ORIGINAL ARTICLE

The association between expression of p53 and aggressiveness of serous adenocarcinoma of the uterine cervix

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Background: Serous adenocarcinoma of the uterine cervix is an extremely rare variant of cervical adenocarcinoma. This study aimed to evaluate the clinicopathological and molecular features and outcomes of serous adenocarcinoma of the uterine cervix (SACC). **Materials and Methods:** This was a retrospective study conducted based on the clinical and pathological data of seven patients diagnosed with SACC after hysterectomy, who were evaluated at the gynecologic oncologic centers between 2010 and 2019. **Results:** Five cases were diagnosed at Stage IB and two at Stage IV. All patients underwent radical hysterectomy with bilateral salpingo-oophorectomy and subsequently received postoperative radiotherapy or chemotherapy. One patient showed persistent disease, and two patients suffered recurrence. Immunohistochemical study showed that three (43%) of the seven patients were positive for p53, and among these three patients, two with diffuse strong p53 expression experienced an aggressive course with recurrences at pelvic lymph nodes, lung, and brain. **Conclusion:** High p53 expression and advanced stage may be associated with poorer clinical outcomes in SACC, which suggest that immunohistochemistry may contribute to the prediction of prognosis.

Key words: Cervix, clinicopathologic features, serous adenocarcinoma

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INTRODUCTION

Serous adenocarcinoma is frequently encountered in ovaries, Fallopian tubes, endometrium, or peritoneum, but rarely in uterine cervix. Serous adenocarcinoma of the uterine cervix (SACC) is an extremely rare, recently described variant of cervical adenocarcinoma with an aggressive and unpredictable clinical course. Morphologically, this variant is similar to papillary serous adenocarcinoma arising from an ovary, Fallopian tube, or peritoneum.[1] In general, this disease is considered relatively chemo- and radioresistant.[2] Abnormal vaginal bleeding and watery vaginal discharge during pre- or postmenopause are the presenting symptoms of SACC. However, due to the limited number of reported cases, the clinicopathological features of SACC are largely unknown, and consequently, its optimal management has not been determined. Nevertheless, such subtype of cervical adenocarcinoma tends to show rapid growth and result in poor outcomes, especially when the disease is diagnosed in the advanced stage; such characteristic implies the importance of predicting its prognosis using immunohistochemical markers. The present study aimed to describe the clinicopathologic

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features and immunohistochemical characteristics of seven cases of SACC.

MATERIALS AND METHODS

The clinical and pathological data of seven patients with SACC diagnosed and treated at gynecologic oncologic centers of participating institutions (Pusan National University, Inje University, Kosin University, and Ulsan University Hospital) between 2010 and 2019 were retrospectively analyzed. The study protocol was approved by the Institutional Review Board of Pusan National University Hospital (E-2016087). This study included cases with a lesion fulfilling the histological criteria for serous adenocarcinoma of World Health Organization International Histological Classification (2014). All cases were confirmed by two experienced gynecologic pathologists, which exhibited a prominent complex papillary pattern with epithelial stratification and tufting with moderate-to-marked cytologic atypia. Cases of the papillary serous type accounting for >20% of tumor area were included. No patient had a previous history of papillary serous carcinoma at another site, including female genital tracts and peritoneum. Clinicopathologic characteristics obtained from medical records included age at diagnosis, FIGO stage, tumor grade, menopausal status, human papillomavirus (HPV) status, immunoprofile, invasion depth, adjuvant therapy, metastasis, and recurrence [Table 1]. The stages at diagnosis were determined according to the FIGO criteria (2009).[3] In addition to hematoxylin and eosin staining, immunohistochemical studies were performed on all the seven cases. Tumor tissue specimens were fixed in formalin, paraffin embedded, and serially sectioned at 4 μm for immunohistochemical staining. Percentages of positively stained cells were evaluated semi-quantitatively, as follows; −, <10%; +, 10%–25% (weakly positive), ++, 26%–50% (moderately positive), and +++, >50% (strongly positive). Real-time polymerase chain reaction was performed to identify high-risk and low-risk HPV genotypes.

