

Clinicocytopathological and Immunohistochemical Study of Adenoma Malignum of the Uterine Cervix

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ABSTRACT

Adenoma malignum is a rare type of very highly differentiated adenocarcinoma of the uterine cervix, and is quite difficult to diagnose because there are few findings definitely suggesting malignancy on cytologic or histologic examination. We recently encountered four patients with adenoma malignum and reviewed their clinicocytopathological and immunohistochemical findings. The most characteristic symptom was a watery discharge and an enlarged cervix was palpable, while multiple cystic lesions (MCL) were observed by transvaginal and abdominal ultrasonography, CT or MRI. On cytodiagnosis, the cervical gland cells formed large sheets or showed a palisading arrangement. Slightly enlarged nuclei and yellowish-orange staining of the cytoplasmic mucus were the characteristic findings. On histological examination, many cervical glands of different sizes were present and extended deep into the muscle layer, while branching or papillary growth into the lumen was also observed.

On immunohistochemical study, HIK1083, a monoclonal antibody for gastric gland mucous cell mucin, was found to be positive in 3 of 4 cases, and this was fairly useful in the diagnosis of adenoma malignum.

Key words: Adenoma malignum, Clinicocytopathological study, Immunohistochemical study, HIK 1083

Adenoma malignum, a so-called minimal deviation adenocarcinoma, is a rare type of very highly differentiated adenocarcinoma of the uterine cervix. In morphology, it does not differ much from normal cervical glands, and it is thus difficult to distinguish from benign lesions. However, the prognosis often becomes poor when diagnosis is delayed, so early diagnosis and treatment are desirable.

We recently encountered four patients with adenoma malignum. We reviewed these four cases, including their cytological and immunohistochemical findings, and the results are reported here.

CASE REPORT

Case 1: The patient was a 47-year-old woman (gravida 3, para 2). From September 1996, she was examined every 3 to 6 months in order to

monitor a uterine myoma and ovarian chocolate cyst. From around the beginning of 1998, a watery discharge appeared. In March, transvaginal ultrasonography revealed multiple cystic lesions (MCL) measuring about 1 to 2 cm in diameter in the cervix (Fig. 1). Cytological examination revealed Papanicolaou class III because of the irregular arrangement of the cervical glandular cells and slight dyskaryosis. However, there were no abnormal findings on colposcopy or cervical biopsy, and tumor markers were within the normal range (CEA was 1.2 ng/ml, CA19-9 was 19 U/ml, and CA125 was 12 U/ml). Since there were no findings clearly suggesting malignancy, she was followed up as an outpatient. Over the next 6 months, her cytology remained class III and a profuse watery discharge was persistent. After a hard region of the cervix was detected by inner examination, ade-

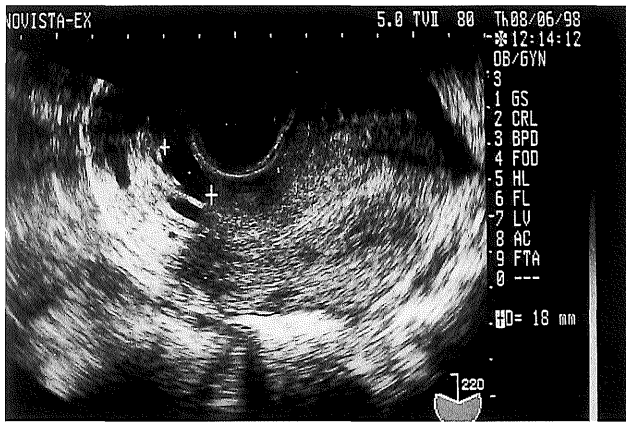


Fig. 1. Case 1. Transvaginal ultrasonography. Multiple cystic lesions (MCL) were observed in the uterine cervix.

noma malignum was suspected. Thereafter, modified radical hysterectomy, left salpingo-oophorectomy, and right salpingectomy were performed on October 15, 1998. The right ovary was preserved at the request of the patient. Postoperative histological examination confirmed the diagnosis of adenoma malignum. No signs of relapse have appeared after one year.

