Synchronous serous carcinoma arising in adenomyosis and small cell carcinoma of ovary - pulmonary type (SCOOPT): a case report and literature review

Qiuyang Jing

Department of Pathology, West China Second Hospital of Sichuan University

Ying He (✉ heyings626@163.com)

Department of Pathology, West China Second Hospital of Sichuan University

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Case Report

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Abstract

Background: Serous carcinoma arising in adenomyosis is rare, only 8 cases have been reported in the literature. Primary small cell carcinoma of ovary - pulmonary type (SCOOPT) is a rare, aggressive entity associated with poor outcomes and limited treatment options. The two malignant tumors synchronously happen at one patient has never been reported before.

Case presentation: We summarized and analyzed the clinicopathological features of 1 serous carcinoma arising in adenomyosis synchronous with SCOOPT and reviewed the literature. A 60-year-old postmenopausal woman presented to our hospital with abdominal distension, abdominal pain, and constipation. Colonoscopy and computed tomography (CT) scan of pulmonary showed no abnormalities. Ultrasonography and CT scan revealed a solid-cystic mass in the pelvic cavity, slightly thickened uterine myometrium at the fundus with heterogeneous echo. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy were performed. The final pathology showed serous carcinoma originating from adenomyosis, while the eutopic endometrium and both fallopian epithelia were identified with no cancer. The solid-cystic mass in the right ovary is diagnosed with SCOOPT and metastasis to the myometrium of the uterus. The prognosis of previously reported cancers of adenomyosis origin and SCOOPT were both poor, while our case was alive without disease during the 6-month follow-up.

Conclusion: We believe this case report will expand our recognition of the coexistence of serous carcinoma arising in adenomyosis with small cell carcinoma of the ovary–pulmonary type (SCOOPT).

Background

Adenomyosis is defined as ectopic endometrial glands and stroma invades myometrium. Adenomyosis is a common benign gynecological disease in hysterectomy specimens and often coexistence with other diseases, such as endometrioid adenocarcinoma, leiomyoma, etc. The malignant transformation of adenomyosis was first reported by Rolly in 1897[1], only dozens of cases have been reported since then and most of them are malignant transformation into endometrial adenocarcinoma. [2–6]. However, serous adenocarcinoma originating from adenomyosis was first reported by Griffin in 1996[7] and only 8 cases have been reported so far [3, 6, 8–11]. Due to the rarity of serous adenocarcinoma originating from adenomyosis and current reports are mostly individual cases, we currently know little about the etiology, pathogenesis, and genetic alteration of this disease.

The gynecologic tract, including the cervix, endometrium, ovary, fallopian tube, vagina, and vulva, is one of the extrapulmonary systems where extrapulmonary small cell carcinoma (EPSCC) occur frequently, representing less than 1% of all gynecologic malignancies[12, 13]. Small cell carcinoma of the ovary (SCCO) is an uncommon, highly aggressive cancer with an incidence of less than 1% of ovarian tumors.[14] Small cell carcinoma of the ovary is consists of two different types, the hypercalcemic type (SCCOHT) and the pulmonary type (SCOOPT). SCCOHT is often associated with hypercalcemia, while the SCOOPT shows the characteristic morphologic features of lung small cell carcinoma.[12]

Serous carcinoma arising from adenomyosis and SCOOPT both are rare tumors of the female genital tract. We have less knowledge about these two types of tumors, let alone both tumors occur in the same patient at the same time. Herein, we reported the first case of this two cancers simultaneously occurred at one patient and analyzed the previous literature about serous adenocarcinoma originating from adenomyosis. We believe that this report will increase our understanding of the two diseases.

Case Presentation

Clinical features and findings in the operation:

A 60-year-old postmenopausal woman attended the local community hospital, gravida 2, para 1, complained of abdominal pain, abdominal distention, and constipation for about 1 month. Her gastroenterological endoscope at the local community hospital showed no abnormalities. Ultrasonography found a solid- cystic heterogeneous mass in the pelvic cavity and indicate it may be derived from the adnexa. (Fig. 1) She had dyspnea due to abdominal distension a few days later, then she underwent abdominal puncture decompression treatment in the emergency department of our hospital.

The patient had regular menstruation in the past and was menopausal 4 years ago. She denied receiving hormone replacement therapy or the existence of breast cancer. The patient was diagnosed with hypertension 10 years ago and treated with amlodipine orally, and both her parents and siblings have had a history of hypertension. She had a negative cervical smear one month ago.

