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Original Article

Mitotically active cellular fibroma of ovary should be differentiated from fibrosarcoma: a case report and review of literature

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Abstract: The clinicopathologic characteristic of mitotically active cellular fibroma is significantly different from the malignant behavior of ovarian fibrosarcoma. Therefore, it's very important to differentiate mitotically active cellular fibroma from ovarian fibrosarcoma. We report a case in which a 39-year-old woman was found with an ovarian tumor measuring 105 × 71 × 47 mm. The tumor ruptured and adhered to the peritoneum. Microscopic examination showed densely cellular spindle-shaped tumor cells. The cellular atypia was mild. The Ki-67 proliferation index was approximately 10%. The patient remained free of tumor for more than 66 months without any adjuvant chemotherapy after operation. After reviewing the literature, we diagnosed this case as mitotically active cellular fibroma rather than ovarian fibrosarcoma. It is very important to differentiate these two tumors because of the marked differences in treatment modalities and prognosis between them. The ovarian fibrous tumors with mitotic figures ≥ 4 per 10 high-power fields but no severe nuclear atypia should be mostly diagnosed as mitotically active cellular fibroma of ovary. The correct diagnosis is the key to avoid excessive treatments.

Keywords: Mitotically active cellular fibroma of ovary, ovarian fibrosarcoma, ovarian fibrous tumor

Introduction

In 2003 WHO histological classification, the ovarian cellular fibrous tumors with mitotic figures less than 3 per 10 high-power fields and no severe nuclear atypia are defined as cellular fibroma, while the fibrous tumors with mitotic figures ≥ 4 per 10 high-power fields (MFs/10 HPFs) and severe nuclear atypia are defined as fibrosarcoma. However, the ovarian tumors with mitotic figures ≥ 4 MFs/10 HPFs but no severe nuclear atypia are not categorized. This kind of tumors was mostly diagnosed as ovarian fibrosarcoma. However, the clinicopathologic characteristic of this tumor is significant different from the malignant behaviors of ovarian fibrosarcoma. In 2006, Irving et al. first defined this kind of ovarian tumors as 'mitotically active cellular fibroma' [1]. We report a similar case with a long-term survival. After reviewing the literature, we prefer to diagnose this case as mitotically active cellular fibroma rather than the ovarian fibrosarcoma. The correct diagnosis is the key to avoid excessive treatments.

Case report

A 39-year-old Chinese woman was admitted to our hospital with complaints of menstruation pausing for 4 months and lower abdominal pain for 4 days. Before coming to the hospital, she took some anti-inflammatory medicine for 3 days, and the abdominal pain remained. The abdominal ultrasound examination was performed, and showed a 105 × 71 × 47 mm mixed mass in the left adnexa. After admitted, the serologic test showed an elevated CA125 (41.26 U/ml, normal range: < 35 U/ml). However, the human chorionic gonadotropin level was within normal limits. In addition, the sex hormone tests showed FSH at 6.59 mIU/ml, LH at 36.7 mIU/ml, E2 at 25.5 ng/L, Prog at 1.1 ng/L, PRL at 5.48 ng/ml, and T at 0.29 ng/ml. By laparoscopic exploration, an enlarged left ovary measuring 11 × 8 × 5 cm was found with reddish-brown surface color and a 2 cm rupture, adhered to the rear of the left latum and the uterus. There were about 100 ml bloody liquid in rectouterine fossa. The uterus, right adnexa,

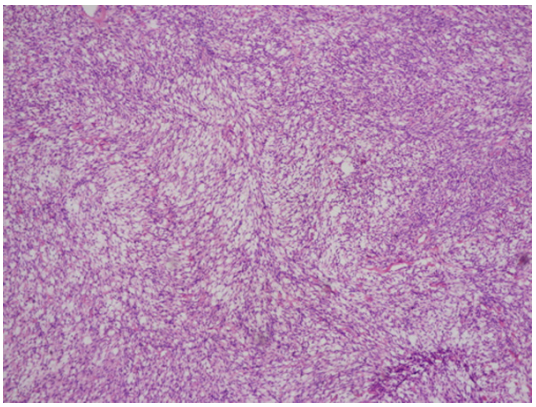

Figure 1. The tumor cells arranged in a herringbone pattern (hematoxylin-eosin, original magnification ×100).