Case 2: The patient was a 44-year-old woman (gravida 0, para 0). In 1989, she underwent resection of an ovarian cyst. She had attended a local physician because of atypical vaginal bleeding and a watery discharge since October 1997, and was treated for a uterine myoma and endometriosis, but the watery discharge persisted. No findings suggesting malignancy was obtained by ectocervical, endocervical cytology or endometrial biopsy. However, MCL were found in the cervix on MRI, so adenoma malignum was suspected, and she was referred to our department. Because class III ectocervical cytology was still detected, conization was performed on January 29, 1998, but no evidence of malignancy was obtained. Tumor markers were normal (28 U/ml for SLX-1 and 22 U/ml for CA125). However, class III cytology persisted,

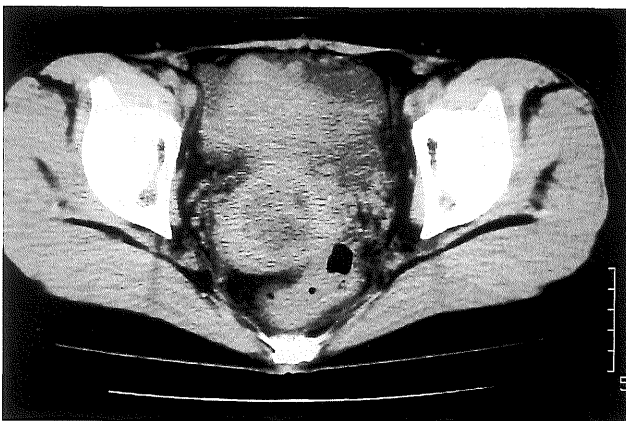


Fig. 2. Case 2. CT. MCL were found in the cervix.

so another conization was performed on June 1, 1998, but there was still no evidence of malignancy. Despite this, adenoma malignum was suspected because class III cytology was still detected and MCL were found in the cervix on CT (Fig. 2). Therefore, radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphnodectomy were performed on February 2, 1999.

Postoperative pathological examination confirmed that adenoma malignum was present. After the operation, she has undergone periodic cytodiagnosis of the vaginal stump and remained under observation, but no abnormalities have been found.

Case 3: The patient was a 52-year-old woman (gravida 3, para 3). Her past history included appendectomy in 1970, left mastectomy for breast cancer in May 1994, and left nephrectomy for renal cancer in 1995. She was subsequently followed up by the Department of Urology. In December 1996, abdominal CT scans revealed a left ovarian tumor and a uterine myoma, so she was referred to our department. No abnormalities were found on cervical and endometrial cytodiagnosis. Tumor markers were within the normal ranges (1.2 ng/ml for CEA, 3 U/ml for CA19-9, and 6 U/ml for CA125), and no abnormalities were detected by subsequent tumor marker studies and cytodiagnosis. In January 1998, MCL were observed in the cervix on abdominal and transvaginal ultrasonography, and the same finding was obtained by MRI in February (Fig. 3).



Fig. 3. Case 3. MRI. MCL were observed in the cervix.

Although no abnormalities were detected by subsequent tumor marker studies and cytodiagnosis, class III cervical cytology was seen from September. Tumor markers remained within the normal range, but ectocervical swelling and watery discharge were observed in February 1999. Since MCL were present on CT, adenoma

malignum was suspected and conization was performed on May 27. On postoperative pathological examination, adenoma malignum was diagnosed and she underwent radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy on July 8. After the operation, she has been followed up as an outpatient and no evidence of

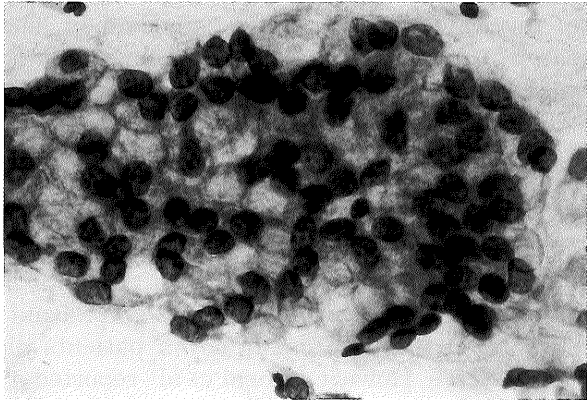


Fig. 4a. Case 1. Papanicolaou stain $\times 200$
Endocervical gland cells formed large sheets.

