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Minimal Deviation Adenocarcinoma of the Uterine Cervix: Diagnostic Challenges and Recent Insights

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Abstract

Minimal deviation adenocarcinoma (MDA) of the cervix is a highly differentiated form of adenocarcinoma that presents a significant diagnostic challenge. Due to its subtle microscopic features, MDA is often mistaken for benign conditions, which confuses pathologists and complicates its diagnosis in gynecological oncology. This leads to frequent misinterpretation and some cases are mistakenly diagnosed as benign, leading to inappropriate management. Both false-positive and false-negative MDA diagnoses are common in cervical biopsies and can have serious consequences for patient treatment. Immunohistochemistry plays an important role in the accurate diagnosis of MDA. This review summarizes the key clinical and pathological features, reviews benign mimics, and explores the immunohistochemical and molecular markers that assist in the correct diagnosis of MDA.

Keywords: Cervix, Adenocarcinoma, Minimal deviation

Introduction

Cervical cancer remains a significant public health concern, particularly for middle-aged women, especially in developing countries. It ranks as the fourth most prevalent cancer in women, following breast, colorectal, and lung cancers. Early detection and intervention can significantly reduce mortality rates. However, minimal deviation adenocarcinoma (MDA) of the cervix closely resembles benign cervical lesions, which often leads to missed diagnoses by gynecologists, radiologists, and pathologists [1-5].

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Initially termed “malignant adenoma of the cervix” by Gusserow, MDA was later renamed by Silverberg and Hurt as “minimal deviation adenocarcinoma” because of its deceptively benign microscopic features. Since its recognition, only a limited number of MDA cases have been documented in the medical literature. In 2014, the WHO reclassified MDA as a subtype of gastric-type mucinous cervical adenocarcinoma [6-8]. MDA is a rare form of cervical adenocarcinoma, comprising just 1%–3% of all such cases. The tumor typically exhibits an endophytic growth pattern and, on transvaginal ultrasound, can resemble multiple benign nabothian cysts. Despite routine screening methods like the Papanicolaou (Pap) smear and human papillomavirus (HPV) testing, MDA is often missed, even with invasive diagnostic procedures such as punch biopsies or cervical conization [9, 10].

Because of it being rare and the subtlety of cytologic changes, MDA is frequently overlooked by pathologists, making diagnosis challenging. Differentiating MDA

from normal endocervical glands is difficult, especially in well-differentiated histological specimens from cytological evaluations or cervical punch biopsies. This can lead to MDA being diagnosed incidentally during a hysterectomy performed for other benign conditions [13-15]. Even though it appears histologically benign, MDA is generally aggressive, and its clinical course remains poorly understood due to its infrequent occurrence. This lack of comprehensive data hinders early detection and contributes to poor patient outcomes. Accurate diagnosis is crucial since MDA's prognosis is generally poor. Early identification and consideration of MDA in patients presenting with suspicious symptoms, even if cervical screening tests are negative, is critical. Pathologists must fully comprehend the pathology of MDA to facilitate timely diagnosis and improve patient outcomes [15-17].

This review summarizes key clinical and pathological characteristics, examines benign mimics, and explores the immunohistochemical and molecular markers that assist in the correct diagnosis of MDA.

Results and Discussion

Epidemiology and clinical features

A review of the literature and meta-analysis of 347 MDA cases indicates that the average age is 45 years when diagnosing, with a range of 20-78 years. The clinical presentation of MDA is similar to that of more common forms of cervical adenocarcinoma. Symptoms may include abnormal vaginal discharge, which can be mucoid or watery, menometrorrhagia, irregular genital bleeding, and abdominal swelling, depending on the tumor size. Among these, watery discharge is the most frequently reported symptom. Many patients are asymptomatic, and MDA is often discovered incidentally during procedures like cone biopsies or hysterectomies. Less commonly, patients may experience abdominal discomfort, a barrel-shaped cervix, cervical masses, and, in rare cases, adnexal metastases. MDA is found in 10%–15% of patients with Peutz–Jeghers syndrome and is frequently linked with lobular endocervical glandular hyperplasia. Upon clinical examination, the cervix typically feels firm and indurated.

Etiopathogenesis and HPV's Role

The underlying cause of MDA remains unclear, though a strong association exists between HPV infection and cervical cancer in general. However, studies have not found a significant link between HPV and MDA, setting this type of carcinoma apart from more common cervical cancers. Using advanced PCR techniques, most MDA cases show a lack of HPV infection. Research by Gong *et al.* [16] using in situ hybridization to detect HPV did not reveal any glandular nuclei testing positive for high-risk HPV, reinforcing the findings of earlier studies.

