Clinical Case Report

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A diagnostic challenge of seromucinous borderline tumor

A case report

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Abstract

Introduction: Magnetic resonance (MR) relaxometry provides a noninvasive predictive tool to discriminate between benign ovarian endometrioma (OE) and endometriosis-associated ovarian cancer (EAOC). Transverse relaxation rate R2 value was determined using a single-voxel, multi-echo MR sequence (HISTO) by a 3T-MR system. R2 with cutoff value of 12.1 s^{-1} was established to discriminate between benign and malignant tumors.

Patient concerns: We present a case of a 39-year-old woman who was initially thought to be malignant transformation of endometriosis by diagnostic MR imaging of the vascularized solid components.

Diagnosis: A R2 value of 42.62 s^{-1} on MR relaxometry demonstrated that this case is non-malignant.

Interventions: To confirm the diagnose, left salpingo-oophorectomy by laparoscopic surgery was performed.

Outcomes: Histopathological results revealed seromucinous borderline tumor (SMBT). Our experience suggests that preoperative MR relaxometry may be useful for discriminating "borderline (SMBT)" from "malignancy (EAOC)." Furthermore, immunohistochemical studies of this case demonstrated ovarian SMBT cells were positive for estrogen receptor, progesterone receptor, and hepatocyte nuclear factor-1beta. A similar expression pattern was also observed in patients with benign OE.

Lessons: In many respects, SMBT characteristics differ from those of EAOC but resemble those of benign OE. MR relaxometry unveils a new clinical approach as an adjunctive modality for discriminating SMBT from EAOC.

Abbreviations: EAOC = endometriosis-associated ovarian cancer, ER = estrogen receptor, HISTO = high-speed T2 corrected multi-echo, HNF-1β = hepatocyte nuclear factor-1beta, MR = magnetic resonance, OE = ovarian endometrioma, PgR = progesterone receptor, SMBT = seromucinous borderline tumor.

Keywords: case report, endometriosis, immunohistochemistry, malignant transformation, MR transverse relaxation, seromucinous borderline tumor

1. Introduction

Seromucinous neoplasms are a new category of ovarian epithelial tumor in the 2014 revised World Health Organization classification. Seromucinous borderline tumor (SMBT) is frequently associated with endometriosis that is a common gynecological disorder affecting women in the reproductive age group.[1,2] Endometriosis is a benign condition, but approximately 1% of the cases undergo malignant transformation (endometriosis-associated ovarian cancer [EAOC]) later in life.[3] EAOC includes clear cell carcinoma, endometrioid carcinoma, low-grade serous carcinoma, and SMBT.[2,4]

Magnetic resonance imaging (MRI) plays an important role in differentiating benign from malignant lesions in suspicious ovarian findings. Since soft tissue components, mural nodules and papillary projections can be seen in EAOC and SMBT, and also sometimes benign ovarian endometrioma (OE), it poses a challenging diagnostic dilemma to clinicians.[5,6] Hemorrhage due to endometriosis was present in a majority of EAOC and SMBT.[6] Magnetic resonance (MR) relaxometry is a noninvasive, promising new diagnostic tool for providing sufficient information for determining the iron concentration within the human tissue.[7] MR relaxometry R2 values were highly correlated with total iron concentrations.[8] Yoshimoto et al reported that EAOC exhibited decreased total iron concentrations in cyst fluids compared to benign OE.[9] Therefore, MR relaxometry provides a predictive tool to discriminate between EAOC and OE.

Editor: N/A.

Informed written consent was obtained from the patient for publication of this case report and companying images.

This work was supported by JSPS KAKENHI Grant Number JP16K11148, and Konica Minolta Science and Technology Foundation in 2017.

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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Medicine (2019) 98:22(e15707)

Received: 23 December 2018 / Received in final form: 9 April 2019 / Accepted: 22 April 2019

http://dx.doi.org/10.1097/MD.0000000000015707

We present here a case of a 39-year-old woman who was initially thought to be malignant transformation of decidualized endometriosis by diagnostic MRI of the vascularized solid components, but MR relaxometry result was evaluated as benign OE.

1.1. Case report

A 39-year-old primigravida Japanese female was referred to our outpatient clinic with an atypical multicystic lesion (81 × 43 mm) posterior to the uterus seen on routine ultrasound during pregnancy at 23 weeks of gestation. She had no history of gynecological disease such as endometriosis, abdominal pain, or abdominal surgery. An early transvaginal ultrasound in first trimester revealed a 53 mm unilocular left ovarian mass. On physical exam, external genitalia, vagina, and cervix were unremarkable; however, pelvic exam revealed a nontender mass in the left adnexal region. Figure 1 shows a characteristic sonographic finding with clinically suspicious ovarian cancer. The CA125 and CA19-9 assays were 55 U/ml and 78 U/ml, respectively. MRI was recommended to provide further information about soft tissue components or mural excrescences that can aid in their differential diagnosis; decidualized endometrioma or malignant transformation of endometriosis. The present case was considered as suggestive of decidualized endometrioma (Fig. 2). Watchful observation was needed to exclude the possibility of malignancy.

