Med Electron Microsc (2000) 33:241–245

ORIGINAL PAPER

**Makoto Hiroi · Toshinori Fukunaga · Eriko Miyazaki
Yoshihiro Hayashi · Naoto Kuroda · Makoto Toi
Keishi Naruse · Hirofumi Nakayama · Hiroshi Kiyoku
Hideaki Enzan**

Adenoid basal carcinoma of the uterine cervix: a case report with ultrastructural findings

Received: November 1, 2000 / Accepted: December 25, 2000

Abstract Adenoid basal carcinoma of the uterine cervix is a rare tumor with a favorable prognosis. A case of adenoid basal carcinoma (ABC) of the uterine cervix was studied using light and electron microscopy. The patient was a 74-year-old Japanese woman who had undergone hysterectomy due to cervical intraepithelial neoplasia 3. Incidentally, ABC was found in the resected uterus. The tumor cells made small nests and infiltrated the cervical portion of the uterus. In the nests, glands, cribriform patterns with glandlike structures, and squamous differentiation were seen. Immunohistochemically, the glandlike structures were positive for laminin and type IV collagen. Ultrastructurally, the tumor cells had irregular nuclei, scanty cytoplasm, and cribriform patterns in which glandlike structures were covered with basal lamina. No myoepithelial differentiation of the tumor cells was seen. These findings suggest a similarity between adenoid basal carcinomas and adenoid cystic carcinomas. Furthermore, both tumors are considered to originate in the reserve cells of the uterine cervix. Because their outcomes are different, they should be distinguished from each other.

Key words Adenoid basal carcinoma · Uterine cervix · Ultrastructure

M. Hiroi (✉) · E. Miyazaki · Y. Hayashi · N. Kuroda · M. Toi · K. Naruse · H. Enzan
First Department of Pathology, Kochi Medical School, Kohasu, Okoh-Cho, Nankoku City, Kochi 783-8505, Japan
Tel. +81-88-880-2330; Fax +81-88-880-2332
e-mail: hiroim@kochi-ms.ac.jp

T. Fukunaga
Obstetrics and Gynecology, Kubokawa Hospital, Kubokawa, Japan

H. Nakayama
Department of Pathology, Kure National Hospital, Kure, Japan

H. Kiyoku
Department of Pathology, Tokushima Municipal Hospital, Tokushima, Japan

Introduction

Adenoid basal carcinoma (ABC) of the uterine cervix is a very rare neoplasm first described by Baggish and Woodruff in 1966.[1] The best of our knowledge, approximately 60 cases have been published.[2–12] Clinically, almost all ABCs occur in postmenopausal women. Most cases are associated with cervical intraepithelial neoplasia (CIN).[13] ABCs have a favorable prognosis, showing local proliferation without metastasis. Therefore, ABCs should be distinguished from adenoid cystic carcinomas (ACC), which often resemble ABCs histopathologically and show aggressive behavior.[4,5,11] Both tumors are thought to be derived from the reserve cells of the uterine cervix, but this has not been confirmed.[1,2,10,12] To the best of our knowledge, there have been no reports on the electron microscopic appearance of ABCs. We report a case of ABC with pathological and ultrastructural findings.

Case report

Clinical history

A 74-year-old Japanese woman presented with irregular uterine bleeding. The patient's medical history was unremarkable. Ultrasonography revealed a thickening of the endometrium but colposcopy showed no remarkable findings. The endometrial and cervical cytology was reported to be a high-grade squamous intraepithelial lesion. A biopsy of the endometrium showed no atypia. Occasionally CIN 3 was noted in the cervical squamous epithelium. After the biopsy, a total hysterectomy was performed.

Material and methods

Tissue samples were fixed in 20% formalin and embedded in paraffin. Sections 4 μm thick were prepared for immuno-

Table 1. List of antibodies employed

Antibody	Clone	Dilution	Source
AE1/AE3	AE1/AE3	1:400[a]	Boehringer Mannheim, Germany
Cytokeratin 7	M7018	1:50[a]	DAKO, Glostrup, Denmark
Cytokeratin 8	M631	1:50[a]	DAKO, Carpinteria, CA, USA
Cytokeratin 14	LL002	1:20[b]	Novocastra, Newcastle, UK
Type IV collagen	Poly	1:1000[a]	Cosmo Bio, LSL, Tokyo, Japan
Laminin	Poly	1:50[a]	Bio-Science, Emmenbrücke, Switzerland
S100	2A-10	1:100	IBL, Gunma, Japan
α-ASMA	1A4	1:50	DAKO, Glostrup, Denmark
MIB-1 (Ki-67)	MIB-1	1:100[b]	Immunotech, Marseilles, France
bcl-2	124	1:50[b]	DAKO, Glostrup, Denmark