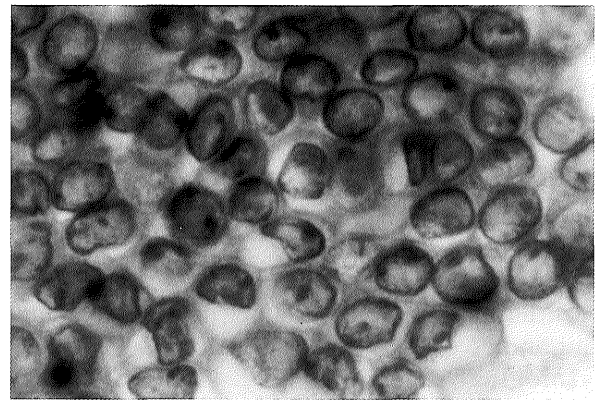


Fig. 4b. Case 2. Papanicolaou stain $\times 500$
Endocervical gland cells formed a honeycomb arrangement.

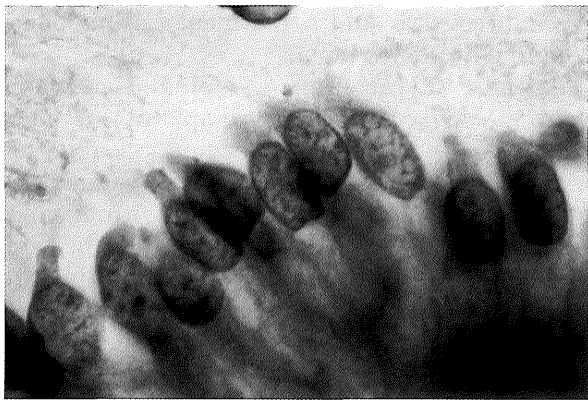


Fig. 4c. Case 1. Papanicolaou stain $\times 500$
Endocervical gland cells showed palisading.

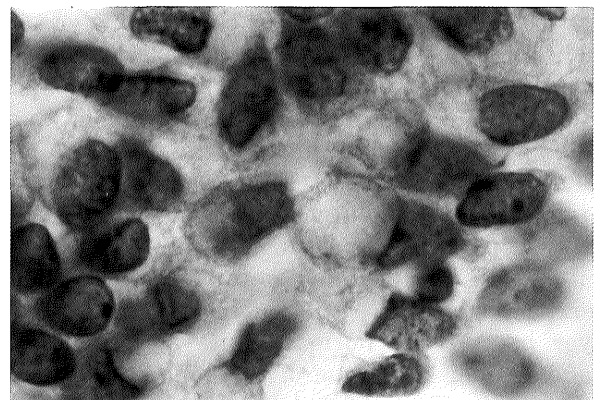


Fig. 4d. Case 1. Papanicolaou stain $\times 500$
The nuclei were slightly enlarged and the nuclear chromatin showed a slight increase. One to two nucleoli were present.

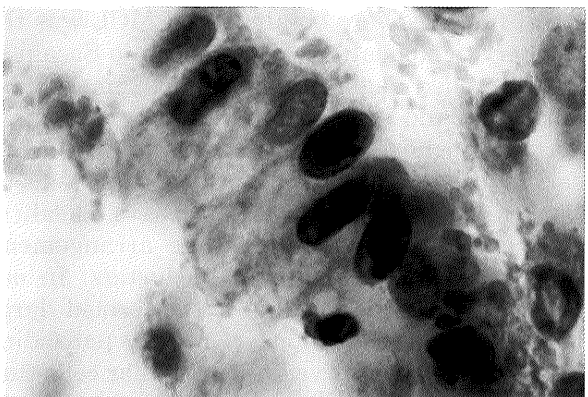


Fig. 4e. Case 2. Papanicolaou stain $\times 500$
The tall columnar cells of the glands contained abundant yellowish-orange mucus.

