Table 2 Summary of the management of all patients ($n = 15$)

No.	Disease	Age	Cycles of prior CBDCA	Total CBDCA (mg)	CBDCA HSR grade	Interval to rechallenge (M)	Prior regimen	Regimen	Cycles of nedaplatin	Total nedaplatin (mg)	Premedication	Nedaplatin HSR	Response	Time from infusion start to HSR (min)
1	Ov	64	30	17 175	2	3.9	G	N	2	129	None	Grade 2 (rash)	NE	15
2	Ov	67	9	3 950	3	23.9	T	TN	2	140	D + H + R	Grade 3 (hypotension)	SD	20
3	Ov	47	8	4 455	2	1	TC	TN	4	370	D + H + R	Grade 2 (dyspnea)	NE	44
4	Ov	50	14	8 875	2	1	TC	TN	9	961	D + H + R	Grade 3 (edema)	PR	1
5	Ov	66	12	7 875	3	17.5	TG	DN	1	120	D	(-)	PD	
6	Ov	47	8	5 125	2	3.2	T	DN	4	470	D(x2) + H + R	(-)	NE	
7	Ov	58	11	6 900	3	1	DC	DN	5	600	D′	(-)	PD	
8	Ov	62	8	3 300	2	3.1	TG	DN	6	780	D	(-)	PD	
9	Ov	60	24	12 520	3	9.1	CPT	N	8	1104	D(x2) + R	(-)	SD	
10	Ov	67	20	9 735	2	12.7	T	DN	9	1080	D′	(-)	SD	
11	Ov	52	20	9 080	2	0.7	C	N	15	1800	Cort + R	(-)	PR	
12	Ov	57	8	3 750	3	1	DC	DN	29	3190	D + H	(-)	CR	
13	Tube	59	31	9 660	2	0.7	TC	N	10	1200	D′ + R	(-)	NE	
14	Em	58	10	5 760	2	1.4	TC	DN	23	2845	D′	(-)	PR	
15	Cx	49	26	13 000	2	1.2	TC	TN	10	1100	D(x2) + H + R	(-)	SD	

C, carboplatin; Cort, hydrocortisone 100 mg; CPT, irinotecan; Cx, cervical cancer; D, dexamethasone 20 mg; D′, dexamethasone 6.6 mg; DC, docetaxel/carboplatin; DN, docetaxel/nedaplatin; Em, endometrial cancer; G, gemcitabine; H, diphenhydramine 50 mg; N, nedaplatin; NE, not evaluable; Ov, ovarian cancer; R, ranitidine 50 mg; T, paclitaxel; TC, paclitaxel/carboplatin; TG, paclitaxel/gemcitabine; TN, paclitaxel/nedaplatin; Tube, fallopian tube cancer.

starting infusion of nedaplatin. The other three patients had HSRs on the second, second, and fourth cycle, respectively. In these patients, the reactions occurred more than 15 min after the infusion of nedaplatin had started. Three of the four (75%) patients who received paclitaxel and nedaplatin showed HSRs to nedaplatin, whereas one of the 11 (9%) without paclitaxel ($P = 0.033$ by Fisher's exact test) and none of the seven with docetaxel and nedaplatin ($P = 0.024$) showed HSRs to nedaplatin.

There were no treatment-related deaths. Cycles of nedaplatin, total amount of prior carboplatin, the grade of HSR to carboplatin, and platinum-free interval before the nedaplatin treatment were not significantly distinct between the HSR-positive and the HSR-negative group.

Efficacy

Eleven patients (73%) had measurable disease. We observed one CR (9.1%) and three PRs (27%), for an overall response rate of 36% (95% CI: 11–69%). Stable disease was documented in four (36%) patients, and the disease control rate (CR + PR + SD) was 73% (95%CI: 39–94%). Median progression-free survival was 9.2 months (range: 0.4–42.0 months, 95%CI: 2.1–14.3 months).

In the patients with ovarian or fallopian tube cancer, nine patients had measurable disease. The overall response rate was 33% (one CR and two PRs, 95% CI: 7.5–70%), and the disease control rate was 67% (95% CI: 30–93%). Median progression-free survival was 8.2 months (range: 0.4–38.9 months, 95% CI: 2.1–11.6 months).

Discussion

In this study, we evaluated the safety and efficacy of retreatment with nedaplatin in patients who had developed carboplatin-associated HSRs. Although all the 15 patients were safely treated at first cycle, four (27%) of them experienced HSRs to nedaplatin during their treatment. This incidence suggests that cross-reactions between nedaplatin and carboplatin might occur at substantial frequency, as observed between cisplatin and carboplatin.[10] Our experience supports the risk of delivering any platinum agent following the documentation prior platinum hypersensitivity. However, case 4, who developed HSRs to nedaplatin on the ninth cumulative cycles in the second-line setting, suggests that newly-obtained hypersensitivity to nedaplatin might occur in certain patients.