α-ASMA, α-smooth muscle actin
[a] Required pronase digestion
[b] Required microwave antigen retrieval

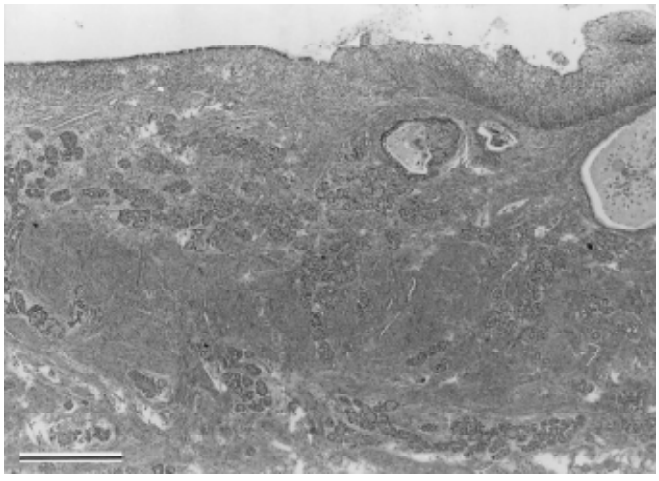

Fig. 1. Low magnification of the uterine cervix. The cervical epithelium in the *right half* of the figure shows cervical intraepithelial neoplasia (CIN) 3. Multiple epithelial nests are seen in the stroma. *Bar* 1 mm

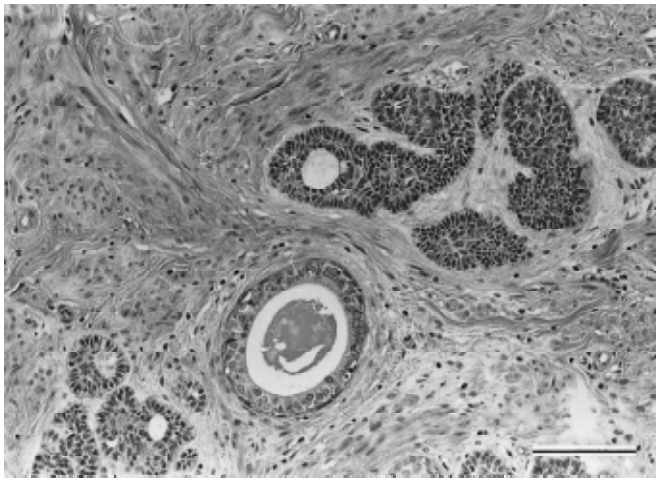

Fig. 2. Epithelial nests consist mainly of basaloid cells with glandlike structures (*bottom left* and *upper right*) and a dilated gland. *Bar* 100 μm

histochemical examination and staining with hematoxylin and eosin. Immunohistochemical staining was performed using a labeled streptavidin-biotin staining kit (Nichirei, Tokyo, Japan) according to the manufacturer's instructions. The antibodies and their sources are listed in Table 1.

For electron microscopic study, formalin-fixed tissue samples were used. The samples were postfixed in 1% osmium tetroxide. After dehydration in graded ethanols and propylene oxide, the blocks were embedded in epoxy resin (Epon 812). Ultrathin sections were stained with uranyl acetate and lead citrate and examined using a JEM-1200 electron microscope (JEOL, Tokyo, Japan).

Pathological findings

Gross examination of the hysterectomy specimen showed no tumor in the uterine cervix. Microscopically, CIN 3 was noted in the transitional zone of the cervix. The stromal invasion was not identified. As an incidental finding, there were multiple epithelial nests in the cervical stroma (Fig. 1). The nests occupied all the cervical specimens with a maximum depth of 14 mm and a horizontal spread of 12 mm. The epithelial nests were oval and often irregular in shape. They were composed of basaloid cells with glandular components in which clear columnar cells formed a few distinct lumen (Fig. 2). Some of them had a cribriform pattern, resembling ACCs. Squamous differentiation was also seen (Fig. 3). Mitosis of the tumor cells was not seen. There were no distinct stomal reaction and no necrosis of the tumor cells.