Pelvic examination showed a moderately enlarged uterus and an unmovable mass about 9cm in the right adnexa. CT scan of the pelvic and abdomen cavity revealed an irregular solid-cyst masses in the right adnexa area, with sizes of 4.7cmx3.4cmx2.1cm and 9.3cmx7.6cmx6.6cm, respectively. The contrast-enhanced CT scan showed the tumor with heterogeneous enhancement and the "ovarian blood vessel pedicle" sign, and the boundary between the serosal surface of the uterus and the lateral adnexa area is unclear. The peritoneum and the omentum majus are thickened, and large amount of ascites can be seen in the pelvic and abdominal cavity. No abnormalities were showed in the liver, spleen, pancreas, and kidneys under the ultrasonography. The contrast-enhanced CT scan of the lung showed no mass or ground-glass opacity. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) were initially performed. The serum CA125 is 284.2U/ml, serum AFP is 16.1ng/ml, and serum calcium is 2.06mmol/L (normal 2.15-2.70mmol/L).

The surface of the uterus and left ovary were found to be smooth during the operation and the left ovary is size 4.0cmx4.0cmx3.0cm. The right ovary adheres to the posterior lobe of the broad ligament and the pelvic floor and is about 10.0cmx8.0cmx8.0cm. A solid cystic mass was seen in the right ovary. The solid part of the mass was fish-like, fragile, and easy to hemorrhage. The cystic cavity was filled with dark red cyst fluid. The fallopian on both sides were slightly edema.

Gross pathology:

A solid-cystic, gray-tan irregular mass about 11.0cmx7.0cmx6.0cm, with a fibrous capsule, replaced the right ovary. The cut surface of the mass is gray-tan, with hemorrhage, cyst formation, and necrosis. The mass was predominantly solid, with scattered small cysts, ranging from 0.1cm to 0.5cm in diameter. The serosal surface of both fallopian tubes is smooth, and no abnormalities were found in the lumen or fimbria. The myometrium at the fundus is slightly thickened and harder than the surrounding myometrium, with gray-white cut surface. There were no polyps, rough areas, or masses in the eutopic endometrium and endocervical canal. The specimens of the left adnexa, the right fallopian tube, the endometrium, and the cervix were all extensively sectioned for histopathological examination.

Microscopic pathology and immunohistochemical staining

Histologically, the tumor cells of the right ovary are grown in nests and organ-like, showing the typical microscrocpic structure of small cell neuroendocrine carcinoma. The tumor is comprised of monomorphic small cells with indistinct cellular borders, ovoid nuclei with vesicular chromatin, hyperchromatic nucleoli, scanty cytoplasm, and brisk mitotic activity. (Fig. 2) Lymphovascular space invasion can be seen around the tumor.

Microscopically, ectopic endometrium glandular and stroma were found in the thickened myometrium of the fundus, supporting the diagnosis of adenomyosis. Within the adenomyosis, serous carcinoma was present with a destructive growth pattern (Fig. 3) and desmoplastic reaction. The neoplastic glands were lined by markedly atypical, cuboidal to columnar cells with hyperchromasia, conspicuous nucleoli, and irregular nuclear membrane. The tumor component is located in the deep half of the myometrium and is adjacent to the serosal layer. Metastatic SCCOPT was found in the myometrium. Lymphovascular space invasion can also occasionally be found in the myometrium. There were no serous carcinoma, serous endometrial intraepithelial carcinoma (SEIC), or endometrial glandular dysplasia (EmGD) in the eutopic endometrium or the fallopian epithelial.

Immunohistochemical staining of the small cell carcinoma of the ovary showed diffuse positivity of SMARCA4, CD56, CgA, Syn (Fig. 2), and focal positivity of SF-1, on the other hand, EMA, Vim, FOXL-2, a-inhibin, CD10, CyclinD1, LCA, CD117, DOG-1, and SALL-4 were all negative. The Ki67 proliferation index is about 95%. Immunohistochemical staining of the serous carcinoma arising from adenomyosis showed diffuse positivity of EMA, PAX-8, and P53 (Fig. 3), while P16, ER, PR, WT-1, Vim, PTEN, CgA, and Syn were all negative. Both the ectopic endometrial glands and bilateral fallopian tube epithelium showed wild-type expression of P53 (Fig. 4).

No recurrence or metastasis occurred during the 6-month follow-up after the operation, and the patient is currently receiving chemotherapy at the local hospital.

