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Minimal deviation adenocarcinoma with elevated CA19-9: A case report

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Abstract

BACKGROUND

Minimal deviation adenocarcinoma is a rare malignancy with a high rate of misdiagnosis and high aggressiveness, and its diagnosis relies on histopathology. Surgical resection is the preferred and most effective treatment, but the outcomes are often unsatisfactory.

CASE SUMMARY

A 60-year-old perimenopausal woman was admitted to the hospital and found to have elevated CA19-9 on physical examination without abdominal pain or vaginal bleeding. Clinical examination and positron emission tomography/computed tomography examination were unremarkable, magnetic resonance imaging examination was suggestive of dominant cervical lesions, and methylation examination was suggestive of malignant lesions. Tissue samples were taken from the suspected cervical lesion, and the final pathologic diagnosis was minimal deviation adenocarcinoma. Based on the pathologic diagnosis of suspected minimal deviation adenocarcinoma, radical abdominal total hysterectomy, bilateral oophorectomy, and pelvic and para-aortic lymph node dissection were performed. The final histological report confirmed minimal deviation adenocarcinoma of the cervix, stage IB2, with lymph node metastasis. Minimal deviation adenocarcinoma is a tumor with aggressive clinical behavior.

CONCLUSION

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Patients with minimal deviation adenocarcinoma have a lower survival rate than patients with conventional human papillomavirus-related cervical adenocarcinoma. A precise preoperative pathologic diagnosis may reduce the mortality rate due to missed optimal treatment with multiple surgical interventions. To date, there is no therapeutic consensus; therefore, each case must be treated individually.

Key Words: Methylation; Minimal deviation adenocarcinoma; Positron emission tomography/computed tomography; Magnetic resonance imaging; Pathology; Case report

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Core Tip: Minimal deviation adenocarcinomas of the uterine cervix are mucinous adenocarcinomas not related to human papillomavirus. They are relatively rare, with atypical clinical presentation, low positive rate under cytology and pathological biopsy, high rate of misdiagnosis, high aggressiveness, and tendency to spread easily during the early stage. The methylation test also improves the specificity and sensitivity of early diagnosis of minimal deviation adenocarcinoma of the cervix.

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INTRODUCTION

Gastric-type endocervical adenocarcinoma, also known as malignant adenocarcinoma or minimal deviation adenocarcinoma, is a rare pathologic type of cervical mucinous adenocarcinoma. Its prevalence is about 1%-3% of cervical adenocarcinomas and 0.15%-0.45% of cervical tumors. The average age at diagnosis is 42-57 years. The etiology of minimal deviation adenocarcinoma is unknown and is not associated with human papillomavirus (HPV) infection.

However, it has been reported to be associated with Peutz-Jeghers syndrome (10%) and other ovarian tumors such as mucinous or sex cord tumors. The most common clinical features include serous vaginal discharge (69.4%), spotting, and post-coital bleeding (50%). Pelvic pain was uncommon, but cervical hypertrophy was present in 74.9% of cases[1]. The diagnosis of minimal deviation adenocarcinomas is difficult because of the lack of specific clinical manifestations and benign pathology, and it needs to be differentiated from benign tumors.

CASE PRESENTATION

Chief complaints

A 60-year-old patient presented to the clinic on May 26, 2020 due to elevated CA19-9 found during a health check.

History of present illness

Elevated CA19-9 had lasted more than 3 mo.

History of past illness

The patient had been menopausal for 7 years, with a free previous medical history.

Physical examination

Gynecologic examination suggested normal vulvar development, a smooth vagina, little vaginal discharge, a soft cervix, a uterus of average size, no tenderness, and no abnormalities in the accessories. Triage suggested a smooth rectal wall and rectal pit.

Laboratory examinations

The patient's CA19-9 level was 3405.89 U/mL on May 13, 2020 and increased to 4972.00 U/mL on June 5, 2020. CEA and CA-125 were normal.

Imaging examinations

Positron emission tomography/computed tomography (PET-CT) (Figure 1) showed that the uterus was enlarged with cystic, stable occupancy. MRI (Figure 2) suggested fluid in the uterine cavity and a cervical lesion occupying the cervical niche, which was considered a neoplastic lesion, predisposing to cervical cancer.

