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Original Article

Uterine superficial serous carcinomas and extensive serous endometrial intraepithelial carcinomas: clinicopathological analysis of 6 patients

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Abstract: Uterine superficial serous carcinoma (SSC) and serous endometrial intraepithelial carcinoma (SEIC) are unique malignancies found primarily in postmenopausal women. SSC and SEIC lesions measuring 1 cm or less are categorized as minimal uterine serous carcinoma (MUSC). Less well understood, however, the clinical behavior of SSC and SEIC lesions measuring more than 1 cm. We investigated 6 postmenopausal patients, aged 69-83 years, with SSC or SEIC and without hyperestrogenism. All but 1 patient had tumors originating from the surface of polyps, including 3 patients who each had an enormous polyp occupying the entire uterine cavity. Two patients had extensive SEICs measuring more than 1 cm; the others had SSCs, including 1 MUSC. The mesenchymal cells of the cancer-bearing polyps lacked the morphologic characteristics of endometrial stroma, and the cancer glands often immunostained negatively for estrogen receptors and progesterone receptors. Diffuse immunostaining for human epidermal growth factor receptor 2 was detected in 3 patients, and p53 was detected in all. Cyclin E, a downstream molecule of the F-box and WD repeat domain-containing 7 (*FBXW7*), was detected in all patients. Microdissected cancer glands showed *p53* mutations in 2 patients and a *FBXW7* mutation in 1 patient. These findings suggest that mutations of *FBXW7* and *p53* may contribute to the carcinogenesis of less invasive tumor subtypes. Pathologists and physicians should carefully evaluate SSC and SEIC lesions involving large polyps but lacking myometrial invasion.

Keywords: Superficial uterine serous carcinoma, polyp, p53, F-box and WD repeat domain-containing 7 (*FBXW7*), cyclin E

Introduction

Endometrial cancers are conventionally divided into type I and type II tumors. The former is a well-differentiated endometrioid type that accounts for the majority of endometrial carcinomas, and the latter is a group composed of more aggressive histological types such as serous and clear cell carcinomas. The mechanism of carcinogenesis of high-grade uterine serous carcinoma (USC) is thought to be different from that of endometrioid carcinoma. It is widely accepted that USC is not related to estrogenic stimulation, and that most USCs have *p53* mutations [1]. USCs are occasionally found at early stages, but are often not detected until the disease is advanced. Noninvasive USC is called serous endometrial intraepithelial carcinoma (SEIC), and USC with limited infiltration is called superficial serous carcinoma (SSC) [1, 2]. Minimal USC (MUSC) comprises SSC and SEIC lesions that measure 1 cm or less in diameter. SSC and SEIC frequently develop from the endometrial polyps of postmenopausal patients [3]. No consensus has been reached on how to define extensive SEIC and SSC lesions (1 cm or more in diameter) that are limited to the polyp, in other words, without myometrial invasion.

Also complicating classification, these extensive tumor subtypes can discontinuously replace the endometrium, making it difficult to precisely measure their size.

Dysplastic glands adjacent to cancer glands frequently have *p53* mutations [4-6]; such glands are described as "endometrial glandular dysplasia (EmGD)" in the literature [1]. A sequential progression model has been proposed that explains the transformation from resting endometrial gland to overt USC, in which p53 is involved as a key factor [2, 7]. Recent whole-genome analyses of USC lesions have identified some new markers: methyl-CpG binding domain 3 (MBD3) and F-box and WD repeat domain-containing 7 (*FBXW7*) [8]. In some patients with invasive USC, somatic *FBXW7* mutations have been found not only in the invasive lesions but also in intraepithelial neoplasms [9].

Herein, we described the clinicopathological features found in the USC lesions of 6 patients: 2 extensive SEICs and 4 SSCs. In 3 patients, the tumors developed from a large polyp; the neoplasms developed from average-sized polyps in 2 patients and from flat endometrium in 1 patient. Immunostaining patterns for hormone receptors and cancer-related molecules were compared between tumor- and non-tumor regions. We also investigated somatic mutations of the *p53* and *FBXW7* genes.

Materials and methods

Clinical samples

Six patients with USC were enrolled in this study (**Table 1**). Written informed consent for tissue analysis was obtained from each patient. The study design was approved by the institutional review boards of Yokohama City University and Yokohama Municipal Citizen's Hospital. Seven samples of normal postmenopausal uterine tissue were used as a control. The resected tissues were fixed with 10% formalin and embedded in paraffin. Several 4-μm sections were then cut from each paraffin block and stained with hematoxylin and eosin.