RESULTS

Clinical characteristics

The characteristics of the seven patients are summarized in Table 1. The median age at diagnosis was 54.0 years (range 45–67 years). Five (71.4%) patients had experienced natural menopause. The most common presenting symptom was postmenopausal bleeding (5/7; 71%). Two patients presented with intermenstrual bleeding. No patient had a history of medical disease. Five patients were diagnosed with FIGO Stage IB and two with Stage IV. During physical examination, a polypoid or exophytic mass of the cervix was noted in four patients, an ulcerated cervix was noted in two,

Table 1: Clinicopathological characteristics of the seven patients with serous adenocarcinoma of the cervix

Case	Age	Presenting symptom	Cytology	Stage*	Grade	High risk-HPV	Treatment	Histology	Invasion/total thickness	LVSI	Ovarian involvement	Psammoma body	Adjuvant therapy
1	60	PMB	NA	IB1	2	18	RH, BSO, PLND	Pure	10/12 mm	-	-	-	CCRT
2	57	PMB	AGC - favor neoplastic	IVB	3	(-)	RH, BSO, Omentectomy	Pure	Whole thickness	+	+	-	CT
3	49	AUB	Negative	IVB	2	(-)	RH, BSO, P/PALND	Pure	Whole thickness	+	+	+	CT
4	54	PMB	HSIL	IB2	2	(-)	RH, BSO, P/PALND	Pure	Whole thickness	-	-	-	CT
5	67	PMB	SCC	IB1	3	18	RH, BSO, P/PALND	Pure	6/15 mm	-	-	-	CCRT
6	45	AUB	Adenocarcinoma	IB1	2	(-)	RH, BSO, PLND	Pure	8/19 mm	-	-	-	CT
7	51	PMB	Negative	IB1	3	(-)	Robotic RH, BSO, PLND	Mixed*	3/18 mm	+	-	+	CT

*FIGO clinical staging (2009). PMB=Postmenopausal bleeding; AUB=Abnormal uterine bleeding; CT=Chemotherapy; NA=Not applicable; P/PALND=Pelvic and para-aortic lymph node dissection; LVSI=Lymphovascular space invasion; Pre-M=Premenopausal; Post-M=Postmenopausal; Mixed=Serous and clear cell carcinoma; HSIL=High-grade squamous intraepithelial lesion; SCC=Squamous cell carcinoma; AGC=Atypical glandular cell

and erosive cervix was noted in one. All patients underwent radical hysterectomy with bilateral salpingo-oophorectomy. Pelvic and/or para-aortic lymphadenectomy was performed in six patients. Adjuvant radiotherapy or chemotherapy was administered based on the considerations of risk factors. Two patients received adjuvant chemoradiation to the whole pelvis and five received combination chemotherapy (carboplatin and paclitaxel ± bevacizumab, cisplatin + 5-FU, or carboplatin + etoposide).

Pathologic features

Tumor findings were typical of papillary serous adenocarcinoma and included epithelial tufts and stratification, a complex pattern of papillae lined by cells with hyperchromatic nuclei, and numerous mitotic bodies. Four patients were Grade 2 with moderate nuclear pleomorphism, small nucleoli, and moderate amounts of cytoplasm. The other three patients were Grade 3 with marked nuclear pleomorphism and prominent nucleoli. All tumors, regardless of grade, had >10 mitotic figures per 10 high-power fields. Occasional psammoma bodies were present in two cases (cases 3 and 7), pelvic and/or para-aortic lymph node metastases were present in three cases at initial presentation, and microscopic ovarian metastasis was observed in two patients [Table 1].

Immunophenotype

Immunohistochemical staining was performed using antibodies for p53, p16, estrogen receptor (ER), progesterone receptor (PR), and Wilms' tumor-1 (WT-1) [Figure 1a-f]. The results are summarized in Table 2. p53 and p16 were positive in three (43%) and two cases (29%), respectively [Figure 2b and c]. Two of the three cases with strong p53 expression experienced an aggressive course with recurrences at pelvic lymph nodes, lung, and brain [Figure 2a and b]. Staining for ER, PR, and WT-1 were each positive in one case (14%). HPV DNA (type 18) was detected in two of the seven patients (cases 1 and 5) and low-risk type (61) was detected in one patient (case 5).

Outcomes

The follow-up durations ranged from 7 to 96 months (mean 29.3 months). Two patients experienced tumor recurrence at 16 and 29 months after surgery, respectively. Five patients were alive without evidence of tumor recurrence or metastasis at the last follow-up. Sites of recurrent disease included pelvic lymph nodes, lung, and brain (cases 3 and 5). One patient (case 5) died of lung and brain metastases at 31 months after diagnosis despite intensive multimodal therapy. In this patient, innumerable enhancing masses were observed in the frontal, temporal, and occipital regions; both cerebelli; midbrain; pons; and right medial thalamus [Figure 2c]. In case 2, vaginal wall, uterine corpus, and para-cervical tissue were involved. In addition, multiple lymph nodes in pelvic and para-aortic areas, omentum, both ovaries, and both salpinges were involved. Nine cycles of combination carboplatin-paclitaxel and bevacizumab

