Clinical analysis of minimal deviation adenocarcinoma of the cervix

A report of five cases

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Key words: cervical neoplasm, minimal deviation adenocarcinoma, diagnosis, treatments, prognosis

Background and Objective: Minimal deviation adenocarcinoma (MDA) of the cervix is a rare disease. The misdiagnosis rate of this disease is relatively high and there is no standard treatment for it. This study evaluates the clinicopathologic features, diagnosis and treatment of MDA. Methods: Records of five patients with MDA treated in the Second Affiliated Hospital of Sun Yat-sen University from January 1991 to December 2006 were retrospectively analyzed. Results: The median age of the five patients was 47 years (range 38–59 years). The most common complaints included a large amount of watery discharge and atypical genital bleeding. Histology revealed that MDA was highly differentiated. Although the appearance of the MDA glands was difficult to distinguish from normal endocervical glands, the location of the MDA glands was deeper than the lower level of normal endocervical glands. Carcinoembryonic antigen (CEA) and p53 in two patients were positively detected by immunohistochemistry. Four patients underwent surgery, among which one received surgery plus postoperative radiotherapy, and three received surgery plus postoperative chemotherapy and radiotherapy. One inoperable case received palliative radiotherapy. All cases were followed up for 6–88 months. Two patients achieved disease-free survival, one surviving for more than five years. Three patients died of local recurrence and distant metastasis. Conclusions: Diagnosis of MDA mainly depends on its clinical manifestations and the pathological feature that MDA glands are located deeper than the lower level of normal endocervical glands. Surgery combined with other adjunct therapy achieves good outcomes for MDA.

Minimal deviation adenocarcinoma of the cervix (MDA), also known as adenoma malignum is a rare disease, represents about 1.0–3.0% of all cervical adenocarcinoma cases.1 In 2003, the new WHO classification classified MDA as a modified “deviation type” of cervical adenocarcinomas.2 Its histopathological pattern is similar to benign change, it is difficult to differentiate from normal cervical endothelial tissue under light microscopy, false negatives have been reported from cervical cytology smears. Even after several repeated biopsies. Thus it is often misdiagnosed, highly malignant, prone to metastasize, with poor prognosis and so on. In this article, retrospective analysis has been conducted on clinicopathology records of five patients with MDA treated in the Second Affiliated Hospital of Sun Yat-sen from Jan 1991 to Dec. 2006. The clinical features, diagnosis and treatment of the disease are as follows:

Data and Methods

Case selection. A total of 383 patients with cervical adenocarcinoma were reported in the Gynecology Department at the Second Affiliated Hospital of Sun Yat-sen University from January 1991 to December 2006. MDA was reported in five cases, accounting for 1.3% of all cases. Diagnosis was confirmed in each of the cases based on their pathological findings, where two cases were confirmed through pre-operative cervical conization. Age of onset reported ranged from 38 to 59 years old, with a median age of 47-years-old. FIGO clinical staging was as follows: stage Ib in two cases; the other three cases with stage Iib, IIIb and IV in one case each, respectively (Table 1).

Method of pathological diagnosis. Method of pathological diagnosis mainly consisted of cytology, cervical biopsy and cervical conization. Obtained specimens had been dyed with routine HE staining as well as CEA, p53 and other immunohistochemical stains.

Methods of treatment. One patient with stage IV had been given palliative radiotherapy (radiation dose 40 Gy), and the remaining four had been given comprehensive treatments. Among those who received comprehensive treatment, one case had been highly suspected of cervical malignant changes before surgery, however, a biopsy revealed no tumor cells; during surgery, a tumor was seen to have invaded the patient’s left pelvic sidewall, and “well-differentiated adenocarcinoma of the cervix” was reported through...
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Frozen sectioning. Subsequently, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed, and postoperative pathology revealed MDA. Concurrent adjuvant radiotherapy and chemotherapy were given [chemotherapy regime: FP (5-FU + carboplatin), where 5-FU was given in accordance to 4,000 mg/m2, set on continuous intravenous pump for 96 h; carboplatin dose was given at AUC = 6.0]. Radical hysterectomy + pelvic lymph node clearance had been performed on the remaining three cases due to preoperative cervical conization or biopsy diagnosis revealing malignant changes. Postoperative adjuvant radiotherapy and/or chemotherapy were given. (Chemotherapy regime: FP or TP, where TP = Taxol + carboplatin, taxol was given in accordance to 135–175 mg/m2).

