Case Report

Unusual Massive Endometrial Hyperplasia: Initial Presentation with a Small Ovarian Granulosa Cell Tumor

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ABSTRACT: Ovarian granulosa cell tumors (OGCTs) vary greatly in size, with an average diameter of approximately 10 cm. OGCTs often cause diverse estrogen-related symptoms and are sometimes accompanied by complications related to endometrial pathology. Nevertheless, endometrial hyperplasia with an OGCT does not generally present with tumor-like masses in the uterine cavity. We encountered a unique case: A 77-year-old woman presented a small OGCT complicated by massive endometrial hyperplasia that resembled a malignant uterine tumor. Initially, we diagnosed the mass as a malignant uterine tumor with ovarian metastasis. However, the final diagnosis was OGCT and endometrial hyperplasia. Sex cord stromal tumors of the ovary should be considered if a malignant uterine tumor is the most likely suspected cause of tumor-like endometrial pathology and if the presentation involves even a small ovarian tumor.

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KEYWORDS: deep venous thrombosis, endometrial hyperplasia, estradiol, granulosa cell tumor

Introduction

Ovarian granulosa cell tumors (OGCTs) are a relatively rare tumor type with an estimated prevalence of 1.5% of all ovarian tumors.[1, 2)] OGCTs vary greatly in size but have an average diameter of approximately 10 cm.[1)] OGCTs manifest with diverse estrogen-related symptoms, including variations of endometrial pathology such as hyperplasia or carcinoma,[3)] breast cancer,[4)] and deep venous thrombosis in instances of large ovarian tumors.[5)] Endometrial hyperplasia is often detected before surgery[6)] but typically does not form uterine tumor-like masses. We encountered a patient who presented a small granulosa cell tumor with endometrial hyperplasia; this presentation was similar to that of a malignant uterine tumor. The patient also had deep venous thrombosis.

Case Summary

A 77-year-old woman, who had three times of pregnancy and two times of delivery, was examined at a local gynecology clinic with a chief complaint of irregular uterine bleeding for 7 years. The patient experienced menarche at age 15 and menopause at age 56. Her body mass index was 24 kg/m^2. She had no relevant medical history and did not use hormonal therapy or medications. Endometrial thickening was detected on transvaginal ultrasonography, and a complete blood count revealed severe anemia with a hemoglobin level of 5.6 g/dl. A malignant uterine tumor was suspected and she was referred to our hospital.

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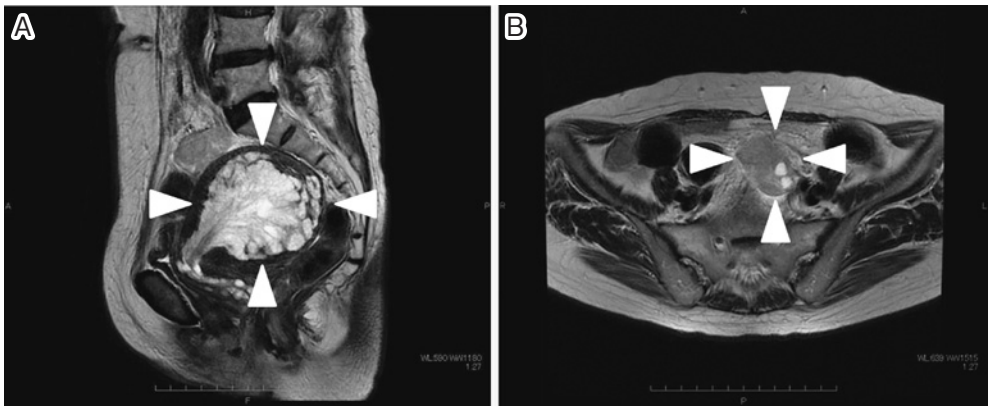

Fig. 1 T2-weighted magnetic resonance images of the pelvis.
(A) Sagittal image showing a multilobular tumor lesion with a mixture of low- and high-intensity areas in the uterine cavity (arrows).
(B) Axial image showing the low-intensity solid ovarian tumor with multiple small cysts (arrows).

The uterine cervix and endometrium cytology results were negative. Transvaginal ultrasonography revealed markedly thickened endometrium with a thickness of 66 mm, and an endometrial biopsy showed atypical hyperplasia.

Magnetic resonance imaging of the pelvic cavity revealed a 9.8 × 8.5 cm multilobular fan-shaped lesion in the uterus with a mixture of low- and high-intensity areas on T2-weighted imaging (T2WI), and the junctional zone was not detected (Fig. 1A). T2WI also showed a hypointense 4 × 3 cm solid left ovarian tumor with a cystic component (Fig. 1B). A contrast-enhanced computed tomography scan of the abdomen was performed, but no distal or lymphatic metastasis was detected. The serum CA-125 (Carbohydrate Antigen 125) levels were 144 U/ml (upper limit of normal, 35 U/ml) and the estradiol levels were 20 pg/ml (average estradiol level for normal post-menopausal women, 15 pg/ml).[7] Deep venous thrombosis in the right soleus vein was detected by Doppler ultrasonography, which was performed as a routine preoperative examination, and 1000 U/day of low-molecular weight heparin was administered as an anticoagulant regimen until 6 hours before surgery.