Table 3 Reported cases of retreatment with carboplatin by desensitization protocol

Authors	Number	Success rate (%)
Gastaminza *et al.*[16]	4	75
Nishio *et al.*[17]	1	100
Gomez *et al.*[18]	7	71
Hesterberg *et al.*[19]	30	97
Confino-Cohen *et al.*[20]	20	95
Lee *et al.*[21]	31	100
Choi *et al.*[22]	8	100
McElroy *et al.*[23]	1	100
Rose *et al.*[24]	33	79
Robinson *et al.*[25]	8	100
Markman *et al.*[26]	3	33
Total	146	90

The mechanism of nedaplatin-associated HSRs remains unclear. Nedaplatin-associated HSRs are likely to be similar to carboplatin-associated HSRs, considering the development of allergic reactions with multiple courses of the therapy and the time from infusion start to the onset of HSRs (≥15 min in three of four patients).[4] Although the exact etiology responsible for carboplatin-associated HSRs is not also clarified, it is believed that both immediate Type I hypersensitivity mediated by IgE and the direct action of platinum on mast cells are involved in the allergic process.

Our study suggests that nedaplatin-associated HSRs in patients with HSRs to carboplatin would be difficult to predict. First, there were no significant differences of the profile between the HSR-positive and the negative group. Second, three of four patients who developed nedaplatin-associated HSRs had premedicated with 20 mg of dexamethasone, 50 mg of diphenhydramine, and 50 mg of ranitidine similar to those of paclitaxel-containing chemotherapy. This indicates that pretreatment with combination of steroids and antihistamines would be insufficient to prevent nedaplatin-associated HSRs. The administration of desensitization protocol may help to reduce the risk of HSRs, as successful rechallenge with carboplatin or cisplatin following desensitization has been reported.[14,15] The result of desensitization to carboplatin is listed in Table 3.[16–25] However, two deaths due to anaphylaxis following retreatment with platinum agents have been reported in spite of using an extensive desensitization protocol.[26] Further study is necessary to evaluate the effect of desensitization to nedaplatin.

It has been reported that the incidence of HSRs depends on a combination drug with platinum. CALYPSO trial showed that carboplatin-associated HSRs occurred significantly less frequently in treatment with pegylated liposomal doxorubicin and carboplatin than that with paclitaxel and carboplatin in patients with platinum-sensitive relapsed ovarian cancer.[27] The result of our study suggests that the combination of paclitaxel and nedaplatin might increase a risk of HSRs to nedaplatin. On the other hand, SCOTROC trial showed that HSRs were more frequent in combination of docetaxel and carboplatin in comparison with that of paclitaxel and carboplatin in first-line setting.[28]

Although the sample size is small, the overall response rate and the disease control rate (CR + PR + SD) in the patients with ovarian or fallopian tube cancer were achieved at 33% and 67%, respectively. A previous report showed that the response rate was 24% and the disease control rate was 59% by treatment with nedaplatin in patients with platinum-resistant ovarian, tubal, and peritoneal cancers.[29] The lower rate of patients with platinum-resistant disease in the present study might lead to slightly higher response rate and disease control rate. Nevertheless, other agents could be as effective as nedaplatin, considering that all the patients had platinum-sensitive disease at their primary treatment.

In conclusion, nedaplatin-associated HSRs are not rare in patients who have developed allergic reactions to carboplatin, indicating that non-platinum agents should be first considered to the patients with HSRs to carboplatin. The use of nedaplatin might be taken into consideration to patients that alternative drugs are not available, as these patients might be still sensitive to platinum. Appropriate informed consent regarding the potential risk and prompt treatment to the HSRs are indispensable for the rechallenge with nedaplatin. And also, the desensitization study of nedaplatin should be needed.

Disclosure

We declare that there are no conflicts of interest.

References

1. du Bois A, Lueck HJ, Meier W *et al.* A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003; **95**: 1320–1330.
2. Markman M, Rothman R, Hakes T *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991; **9**: 389–393.

