

CASE REPORT

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

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Abstract

Serous carcinoma arising in adenomyosis is rare, with only 8 cases reported in the literature. Primary small cell carcinoma of the ovary-the pulmonary type (SCCOPT) is a rare and aggressive entity associated with poor outcomes and limited treatment options. The presence of two malignant tumors synchronously happening in one patient has never been reported before. In this study, we summarized and analyzed the clinicopathological features of a serous carcinoma arising in adenomyosis synchronous with SCCOPT and reviewed the corresponding literature. A 60-year-old postmenopausal woman presented to our hospital with abdominal distension, abdominal pain, and constipation. A colonoscopy and lung computed tomography (CT) scan showed no abnormalities. Ultrasonography and CT scans revealed a solid-cystic mass in the pelvic cavity, with a slightly thickened uterine myometrium at the fundus with heterogeneous echo. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic and para-aortic lymphadenectomy, and the final pathology showed serous carcinoma originating from adenomyosis, while the eutopic endometrium and both fallopian epithelia had no cancer infiltrations. The solid-cystic mass in the right ovary was diagnosed with SCCOPT, which was found to metastasize to the uterine myometrium. The prognosis of previously reported cancers of adenomyosis origin and SCCOPT were poor, while our case was alive without disease during an 18-month follow-up. Findings from this case report could expand our recognition on the coexistence of serous carcinoma arising in adenomyosis with small cell carcinoma of the ovary-pulmonary type.

Keywords

Serous carcinoma; Adenomyosis; Malignant transformation; Small cell carcinoma of the ovary; Pulmonary type; Immunohistochemistry

1. Background

Adenomyosis is defined as ectopic endometrial glands and stroma invading the myometrium. It is a common benign gynecological disease, usually identified in hysterectomy specimens and often coexists with other diseases, such as endometrioid adenocarcinoma, leiomyoma, *etc.* The malignant transformation of adenomyosis was first reported by Rolly [1] in 1897, and only dozens of cases have been reported since then, with most of them malignantly transformed into endometrial adenocarcinoma [2–6]. Serous adenocarcinoma originating from adenomyosis was first reported by Griffin *et al.* [7] in 1996, and only 8 cases have been reported so far [3, 6, 8–11]. Due to the rarity of serous adenocarcinoma originating from adenomyosis and the current reports are mostly individual cases, little is known about its etiology, pathogenesis and genetic alterations.

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) frequently occurs, representing <1% of all gynecologic malignancies [12, 13]. Small cell carcinoma of the ovary (SCCO) is an uncommon, highly aggressive cancer with an incidence of <1% of ovarian tumors [14]. Small cell carcinoma of the ovary consists of two different types: the hypercalcemic type (SCCOHT) and the pulmonary type (SCCOPT). SCCOHT is often associated with hypercalcemia, while SCCOPT shows the characteristic morphologic features of lung small cell carcinoma [12].

Serous carcinoma arising from adenomyosis and SCCOPT are rare tumors of the female genital tract, with little known about them, let alone both occurring simultaneously in the same patient. Herein, we reported the first case of these two cancers in one patient and performed an analysis of previous literature on serous adenocarcinoma originating from adenomyosis to increase our understanding of the two diseases.

2. Case presentation

2.1 Clinical features of the patient and surgical findings

A 60-year-old postmenopausal woman (gravida 2, para 1) attended the local community hospital following complaints of abdominal pain, abdominal distention and constipation for about 1 month. Her gastroenterological endoscopy at the local community hospital showed no abnormalities. Ultrasonography found a solid cystic heterogeneous mass in her pelvic cavity, indicating that it might be originated from the adnexa. She had dyspnea due to abdominal distension a few days later, following which she underwent abdominal puncture decompression in the emergency department of our hospital.

