Diagnostic Pitfalls in Minimal Deviation Adenocarcinoma of the Uterine Cervix: Review and Update

Abstract
Cervical minimal deviation adenocarcinoma (MDA) is an extremely well-differentiated adenocarcinoma. This tumor often imposes diagnostic dilemma among pathologists as it is confused with a variety of benign mimics and represents a diagnostic challenge in the field of gynecologic oncology. Since the microscopic features are subtle, it is frequently misinterpreted as benign and often misdiagnosed and inadequately treated. False positive as well as false negative reporting of MDA on cervical biopsy is commonly seen among pathologists, both of which have grave implications on the treatment of the patient. Immunohistochemistry has been found to be extremely useful in the diagnosis of MDA. In this review, based upon our experience and that of the literature, we highlight the salient clinicopathological features, discuss the benign mimics and review the immunohistochemical and molecular features that aid in the diagnosis.

Keywords: Adenocarcinoma, cervix, minimal deviation

Introduction
Cervical cancer continues to be a major public health problem affecting middle-aged women, particularly in the developing countries of the world. Cervical cancer is the fourth most common cancer in women, ranking after breast cancer, colorectal cancer, and lung cancer. Early diagnosis and treatment of cervical cancer can substantially decreases the mortality. However, the minimal deviation adenocarcinoma (MDA) of the cervix mimics benign lesions of the cervix, and the diagnosis is usually missed by the gynecologists, radiologists, and pathologists.

MDA was first designated as “malignant adenoma of the cervix” by Gusserow.[1] However, Silverberg and Hurt[2] proposed the term “minimal deviation adenocarcinoma” for this tumor due to its deceptively benign microscopic appearance. Since that time, only a few cases of MDA have been reported in the English literature. In 2014, MDA has been reclassified by the WHO as a subcategory of gastric-type mucinous cervical adenocarcinoma.[3] MDA is a rare variant of cervical adenocarcinoma and accounts for 1%-3% of all cervical adenocarcinoma cases.[4] MDA demonstrates an endophytic and not an exophytic growth pattern. It resembles multiple benign nabothian cysts on transvaginal ultrasonography. Routine screening methods for the uterine cervix including the Papanicolaou (Pap) and the human papillomavirus (HPV) tests.[5] Moreover, even invasive diagnostic tools (e.g., punch biopsy and cervical conization) often misdiagnose MDA before performing definitive surgery. Because of its rarity and perhaps because cytologic changes are subtle, the diagnosis is often missed by the pathologists. Differentiating MDA from normal endocervical glands is difficult due to histologically well-differentiated specimens, particularly those from cytological evaluation and cervical punch biopsies. This could lead to an incidental diagnosis of MDA following a simple hysterectomy for other benign conditions. Although MDA has a benign histological appearance, it is typically aggressive. In addition, MDAs are so rare that their true nature and clinical course has not been fully clarified. This lack of information delays accurate diagnosis and leads to poor patient prognosis. It is very important to diagnose MDA as the prognosis of MDA is known to be relatively poor.[6,7] Early
diagnosis is important to manage MDA. Clinicians should consider MDA among the differential diagnoses in patients with a suspicious clinical presentation even with negative cervical screening tests. Since MDA is a tumor with deceptively innocent histologic patterns, it is important for the pathologists to understand the pathology of MDA in great detail, so that early diagnosis is made.

**Epidemiology and Clinical Features**

Based on the literature reviews and meta-analysis of 347 cases of MDA, the mean age at diagnosis is 45 years (range 20–78 years). The symptoms and signs of MDA are not different from those of common cervical adenocarcinoma. Depending upon the size of the tumor, the presenting feature may be abnormal vaginal discharge/mucoid or profuse watery vaginal discharge, menometrorrhagia, irregular genital bleeding, and abdominal swelling. The most common presenting symptom was watery discharge. More often, patients are asymptomatic and MDA is an incidental finding in a cone biopsy or hysterectomy specimen. Uncommonly, patient present with abdominal discomfort, barrel-shaped cervix, cervical mass, and rarely adnexal metastases. It is associated in 10%–15% with Peutz–Jeghers syndrome. It is also frequently associated with lobular endocervical glandular hyperplasia. On clinical examination, the cervix is usually firm and indurated.