3. Parmar MK, Ledermann JA, Colombo N *et al.* Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: The ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003; **361**: 2099–2106.
4. Markman M, Kennedy A, Webster K *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; **17**: 1141–1145.
5. Morgan JS, Adams S, Mason MD. Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. *Eur J Cancer* 1994; **30A**: 1205–1206.
6. Hendrick AM, Simmons D, Cantwell BM. Allergic reactions to carboplatin. *Ann Oncol* 1992; **3**: 239–240.
7. Koshiba H, Hosokawa K, Kubo A *et al.* Incidence of carboplatin-related hypersensitivity reactions in Japanese patients with gynecologic malignancies. *Int J Gynecol Cancer* 2009; **19**: 460–465.
8. Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol* 2002; **84**: 378–382.
9. Zweizig S, Roman LD, Muderspach LI. Death from anaphylaxis to cisplatin: A case report. *Gynecol Oncol* 1994; **53**: 121–122.
10. Kandel MJ, Loehr A, Harter P, Traut A, Gnauert K, du Bois A. Cisplatinum rechallenge in relapsed ovarian cancer patients with platinum reinduction therapy and carboplatin hypersensitivity. *Int J Gynecol Cancer* 2005; **15**: 780–784.
11. Kato T, Nishimura H, Yakushiji M *et al.* Phase II study of 254-S (cis-diammine glycolato platinum) for gynecological cancer. *Gan to Kagaku Ryoho* 1992; **19**: 695–701.
12. Noda K, Ikeda M, Yakushiji M *et al.* A phase II clinical study of cis-diammine glycolato platinum, 254-S, for cervical cancer of the uterus. *Gan to Kagaku Ryoho* 1992; **19**: 885–892.
13. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228–247.
14. Goldberg A, Confino-Cohen R, Fishman A, Beyth Y, Altaras M. A modified, prolonged desensitization protocol in carboplatin allergy. *J Allergy Clin Immunol* 1996; **98**: 841–843.
15. Jones R, Ryan M, Friedlander M. Carboplatin hypersensitivity reactions: Re-treatment with cisplatin desensitisation. *Gynecol Oncol* 2003; **89**: 112–115.
16. Gastaminza G, de la Borbolla JM, Goikoetxea MJ *et al.* A new rapid desensitization protocol for chemotherapy agents. *J Investig Allergol Clin Immunol* 2011; **21**: 108–112.
17. Nishio S, Koyanagi T, Miyabe K, Kuromatsu H. Successful desensitization protocol for patients with hypersensitivity reactions caused by carboplatin. *Gan to Kagaku Ryoho* 2010; **37**: 731–733.
18. Gomez R, Harter P, Lück HJ *et al.* Carboplatin hypersensitivity: Does introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. *Int J Gynecol Cancer* 2009; **19**: 1284–1287.
19. Hesterberg PE, Banerji A, Oren E *et al.* Risk stratification for desensitization of patients with carboplatin hypersensitivity: Clinical presentation and management. *J Allergy Clin Immunol* 2009; **123**: 1262–1267.
20. Confino-Cohen R, Fishman A, Altaras M, Goldberg A. Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer* 2005; **104**: 640–643.
21. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: Standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005; **99**: 393–399.
22. Choi J, Harnett P, Fulcher DA. Carboplatin desensitization. *Ann Allergy Asthma Immunol* 2004; **93**: 137–141.
23. McElroy TM, Gruenigen VE, Waggoner SE. A case of prolonged carboplatin therapy in a patient with carboplatin hypersensitivity. *Gynecol Oncol* 2003; **91**: 435–437.
24. Rose PG, Fusco N, Smrekar M, Mossbruger K, Rodriguez M. Successful administration of carboplatin in patients with clinically documented carboplatin hypersensitivity. *Gynecol Oncol* 2003; **89**: 429–433.
25. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, Wolf JK. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. *Gynecol Oncol* 2001; **82**: 550–558.
26. Markman M. Hypersensitivity reactions to carboplatin. *Gynecol Oncol* 2002; **84**: 353–354.
27. Joly F, Ray-Coquard I, Fabbro M *et al.* Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: Analysis from the GCIG CALYPSO relapsing ovarian cancer trial. *Gynecol Oncol* 2011; **122**: 226–232.
28. Vasey PA, Jayson GC, Gordon A *et al.* Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst* 2004; **96**: 1682–1691.
29. Goto T, Takano M, Ohishi R *et al.* Single nedaplatin treatment as salvage chemotherapy for platinum/taxane-resistant/refractory epithelial ovarian, tubal and peritoneal cancers. *J Obstet Gynaecol Res* 2010; **36**: 764–768.

THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/j.1447-0756.2012.01915.x J. Obstet. Gynaecol. Res. Vol. 39, No. 1: 424–429, January 2013

Low-grade endometrial stromal sarcoma developing in a postmenopausal woman under toremifene treatment for breast cancer

Tomoko Kashiyama[1], Katsutoshi Oda[1], Kei Kawana[1], Takahide Arimoto[1], Yukiko Kanetaka[1], Yutaka Takazawa[2], Daichi Maeda[2], Shunsuke Nakagawa[1], Tetsu Yano[1] and Shiro Kozuma[1]

Departments of [1]Obstetrics and Gynecology and [2]Pathology, The University of Tokyo, Tokyo, Japan

Abstract

Low-grade endometrial stromal sarcoma (ESS) is a rare neoplasm that is generally estrogen-receptor- and progesterone-receptor-positive and develops in premenopausal women. Although tamoxifen treatment is associated with an increased risk of ESS, the effect of other selective estrogen receptor modulators, including toremifene, on the risk of ESS is not clear. A 61-year-old postmenopausal woman was treated with toremifene as an adjuvant therapy for breast cancer. A cystic mass developed during the treatment, with gradual growth in the uterine myometrium. The patient was treated with hysterectomy and bilateral salpingo-oophorectomy, and the tumor was diagnosed as low-grade ESS (stage IA) with estrogen-receptor and progesterone-receptor. The patient discontinued toremifene and has been progression-free for 21 months. Our data suggest that toremifene might be associated with the development of ESS in certain patients through its estrogen-like effects in the uterus.