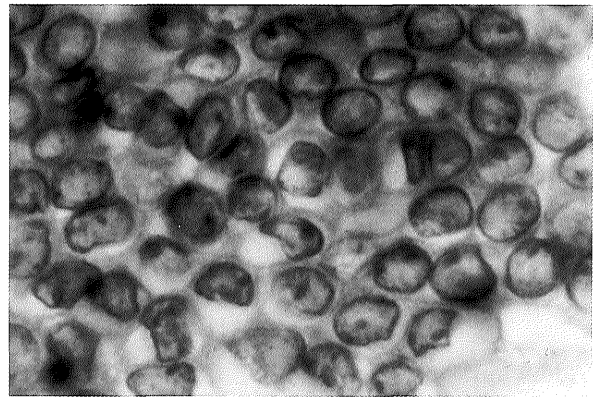


Fig. 4f. Case 3. Papanicolaou stain $\times 500$
The nuclei were slightly enlarged and its cytoplasm was a light blue.

recurrence has been seen.

Case 4: The patient was a 54-year-old woman (gravida 3, para 3). She attended a related hospital belonging to Hiroshima University School of Medicine on December 13, 1999, because of lower abdominal pain and watery discharge. Cytological examination revealed Papanicolaou class IV, with suspected well-differentiated adenocarcinoma of the uterine cervix. MCL were found in the cervix by transvaginal ultrasonography and MRI. Adenoma malignum was suspected and conization was performed on December 22. On postoperative pathological examination, adenoma malignum was diagnosed and she underwent radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy on January 18, 2000. Postoperative pathological examination confirmed the diagnosis of adenoma malignum. After the operation, she has been followed up as an outpatient and no evidence of recurrence has been seen.

Cytological findings (Fig. 4a-4f): Although there was some hemorrhage and mucous, the cervical gland cells in relatively clean backgrounds showed palisading and formed large sheets or a honeycomb arrangement. The nuclei were slightly enlarged and uniform in size, and there was irregular overlapping. The nuclear chromatin showed a slight increase and one to two nucleoli were usually present. The cytoplasm was a light blue. The tall columnar cells of the glands contained abundant yellowish-orange mucus.

Histological findings (Fig. 5a-5f): The uterine cervix contained many cervical glands of various sizes. Structures consisting of highly columnar epithelia and resembling normal cervical glands were detected infiltrating deep into the muscle layer beyond the normal limits of the cervical gland region, and some of the cells showed mild dyskaryosis. The glandular epithelium consisted of both branching shapes and papillary proliferations into the lumen.

Immunohistochemical findings (Fig. 6a-6d): The intracellular mucus was stained by PAS or Alcian blue in all four patients, but only case 2 was positive for CEA. Immunostaining with HIK 1083 (1:20 dilution: Kanto Reagents, Co. Ltd. Tokyo, Japan), a monoclonal antibody for gastric gland mucous cell mucin, was carried out by avidin-biotin complex (ABC) methods (Vectastain, Vector Lab. Inc.). The positive control for HIK 1083 was prepared for gastric tissue. Cases 1, 2 and 4 were also positive for HIK1083, and cytoplasmic staining of the glands was observed.