**Etiopathogenesis and Role of Human Papillomavirus**

The etiopathogenesis of MDA remains unclear. Although a significant association is observed between HPV infection and carcinogenesis of the uterine cervix, previous studies have revealed no significant association between MDA and the HPV virus. An important distinguishing feature between MDA and common cervical cancer is that when sensitive PCR techniques are utilized, MDA are usually found to be negative for HPV. Gong et al. investigated HPV infection in MDA using in situ hybridization technique, but they did not find glandular nuclei that were positive for high-risk HPV, a negative finding consistent with those of previous studies.

MDA is more likely to either precede or develop coincidentally with an ovarian carcinoma than other types of cervical adenocarcinomas. The ovarian neoplasms with which MDA are most likely to be associated include mucinous adenocarcinomas and sex cord tumors with annular tubules. Both MDA of the cervix and ovarian sex cord tumors with annular tubules have been strongly associated with Peutz–Jeghers syndrome. In one series, 4 of 27 women with Peutz–Jeghers syndrome developed MDA. Therefore, close surveillance of women with Peutz–Jeghers syndrome is recommended, including careful endocervical cytologic examination and periodic endocervical curettage. A few studies have demonstrated a close link between MDA and gastric metaplasia or endocervical glandular hyperplasia.

**Cervical Cytology of Minimal Deviation Adenocarcinoma**

Routine screening methods (HPV test and/or cytology) can easily miss MDA due to its HPV negativity and bland cytology. Previous studies have suggested cytology had a low sensitivity to detect MDA, which is attributed to its bland cytologic features, and to their location being more often in the upper endocervical canal. Subtle cytologic features including mono layered and honeycomb sheets with vesicular nuclei, prominent nucleoli, vacuolar or foamy cytoplasm, and intracytoplasmic neutrophil entrapment suggest the diagnosis of MDA on cytology.

There are few reports on the cytologic findings in patients with MDA. Szyfelbein et al. characterized the cytologic features in three patients. These authors found a significant range of cytologic abnormalities of glandular cells including multilayered sheets, three-dimensional clusters, columnar cells with abundant or lacy cytoplasm, occasional prominent nucleoli, and mitotic figures in all three cases. In one of their cases, numerous cells suggestive of malignancy were seen. In two cases, small numbers of cells suspicious/diagnostic of malignancy were present. The Papanicolaou smear from patient 1 was taken from a tumor recurrence after the patient had received 4270 rads of whole-pelvic irradiation. In patient 3, the smear taken at the time of biopsy and was initially interpreted as negative. Review of this smear, presumably after the established diagnosis of MDA, was interpreted as suspicious but not diagnostic for malignancy.

Granter and Lee studied cytological findings in a series of patients, and concluded that that even if well sampled, the definitive cytologic diagnosis of MDA in the absence of a more poorly differentiated component may be very difficult if not impossible. Although in five cases they have identified a population of cells which we believe corresponds to the very well differentiated component of MDA, in four of these smears, these cells lacked sufficient nuclear and cytoplasmic abnormalities to allow reliable distinction from reactive endocervical cells. However, if such cells are seen in abundance, especially in large branching sheets, a careful search for more atypical cells on the smear or a recommendation for a biopsy follow-up might lead to the detection of MDA. Thus, the Pap test used as a diagnostic tool for MDA has shown a limited detection rate (32.7%).

**Pathology**

Endocervical gastric-type adenocarcinoma (GAS) is defined as a subtype of mucinous adenocarcinoma with gastric differentiation in the 2014 World Health Organization classification of cervical tumors. MDA, also known as...
adenoma malignum, is a designation that refers to a well-differentiated form of GAS. On gross examination, most cases showed a firm, indurated or friable mass, or a “barrel-shaped” enlarged cervix.