Follow-up. Follow-up arrangements included outpatient follow-up visits and telephone follow-ups. Follow-up time was initiated on the day of diagnosis confirmation, and the last follow-up was recorded on February 2007.

Outcomes

Clinical manifestations. In our group of cases, common symptoms were profuse, thin and mucotic leucorrhea, with two cases of leucorrhea requiring the use of sanitary pads; irregular vaginal bleeding and postcoital bleeding were reported in two cases, with both complaints in one case. The disease course was four years in one case, 1–2 years in three cases, and one month in one case. Gynecology examination showed cervical hypertrophy with hard consistency in four cases, severe cervical erosion in three cases, irregular surfaces in two cases, contact bleeding in three cases, thickened ligaments as well as parauterine structures with poor elasticity in three cases.

Pathology diagnosis. All cases of our group had been pathologically diagnosed as MDA, among which four cases had had preoperative cytology examination; diagnosis of MDA was confirmed in two cases; no malignancy changes reported in one case, and typical cervical adenocarcinoma was reported in one case due to the presence of significant heteromorphic glandular epithelial cells on the smear. The cervical smear revealed an increased number of glandular epithelial cells in MDA subjects, high-columnar cells arranged in small sheets or irregular rectangular shape, and peripheral cells were closely-arranged together forming a palisade pattern; cytoplasm was granular, dark-stained nuclei with mild dysplasia noted, chromatin appeared to be condensed into masses and nucleioli were partially visible. Necrosis debris could be seen in the background of a smear.

Preoperative cervical biopsy had been performed in five cases, diagnosis of MDA was confirmed in one case, typical cervical adenocarcinoma with co-existing MDA suspected in one case, while “no malignant changes found” was reported in the rest of the three cases. However, one case had already been prompted MDA on preoperative cytology, and MDA was confirmed subsequently through cervical conization; one other case was reported to have no malignant changes, however, the case was prompted MDA through cervical conization subsequently. Diagnosis confirmation of the other two cases had relied upon surgical resection specimens. Grossly, significant cervical hypertrophy, hard in consistency could be seen with hemorrhage as well as mucous on its mucosal surface. The resected section appeared to be yellow, brownish-white, and distinct vesicular structures reached the deep cervical fascia. Under light microscopy, (Fig. 1) most of the mucous glandular tissues appeared to be benign (equivalent to of stage I adenocarcinoma), where the tissues were densely or loosely distributed, irregular in size, inordinately arranged and abnormal in shape, and the tissues had infiltrated into the surrounding stroma. The vast majority of glandular tissues were widely separated by stroma and the lack of back-to-back phenomenon. Most of the glandular tissues were surrounded by mucous columnar epithelial cells, large nuclei, mostly located at the basement, stained dark, with chromatin appearing to be condensed into masses while karyokineretic phases were rarely seen. Single or small nests or stalk-shaped heterotypic cells were seen invading blood vessels, lymphatic ducts or nerves. The glandular tissue infiltration reached to the depth of 0.7–2.7 cm underneath the cervical epithelium, and involved 2/3–4/5 of the cervical wall thickness. Three cases in our study had revealed a small number of poorly-differentiated glandular cells; however,

Table 1 Clinical data of five cases of minimal deviation adenocarcinoma of the cervix