The patient had regular menstruation in the past and became menopausal 4 years ago. She denied having breast cancer or receiving hormone replacement therapy. She was diagnosed with hypertension 10 years ago and treated with amlodipine orally. 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 of about 9 cm in the right adnexa. Computed tomography (CT) scan of the pelvic and abdomen cavity revealed irregular solid cystic masses in the right adnexa area, with sizes of 9.3 cm × 7.6 cm × 6.6 cm. (Fig. 1) Contrast-enhanced CT scan showed that the tumor had heterogeneous enhancement, signs of “ovarian blood vessel pedicle”, and the boundary between the serosal surface of the uterus and the lateral adnexa area was unclear. The peritoneum and the omentum majus were thickened, and a large amount of ascites were present in the pelvic and abdominal cavities. No abnormalities were observed in the liver, spleen, pancreas and kidneys under ultrasonography. The contrast-enhanced CT scan of the lungs showed no mass or ground-glass opacity. Her preoperative serum CA125 (cancer antigen 125) was 284.2 U/mL, serum AFP (alpha foetoprotein) was 16.1 ng/mL, and serum calcium was 2.06 mmol/L (normal 2.15–2.70 mmol/L). After completing all preoperative examinations, she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO).

The surface of the uterus and left ovary were found to be smooth during the operation, and the size of the left ovary was 4.0 cm × 4.0 cm × 3.0 cm. The right ovary adhered to the posterior lobe of the broad ligament and the pelvic floor and was about 10.0 cm × 8.0 cm × 8.0 cm. 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 edematous.

2.2 Gross pathology

We observed that the mass appeared to be a cyst with a fibrous capsule, irregular shape and solid gray-tan color, sized about 11.0 cm × 7.0 cm × 6.0 cm and had replaced the right ovary. The cut surface of the mass was gray-tan, with hemorrhage, cyst formation, and necrosis. The mass was predominantly solid, with scattered small cysts ranging from 0.1 cm to 0.5



FIGURE 1. CT scan of the pelvis shows a solid-cystic heterogeneous mass.

cm in diameter. The serosal surface of both fallopian tubes was smooth, and no abnormalities were found in the lumen or fimbria. The myometrium at the fundus was slightly thickened and harder than the surrounding myometrium, with a 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.

2.3 Microscopic pathology and immunohistochemical staining

Histologically, the tumor cells of the right ovary grew in organ-like nests, showing the typical microscopic structure of small cell neuroendocrine carcinoma. The tumor comprised monomorphic small cells with indistinct cellular borders, ovoid nuclei with vesicular chromatin, hyperchromatic nucleoli, scanty cytoplasm, and brisk mitotic activity. (Fig. 2A) Lymphovascular space invasion was present 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 observed and demonstrated a destructive growth pattern and desmoplastic reaction. The neoplastic glands were lined by markedly atypical, cuboidal to columnar cells with hyperchromasia, conspicuous nucleoli, and irregular nuclear membranes. The tumor component was located in the deep half of the myometrium and was adjacent to the serosal layer. (Fig. 2F–G) Metastatic SCCOPT was found in the myometrium. Lymphovascular space invasion could also be occasionally found in the myometrium. There was no serous carcinoma, serous endometrial intraepithelial carcinoma (SEIC) or endometrial glandular dysplasia (EmGD)