After an uncomplicated pregnancy, the pregnancy was terminated at 39 weeks of gestation by a normal spontaneous vaginal delivery. The patient delivered a healthy girl weighing 2852 g, with Apgar 8 and 9 at 1 and 5 minutes. She presented to our hospital for every 3-month follow-up of left endometrioma or decidualized ovarian mass. Eight months after delivery, ultrasonography showed an ovarian cystic tumor with an enlarged solid portion, which was suspicious of malignancy. Levels of CA125 and CA19-9 were 19 U/mL and 39 U/mL, respectively. MRI revealed a multilocular cyst with the irregularly thickened mural nodules (Fig. 3). MRI clearly identified the solid tissue components, detected with intermediate signal intensity and enhancing on dynamic contrast-enhanced images (Fig. 4). MRI revealed a 78 mm left ovarian tumor with an enlarged (26 × 12 mm) irregular-shaped soft-tissue component or mural nodule that were well enhanced. These findings suggested the possibility of malignancy. The patient was evaluated by a gynecologic oncologist and radiologist. The patient was advised to have MR relaxometry of the pelvis. After the routine clinical MRI, she underwent MR relaxometry by using single-voxel acquisition mode sequence at a multiple echo times and by fitting an exponential decay to the echo amplitude at different multiple echo times.[10] A parameter R2 value s^{-1} was calculated using high-speed T2*-corrected multi-echo MR sequence (HISTO) by the 3T-MR system in vivo and ex vivo that has been described previously.[8] MR relaxometry demonstrated a R2 value of 42.62 s^{-1} in the cyst, which suggested a benign tumor rather than malignancy (Fig. 5).

Finally, for further work-up, a planned laparoscopic surgery was performed to exclude the possibility of malignancy. Gross appearance was no suspicious for malignancy without adhesion and therefore left salpingo-oophorectomy was performed. Histopathological results revealed SMBT; all the tissue samples were negative for malignancy (Fig. 6). Immunohistochemical studies of the present case demonstrated ovarian SMBT cells were positive for estrogen receptor (ER), progesterone receptor (PgR), and hepatocyte nuclear factor-1beta (HNF-1β) (Fig. 7). Peritoneal washings were negative for malignant cells. Surgical resection was not performed due to refusal of additional

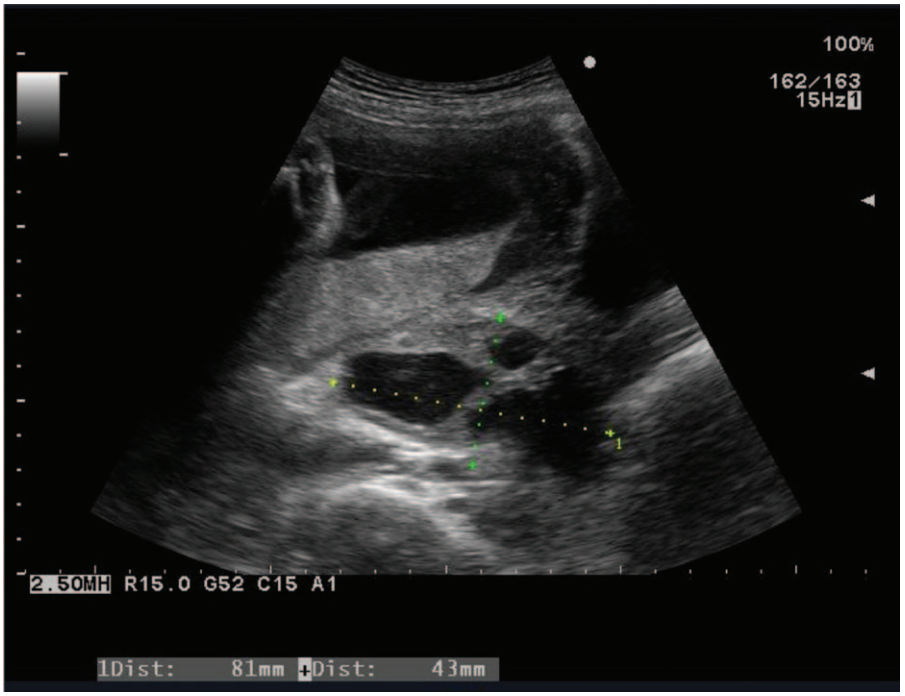


Figure 1. Pelvic ultrasound at 23 wk of gestation revealed a 81 mm left ovarian mass that was multiloculated with thickening of septas. The solid components were demonstrated as linear and broad-based nodular structures. This is a characteristic sonographic finding associated with suspected ovarian cancer.