The characteristic histopathological features of MDA are as follows: (1) A well-differentiated mucinous adenocarcinoma in which most glands are indistinguishable histologically from normal endocervical glands, [Figure 1] (2) a lesion showing cytologically bland glands of varying sizes and shapes, (3) a lesion showing increased mitotic activity, (4) a lesion with hyperplastic glands at the surface, and (5) lesions showing an increased number of glands deeper than the lower level in normal endocervical glands.

The characteristic microscopic features of MDA are the presence of architecturally atypical glands that vary in size, shape, and location. In the mucin-producing forms, the glands are lined by a single layer of tall columnar epithelium that usually has minimal, if any nuclear atypia. The nuclei are bland and are located at the base of epithelium. The glands have bizarre angular outpouchings, which vary greatly in size [Figure 2]. MDA often involves more than two-thirds of the thickness of cervical stroma and glandular tissue may infiltrate beyond 5.0 mm into the cervical wall.[20]

Desmoplasia is frequently present surrounding the angular outpouchings of MDA or in the deep portion of the tumor. Large areas of invasive tumor may be devoid of any stromal reaction. In such areas, the presence of glands adjacent to thick-walled blood vessels is a helpful finding in determining that stromal invasion is present. The most reliable criterion to assess malignant nature of MDA is the haphazard arrangement of glands that extend beyond the level of normal endocervical glands and presence of occasional mitosis in glandular cells [Figure 3].[21] MDA often involves more than two thirds of the thickness of the cervical stroma and should be regarded as invasive because the normal endocervical crypts and tunnels do not extend beyond 7 mm.[6,22]

**Differential Diagnosis**

The differential diagnosis of MDA includes several conditions in which nonneoplastic glands extend beyond 7 mm from the surface. These conditions include endocervical tunnel clusters, deeply situated nabothian cysts, endocervicosis of the cervical wall, and mesonephric hyperplasia.[23] The glands of endocervical tunnel clusters, mesonephric hyperplasia, and deep nabothian cysts are usually much more uniform in size than are the glands of MDA and lack the bizarre branching and irregular outpouchings that are characteristic of the glands of MDA. The benign processes also lack a desmoplastic response. Interestingly, the benign endocervical glandular lesion termed lobular endocervical glandular hyperplasia, which may mimic adenoma malignum, is now also thought to have a pyloric gland phenotype on the basis of histochemical staining and immunohistochemistry (IHC) with antibodies against pyloric gland-type mucins. 84.

However, it is stressed that in most such instances appreciation of the overall architecture of the lesion with
deep invasion of the cervical stroma, the presence of a stromal desmoplastic reaction, and the presence of focal areas of atypia on adequate sampling will usually allow a correct diagnosis. Vascular or perineural infiltration, when present, is also helpful pointers that one is dealing with a malignant lesion.

Whenever one finds the presence of endocervical glands located deep in the endocervical stroma, search for the presence of atypia and vascular emboli should be made to rule out MDA.

**Role of Histochemical Stains in Diagnosis of Minimal Deviation Adenocarcinoma**

Combined Alcian blue–periodic acid Schiff (PAS) stain may be useful because normal endocervical glands, as a result of their high content of acid and neutral mucins, stain a purple/violet colour. In contrast, the glands of cervical adenoma malignum (and conventional adenocarcinomas) stain red using this preparation because of the almost exclusive presence of neutral mucin. In doubtful cases, a combined Alcian blue–PAS stain may be useful in distinguishing normal endocervical glands from the glands of adenoma malignum.

**Role of immunohistochemistry in diagnosis**

IHC can be helpful in the differential diagnosis of MDA. Carcinoeembryonic antigen, Ki67 and p53 can be used for the diagnosis of MDA. Vimentin is also positive in tumor stroma and can be used for the diagnosis. Gong et al. found that the glands were positive for CEA, Ki-67, and p53 and negative for estrogen receptor (ER), progesterone receptor (PR), and high-risk HPV DNA. The index of proliferation for Ki-67 was more than 50%. However, the stromal cells were positive for ER, PR, vimentin, and SM-actin.