DISCUSSION

Adenoma malignum was first reported by Gusserow⁵⁾ in 1870 as a highly differentiated type of adenocarcinoma. In Japan, it is classified as an endocervical type of mucinous adenocarcinoma, and is defined as follows in the General Rules for

Clinical and Pathological Study of Uterine Cervical Cancer¹⁴⁾: This category can be defined as a highly differentiated mucinous adenocarcinoma in which most of the glands are difficult to distinguish histologically from normal endocervical glands. In the majority of cases, however, glands show an abnormal branching pattern with a desmoplastic stromal reaction. Usually, the tumor grows beyond (deeper than) the normal confines of the cervical glands. Some glands may show greater cytologic atypia. Adenoma malignum is a rare disease, accounting for 1 to 3% of uterine cervical adenocarcinoma, according to Norris et al¹¹⁾. Haga et al⁶⁾ reported that adenoma malignum accounted for only 7 out of 454 (1.54%) uterine cervical adenocarcinomas in a study covering the past 45 years. The prognosis of adenoma malignum is usually poor. McKelvey et al⁹⁾ found that four out of five patients died within 2.5 years and Sasaki et al¹³⁾ reported that two out of seven patients died within 3 years. However, Hirai et al⁷⁾ reported a 5-year survival rate of 100% in a study of six patients, and they noted that the prognosis of adenoma malignum is not always poor if it is discovered at an early stage. Cervical adenocarcinoma is resistant to chemotherapy and radiotherapy, so early discovery and treatment of adenoma malignum are important.

The most characteristic symptom is a watery discharge and the chief complaint of many patients is atypical genital bleeding. Sasaki et al¹³⁾ observed an increased amount of vaginal discharge in four out of seven patients with adenoma malignum and atypical genital bleeding in three. Haga et al⁶⁾ reported a watery discharge in three out of seven patients, atypical genital bleeding in three patients, and lower abdominal pain in one patient. Our four patients also had a watery discharge and one had atypical genital bleeding.

On vaginal examination, an enlarged cervix was palpable in all cases, while transvaginal and abdominal ultrasonography revealed multiple cystic lesions (MCL) measuring 1–2 cm in the cervix. On imaging studies such as CT or MRI, the same cervical findings were obtained and MCL was the characteristic appearance⁸⁾. According to Sasaki et al¹³⁾, the eroded vaginal region is extremely hard on speculum and vaginal examination.

On cytodiagnosis, Haga et al⁶⁾ and Arai et al¹¹⁾ observed cell clusters that formed large sheets, palisades, ribbons, or grape-like clusters. Sasaki et al¹³⁾ found palisading, a sheet-like arrangement, and irregularly overlapping cell clusters. In our patients, the cervical gland cells formed large sheets or showed a honeycomb or palisading arrangement. We observed tall columnar cells that were longer than those of normal cervical glands and contained large amounts of yellowish-orange mucus. The nuclei were slightly enlarged, basically uniform in size, and showed irregular overlap-

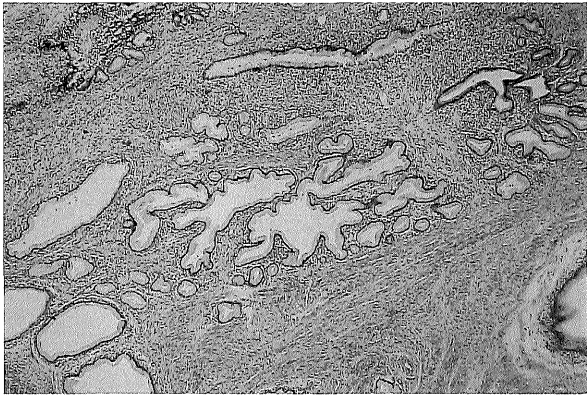


Fig. 5a. Case 1. HE stain $\times 20$
Many cervical glands of various sizes.

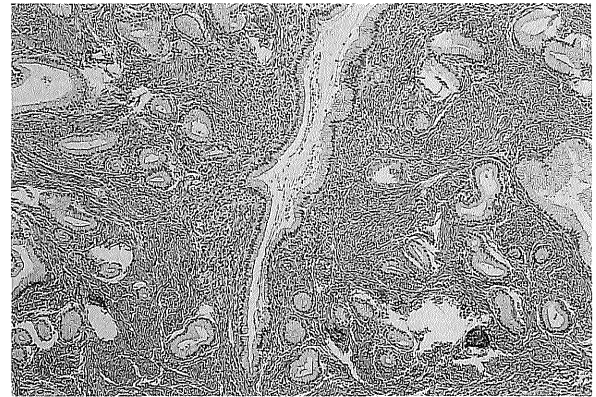


Fig. 5b. Case 2. HE stain $\times 20$
Branching-shaped endocervical glands were infiltrating deep into the muscle layer beyond the normal limits of the cervical gland variion.