Further diagnostic work-up

On May 26, 2020, the level of tumor marker CA-199 was 3287.19 U/mL, an E6E7 test was negative, and thinprep cytologic test revealed negative intraepithelial lesion or malignancy. A colposcopy (Figure 3A) on May 28, 2020 suggested cervical inflammation. Further cervical biopsy + pathology (Figure 3B) indicated (cervical 6 o'clock distal) tissue chronic inflammation, bleeding tissue in the uterine cavity with a small amount of mucus epithelium detected in the tissue, chronic inflammation of the tissues of the cervical canal, and significant glandular hyperplasia with hyaline cell mucus papillomatosis. Immunohistochemistry showed the following: CEA (-), P16 (-), NapsinA (-), Ki-67 (+) (< 5%), and HNF-1b (+). On June 2, 2020, the patient underwent loop electrosurgical excision procedure, with an intraoperative resection depth of 3-3.5 cm, and pathological inflammation of the cervix was observed. A PAX1 gene methylation assay performed on cervical exfoliated cells showed the following results: $\Delta C_p = 3.57$, indicating that the gene was highly methylated.

FINAL DIAGNOSIS

The final diagnosis of the presented case was uterine minimal deviation adenocarcinoma.

TREATMENT

Since MRI, methylation, and CA19-9 suggested malignant lesions, hysterectomy was performed first, and the next surgical treatment was performed according to the results of intraoperative rapid pathological examination.

Hysterectomy was performed on July 6, 2020, and the uterus was observed anteriorly and found to be slightly smaller than average, regular in shape, with a smooth surface, no abnormalities in bilateral adnexa, a thickened and hardened cervix, and no abnormalities in sacral ligaments detectable upon palpation. Intraoperative rapid pathology considered uterine cervical adenocarcinoma, and minimal deviation adenocarcinoma was not ruled out. The patient underwent further surgical treatment. Then transabdominal extensive hysterectomy + double adnexal resection + pelvic lymph node dissection + abdominal para-aortic lymph node biopsy was performed.

OUTCOME AND FOLLOW-UP

The final pathologic diagnosis (Figure 3C and D) was stage IB2 minimal deviation adenocarcinoma. The patient was given treatment with postoperative radiotherapy and chemotherapy. There is no recurrence at present.

DISCUSSION

Minimal deviation adenocarcinoma of the cervix (MDA), accounting for 1%-3% of all cervical adenocarcinomas and 0.15%-0.45% of all cervical cancers, is a highly differentiated type of mucinous adenocarcinoma[2]. The average age of onset of MDA is 45 years. It is highly aggressive, but the clinical symptoms are atypical and readily missed and misdiagnosed in the early stage. Most of the patients are already in the middle and late stages upon diagnosis, so prognosis is poor[3].

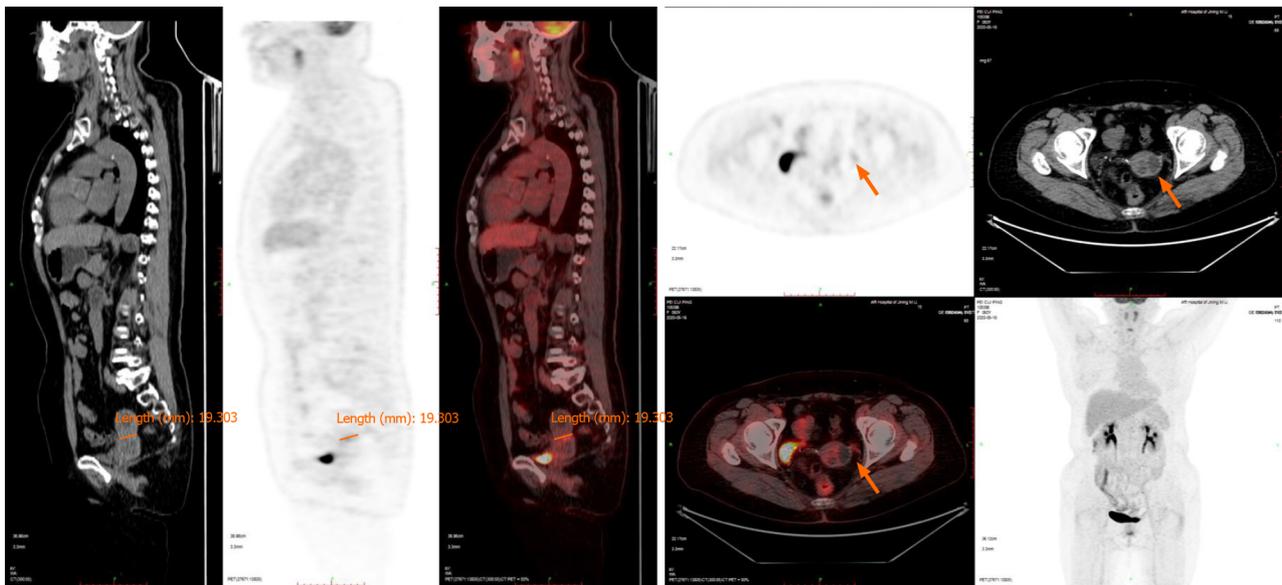


Figure 1 Positron emission tomography/computed tomography. Uterine volume enlargement with cystic solid occupancy.

