Int J Clin Exp Pathol 2018;11(3):1758-1762
www.ijcep.com /ISSN:1936-2625/IJCEP0064203

Case Report

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

Masayuki Shintaku[1], Yukako Rai[2], Shinya Yoshioka[3], Hidetoshi Okabe[4]

[1]Department of Pathology, Shiga Medical Center for Adults, Japan; [2]Department of Obstetrics and Gynecology, Tenjinbashi Yukako Ladies Clinic, Japan; [3]Department of Obstetrics and Gynecology, Kobe City Medical Center General Hospital, Japan; [4]Department of Laboratory Medicine, Shiga University of Medical Science, Japan

Received August 22, 2017; Accepted October 24, 2017; Epub March 1, 2018; Published March 15, 2018

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.

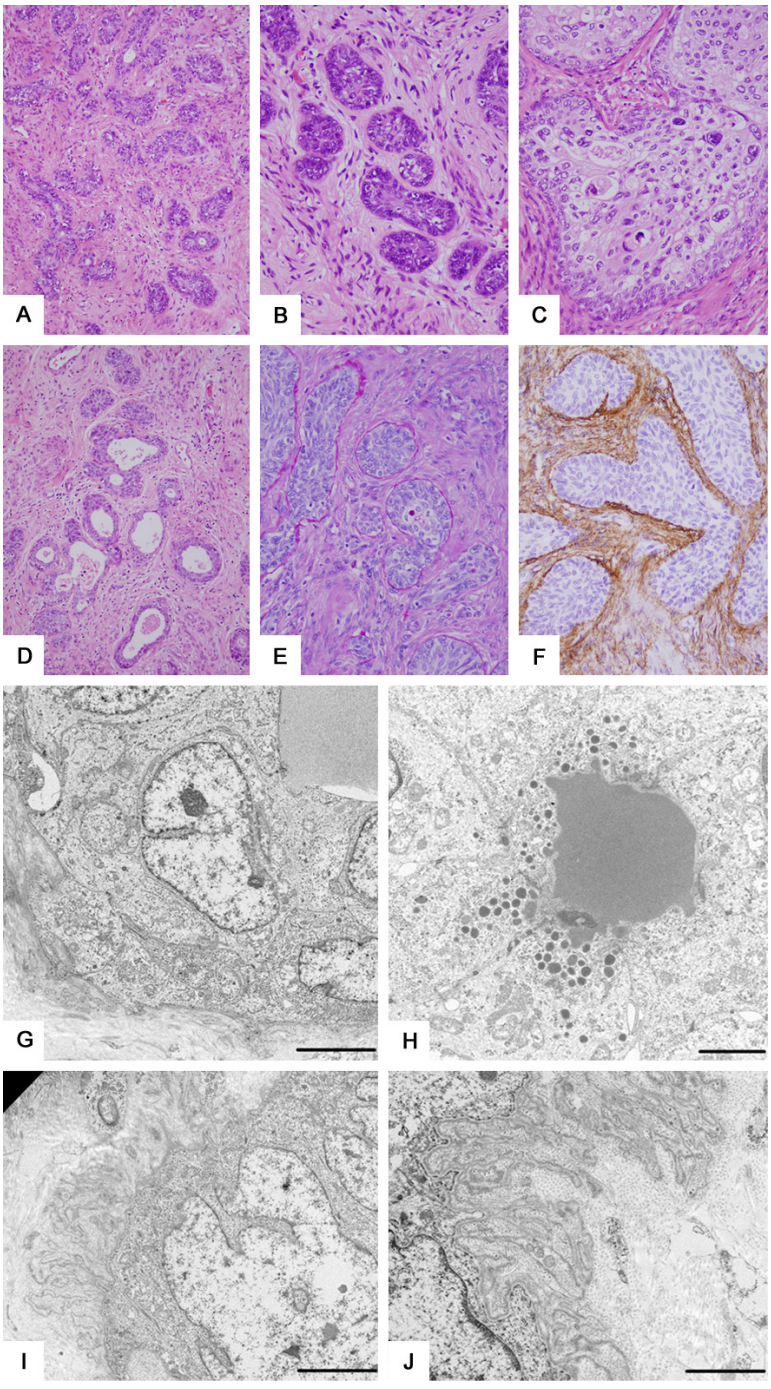

Figure 1. A: Small, solid cell nests of irregular shape extensively invaded the cervical stroma. Some nests had small glandular lumina in the center. (Hematoxylin-eosin stain, x 25), B: Each cell nest consisted of a dense proliferation of small basaloid cells occasionally showing peripheral nuclear palisading. (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).

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

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,

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**, **1J**). A moderate amount of collagen fibrils was admixed with it. The intercellular space contained many

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.

Among the histopathological differential points between ABC and ACC, the intercellular accumulation of an enormous amount of basal lamina material has been emphasized as a characteristic finding of the latter [2, 4, 9, 16-18]. In ACC, this exuberant basal lamina material is found as the stromal deposition of a thick hyaline substance [2, 4, 9, 16-18], and it is seen as an accumulation of dense, felt-like material on ultrastructural analysis [4, 17]. Grayson et al. demonstrated the localization of type IV collagen and laminin in ACC but not in ABC [4]. However, Hiroi et al. immunohistochemically demonstrated the presence of type IV collagen and laminin on the surface of cell nests in their case of cervical ABC [12], and we also confirmed the presence of laminin. These findings suggest that redundant basal lamina material is also produced in ABC.