Key words: estrogen-like effect, low-grade endometrial stromal sarcoma, selective estrogen receptor modulator, toremifene, uterine corpus.

Introduction

Selective estrogen receptor modulators (SERM), especially tamoxifen, have been broadly administered as an endocrine treatment for breast cancer.[1] Despite its good reputation, tamoxifen has been associated with a 2–7-fold increased risk of endometrial cancer.[2] In addition, tamoxifen treatment has been associated with elevated risk of uterine sarcomas, including endometrial stromal sarcoma (ESS).[3] Toremifene is another type of SERM commonly used for the treatment of breast cancer.[4,5] Although toremifene might produce comparable estrogenic effects with tamoxifen in the uterus, the risk assessment of toremifene for endometrial cancer and uterine sarcomas is still inconclusive,[4,6] and toremifene-associated ESS has not been reported to date.

ESS is a rare gynecological malignancy accounting for 10% of uterine sarcomas.[7] ESS is classified into two histological subtypes: low-grade ESS (LG-ESS) and undifferentiated uterine sarcoma, depending on the morphology, number of mitoses, cellularity, and necrosis. LG-ESS tends to occur before menopause (mean, 39 years).[8] Estrogen acts as a growth stimulus in LG-ESS, which generally expresses estrogen receptors (ER) and progesterone receptors (PgR). Thus, LG-ESS is thought to be estrogen-dependent.

We report a case of LG-ESS development during treatment with toremifene for breast cancer.

Received: November 27 2011.
Accepted: March 5 2012.
Reprint request to: Dr Katsutoshi Oda, Department of Obstetrics and Gynecology, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan. Email: katsutoshi-tky@umin.ac.jp