Histopathological diagnosis of USC and atypical glands

We defined "extensive SEIC" as a noninvasive USC greater than 1 cm in diameter, and "SSC" as USC with superficial invasion of the endometrium but not the myometrium, regardless of the horizontal and vertical extent of the tumor in the endometrial polyp itself. We defined atypical glands in USC-adjacent endometrium as "atypical glands indefinite for neoplasia (AGIN)". AGIN lesions contained glands that were morphologically atypical but not definitive of SEIC, fulfilling more than 2 of the following 4 points: (1) hyperchromatic and slightly enlarged, rounded nuclei; (2) more proliferative features than resting glands; (3) partial loss of cell polarity; (4) a few apoptotic bodies. We created this definition because of the possibility that repeated biopsy or curettage before hysterectomy affected the histology of the endometrium, making it difficult to distinguish glandular dysplasia [4, 5] from metaplasia or biopsy-associated regenerative changes.

Immunohistochemistry

After deparaffinization and rehydration, sections were autoclaved at 121°C for 15 minutes. Immunohistochemical staining was done using the EnVision+ kit (Dako Denmark A/S, Glostrup, Denmark), followed by 3, 3'-diaminobenzidne staining for visualization. A 1:800 dilution was used for the progesterone receptor (PgR) antibody (Dako Denmark A/S); 1:50 for the estrogen receptor (ER) antibody (Dako Denmark A/S); 1:50 for the p53 antibody (Dako Denmark A/S); 1:50 for the cyclin E antibody (Leica, Biosystems, Wetzlar, Germany); and 1:100 for the *FBXW7* antibody (Invitrogen, Camarillo, CA), prediluted human epidermal growth factor receptor 2 (HER2) antibody (Roche Diagnostics GmbH, Mannheim, Germany), CD10 antibody (Roche Diagnostics GmbH), and α-smooth muscle actin (α-SMA) antibody (Nichirei Biosciences Inc., Tokyo, Japan). The intensity of the immunostaining was graded as; (-): no staining or less than 1% of cells positive; (±): up to 10% positive; (+): 11-50% positive; (++): 51-100% positive.

Laser capture microdissection and direct sequencing

Laser capture microdissection (LCM) was performed, and DNA of SSC lesions was extracted using the QIAamp DNA Mini kit (QIAGEN GmbH, Hilden, Germany). Exons 5-8 of *p53* and exon 8-9 of *FBXW7* were amplified by polymerase chain reaction (PCR). The primers for *p53* exons 5-8 have been previously described [10]. The primers used for *FBXW7* were (F) 5'-AGTGT-

Table 1. Clinical characteristics

Patient SEIC/SSC (FIGO stage)	Age, years (G/P)	Condition	Em Cytology/Biopsy	Polyp size/SEIC/ SSC extension	Procedure	Status (follow-up period, months)
1 SSC (IA)	77 (G4P2)	Unknown	Positive/adenocarcinoma	60 mm/20 mm	RH + BSO + LN	DOD (96)
2 SEIC[1)]/SSC[2)] (IA)	72 (G3P3)	Abnormal cervical smear	Positive/serous carcinoma	1) 12 mm/1 mm[#] 2) 8 mm/8 mm[#]	TAH + BSO	NED (38)
3 SEIC (IA)	69 (G2P2)	Postmenopausal bleeding	Positive/ adenocarcinoma	No polyp/13 mm[#]	RH + BSO + LN	NED (44)
4 SEIC (IIIB)	70 (G3P3)	Abdominal distension	Negative*/not done	97 mm/40 mm	TAH + BSO + OMT	DOD (1.5)
5 SSC (IA)	83 (G2P1)	Postmenopausal bleeding	Positive/adenocarcinoma	85 mm/22 mm	TAH + BSO	AWD (16)
6 SSC (IA)	76 (G2P2)	Postmenopausal bleeding	Positive/not done	20 mm/12 mm[#]	RH + BSO + LN	NED (20)

Abbreviations: SEIC: serous endometrial intraepithelial carcinoma; SSC: superficial serous carcinoma; FIGO: International Federation of Gynecology and Obstetrics; G: gravidity; P: parity; Em: endometrial; RH: radical hysterectomy; BSO: bilateral salpingo-oophorectomy; LN: lymphadenectomy; TAH: total abdominal hysterectomy; OMT: omentectomy; NED: no evidence of disease; DOD: dead of disease; AWD: alive with disease. *ascites cytology was positive. #intermittent extension.