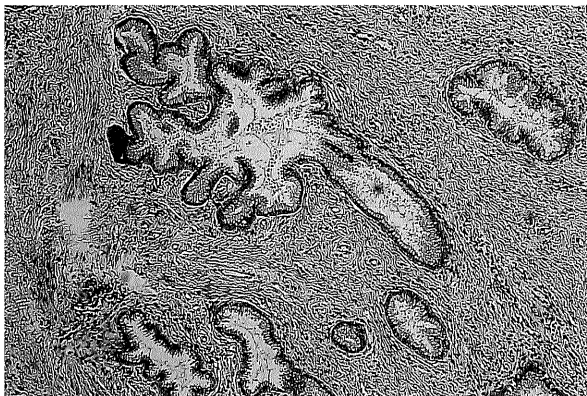


Fig. 5c. Case 3. HE stain $\times 20$
Branching shaped endocervical glands.

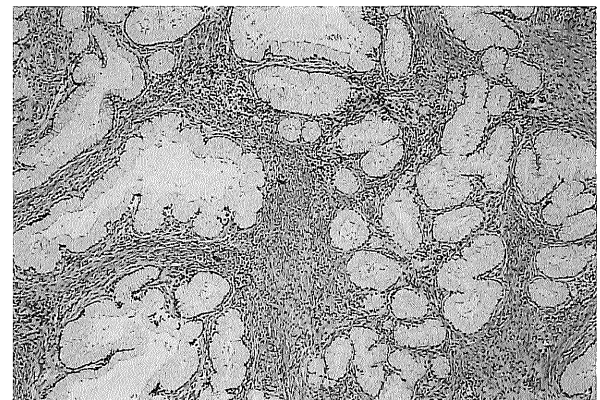


Fig. 5d. Case 4. HE stain $\times 20$
Many cervical glands of various sizes.

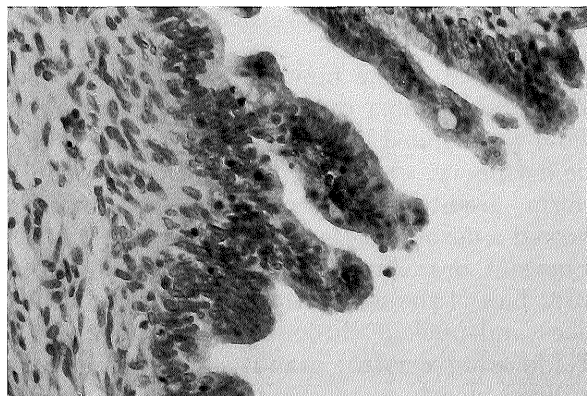


Fig. 5e. Case 1. HE stain $\times 100$
The glandular epithelium consisted of papillary proliferations into the lumen.

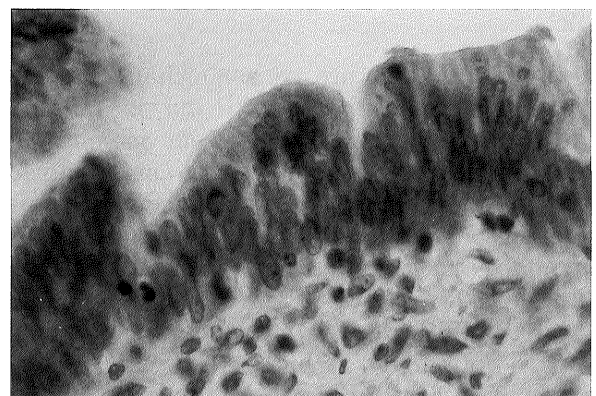


Fig. 5f. Case 2. HE stain $\times 200$
Papillary proliferations into the lumen.

ping. Nuclear chromatin was increased slightly and one to two nucleoli were present. Ishii et al⁸⁾ suggested that yellowish-orange staining of cytoplasmic mucus by the Papanicolaou method is an important diagnostic clue aiding identification of adenoma malignum.