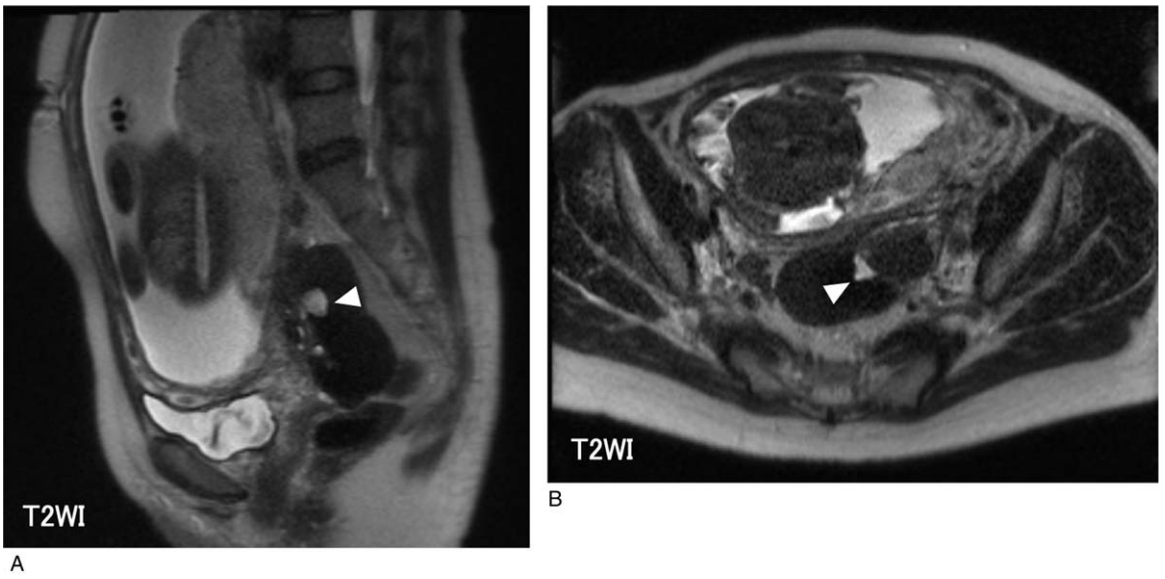


Figure 2. The patient underwent routine MRI using T1W and T2W sequences. MRI examination of the pelvis on a 3.0-Tesla MR unit (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany), using a pelvic-phased array coil was followed. The mural nodules were demonstrated as polypoid structure. A multilocular cystic mass (75 × 38 mm) with a mural nodule or thickening of septas was demonstrated on sagittal (A) and axial (B) T2WI during pregnancy at 23 wk of gestation. High signal intensity (14 × 10 mm) at the septum was recognized on T2WI (arrowhead). The signal of the soft-tissue component is isointense with the placenta within the uterus on all sequences.[24] MRI = magnetic resonance imaging.

treatment. She was symptom-free without recurrence or metastasis at the 4-year follow-up examination.

2. Discussion

We report the case of SMBT investigated using MRI and MR relaxometry as part of multimodal imaging. MRI offered the possibility of malignancy, while MR relaxometry suggested a benign tumor rather than malignancy. Furthermore, SMBT and benign OE had similar immunohistochemical expression patterns that differed from the pattern of EAOC. SMBT should always be part of the differential diagnosis when evaluating mass lesions that mimic EAOC.

First, establishing a diagnosis of SMBT represents a major challenge because of the lack of readily available clinical and MRI findings. Diagnostic imaging between SMBT and EAOC still poses difficulties as both have intracystic vascularized mural nodules and exhibits similar characteristics on both T1 and T2-weighted images. The presence of an enhancing component within a blood-filled ovarian mass is considered as suggestive of malignant transformation of a pre-existing endometrioma.[11]