Immunohistochemically, all the tumor cells were positive for AE1/AE3. CK8 was positive only in the basaloid cells. CK7 was positive in the cells mainly surrounding the true lumen. CK14-positive cells were scattered. The tumor cells were negative for S-100 protein and α-smooth muscle actin. MIB1 (Ki67)-positive cells were scattered unevenly and the positive rate was about 2%. Bcl-2 was positive in the basaloid and columnar tumor cells. The basement membrane material, positive for type IV collagen and laminin, was seen around the tumor nests and in the glandlike structures (Fig. 4).

By electron microscopy, the tumor cells had irregular round to oval nuclei and scant cytoplasm (Fig. 5). In the cytoplasm, organelles were sparse and the filaments were

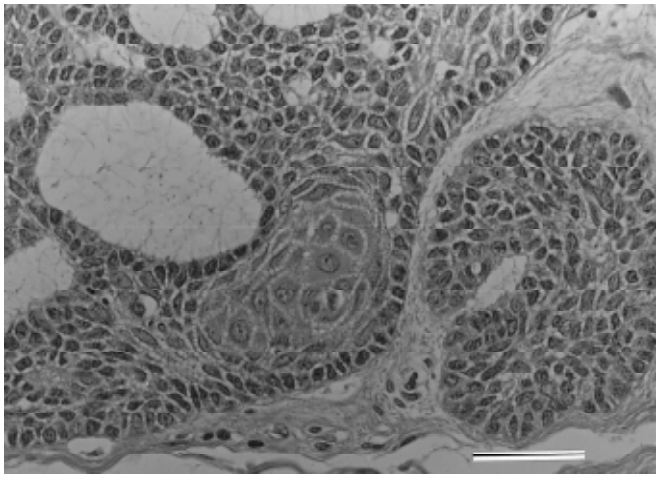

Fig. 3. Nest with squamous differentiation. *Bar* 30 μm

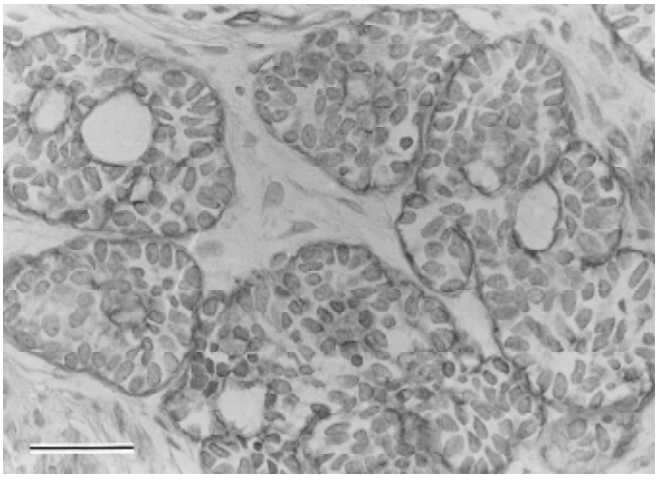

Fig. 4. Immunostaining of the laminin. Epithelial nests and glandlike structures are covered with laminin-positive membranes. *Bar* 50 μm