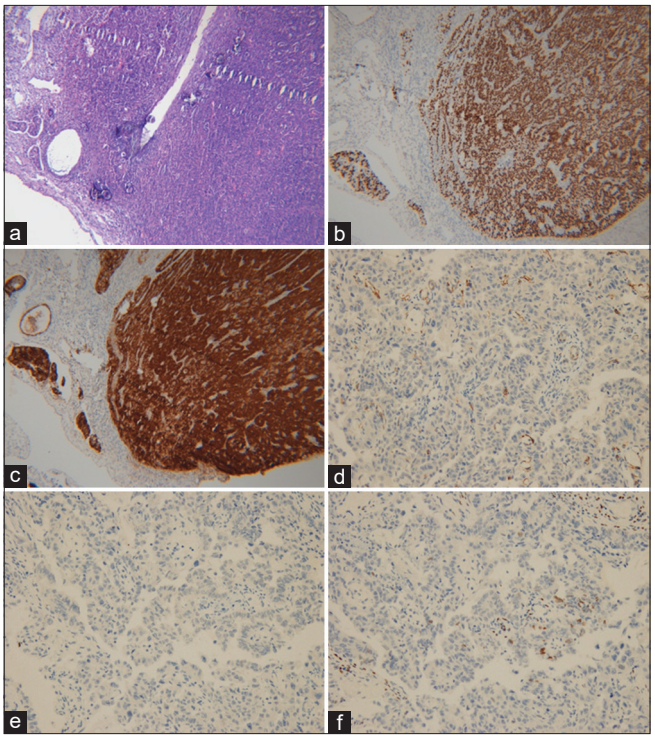

Figure 1: H and E stains and immunohistochemical findings of SACC. (a) Tumor showed papillae and solid growth pattern with high-grade nuclear features and psammoma bodies, H and E staining (×100). The tumor cells were diffusely strongly positive for p53 (b) and p16 (c) (×100). The tumor cells were negative for WT-1 (d), ER (e), and PR (f) (×100) (case 3). SACC = Serous adenocarcinoma of the uterine cervix. SACC = Serous adenocarcinoma of the uterine cervix; WT-1 = Wilms' tumor-1; ER = Estrogen receptor; PR = Progesterone receptor

Table 2: Immunophenotypes of the seven patients with serous adenocarcinoma of the cervix

Case	Immunoprofile					Metastasis at diagnosis	Recurrence	Survival
	p53	p16	ER	PR	WT-1			
1	−	+++	−	−	−	Pelvic LN	No	NED, 96 months
2	−	−	−	−	−	Pelvic and para-aortic LN, omentum, peritoneum	Persistent	Dead, 16 months
3	+++	+++	−/+	−/+	−/+	Pelvic and para-aortic LN, omentum, vagina	Pelvic LN, 16 months	NED, 32 months
4	+	−	−	−	−	-	No	NED, 13 months
5	+++	−/+	−	−	+	-	Lung, brain, 30 months	Dead, 31 months
6	−/+	−/+	+	+	-	-	No	NED, 7 months
7	−	−	−	−	−	-	No	NED, 12 months

WT-1=Wilms' tumor-1; ER=Estrogen receptor; PR=Progesterone receptor; LN=Lymph node; NED=No evidence of disease, −, <10%; +, 10%–25% (weakly positive), ++, 26%–50% (moderately positive), and +++, >50% (strongly positive)