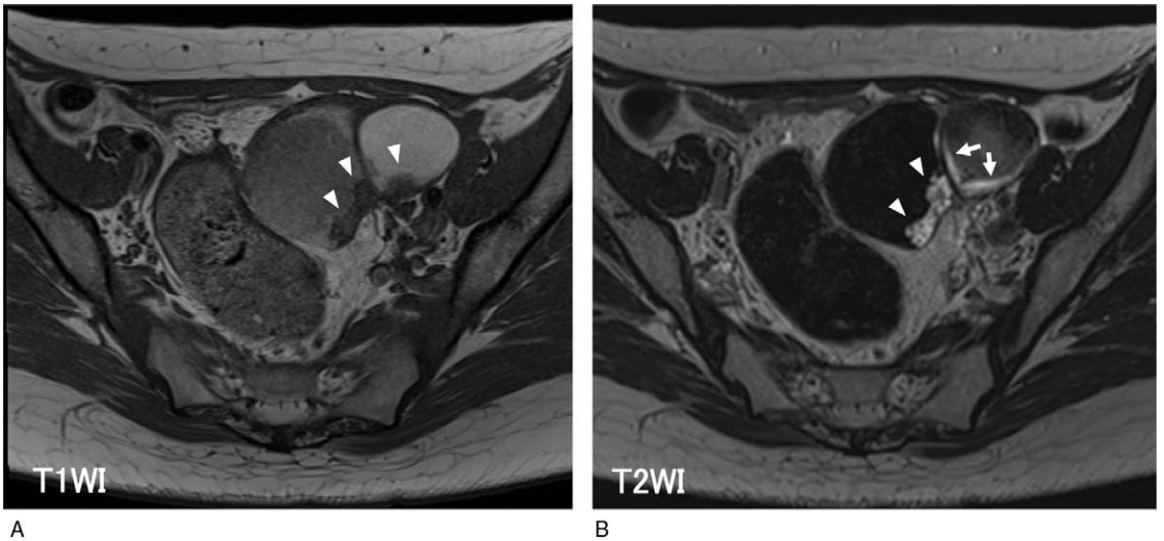


Figure 3. The fluid in the cysts had intermediate to high signal intensity on T1WI (A) and low and intermediate signal intensity on T2WI (B). T1WI demonstrated a multilocular cyst containing papillary projections and/or solid portion (arrowheads). MRI revealed a circumferential region of high signal intensity in the periphery of the cyst (arrows). MRI = magnetic resonance imaging.

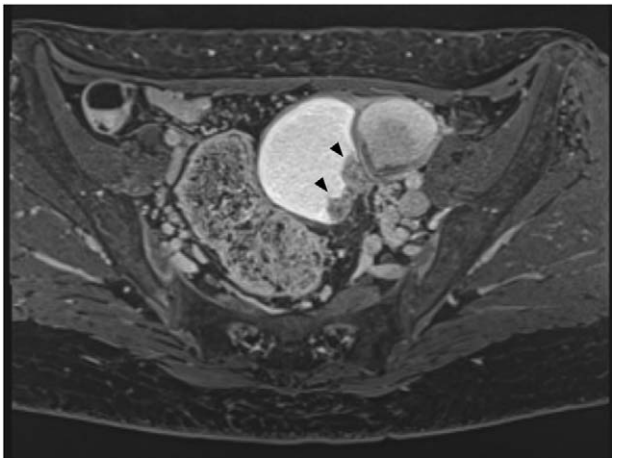
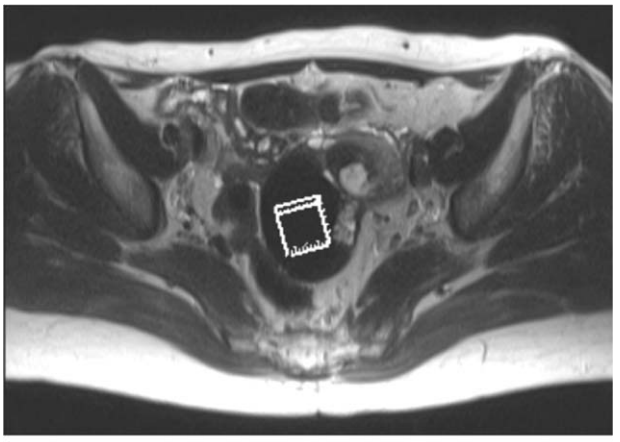


Figure 4. Dynamic contrast-enhanced fat-suppressed gradient-echo T1-weighted imaging was performed, after a rapid injection of gadolinium chelate components (Magnevist, Bayer). After administration of contrast material, the mural nodule was enhanced (arrowhead).



Fat percentage (%)	1.40 % (CI95: -1.00 to 3.80)		
R2 water	42.62 s-1 (rsq = 0.99)		
	Water Sig.	Lipid Sig.	Lipid Percent
T2 Corrected	1.56e+07	2.22e+05	1.40
TE = 12	1.23e+07	3.32e+05	2.62
TE = 24	5.08e+06	7.87e+04	1.53
TE = 36	2.74e+06	7.81e+04	2.77
TE = 48	1.70e+06	5.23e+04	2.99
TE = 72	8.93e+05	6.54e+04	6.82
R2 (s-1)	42.62	22.60	
R-square fit	0.99	0.92	

Figure 5. After the routine MRI, she underwent MR relaxometry by using single-voxel acquisition mode sequence at a multiple echo times and by fitting an exponential decay to the echo amplitude at different multiple echo times. A parameter R2 value s^{-1} was calculated using high-speed T2*-corrected multi-echo MR sequence (HISTO) by the 3T-MR system in vivo as described previously.[8] A $15 \times 15 \times 15$-mm spectroscopy voxel was placed to select a region encompassing the liquid portion of the cyst. The T2 relaxation time (R2 value) of the cystic fluid was $42.62\,s^{-1}$. HISTO = high-speed T2 corrected multi-echo, MRI = magnetic resonance imaging.