GGAATGCAGAGACTGG-3' and (R) 5'-TTTAAGAGCACACTGTCACTATTTCAG-3' for exon 8 and (F) 5'-TCTGCAGAGTTGTTAGCGGTT-3' and (R) 5'-CAGTCTCTGGATCCCACACC-3' for exon 9. The PCR procedure was carried out using denaturation at 95°C for 2 minutes, followed by 35 cycles at 95°C for 30 seconds, 58°C for 30 seconds, and 72°C for 45 seconds, with an extension step of 5 minutes at 72°C at the end of the last cycle. For *p53* exon 5, 40 cycles were performed. After purification, DNA was labeled using the Big Dye Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Bedford MA) and DNA direct sequencing was done using the ABI Prism 3100 Genetic Analyzer (Applied Biosystems).

Results

Clinical summary

Patients' clinical information is summarized in **Table 1**. The patients were aged 69-83 years, and all were multiparous, postmenopausal Japanese women without significant gynecologic disease history. The single exception was patient 5, who had a history of breast cancer and had undergone mastectomy 21 years previously, followed by 5 years of tamoxifen treatment. No patient had a familial history of hereditary breast and ovarian cancer syndrome. Three patients (3, 5 and 6) had genital bleeding as the first manifestation of pathology, and were diagnosed with adenocarcinoma by endometrial cytology and/or biopsy. Patient 2 had an abnormal screening cervical smear, but a thorough medical workup had not revealed any evidence of malignancy. She was followed closely and, 3 years later, was diagnosed with serous carcinoma by endometrial biopsy. Patient 4 complained of abdominal distension, and a large intrauterine polyp and ascites were detected. Although endometrial cytology was negative, a smear of the ascites fluid revealed adenocarcinoma. All patients underwent total hysterectomy and bilateral salpingo-oophorectomy (**Table 1**). Patients 1 and 4 died of their disease. Patient 5 had a local recurrence 1 year after surgery, and was alive with the disease at the time of this study. The other 3 patients have been followed since surgery, with none exhibiting evidence of disease.

Macroscopic findings

All but 1 patient had intrauterine polypoid lesions. Patients 1, 4, and 5 each had a large polyp occupying the entire uterine cavity (**Figure 1A**). The cut surfaces of these polyps were spongiform. Patient 3 was the only one without a polyp; she developed a tumor, 2 mm high and 13 mm wide, from the surface of the endometrium (**Figure 1B**). Patient 2 demonstrated 2 separate polyps; 1 in the fundus and 1 in the isthmic region of the uterus.

Microscopic findings

In all 6 patients, the cancer lesions consisted of serous-type glands. Other histological types, such as clear cell- and endometrioid adenocarcinomas, did not coexist. Only 1 patient exhibited metastasis to the adnexa and lymph nodes. In patient 4, microscopic metastases were detected on the surface of both ovaries and of the omentum (International Federation of Gynecology and Obstetrics [FIGO] stage IIIB). Other 5 patients were diagnosed as FIGO stage IA.

In patients 1, 4, and 5, USC developed from a large polyp that was composed of innumerable cystic glands and hyalinized stroma (**Figure 1C**). Papillary cancers intermittently spanned the polyp surface by forming confluent glands measuring from 20 mm to 40 mm in diameter. In patient 4, the cancer glands replaced the preexisting glands without definitive stromal invasion, while patients 1 and 5 demonstrated desmoplastic stromal invasion of less than 1 mm. Negative staining for α-SMA precluded the possibility of adenomyomatous polyp and atypical polypoid adenomyoma. The majority of the benign cystic glands in the polyp showed flattened epithelial cells.

Patient 2 had 2 polyps: a 12-mm polyp that contained SEIC and an 8-mm polyp that contained SSC. In the nonpolyp regions, SEIC lesions intermittently replaced the atrophic glands. In patient 3, SEIC was detected in a slightly elevated area of the endometrium with exudative modification (**Figure 1B**, **1D**).