Unlike other cervical adenocarcinomas, MDA is more frequently seen alongside or before ovarian cancer. The types of ovarian cancer most commonly connected with MDA are mucinous adenocarcinomas and sex cord tumors with annular tubules. Both MDA of the cervix and these ovarian tumors have been notably associated with Peutz–Jeghers syndrome. In a study, 4 out of 27 women with this syndrome developed MDA. For this reason, women with Peutz–Jeghers syndrome are recommended to undergo close monitoring, which includes comprehensive endocervical cytologic evaluation and regular endocervical curettage. Furthermore, some studies have suggested that MDA may also be closely linked with gastric metaplasia or endocervical glandular hyperplasia [18-20].

Cervical cytology in MDA

Routine screening methods like the HPV test or cytology often fail to detect MDA due to the absence of HPV infection and its subtle cytological presentation. Previous studies have highlighted the limited sensitivity of cytology for diagnosing MDA, mainly because of its mild cytological features and its tendency to develop in the upper endocervical canal. MDA may be suspected cytologically if subtle patterns such as honeycomb arrangements, monolayered sheets, vacuolated cytoplasm, vesicular nuclei, and the presence of intracytoplasmic neutrophils are noted [18-21].

Several reports have characterized cytologic findings in MDA. Szyfelbein *et al.* [18] reviewed three cases, noting various glandular cell abnormalities, including multilayered sheets, columnar cells with abundant or lace-like cytoplasm, prominent nucleoli, and mitotic figures. In one case, many malignant-looking cells were found, while in others, only a few cells exhibited features suspicious of malignancy. A patient's smear, initially deemed negative following radiation treatment, was later identified as suspicious after MDA was diagnosed.

Granter and Lee's [19] study on cytological findings in MDA cases emphasized that making a definitive cytologic diagnosis can be very challenging without

more poorly differentiated features. In some cases, cells corresponding to the well-differentiated component of MDA were identified but lacked sufficient abnormalities to distinguish them from benign endocervical cells. However, if large clusters of such cells are observed, it could be an indication for further investigation, such as biopsy. The sensitivity of cytology in detecting MDA has been reported to be as low as 32.7%.

Pathology

Endocervical gastric-type adenocarcinoma (GAS), classified as a subtype of mucinous adenocarcinoma with gastric differentiation by the 2014 WHO, includes MDA, also referred to as adenoma malignum. This variant is distinguished by its well-differentiated features. Gross examination typically reveals a firm, indurated mass or a cervix that appears enlarged and barrel-shaped [22-26].

Histologically, MDA displays several key characteristics: (1) it features well-differentiated mucinous adenocarcinoma with glands that resemble normal endocervical glands, (2) the glands vary in size and shape with mild cytological changes, (3) mitotic activity is present, (4) surface hyperplastic glands are visible, and (5) glandular proliferation extends deeper than the lower endocervical level [27-29].

Microscopically, the glands in MDA are irregular, varying in shape, size, and arrangement. Mucin-producing glands are typically lined by a single layer of columnar epithelium, showing minimal nuclear atypia. The glandular cells have bland nuclei, often situated at the base of the epithelium. Angular outpouchings of glands are a hallmark, and these can vary greatly in size. MDA can extend through more than two-thirds of the cervical stroma and can infiltrate deeper than 5 mm into the cervical wall [28-31].

Desmoplastic reactions are commonly observed surrounding the glandular outpouchings or in deeper tumor areas. Areas devoid of stromal reaction may contain glands adjacent to thick-walled blood vessels, aiding in the identification of stromal invasion. The most reliable sign of malignancy is the irregular arrangement of glands beyond normal endocervical structures, with occasional mitotic activity. MDA is considered invasive if it extends more than 7 mm beyond the normal cervical gland crypts and tunnels **(Figures 1-3)**.

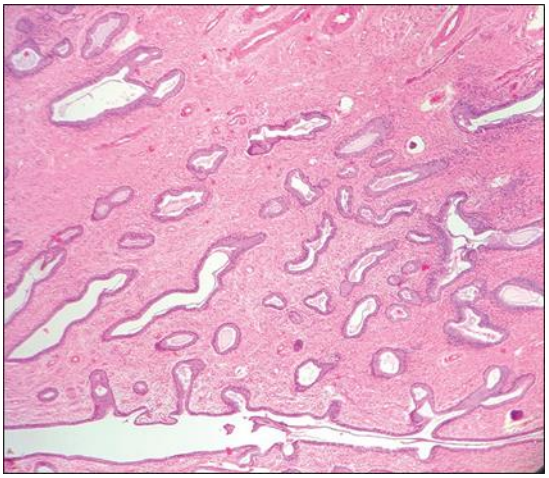

Figure 1. Architecturally atypical glands that vary in size and shape (H and E, ×10)