Since the above finding was also seen in this patient, she was provisionally classified as having EAOC by MRI. Therefore, diagnostic imaging of the solid components of tumors such as vascularized mural nodules did not provide a better differential diagnostic between SMBT and EAOC.

Second, the cystic components of the present case showed isointensity or hyperintensity on T1WI and low and mild hyperintensity on T2WI. This finding is in good agreement with that of Kurata et al, reporting that SMBT showed a high intracystic fluid signal intensity on T1WI and a low signal intensity on T2WI.[2] The intracystic fluid signal intensity depends upon the electron paramagnetic effects of the different derivates of hemoglobin (oxyhemoglobin, methemoglobin, heme iron, and free iron) and the magnetic field strength.[12] Recent metallobiology study demonstrated that methemoglobin (ferric Fe^{3+}) was significantly more abundant in cyst fluids of benign OE than EAOC patients, while oxyhemoglobin (ferrous Fe^{2+}) was significantly more abundant in the cyst fluids of EAOC than benign OE.[13] Therefore, the oxyhemoglobin/methemoglobin ratio may be useful as a surveillance test for the early detection of malignant transformation.[13] Methemoglobin is predominantly produced from oxyhemoglobin in endometriotic environments due to repeated episodes of hemorrhage via the autoxidation and Fenton reaction.[13,14] In contrast, oxyhemoglobin and antioxidants, including glutathione transferase family, are increased in patients diagnosed with EAOC compared to the benign OE group.[14,15] Excess antioxidants may inhibit oxidative stress-induced cell death by scavenging surplus reactive oxygen species, thus allowing for survival of premalignant endometriotic cells.[15] In this case, intracystic fluid signal intensity suggests that the fluid contains subacute (methemoglobin) hemorrhage.[12] Thus, signal intensity feature of SMBT resembles benign OE more closely than EAOC.

Third, the concentrations of hemoglobin and iron species in endometriosis is considered to be a possible indicator of malignancy.[3] Previous study demonstrated that total iron levels in the cyst fluid of EAOC patients were significantly lower than those in patients with benign OE.[9] Total iron level <64.8 mg/L is an important biomarker that can predict malignant transformation (90.9% sensitivity, 100% specificity).[9] The MR relaxometry R2 value is highly accurate in the differential diagnosis of benign and malignant endometriosis.[9] In vivo R2 value was highly correlated with the cyst fluid total iron concentration ([total iron] $= 11.606 \times$ [in vivo R2] $- 43.325$).[8] The receiver operating characteristic curve analysis of the R2 value yielded a best cutoff value of $12.1\,s^{-1}$. Thus, MR relaxometry provided a new insight in the assessment of the cyst fluid total iron concentration and in the management of malignant transformation of endometriosis.[8] Using the above formula, we can readily calculate the total iron concentration ($= 451$ mg/L) from in vivo R2 value ($= 42.6\ s^{-1}$), suggesting that both in vivo R2 value and total iron concentration of this case can predict non-malignancy. This finding demonstrated the similarity in MR relaxometry feature of SMBT and benign OE, but not EAOC.

Fourth, additional effort has been made to better clarify the molecular mechanisms that are involved in the pathogenesis of SMBT. Immunohistochemical studies of the present case demonstrated ovarian SMBT cells were positive for ER, PgR, and HNF-1β. Clear cell carcinoma cells were positive for HNF-1β but negative for ER and PgR, while endometrioid carcinoma cells were positive for ER and PgR but negative for HNF-1β.[16–18] Hormone receptors and HNF-1β immunostainings were