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, although it does not amount to be recognized as a thick hyaline substance on light microscopy such as seen in ACC. 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.

Address correspondence to: Dr. Masayuki Shintaku, Department of Pathology, Shiga Medical Center for Adults, Moriyama 524-8524, Shiga, Japan. (Tel: 077-582-5031; Fax: 077-582-5426; E-mail: masas@sings.jp

References

[1] Van Dinh T, Woodruff JD. Adenoid cystic and adenoid basal carcinomas of the cervix. Obstet Gynecol 1985; 65: 705-709.

[2] Ferry JA, Scully RE. "Adenoid cystic" carcinoma and adenoid basal carcinoma of the uterine cervix. A study of 28 cases. Am J Surg Pathol 1988; 12: 134-144.

[3] Brainard JA, Hart WR. Adenoid basal epitheliomas of the uterine cervix. A reevaluation of distinctive cervical basaloid lesions currently classified as adenoid basal carcinoma and adenoid basal hyperplasia. Am J Surg Pathol 1998; 22: 965-975.

[4] Grayson W, Taylor LF, Cooper K. Adenoid cystic and adenoid basal carcinoma of the uterine cervix. Comparative morphologic, mucin, and immunohistochemical profile of two rare neoplasms of putative "reserve cell" origin. Am J Surg Pathol 1999; 23: 448-458.

[5] Chen TD, Chuang HC, Lee LY. Adenoid basal carcinoma of the uterine cervix. Clinicopathologic features of 12 cases with reference to CD117 expression. Int J Gynecol Pathol 2012; 31: 25-32.

[6] Parwani AV, Smith Sehdev AE, Kurman RJ, Ronnett BM. 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. Hum Pathol 2005; 36: 82-90.

[7] Baggish MS, Woodruff JD. Adenoid-basal carcinoma of the cervix. Obstet Gynecol 1966; 28: 213-218.

[8] Baggish MS, Woodruff JD. Adenoid basal lesions of the cervix. Obstet Gynecol 1971; 37: 807-819.

[9] Miles PA, Norris HJ. Adenoid cystic carcinoma of the cervix. An analysis of 12 cases. Obstet Gynecol 1971; 38: 103-110.

[10] Yoshida T, Fujiwara K, Shimizu M, Kohno I, Mikami Y, Manabe T. Adenoid basal carcinoma of the cervix uteri. A case report. Pathol Int 1997; 47: 775-777.

[11] Senzaki H, Osaki T, Uemura Y, Kiyozuka Y, Ogura E, Okamura A, Tsubura A. Adenoid basal carcinoma of the uterine cervix. Immunohistochemical study and literature review. Jpn J Clin Oncol 1997; 27: 437-441.

[12] Hiroi M, Fukunaga T, Miyazaki E, Hayashi Y, Kuroda N, Toi M, Naruse K, Nakayama H, Kiyoku H, Enzan H. Adenoid basal carcinoma of the uterine cervix. A case report with ultrastructural findings. Med Electron Microsc 2000; 33: 241-245.

[13] Jones MW, Kounelis S, Papadaki H, Bakker A, Swalsky PA, Finkelstein SD. The origin and molecular characterization of adenoid basal carcinoma of the uterine cervix. Int J Gynecol Pathol 1997; 16: 301-306.

[14] Grayson W, Taylor LF, Cooper K. Adenoid basal carcinoma of the uterine cervix. Detection of integrated human papillomavirus in a rare tumor of putative "reserve cell" origin. Int J Gynecol Pathol 1997; 16: 307-312.

[15] Cviko A, Briem B, Granter SR, Pinto AP, Wang TY, Yang YC, Chen BF, Yang A, Sheets EE, McKeon FD, Crum CP. Adenoid basal carcinomas of the cervix. A unique morphological evolution with cell cycle correlates. Hum Pathol 2000; 31: 740-744.

[16] Xing D, Schoolmeester JK, Ren Z, Isacson C, Ronnett BM. Lower female genital tract tumors with adenoid cystic differentiation. P16 expression and high-risk HPV detection. Am J Surg Pathol 2016; 40: 529-536.

[17] Mazur MT, Battifora HA. Adenoid cystic carcinoma of the uterine cervix. Ultrastructure, immunofluorescence, and criteria for diagnosis. Am J Clin Pathol 1982; 77: 494-500.

[18] Albores-Saavedra J, Manivel C, Mora A, Vuitch F, Milchgrub S, Gould E. The solid variant of adenoid cystic carcinoma of the cervix. Int J Gynecol Pathol 1992; 11: 2-10.

[19] Emanuel P, Wang B, Wu M, Burstein DE. p63 Immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma. Mod Pathol 2005; 18: 645-650.

[20] Enzinger FM, Weiss SW, Liang CY. Ossifying fibromyxoid tumor of soft parts. A clinicopathological analysis of 59 cases. Am J Surg Pathol 1989; 13: 817-827.

[21] Quddus MR, Henley JD, Affify AM, Dardick I, Gnepp DR. Basal cell adenocarcinoma of the salivary gland. An ultrastructural and immunohistochemical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87: 485-492.