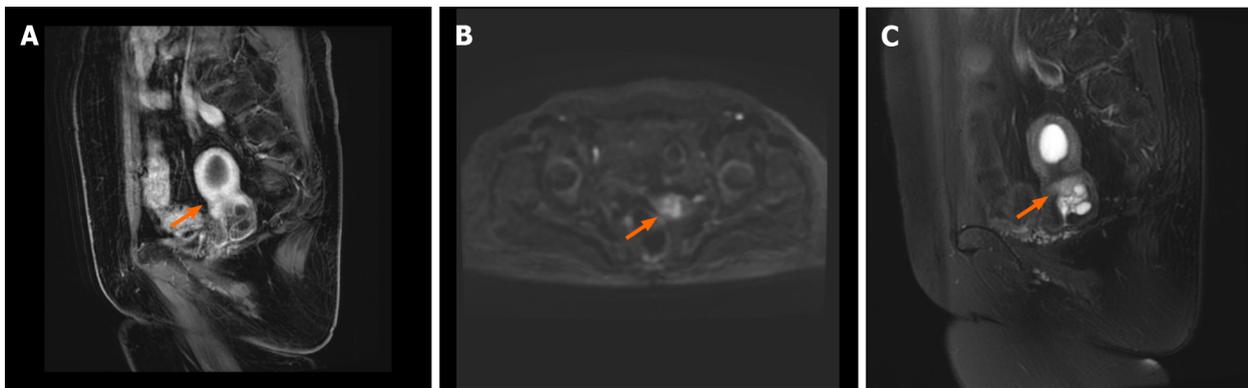


Figure 2 Pelvic magnetic resonance imaging. A: Liver acquisition with volume acceleration showed enlarged cervix with localized soft tissue nodules; B: Diffusion weighted imaging showed a relatively high signal and lesions mainly located in the posterior part of the cervix; C: T2 weighed imaging showed multiple cystic signals.

The etiology and pathogenesis of MDA remain unclear. Common cervical adenocarcinoma is usually associated with high-risk HPV infection. However, current studies have found that MDA occurrence is not related to HPV infection. According to the WHO classification, MDA is defined as an HPV-independent cervical adenocarcinoma, which is a rare mucinous adenocarcinoma with gastric gland differentiation [4]. HPV infection was not found in this case. MDA is a highly differentiated type of gastric-type endocervical adenocarcinoma, and it is difficult to distinguish well-differentiated glands from normal glands.

However, MDA shows a typical deep infiltration, random distribution, and structural abnormalities, with some glands showing distinct malignant cellular features with interstitial tissue proliferation. P16 negativity in immunohistochemistry is an essential feature of MDA, suggesting no correlation with HPV infection or with the estrogen receptor[5].

Itoh *et al*[6] reported that MRI shows the most typical features of the disease among ultrasound, CT, MRI, and other forms of imaging, so MRI is preferred. MDA tissue is highly differentiated, and PET-CT only suggests non-specific signs such as increased cervical volume, cervical redundancy, and abnormal cervical echogenicity, with slightly increased marginal metabolism, which has limited diagnostic value[7]. T2-weighted MRI showed localized polycystic appearance of the MDA, fluid in the uterine cavity, disorderly arrangement of glands, and invasion of the cervical canal wall. In this case, only MRI produced positive results on imaging[8].