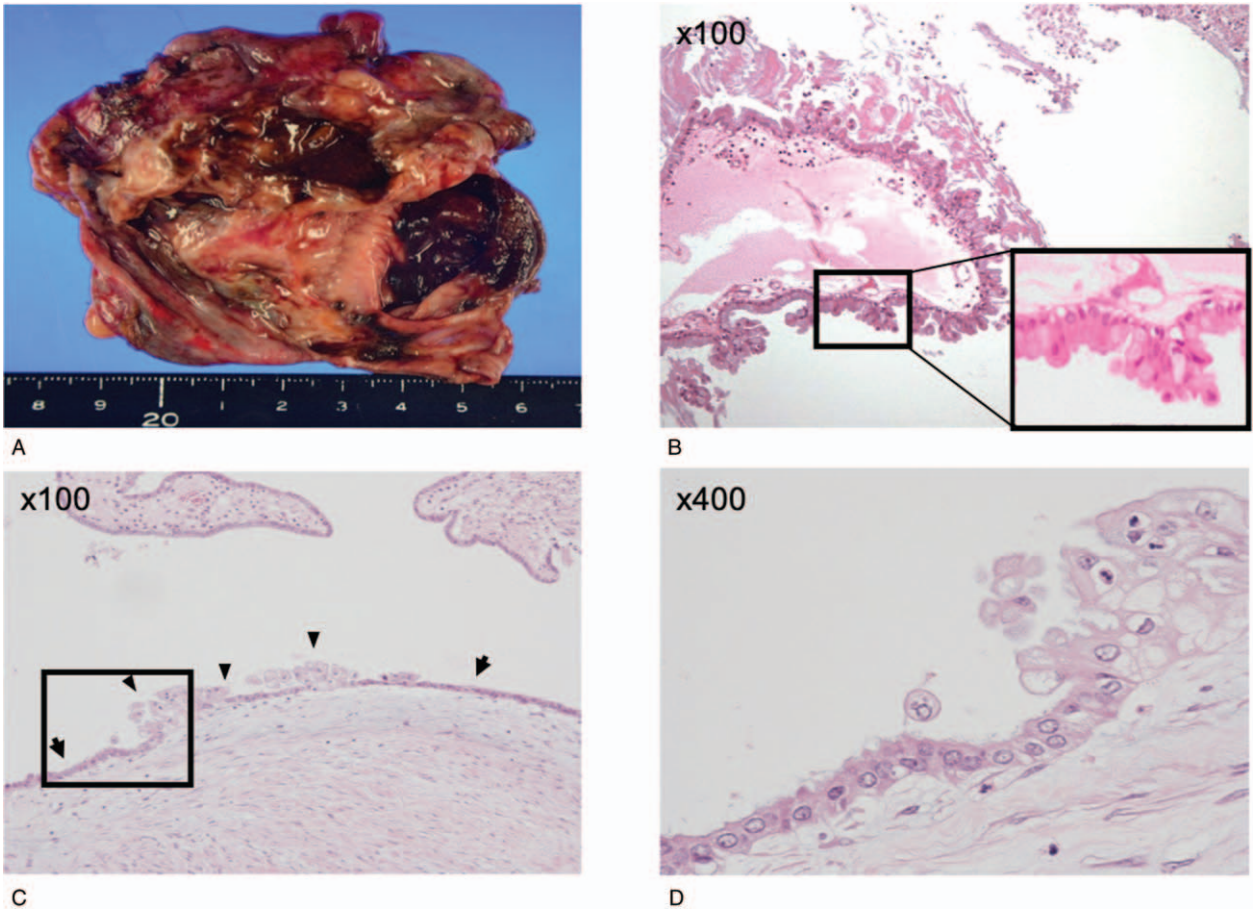


Figure 6. (A) Gross specimen shows a cyst containing brownish fluid and a hemorrhagic component. The inner surface shows many papillary protruding nodules. (B) The black square lesion was set to ×400. Hematoxylin and eosin-stained section showing papillary hyperplasia in the cyst wall (original magnification, ×100). Photomicrograph shows the papillary tumors lined by tall columnar mucinous and ciliated serous cells. (C) Complex papillary excrescences lined by stratified endocervical-type mucinous (arrowheads) and serous (arrows) epithelium (original magnification, ×100). (D) The black square lesion in C was set to ×400. The papillary tumors of ovary were lined by tall columnar mucinous and ciliated serous cells. Focal atypical glands with some papillary structure and nuclei.

mutually exclusive, which may play pivotal roles in the pathogenesis of EAOC.[16] On the other hand, endometriotic cells were positive for ER and PgR and focally positive for HNF-1β.[19] SMBT and benign OE had similar immunohistochemical expression patterns that differed from the pattern of EAOC, suggesting that molecular characteristics of SMBT resemble OE more closely than EAOC. In contrast, Nakamura et al, reported that seromucinous tumor cells were positive for ER and PgR but negative for HNF-1β.[20] Even though HNF-1β plays a key role in several biological processes, including cellular metabolism, cell survival, and malignant transformation of endometriosis,[18,21,22] its role in the pathogenesis of SMBT remains unknown.