Moderately atypical glands were detected in the vicinity of cancer lesions, which we described as AGIN according to the definition in the Materials and Methods section of this manuscript. Representative microscopic features of AGIN and SSC were shown in **Figure 1E** and **1F**.

Immunohistochemical findings

The results of immunohistochemistry are summarized in **Table 2**. In our patients, ERs and

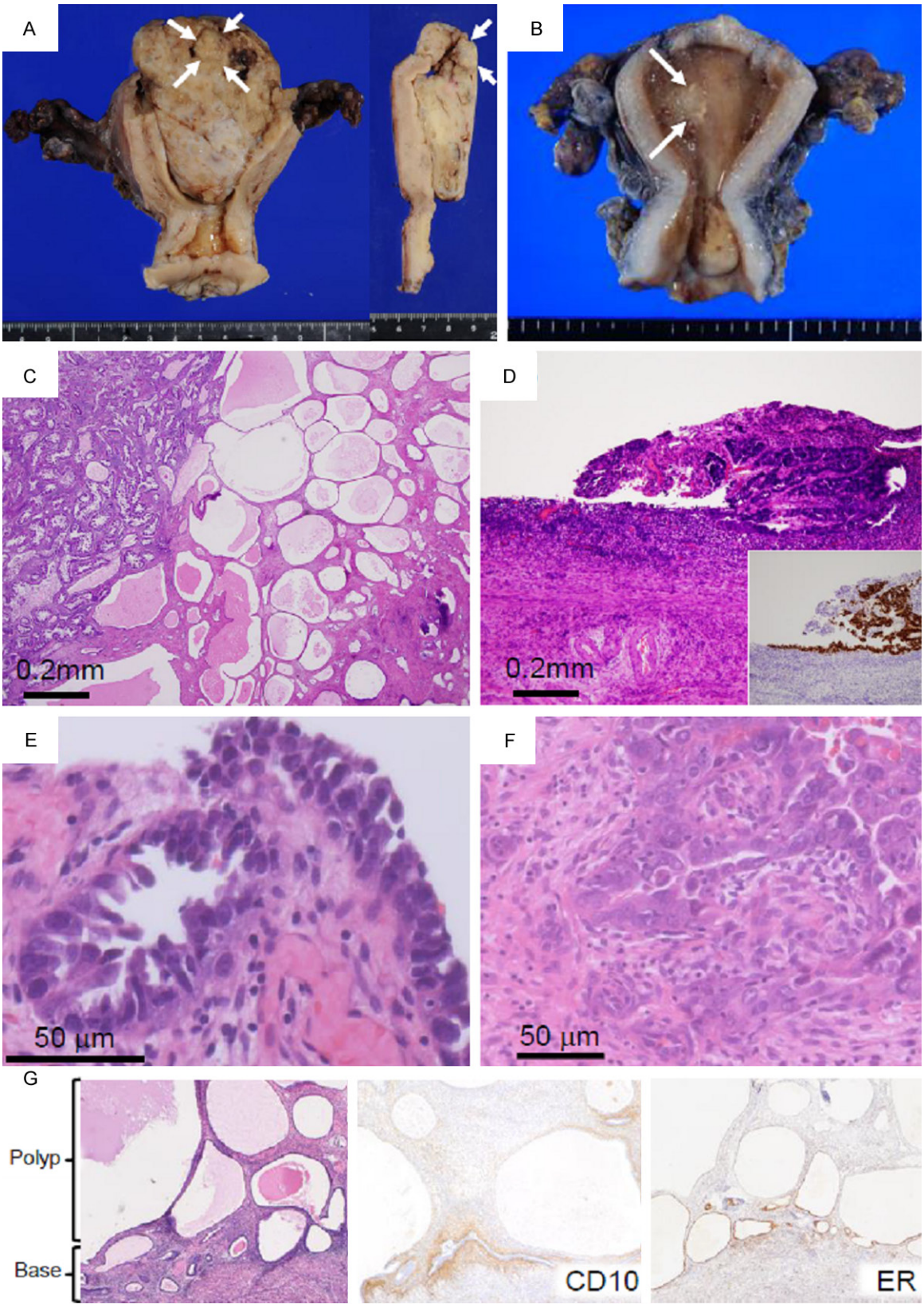

Figure 1. Macroscopic and microscopic features of superficial serous carcinoma (SSC) and serous endometrial intraepithelial carcinoma (SEIC). A. The resected uterus has a large polyp occupying the uterine cavity (patient 5). The cut surface of a spongy polyp is shown at right. The arrows indicate the SSC lesion. B. The resected uterus with

