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Case Report

Concurrent tamoxifen-related Müllerian adenofibromas in uterus and ovary

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Abstract: Tamoxifen is a widely used in anti-oestrogen treatment of breast cancer. Previous reports showed that tamoxifen is associated with proliferative endometrial lesions. We herein reported an unusual case of concurrent hyperplastic lesions in the uterine cavity and right ovary in a 45-year-old woman with tamoxifen therapy. Regular vaginal ultrasonography showed the progressive endometrial thickening and right ovary enlargement during the period of drug use. Both lesions in the uterine cavity and right ovary showed characteristics resembling that of Müllerian adenofibroma. There were also foci of endometriosis in her bilateral ovarian surfaces. We suggest that women taking tamoxifen with a known history of endometriosis should be followed with transvaginal ultrasonography periodically.

Keywords: Adenofibroma, ovary, endometrium, tamoxifen, endometriosis

Introduction

Tamoxifen, one of the first generation selective estrogen receptor modulators (SERMs), has widely been applied in the first line endocrine therapy for the estrogen-dependent breast cancers [1]. Accumulating evidence has shown that tamoxifen paradoxically acts as a partial estrogen agonist on the endometrium, and thus increase the incidence of proliferative endometrial lesions, including polyps, hyperplasia, and endometrial cancer, etc. [2-5]. It has also been suggested that tamoxifen treatment may result in similar changes in extrauterine endometrial tissue [6-10]. But concurrent tamoxifen-related proliferative lesions in multiple organs were exceedingly rare in English literature. We here reported such an unusual case of proliferative disorders resembling Müllerian adenofibroma in both the endometrium and the right ovary in a menopausal woman taking tamoxifen.

Case report

A 45-year-old woman, who had been receiving tamoxifen therapy for more than two years after surgery for her breast cancer, was admitted due to synchronous lesions in her uterine cavity and right ovary. Otherwise, there was no evidence of cancer relapse or metastasis throughout her body.

The patient had a history of modified radical mastectomy for her right breast cancer 26 months ago. She recovered well from her surgery. The final pathological reports showed a grade II invasive ductal carcinoma (T2N0M0) with both strong positive estrogen and progesterone receptors. The patient thus took tamoxifen 20 mg, twice a day for 18 months. She began to use toremifen 60 mg daily six months ago because of the abnormal findings in her uterine cavity and right ovary. At the beginning of tamoxifen therapy, irregular menstruation existed and one-year later amenorrhea occurred.

During tamoxifen treatment, she was followed-up with vaginal ultrasonography every three months to detect the potential endometrial proliferative lesions. Ultrasonography demonstrated the irregular endometrial thickening in the period of 10 months with tamoxifen administra-

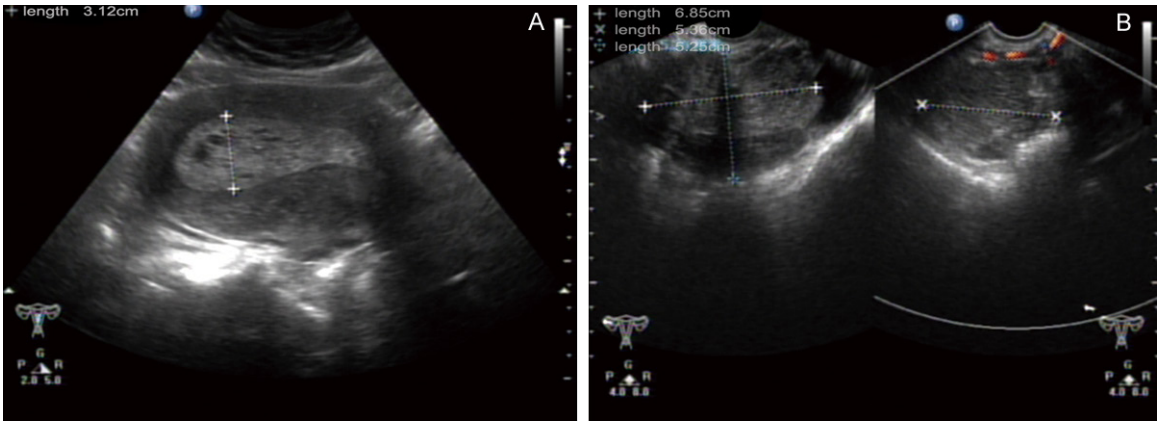

Figure 1. Ultrasonographic images of two lesions in the uterine cavity (A) and the right ovary (B). Both lesions showed honeycomb-like echo and the absence of Doppler flow.

