Minimal Deviation Adenocarcinoma, Mucinous Type, of the Uterine Cervix
- Report of a Case with Extensive Metastasis to the Uterine Corpus and Bilateral Adnexae -

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Minimal deviation adenocarcinoma is an extremely well differentiated variant of cervical adenocarcinoma, and is frequently misdiagnosed due to its benign-looking histopathological features. A 38-year-old woman was diagnosed as having had a minimal deviation adenocarcinoma in the cervix, metastasizing to the uterine body and bilateral adnexae. She had a history of right salpingo-oophorectomy 3 years ago, and was diagnosed as having a mucinous cystadenoma. Histologically, the tumor cells were so well differentiated that they appeared to be almost the same as those of the non-neoplastic cervical glands. Similar glands were found in both ovaries and in the left fallopian tube. PAS staining showed a negative or apical positive pattern in the endocervical-like glands. Immunohistochemical studies for CEA, ER/PR, cytokeratin 20, and p53 were negative, but positive for cytokeratin 7. The HPV DNA microarray test was negative. Clinically, this proved to be an advanced, biologically aggressive disease.

Key Words : Adenocarcinoma, Mucinous-Cervix

Minimal deviation adenocarcinoma (MDA) is an uncommon tumors and accounts for only 1-3% of all cervical adenocarcinomas. Originally the tumor was termed an adenoma malignum because of the resemblance of its glands to the endocervical glands and its lack of malignant cellular features, the designation MDA was first proposed by Silverberg and Hurt in 1975 to more accurately reflect this form of adenocarcinoma. Clinically, MDA is an advanced and aggressive disease, because of misdiagnosis and delayed treatment. Therefore, its clinical and pathological characteristics needed further analysis in order to improve diagnostic accuracy. Here we report a case of MDA of the cervix in a 38-year-old woman with an extensive metastasis to the uterine corpus and bilateral adnexae.

CASE REPORT

A 38-year-old unmarried single woman (0-0-1-0) was admitted because of a one-month history of a profuse watery discharge, vulvar swelling and difficult urination. She had a history of a right salpingo-oophorectomy at another hospital, 3 years ago, and had been diagnosed as having a mucinous cystadenoma at the time. One year later, the MRI showed an ill-defined uterine mass, 5 × 4 × 3 cm in size, in the cervix and body. The left ovary was cystic, but not enlarged, and this was interpreted as a functional cyst. She was diagnosed as having an endometrial carcinoma, stage IIIb, but she refused surgery. Abnormal cervical glandular cells were noted in cervico-vaginal smears from several follow up examinations, which had been diagnosed as benign. A punch biopsy of the cervix had
been performed a year before this admission, which showed a branching arrangement similar to that of normal endocervical glands, but which we misdiagnosed as chronic cervicitis. A follow-up CT revealed a 13×13×8.8 cm-sized multilocular cystic mass in the left ovary and a heterogenous uterine mass which was observed in a previous image (Fig. 1). Adjacent anterior rectal wall thickening was also noted, which was consistent with a direct rectal tumor invasion. Consequently, she underwent a total hysterectomy and a left adnexectomy.

Gross findings

The uterus measured 11×7×6 cm and weighed 110 gm, and showed a pale brown soft smooth glistening surface. The cut surface was a diffuse pale white to creamy yellow, mucoid with soft consistency and a honeycomb cystic appearance throughout the entire body. The endometrial cavity was filled with clear glairy and mucoid materials, and the cervix showed a pale brown protruding mucoid mass of 3×3×2.5 cm (Fig. 2A). The left ovary was cystic, measuring 13×11×8 cm and weighing 450 gm. It showed a yellow white soft surface and small and large multilocular cysts with thin septae, which were filled with a clear to red mucin (Fig. 2B). The attached fallopian tube, 6×1×1 cm in size, was edematous and soft.

Histologic findings

A microscopic examination of the uterine and left adnexal lesions showed the same histology of MDA. They were characterized by widely spaced glands of irregular size and shape, which were occasionally cystically dilated, and exhibited papillary infoldings. Most of the glands were lined by a single
layer of columnar and cuboidal epithelial cells without a cyto-
logic atypia (Fig. 3A). The nuclei were bland, lacked promi-
nent nucleoli, and were located at the base of epithelial cells. 
The tumor showed deep invasion into the cervical wall, and 
a transmural extension to the uterine corpus. In the myometri-
um, adenomyosis was associated. No desmoplastic stromal 
reaction was found. The ovary was infiltrated with small and 
cystically dilated glands, as were observed in the uterine mass 
(Fig. 3B). Similar glands were also noted in the left fallopian 
tube. The microscopic slides of the right ovary tumor that had 
been resected 3 years previously were reviewed. Its histologic 
features were similar to those of the uterine mass.

PAS staining showed a strong positive reaction with a whole 
cytoplasmic pattern in the mucinous papillary glands, but a 
negative or apical positive pattern in the clear endocervical-
like glands (Fig. 3C). Immunohistochemical studies for CEA, 
ER/PR, cytokeratin 20 and p53 were negative, but positive for 
cytokeratin 7 in the cervix, uterine body and ovary tumor. The 
HPV DNA microarray test (Biomed Lab Co, Seoul, Korea) 
was negative.