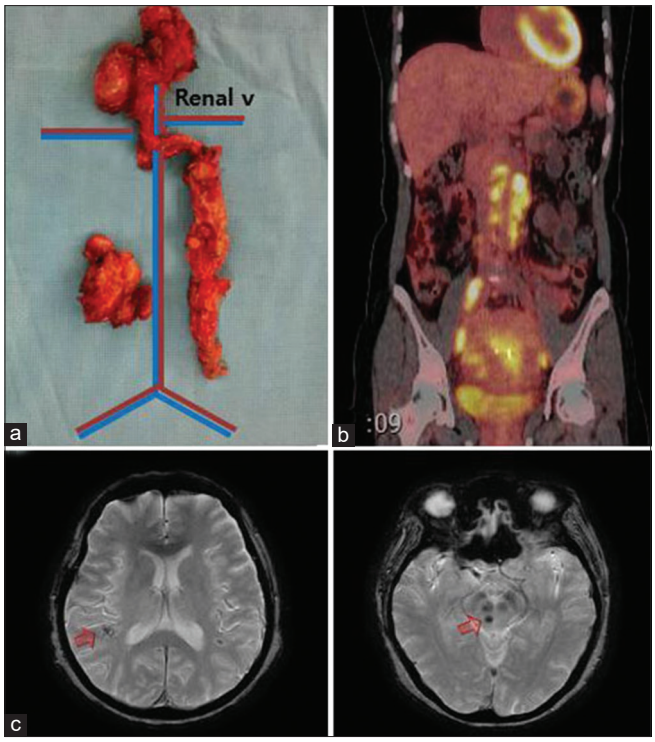

Figure 2: Aggressive clinical course of SACC with p53 expression: Operative findings and images. Resected lymph nodes (a) and PET-CT image (b) showing extensive lymphadenopathy throughout the pelvis and abdomen (case 3). Enhancing masses in the temporal lobe and pons were revealed (c) (case 5). SACC = Serous adenocarcinoma of the uterine cervix; PET-CT = Positron emission tomography-computed tomography

chemotherapy were administered, and her CA-125 level declined to normal (14.38 U/ml), but computed tomography revealed persistent disease with seeding nodules at the omentum. The patient subsequently succumbed 16 months after SACC diagnosis. In case 3, preoperative serum CA125 level was much elevated (607.1 U/ml). Six cycles of combination chemotherapy with carboplatin and paclitaxel were administered, and CA-125 level normalized (7.1 U/ml); complete remission was achieved. In this case, recurrence was detected at 16 months after diagnosis and treated with carboplatin and paclitaxel.

DISCUSSION

SACC was recently described as a rare variant of endocervical adenocarcinoma,[4,5] and thus, its clinicopathological and molecular features, prognostic significances, and optimal treatment are largely unknown. Here, we describe the clinicopathological features, molecular features, and outcomes of seven patients with serous adenocarcinoma of uterine cervix.

Nofech-Mozes *et al*. first detailed the clinicopathological features of SACC.[5,6] Ages of the 17 patients varied widely (from 27 to 79 years). Interestingly, a bimodal distribution was observed; one peak occurred before the age of 40 years (premenopausally) and the other after the age of 65 years (postmenopausally).[5] In the present study, ages at diagnosis ranged from 45 to 67 years and no biphasic distribution was observed; five of the seven patients (71.4%) were diagnosed after menopause. In our patients, the main clinical symptoms of SACC were abnormal vaginal bleeding; watery vaginal discharge; and polypoid, exophytic, or ulcerated cervical mass by pelvic examination, which concurs with previous reports.[6,7]

The outcomes of early-stage SACC do not differ significantly different from those of common adenocarcinoma. However, due to its aggressive behavior, when detected, SACC tumors are associated with lymph node metastases[2,8] and diagnosed at advanced stages.[2] Distant metastases outside the pelvis are frequent, especially in the para-aortic and cervical lymph nodes, lungs, peritoneum, ovary, liver, brain, and skin.[2,9] Khan *et al*. reported a case of pulmonary metastases (Stage IVB) with extensive lymphadenopathy throughout the abdomen and pelvis that was treated by debulking surgery and combined carboplatin and paclitaxel chemotherapy.[10] Tang *et al*. reported a mixed case of SACC and squamous cell carcinoma, which demonstrated brain metastasis at 17 months after surgery.[9] In our case 3, extensive lymphadenopathy throughout the abdomen and pelvis was observed.

Serous adenocarcinoma of the female genital tract can be diagnosed without difficulty because it exhibits similar morphologic features regardless of origin. Ueda *et al*. reported that SACC exhibits several pathologic features that resemble those to their ovarian counterparts such as papillary tufts, papillae lined by cells with high-grade pleomorphic nuclei, numerous mitotic bodies, and occasional psammoma bodies.[2] SACC may be pure or mixed with other adenocarcinoma subtypes.[9,11] A few reports of mixed serous carcinoma with endometrioid adenocarcinoma, clear cell carcinoma, well-differentiated villoglandular adenocarcinoma, or rarely squamous cell carcinoma have been issued.[9] In the present study, six cases were pure and one case was mixed with clear cell carcinoma.