no polyp (patient 3). The arrows indicate the SEIC lesion. C. SSC developing in a cystic polyp (patient 1). The polyp surface (left) is replaced by serous-type cancer glands. D. A focus of SEIC without polyp in atrophic endometrium (patient 3). Inset: serial-section immunostaining for p53. E. A representative feature of atypical glands indefinite for neoplasia (AGIN): proliferative glands with hyperchromatic and slightly enlarged nuclei (patient 2). F. A representative feature of SSC: microinvasive glands and desmoplastic stroma (patient 2). G. Decreased immunoreactivity for CD10 and estrogen receptors (ERs) in the stroma of an exophytic polyp (patient 1). Serial staining sections are shown.

Table 2. Summary of immunostaining in malignant and benign tissues

Immunostaining	SEIC/SSC (n = 6)	AGIN (n = 6)	Polyp glands (n = 5)	Polyp stroma (n = 5)	Non-polyp glands (n = 6)	Non-polyp stroma (n = 6)
ER						
(-), (±)	3, 1	2, 0	0, 0	0, 2	1, 0	0, 0
(+)	0	2	0	1	0	1
(++)	2	2	5	2	5	5
PgR						
(-), (±)	4, 0	3, 1	0, 0	0, 2	0, 0	0, 1
(+)	1	1	0	0	4	1
(++)	1	1	5	3	2	4
HER2						
(-), (±)	3, 0	2, 1	4, 1	NE	6, 0	NE
(+)	0	1	0	NE	0	NE
(++)	3	2	0	NE	0	NE
p53						
(-), (±)	0, 0	0, 1	3, 2	NE	5, 1	NE
(+)	1	0	0	NE	0	NE
(++)	5	5	0	NE	0	NE
FBXW7						
(-), (±)	6, 0	4, 1	0, 3	NE	0, 4	NE
(+)	0	1	2	NE	2	NE
(++)	0	0	0	NE	0	NE
Cyclin E						
(-), (±)	0, 1	1, 0	2, 2	NE	1, 2	NE
(+)	2	3	1	NE	3	NE
(++)	3	2	0	NE	0	NE

Abbreviations: SEIC: serous endometrial intraepithelial carcinoma; SSC: superficial serous carcinoma; AGIN: atypical glands indefinite for neoplasia; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; *FBXW7*: F-box and WD repeat domain-containing 7; (-): no staining; (±): 1-10% positive; (+): 11-50% positive; (++): 51-100% positive; NE, not evaluated.

PgRs were less frequently expressed in cancer lesions and AGIN than in resting glands (**Figure 2A**; **Table 2**). Most resting glands in the polyps and in the flat areas of the endometrium showed diffuse ER and PgR expression; however, the mesenchymal cells of edematous polyps occasionally showed sparse immunoreactivity for ER and PgR (**Figure 1G**). These cells stained negative for CD10 (**Figure 1G**) and α-SMA. Positive staining for HER2 was observed in the cancer lesions and corresponding AGIN in 3 of 6 patients (**Figure 2B**).

Almost all cancer lesions showed intensive immunostaining for p53, and the adjacent AGIN lesions were also positive (**Figure 2C**). In contrast, the resting glands lacked p53 immunostaining or had only a few positive cells. We examined *FBXW7* staining in normal postmenopausal endometrial glands (n = 7), and found occasional weak immunoreactivity. Next, we examined *FBXW7* in the study patients. All cancer lesions stained negative, while the resting glands showed focal immunoreactivity (data not shown). Immunostaining for cyclin E, a