DISCUSSION

The main clinical symptoms of MDA are a profuse watery 
discharge, and an enlargement of the cervix with erosion and 
hardening. Abnormal cervical glandular cells are evident in 
smears in most cases, and a preoperative cytological diagnosis 
was reported in 83.3% of cases. In the present case, clusters 
of normal endocervical-like, tumor cells were noted in cervico-
vaginal smears from several follow up examinations, but these 
were misdiagnosed. Moreover, it was reported that a preop-
erative punch biopsy failed to confirm a diagnosis of MDA 
in all cases. In almost all cases, a reliable diagnosis could not 
be based on a biopsy material. A punch biopsy had been per-
formed a year prior to the present admission in the present 
case, which showed a branching arrangement similar to that 
of the normal endocervical glands, but this was also misdiag-
nosed as chronic cervicitis. Mulvany and Monostori reported 
the tumor as an incidental finding in a hysterectomy specimen. 
This tumor, particularly the mucinous form, may occur syn-
chronously or before the development of an ovarian tumor, 
which is usually a mucinous neoplasm or a rare sex cord stro-
mal tumor (sex cord tumor with annular tubules). MDA is 
strongly associated with Peutz-Jeghers syndrome (PJS), but 
this association could not be confirmed in the present case. 
The pathogenesis of MDA may not be related to HPV infec-
tion. Pirog et al. reported that two cases of MDA were neg-
ative for HPV, and the present case was also negative by the 
HPV DNA microarray test. A serine threonine kinase gene, 
STK11, has been identified in 55% of the mucinous MDAs, 
and may play an important role in the etiology of the disease.
Characteristically, the glands vary in size, ranging from small to large irregular and distorted forms with angular projections. Complex outlines and a minor component of desmoplasia are usually present; however, those findings were not observed in the present case. In mucin-producing forms, the glands are lined by a single layer of a tall columnar epithelium that usually has minimal nuclear atypia. Peculiar elongations or branching processes are common. The nuclei are bland, lack prominent nucleoli, and are located at the base of epithelial cells. There are no mitoses or nuclear pleomorphisms. In the endometrioid type, the tumor cells resemble those of the proliferative endometrium or endometrial hyperplasia.

Histochemical methods are effective for making a differential diagnosis of MDA and can contribute to its early detection and treatment. MDA cells produce neutral mucin almost exclusively. Alcian blue pH 2.5/periodic acid-Schiff (AB-PAS) staining is generally used to evaluate mucin phenotyping in order to differentiate MDA from other conditions. The cytoplasmic localization of neutral mucin has been classified either as a "whole cytoplasmic pattern", in which neutral mucin fills the cytoplasm entirely, or as an 'apical pattern', in which neutral mucin is localized in the subsurface area only. In 5 of 6 MDA cases, neutral mucin stained by PAS showed an apical pattern. The present case showed a negative or apical positive pattern in the clear endocervical-like glands for PAS staining. Immunohistochemically, MDA is highly variable in terms of its staining for CEA. It is usually positive in focal areas, whereas a well-differentiated cervical adenocarcinoma is usually more diffusely positive. All benign lesions, except for microl glandular hyperplasia, are negative for CEA, as was the present case, ER and PR were not expressed in MDA, whereas both receptors were invariably expressed in the normal cervix. The CA125 expression level was significantly lower in MDA, but was diffusely positive in the normal endocervical glands. These results suggest that MDA lacks the expression of characteristic Mullerian-type substances such as ER, PR, and CA 125, and that a proportion of its cells contain gastric epithelial substances, such as gastric mucin and CEA. Immunostaining for gastric mucin with a monoclonal antibody HIK 1083 revealed that all the tumors areas of a typical MDA are partially immunoreactive. Mucinous MDA was also confirmed to be a tumor expressing gastric phenotypes ultrastructurally.

Tsuda et al. reported an interobserver variation in the diagnosis of MDA. It was suggested that any disagreement was caused by the absence of consensus criteria for its differential diagnosis and by different observer interpretations regarding cellular atypia and invasion. The most reliable criteria for assessing the malignant nature of MDA are the haphazard arrangement of the glands that extend beyond the level of the normal endocervical glands and the presence of occasional mitoses in the glandular cells. Deeply positioned nabothian cysts, tunnel clusters, microglandular hyperplasia, and mesonephric hyperplasia are the major considerations when making a differential diagnosis. In abnormally shaped benign endocervical glands, the typical stromal response may be a helpful indicator of the infiltrative nature of the glands. In lobular endocervical gland hyperplasia, the lobules are usually confined to the inner half of the cervical wall with an unremarkable intervening cervical stroma. Adjacent mucinous glands are usually present and help exclude a mesonephric lesion.

When any of the diagnostic characters summarized above is determined, the probability of an MDA should be seriously considered. At least atypical hyperplasia in cervical glands should be explored, and patient follow-up and a biopsy of the deep tissues (>5 mm) of the cervix will be necessary. Obviously, a correct pathological diagnosis is extremely important so that a patient can receive proper timely treatment.

The therapy should be the same as for ordinary adenocarcinoma, the prognosis is unsettled. A majority have reported an unfavorable prognosis, because most neoplasms were discovered in the later stages. In addition, many MDAs fail to form a visibly evident lesion despite deep infiltration, resulting in delayed treatment and a relatively poor prognosis. In some cases, MDA has not been correctly diagnosed, even in hysterectomy specimens, prior to the development of recurrent disease. However, some studies have reported that survival rates and the distributions of metastases are similar to those of a well differentiated ordinary adenocarcinoma.

A deep biopsy is essential for making an accurate diagnosis, when the presence of this disease is suspected by cytological examination. An ordinary cervical biopsy is usually insufficient to detect deeply positioned tumor glands. Because the present case was not correctly diagnosed, diffuse dissemination and metastases occurred. The synchronous existence of cervical, endometrial and ovarian linings embryologically related to Mullerian origin epithelia was considered. However, advanced components were found in all involved lesions, suggesting that the lesions represented a metastatic disease rather than coexistent separate primary lesions.
REFERENCES


