



Research Letter

Minimal deviation adenocarcinoma of the uterine cervix

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In 2003, the World Health Organization (WHO) defined minimal deviation adenocarcinoma (MDA) as endocervical adenocarcinoma mucinous, well differentiated, consisting of an endocervical glandular hyperplasia of lobular architecture resembling glands but with the characteristics of adenocarcinoma [1]. However, MDA has been recently reclassified as a subcategory of gastric-type mucinous carcinoma by WHO and is reserved only for extremely well-differentiated cell types. [2]. MDA is a rare histological entity of cervix adenocarcinoma. Cervical cytology provides an imperfect diagnosis of glandular cells compared to squamous lesions, although the 2001 Bethesda system still allows better management of patients with abnormal glandular cells; the diagnosis is therefore based on histological studies. In this report, we present the case of a 45-year-old woman with typical symptoms of MDA, in whom cytological tests revealed atypical glandular cells; however, punch biopsies and cervical conization failed to confirm the diagnosis of MDA despite reviewing literature pertaining to MDA.

A 45-year-old woman presented to our hospital with heavy vaginal discharge for several months. Physical examination revealed normal external genitalia and a large amount of mucoid fluid in the posterior vaginal fornix. Her cervix was grossly normal in appearance except for the profuse mucoid discharge. She had undergone bilateral adnexectomy in September 2010 due to the presence of an ovarian cyst. Transvaginal sonography revealed a normal cervix, hydrops in the endometrial cavity, and a small fibroid. The following Pap smear and cytological tests reported the presence of atypical glandular cells of undetermined significance (AGUS), which was in favor of the diagnosis of adenocarcinoma of the endocervix (Figures 1 and 2). However, despite undergoing four

endometrial curettages, two cervical biopsies, and one cervical conization, she was diagnosed with only chronic cervical inflammation and not with cervical disease or endometrial malignancy. Subsequently, the patient underwent a total abdominal hysterectomy. Pathologic examination of the specimen revealed MDA of the cervix (Figures 3 and 4) with parametrial invasion and small subserosal myomas. The tumor was staged as IIB MDA according to the American Joint Committee on Cancer (AJCC) classification. The patient had an uneventful postoperative course and received adjuvant therapy with concurrent chemoradiation therapy (CCRT). She died 22 months after the surgery.

Minimal deviation adenocarcinoma (MDA), also known as adenoma malignum (AM), is a well-known and extremely well-differentiated type of mucinous endocervical adenocarcinoma. It exhibits a gastric morphology and immunophenotype and is easily misdiagnosed because of its benign-looking histological features. MDA represents only 1–3% of all cervical adenocarcinomas and is most likely unrelated to the human papillomavirus (HPV) [3,4].

The predominant clinical symptoms of MDA are profuse mucoid vaginal discharge and irregular/contact vaginal bleeding [5,6]. Hirai et al [7] reported profuse vaginal discharge in all cases, and Ki et al [8] reported four cases, of which two had profuse watery or mucoid vaginal discharge, one had irregular vaginal bleeding, and one had both profuse vaginal discharge and irregular vaginal bleeding. Pelvic examination may present grossly normal vaginal and cervical findings or cervical hypertrophy with multiple cystic lesions, such as Nabothian cysts, in some cases [5,6].

Diagnosing MDA with the use of imaging techniques such as magnetic resonance imaging (MRI) and ultrasonography is often difficult due to the benign appearance of this tumor; however, these techniques play an important role in the evaluation of the dissemination of MDA. Transvaginal sonography can detect the presence of multilocular cystic masses in the uterine cervix and may aid in the diagnosis of MDA [5,6]. Park et al [9] reported that ultrasound imaging with Doppler examination is more efficient and accurate in the evaluation of multilocular lesions of the uterine cervix; they revealed that MDA had an increased intralesional vascularity. In another study, MRI revealed multiple irregular cystic lesions; the cysts were arranged in a floret-like manner with aggregates of small cysts, resulting in a “cosmos (*Cosmos bipinnatus*) pattern” [10]. MRI of MDA characteristically presents with