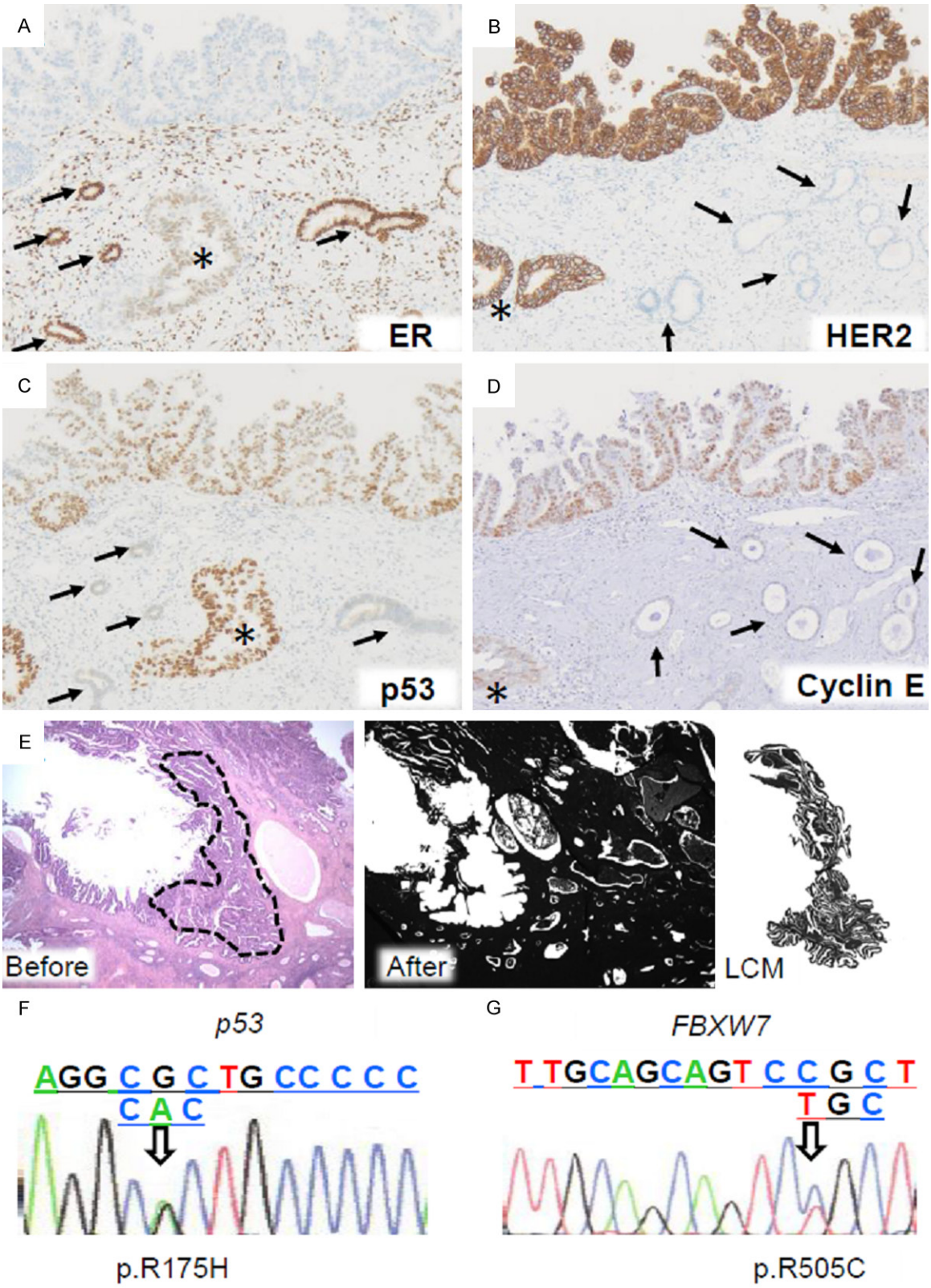

Figure 2. Immunohistochemical and genomic features of SSC. (A-D) Serial-section immunohistochemical staining for ERs (A), human epidermal growth factor receptor 2 (HER2) (B), p53 (C), and cyclin E (D) in an SSC-bearing polyp (patient 5). Arrows indicate resting glands, and asterisks indicate AGIN. The polyp surface is replaced by cancer glands. (E) An example of laser capture microdissection (LCM) (patient 1). The dotted circle indicates the dis-

sected lesion. (F) Somatic mutation of *p53* from CGC to CAC (arrow) in patient 5, predicting the amino acid change p.R175H. (G) Somatic mutation of the F-box and WD repeat domain-containing 7 (*FBXW7*) gene from CGC to TGC (arrow) in patient 1, predicting the amino acid change p.R505C.

downstream molecule negatively regulated by *FBXW7*, showed intensive staining in most cancer and AGIN lesions (**Figure 2D**). In contrast, resting glands were either negatively or sparsely stained for cyclin E.