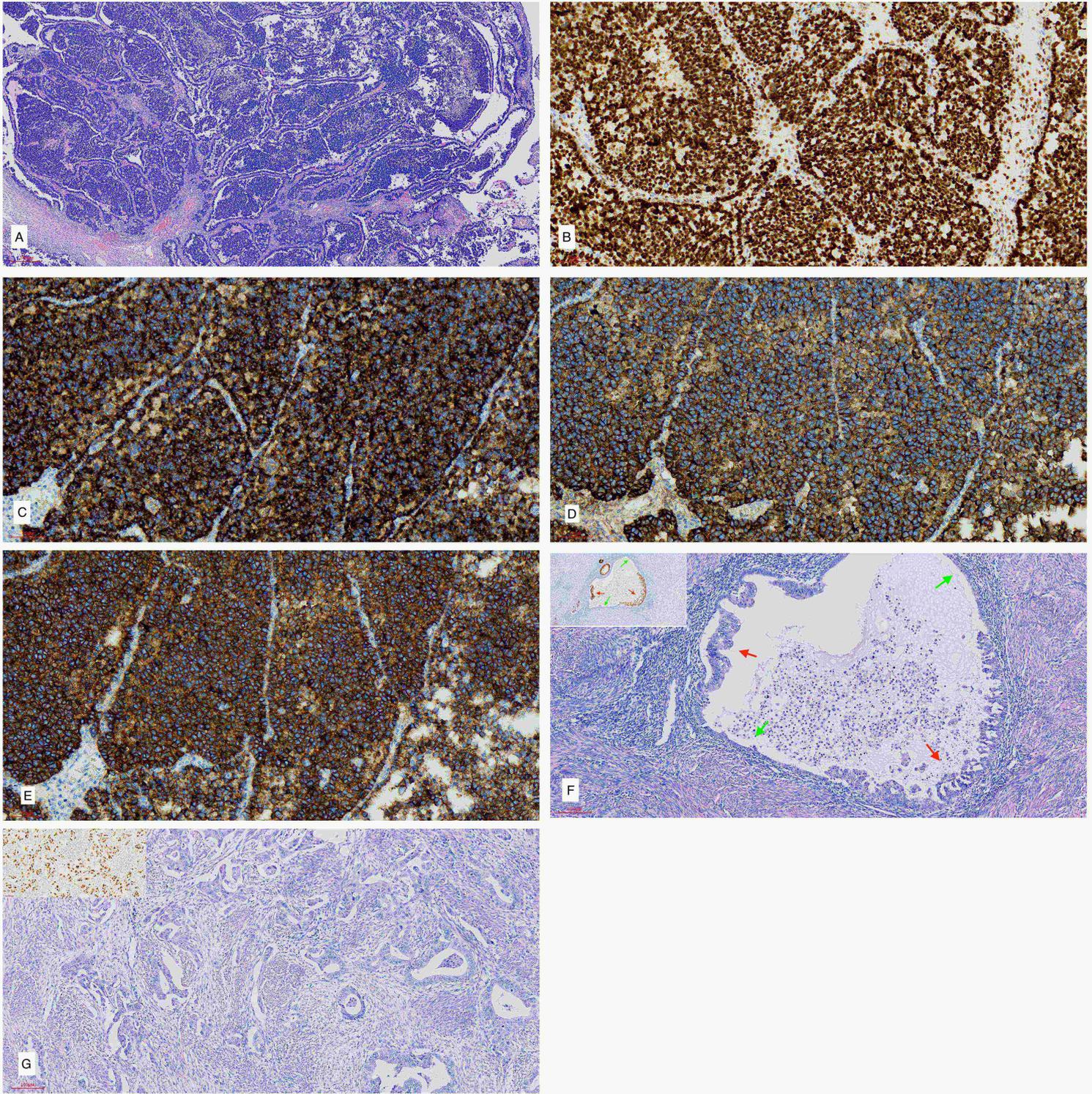


FIGURE 2. Microscopic pathology and immunohistochemical staining of small cell carcinoma of the ovary-pulmonary type (SCCOPT) and serous carcinoma originating from adenomyosis. A. SCCOPT; hematoxylin and eosin stain (40X). B. SCCOPT; *SMARCA4* positivity (200 × magnification). C. SCCOPT; CgA positivity (200 × magnification). D. SCCOPT; Syn positivity (200 × magnification). E. SCCOPT; CD56 positivity (200 × magnification). F. Serous carcinoma originating from adenomyosis; ectopic endometrium glandular and stroma and one glandular with atypical proliferation. Green arrows indicate normal endometrial glands, and red arrows indicate endometrial glands with malignant adenomyosis. The left upper illustration shows the different expressions of *p53* in the same gland. The normal glandular epithelium is of the wild type (green arrow), while the atypical glandular epithelium is of the mutant type (red arrow). G. Serous carcinoma of the uterus. The left upper illustration shows strong positivity and diffuse expression of *p53*.

in the eutopic endometrium or the fallopian epithelial.

Immunohistochemical staining of the small cell carcinoma of the ovary showed diffuse positivity of *SMARCA4* (*SWI/SNF Related, Matrix Associated, Actin Dependent Regulator Of Chromatin, Subfamily A, Member 4*) (Fig. 2B), CgA (chromogranin A) (Fig. 2C), Syn (synaptophysin) (Fig. 2D), *CD56* (Cluster of differentiation 56) (Fig. 2E), and focal positivity of *SF-1* (*steroidogenic factor 1*), but was negative for EMA (epithelial membrane antigen), vimentin, *FOXL-2* (*fork-head transcription factor 2*), α -inhibin, CD10, CyclinD1, LCA (leukocyte common antigen), CD117, *DOG-1* (*discovered on GIST-1*) and SALL-4 (Sal-like protein 4). The Ki67 proliferation index was about 95%. Immunohistochemical staining of the serous carcinoma arising from adenomyosis showed diffuse positivity of EMA, PAX-8 (paired box gene 8) and *p53* (Fig. 2F–G), while *p16*, ER (estrogen receptor), PR (progesterone receptor), *WT-1* (*Wilms tumor gene*), Vimentin, *PTEN* (*phosphatase and tensin homolog*), CgA, and Syn were all negative. Both the ectopic endometrial glands and bilateral fallopian tube epithelium showed wild-type expression of *P53*.