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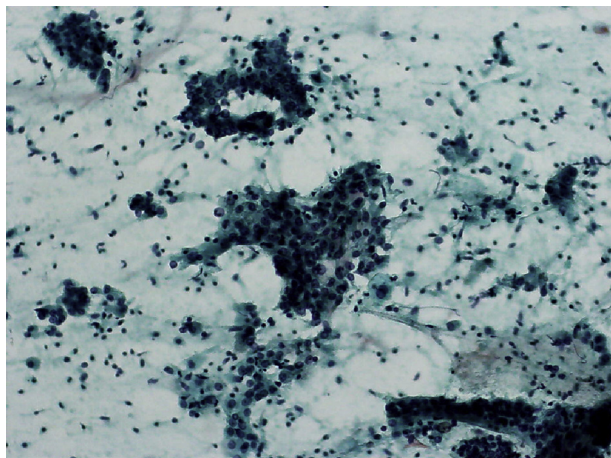


Figure 1. Uterine cervical smear displaying many atypical endocervical gland cells and scant squamous epithelial component. Papanicolaou, $\times 100$.

medium-to-high signal intensity on T1-weighted image (WI) and markedly high signal intensity on T2WI. T2-weighted MRI shows the MDA characteristics in detail and exhibits a reliable correlation with histological findings [11–14].

A preoperative histological diagnosis of MDA is difficult because the pathological entity is composed of mucinous, very well-differentiated glands deeply invading the cervical stroma, often surrounded by a desmoplastic reaction. Cervical cancer screening is done with a cytological evaluation performed using the Papanicolaou (Pap) test. However, an accurate cytological diagnosis is difficult because the lesion is located deep in the endocervix and presents with an endophytic growth pattern [15]. Ishii et al [15] and Chang et al [6] reported similar cytologic features of MDA, which are as follows: (1) the frequent appearance of large sheets of cells with a honeycomb pattern and a palisading arrangement at the periphery; (2) abnormal glandular cells with abundant cytoplasm showing atypia and benign-appearing glandular cells; and (3) slightly enlarged mucous cells with ovoid nuclei. Histologic examination reveals well-spaced, deeply invasive branching glands lined with uniform columnar mucin-distended cells and infrequent foci of less well-differentiated neoplastic cells [16]. Unlike other adenocarcinomas, histologically, MDA rarely presents with mitotic

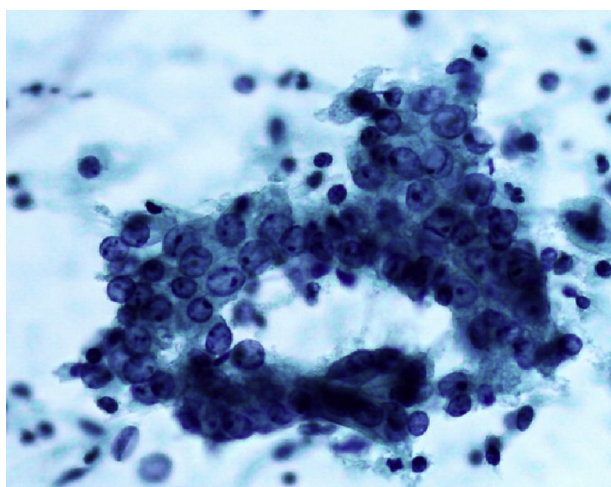


Figure 2. Endocervical glandular epithelial cells show nuclear crowding and clearing with gland-opening or acinar-like pattern. Prominent and displaced nucleoli are also noted. Papanicolaou, $\times 400$.

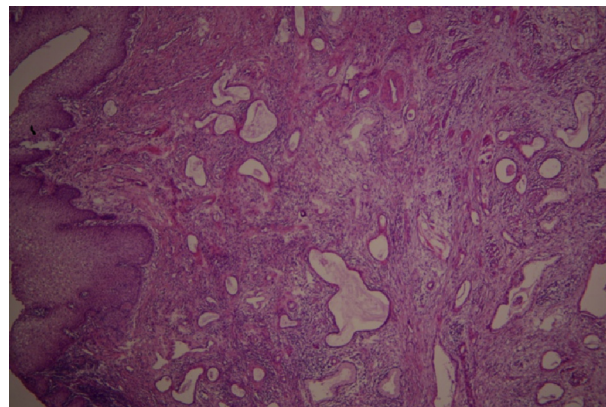


Figure 3. Uterine cervix: numerous varied endocervical glands are seen scattered from the subepithelium to the serosa. Hematoxylin and eosin, $\times 40$.

figures, pseudo-stratification, or atypia; instead, in most cases, it exhibits gastric differentiation with a high cytologic grade and association with gastric metaplasia [4]. MDA is most likely unrelated to HPV infection [17], which distinguishes it from common cervical cancers, and therefore, it cannot be prevented by HPV vaccination programs [4]. MDA was also associated with the Peutz–Jeghers syndrome with mutations in the *STK11* gene [18]. Compared with the usual type of cervical adenocarcinoma, MDA had a less favorable prognosis.

