordance with the Declaration of Helsinki.

Figure 1. A: Small, solid cell nests of irregular shape extensively invaded the cervical stroma. Some nests had small glandular lumina in the center. (Hematoxylin-eosin stain, x 25), B: Each cell nest consisted of a dense proliferation of small basaloid cells occasionally showing peripheral nuclear palisading. (Hematoxylin-eosin stain, x 50), C: Some nests exhibited squamous differentiation associated with increased nuclear atypism and pleomorphism. (Hematoxylin-eosin stain, x 50), D: Other nests contained glandular lumina which occasionally showed cystic dilatation and contained eosinophilic secretory material. (Hematoxylin-eosin stain, x 25), E: Thickened basal lamina surrounded some of the cell nests. (PAS reaction, x 50), F: Thickened basal lamina was immunoreactive for laminin. (Immunoperoxidase method, x 50), G: Polygonal tumor cells with a moderate amount of cytoplasm surrounded a small lumen (upper right corner). A localized accumulation of redundant basal lamina material is seen in the lower left corner. (scale bar: 5 μm), H: Electron-dense, small, round secretory granules were seen in the apical cytoplasm surrounding the glandular lumen. (scale bar: 2 μm), I: A localized accumulation of redundant basal lamina material protruded from the cell surface into the surrounding stroma. (scale bar: 5 μm), J: Redundant basal lamina material showed a “seaweed-like” appearance and was closely admixed with collagen fibrils. (scale bar: 2 μm).
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and the larger nests were predominantly distributed in the superficial region, while the smaller nests were in the deeper portion. Neither lymphovascular nor perineural invasion was observed. Each cell nest was composed of uniform, small, basaloid cells with bland nuclei and inconspicuous cytoplasm, and peripheral nuclear palisading was found in some nests (Figure 1B). The mitotic activity was very low as a whole. Some cell nests showed squamous differentiation toward the center, which was accompanied by an increase of nuclear atypism and pleomorphism and an elevated mitotic activity (Figure 1C). The squamous differentiation also occasionally accompanied central necrosis and calcification. In other nests, one or a few small, round lumina or microcysts were found in the center, and they contained eosinophilic, flocculent material (Figure 1D), which was positive for the periodic acid-Schiff (PAS) reaction. Some of the lumina were lined by cuboidal cells with clear cytoplasm. Cribriform glands were not found.

The penetration of tumor cell nests did not evoke a desmoplastic or inflammatory stromal reaction, but a small number of the nests were surrounded by edematous or myxoid stroma. Although the intercellular deposition of a hyaline substance suggestive of exuberant basal lamina material was not obvious, PAS-positive basal lamina was found on the surface of cell nests (Figure 1E). The squamous epithelium overlying the tumor showed marked acanthosis and hyperkeratosis, and, in the squamo-columnar junction, features of severe dysplasia with glandular involvement were noted. No continuity was demonstrated between the overlying epithelium and subepithelial tumor cell nests.

**Immunohistochemical findings**

An immunohistochemical study was performed on paraffin sections using primary antibodies against the following substances: cytokeratin (clone AE1/AE3, Dako, 1:500), high-molecular-weight cytokeratin (clone 34βE12, Dako, prediluted), cytokeratin 5/6 (clone D5/16B4, Roche, prediluted), p40 (clone BC28, Roche, prediluted), p63 (clone 7JUL, Novocastra Laboratories, 1:25), S-100 protein (clone ER-PR8, Dako, 1:500), α-smooth muscle actin (α-SMA) (clone 1A4, Dako, 1:100), desmin (clone D33, Dako, prediluted), c-kit gene product (CD117) (polyclonal, Dako, 1:200), laminin (clone HL-4H3, Daiichi Fine Chemical, 1:100), p16 (clone G175-45, Becton Dickinson Pharmigen, 1:500), and Ki67 antigen (clone MIB-1, Dako, 1:100). Heat-induced antigen retrieval using a hot bath or protease predigestion was performed before the immunostaining.

Tumor cells were diffusely positive for cytokeratin (AE1/AE3), high-molecular-weight cytokeratin (34βE12), and cytokeratin 5/6. Cells in the center of nests showing squamous differentiation were often negative or only weakly positive for the latter two. Tumor cell nuclei were diffusely immunoreactive for both p40 and p63. The cytoplasm was not immunoreactive for S-100 protein, α-SMA, desmin, and CD117. Most of the tumor cells were diffusely immunoreactive for p16. Thin, basal lamina material immunoreactive for laminin surrounded cell nests (Figure 1F). The Ki67 labeling index was less than 1% in basaloid cells but increased up to 18.6% in the central region of the cell nests showing squamous differentiation.