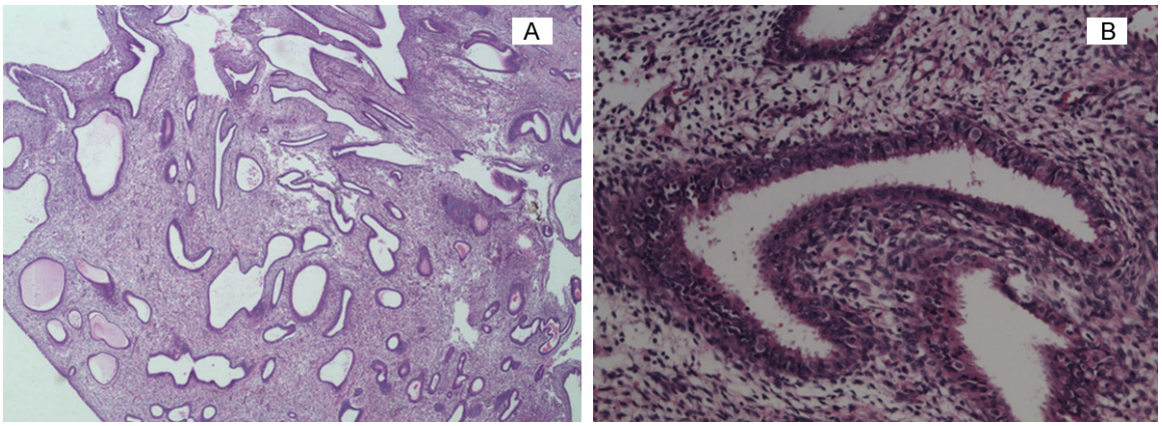

Figure 2. Adenofirbromatous disorder in the unterine cavity. A: Showed that endometrial glands disseminated in the cellular fibrous stroma. B: The endometrioid glandular epithelium, presented with apical secretion. The periglandular endometrioid stroma was mild edematous with prominent small vessels.

tion, and a 2.2×2.2×2.0-cm hyper-echoic mass in the uterus cavity, and a cystic enlargement of right ovary about 5.4×3.7×2.8 cm subsequently during the next 9 months of tamoxifen. Both lesions in the uterine cavity and ovary enlarged slowly as indicated by the regular ultrasonography detection. The last ultrasonography before this admission showed that the mass in the uterine cavity increased up to 7.5×5.4×3.1 cm and that in the right ovary to 6.9×5.4×5.3 cm (**Figure 1**). Both lesions had an appearance of honeycomb-like echo lacking of Doppler (blood) flow.

The endometrial curettings showed simply hyperplasia of the endometrium. The patient was treated with total hysterectomy and bilateral salpingo-oophorectomy. Ten months after surgery, she was well without evidence of recurrence.

Pathologic findings

Grossly, there was a polypoid mass measured 6.5×5×4 cm with a 1.5 cm wide stalk in the uterine cavity. The mass displayed a smooth external surface. The sectioned surface had a grey-white, honeycomb appearance with multiple microcysts. The texture was moderate. The right ovary had a size of 6.5×5×5 cm and showed a similar gross feature to the intracavitary mass except a softer texture. Adenomyosis and a leiomyoma coexisted in the uterus. The uterine cervix, left ovary and bilateral fallopian tubes looked normal.

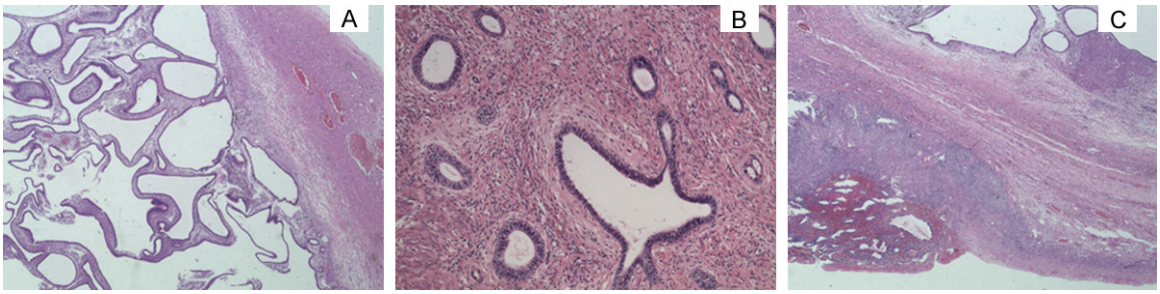

Figure 3. Adenofirbromatous disorder in the right ovary. The lesion in the ovary had the consistent features as that in the uterine cavity (A). The stromal cells lacked nuclear atypia and mitoses in keeping with the benign behavior (B). (C) Showed the endometriosis at surface of the ovary.