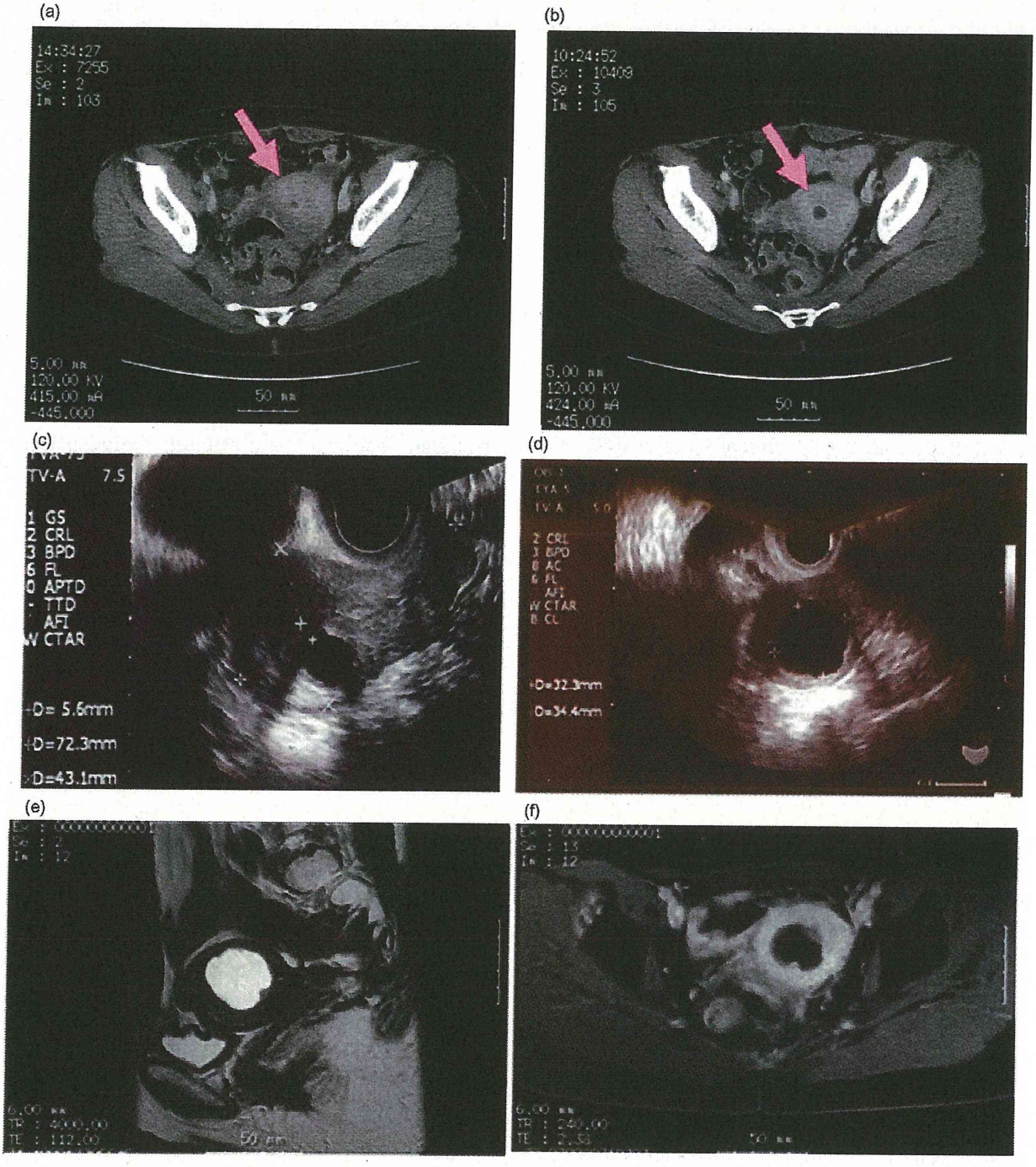

Figure 1 Images of the tumor by (a,b) computed tomography scan, (c,d) transvaginal ultrasonography, and (e,f) magnetic resonance imaging. (a) A cystic mass was first observed in the uterine myometrium 4 months after toremifene treatment in November 2007. (b) The cystic mass was more clearly detected in May 2008. (c) An intramyometrial cystic mass (14 × 16 mm) observed at the patient's first visit. (d) The cystic mass measured 32 × 34 mm 13 months after the first visit. (e) Sagittal T2-weighted image of a cystic tumor 38 mm in diameter located in the posterior myometrium. (f) Gadolinium-enhanced axial T1-weighted image of a homogeneous enhancement of the solid part of the tumor similar to normal myometrium.

Case Report

A 61-year-old woman (gravida 3, para 1) presented to our hospital with brownish discharge in June 2008. She had undergone surgeries for colorectal cancer in March 2007 and for breast cancer in June 2007, and had been treated for breast cancer with toremifene at a daily dose of 120 mg since July 2007. Magnetic resonance imaging (MRI) performed before the start of toremifene treatment in 2007 had revealed no abnormal mass in the uterine myometrium (Fig. S1). A low-density lesion (<1 cm in diameter) was observed in a computed tomography (CT) scan performed in November 2007 and in May 2008 while under treatment with toremifene (Fig. 1a,b). Transvaginal ultrasonography performed in June 2008 revealed a 14 × 12-mm hypoechoic lesion in the posterior myometrium (Fig. 1c). Endometrial cytology and biopsy of the endometrium were negative for malignant cells. The patient was followed up every 3 months, and a gradual enlargement of the hypoechoic lesion in the posterior myometrium was observed. In July 2009, the hypoechoic mass reached a size of 32 × 34 mm (Fig. 1d). In September 2009, MRI revealed a 38-mm tumor, which was presumed to be LG-ESS (Fig. 1e,f). No tumor markers were significantly elevated, including carbohydrate antigen (CA) 125 (11 U/mL), CA19-9 (10 U/mL), carcinoembryonic antigen (CEA) (2.3 ng/mL), neuron-specific enolase (NSE) (13 ng/mL) and lactate dehydrogenase (LDH) (193 U/L), and the biopsy of the endometrium was still negative. The patient discontinued toremifene and underwent total abdominal hysterectomy and right salpingo-oophorectomy in November 2009 (Fig. 2a) (she had received left salpingo-oophorectomy for an ectopic pregnancy when she was 33 years old). She was diagnosed with LG-ESS, International Federation of Gynecology and Obstetrics (FIGO) stage IA (Fig. 2b). The tumor demonstrated strong staining for CD10, ER, and PgR (Fig. 2c–e). The patient has received no postoperative treatment and has been recurrence-free for all of her malignant diseases.

Discussion

LG-ESS develops commonly in premenopausal women (range, 19–58 years).[9,10] In total, nine LG-ESS cases have been diagnosed in our hospital, including the present case (Table 1). The median age of the other eight LG-ESS patients in our hospital was 40 years (range, 28–57 years), and all of them were pre- or perimenopausal. However, in the present case, LG-ESS was diagnosed at the age of 61 (11 years after her menopause). The tumor in the uterine myometrium, which was first detected in a CT scan performed after 4 months of toremifene treatment, showed a gradual enlargement during the treatment period, suggesting that toremifene might be associated with the development of ESS. The reported association between tamoxifen and increased risk of uterine sarcoma and endometrial cancer[2,11,12] implies that other types of SERM, including toremifene, might also be involved in the development of uterine sarcoma through their estrogen-like effects. Whether the estrogenic effect of toremifene can be induced in postmenopausal women remains to be elucidated.