Immunohistochemical assessments are very helpful for diagnosing and achieving the differential diagnosis of SACC.[5,12] In a literature review, Jonska-Gmyrek *et al*. described the molecular features of SACC, and concluded that it is usually positive for p16, carcinoembryonic antigen (CEA), CA-125, or p53 and negative for WT-1, estrogen, progesterone, PAS, or vimentin. In previous reports, percentage p53 immunopositivity ranged from 42% to 90%[5,6,13] and p53 expression was associated with poorer clinical outcomes.[5,8,11,14] These reports indicate that strong p53 expression is associated with recurrence, metastases, and death, and that assessment of p53 status might be

prognostically meaningful. Deceased cases of SACC had a strong expression of p53 (>50% of cells).[5,11] In the present study, three patients (43%) were positive for p53, and of these, two with diffuse strong p53 expression experienced an aggressive course with corpus extension; pelvic and para-aortic lymph node metastases; and recurrences at pelvic lymph nodes, lung, and brain [Figure 2]. The other patient was weakly positive for p53 (~20% of cells), no metastasis was present at initial diagnosis, and recurrence did not occur. Usually, serous carcinomas of the ovary are positive and serous carcinomas of endometrium are generally negative for WT-1.[5] Thus, WT-1 immunostaining may be useful for distinguishing serous adenocarcinomas of the ovary from serous adenocarcinoma of the endometrium or uterine cervix. In previous reports, only 0%–20% of SACC tumors exhibited WT-1 immunoreactivity,[5,14,15] and similarly, in the present study, only one of the seven SACC cases showed immunoreactivity to WT-1.

Little is known about the relation between HPV and SACC. Some authors have suggested that persistent high-risk HPV infection might be related to the development of cervical adenocarcinoma.[16] Togami *et al*. reported p16 overexpression in 100% (12/12) of SACC samples,[14] and that HPV DNA (Type 16 or 18) was detected in four samples (33%), which suggests a link between high-risk HPV infection and SACC development. Other studies have reported high-risk HPV DNA in 0%–75% of cases.[6,17-19] In the present study, two (29%) cases were of positive HPV DNA (type 18), which supports a weak association with SACC development. Further studies are needed to investigate the association between HPV infection and the occurrence of SACC.

Patients with early-stage SACC and no risk factors appear to have a favorable prognosis after radical hysterectomy alone.[6] The biological behavior of early-stage SACC seems similar to that of common-type adenocarcinoma of the uterine cervix. However, advanced-stage SACC is likely to recur, and its behavior is more aggressive.[14] In a previous report, tumor recurrence was usually found beyond the pelvis,[16] and most recurrences occurred within 24 months of primary therapy.[6] The most frequently reported sites of recurrence are distant lymph nodes followed by peritoneal spread and lung. For common-type adenocarcinoma, the most frequent sites of recurrence are distant nodes and peritoneal spread followed by lung. Thus, the spread patterns of both SACC and common-type adenocarcinoma appear to be similar in terms of frequent extrapelvic metastasis.[14]

Because of its rarity, the optimal primary management of SACC has not been determined. For early-stage SACC, preferred treatment options include radical hysterectomy, radiotherapy alone,[19,20] or primary surgery followed, depending on risk factors, by postoperative radiotherapy.[10,14] However, most cases are diagnosed with advanced-stage disease with metastases and require debulking surgery followed by combination chemotherapy[10,21] or radiotherapy.[5,10] Interestingly, Ueda *et al*. described a remarkable response to combined paclitaxel and carboplatin chemotherapy in a case of unresectable advanced case.[2]

A recent literature review detailed the key features of SACC:[6] (1) It exhibits a bimodal age distribution with one before the age of 40 years (premenopausal) and the other after the age of 54 years (postmenopausal); (2) its most common symptoms are watery vaginal discharge or abnormal vaginal bleeding; and (3) early-stage SACC with no risk factors appears to have a favorable prognosis after surgery alone, but advanced stages of SACC have deleterious impacts despite multimodality therapies.

The strength of our study is the analysis of clinicopathological features in SACC, such as similarities and dissimilarities with serous carcinomas of other female organs, and immunophenotype and their role as discriminatory or prognostic indicators. The major limitation of the study is the small sample size of patients with SACC, due to its rarity. Because of such limitation, it is difficult to draw firm conclusions with regard to the prognostic significance of immunohistochemical markers, the association between HPV infection and occurrence of SACC, and the optimal management of advanced disease.

CONCLUSION

We suggest that high p53 expression, lymph node metastasis, advanced stage, and an elevated serum CA125 level may be associated with poorer clinical outcomes. Appropriate immunoprofiling, especially p53 expression, may be helpful for the differentiation of SACC from serous carcinomas in other female organs, the prediction of prognosis, and the establishment of future target therapy of SACC. We suggest a large-scale multicentric study be conducted to determine the clinical behavior and to establish optimal treatment strategies, especially for advanced-stage SACC.

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Conflicts of interest

There are no conflicts of interest.

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