Recurrent Postmenopausal Bleeding: Just Endometrial Disease or Ovarian Sex Cord Stromal Tumor? A Case Report and Literature Review

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Case report

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Abstract

**Background:** Postmenopausal bleeding (PMB) is a common gynecologic complaint among elderly women, and endometrial hyperplasia is a common cause of this bleeding. Ovarian fibromas are the most common ovarian sex cord stromal tumors (SCST). They arise from non-functioning stroma, rarely show estrogenic activity, and stimulate endometrial hyperplasia, leading to abnormal vaginal bleeding.

**Case presentation:** We report herein the case of a 64-year-old Chinese woman who presented with recurrent PMB. A sex-hormone test revealed her estrogen level was significantly higher than normal, and other causes of hyperestrogenism had been excluded. In the past 7 years, the patient had undergone four curettage-and-hysteroscopy procedures due to recurrent PMB and endometrial hyperplasia. Finally, the culprit behind the rise in estrogen – an ovarian cellular fibroma with estrogenic activity – was found in the fifth operation.

**Conclusions:** Ovarian cellular fibromas occur insidiously, and some may have endocrine functions. For postmenopausal patients with recurrent PMB and endometrial thickening indicated by ultrasonography, it is recommended they undergo sex-hormone testing while waiting for results regarding the pathology of the endometrium. If the estrogen level remains elevated, even if the imaging does not indicate an ovarian tumor, the clinician should consider the possibility of an ovarian SCST and follow the patient closely. Once the tumor is found, no matter the size, it should be removed as soon as possible to avoid endometrial lesions caused by long-term estrogen stimulation. More studies are needed to confirm whether preventive total hysterectomy with bilateral salpingo-oophorectomy should be recommended for postmenopausal women with recurrent bleeding whose estrogen levels are higher than normal, even when the auxiliary examination does not indicate ovarian mass. It is possible this could avoid the physical and psychological burden caused by repeated curettage.

**Background**

Postmenopausal bleeding (PMB) is a common gynecologic complaint encountered in the clinical setting. Inflammation and benign or malignant tumors of the reproductive organs can cause PMB. The keys to diagnosis and treatment are accurately determining the etiology and preventing and treating malignant diseases. Correct identification of the etiology aids in defining the treatment plan and facilitates early patient recovery.

We report herein the case of a postmenopausal woman who had undergone repeated curettage and hysteroscopy due to recurrent PMB and endometrial hyperplasia. Sex-hormone testing revealed her estrogen levels were consistently higher than normal. However, the imaging examinations performed as part of her first four operations did not reveal an ovarian mass. Finally, an ovarian cellular fibroma with endocrine function was found during the fifth operation, and the relevant literature was reviewed. This case is significant because it demonstrates the necessity of considering the rare possibility of ovarian cellular fibromas as a precursor for PMB.
Case Presentation

A 64-year-old female patient presented in May 2020 after “postmenopausal vaginal bleeding for one year.” The patient had experienced menopause at the age of 53, her body mass index was 18.75, she reported no risk factors for endometrial cancer such as obesity, diabetes, hypertension, genetic diseases, she had no history of hormone drug use, and her adrenal glands were normal in size. She had one pregnancy and had delivered once.

In June 2013, 4 years after menopause, the patient had irregular vaginal bleeding without obvious cause. Transvaginal ultrasonography (TVUS) showed the endometrium was thickened, about 1.5 cm, and diagnostic curettage was performed. The pathological results suggested simple endometrial hyperplasia.

In May 2014, diagnostic curettage was performed again due to irregular vaginal bleeding, and the pathological results suggested endometrial hyperplasia disorder. The first two curettage procedures were performed at another hospital.