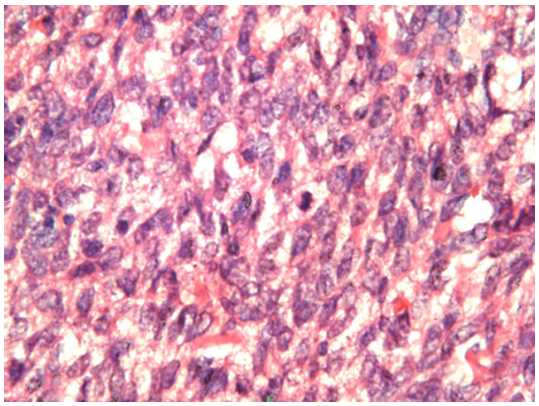

Figure 2. Short spindle-shaped tumor cells containing mitosis (hematoxylin-eosin, original magnification ×400).

left fallopian tube, and the peritoneum appeared normal. Clinical suspicion of malignancy could not be excluded. The laparotomy was performed and the left adnexa was removed. The fresh frozen-section report came back with diagnosis left ovarian malignant tumor. Therefore, total hysterectomy, right adnexectomy, appendicectomy, pelvic lymphadenectomy and omentectomy were performed.

Materials and methods

The surgical specimen was fixed in formalin, and HE slides of the tumor were prepared for histological examination. Reticulum stain was performed on selected sections of the ovarian tumor. Mitotic count was carried out on the representative sections by recording the number of mitotic figures in 50 consecutive high-power fields (HPF) and calculating the average per 10 HPF. Immunohistochemical stains were performed with a standard streets idiom-biotin-peroxidase method (Dako). Sections were stained with the following monoclonal antibodies: CD99, CK, SMA, vimentin, ER, PR, S-100, CD10, CK7, EMA, desmin and Ki-67.

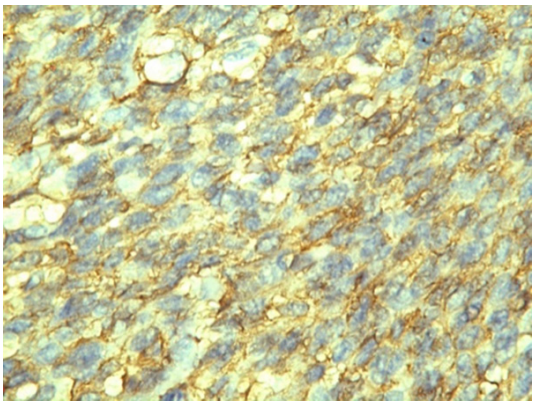

Figure 3. Immunohistochemical staining with SMA are positive (immunohistochemistry, original magnification ×400).

Pathological findings

Grossly, the left ovary measuring 10 × 7 × 4 cm is solid with a 2 cm rupture. No hemorrhage or necrosis was identified. The external surface was reddish-brown, and the cut surface was from grayish-yellow to grayish-white. The right ovary, fallopian tubes, uterus, appendix and omentum showed no pathologic change. No metastasis of lymph node was found.

Microscopically, the tumor is densely cellular and the cells are short spindle-shaped, arranged in herringbone appearance (**Figure 1**). There was mild nuclear atypia. The mitotic figures was 3 to 5 MFs/10 HPFs (**Figure 2**).

Immunohistochemically, the tumor cells are positive for CD99, CK, SMA (**Figure 3**), Vimentin, ER, PR, S-100 (**Figure 4**), and negative for CD10, CK7, EMA, Desmin. The Ki-67 proliferative index was 10% (**Figure 5**).

After surgery, the patient did not receive any adjuvant therapy. She has remained free of tumor for more than 66 months.