Among the nine LG-ESS cases treated in our hospital, six patients received bilateral salpingo-oophorectomy (BSO) at our hospital as a primary treatment and remain free of recurrence, whereas three patients did not receive BSO and were transferred to our hospital after the diagnosis of recurrence (Table 1). Preservation of the ovaries was associated with recurrence in these nine cases ($P = 0.022$ by log–rank test). Although primary treatment in other hospitals might cause bias in the recurrence rate, these data suggest that continuous exposure to estrogen might increase the risk of LG-ESS development. However, objective responses have been obtained by hormonal therapy with progesterone derivatives or aromatase inhibitors in LG-ESS.[13] As the impact of ovarian preservation and hormonal treatment, including SERM, on the prognosis of LG-ESS is still controversial,[14] further study is necessary to evaluate the potential risks for LG-ESS development.

Figure 2 Macroscopic and microscopic findings of the tumor. (a) Photograph of the cut surface of the excised uterus. The 4 × 4-cm tumor was a relatively soft, polypoid growth in the uterine posterior wall. The cut surface was yellowish-white. (b–e) Histological and immunohistochemical findings of the tumor (high power). (b) Tumor cells in the uterus, demonstrating proliferation of endometrial stromal cells without significant atypia or pleomorphism, diagnosed as low-grade endometrial stromal sarcoma. Tumor cells were strongly positive for (c) CD10, (d) estrogen receptor, and (e) progesterone receptor by immunohistochemistry.