Discussion

Adenomyosis is a common disease in hysterectomy specimens, and its common symptoms include dysmenorrhea, and irregular menstruation, etc. Adenomyosis is histologically defined as the presence of ectopic endometrial glands and stroma within the myometrium. It is not uncommon for adenomyosis to merge with malignant tumors of the female genital, but the incidence of malignant transformation of adenomyosis is low[5]. The malignant transformation of adenomyosis is mostly endometrioid adenocarcinoma[4, 15, 16]. In contrast, the malignant transformation of adenomyosis into serous adenocarcinoma or clear cell adenocarcinoma is even rarer.[5, 17]

The widely agreed diagnostic criteria for malignant transformation of adenomyosis are the Sampson criteria and the Scott and Colman supplementary criteria. These criteria include the following [2, 18, 19]: (1) there are endometrial glands and/or stromal cells exist deep in the myometrium to support the diagnosis of adenomyosis, or there are endometrial glands or stromal cells around the malignant lesions; (2) there is transformation evidence between benign and malignant glands structure, e.g., normal endometrial epithelium, borderline, and invasive carcinoma coexist.; (3) other sources of tumor invasion or metastasis are excluded, e.g., endometrium and other parts of the pelvis; (4) cancer tissue and ectopic endometrial tissue coexist in the same lesion. Due to the special diagnostic criteria of malignant transformation of adenomyosis, it is almost impossible to make an accurate diagnosis before the operation. Only complete pathological examination of all specimens after the operation can make the final diagnosis.

Our case meets all the diagnostic criteria mentioned above. In this case, clear ectopic endometrial glands and stroma can be seen between the myometrium, and the transition zone from benign glandular epithelium to serous adenocarcinoma can be seen. Based on the complete gross examination, microscopic examination, and appropriate immunohistochemistry staining, metastatic serous adenocarcinoma of endometrial, ovarian, or fallopian tube can be excluded.

The clinicopathological characteristics of serous adenocarcinoma originating from adenomyosis are presents in the Table 1. Most cases were occurred in postmenopausal women[5]. The most common symptoms are irregular vaginal bleeding and abdominal discomfort. All reported cases underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, and most of them underwent lymph node dissection. There was a study about endometrial cancer arising in adenomyosis showed that it had a significantly poorer disease-free survival than endometrial cancer with adenomyosis (5-year rate, $P = 0.014$), and it is an independent prognostic factor for decreased disease-free survival ($P = 0.001$).[11] Machida et al. also found that the prognosis of endometrioid adenocarcinoma arising in adenomyosis was significantly worse than that of patients with endometrioid adenocarcinoma coexisting with adenomyosis.[20] On the contrary, Table 1 shows that the prognosis of serous carcinoma arising from adenomyosis seem to be good and the patients with prognostic information were all alive without recurrence at the end of follow-up. The completely opposite prognostic results of adenomyoiosis malignant transformation of endometrioid adenocarcinoma and serous carcinoma may be due to the rarity of the latter and only few cases have been reported. Our case is only follow up for 6 months and is currently undergoing chemotherapy, so its data may not reflect the true prognosis of the disease.

Table 1. Clinicopathological characteristics of serous adenocarcinoma originating from adenomyosis in the previous literature

Author, time	Case no.	Age(y)	Complaint	Findings in the adenomyosis	Operation	Follow-up	Clinico-pathological features
Miriam Griffin[7], 1996	1	68	postmenopausal bleeding.	papillary serous carcinoma	TAH and BSO	NA	Cervical smear was positive for adenocarcinoma.
Masafumi Koshiyama[8], 2002	2	69	postmenopausal bleeding	Papillary serous carcinoma	TAH and BSO, pelvic and para-aortic lymphadenectomy	96 months, AWOD	EE-, PR-, P53+++
Narges Izadi-Mood[9], 2007	3	61	postmenopausal bleeding	papillary serous carcinoma	THA and BSO	30months, AWOD	had a history of breast cancer (invasive lobular carcinoma), underwent a mastectomy, and received tamoxifen for the past five years. received pelvic and intracavitary radiation.
Nisreen Abushahin[3], 2011	4	58	low abdominal discomfort	Serous EIC	THA and BSO; laparoscopic staging with omentectomy	68 months, AWOD	No history of breast cancer; No hormone replacement was taken until the age of 55 years; Endometriosis in uterine serosa and ovaries IHC: P53+++ , IMP3+++ , ER+ , PR- , WT1-
Bingjian Lu[10], 2016	5	64	Left low abdominal pain	Serous carcinoma	TAH and BSO, complete staging surgery	NA	Left ovary metastasis, leiomyoma, endometriosis in the rectum. ER-, PR-, CK7+++ , Ck20-, PAX-8+++ , WT1-, CA125++ , P53+++ , PTEN++ , β -catenin membrane + , P16+++ , Ki67 80%.
	6	55	Postmenopausal vagina bleeding	Minimal SC; serous EIC; EmGD	TAH and BSO, and complete staging surgery	NA	Lymphovascular space invasion, Leiomyoma. ER-, PR-, PAX-8+++ , WT1-, P53+++ , PTEN++ , β -catenin membran+, P16+++ , HNF1 β -, Ki67 70%.
	7	55	Vaginal bleeding	Serous EIC; EmGD	Radical resection of the cervical stump + BSO +	44 months, AWOD	ER-, PR-, PAX-8+++ , WT1-

