Clinical Research Paper

Malignant transformation of ovarian endometriosis

A clinicopathologic analysis of forty-nine cases

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Abstract

Malignant transformation of ovarian endometriosis is a common and benign, but progressive disease. We aimed to investigate the clinicopathologic of ovarian endometriosis with malignant transformation and to evaluate the expression differences of estrogen receptor (ER) and progesterone receptor (PR) between ovarian endometriosis samples with and without malignant transformation.

Methods: Clinicopathologic data of 49 ovarian endometriosis patients with malignant transformation were reviewed. The expression of ER and PR in the 49 specimens of ovarian endometriosis with malignant transformation (transformation group) and 49 specimens of ovarian endometriosis without malignant transformation (control group) were detected by immunohistochemistry and compared statistically.

Results: The 49 ovarian endometriosis patients were aged of 29–70 years with a median of 49 years. The major initial manifestation was pelvic masses. B-ultrasound examination showed mixed cystic and solid masses in the pelvic cavity. Macroscopically, the ovarian masses were solid cystic with diameters of 4.0–20.0 cm; the cysts possessed thick and fibrous walls (in brown or yellow) and contained chocolate-like fluid or semi-fluid materials; the parenchymal part was tender papillary nodules with diameters of 0.5–15.0 cm. Microscopically, the ectopic endometrium proliferated and transformed to atypical hyperplasia and carcinoma. The positive rates of ER and PR proteins were significantly lower in transformation group than in control group (20.4% vs. 95.9%, 14.3% vs. 95.9%, p < 0.05). Conclusions: The malignant transformation of ovarian endometriosis is likely to occur in perimenopausal women. Clinical manifestations, B-ultrasound examination and pathologic examination are valuable for diagnosis. The absence of ER and PR protein expression in endometriosis may help to diagnose malignant transformation of ovarian endometriosis.

Endometriosis (EMs) is a common gynecologic disease in which endometrium-like glandular epithelia and stroma are found at locations outside the uterine cavity, most commonly the ovary. Most EMs are benign, but the ectopic endometrium, like the normal one, has potential to become malignant.1 Therefore, the ectopic endometria of EMs can undergo atypical hyperplasia and even malignant transformation. Since Sampson first reported malignant transformation of ovarian EMs in 1925,2 there are many reports on it, but its incidence and clinicopathologic characteristics remain unclear. We retrospectively analyzed the clinicopathologic characteristics of 49 cases of malignant ovarian EMs, and investigate the significance of estrogen receptor (ER) and progesterone receptor (PR) in pathologic diagnosis and differential diagnosis of the disease.

Materials and Method

Clinical data. Clinical data of 49 malignant ovarian EM patients were collected from West China Second University Hospital of Sichuan University from 2003 to 2007. The inclusive criteria were accordant to those reported by Sampson and Scott:2 3 (1) the presence of both malignant and benign endometrial tissues in the same ovary; (2) a clear evidence of EMs close to the tumor; (3) excluding metastasis and invasion of other primary tumors; (4) histological evidences of malignant transformation of ovarian EMs under microscope. Also, clinical data of 49 ovarian EM patients without malignant transformation were collected and used as control.

Immunohistochemical staining. Slides with four µm thickness were prepared from paraffin-embedded tissue, and stained by the EnVision Two-Steps Method (DAKO Company), using primary antibodies of ER and PR. The slides stained with PBS were used as negative control; the known positive slides were used as positive control. ER- and PR-positive granules were stained in brown and located in nuclei of endometria. The expression levels of ER and PR were assessed according to the number of positive cells ( < 50% = 1 point, 50–80% = two points, > 80% = three points) and staining intensity (no stain = 0 point, light yellow = one point, brownish yellow = two points, pure brown = three points).4,5 Multiplying the scores of these two indices, 0-1 point referred to negative expression (-); 2–9 points referred to positive expression (+). The slides were observed by two pathologists independently. Any controversy would be discussed to reach a consensus.

Statistical analysis. Data were analyzed by SPSS 13.0 software using χ²-test. A p value of < 0.05 was considered as significant.
Results

Clinical conditions. The age of the 49 malignant ovarian EM patients ranged from 29 to 70 years, with a median of 49 years; among them, 29 (59.2%) patients were aged of 44–57 years. Of the 49 patients, 42 (85.7%) were admitted to the hospital due to the notice of pelvic mass, one (2.0%) was admitted due to progressive menstrual pain, and six (12.2%) were due to abdominal pain. According to gynecologic examination, masses, 4.0–20.0 cm in diameter, next to the uterus or in the adnexa uteri, were palpated in all patients. Some masses were solid cystic, with medium or hard texture. Ultrasound examination displayed mixed solid cystic masses, presented echoes of various intensities, in the pelvis of the 49 patients. All patients underwent exploratory laparotomy: masses were seen on one side or both sides of the adnexa uteri, and adhered to the intestinal tract and pelvic wall. Malignant transformation was observed in the ovarian endometrial cyst under microscope. Of the 49 patients, 29 (59.2%) had EMs with malignant transformation on one side, including 15 on the left side and 14 on the right side; 20 (40.8%) had EMs on both sides, including eight had malignant transformation on the left side, three had malignant transformation on the right side, and nine had malignant transformation on both sides.

Macroscopic observation. The diameter of tumors ranged from 4.0 cm to 20.0 cm, which was < 10.0 cm in nine (18.4%) cases, 10.0–14.9 cm in 28 (57.1%) cases, and ≥ 15.0 cm in 12 (24.5%) cases. The tumors were solid cystic with smooth surface. The cystic regions were multi-chambered and filled with brown mucous liquid in 39 (79.6%) cases or yellowish serous liquid in ten (20.4%) cases. The solid regions presented as grayish white or yellow cauliflower-like nodules or masses, with diameters of 0.5-15.0 cm, grayish white sections, fish flesh-like, soft or fragile in texture, and sometimes with calcification, on the internal walls of these cysts.