In June 2016, irregular vaginal bleeding occurred again. Gynecological examination showed the cervix was a normal size, the uterus was enlarged and the shape was irregular, and there were no abnormalities in the accessory area of either side. TVUS showed the size of the uterus was about 9.0 × 6.1 × 6.0 cm, the endometrium was thickened, about 1.9 cm, and the echo was uneven. There were several hypoechoic masses in the uterine area; the larger one was in the lower part of the front wall, about 2.2 × 2.1 × 1.9 cm, and the boundary was clear. The size of the left ovary was about 2.1 × 1.4 cm, and the size of the right ovary was 2.0 × 1.2 cm. There was no obvious mass in the double accessory area. Further hysteroscopy showed that the endometrium of the posterior wall of the uterus was focally thickened, and multiple polypoid lesions were seen in the uterine cavity; the larger one was about 1.5 × 1.0 cm, soft and pink with a smooth surface, and the cervical mucosa was smooth. The sex-hormone test revealed the following: estradiol (E2): 63 pg/mL (normal range: <20–40 pg/mL), human follicle stimulating hormone (hFSH): 29.01mIU/mL (normal range: 16.24-113.59mIU/mL), human luteinizing hormone (hLH): 26.54mIU/mL (normal range: 10.87-58.64mIU/mL), progesterone (Prog): 0.33 ng/mL (normal range: 0.01–0.78 ng/mL), testosterone (Testo): 0.46 ng/mL (normal range: <0.1–0.75 ng/mL). Hysteroscopic endometrial polypectomy was performed on June 27, 2016, and the pathological results revealed endometrial polyps with secretory changes. The bleeding disappeared after the operation.

In June 2019, vaginal bleeding returned and lasted intermittently for nearly 1 year. In May 2020, the patient presented to a doctor for a gynecological examination. The cervix was normal in size with a smooth surface and no cervical atrophy, the uterus was enlarged and irregular, and no abnormalities were observed in the double accessory area. TVUS (Fig. 1A) showed the uterus to be about 8.2 × 6.3 × 5.7 cm, and the endometrium was about 2.0 cm. There were several hypoechoic masses in the uterine area. A large one (3.6 × 3.4 × 2.7 cm) was in the isthmus of the anterior wall, with a clear boundary. The size of the left ovary was about 2.1 × 1.7 × 1.0 cm, and the size of the right ovary was about 1.9 × 1.3 × 1.2 cm. There was no obvious mass in the double accessory area. The results of tumor markers were normal. Hysteroscopy (Fig. 1B) showed the endometrium was extensively thickened, and the cervical mucosa was
smooth. Part of the endometrium was scraped and sent to pathology, the results indicated endometrial complex hyperplasia. Pelvic magnetic resonance imaging (MRI) (Figs. 1C, D) showed the uterus was enlarged, the endometrium was thickened (about 1.6 cm), and the signal in the right corner of the uterine cavity was not uniform. The patient’s sex hormones were rechecked June 19, 2020; the results suggested the following: E2: 124 pg/mL, hFSH: 33.31mIU/mL, hLH: 26.97mIU/mL, Prog: 1.04 ng/mL, Testo: 1.10 ng/mL. Full-scale curettage under hysteroscopy was performed June 23, 2020. During the operation, the uterine cavity was found to be irregular, the endometrium was diffusely thickened, local polypoid changes were observed. The pathological results indicated endometrial complex hyperplasia, but could not exclude mild atypical hyperplasia.

As atypical hyperplasia of the endometrium was not excluded and considering the patient’s age and operation history, we decided to perform laparoscopic hysterectomy and bilateral salpingo-oophorectomy. TVUS was performed again before the operation (Fig. 2A, B). The uterus was about 8.0 × 6.4 × 5.5 cm, and the thickness of the endometrium was about 0.6 cm. There were several hypoechoic masses in the uterine area. The right ovary was about 2.2 × 1.7 × 1.5 cm, and a 1.6 × 1.2 × 1.2 cm mass was observed inside; it had clear borders and was hypoechoic inside. Blood-flow signals were detected with color Doppler flow imaging (CDFI). The left ovary was unclear. A further abdominal computed tomography (CT) scan (Fig. 2C) showed a low-density nodule of about 1.5 × 1.0 cm in the right ovary, with clear borders. Laparoscopic hysterectomy and double salpingo-oophorectomy were performed July 10, 2020. During the operation, we observed that the uterus was obviously large and irregular, with multiple fibroid nodules. On the surface of the right ovary, there was a yellow protruding lesion of about 1 cm (Fig. 2D). The whole uterus and double appendages were removed through the vagina and sent to pathology. As seen under a microscope, the tumor cells of the right ovarian lesion were spindle-shaped and bundle-like with sheet-like arrangement, and the cells were densely arranged without obvious atypia. Eosinophilic cell nests with rich cytoplasm could be seen in the focal area (Fig. 3A). Endometrial glandular hyperplasia, densely arranged, part of the glandular cavity irregular (Fig. 3B). Immunohistochemistry revealed: cytokeratin (focal +, Fig. 3C); inhibin (part +, Fig. 3D); Wilm's tumor protein (WT1, part +, Fig. 3E); calretinin (+, Fig. 3F); Ki-67 (about 10% +, Fig. 3G); net staining showed mostly surrounding single cells (Fig. 3H). Pathological diagnosis was right ovarian cellular fibroma with hilar cell hyperplasia, focal complex endometrial hyperplasia, multiple leiomyomas of the uterus, and chronic cervicitis, the left adnexa and right fallopian tube were normal. The patient recovered well after the operation. Sex hormones the first day after the operation were E2: 22 pg/mL and testo:0.73 ng/mL; the second day, they were E2: <20 pg/mL and testo:0.30 ng/mL. The patient was discharged on the 5th postoperative day, 2 and 5 months after the operation, there was no abnormality discovered in the outpatient review.