The pathological characteristics of adenoma malignum were summarized by McKelvey et al⁹⁾ in

1963 as follows: the cervical glands proliferate to a deeper region than the cervical gland surface layer where they are normally located. A monolayer of glandular epithelial cells show marked mucous production and the nuclei are compressed against the basal region, but findings for the chromatin and nuclei are not malignant, and almost no nuclear division is observed. The size and shape of

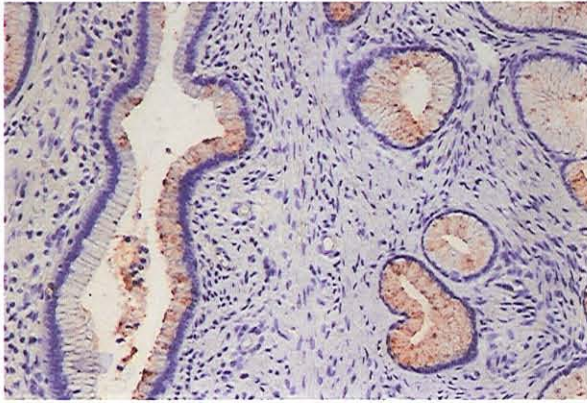


Fig. 6a. Case 1. Immunohistochemical reactivity for HIK 1083
ABC method $\times 50$, Positive for HIK 1083
Cytoplasmic staining was observed.

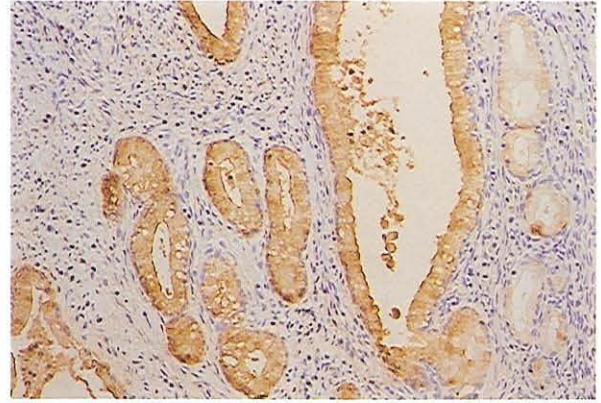


Fig. 6b. Case 2. Immunohistochemical reactivity for HIK 1083
ABC method $\times 50$, Positive for HIK 1083

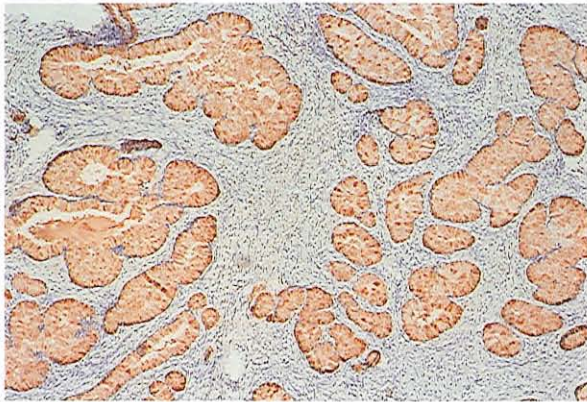


Fig. 6c. Case 4. Immunohistochemical reactivity for HIK 1083
ABC method $\times 50$, Positive for HIK 1083