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Stage</th>
<th>Symptoms</th>
<th>Cytology</th>
<th>Punch biopsy</th>
<th>Cervical Conization</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>IV</td>
<td>Atypical genital bleeding, cough, chest pain</td>
<td>AM</td>
<td>AM</td>
<td>⋯</td>
<td>RT(40 Gy)</td>
<td>DOD (6 months)</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>IIb</td>
<td>Watery discharge</td>
<td>No malignancy</td>
<td>No malignancy</td>
<td>AM</td>
<td>RH, RT(50 Gy),</td>
<td>DOD</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>IIIb</td>
<td>Watery discharge</td>
<td>⋯</td>
<td>No malignancy</td>
<td>⋯</td>
<td>TAH, RT(50 Gy),</td>
<td>DOD</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Ib</td>
<td>Watery discharge, atypical genital bleeding</td>
<td>AM</td>
<td>No malignancy</td>
<td>AM</td>
<td>RH, RT(50 Gy)</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>Ib</td>
<td>Atypical genital bleeding</td>
<td>ΔC</td>
<td>ΔC+suspicious</td>
<td>⋯</td>
<td>RH, RT(50 Gy)</td>
<td>NED</td>
</tr>
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Note: AM, adenoma malignum; AC, ordinary adenocarcinoma; RT, radiotherapy; FP, 5-FU + Carboplatin; RH, radical hysterectomy with pelvic lymphadenectomy; TAH, total abdominal hysterectomy with bilateral salpingo-oophorectomy; DOD, died of the disease; NED, no evidence of disease; ⋯, Unknown.
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As shown in Figure 1, histological features of adenoma malignum (HE x100). Typical lesions of minimal deviation adenocarcinoma consist mostly of abnormally shaped tubules. Apillary infolding and irregular branching are lined by mildly atypical cells. Mitoses are rarely found. Stromal reactions, such as mild oedema and inflammatory cell infiltration are occasionally observed.

The ratio of this type of cells generally accounted for <10%. Immunohistochemistry had been conducted on two of the five cases, and the results showed CEA (+) and p53 (+) (Figs. 2 and 3).

Follow-up results. There were no missed follow-ups in any of our case studies, with a median follow-up period of 63 months (from six to 88 months). Among the three reported deaths, one was due to distant metastasis after six months, one was judged as due to unsatisfactory results from postoperative adjuvant radiotherapy after total hysterectomy and bilateral salpingoophorectomy; and one death was 46 months later due to local recurrence. Among the two disease-free surviving patients, one case reported disease-free survival for more than five years.

Discussions

Clinical features. MDA is a rare disease. Foreign studies have reported that MDA only accounts for 1.0% to 3.0% of all adenocarcinoma of the cervix. In 1975, Silverberg and Hurt et al. considered its pathological form to be a type of well-differentiated cancer, one slightly different from normal cervical glands, and thus suggested naming it minimal-deviation adenocarcinoma. Its pathological pattern, which is very similar to mucus glands of a normal cervical mucosa, invades cervical stroma giving rise to this definition. Peutz-Jeghers syndrome, ovarian adenocarcinomas as well as sex-cord tumors are the possible comorbidities of MDA. In our group, there were no patients reported with coexisting PJS; however, PJS or primary ovarian adenocarcinomas are the high-risk factors of MDA.

Foreign studies have reported the median age of MDA patients to be 42.6 to 53.3 years old, with 16 years being the youngest age reported. In our group, the median age was 47 years old, with 38 years being the youngest. The main clinical features of MDA are profuse, thin, mucotic leucorrhea, watery leucorrhea or irregular vaginal bleeding, contact bleeding or both. Profuse, thin mucotic leucorrhea is due to the higher sialic acid proportion over sulfuric acid of acidic mucin secreted by cervical glandular epithelium in MDA subjects. Early physical examinations may not reveal any specific findings, however, variable degrees of cervical hypertrophy as well as granular-appearance of the cervical os may be present at later stages. Imaging diagnostics such as ultrasonography, CT and MRI may routinely reveal intrauterine and/or vaginal fluid accumulation, and in most cases, MRI examinations reveal multiple, irregular cystic lesions which presents as low-signal on T1WI image, and high-signal on T2WI image. On contrast imaging using bolus intravenous gadolinium-diethylene triaminepentaacetic acid (Gd-DTPA) (0.1 mmol/kg) rough, irregular cyst walls presenting with a fine granular appearance may be detected; however, their appearance is non-specific on MRI.