**Discussion**

PMB, defined as uterine bleeding occurring after at least 12 months of amenorrhea, is mainly caused by intrauterine sources, and a few cases are related to ovarian tumors. Clarke et al. found that, among 593 women with PMB, 18 (3.0%) had endometrial intraepithelial neoplasia (EIN), and 47 (7.9%) had endometrial cancer (EC). Women with recurrent PMB had higher risks of EIN and EC [1]. Endometrial
hyperplasia, usually caused by the continuous action of estrogen on the endometrium, is regarded as a precursor to EC. Hysteroscopy is now considered the gold standard for diagnosing and managing intrauterine lesions [2]. TVUS of postmenopausal women with endometrial thickness > 4 mm requires additional endometrial sampling for evaluation. For women with PMB, a negative tissue biopsy after a “blind” sampling of the endometrium is not considered the end point [3].

Under long-term estrogen stimulation, the endometrium gradually escalates from simple hyperplasia to complex hyperplasia and atypical hyperplasia. If not treated in time, it may develop into EC. The present case demonstrates the rare possibility of ovarian cellular fibroma as a precursor for estrogen excess leading to endometrial hyperplasia and PMB.

Ovarian fibromas are the most common mesenchymal tumors of the ovary, accounting for 4% of all ovarian tumors [4]. They occur mainly in perimenopausal and postmenopausal women. The most common clinical manifestation of ovarian fibromas is an ovarian mass, sometimes accompanied by pleural effusion and ascites. About 10% of ovarian fibromas are cellular fibromas and the average age is 51 years [5], clinical manifestations are benign, occasionally local recurrence, with low malignant potential. It usually presents as an ovarian mass, which may be accompanied by hemorrhage, edema, and cystic degeneration. Cystic degeneration usually forms a single cyst; in rare cases, it may be polycystic [6].

Unlike granular or theca cell tumors, ovarian fibromas rarely exhibit estrogenic activity. Chechia et al. retrospectively analyzed 24 cases of ovarian fibroma and fibrothecomas, which have no endocrine activity [4]. Haroon et al. retrospectively analyzed 480 cases of ovarian SCST, including 98 cases of ovarian fibroma; one case was associated with EC and one with endometrial hyperplasia, proving that these tumors have hormonal activity [7]. Identifying whether ovarian fibromas have other concomitant components and/or hormonal activity helps explain various clinical characteristics and histopathological findings. Our case was accompanied by hilar cell hyperplasia, which has the function of secreting androgen. The levels of estrogen and androgen were significantly higher than normal and dropped to the normal range the first day after surgery; estrogen may be directly secreted by tumors and/or transformed by androgens.

As most ovarian fibromas are solid tumors, they are easily misdiagnosed as uterine fibroids. In the present case, TVUS finally revealed an ovarian hypoechoic mass before the fifth operation. The ovarian mass should have existed at the time of the fourth operation, but it was not reported by ultrasound and imaging doctors. It was likely mistaken for a uterine fibroid, as the patient also had several. Ovarian cellular fibroma is diagnosed by postoperative pathology. Its pathological characteristics include microscopically, and the tumor cells are fusiform, dense, without obvious nuclear atypia, 0–3 mitoses/10 high-power fields (HPFs), and arranged in bundles, which may contain a small amount of sex cord components (partly with luteinized cells). It is surrounded by reticular fibers. Immunohistochemistry can show Inhibin-α, calretinin, estrogen receptor, progesterone receptor, etc. to varying degrees. The tumor immunohistochemistry in this case was consistent with those reported in the literature. Ovarian cellular
fibroma is also easily misdiagnosed as ovarian malignant tumor, especially when it occurs in both ovaries or is accompanied by pleural effusion, ascites, or elevated CA125.