No recurrence or metastasis occurred during the 18-month follow-up after the operation. The patient is currently receiving chemotherapy at the local hospital and has shown no evidence of disease recurrence or metastasis. Her serum CA125, AFP and calcium were all within normal ranges after operation.

3. Discussion

Adenomyosis is a common presentation in hysterectomy specimens, and its common symptoms include dysmenorrhea, 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 tract, but the incidence of malignant transformation of adenomyosis is low [5]. The malignant transformation of adenomyosis is mostly endometrioid adenocarcinoma [4, 15, 16]. Comparatively, 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: (1) the presence of endometrial glands and/or stromal cells deep in the myometrium to support the diagnosis of adenomyosis, or endometrial glands or stromal cells around the malignant lesions; (2) transformation evidence between benign and malignant glands structure, *i.e.*, coexistence of normal endometrial epithelium, borderline and invasive carcinoma; (3) exclusion of other sources of tumor invasion or metastasis, *i.e.*, endometrium and other parts of the pelvis; (4) coexistence of cancer and ectopic endometrial tissues in the same lesion. Due to the peculiar diagnostic criteria of malignant transformation of adenomyosis, it is almost impossible to make an accurate diagnosis before surgery [2, 18, 19]. Thus, a final diagnosis is only achieved by complete pathological examinations of postoperative specimens.

Our case met all the diagnostic criteria mentioned above. We observed clear ectopic endometrial glands and stroma

between the myometrium and visualized a transition zone from benign glandular epithelium to serous adenocarcinoma. Based on the complete gross examination, microscopic examination, and appropriate immunohistochemistry staining, we excluded metastatic serous adenocarcinoma of the endometrium, ovaries and fallopian tubes.

The clinicopathological characteristics of serous adenocarcinoma originating from adenomyosis are presented in Table 1. Most cases 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, most of which underwent lymph node dissection. A study that reported endometrial cancer arising from adenomyosis showed that this condition was associated with a significantly poorer disease-free survival than endometrial cancer with adenomyosis (5-year rate, $p = 0.014$), and it was an independent prognostic factor for decreased disease-free survival ($p = 0.001$) [11]. Machida *et al.* [20] also found that the prognosis of endometrioid adenocarcinoma arising in adenomyosis was significantly worse than that of patients with endometrioid adenocarcinoma coexisting with adenomyosis. Comparatively, Table 1 shows that the prognosis of serous carcinoma from adenomyosis seems good, and all patients were still alive without recurrence at the end of follow-up. These contrasting prognostic results of adenomyosis malignant transformation of endometrioid adenocarcinoma and serous carcinoma might be due to the rarity of the latter, with only a few reported cases. The patient reported in this case report was followed up for only 18 months and is currently undergoing chemotherapy; thus, her data might not reflect the true prognosis of the disease.

Preoperatively, the malignant transformation of adenomyosis shows no prominent symptoms, specific laboratory indications or imaging features [6, 21, 22]. Some cases can be 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, menorrhagia, or anemia [5, 6, 21, 22, 24], indicating a possible high risk of misdiagnosis. Further, as the malignant transformation of adenomyosis is inside the myometrium rather than forming an exogenous mass and lacks positive findings in hysteroscopy and curettage specimens, these might also contribute to a missed diagnosis [6]. Our patient came to the hospital due to gastrointestinal symptoms, and her main complaint for surgical treatment 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 are only accurately diagnosed after a complete pathological examination [6, 9, 10, 16]. Although this disease can be easily misdiagnosed, standardized sampling, careful reading of all the slides and appropriate immunohistochemistry could increase the accuracy and provide more indications for proper diagnosis of this disease.

TABLE 1. Clinicopathological characteristics of serous adenocarcinoma arising from adenomyosis in the literature.