Pathological features. Papanicolaou smears of a cervical exfoliative in cytology is an essential technique used to diagnose MDA, where atypia may be elicited on smears which histological heterotypic cells are not significant. Of course, some researchers hold
HIK1083 into account may be helpful to determine MDA.5

60% patients with MDA had chromogranin A (CGA) (+). As CEA accurate diagnosis of MDA, then further immunohistochemisty scratch or hysterectomy. If biopsy specimens do not lead to an considered.

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In our group, one patient suspected of cervical adenocarcinoma through cervical biopsy was deemed to have concurrent MDA due to the presence of well-differentiated adenocarcinomatous elements which rarely results in cervical adenocarcinoma. He Song et al.10 believed that the above elements of typical malignant adenoma should require more than 90% in order to diagnose MDA, and if the typical elements of well-differentiated adenocarcinoma are more than 10%, diagnosis of cervical adenocarcinoma should be considered.

Immunohistochemistry. MDA has a characteristic expression which resembles the phenotype of gastric epithelial cells. Kuniko et al.14 reported that 90% of patients with MDA had gastric-mucin monoclonal antibody, HIK1083 (+). Yoshiki et al.15 reported that 60% patients with MDA had chromogranin A (CGA) (+). As CEA and p53 are not always both positive in MDA subjects, taking HIK1083 into account may be helpful to determine MDA.5 Special staining with AB/PAS (pH 2.5) reveals red in MDA whilst purple in benign epithelium.16

Diagnosis. An accurate diagnosis of MDA relies upon pathological examinations; therefore, cases with abnormal findings on clinical manifestation, ultrasonography, CT and MRI, but with negative results on cytology, should undergo deep cervical tissue biopsy or cervical conization. As glandular tissues may infiltrate more than 8.0 mm into the cervical wall,10 general cervical biopsies are not able to put forward an accurate diagnosis. Cervical conization, however, may determine the depth of interstitial infiltration.6 Hence, the correct path to the diagnosis of MDA is based on specimen tests obtained from cervical conization, cervical canal scratch or hysterectomy. If biopsy specimens do not lead to an accurate diagnosis of MDA, then further immunohistochemistry and special staining can be proposed.

Treatment and prognosis. Yamagata et al.17 reported that patients who were accurately diagnosed with MDA and who underwent radical hysterectomy + pelvic lymph node clearance along with postoperative adjuvant chemotherapy showed no tumor recurrences on follow-up period of 15 to 60 months, while the condition of inaccurately diagnosed patients deteriorated. Young et al.18 reported that managing patients after receiving radical hysterectomy + pelvic lymph node clearance with postoperative radiotherapy yields a better prognosis. In our cases, the patient with stage IIIb had been managed with total abdominal hysterectomy and bilateral salpingoophorectomy and radiotherapy and chemotherapy and expired 18 months after surgery; the patient at stage IV had been given palliative radiotherapy (40 Gy) and succumbed to the disease six months after the procedure. Two cases of stage Ib and one case of stage IIb had been managed with radical hysterectomy and pelvic lymph node clearance and radiotherapy and/or chemotherapy, one case survived 46 months, and among the two cases of disease-free surviving patients, one patient was reported disease-free for more than five years. This obviously shows that the prognoses of patients in the latter group are better than in patients with stage IIIb and IV. This shows that early diagnosis with comprehensive managed treatment is the key factor for improving the prognoses of patients with MDA.

References