Immunohistochemical studies using CEA show highly variable staining of MDA with only focal areas of positivity, and CA 125 staining is significantly reduced compared to normal endocervical glands. Immunohistochemical staining for estrogen and PR is uniformly negative in MDA, and this criterion can be used to help differentiate these tumors from variants of normal endocervical glands. Recent studies have shown that gastric mucins are present in cervical adenoma malignum and that HIK1083, a monoclonal antibody against gastric gland mucous cell mucin, is useful in the diagnosis of this neoplasm. Normal endocervical glands are negative, although very small foci of positivity may be found in ordinary endocervical adenocarcinomas. Thus, HIK1083 staining may be useful in discriminating between benign endocervical glands and the well differentiated glands of adenoma malignum.

Monoclonality is a major characteristic of most tumors. By contrast, normal tissue and reactive hyperplasia are polyclonal. Gong et al. studied the clonality of MDA, and this criterion can be used to help differentiate these tumors from variants of normal endocervical glands.

**Role of imaging**

Diagnosis using imaging techniques, such as magnetic resonance imaging (MRI) and ultrasonography, is often difficult due to the benign appearance of this tumor; however, they play an important role in evaluating the dissemination of MDA. MRI shows multiple irregular T2 hyperintense cystic lesions with enhancing stroma on postcontrast image. Takatsu et al. described the finding as “Cosmos pattern” as the irregular cystic lesions often seen in floret-like pattern. Thus, T2-weighted MRI, in particular, shows the characteristics of MDA in detail and exhibits a reliable correlation with histological findings.

**Genetic findings**

McGowan et al. have reported that PJS may complicate MDA. PJS is an autosomal dominant disorder characterized by gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. It could possibly trigger the development of MDA secondary to a mutation of the responsible tumor-suppressor gene (STK11). A previous study has shown that 4 of 27 women (14.8%) with PJS developed MDA with lobular endocervical hyperplasia. The prognosis of patients with MDA associated with PJS is usually poor. There was no comparable result of MDA with PJS based on family history, clinical, or gastrointestinal endoscopic findings in the present study. Three recently diagnosed patients with MDA underwent genetic testing for the STK11 gene, and no patient demonstrated a genetic mutation.
Screening Tools for Minimal Deviation Adenocarcinoma

Since MDA is not associated with HPV infection, pap smears and HPV serology are not of much use in the early detection of MDA. Screening tools to aid in the diagnosis of MDA are the HIK1083-latex agglutination test or MUC6 that identifies gastrin mucus present in cervical discharge.[38-40] With all of the screening techniques, any positive or unspecified results warrant radiographic follow-up with ultrasound and biopsy sampling followed by MRI.

Treatment and Prognosis

Owing to the rarity of this condition and the difficulty in accurately diagnosing it, no standard treatment is available for MDA. The optimal treatment for MDA has not been well-established. Surgical treatment is the most successful option for MDA. The surgical treatment includes a radical hysterectomy with salpingo-oophorectomy and bilateral pelvic lymphadenectomy, at an early stage. Chemotherapy and/or radiotherapy are reserved for the treatment of advanced stage disease.[42]

The prognosis of MDA is controversial, although it is known to be relatively poor. This is attributable to the likelihood of lymph node metastasis and early peritoneal carcinomatosis in contrast to localized metastases observed in patients with squamous cell carcinomas.[41] The poor prognosis of MDA is also attributed to clinical under-staging, misdiagnosis, and under-treatment.

Conclusions

With large-scale implementation of HPV vaccine, the incidence of HPV-associated cervical adenocarcinoma is expected to decrease. The relative proportion of MDA and other rare HPV negative adenocarcinomas would increase. Early diagnosis is important to manage MDA. Clinicians should consider MDA among the differential diagnoses in patients with a suspicious clinical presentation even with negative cervical screening tests. Awareness of the morphologic features and immunohistochemical profile of MDA will allow pathologists to recognize and accurately diagnose this rare and aggressive entity.

Because of the rarity of MDA, future research should be focussed on nationwide studies. Data collection, information sharing, and inter-institutional consultations are necessary to define the nature of MDA to establish appropriate therapeutic guidelines and provide optimal advanced therapy in the era of precision medicine.

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Conflicts of interest

There are no conflicts of interest.

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