Author, time	Case no.	Age (years)	Chief complaint	Findings in the adenomyosis	Type of surgery	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	ER-, PR-, <i>P53</i> +++
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. No history of breast cancer; No hormone replacement was taken until the age of 55 years; Endometriosis in uterine serosa and ovaries IHC: <i>P53</i> +++ , <i>IMP3</i> +++ , ER+, PR-, <i>WT-1</i> -
Nisreen Abushahin [3], 2011	4	58	Low abdominal discomfort	Serous EIC	THA and BSO; laparoscopic staging with omentectomy	68 months, AWOD	ER-, PR-, CK7+++ , CK20-, PAX-8+++ , <i>WT-1</i> - , CA125++ , <i>P53</i> +++ , <i>PTEN</i> ++ , β -catenin membrane+ , <i>P16</i> +++ , Ki67 >80%.
	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+++ , <i>WT-1</i> - , CA125++ , <i>P53</i> +++ , <i>PTEN</i> ++ , β -catenin membrane+ , <i>P16</i> +++ , Ki67 >80%.
Bingjian Lu [10], 2016	6	55	Postmenopausal vagina bleeding	Minimal SC; serous EIC; EmGD	TAH and BSO, and complete staging surgery	NA	ER-, PR-, PAX-8+++ , <i>WT-1</i> - , <i>P53</i> +++ , <i>PTEN</i> ++ , β -catenin membrane+ , <i>P16</i> +++ , HNF1 β - , Ki67 >70%.
	7	55	Vaginal bleeding	Serous EIC; EmGD	Radical resection of the cervical stump + BSO + complete staging surgery	44 months, AWOD	ER-, PR-, PAX-8+++ , <i>WT-1</i> - , <i>P53</i> +++ , <i>P16</i> +++ , Ki67 >80% Left ovarian endometriotic cyst; Endometriosis in the rectum.

TABLE 1. Continued.

Author, time	Case no.	Age (years)	Chief complaint	Findings in the adenomyosis	Type of surgery	Follow-up	Clinico-pathological features
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.
Case of this present study	9	60	Postmenopausal bleeding.	Serous carcinoma	TAH and BSO, complete staging surgery	18 months, AWOD	Accompanied by small cell carcinoma of the ovary-pulmonary type.

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; ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemical staining; IMP3, insulin-like growth factor II mRNA binding protein 3; CK7, cytokeratin 7; CK20, cytokeratin 20; WT-1, Wilms tumor gene; PAX-8, paired box gene 8; CA125, cancer antigen 125; PTEN, phosphatase and tensin homolog.

Uterine serous carcinoma commonly demonstrates alterations in *ERBB2* (*erb-b2 receptor tyrosine kinase 2*), *TP53* (*Tumor protein p53*), *FBXW7* (*F-box and WD repeat domain containing 7*) and *PPP2R1A* (*protein phosphatase 2 scaffold subunit Aalpha*), and the *phosphoinositide 3-kinase (PI3K)* pathway [25]. However, the etiology, pathogenesis or molecular alteration of the malignant transformation of adenomyosis is poorly understood. At present, only a few studies have suggested gene changes and inactivation of specific tumor suppressor genes in adenomyosis, which might be related to its malignant transformation, including the loss of heterozygosity (LOH), DNA mismatch repair genes, low expression of Bcl-2 (B-cell lymphoma 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 might have similar molecular changes with serous adenocarcinoma of endometrial origin. Nevertheless, there is no study on the molecular alterations of the malignant transformation of adenomyosis into serous carcinoma because of its rarity.

Due to the low incidence of this disease and the existing studies being mostly case reports, the associated risk factors of the malignant transformation of adenomyosis are still unclear. Upon reviewing previous literature, we found a patient with adenomyosis malignant transformation who was treated with tamoxifen for a long time in the past [9]. Coincidentally, there was also a SCCOPT case that had previously received tamoxifen treatment for breast cancer [29]. These findings indicated that tamoxifen could be a potential risk factor for malignant transformation of adenomyosis and SCCOPT.

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, with only <30 cases have been reported. SCCOHT is often accompanied by elevated serum calcium levels and may have the symptoms of hypercalcemia [30]. SCCOPT is similar to pulmonary small cell carcinoma and is considered a neuroendocrine tumor, consistent with pulmonary small cell carcinoma in morphology and immunophenotype. The case reported in this study was SCCOPT.

It is necessary to exclude metastatic cancer of the pulmonary, digestive tract, cervix, *etc.*, which requires a combination of the patient's gastrointestinal endoscopy, imaging, physical examination, intraoperative findings, morphology, and immunohistochemical staining. Gastrointestinal endoscopy and enhanced CT scan of the chest showed no tumorous lesions, and no other masses in the pelvic and abdominal cavities were seen during the operation in our case, which can rule out the possibility of metastasis. Although some studies have shown that primary small cell carcinoma of the ovary does not express TTF-1 (thyroid transcription factor 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 could distinguish it from SCCOHT. Briefly, SCCOPT does not have follicular-like spaces and large cell components [12, 30, 33]. In addition, *SMARCA4* always shows diffuse positivity in

SCCOPT, while *SMARCA* is always negative in SCCOHT [34, 35]. On the other hand, the expression of vimentin could be opposite that of *SMARCA4* in these two different types [12]. In addition, approximately 70% of SCCOHT patients generally have hypercalcemia, which is absent in SCCOPT patients [12, 14, 36]. According to previous reports, the average age of SCCOPT patients is 59 years old [36], while that of SCCOHT patients is 23.9–30 years 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 (octamer-binding transcription factor 3/4) [13].

Previous studies using flow cytometry found that SCCOPT were aneuploid or diploid [36], while SCCOHT were all diploid [30]. Recent studies showed that germline or somatic mutations in the *SMARCA4* gene were 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* (breast cancer susceptibility gene 2) mutations in 50 % of SCCO (1/2) patients by using NGS (next-generation sequencing) and Sanger sequencing of the 47-gene panel [39]. Although the authors reported that *TP53* mutation could be oncogenic, it is not persuasive to conclude that the *TP53* mutation was the representative molecular alteration of SCCOPT from only one case.

The prognosis of SCCOPT is very poor. Even for patients with FIGO (International Federation of Gynecology and Obstetrics) stage IA, the long-term survival is only 30% to 40% [14]. According to a study by Eichhorn [36], 5 of 7 cases succumbed from the disease 1–13 months (average 8 months) after surgery, possibly due to the biological behavior similarity between extrapulmonary and lung small cell carcinoma, which contributed to their treatment approaches being generally similar [40, 41].

Synchronous tumors of the ovaries and uterus are rare, accounting for about 1–2% of female reproductive genital tract malignancies, of which endometrioid adenocarcinoma is the most commonly diagnosed. This is the first study to report the co-occurrence of SCCOPT and serous adenocarcinoma of adenomyosis; however, further investigations are required to clarify whether there could be a genetic correlation between the two.

4. Conclusion

Due to the low incidence of SCCOPT and malignant transformation of adenomyosis into serous adenocarcinoma, little is known about their etiology, pathophysiology, pathogenesis and genetic alterations. To the best of our knowledge, this is the first case reporting the occurrence of serous adenocarcinoma arising from adenomyosis synchronous with SCCOPT. Because of the high possibility of misdiagnosis, careful and complete pathological analysis, immunohistochemical staining and imaging examination are essential to accurately diagnose this condition. Lastly, it is worth collecting more cases

for systematic review and in-depth analysis to uncover their clinicopathological characteristics and molecular changes.

AUTHOR CONTRIBUTIONS

QYJ—Manuscript writing, data collection; YH—Revision of manuscript, support of funding. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study met the requirements of the Helsinki Declaration on human material and data. The study protocol was reviewed and approved by the institutional research ethics committee of West China Second University Hospital, approval number 326. The patient agreed to the publication of this case.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Rolly F. Ueber einen Fall von Adenomyoma uteri mit Uebergang in Carcinom und Metastasenbildung. *Virchows Arch Pathol Anat.* 1897; 150: 555–582.
- [2] Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. *American Journal of Obstetrics & Gynecology.* 1925; 9: 111–114.
- [3] Abushahin N, Zhang T, Chiang S, Zhang X, Hatch K, Zheng W. Serous endometrial intraepithelial carcinoma arising in adenomyosis: a report of 5 cases. *International Journal of Gynecological Pathology.* 2011; 30: 271–281.
- [4] Ismiil ND, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Thomas G, *et al.* Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. *International Journal of Gynecological Pathology.* 2007; 26: 278–283.
- [5] Yuan H, Zhang S. Malignant transformation of adenomyosis: literature review and meta-analysis. *Archives of Gynecology and Obstetrics.* 2019; 299: 47–53.
- [6] Liu C, Chang W, Liu W, Wang P. Serous carcinoma arising from adenomyosis. *Taiwanese Journal of Obstetrics and Gynecology.* 2017; 56: 706–707.
- [7] Griffin M, Parai S, Ghatage P, Dimakulangan A. Papillary serous carcinoma of the uterus arising in an adenomyoma. *Acta Cytologica.* 1996; 40: 849–850.
- [8] Koshiyama M, Suzuki A, Ozawa M, Fujita K, Sakakibara A, Kawamura M, *et al.* Adenocarcinomas arising from uterine adenomyosis: a report of four cases. *International Journal of Gynecological Pathology.* 2002; 21: 239–245.
- [9] Izadi-Mood N, Samadi N, Sarmadi S, Eftekhari Z. Papillary serous carcinoma arising from adenomyosis presenting as intramural leiomyoma. *Archives of Iranian Medicine.* 2007; 10: 258–260.
- [10] Lu B, Chen Q, Zhang X, Cheng L. Serous carcinoma arising from uterine adenomyosis/adenomyotic cyst of the cervical stump: a report of 3 cases. *Diagnostic Pathology.* 2016; 11: 46.
- [11] Matsuo K, Moeini A, Machida H, Scannell CA, Casabar JK, Kakuda M, *et al.* Tumor characteristics and survival outcome of endometrial cancer arising in adenomyosis: an exploratory analysis. *Annals of Surgical Oncology.* 2016; 23: 959–967.
- [12] Atienza-Amores M, Guerini-Rocco E, Soslow RA, Park KJ, Weigelt B. Small cell carcinoma of the gynecologic tract: a multifaceted spectrum of lesions. *Gynecologic Oncology.* 2014; 134: 410–418.
- [13] World Health Organization. *Female Genital Tumours.* 5th edn. International Agency for Research: CancerLyon, France. 2020.
- [14] Reed NS, Pautier P, Ávall-Lundqvist E, Choi C, du Bois A, Friedlander M, *et al.* Gynecologic cancer intergroup (GFIG) consensus review for ovarian small cell cancers. *International Journal of Gynecologic Cancer.* 2014; 24: S30–S34.
- [15] Koshiyama M, Okamoto T, Ueta M. The relationship between endometrial carcinoma and coexistent adenomyosis uteri, endometriosis externa and myoma uteri. *Cancer Detection and Prevention.* 2004; 28: 94–98.
- [16] Hsu M, Chou S, Lin S, Liang S, Chiu H, Hsu C. Very early stage adenocarcinoma arising from adenomyosis in the uterus. *Taiwanese Journal of Obstetrics and Gynecology.* 2006; 45: 346–349.
- [17] Baba A, Yamazoe S, Dogru M, Ogawa M, Takamatsu K, Miyauchi J. Clear cell adenocarcinoma arising from adenomyotic cyst: a case report and literature review. *Journal of Obstetrics and Gynaecology Research.* 2016; 42: 217–223.
- [18] Scott RB. Malignant changes in endometriosis. *Obstetrics and Gynecology.* 1953; 2: 283–289.
- [19] Colman HI, Rosenthal AH. Carcinoma developing in areas of adenomyosis. *Obstetrics and Gynecology.* 1959; 14: 342–348.
- [20] Machida H, Maeda M, Cahoon SS, Scannell CA, Garcia-Sayre J, Roman LD, *et al.* Endometrial cancer arising in adenomyosis versus endometrial cancer coexisting with adenomyosis: are these two different entities? *Archives of Gynecology and Obstetrics.* 2017; 295: 1459–1468.
- [21] Mao X, Zheng W, Mao W. Malignant changes in adenomyosis in patients with endometrial adenocarcinoma: a case series. *Medicine.* 2017; 96: e8336.
- [22] Zouzoulas OD, Tsolakidis D, Efstratiou I, Pervana S, Pazarli E, Grimbizis G. Correlation between Adenomyosis and Endometrial cancer: 6-year experience of a single center. *Facts, Views & Vision in ObGyn.* 2018; 10: 147–152.
- [23] Woodruff JD, Erozan YS, Genadry R. Adenocarcinoma arising in adenomyosis detected by atypical cytology. *Obstetrics and Gynecology.* 1986; 67: 145–148.
- [24] Koike N, Tsunemi T, Uekuri C, Akasaka J, Ito F, Shigemitsu A, *et al.* Pathogenesis and malignant transformation of adenomyosis (Review). *Oncology Reports.* 2013; 29: 861–867.
- [25] Lee EK, Fader AN, Santin AD, Liu JF. Uterine serous carcinoma: molecular features, clinical management, and new and future therapies. *Gynecologic Oncology.* 2021; 160: 322–332.
- [26] Jones RK, Searle RF, Bulmer JN. Apoptosis and bcl-2 expression in normal human endometrium, endometriosis and adenomyosis. *Human Reproduction.* 1998; 13: 3496–3502.
- [27] Nie J, Liu X, Guo S. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in adenomyosis and its rectification by a histone deacetylase inhibitor and a demethylation agent. *Reproductive Sciences.* 2010; 17: 995–1005.
- [28] Goumenou AG, Arvanitis DA, Matalliotakis IM, Koumantakis EE, Spandidos DA. Loss of heterozygosity in adenomyosis on hMSH2, hMLH1, p16Ink4 and GALT loci. *International Journal of Molecular Medicine.* 2000; 6: 667–671.
- [29] Yin L, Li J, Wei Y, Ma D, Sun Y, Sun Y. Primary ovarian small cell carcinoma of pulmonary type with coexisting endometrial carcinoma in a breast cancer patient receiving tamoxifen: a case report and literature review. *Medicine.* 2018; 97: e10900.
- [30] Young RH, Oliva E, Scully RE. Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases. *The American Journal of Surgical Pathology.* 1994; 18: 1102–1116.
- [31] Bing Z, Adegboyega PA. Metastasis of small cell carcinoma of lung into an ovarian mucinous neoplasm: immunohistochemistry as a useful