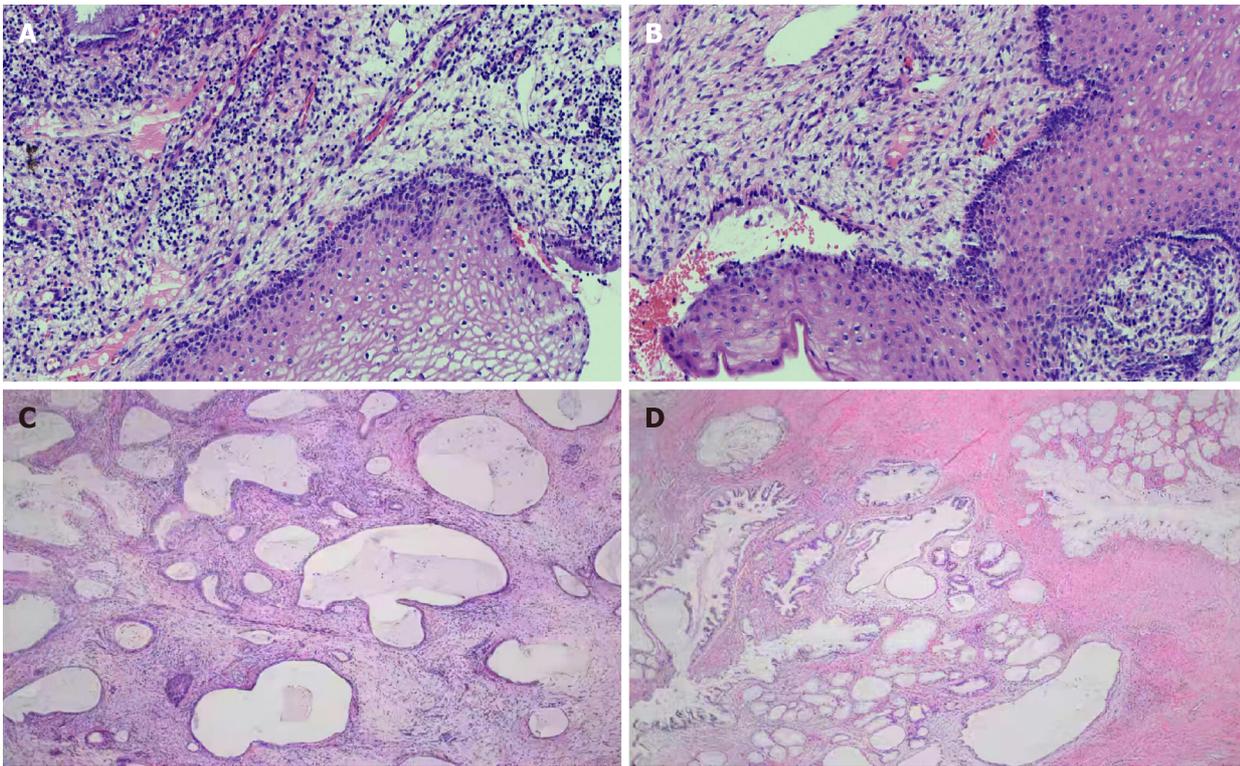


Figure 3 Pathological analysis. A and B: Pathology of preoperative colposcopy and loop electrosurgical excision procedure mainly showed inflammation (200 ×); C and D: Pathology of postoperative showed minimal deviation adenocarcinoma (200 ×).

The methylation test provides an essential basis for the clinical diagnosis of this case. Recent studies have shown that DNA methylation is closely related to the occurrence of cervical cancer and can be used as a significant molecular marker for cervical cancer screening[9]. At present, many methylation test samples come from cervical cytology, which can avoid the influence of the stromal cells contained in the histological assay on the results. CpG island hypermethylation of tumor suppressor genes was found in cervical cancer patients and did not correlate with the degree of HPV infection[10]. This case was tested for methylation of the *PAX1* gene, which is a crucial tumor suppressor gene. Lai *et al*[11] found *PAX1* to be 94.4% highly methylated in cervical cancer tissues. In a subsequent study, they discovered that *PAX1* methylation had a sensitivity of 78% and a specificity of 91% for the detection of CIN3+. *PAX1* methylation provides a digital assay (Δ Cp), which can be used to accurately determine whether cervical tissues are carcinogenic or not, based on the Δ Cp of the *PAX1* methylation assay and the extent of cancer. In 2016, Lai *et al* proposed using HPV testing as a primary screen. Many HPV-positive patients were tested for *PAX1* methylation to identify actual high-grade lesions, assess whether they should undergo vaginal microscopy, and allay their fears[12,13].

There are few reports about the diagnosis and treatment of MDA. Considering that its molecular biological characteristics (easiness to infiltration, early metastasis and diffusion, and insensitivity to chemoradiotherapy), surgery is the best choice. It is recommended to perform transabdominal hysterectomy + pelvic lymphadenectomy, and adjuvant chemoradiotherapy should be carried out according to whether there are high-risk factors after surgery.

All in all, with the popularity of screening for HPV-related cervical lesions and the wide vaccination of HPV vaccines, the incidence rate of non-HPV-related tumors (such as MDA) may increase. In this patient, PET-CT failed to show its advantage in the diagnosis of malignant tumors, which may be due to less blood perfusion and weak marginal metabolism at the lesion site, but MRI examination could clearly indicate the lesion. Our research showed that for patients with vaginal discharge but negative cytological examination, we should be alert to the possibility of MDA. Deep biopsy or conization should be performed when necessary, combined with auxiliary examination techniques (such as MRI, immunohistochemistry, and methylation) to provide a basis for MDA diagnosis.

CONCLUSION

The methylation test improves the specificity and sensitivity of early diagnosis of MDA, facilitates early treatment, and positively improves the prognosis.

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