					complete staging surgery		P53+++, P16+++, Ki6780% Left ovarian endometriotic cyst; Endometriosis in the rectum.
Chia-Hao Liu, [6] 2017	8	67	right inguinal mass and postmenopausal bleeding.	serous carcinoma	laparoscopic complete staging surgery and inguinal LN dissection.	8 months, AWOD	metastatic serous carcinoma to the inguinal lymph node.
Our case	9	60	postmenopausal bleeding.	serous carcinoma	TAH and BSO, complete staging surgery	6 months, AWOD	Small cell carcinoma of the ovary – pulmonary type,

Abbreviation: NA, not available; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LN, lymph node; AWOD, alive without disease; EIC, endometrial intraepithelial carcinoma; EmGD, endometrial glandular dysplasia;

There were no prominent symptoms, specific laboratory or imaging examination of malignant transformation of adenomyosis preoperatively, [6, 21, 22] although some cases were found through cervical smears.[7, 23] The clinical manifestations of carcinoma originating from adenomyosis are the same as those of conventional adenomyosis, manifested as abnormal vaginal bleeding, menorrhea, or anemia.[5, 6, 21, 22, 24] Therefore, the malignant transformation of adenomyosis has a high risk of missed diagnosis. The malignant transformation of adenomyosis is inside the myometrium rather than forming an exogenous mass, and there may lack positive findings in hysteroscopy and curettage specimens, any of these may lead to missed diagnosis[6]. Our patient came to the hospital due to gastrointestinal symptom and her main complaint for surgical treatment her was pelvic mass. There was no indication of malignant transformation of adenomyosis before the complete pathological examination. Nearly all the cases underwent surgery for other reasons and only diagnosed accurately after complete pathological examination.[6, 9, 10, 16]

Uterine serous carcinoma most demonstrate alterations in *ERBB2*, *TP53*, *FBXW7*, *PPP2R1A*, and of the phosphoinositide 3-kinase (*PI3K*) pathway.[25] On the other hand, the etiology, pathogenesis or molecular alteration of the malignant transformation of adenomyosis are rarely known. At present, only a few studies suggest that there are gene changes and inactivation of specific tumor suppressor genes in adenomyosis, which may be related to its malignant transformation. This includes loss of heterozygosity (LOH), DNA mismatch repair genes, low expression of Bcl-2. and epigenetic changes in the promoter region of the progesterone receptor gene.[26-28] Serous adenocarcinoma derived from adenomyosis also showed P53 mutant expression and WT-1 negativity, indicating that it may have similar molecular changes with serous adenocarcinoma of endometrial origin. Nevertheless, there is no study on molecular alteration of malignant transformation of adenomyosis into serous carcinoma because of its rarity.

Due to the low incidence of this disease and the existing studies mostly are case report, the risk factors of the malignant transformation of adenomyosis are still unclear. Reviewing the previous literature, we found that there is a patient with adenomyosis malignant transformation has taken tamoxifen for a long time in the past.[9] Coincidentally, there was also a SCOOPT case who had previously received tamoxifen treatment for breast cancer.[29] Therefore, receiving tamoxifen treatment may be a risk factor of malignant transformation of adenomyosis and SCOOPT.

Primary small cell carcinoma of the ovary is a highly malignant tumor, divided into two types: small cell carcinoma of the ovary – the pulmonary type (SCCOPT) and the hypercalcemia type (SCCOHT). Both types are rare, but compared with SCCOHT, SCCOPT is rarer and only less than 30 cases have been reported. SCCOHT is often accompanied by elevated serum calcium level and may have the symptoms of hypercalcemia.[30] SCCOPT is similar to pulmonary small cell carcinoma and is considered to be a neuroendocrine tumor, and is consistent with pulmonary small cell carcinoma in morphology and immunophenotype. The case reported in this study is SCCOPT.