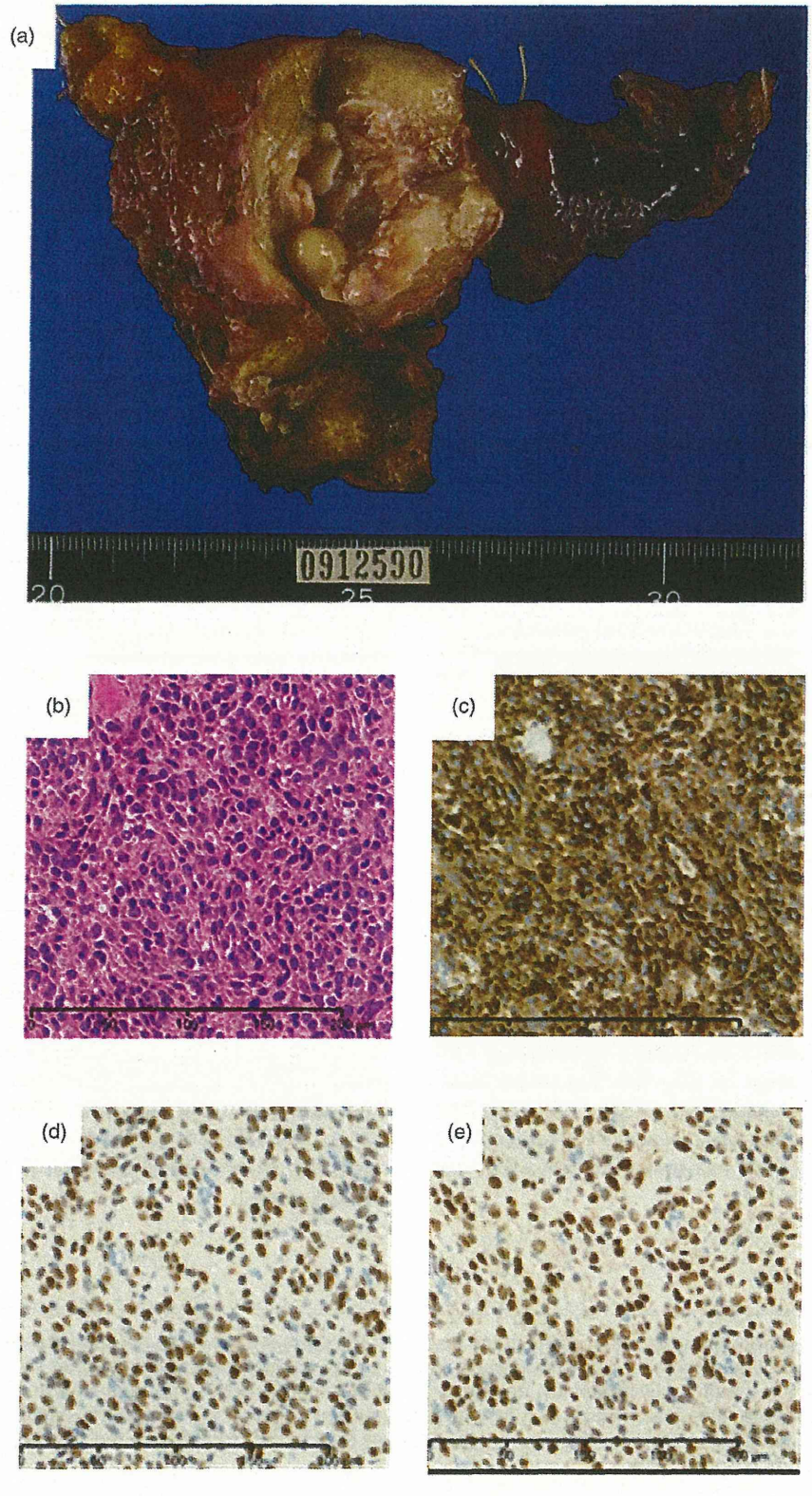

Table 1 Clinical characteristics of nine low-grade endometrial stromal sarcoma cases in our hospital

Case	Age	Gravidity	Parity	Primary treatment	Preservation of ovaries and uterus	Adjuvant therapy	Stage	Recurrence-free survival (months)	Outcome	Remarks
1	38	2	2	ARH + RSO	Left ovary	Chemotherapy	I	26	Recurred	†Primarily treated outside
2	35	4	2	TAH	Bilateral ovaries	(–)	I	72	Recurred	†Primarily treated outside
3	29	1	0	LAM	Uterus, bilateral ovaries	(–)	I	13	Recurred	†Primarily treated outside
4	40	1	1	TAH + BSO + PLA	(–)	(–)	I	78	NED	
5	45	2	2	LAVH → BSO + pOM + PLN Biopsy	(–)	(–)	I	65	NED	
6	34	1	1	Tumorectomy → MRH + BSO + PLA	(–)	(–)	I	45	NED	
7	57	4	2	TAH + BSO	(–)	(–)	I	38	NED	
8	43	2	0	TAH + LSO → RSO + pOM	(–)	(–)	IVb	28	NED	
9	61	3	1	TAH + RSO (post-LSO)	(–)	(–)	I	16	NED	Toremifene per os

†Primarily treated outside; transferred to our hospital after the recurrence was diagnosed. ARH, abdominal radical hysterectomy; BSO, bilateral salpingo-oophorectomy; LAM, laparoscopically-assisted myomectomy; LAVH, laparoscopically-assisted vaginal hysterectomy; LSO, left salpingo-oophorectomy; MRH, modified radical hysterectomy; NED, no evidence of disease; PLA, pelvic lymphadenectomy; PLN Biopsy, pelvic lymph node biopsy; pOM, partial omentectomy; RSO, right salpingo-oophorectomy; TAH, total abdominal hysterectomy; TCR, transcervical resection.

This is the first report of LG-ESS development during treatment with toremifene. The LG-ESS in the present patient may have been caused by the stimulation of the endometrial epithelium and/or stromal cells by toremifene.

Acknowledgments

We thank Drs Keiko Shoji, Yuji Ikeda, Takahiro Koso, and Aki Miyasaka for support and assistance.

Disclosure

The authors declare that there are no conflicts of interest.

References

1. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: An overview of the randomised trials. *Lancet* 1998; **351**: 1451–1467.
2. Bergman L, Beelen ML, Gallee MP *et al.* Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. *Lancet* 2000; **356**: 881–887.
3. Wickerham DL, Fisher B, Wolmark N *et al.* Association of tamoxifen and uterine sarcoma. *J Clin Oncol* 2002; **20**: 2758–2760.
4. Harvey HA, Kimura M, Hajba A. Toremifene: An evaluation of its safety profile. *Breast* 2006; **15**: 142–157.
5. Zhou WB, Ding Q, Chen L *et al.* Toremifene is an effective and safe alternative to tamoxifen in adjuvant endocrine therapy for breast cancer: Results of four randomized trials. *Breast Cancer Res Treat* 2011; **128**: 625–631.
6. Pukkala E, Kyyronen P, Sankila R *et al.* Tamoxifen and toremifene treatment of breast cancer and risk of subsequent endometrial cancer: A population-based case-control study. *Int J Cancer* 2002; **100**: 337–341.
7. Koss LG, Spiro RH, Brunschwig A. Endometrial stromal sarcoma. *Surg Gynecol Obstet* 1965; **121**: 531–537.
8. Zaloudek C, Norris HJ. Mesenchymal tumors of the uterus. In: Kurman RJ (ed.). *Blaustein's Pathology of the Female Genital Tract*, 4th edn. New York: Springer Verlag, 1994; 457–528.