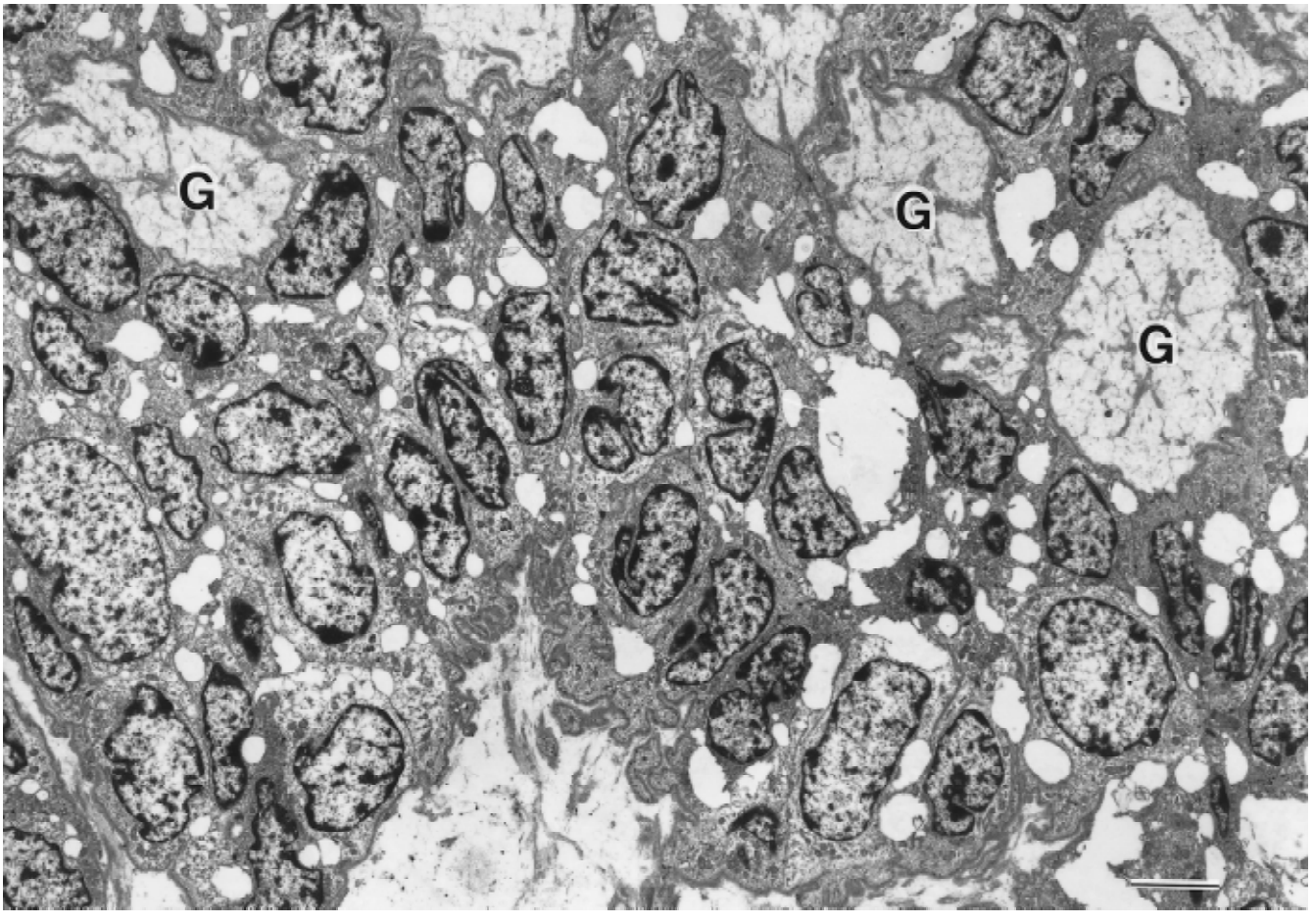

Fig. 5. Ultrastructural findings. Tumor cells have irregular nuclei and scanty cytoplasm. Epithelial nest and glandlike structure (*G*) are covered with basal lamina. *Bar* 5 μm