Immunohistochemical studies, which have been used for a more accurate diagnosis, help differentiate MDA from a normal endocervix and from other lesions, such as microglandular hyperplasia, adenocarcinoma *in situ*, and well-differentiated endocervical adenocarcinoma. Ishii et al [15] and Urusagi et al [19] reported that mucinous MDA cells are positive for HIK1083. The HIK1083-labeled latex agglutination test combined with other modalities may facilitate the detection of MDA. Takatsu et al [10] presented a combination of a diffusely solid pattern on MRI and atypical glandular cells on smear and a positive gastric mucin test, which was suggestive of MDA or gastric type adenocarcinoma. Mercer et al [20] reported that MDA can be distinguished from well-differentiated adenocarcinoma and other lesions with the use of the carcinoembryonic antigen (CEA). Moreover, patients with AGUS require further evaluation such as colposcopy in combination with fractional curettage and/or cone biopsy owing to the possibility of

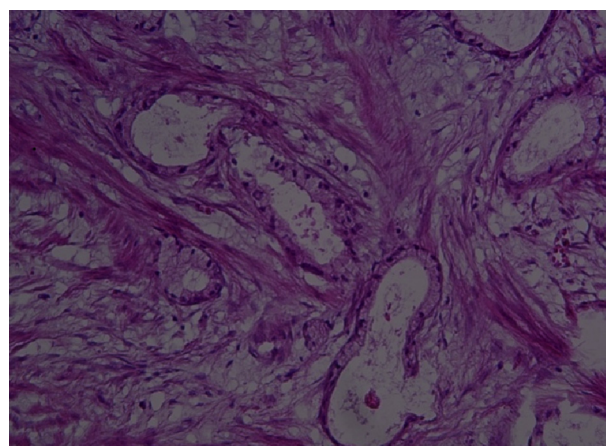


Figure 4. Uterine cervix: bland-looking endocervical glands penetrate the deep cervical stroma. Hematoxylin and eosin, $\times 200$.

29.0% of these Pap test findings, which include a 5.2% malignancy rate, requiring follow-up or therapeutic intervention [21,22].

The treatment of MDA is similar to that of endocervical adenocarcinomas, and surgical intervention is the standard treatment for both [8]. The type of surgery performed differs among surgeons due to the difficulty in preoperative diagnosis. Lim et al [5] reported patients who underwent Type I hysterectomy without pelvic lymph node dissection (PLND; 5 patients), Type I hysterectomy with PLND (5 cases), and Type III radical hysterectomy (RH) with PLND (8 patients). Kudo et al [23] reported patients who underwent PLND and external radiation (1 patient), radical hysterectomy and external radiation (1 patient), radical hysterectomy, omentectomy, and combination chemotherapy (1), and radical hysterectomy, external radiation, and combination chemotherapy (1 patient). Ki et al [8] reported patients who underwent simple hysterectomy and bilateral adnexectomy (2 cases), Type I hysterectomy and pelvic node sampling (1 case), and simple hysterectomy and PLND (1 case). In our case, the patient underwent Type 1 hysterectomy without PLND combined with concurrent chemoradiation therapy. The correlation between the type of surgery and survival rate is unclear based on the results of the current study. This was possibly due to the small sample size and the difficulties encountered in reaching a preoperative diagnosis. Further investigation is therefore warranted.

MDAs are rare and are easily misdiagnosed. As standard screening tests and diagnostic tools have not yet been established, early diagnosis of MDA followed by an appropriate evaluation and treatment has been a challenge for gynecologists. In conclusion, in patients presenting with symptoms of heavy vaginal discharge, a cystic lesion revealed on imaging, and atypical glandular cells on a cytologic smear, MDA should be considered as a possible diagnosis.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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