Microscopic observation. Endometrial stroma, with or without ectopic endometrial epithelia and remote hemorrhage, was observed in all patients. If no ectopic endometrial epithelia were seen, CD10 staining was done for further verification (Fig. 1). Of the 49 cases of ovarian EMs with malignant transformation, 17 (34.7%) were classified as clear cell carcinoma, 12 (24.5%) were serous papillary adenocarcinoma, eight (16.3%) were endometrioid adenocarcinoma, 11 (22.4%) were mixed type of the above three types, one (2.0%) was endometrial stromal sarcoma. With HE staining, the endometrial epithelia of 48 EMs with epithelial malignant transformation presented a continuous process of atypical hyperplasia, malignant transformation to ovarian carcinoma (Fig. 2 and Fig. 3).

ER and PR expression in ovarian EMs. Both ER and PR were not detected on ectopic endometrial epithelia of ovarian EMs with atypical hyperplasia and malignant transformation (malignant transformation group), while detected in ovarian EMs without malignant transformation (control group) (Fig. 4). The positive rates of ER and PR were significantly lower in malignant transformation group than in control group (20.4% vs. 95.9%, p < 0.001; 14.3% vs. 95.9%, p < 0.001). In control group, the expression of ER and PR were completely identical, while in malignant transformation group, only seven of the ten ER-positive cases showed PR-positive.

Discussion

Clinical diagnosis of ovarian EMs with malignant transformation. Of the 49 patients in this study, 29 were in perimenopausal period; the median age was 49 years. Palpable pelvic mass was the major clinical manifestation. Ultrasonography examination showed pelvic solid cystic mass with suspicion of malignant transformation in solid regions. Except for two patients who received operation for ovarian endometrial cysts, other patients received exploratory laparotomy for pelvic masses. The masses were verified as ovarian EMs with malignant transformation by pathology. Therefore, it is hard to diagnose ovarian EMs with malignant transformation at early stage when pelvic mass is the main complaint while dysmenorrhea is not obvious. When pelvic mass is progressively growing up, solid regions or abundant blood supply is detected in the mass by ultrasonography examination, ovarian EMs with malignant transformation should be considered.

Pathology of ovarian EMs with malignant transformation. Pathological diagnosis of ovarian EMs with malignant transformation primarily requires to distinguish the malignant transformation of ovarian EMs into ovarian carcinoma from primary ovarian
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When dealing with the samples of ovarian EMs, one should observe the gross specimen carefully, and to note the presence of atypical hyperplasia and malignant transformation in ectopic endometrial epithelia as well as the connection or adhesion of malignant endometrial epithelia to normal ectopic epithelia under light microscope.

According to the literature, malignant epithelial tumor accounts for about 90% of ovarian EMs with malignant transformation, while sarcoma takes up 8%. Endometrial carcinoma (55.1%) and clear cell carcinoma (21.0%) account for 76% of all malignant epithelial tumors. Our results are accordant with the literature. Therefore, we speculate that malignant transformation of ovarian EMs is closely related to the development of endometrial carcinoma and clear cell carcinoma.

EMs is a sex hormone-dependent disease. When atypical hyperplasia and malignant transformation occurred, the receptors of epithelia gradually lose recognition ability for sex hormones and transform from sex hormone-dependent to sex hormone-independent characteristics. When tumor has become malignant to a certain degree, it will lose the expression of ER and PR. The synthesis of PR relies on the activity of ER. Therefore, when the synthesis of ER is reduced, it will certainly affect the production of PR and the expression of PR is possibly weaker than that of ER.

In our study, the positive rates of ER and PR were significantly lower in malignant transformation group than in control group, and the positive rate of ER was higher than that of PR, suggesting that the reduction in expression of ER and PR is possibly involved in malignant transformation of ovarian EMs. The immunohistochemical detection of ER and PR is helpful in early diagnosis of ovarian EMs with malignant transformation.

The relationships among ovarian EMs, atypical ovarian EMs and ovarian EMs with malignant transformation. Ovarian endometrial cyst is the most common presentation of ovarian EMs which is usually benign. However, ectopic endometria, like normal ones, have the potential for malignancy. Therefore, ectopic endometrial epithelia may process to atypical hyperplasia and even malignant transformation with a malignant rate of 1.1–3.0%. Atypical ovarian EMs, first introduced by LaGrenade et al. in 1988, refers to atypical or karyotypical changes in ectopic endometrial epithelia. The diagnosis standards, reported by Sampson and Scott, are as follow: (1) The Nuclei of ectopic endometrial epithelia are heavily or lightly stained,
with medium to severe degree of multiformity; (2) The ratio of nucleus to cytoplasm is increased; (3) Cells congregate showing in layers or grouped protrusions; (4) Atypical glandular structures are seen. The diagnosis is confirmed when 3 or more criteria are met. Currently, the relationship between atypical EMs and EMs with malignant transformation remains controversial. Zhang et al. had reported a high proportion (51.59%) of atypical EMs in cases of EMs with malignant transformation, suggesting a close relationship between them. Ballouk et al. had conducted a study on the relationship between them at molecular level, and discovered that severe atypical endometrial epithelia had non-ploidy DNA, while non-abnormal endometrial epithelia had diploid DNA. Non-ploidy DNA is regarded as the evidence of tumor-like proliferation. These results support at molecular level that atypical EMs may be the premalignancy of EMs with malignant transformation.

References: