



Case report

Pelvic seromucinous borderline tumor 26 years after ovarian seromucinous borderline tumor managed with post-treatment estrogen replacement therapy

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1. Introduction

Seromucinous borderline tumors (SMBTs) of the ovary are considered endometriosis-related ovarian neoplasms (ERONs) (Kobell et al., 2014; Maeda and Shih, 2013). SMBTs have been reported to complicate endometriosis in a third of cases. Recurrences of SMBTs within 10 years after the initial treatment have been reported (Bostwick et al., 1986); however, to our knowledge, later recurrences have not been reported. Long-term follow-up and recurrence data for SMBTs are scarce, probably because of the relatively short period since the first description in the literature (Rutgers and Scully, 1988a; Rutgers and Scully, 1988b), relatively rare incidence (7.8% of all BTs) (du Bois et al., 2013), and prevalence of early-stage diseases with a favorable prognosis (Kobell et al., 2014). The biological and clinical features of SMBTs should be clarified.

Here we report a case involving a 56-year-old woman who developed SMBT presenting as a pelvic endometriotic cyst 26 years after curative (surgical and chemotherapeutic) treatment and post-treatment estrogen replacement therapy (ERT; 10 years) for a lesion originally diagnosed as stage III serous adenocarcinoma of the ovary, which was later re-diagnosed as SMBT after a retrospective review of the pathological slides. We suspected that the second SMBT that occurred 26 years after the first ovarian SMBT was not a recurrent tumor, but a metachronous primary SMBT that developed from the pelvic endometriosis.

2. Case report

A 56-year-old woman (gravida 1, para 0) treated for noninvasive papillary urothelial carcinoma of the bladder was referred to our institution for the examination of a pelvic cystic tumor detected via follow-up imaging and elevated serum cancer antigen 125 (CA125). During a laparotomy performed for an ectopic pregnancy 26 years ago, bilateral ovarian tumors were incidentally detected, and left salpingo-oophorectomy and right ovarian biopsy were performed. The lesion was diagnosed as serous adenocarcinoma of the ovary; therefore, she underwent staging laparotomy with total abdominal hysterectomy, right salpingo-oophorectomy, partial omentectomy, and pelvic lymphadenectomy. Only mild atypia was observed. A diagnosis of stage III serous adenocarcinoma of the bilateral ovaries was made because of microscopic metastases in the omentum and fallopian tube. She received adjuvant combination chemotherapy involving 5 cycles of cyclophosphamide, doxorubicin, and cisplatin and was followed up for 13 years after treatment without any evidence of recurrence. From the age of 40 years, she received ERT (conjugated estrogen or estradiol transdermal patch) for 10 years.

Fig. 1 (a and b) shows the findings of pretreatment transvaginal ultrasound, computed tomography, and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography for the present lesion. The serum CA125 level was 165 U/L. Colonoscopy revealed stenosis at the rectum and sigmoid colon due to the pelvic tumor. Accordingly, we

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suspected that the tumor was an endometriotic cyst that arose in the pelvic endometriosis and underwent a malignant transformation. The patient consented to undergo laparotomy, which revealed a cystic tumor adhered to the left pelvic wall, most firmly to the left vesicouterine fossa. The sigmoid colon and rectum were adherent around the tumor. The tumor and adherent sigmoid colon were resected together without rupture of the cystic tumor. The findings of peritoneal washing cytology were negative.

Fig. 1 (c–e) shows photographs of the resected tumor. Macroscopically, the cystic tumor measured approximately 10 × 10 × 8.5 cm (Fig. 1c). Microscopically, the inner wall showed papillary proliferative serous epithelium with focal intracytoplasmic mucin-containing columnar epithelium (Fig. 2a and 2b). Despite massive papillary epithelial proliferation, there was no stromal invasion. Immunohistochemistry showed positivity for paired box gene 8, Wilms tumor suppressor gene 1, AT-rich interaction domain 1A, estrogen receptor (ER), progesterone receptor (focal), and p53 (wild type) and negativity for CDX-2 and carcinoembryonic antigen. The MIB-1 labeling index was < 10%, with 10–20% cells in hot spots. The cystic wall showed hemosiderin-containing macrophages with normal endometriosis (Fig. 2c). We diagnosed this cystic tumor as SMBT arising in a pelvic

endometriotic cyst. A transition from SMBT to background endometriosis was observed. A retrospective review of hematoxylin and eosin-stained sections of the tumor resected 26 years ago showed histopathological similarities with the current lesion (Fig. 2d). The previous tumor showed papillary proliferative serous epithelium with only a small focus of mucinous epithelium, which should be included within the SMBT spectrum according to the 2014 WHO classification of tumors (Kobell et al., 2014). The omental tumor associated with the primary lesion was diagnosed as a noninvasive implant. A small endometriosis focus was suspected. The originally diagnosed stage III serous adenocarcinoma of the ovary was re-diagnosed as SMBT with noninvasive implants. The ER status of the first ovarian SMBT could not be obtained. The patient was free from recurrence 4 years and 6 months after surgery.

3. Discussion

In this case, we suspected that the pelvic cystic tumor that occurred 26 years after the first ovarian SMBT was not a recurrent tumor; rather, it was a metachronous primary tumor that developed from the pelvic endometriosis. There are multiple reasons for this speculation.

First, the cystic tumor showed a transition between SMBT and

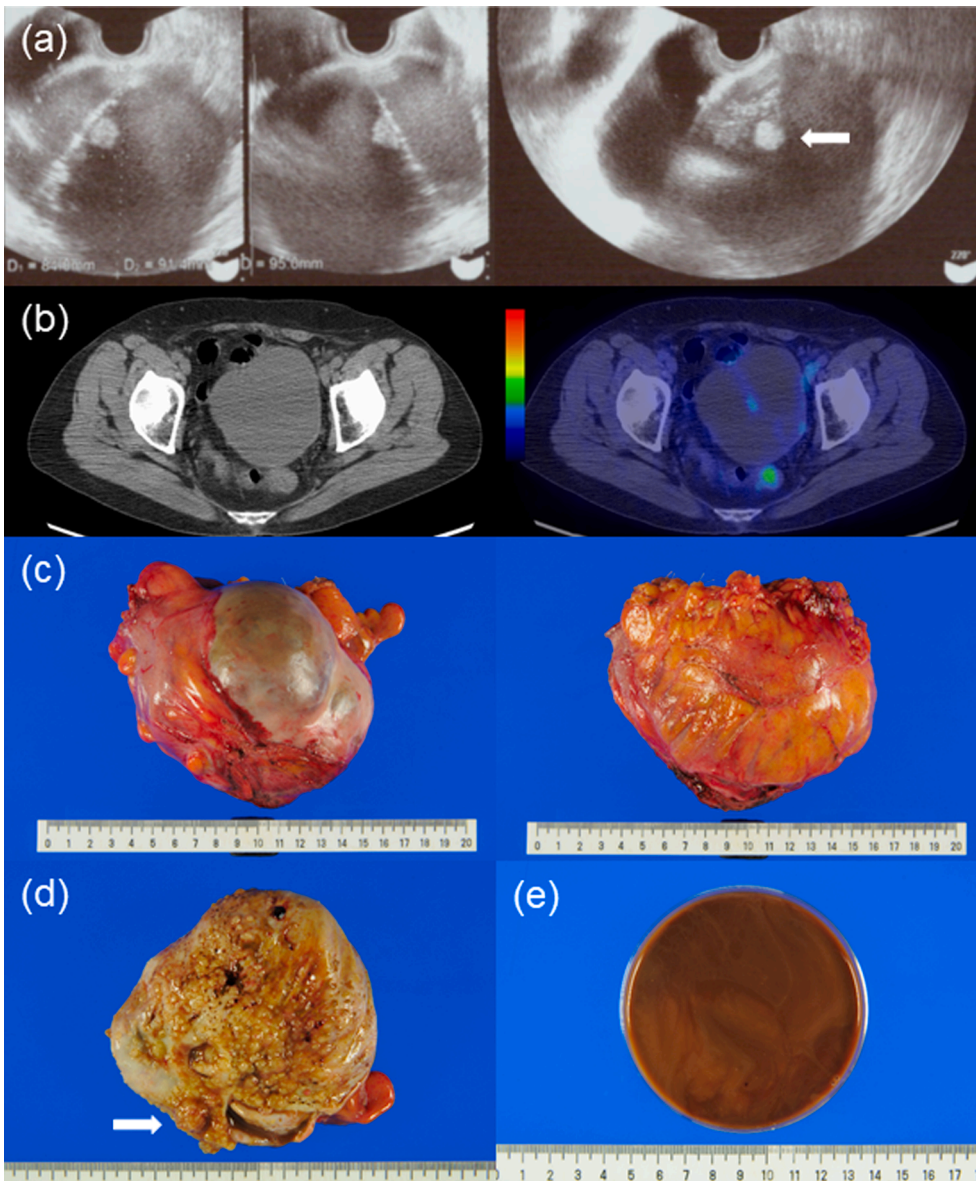


Fig. 1. Imaging findings and photographs of a seromucinous borderline tumor arising in an endometriotic cyst in the pelvis of a 56-year-old woman. (a) Transvaginal ultrasound shows a 95-mm pelvic cystic mass with a nodule and a septum behind the bladder (left: sagittal and transverse plane; right: a nodule of the septum [arrow]). (b) Computed tomography (left) and ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (right) show a cystic tumor in the pelvis and FDG accumulation in the nodule. (c) Photographs of the resected tumor show the sigmoid colon that adhered to the left side of the tumor (left: anterior side) and the sigmoid mesocolon that adhered to the tumor (right: posterior side). (d) A photograph of the inner side of the resected tumor shows small granular protrusions spread in a cobblestone pattern in the lining of the tumor. A nodule is also visible (arrow). (e) The tumor comprised dark reddish-brown serous fluid.

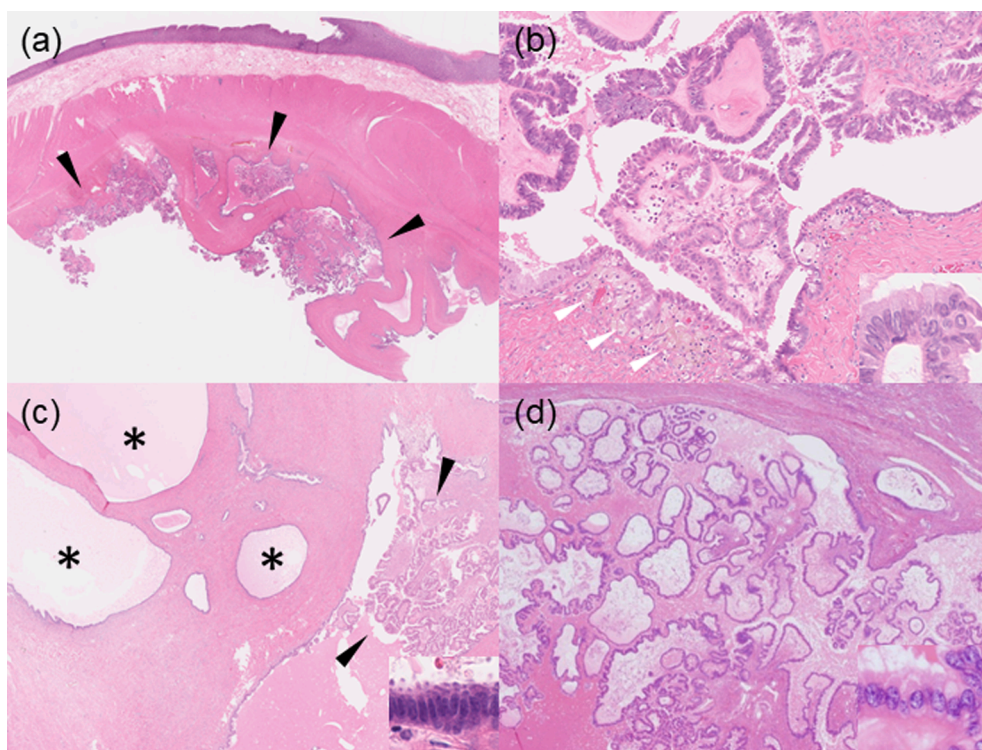


Fig. 2. Histopathological findings (hematoxylin and eosin staining) for seromucinous borderline tumors that occurred after an interval of 26 years in the same patient. (a) A panoramic view of the second lesion shows the tumor exhibiting papillary growth (arrowheads) on the serosa of the sigmoid colon. (b) The tumor shows a papillary structure with a broad fibrovascular core or hyalinized stroma. Some tumor cells contain mucin and resemble the endocervical glandular epithelium (inset). Aggregations of hemosiderin-laden macrophages are seen beneath the glandular epithelium (white arrows). (c) Dilated endometriotic cysts (*) are observed adjacent to the tumor and composed of bland glandular cells (inset; arrowheads). (d) Review of the histopathology of an ovarian seromucinous borderline tumor resected 26 years ago. Tumor cells with mucin can be observed (inset).

endometriosis. If it were a recurrent tumor, whole tumor cells would have been atypical or malignant cells. SMBT can occur concurrently in any organ where endometriosis can develop, and coexisting extra-ovarian tumors do not necessarily indicate tumor metastasis if SMBT is associated with endometriosis (Kim et al., 2010). Endometriotic implants frequently distribute in the pelvic peritoneum of patients with infertility and endometriosis (Jenkins et al., 1986). Second, the present tumor was found 6 years after the completion of 10 years of ERT. If it were a recurrent SMBT, it would have been apparent earlier because 10 years of ERT could have stimulated its recurrence. Estrogen can induce the proliferation of different ER-positive ovarian cancer cell lines (Cunat et al., 2004), and SMBTs normally express ER (Kobell et al., 2014). The Society of Gynecologic Oncology clinical practice statement on hormone replacement therapy (HRT) in patients with gynecologic cancers stated that a recommendation for patients with BT could not be determined because of data paucity (Sinno et al., 2020). Conversely, HRT is acceptable in high-grade serous subtypes, but is not recommended in low-grade serous and endometrioid subtypes because the latter two subtypes may respond to antiestrogen therapy (Sinno et al., 2020), and both are considered ERONs (Pearce et al., 2012). A review of HRT for endometriosis reported that HRT may enhance endometriosis recurrence because of its effect on the remaining endometriotic deposits in the pelvis (Al Kadri et al., 2009). The European Society of Human Reproduction and Embryology guideline recommends avoiding unopposed estrogen treatment and treating with combined estrogen/progesterone or tibolone for menopausal women with endometriosis (Dunselman et al., 2014). Cases of adenocarcinoma arising from pelvic endometriosis subsequent to unopposed ERT have also been reported (Lavery and Gillmer, 2001). Our patient might have also had pelvic endometriosis, which may have developed into endometriotic cysts, as well as malignant transformation subsequent to ERT.

A “recurrence” in a residual ovary after fertility-sparing surgery for BTs is suspected to be a newly developed primary tumor (Gershenson, 2017; Kim et al., 2010), although it is unclear whether a second SMBT at sites other than the ovary is another primary tumor. We reviewed the literature and retrieved 9 SMBT cases with “recurrence” at sites other

than the ovary (Table 1) (Rutgers and Scully, 1988a; Rutgers and Scully, 1988b; Bostwick et al., 1986; Koskas et al., 2011; Hayashi et al., 2016; Sun et al., 2018). In 4 patients, the recurrent tumor was confined to the pelvis, where endometriosis is frequently distributed. In 3 patients, the recurrent tumor was invasive; different histologic subtypes of ERONs from the primary SMBT may occur without a history of HRT (Uehara et al., 2019). The site of peritoneal “recurrence” in the remaining 2 cases was unclear, although it may be the pelvic peritoneum. Most of these secondary SMBTs at sites other than the ovary occurred in the pelvis or as different histologic subtypes of ERONs. A seemingly recurrent SMBT may be a metachronously developed primary SMBT.

In conclusion, we suspect that the second pelvic SMBT developed metachronously from pelvic endometriosis after post-treatment ERT. The findings from this case suggest that post-treatment ERT for ERONs should be carefully provided because the remnant endometriosis can become endometriotic cysts with subsequent malignant transformation. SMBTs can occur several years after post-treatment ERT, and long-term follow-up should be considered for patients with SMBTs, particularly for those who undergo post-treatment ERT. A study of similar cases may elucidate the clinicopathologic features of SMBT.

Consent

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

CRediT authorship contribution statement

Takashi Uehara: Conceptualization, Data curation, Investigation, Writing - original draft, Writing - review & editing. **Hiroshi Yoshida:** Data curation, Investigation, Writing - review & editing. **Tomoyasu Kato:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial

Table 1
Reported cases of recurrent seromucinous borderline tumor at sites other than the ovary.

No.	Author	Age (years)	Stage	Primary Histology	Primary Treatment	Recurrence Sites	Recurrence-free Survival	Treatment for Recurrence	Histology of Recurrence	Outcomes
1	Bostwick	52	IA	Mixed seromucinous BT	TAH + BSO	Peritoneal cavity	85M	Excisional biopsy, Chemotherapy	Mixed seromucinous BT	No evidence of disease (135 M)
2	Rutgers	NA	NA	Mixed-epithelial BT	NA	Pelvic disease	7M	Surgical excision	NA	Alive and well (12Y) (second recurrence at 10 M)
3	Rutgers	NA	NA	Mixed-epithelial BT	NA	Pelvic disease	3Y	Surgical excision	NA	Alive and well (5Y) (second recurrence at 4Y)
4	Rutgers	NA	NA	Mixed-epithelial BT	NA	Pelvic disease	3Y	No further treatment	NA	Alive and well (5Y)
5	Koskas	43	IA	Endocervical-like MBOT	UC	Ipsilateral ovary and peritoneum	46M	NA	Mucinous borderline	Alive without disease
6	Koskas	31	IA	Endocervical-like MBOT	UC	Peritoneum	36M	NA	Invasive carcinoma	Died of disease
7	Koskas	45	IA	Mixed (seromucinous) BOT	UC	At least ovary	7M	NA	Invasive carcinoma	Alive with persistent disease
8	Hayashi	57	pT2cN1M0*	Mixed-epithelial BT (SMBT)	BSO + hysterectomy + pOMT + APD + PLA + PALB	Vaginal stump	2Y6M	Surgery, TC	Low-grade adenocarcinoma	Alive with disease (4Y)
9	Sun	31	IC	Endocervical MBOT	Conservative surgery	Pelvic cavity	23M	NA	NA	Disease free (190 M)

NA, not available; BT, borderline tumor; MBOT, mucinous borderline ovarian tumor; SMBT, seromucinous borderline tumor; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; UC, unilateral cystectomy; pOMT, partial omentectomy; APD, appendectomy; PLA, pelvic lymphadenectomy; PALB, *para*-aortic lymph node sampling; TC, chemotherapy with paclitaxel and carboplatin combination; M, months; Y, years.

* : staged by the 7th TNM classification.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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