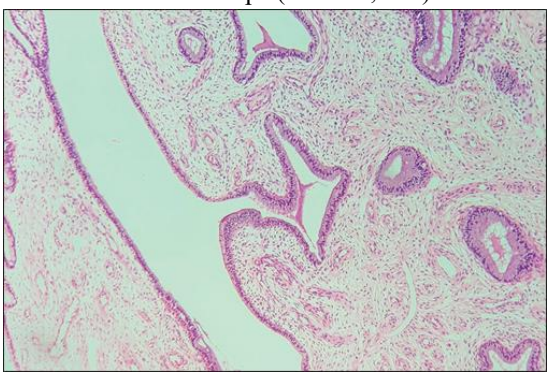

Figure 2. The glands have bizarre angular outpouchings (H and E, ×40)

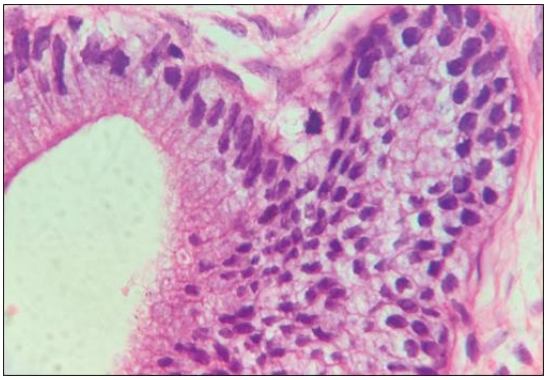

Figure 3. Presence of occasional mitosis in glandular cells (H and E, ×40)

Differential diagnosis

Several conditions can resemble MDA due to the presence of nonneoplastic glands extending further than 7 millimeters from the surface. They include deeply embedded nabothian cysts, endocervical tunnel clusters, endocervicosis within the cervical wall, and mesonephric hyperplasia. The distinguishing factor between these benign conditions and MDA lies in their glandular morphology—Noncancerous glandular formations generally exhibit a consistent size, lacking the irregular branching patterns and outpouchings characteristic of MDA. Additionally, these benign entities do not exhibit desmoplastic stromal reactions [32-26].

Lobular endocervical glandular hyperplasia, a benign lesion that may closely resemble adenoma malignum, has been identified as having a pyloric gland phenotype based on histochemical staining and immunohistochemical (IHC) analysis targeting pyloric gland-type mucins. Despite this similarity, the overall lesion architecture, including the extent of invasion into the cervical stroma, the presence of a stromal desmoplastic response, and focal areas of cellular atypia in sufficiently sampled tissue, aids in distinguishing MDA from benign conditions [36, 37].

Further, identifying vascular or perineural infiltration can be a critical indicator of malignancy. When encountering deeply located endocervical glands in the cervical stroma, a thorough examination for atypical features and vascular involvement is essential to rule out MDA [37-39].

Histochemical Stains's role in diagnosing MDA

A valuable tool in differentiating normal endocervical glands from malignant counterparts could be the combined Alcian blue–periodic acid Schiff (PAS). Due to their abundant acid and neutral mucins, normal glands exhibit a characteristic purple or violet hue when stained. Conversely, glands in cervical adenoma malignum, as well as conventional adenocarcinomas, display a red coloration, primarily due to the presence of neutral mucins. In cases where the diagnosis is uncertain, applying this stain can assist in distinguishing between normal and neoplastic glandular structures [40, 41].

Immunohistochemistry's role in Diagnosis

Immunohistochemistry (IHC) plays a crucial role in differentiating MDA from other conditions. Markers such as carcinoembryonic antigen (CEA), Ki-67, and p53 are commonly utilized to aid in diagnosis. Additionally, vimentin expression in the tumor stroma may further support identification. Research by Gong *et al.* [16] highlighted that MDA glands typically test positive for CEA, Ki-67, and p53 while showing negativity for estrogen receptor (ER), progesterone receptor (PR), and high-risk HPV DNA. Notably, the proliferation index of Ki-67 often exceeds 50%. Meanwhile, the surrounding stromal cells tend to express ER, PR, vimentin, and SM-actin.

Immunohistochemical staining for CEA in MDA is inconsistent, often exhibiting focal positivity, while CA 125 expression is markedly lower in comparison to normal endocervical glands. Another key differentiating factor is that MDA lacks expression of estrogen and progesterone receptors, helping to distinguish it from certain variants of normal endocervical glands [40, 41].

Emerging studies indicate that gastric mucins are a defining feature of cervical adenoma malignum. HIK1083, a monoclonal antibody specific to gastric gland mucous cell mucin, has proven useful in diagnosing this neoplasm. While normal endocervical glands generally do not express this marker, occasional focal positivity may be observed in standard endocervical adenocarcinomas. As a result, HIK1083 staining can serve as a distinguishing factor between benign endocervical glands and well-differentiated forms of adenoma malignum [38-41].