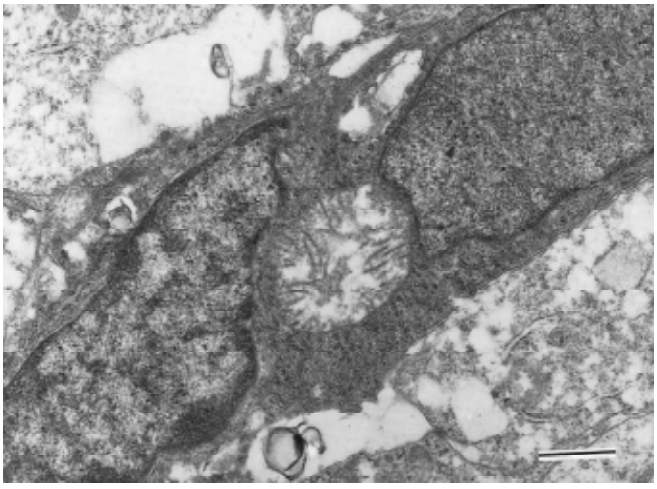

Fig. 6. Small gland with microvilli. *Bar* 1 μm

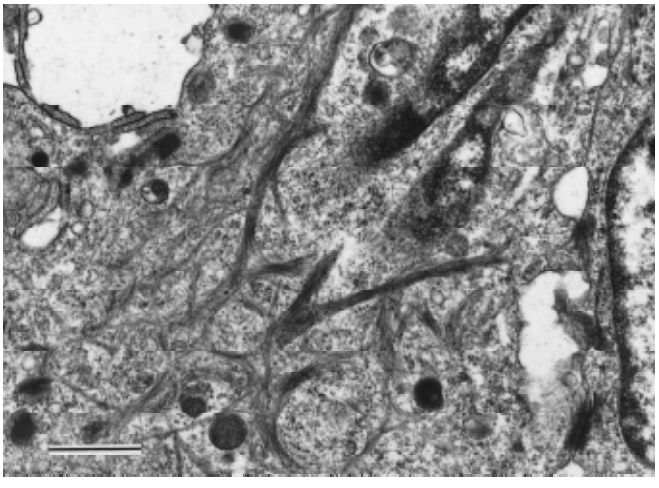

Fig. 7. Thick tonofilaments in tumor cells indicate squamous differentiation. *Bar* 1 μm

scattered. No tumor cells had abundant filaments with dense bodies. When the intercellular spaces were seen between the tumor cells, the desmosomes were scattered. Some tumor cells had tonofilaments, indicating the differentiation to squamous epithelium (Fig. 6). A few of the tumor cells making up the true lumen with microvilli showed glandular differentiation (Fig. 7). In the cribriform patterns, the glandlike structure were covered by single-layered basal lamina. The cell nests were also surrounded by the basal lamina (Fig. 5).

Discussion

ABC of the uterine cervix is a very rare tumor with favorable prognosis. The most important differential diagnosis is to ACCs because of their local recurrence and distant metastasis. The histological patterns of both tumors, namely basaloid cell proliferation, squamous and glandular differentiation, and cribriform pattern, generally overlap.[4,5,11] Compared with ABCs, ACCs show gross polypoid masses in the cervix and histologically larger nests with larger cells, more mitotic activity, and more stromal reaction.[13] In this case, the tumor cell nests occupied a large area of the cervix; however, the cervix was not swollen. Histologically the cell nests were small with no sign of stromal reaction or necrosis. Morphologically, this case was thought to be a typical ABC. Grayson et al. compared 18 cervical ACCs and 8 ABCs and 1 combined ACC and ABC and described that both tumors had similar immunohistochemical profiles with the exception of type IV collagen and laminin, which were positive only in ACC but negative in ABCs.[12]

In our case, immunohistochemical expression of type IV collagen and laminin was seen around the glandlike structure, which ultrastructurally corresponded with the lumen covered with basal lamina. In contrast to Grayson's report, our case shows numerous glandlike structures with basal lamina. Myoepithelial differentiation of ABCs and ACCs is controversial. By immunostaining of S-100 protein and actin, most ABCs were thought to show no myoepithelial differentiation, whereas ACCs showed various degrees of myoepithelial differentiation.[5,12] Ultrastructural studies of ACCs have demonstrated the presence of cells with abundant intracytoplasmic filaments suggesting myoepithelial differentiation.[14–16] Ferry and Scully indicated myoepithelial differentiation with more restricted criteria, namely abundant filaments with dense bodies.[5] However, Shingleton et al. examined three cases of ACC by electron microscopy and saw no evidence of myoepithelial differentiation.[17] In our report, the ABC tumor cells had a considerable number of filaments but no dense bodies. These findings might depend on the quantity of filaments, showing the degree of the differentiation to myoepithelium.

Although the point of origin of ABCs is obscure, many authors speculate that it is the reserve cells of the uterine cervix.[1,2,10,12] Ultrastructurally, the reserve cells have round or oval nucleus with indentations and some bundles of filaments.[18] These findings resemble the basaloid cells of ABC. Bcl-2 is known as an apoptosis-related gene product, and its expression in the uterine cervix was recently reported.[19] Bcl-2 was expressed in the basal layer of ectocervical squamous epithelium and the reserve cells. In this case, Bcl-2 was positive in the majority of the tumor cells. The normal reserve cells in the uterine cervix and the basaloid cells of ABC showed a similar pattern.