Discussion

Ovarian fibrosarcoma and cellular fibroma belong to ovarian fibrous tumors. The former is malignant and rare, while the later is potentially

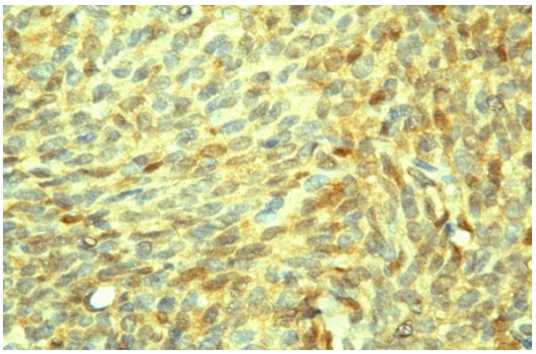

Figure 4. Immunohistochemical staining with S-100 are positive (immunohistochemistry, original magnification ×400).

malignant and relatively common. In 1981, Prat and Scully identified mitotic activity as the most important feature for distinguishing the two tumors [2]. They suggested that tumors containing mitotic figures 1-3 MFs/10 HPFs should be diagnosed as cellular fibroma, while those containing mitotic figures ≥ 4 MFs/10 HPFs should be diagnosed as fibrosarcoma. However, in 1997, Tsuji et al. reported that some cases with mitotic figures ≥ 4 MFs/10 HPFs still had a benign clinical course [3]. They also established the MIB-1 (Ki-67) labeling index and proliferative index by DNA flow cytometry as some important consideration in differentiating cellular fibroma from fibrosarcoma. The MIB-1 labeling index for cellular fibromas ranged from 0.5 to 4.0, with a median of 2.3, while that ranged from 3.0 to 10.8 with a median of 6.6 for fibrosarcomas. In its 2003 histological classification of ovarian tumors, WHO defined the tumors with mitotic figures 1 to 3 MFs/10 HPFs and no nuclear atypia as cellular fibroma, while the tumors with mitotic figures ≥ 4 MFs/10 HPFs and severe nuclear atypia as fibrosarcoma.

Early in 1998, the mitotic count as one of the diagnostic criteria of the ovarian fibrosarcoma was questionable. McCluggage et al. reported a case of metastatic fibrothecomatous tumor of the ovary, in which the mitotic figure was only 1 to 2 per 10 HPF [4]. In 2009, García Jiménez A et al. also reported an ovarian fibrous tumor metastasized to liver 14 months after surgery and adjuvant chemotherapy [5]. The giant ovarian tumor only had 1 to 2 MFs/10 HPFs mitotic count, and the nuclear atypia was mild. However, the nuclear expression for Ki 67 (MIB-1) was seen in more than 60% of total cells.

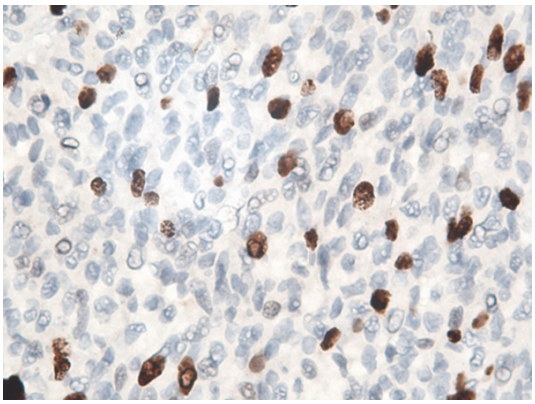

Figure 5. Immunohistochemical staining with Ki-67 (immunohistochemistry, original magnification ×400).

These two cases illustrate that mitotic activity is not an absolute indicator of malignancy in fibrous tumors. The other comprehensive factors, such as tumor size, fast growth, adhesion and high Ki-67 proliferative index may also be the indicators of aggressive behavior.

The WHO histological classification of ovarian tumors did not categorize the tumors with mitotic figure ≥ 4 MFs/10 HPFs without severe nuclear atypia. In 2006, Irving et al. reported 40 cellular fibromas of ovary with a low malignant potential, although their mitotic figures were ≥ 4 MFs/10 HPFs. However, most cells of the tumors showed only mild nuclear atypia [1]. Among them, 18 patients were clinically followed-up. These patients remained free of tumor for a mean 4.75 years (ranging from 3 mos to 12 yrs), even though 3 patients had ovarian surface adhesions or extra ovarian involvement. Therefore, they suggested that such tumors should be regarded as 'mitoticlly active cellular fibroma'. In 2007, Kaku S. et al. reported a left ovarian tumor with a mitotic figure as high as 17 MFs/10 HPFs [6]. However, the nuclear atypia was very mild, and the patient remained free of tumor after a one year follow-up. The question raised by the author was whether the tumor was a fibrosarcoma or a mitotically active cellular fibroma. In 2013, Bi R. et al. studied 11 ovarian fibrous tumors with mitotic figures ranging from 4 to 20 MFs/10 HPFs and mild to moderate nuclear atypia [7]. Ten patients with follow-up ranging from 4 to 38 months were alive with no evidence of tumor recurrence. One patient was alive for 121 months with local recurrence 94 months after