A defining trait of most tumors is monoclonality, whereas normal tissues and reactive hyperplasias exhibit polyclonality. Investigations by Gong *et al.* [16] used laser microdissection and a clonality assay—based on androgen receptor polymorphism and X-chromosome inactivation mosaicism—to analyze MDA samples. Their findings confirmed that these tumors exhibit monoclonal characteristics, reinforcing their neoplastic nature.

Cervical Biopsy's role in Diagnosis

Diagnosing MDA through endocervical biopsy can be challenging since its histological features often appear deceptively benign, leading to potential misinterpretation. Given that MDA typically extends beyond two-thirds of the cervical stroma, it is classified as an invasive tumor, as normal endocervical crypts and tunnel clusters would not surpass a depth of 5 mm. Consequently, superficial biopsies of the cervix

frequently fail to detect malignancy, making deeper tissue sampling through cone biopsy or hysterectomy specimens necessary for an accurate diagnosis [37, 39].
Studies have reviewed biopsy outcomes, revealing that among 185 patients who underwent cervical biopsy, the detection rate stood at 50.7%. In contrast, cervical conization, performed in 14 cases, successfully identified MDA in all instances. Interestingly, some cases are only identified postoperatively when a hysterectomy is carried out for a presumed benign gynecological condition, further underscoring the diagnostic challenge [38, 40].

Role of imaging

Imaging modalities, including MRI and ultrasonography, are not always definitive in diagnosing MDA due to the tumor's resemblance to benign conditions. However, these techniques are valuable for assessing disease extent and spread. MRI findings often reveal multiple irregular cystic structures with hyperintense signals on T2-weighted imaging, accompanied by stromal enhancement in post-contrast scans. A distinctive "Cosmos pattern," as described by Takatsu *et al.* [32], characterizes the normal cystic lesions arranged in a floret-like configuration. T2-weighted MRI is particularly effective in depicting these unique features and demonstrates a strong correlation with histopathological findings.

Genetic findings

Research by McGowan *et al.* [34] has indicated a possible link between Peutz–Jeghers syndrome (PJS) and MDA. PJS is an inherited condition marked by gastrointestinal hamartomatous polyps and distinctive mucocutaneous pigmentation. This syndrome may predispose individuals to MDA through mutations in the tumor-suppressor gene STK11. A previous study reported that 14.8% (4 out of 27) of women diagnosed with PJS developed MDA, often in association with lobular endocervical hyperplasia. Unfortunately, the prognosis for MDA cases linked to PJS tends to be poor. Despite these findings, no correlation between MDA and PJS based on family history, clinical presentation, or gastrointestinal endoscopic evaluation was observed in the current study. Additionally, three newly diagnosed MDA patients who underwent genetic screening for STK11 mutations did not exhibit any detectable genetic alterations.

Screening tools to detect MDA

Since MDA does not have a connection to HPV infection, conventional screening methods such as Pap smears and HPV serology offer little value in its early detection. Instead, specialized diagnostic tools, such as the HIK1083-latex agglutination test and MUC6, can help identify gastrin mucus within cervical secretions. If any of these screening tests yield positive or inconclusive results, further evaluation is necessary. This typically involves imaging techniques like ultrasound, followed by biopsy confirmation and MRI for a more comprehensive assessment [38-40].

Treatment and prognosis

Due to the rarity of MDA and the complexity of its diagnosis, there is no universally accepted treatment protocol. However, surgical intervention remains the most effective approach. For cases diagnosed at an early stage, treatment typically involves radical hysterectomy with salpingo-oophorectomy and bilateral pelvic lymphadenectomy. In more advanced cases, chemotherapy and/or radiotherapy may be considered as additional therapeutic options [37, 39].
The overall prognosis for MDA remains a topic of debate, but it is generally regarded as unfavorable. Unlike squamous cell carcinoma, which tends to metastasize locally, MDA has a higher likelihood of lymphatic spread and early peritoneal carcinomatosis. Delays in diagnosis, misclassification of the disease, and insufficient treatment further contribute to its poor clinical outcomes [38-41].

Conclusions

As widespread HPV vaccination reduces the prevalence of HPV-related cervical adenocarcinoma, the relative frequency of MDA and other rare HPV-negative adenocarcinomas is expected to rise. Timely identification of MDA is crucial for effective management. Clinicians should keep MDA in mind as a potential diagnosis, even when routine cervical screening results appear normal, particularly in cases with concerning clinical symptoms. A thorough understanding of MDA's distinct morphological characteristics and immunohistochemical profile is essential for pathologists to accurately detect and diagnose this uncommon yet aggressive malignancy.

Given the rarity of MDA, future research efforts should prioritize large-scale, nationwide studies. Collaboration through data sharing, multi-institutional research, and expert consultations will be key in further characterizing MDA, refining treatment strategies, and advancing therapeutic approaches in the field of precision medicine.

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