The most likely preoperative diagnosis was primary malignant uterine tumor with ovarian metastasis, and the patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic and paraaortic lymph node sampling. The uterus was enlarged to 14 × 8 cm, and a 4 × 3 cm solid tumor was present in the left ovary. No remarkable changes were observed in the right fallopian tube and ovary. A small amount of ascites was detected. Examination of the surgical specimen showed that the uterine cavity was filled with a soft hydropic tumor (Fig. 2A). The cut surface of the left ovarian tumor was solid, tan-yellow in color, and exhibited an irregular cystic appearance (Fig. 2B). An intraoperative frozen section of the uterine tumor revealed endometrial hyperplasia, and the ovarian tumor was diagnosed as a sex cord stromal tumor.

Microscopic findings from the formalin-fixed paraffin-embedded tissue block sections revealed eosinophilic cytoplasm and oval to round nuclei in the tumor. The presence of a nuclear groove, which manifests as a typical coffee bean appearance, and diffuse uniform tumor cell proliferation were confirmed. Call-Exner bodies were not detected, and neither necrosis nor mitosis was observed. A small number of theca cells was present. In view of these findings, the histopathological diagnosis of the left ovary mass was adult granulosa cell tumor (Fig. 3A). The endometrial pathology showed an irregular luminal structure, scant stromal lesions, and no ductal adhesion. Cellular atypia of the endometrium was observed; this included nucleolar enlargement and round to oval nuclei with coarse chromatin (Fig. 3B).

The immunohistochemical staining of the endometrium was positive for estrogen receptors and progesterone receptors. Overall, the endometrial pathology indicated atypical, complex endometrial hyperplasia. The cytological analysis of the ascites was negative.

The final diagnosis was adult granulosa cell tumor of the

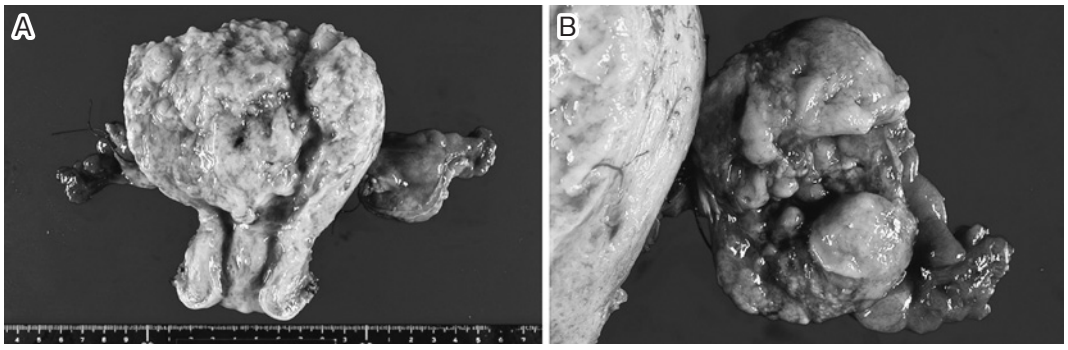

Fig. 2 Surgical specimen of the uterus and bilateral adnexa.
(A) The uterine cavity was filled with hydropic soft tumor.
(B) The left ovary contained a solid and partially cystic tumor of 4 cm in diameter and colored tan-yellow on the cut surface.

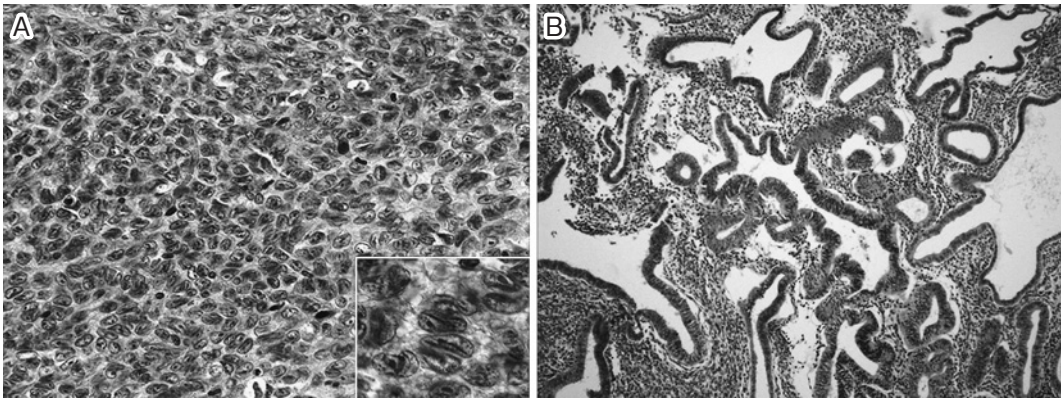

Fig. 3 Histological features of the endometrium and left ovarian tumor.
(A) The ovarian tumor showed eosinophilic cytoplasm and oval to round nuclei (hematoxylin and eosin staining, 200×). The nuclear groove was confirmed (400×, small inset).
(B) Irregular luminal structure and cellular atypia of the endometrium was observed as nucleolar enlargement and round to oval nuclei with coarse chromatin (hematoxylin and eosin staining, 40×).