9. Kim WY, Lee JW, Choi CH *et al.* Low-grade endometrial stromal sarcoma: A single center's experience with 22 cases. *Int J Gynecol Cancer* 2008; **18**: 1084–1089.
10. D'Angelo E, Prat J. Uterine sarcomas: A review. *Gynecol Oncol* 2010; **116**: 131–139.
11. Ismail SM. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994; **47**: 827–833.
12. Engin H. High-grade endometrial stromal sarcoma following tamoxifen treatment. *Gynecol Oncol* 2008; **108**: 253–254.
13. Shoji K, Oda K, Nakagawa S *et al.* Aromatase inhibitor anastrozole as a second-line hormonal treatment to a recurrent low-grade endometrial stromal sarcoma: A case report. *Med Oncol* 2011; **28**: 771–774.
14. Amant F, De Knijf A, Van Calster B *et al.* Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. *Br J Cancer* 2007; **97**: 1194–1199.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Magnetic resonance imaging before the start of toremifene treatment in July 2007. No abnormal mass, except for a uterine fibroid, was observed in the uterine myometrium.

frontiers in MICROBIOLOGY

ORIGINAL RESEARCH ARTICLE
published: 27 August 2013
doi: 10.3389/fmicb.2013.00251

HPV18 E1^E4 is assembled into aggresome-like compartment and involved in sequestration of viral oncoproteins

Naoko Kajitani[1,2], *Ayano Satsuka*[1,2†], *Satoshi Yoshida*[2†] *and Hiroyuki Sakai*[2,3*]

[1] Laboratory of Mammalian Molecular Biology, Department of Molecular and Cellular Biology, Graduate School of Biostudies, Kyoto University, Kyoto, Japan
[2] Laboratory of Gene Analysis, Department of Viral Oncology, Institute for Virus Research, Kyoto University, Kyoto, Japan
[3] Department of Viral Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Edited by:
Akio Adachi, The University of Tokushima Graduate School, Japan

Reviewed by:
Akio Adachi, The University of Tokushima Graduate School, Japan
Masako Nomaguchi, The University of Tokushima Graduate School, Japan

***Correspondence:**
Hiroyuki Sakai, Laboratory of Gene Analysis, Department of Viral Oncology, Institute for Virus Research, Kyoto University, 53 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: hsakai@virus.kyoto-u.ac.jp

†Present address:
Ayano Satsuka, Department of Microbiology and Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA; Satoshi Yoshida, Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, WI 53706, USA

Papillomavirus is the etiological agent for warts and several squamous carcinomas. Skin cancer induced by cottontail rabbit papillomavirus was the first animal model for virus-induced carcinogenesis. The target organ of the virus infection is stratified epithelium and virus replication is tightly regulated by the differentiation program of the host cell. E1^E4 protein is a viral gene product, and although it is considered to be involved in the control of virus replication, little is known about the biological role. We found that HPV18 E1^E4 was assembled into an aggresome-like compartment and was involved in sequestration of virus oncoproteins, which might contribute to the differentiation-dependent lifecycle of papillomavirus.

Keywords: HPV, E1^E4, aggresome, HPV oncoproteins, HPV replication

INTRODUCTION

Papillomavirus is a small virus containing a double-stranded circular DNA as its genome (zur Hausen, 2002). Genomic DNA of typical papillomavirus, human papillomavirus type 16 (HPV16) or HPV18 is ca. 8 kb long and coding six regulatory genes (E1, E2, E4, E5, E6, E7) and two structural genes (L1, L2). Papillomaviruses are found in almost all mammals and also in amniotes. The virus infects to stratified epithelium organ, such as cutaneous or mucosal membrane, and the infection causes various types of hyperplasia. It is known that the infections of some types of papillomaviruses occasionally induce malignant tumors. The cancer formation by the infection of cottontail rabbit papillomavirus (CRPV) was the first animal model of virus-induced carcinogenesis (Campo, 2002).

The replication of papillomavirus is regulated by the differentiation program of the host cell (Doorbar, 2005). The target cell of the virus infection is basal cell of stratified epithelium, in which the virus replication maintains latent status. Cell division of the infected basal cell produces a daughter cell, and the daughter cell is moved to the surface region of the epithelium and proceeds to differentiate. Virus gene expression and genome replication are enhanced in accordance with the cell differentiation, and the productive replication occurs in fully differentiated cells (Sakakibara et al., 2013). The regulatory mechanism of the differentiation-dependent viral replication remains largely unknown.

A variety of mRNAs are produced by alternative splicing in HPV (Schwartz, 2013). About E4 gene, 5′ region of E1 is jointed to E4 coding sequence by RNA splicing, then the gene product contains five amino acid residues of E1 at the N-terminus of the protein coded by E4 ORF, which is called "E1^E4". By the analysis of the specimens obtained from infected individuals and animals, the expression level of E1^E4 appeared to be intense in differentiated layers of the infected lesions (Sterling et al., 1993; Doorbar et al., 1997), suggesting that E1^E4 is involved in the productive stage of viral replication. It was reported on CRPV that the E1^E4 was required for the viral DNA amplification and the late protein expressions (Peh et al., 2004). E1^E4s of HPV16 and HPV31 were reported to be involved in viral genome amplification and cell cycle maintenance in S-phase of differentiated cells (Nakahara