DNA sequencing of p53 and FBXW7

DNA was extracted from 4 SSC lesions using the LCM system (patients 1, 2, 5, and 6 gave consent for genetic analysis) (**Figure 2E**). Patient 5 had a *p53* mutation at p.R175H and patient 6 had the mutation at p.Y163C (**Figure 2F**). No mutation was detected between exons 5 and 8 in the other 2 patients. Patient 1 had *a FBXW7* mutation at p.R505C (**Figure 2G**). The other 3 patients did not have *FBXW7* mutations between exons 8 and 9.

Discussion

The histopathological criteria for and outcomes associated with SSC and extensive SEIC are incompletely understood. The World Health Organization classification of tumors of female reproductive organs describes SEIC as an immediate precursor of invasive USC but does not yet comment on whether tumor extent should be considered in the definition. Some studies have demonstrated that patients with MUSC (i.e., SEIC and SSC measuring 1 cm or less) have favorable outcomes [2, 3]; however, other studies report that advanced SEIC and SSC (FIGO stages II-IV) carry a poor prognosis [11, 12]. Little is known on whether extensive SEIC and SSC, measuring more than 1 cm, is associated with recurrence or disease dissemination.

Our study included 3 patients who developed SSC or SEIC from a large polyp that occupied the entirety of the uterine cavity; the lesions in these patients exceeded 2 cm in diameter and replaced the cystic glands. SEIC and SSC frequently develop in an endometrial polyp under postmenopausal conditions [3, 13]. However, as there exists a previous report of SSC and SEIC in a large polyp [3], it is possible that abnormally enlarged postmenopausal polyps may be associated with the development of these neoplasms. It should be noted that 2 of our patients with large polyps died of the disease, and 1 had recurrence in spite of the minimally invasive nature of her malignancy. Although the number of patients in our study was small, our findings could indicate that the presence of SSC and SEIC, measuring 2 cm or more, in a large polyp might place the patient at higher risk of dissemination and recurrence than the same malignancy found in a smaller polyp or in flat endometrium.

Limited information is available on the pathological features of USC-bearing polyps. In our patients, cross sectioning of the 3 large polyps revealed spongiform morphology with numerous cystically dilated glands. The polyp stroma was composed of spindle cells and matrix that were unlike endometrial stroma: the spiral arteries were replaced by fragile capillary vessels, and loose mesenchymal cells, negative for CD10, lay between glands. In addition, the stroma of the polyp often had absent or decreased immunoreactivitiy for ERs and PgRs. Unlike normal postmenopausal endometrium that is composed of compact glands and stroma, abnormally dilated glands and sparse stroma might be a favorable environment for precursor cells to transform into their malignant phenotype. In 3 of our patients, $HER2^{+}$ cells were detectable not only in cancer lesions but also in AGIN lesions. Our results indicate that ER/PgR downregulation and HER2 overexpression might occur in some, if not all, USC precursor cells.

Recent genome-wide analyses have highlighted the *FBXW7* gene as one of the new markers of USC [9, 14]. *FBXW7* encodes a member of the F-box protein family: 1 of the 4 subunits of ubiquitin ligase complex SKP1-cullin-F-box (SCF). The staining pattern of *FBXW7* in the normal endometrium has not previously been reported, but both mutations and loss of heterozygosity of *FBXW7* have been reported in several human malignancies [15, 16], suggesting that the gene works as a tumor suppressor [17]. The hot spots of *FBXW7* are not fully understood, but single nucleotide missense, at c.1393, c.1394 and c.1436, has been detected in several USC cases [14]. In the present study, patient 1 had c.1513C > T, predicting the

amino acid change p.Arg505Cys. Of note, however, all 6 cancer lesions were positive for cyclin E, a downstream molecule. Therefore, we cannot exclude the possibility that patients 2 through 6 might have loss of heterozygosity or pathological mutations of *FBXW7* in unexamined exons.

We presented herein the histopathological features of 6 USCs made up of extensive SEICs and SSCs. To the best of our knowledge, this is the first report of SSC with a *FBXW7* mutation. All 3 patients whom tumor was extensive and on the surface of a large polyp had poor outcomes. These findings should alert pathologists and physicians that polyp size and the superficial extent of the tumor are possibly important risk factors that will help to predict patient prognosis. Further study is necessary to better understand the clinicopathological features of extensive SEIC and SSC.

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Disclosure of conflict of interest

None.

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