Histologically, both lesions in the uterine cavity and the right ovary showed consistent features in keeping with endometrioid adenofibroma (**Figures 2**, **3**). Glands or cysts with different volumes were distributed in the fibrous stromal background. The glands or cysts were lined by endometrial type cells and occasional ciliated cell or eosinophilic metaplasia. The stroma was mildly edematous. Most stromal cells were non-specific fibroblastic, and a small portion of endometrial stromal cells was present rounding the endometrial glands. Small blood vessels were prominent. Epithelial and stromal atypia were absent. Periglandular cuffing was inconspicous. Local stromal cellularity was detected, but stromal mitoses were rare, with a mitotic count of <1 mitosis per 10 high power fields. Immunostaining showed that most of epithelial and stromal cells were positive for estrogen receptor and progesterone receptor, and negative for P53 and CA125. The ki67 index was less than 5% in both epithelial and stromal cells.

Adenomyosis and leiomyoma of the uterus were typical. Local endometrioses were detected in the surface of bilateral ovaries (**Figure 3C**). No abnormalities were seen in the cervix and bilateral fallopian tubes.

Discussion

A number of reports have described unusual-appearing endometrial polyps in up to 25% of patients undergoing long term tamoxifen treatment [11]. Thus, the term, tamoxifen-related lesions, was introduced in the 2003 WHO classification of tumors of female genital organs. Malignant transformation occurs in up to 3% of cases, and endometrial carcinoma is most common. There were also a few reports of extrauterine lesions that were associated with tamoxifen therapy [6-10, 12-14]. The ovaries are the most common sites out of the uterus. Various lesions were reported in the ovary including endometriosis, cystadenoma, endometrioid adencarcinoma and carcinosarcomas. Ovarian adenofibroma under tamoxifen therapy is extremely rare. We have only found one case in the English literature By McCluggage WG et al [9]. However, the major concern of that study was to describe an endometrioid adenocarcinoma arising in ovarian endometriosis in a patient taking tamoxifen, and the endometrioid adenofibromatous foci was very limited. In addition, the current case had a concurrent lesion in the uterine cavity. To our knowledge, our case might be the first one of multiple Müllerian adenofibromas in endometrium and ovary upon tamoxifen therapy.

Müllerian adenofibroma is a rare biphasic neoplasm composed of benign epithelial and mesenchymal components. It is very important, but sometimes difficult, to distinguish Müllerian adenofibromas from adenosarcomas, because they share common features of macroscopy, histopathology and immunoprofile. The fact that most adenofibromas, which were initially diagnosed, were proved to be adenosarcomas, thus raised the suspect on the presence of adenofibroma as a real entity [15]. The differential diagnosis mainly based on nuclear atypia, cellularity and mitotic figures of the stromal component. A stromal mitotic count of >1 mitosis per 10 high power fields, marked stromal hypercellularity with periglandular cuffing and/or more than mild stromal atypia ensured a diagnosis of low grade adenosarcoma. Immunostaining of p53 CD10, CA125, ER and

PR did not contribute to the differential diagnosis [15]. According to the above criteria of adenosarcomas, both lesions in the endometrium and ovary in our case was consistent with the diagnosis of Müllerian adenofibromas although long-term follow-up was necessary

Previous reports had described a spectrum of tamoxifen-related lesions comprising of epithelial metaplasias, simple and complex hyperplasias, polypoid lesions, and endometrioid carcinomas [6, 7, 9, 10]. Okugawa K and colleagues [7] reported an tamoxifen-associated endometrioid adenocarcinoma arising in an ovarian endometrial cyst with a gradual transfromation from normal-looking endometrial epithelium, atypical endometriosis, to adenocarcinoma. These reports suggested that tamoxifen may cause proliferative and, in rare instances, malignant changes in endometriosis as a result of its estrogenic effects. The present case had endometriosis lesions in bilateral ovarian surface. We postulated that the adenofibroma in the right ovary might arise from the original endometriosis although we failed to observe the presence of a transitional zone between the tumor and endometriosis. In turn, tamoxifen can also increase the risk of endometriosis [4]. Tamoxifen have been used for ovulation induction to reserve the fertility in patients with breast cancer. This fact implied the direct effects of tamoxifen on ovarian function [16, 17]. Thus, it was impossible to draw the conclusion that the ovarian neoplasm mentioned here was resulted from the unantagonized estrogen stimulation of tamoxifen on preexisting or secondary endometriosis, or simply, the direct role of tamoxifen on ovarian tissue.

In addition, the regular ultrasonography in our case showed the continuous, gradual alterations in endometrium and ovaries with the extension of drug use. The graphic spectrum clearly indicated a potential link between the lesions and tamoxifen use.

In conclusion, we describe a rare case of concurrent hyperplastic lesions in the uterine cavity and right ovary accompanied with endometriosis in a patient received tamoxifen therapy. Although it is uncertain that the ovarian neoplasm originated from endometriosis, it is advisable that women undergoing long term tamoxifen treatment, especially who have a known history of endometriosis, should be followed with vaginal ultrasonography periodically.

Disclosure of conflict of interest

None.

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