Finally, this study provides us a scenario of the 2-step malignant transformation model, and explain the possible mechanism underlying the pathogenesis of SMBT (Fig. 8). In the first step, excess hemoglobin and iron species cause oxidative damage via the autoxidation and Fenton reaction, and induce abundant reactive oxygen species, which results in DNA damage and mutations. Excess oxidative stress in turn contributes to the generation of a protumorigenic microenvironment and is probably involved in the development of atypical endometriosis and SMBT. However, the dichotomy between atypical endometriosis and SMBT has been unexplored. In the second step, reduced iron content and increased antioxidant protection could account for part of the cell survival and tumorigenic effect of endometriotic cells. An effective antioxidant defense may be required for SMBT cell progression. SMBT cells are precancerous states but may stop at the first step. SMBT is typically confined to the ovary and rarely relapses after surgery.[20] However, the results should be interpreted with caution as this hypothesis was based on 1 case with SMBT and several authors have reported invasive carcinoma of these seromucinous tumors.[23]

In conclusion, we report the typical imaging findings of SMBT using the morphological and functional imaging modalities, MRI and MR relaxometry, that are clinically available. MRI still poses difficulties in establishing a proper differential diagnosis between SMBT and EAOC, but MR relaxometry may predict SMBT from EAOC. Moreover, we also attempt to provide an immunohistochemical approach for the expression patterns of hormone receptors and HNF-1β that may play a role in the pathogenesis of SMBT. Immunohistochemical results suggest that patients with SMBT rather resemble patients with benign OE than patients with EAOC. Additional cases are