It is necessary to exclude the metastatic cancer of the pulmonary, digestive tract, or cervix, etc., which requires the combination of the patient's gastrointestinal endoscopy, imaging, physical examination, intraoperative findings, morphology, and immunohistochemical staining. Gastrointestinal endoscopy and enhanced CT scan of chest showed no tumorous lesions, and no other masses in the pelvic and abdominal cavity were seen during the operation in our case, which can rule out the possibility of metastasis. Although there were studies that have shown that primary small cell carcinoma of the ovary does not express TTF-1, [31, 32] its positivity does not exclude it as ovarian primary.[13]

Based on the clinical characteristics, morphological features, and immunohistochemical staining of this case, we can distinguish it from SCCOHT. First, SCCOPT does not have follicular-like spaces and large cell components.[12, 30, 33] Secondly, SMARCA4 always shows diffuse positivity in SCCOPT, while it is always negative in SCCOHT.[34, 35] On the other hand, the expression of vimentin is exactly the opposite of SMARCA4 in these two different types.[12] In addition, approximately 70% of SCCOHT patients generally have hypercalcemia that SCCOPT does not.[12, 14, 36] According to previous reports, the average age of SCCOPT is 59 years old[36], while the average age of SCCOHT is 23.9-30years old.[30, 33]

SCCOPT also needs to be differentiated from ovarian germ cell tumors and lymphoma. Lymphoma specifically expresses lymphoma-related markers, such as LCA, Bcl-2, CD20, etc.[13] Ovarian germ cell tumors always showed positivity of germ cell markers, such as SALL-4 and OCT 3/4.[13]

There are studies using flow cytometry found out that SCCOPT were aneuploid or diploid,[36] while SCCOHT were all diploid.[30] Recent studies have shown that germline or somatic mutations in the *SMARCA4* gene are highly correlated with SCCOHT.[35, 37, 38] Unfortunately, there is currently no therapy for this mutation. There is only one literature that revealed *TP53* mutations in 25 % of small cell carcinoma of ovary (SCCO) (1/4) patients and *BRCA2* mutations in 50 % of SCCO (1/2) patients by using NGS and Sanger sequencing of a 47-gene panel.[39] Although the authors declaim that the *TP53* mutation is likely oncogenic, it is not persuasive to conclude that *TP53* mutation is the representative molecular alteration of SCCOPT from only one case.

The prognosis of SCCOPT is very poor. Even for patients with FIGO stage IA, the long-term survival is only 30% to 40%.[14] According to the prognosis of the disease previously reported by Eichhorn[36], 5 of the 7 cases died of the disease 1-13 months (average 8 months) after surgery. Because of the biological behavior similarity between the extrapulmonary and the lung small cell carcinoma, the treatment approaches of the two are generally similar.[40, 41]

Conclusion

Due to the low incidence of SCOOPT and malignant transformation of adenomyosis into serous adenocarcinoma, little is known about their etiology, pathophysiology, pathogenesis, and specific genetic changes. To the best of our knowledge, this is the first case which serous adenocarcinoma arising in adenomyosis synchronous with SCOOPT. Carefully and completely pathological examination, immunohistochemical staining, and imaging examination are essential to the final diagnosis. It is worth collecting more cases for systematic and further in-depth study to uncover their clinicopathological characteristics and molecular changes.

Declarations

Consent for publication

The patient agreed to the publication of this case.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

Data collecting and analysis: Qiuyang Jing and Ying He.

Writing – original draft: Qiuyang Jing.

Writing – review & editing: Ying He.

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Figures

Figure 1

CT scan of pelvic shows a solid- cystic heterogeneous mass

Figure 2

Small cell carcinoma of the ovary; A. hematoxylin and eosin stain (40X); B. hematoxylin and eosin stain, mitotic figures and karyorrhexis are seen (400X); C. SMARCA4 positivity (200X); D. CgA positivity(200X); E. Syn positivity(200X); F. CD56 positivity(200X).

Figure 3

Serous carcinoma originating from adenomyosis; A. adenomyosis in the middle lower part, adenomyosis cystic in the right part, serous carcinoma in the upper and left part. B. serous carcinoma, C. ectopic endometrium glandular and stroma, some glandular with atypic proliferation, D. P53 diffuse strong positivity of serous carcinoma. E. This figure shows the different expression of p53 in the same gland. The normal glandular epithelium is wild type, while the atypical glandular epithelium is mutant type.

Figure 4

A. p53 wild-type expression of fallopian epithelium, B. p53 wild-type expression of eutopic endometrium.