- ancillary technique for diagnosis and classification of rare tumors. *Applied Immunohistochemistry & Molecular Morphology*. 2005; 13: 104–107.
- [32] Oneda E, Zorzi F, Gorio A, Quaglia F, Abeni C, Rota L, *et al.* Diagnosis of small cell carcinoma of the ovary or ovarian metastases of small cell carcinoma of the lung: a case report and review of the literature. *Case Reports in Oncology*. 2020; 13: 822–828.
- [33] Callegaro-Filho D, Gershenson DM, Nick AM, Munsell MF, Ramirez PT, Eifel PJ, *et al.* Small cell carcinoma of the ovary-hypercalcemic type (SCCOHT): a review of 47 cases. *Gynecologic Oncology*. 2016; 140: 53–57.
- [34] Conlon N, Silva A, Guerra E, Jelinic P, Schlappé BA, Olvera N, *et al.* Loss of SMARCA4 expression is both sensitive and specific for the diagnosis of small cell carcinoma of ovary, hypercalcemic type. *The American Journal of Surgical Pathology*. 2016; 40: 395–403.
- [35] Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N, Tomiak E, *et al.* Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nature Genetics*. 2014; 46: 438–443.
- [36] Eichhorn JH, Young RH, Scully RE. Primary ovarian small cell carcinoma of pulmonary type. A clinicopathologic, immunohistologic, and flow cytometric analysis of 11 cases. *The American Journal of Surgical Pathology*. 1992; 16: 926–938.
- [37] Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, Hendricks WPD, *et al.* Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4. *Nature Genetics*. 2014; 46: 427–429.
- [38] Jelinic P, Mueller JJ, Olvera N, Dao F, Scott SN, Shah R, *et al.* Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. *Nature Genetics*. 2014; 46: 424–426.
- [39] Yaghmour G, Prouet P, Wiedower E, Jamy OH, Feldman R, Chandler JC, *et al.* Genomic alterations in neuroendocrine cancers of the ovary. *Journal of Ovarian Research*. 2016; 9: 52.
- [40] Walenkamp AME, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. *Cancer Treatment Reviews*. 2009; 35: 228–236.
- [41] Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M, Ball DL. Should extrapulmonary small cell cancer be managed like small cell lung cancer? *Cancer*. 2010; 116: 888–895.

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