surgery. The scope of operation in most cases of this group was limited within the ovary involved. Only in 1 case the uterus was removed. This is significant different from ovarian cancer protocol performed in an overwhelming majority of ovarian fibrosarcoma. The clinicopathologic characteristics of these tumors revealed malignant potential, but were significant different from the malignant behavior of ovarian fibrosarcoma. They suggested that the ovarian fibrous tumors with mitotic figures ranging from 4 to 20 MFs/10 HPFs but no severe nuclear atypia should be defined as 'mitotically active cellular fibroma'.

According to the literature, the prognosis of ovarian fibrosarcomas is very poor [2, 8, 9]. They have higher recurrence and mortality rates. Only few cases had more than five years survival [10-13]. Most patients of the ovarian fibrosarcoma died within 2 years after the operation using an ovarian cancer protocol was performed [2, 14]. In 2005, after reviewing the literature, M. Gultekin et al. concluded that the stage of tumor is an important prognostic factor for ovarian fibrosarcoma [14]. In addition, the mitotic activety, completeness of removal of the tumor, and capsular rupture were the other prognosis factors. In 2010, Huang et al. performed a retrospective cohort study to evaluate the prognostic factors of ovarian fibrosarcoma [15]. Thirty-one cases of ovarian fibrosarcoma were retrospectively reviewed. The clinicopathologic features contained of age , symptom, FIGO stage, largest diameter, mitoses/10 HPFs , CD10, Ki-67 (MIB-1) positive, Vimentin, CD117, SMA , Desmin, EMA, S-100, CD99, CD34, a-inhibin, ER, PR, CA125, therapy, recurrence and follow-up (months). They drew the conclusions that mitotic activity and positivity for Ki-67 were important factors in the diagnosis of ovarian fibrosarcoma.

The case we report here is a 39-year-old woman with an 11 cm ovarian tumor which was ruptured and adherent to the peritoneum. After the operation, she has been free of tumor for more than 66 months with no adjuvant chemotherapy. The histopathological diagnosis of the frozen section was ovarian fibrosarcoma. However, according to the diagnostic criteria of ovarian fibrosarcoma defined by WHO in 2003, the diagnosis of fibrosarcoma in this case seems to lack of sufficient basis. Although the mitotic figure was from 3 to 5 MFs/10 HPFs, the nuclear atypia was mild. Combined with a 66 month tumor free follow-up, the benign clinicopathologic characteristics in this case indicates a diagnosis of mitotically active cellular fibroma more suitable.

Therefore, we suggest that the ovarian fibrous tumors should be further classified, especially in the cases with mitotic counts ≥ 4MFs/HPFs. Other risk factors, such as tumor size, growth speed, and high Ki-67 proliferative index should be considered. 'Mitotically active cellular fibroma' might be a more appropriate consideration for those with high mitotic activity, but without severe nuclear atypia or other risk factors. In terms of treatment, complete resection of the ovarian tumor might be necessary but enough, especially for women with fertility requirements. The adjuvant chemotherapy is not necessary even if the tumor has rupture and adhesion. Furthermore, a better understanding of the ovarian fibrous tumors will be necessary to make correct pathologic diagnosis and avoid excessive treatment, especially in young nulliparous women.

In conclusion, although the 2003 WHO histological classification set up comprehensive diagnostic criteria of ovarian fibrous tumors, more detailed and revised classification may be necessary. It is more appropriate to diagnose the ovarian fibrous tumors with high mitotic activity, but with no severe nuclear atypia or any other risk factors as 'mitotically active cellular fibroma' and perform a more conservative surgery, especially in the young nulliparous woman. The adjuvant chemotherapy is not recommended.

Disclosure of conflict of interest

None.

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