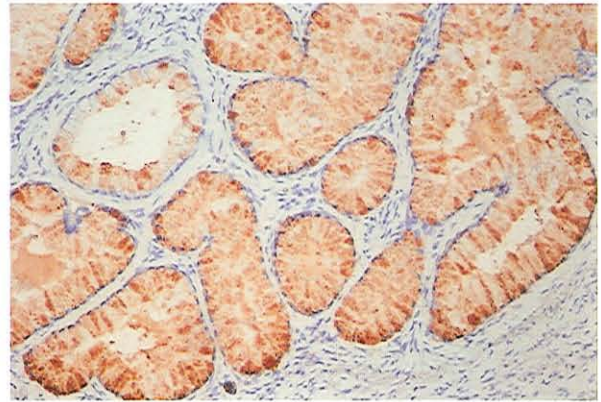


Fig. 6d. Case 4. Immunohistochemical reactivity for HIK 1083
ABC method $\times 100$, Positive for HIK 1083
Cytoplasmic staining of the glands was observed.

the glandular structure are somewhat diverse and irregular when compared with the normal structure, but the glandular basement membrane is distinct with no invasion of the stroma. In our four patients, many cervical glands of different sizes were present and were found to extend deep into the muscle layer on a histological examination with HE staining. The glandular lumens were mainly round or oval, but branching or papillary growth into the lumen was also observed. Overlapping or disordered nuclei were sometimes present.

Recently Nucci et al¹²⁾ reported lobular endocervical glandular hyperplasia, not otherwise specified (LEGH), which needs differential diagnosis from adenoma malignum. The major complaints are mucoid cervical discharge, increased vaginal discharge, and abdominal discomfort. The features most helpful for distinguishing adenoma malignum from this disease are irregular stromal infiltration, a desmoplastic stromal response, and focal malignant cytologic features. They reported that the depth of "penetration" of the glands into the cervical wall ranged from 2 to 12mm, but most

were limited to the inner half of the wall. Some lobular aggregates consisted of a central dilated gland surrounded by a number of taller glands at the periphery, which often imparted a pseudocribiform architecture. Our histological specimen showed a desmoplastic stromal response and some abnormal branching glands penetrated into the outer half of the wall. Mitoses were present in all cases and nuclear chromatin was increased. The proliferating cervical glands showed only a few findings clearly suggesting cancer, but the morphology was not normal and the glands invaded the muscle layer beyond the normal cervical gland region. Thus, adenoma malignum was diagnosed.

Adenoma malignum is quite difficult to diagnose because there are few findings definitely suggesting malignancy on cytologic or histologic examination. Therefore, the use of immunostaining for the diagnosis of this disease has attracted attention. Sasaki et al¹³⁾ reported that the cells were filled with a mucus which was clearly stained by PAS or Alcian blue stain. All four of our patients had cells filled with mucus that was clearly stained by PAS or Alcian blue. Gilks et al¹⁾ and Daya et al²⁾ report-

ed positive staining for CEA, while Mulvany et al¹⁰ reported that CEA immunoreactivity was not detectable in a minority of adenoma malignum cases. Among our four patients, case 2 was positive for CEA, but cases 1, 3 and 4 were negative. Therefore, CEA staining seems to show a lower specificity for diagnosis of adenoma malignum.

Recently, several reports have appeared on the use of HIK1083 in the diagnosis of adenoma malignum^{2,8}. HIK1083 is a monoclonal antibody that detects mucin produced and secreted by the gastric mucous cells. It has recently been reported to be positive in patients with adenoma malignum or goblet-cell type, well-differentiated alveolar epithelial cancer, making it potentially useful in the early diagnosis of these diseases. HIK1083 was found to be positive in patients reported by Ishii et al⁸ and Utsugi et al¹⁵. Among our patients, HIK1083 was negative in case 3, but was positive in cases 1, 2 and 4. Therefore, it should be fairly useful in the diagnosis of adenoma malignum.

CONCLUSION

This study shows that adenoma malignum can be suspected in patients with watery discharge and multiple cystic lesions in the uterine cervix. Such patients should undergo cytodiagnosis and ultrasonography.

When adenoma malignum is strongly suspected, conization should be performed to distinguish adenoma malignum from other differential diagnoses include LEGH, because early diagnosis and treatment of this disease are important. Immunostaining with HIK1083 may assist in the early diagnosis of adenoma malignum. However, further investigation is necessary with more cases.

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