**Ultrastructural findings**

Small pieces of the formalin-fixed tumor tissue were post-fixed by glutaraldehyde and osmium tetroxide. They were then processed routinely and observed after the double-staining with uranium and lead. Small tumor cells of relatively uniform size and shape formed cell nests surrounded by thin basal lamina (Figure 1G). The cytoplasmic membrane was smooth, and the adjoining cells were connected by many desmosomes. Nuclei were round or elliptical and frequently showed deep indentations. They had evenly dispersed chromatin and small nucleoli. The cytoplasm contained rough-surfaced endoplasmic reticulum, free ribosomes, mitochondria, and a few lysosomes. A large amount of intermediate filaments was also found. Some tumor cells formed a small, round lumen in the center of cell nests, and electron-dense, small, and round secretory granules were found in the apical cytoplasmic region surrounding the lumen (Figure 1H).

The intriguing finding was a localized accumulation of redundant basal lamina material on the basal surface of some tumor cells. It was composed of undulating or loop-forming, electron-dense, membranous material and protruded into the intercellular space, with an appearance reminiscent of seaweed (Figure 1I). A moderate amount of collagen fibrils was admixed with it. The intercellular space contained many
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collagen fibrils, but a felt-like structure composed of a large amount of redundant basal lamina material, such as seen in ACC [4, 17], was not observed. On the basal surface of cells, the formation of hemidesmosomes was prominent, and the cytoplasm occasionally formed filopodia-like, small, and thin protrusions.

Discussion

The histopathological findings of the tumor in the present case were well consistent with those of ABC. However, in comparison with the previously reported cases, the deep penetration and horizontal spread of the tumor in this case were extensive, being 10 and 25 mm, respectively. In most cases, uterine cervical ABC is incidentally found as a small, localized lesion and does not form a grossly discernible nodule. According to Brainard and Hart [3], the mean invasion depth in their 12 cases was 4.3 mm. Some investigators preferred to apply the term “adenoid basal epithelioma” to this lesion to emphasize the indolent biological character [3, 6]. However, cervical ABC shows invasive growth into the stroma, and, as reported by Cviko et al. [15], the cellular proliferative activity is high in the center of the cell nests showing squamous differentiation. Moreover, the oncogenesis of ABC is closely related to infection of the high-risk group of HPV [6, 13-16], and Parwani et al. [6] and Xing et al. [16] demonstrated the diffuse immunohistochemical expression of p16 in neoplastic cells of ABC, a finding which was confirmed in the present case. ABC is thus reasonably regarded as a truly carcinomatous lesion, and close postoperative follow-up is desirable.

The histopathological distinction of ABC from adenoid cystic carcinoma (ACC) has been discussed since the first description of this neoplasm. ACC of the uterine cervix [2, 4, 9, 16, 17] is histogenetically different from ACC arising in other organs, such as salivary glands, because myoepithelial cells are not present in the normal cervical mucosa [4], and cervical ACC does not exhibit apparent myoepithelial differentiation [2]. There are some degrees of morphological overlapping between ABC and ACC of the uterine cervix [2, 4, 11, 16]. In particular, a solid variant of ACC closely resembles ABC in that it predominantly consists of solid cell nests with peripheral nuclear palisading [18]. Chen et al. reported that immunohistochemistry for CD117 is one of the useful methods for differentiation between these neoplasms: it is positive in ACC but negative in ABC [5], CD117 was negative in our case. The histogenesis of ABC and ACC of the uterine cervix has not yet been firmly established, but the “reserve cells” within the cervical epithelium are assumed to be the most likely cell of origin of these two neoplasms [1, 2, 4, 9-13, 16, 17]. The diffuse nuclear immunoreactivity for p40 and p63 in the present case suggests the “stem cell” nature with a differentiation potential toward squamous cells [15, 19], supporting the “reserve cell” origin.

The descriptions of ultrastructural features of the uterine cervical ABC remain very limited. Hiroi et al. documented the ultrastructural findings of cervical ABC but did not allude to the presence of redundant basal lamina material [12]. We ultrastructurally demonstrated a localized accumulation of undulating or loop-forming, electron-dense membranous material, resembling seaweed, on the surface of cell nests. It most likely represents an early stage of the accumulation of redundant basal lamina material and indicates that redundant basal lamina material is also produced in ABC. The production and accumulation of exuberant basal lamina materials occurs in many benign and malignant neoplasms of various organs. In most cases these are ultrastructurally seen as a large amount of felt-like materials in the intercellular space, and the localized accumulation of undulating or
loop-forming membranous materials resembling seaweed, as seen in the present case, has been reported only infrequently in, for example, ossifying fibromyxoid tumor [20] and basal cell adenocarcinoma of the salivary gland [21].

Disclosure of conflict of interest

None.

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References