left ovary, International Federation of Gynecology and Obstetrics Stage I A, with atypical endometrial hyperplasia.

Deep venous thrombosis was not observed on ultrasonography performed on postoperative day 8. The estradiol levels soon declined to below the limit of detection after surgery. The patient is alive without any evidence of disease at 2 years after surgery.

Discussion

Granulosa cell tumors account for 1.5% of all ovarian tumors. They belong to the category of borderline and sex cord stromal tumors,[2] and 70% of OGCT (Ovarian granulosa cell tumor) s produce estradiol.[8] OGCTs occur in adults in 95% of cases, with juvenile granulosa cell tumors accounting for the remaining 5%.[2] The distribution of the age of onset peaks at 50-55 years old[9] for adult granulosa cell tumors and at approximately 10 years for juvenile OGCTs.[10] The most frequent symptoms are uterine bleeding, irregular menses, and amenorrhea.[11] In this case, irregular menstruation-like periodic bleeding occurred, which the patient believed to be a re-initiated menstrual cycle. The patient also had not undergone a gynecological examination for 7 years. A preoperative diagnosis of granulosa cell tumors is difficult because of atypical clinical manifestations.

A 25% incidence of endometrial hyperplasia and a 5.9% incidence of endometrial carcinoma[3] are associated with elevated serum estradiol levels in OGCT cases.

Such tumors are often diagnosed as type 1 tumors arising from endometrial hyperplasia due to exposure to ele-

vated estradiol levels.[3] Therefore, endometrial carcinoma with OGCTs is often low-grade and diagnosed at an early stage.[12] Endometrial pathology was found in patients over 40 years of age in previous studies, and its frequency was significantly higher when genital bleeding was present.[8] Endometrial thickening to 66 mm is the most severe case of hypertrophy ever reported. A previous case report describes an OGCT with delayed menopause in a 64-year-old patient who experienced irregular bleeding for 10 years. This patient had simple endometrial hyperplasia with an endometrial thickness of 8 mm.[13]

No known relationship exists among the size, stage or prognosis of ovarian tumors, and estrogen levels,[8] although some reports suggest that smaller tumors are more biologically active.[14] OGCTs vary in size, with a mean tumor size of 11.8 cm.[11] In the present case, the ovarian tumor was relatively small. The estrogen level in this case was 20 pg/ml, which is relatively high for a menopausal woman; because estrogen levels declined rapidly after surgery, this value could be useful for the management of such tumors. Although the estradiol level is not a standard marker, it can be used to monitor postoperative recurrence.[8]

Only one case of OGCT with deep venous thrombosis has been reported. This case involved a large OGCT of 26 cm in diameter and weighing 6.4 kg.[5] Deep venous thrombosis is often a complication of large ovarian tumors but is rare in patients with small ovarian tumors. In this case, the ovarian tumor was 4 cm in diameter, which normally would have a small compression effect, but smooth muscle relaxation of vessels and hypercoagulation can occur with elevated estradiol levels.[10] This is the first reported case of deep venous thrombosis concomitant with a small OGCT.

The primary treatment for OGCTs is surgery, which provides accurate information on the initial extent of disease.[11] Radical surgery improves the prognosis of patients with OGCT,[2] but conservative surgery can be considered if the patient desires to maintain fertility. When preservation of the uterus is a concern, a precise evaluation of the endometrium must be performed preoperatively. The prognosis is significantly associated with the tumor stage followed by the amount of residual tumor.[11] This case involved a Stage I A tumor, and the prognosis was favorable. However, in cases of delayed OGCT recurrence, long-term follow-up is needed.[10]

We encountered a case of a small OGCT complicated with atypical endometrial hyperplasia, which presented as an unusual tumor of the uterus with saliently thickened endometrium and deep venous thrombosis. Both symptoms are believed to be associated with estradiol produced by the OGCT. When remarkable endometrial hyperplasia is associated with even a small ovarian tumor, the existence of an estradiol-secreting tumor of the ovary should be considered. Therefore, an adequate pretreatment evaluation including serum hormone levels and concomitant examination for deep venous thrombosis is mandatory.

Conflicts of interest: None declared.

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