Surgery is the treatment for ovarian fibromas. Laparoscopy facilitated shorter operation times than laparotomy, with no significant differences in perioperative complications [8]. It is recommended that perimenopausal or postmenopausal patients with ovarian cellular fibromas undergo total uterine and bilateral salpingo-ovarian resection with long-term follow-up. In our case, the patient had recurrent vaginal bleeding 4 years ago, and estrogen level was higher than normal, although auxiliary examinations did not indicate ovarian mass, should we recommend the patient undergo prophylactic removal of the whole uterus and both fallopian tubes and ovaries to avoid subsequent vaginal bleeding and surgery?

**Conclusion**

PMB should never be ignored. The ideal sequence of investigation for a patient with PMB remains controversial [9]. Ovarian cellular fibroma occurs insidiously and may have hormonal activity. Excessive or long-term serum estrogen stimulation of the endometrium may lead to endometrial hyperplasia, or even cancer, and cause symptoms such as PMB. Therefore, early diagnosis, determining a clear cause, and timely treatment are essential. For patients with recurrent PMB and endometrial thickening, sex hormone testing is recommended. If the level of estrogen remains higher even if imaging does not indicate an exact ovarian tumor, clinicians should first consider whether it may be associated with ovarian SCST. Once ovarian masses are found, regardless of size, they should be removed as soon as possible to avoid endometrial lesions. Further study is required to determine whether preventive removal of the whole uterus and bilateral fallopian tubes and ovaries should be recommended to women with high levels of estrogen, repeated bleeding after menopause, and auxiliary examinations that do not reveal ovarian masses; it may avoid multiple subsequent curettage procedures, which are associated with physical and psychological burdens.

**Abbreviations**

PMB: Postmenopausal bleeding; SCST: Sex cord stromal tumors; TVUS: Transvaginal ultrasonography; E2: Estradiol; hFSH: Human follicle stimulating hormone; hLH: Human luteinizing hormone; Prog: Progesterone; Testo: Testosterone; MRI: Magnetic resonance imaging; CDFI: Color Doppler flow imaging; CT: Computed tomography; WT1: Wilm's tumor protein; EIN: Endometrial intraepithelial neoplasia; EC: Endometrial cancer; HPFs: High-power fields

**Declarations**

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Not applicable.

**Authors’ contributions**
Jiao Wang was responsible for the data collection and drafting of the manuscript. Qing Yang carried out the study and is the surgeon of the patient. Ningning Zhang participated in providing knowledge of the disease etiology. Dandan Wang was responsible for critical revision of the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The data obtained during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This paper was approved by the Ethics Committee of the institutional review board (IRB) of Shengjing Hospital of China Medical University. and a signed informed consent has been obtained from the patient.

**Consent for publication**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

**Competing interests**

The authors declare that they have no competing interests.

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Figure 1

(A) TVUS: the endometrium was thickened, about 2.0cm. There were several hypoechoic masses in the uterine area. There was no obvious space-occupying lesion in the double accessory area; (B) Hysteroscopy: the endometrium was extensively thickened, the texture was fragile; (C, D) Pelvic MR: the endometrium was thickened, about 1.6cm, and the signal in the right corner of the uterine cavity was not uniform.
Figure 3

Histopathological and immunohistochemical staining findings. (A) The tumor cells of the right ovarian lesion were spindle-shaped and bundle-like with sheet-like arrangement, and the cells were densely arranged without obvious atypia. Eosinophilic cell nests with rich cytoplasm could be seen in the focal area. (B) Endometrial glandular hyperplasia, densely arranged, part of the glandular cavity irregular. (C)
Cytokeratin (focal +); (D) Inhibin (part +); (E) Wilm's tumor protein (WT1, part +); (F) Calretinin (+); (G) Ki-67 (about 10% +); (H) Net staining showed mostly surrounding single cells.