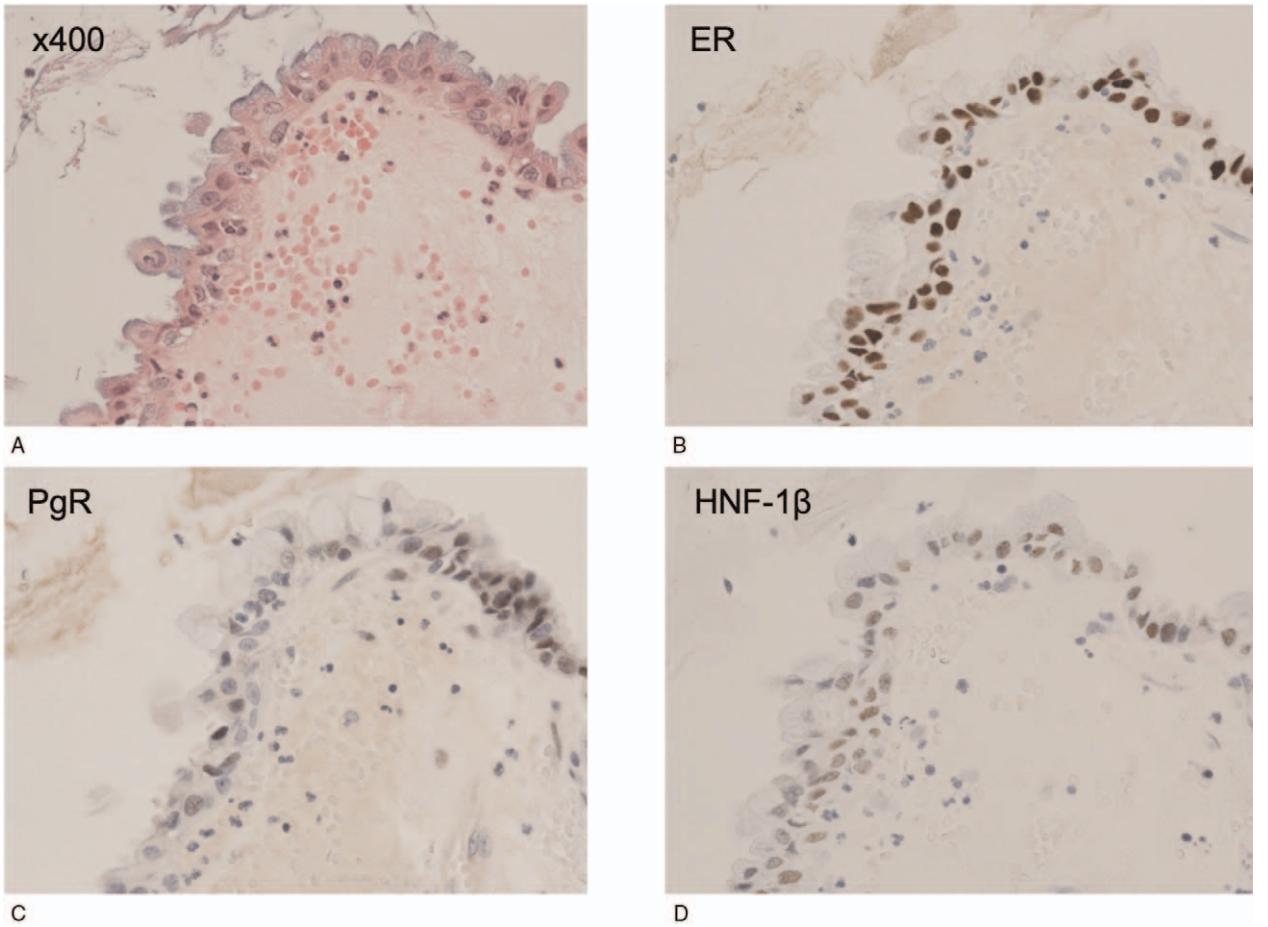


Figure 7. Immunohistochemical findings of SMBT. (A) Hematoxylin and eosin-stained section showing papillary hyperplasia in the cyst wall. Tumor cells showing positive immunohistochemical staining for ER (B), PgR (C), and HNF-1β (D). ER = estrogen receptor, HNF-1β = hepatocyte nuclear factor-1beta, PgR = progesterone receptor, SMBT = seromucinous borderline tumor.

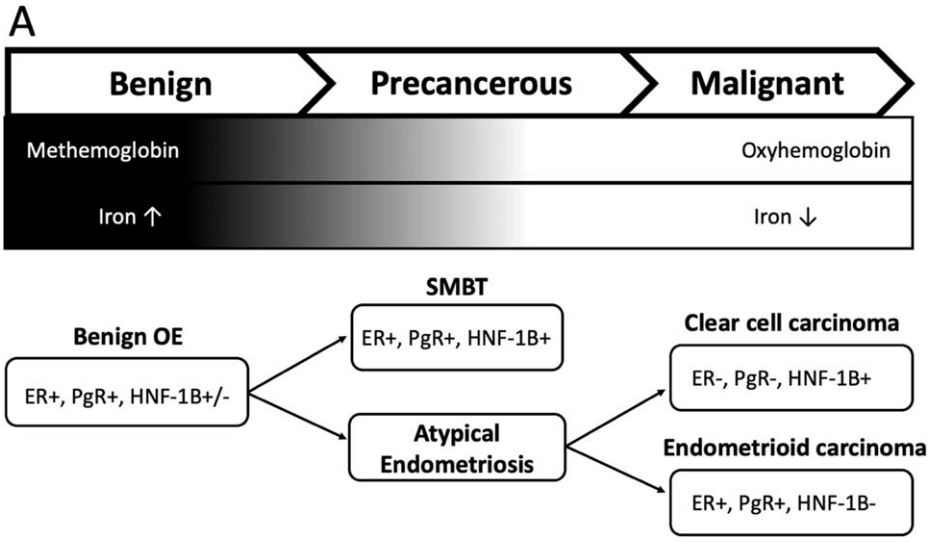


Figure 8. To better understand the pathogenesis and histogenesis of SMBT, we analyzed the possibility of a link of benign OE, atypical endometriosis, and EAOC by MRI, MR relaxometry and immunohistochemistry. Various blood products within cyst fluids were measured on MRI and MR relaxometry. MRI findings of this case suggest that methemoglobin is one of the most abundant hemoglobin species in SMBT cysts. MR relaxometry also reveals that SMBT exhibited increased in vivo R2 values and total iron levels. This case of SMBT may arise from the ER, PgR, and HNF-1β-positive endometriotic cells. Endometrioid adenocarcinoma and clear cell carcinoma arise from the HNF-1β-negative and HNF-1β-positive epithelial cells of endometriosis, respectively.[16] On the basis of the pattern of biomarker expression, SMBT appears to resemble benign OE tumor, but not EAOC. EAOC = endometriosis-associated ovarian cancer, ER = estrogen receptor, HNF-1β = hepatocyte nuclear factor-1beta, MRI = magnetic resonance imaging, OE = ovarian endometrioma, PgR = progesterone receptor, SMBT = seromucinous borderline tumor.

required to determine the diagnostic accuracy and elucidate its pathogenesis.

Author contributions

Tingting Liu, Daichi Sumida, Takuya Wada, and Naoki Kawahara collected data regarding SMBT using the PubMed database.
Hiroshi Kobayashi and Chiharu Yoshimoto made substantial contribution to conception of the study.
Sumire Sugimoto, Tomoka Maehana, and Aika Yamawaki conducted histopathological and immunostaining procedure.
Hiroshi Kobayashi contributed to the study design and interpretation of included clinical studies.
The final version of the manuscript has been read and approved by all authors.
Conceptualization: Chiharu Yoshimoto, Hiroshi Kobayashi.
Data curation: Tingting Liu, Daichi Sumida, Takuya Wada, Naoki Kawahara.
Methodology: Aika Yamawaki, Tomoka Maehana, Sumire Sugimoto.

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