Our observations support the speculation that ABCs originate in the reserve cells and indicate that ABCs are morphologically similar to ACCs. Ferry and Scully thought that ACC of the uterine cervix originated from ABC of the cervix.[5] Brainard and Hart suggested that ABC with typical histological structure is not malignant and proposed the term "basal cell epithelioma" as ABC.[11] Both tumors might originate in the reserve cells and differentiate in similar directions. Therefore, it is suggested that both ABCs and ACCs originate in the reserve cells of the uterine cervix and might be classified as benign or malignant tumors.

Acknowledgment We gratefully thank Mr. David Blake for the English revision of our manuscript.

References

1. Baggish MS, Woodruff JD (1966) Adenoid-basal carcinoma of the cervix. Obstet Gynecol 28:213–218
2. Baggish MS, Woodruff JD (1971) Adenoid basal lesions of the cervix. Obstet Gynecol 37:807–819
3. Shilkin KB (1972) Adenoid basal carcinoma of the cervix uteri. J Clin Pathol 25:301–305
4. van DT, Woodruff JD (1985) Adenoid cystic and adenoid basal carcinomas of the cervix. Obstet Gynecol 65:705–709
5. Ferry JA, Scully RE (1988) "Adenoid cystic" carcinoma and adenoid basal carcinoma of the uterine cervix. A study of 28 cases. Am J Surg Pathol 12:134–144
6. Langlois NE, Miller ID, Mann EM (1995) Adenoid basal carcinoma of the cervix: an unusual cytological appearance. Cytopathology 6:104–109
7. Senzaki H, Osaki T, Uemura Y, Kiyozuka Y, Ogura E, Okamura A, Tsubura A (1997) Adenoid basal carcinoma of the uterine cervix: immunohistochemical study and literature review. Jpn J Clin Oncol 27:437–441
8. Yoshida T, Fujiwara K, Shimizu M, Kohno I, Mikami Y, Manabe T (1997) Adenoid basal carcinoma of the cervix uteri: a case report. Pathol Int 47:775–777
9. Jones MW, Kounelis S, Papadaki H, Bakker A, Swalsky PA, Finkelstein SD (1997) The origin and molecular characterization of adenoid basal carcinoma of the uterine cervix [see comments]. Int J Gynecol Pathol 16:301–306
10. Grayson W, Taylor LF, Cooper K (1997) 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 16:307–312
11. Brainard JA, Hart WR (1998) 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 22:965–975
12. Grayson W, Taylor LF, Cooper K (1999) 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 23:448–458
13. Kurman RJ, Norris JJ, Wilkinson E (1992) Tumors of the cervix. In: Rosai J, Sobin LH (eds) Atlas of tumor pathology – fascicle 4, 3rd series: tumor of the cervix, vagina and vulva. Armed Forces Institute of Pathology, Washington, DC, pp 100–101
14. Gordon HW, McMahon NJ, Agliozzo CM, Rao PR, Rogers J (1972) Adenoid cystic (cylindromatous) carcinoma of the uterine cervix: report of two cases. Am J Clin Pathol 58:51–57
15. Mazur MT, Battifora HA (1982) Adenoid cystic carcinoma of the uterine cervix: ultrastructure, immunofluorescence, and criteria for diagnosis. Am J Clin Pathol 77:494–500
16. Albores SJ, Manivel C, Mora A, Vuitch F, Milchgrub S, Gould E (1992) The solid variant of adenoid cystic carcinoma of the cervix. Int J Gynecol Pathol 11:2–10
17. Shingleton HM, Lawrence WD, Gore H (1977) Cervical carcinoma with adenoid cystic pattern: a light and electron microscopic study. Cancer (Phila) 40:1112–1121
18. Gould PR, Barter RA, Papadimitriou JMF (1979) An ultrastructural, cytochemical, and autoradiographic study of the mucous membrane of the human cervical canal with reference to subcolumnar basal cell. Am J Pathol 95:1–16
19. Ter HB, Smedts F, Kuijpers J, Jeunink M, Trimbos B, Ramaekers F (1996) BCL-2 immunoreactivity increases with severity of CIN: a study of normal cervical epithelia, CIN, and cervical carcinoma. J Pathol 179:26–30