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## Original Article

## Clinical management of uterine cervical mullerian adenosarcoma: A clinicopathological study of six cases and review of the literature

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## ABSTRACT

**Objective:** To assess the clinicopathological characteristics and clinical management of patients diagnosed with mullerian adenosarcoma of the uterine cervix.**Materials and methods:** Records of six patients surgically treated for cervical mullerian adenosarcoma were reviewed.**Results:** The median age of the patients was 50 years (range, 17–74). Four patients presented with vaginal bleeding and two of them had watery discharge as the primary symptoms. Three nulliparous patients who hoped to preserve their uterus were included in this study and only one of the three patients received fertility-preservation surgery. Five patients underwent hysterectomy (simple in 3, modified radical in 2) with bilateral salpingo-oophorectomy or bilateral salpingectomy. One patient underwent conization of the cervix to preserve her fertility as there was no sarcomatous overgrowth, heterologous elements, or deep cervical stromal invasion. A recurrence of cervical mullerian adenosarcoma with sarcomatous overgrowth was observed in one patient who underwent simple hysterectomy.**Conclusion:** The presence of sarcomatous overgrowth and deep cervical stromal invasion are associated with poor prognosis. Along with adequate counseling, fertility-preservation surgery may be an acceptable option for exophytic cervical mullerian adenosarcoma in the cases that do not show sarcomatous overgrowth and deep cervical stromal invasion.© 2018 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Mullerian adenosarcoma (MA) is an uncommon tumor characterized by benign epithelial glands and malignant stromal elements. It occurs mainly in the uterine corpus but may also involve the ovaries, cervix, and extra-pelvic sites [1,2]. MA of the uterine cervix has a low malignant potential, but the presence of sarcomatous overgrowth (SO) and heterologous elements are associated with worse prognosis. It occurs not only in postmenopausal women but also in young women, which can be difficult since techniques to preserve fertility in young women can be at times very challenging. To our knowledge, there is little literature describing the clinical management including fertility preservation for young women

with MA because of the rarity of cases. The present retrospective study, which included a review of the literature, assessed the clinicopathological features and clinical management of MA.

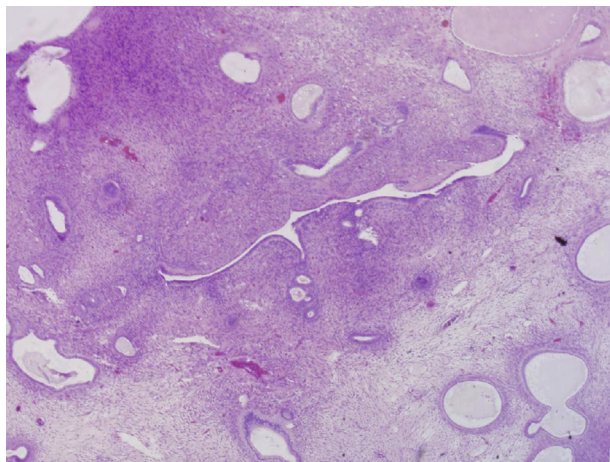
## Materials and methods

We reviewed the clinical records and pathological specimens obtained from all patients with cervical MA diagnosed and treated at the Gynecology Division of Kagoshima University Hospital, Kagoshima, Japan, between 2001 and 2016. The ethics committee approved this study, and informed consent was obtained from all patients. All definitive diagnoses were made from excised specimens.

This study included patients who had a lesion fulfilling the histological criteria for MA based on the guidelines of the World Health Organization International Histological Classification of Tumors. Biphasic tumors with an admixture of benign glands and low grade malignant stromal components were diagnosed as MA

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**Fig. 1.** Mullerian adenocarcinoma of the uterine cervix. The tumor shows benign glands and low-grade endometrial stromal sarcoma of the cervix. (hematoxylin and eosin stain,  $\times 20$ ).

(Fig. 1). Interestingly, benign glands often show comparable endocervical epithelium. They are surrounded by a cellular stroma that forms periglandular cuffs as well as intraluminal polypoid projections. The stroma is low grade, resembling endometrial stromal sarcoma of the uterine corpus.

For this study, two gynecologic pathologists re-examined all pathological specimens.

## Results

Six patients met the study criteria, and Table 1 summarizes their characteristics. The median age was 50 years (range, 17–74) and the median follow-up period was 45 months (range, 13–106). No patient was lost to follow-up. Four patients presented with vaginal bleeding and two of them had watery discharge as the primary symptom. Three nulliparous patients who hoped to preserve their uterus were included in this study, and only one among the three patients received fertility-preservation surgery. Five patients underwent hysterectomy (simple in 3, modified radical in 2) with bilateral salpingo-oophorectomy (BSO) or bilateral salpingectomy, and the sixth patient underwent conization to preserve fertility. Two patients could not preserve their uterus since one of them had an endophytic tumor with deep cervical stromal invasion ( $>1/2$ ) while the other patient had the tumor in the endocervix, as detected by magnetic resonance imaging. Complete resection of the tumors was carried out. While five tumors showed an exophytic pattern, one showed an endophytic pattern. Five patients had no cervical stromal invasion, but one had a full thickness invasion. None of the cases was accompanied with heterologous

components. SO was present in two patients, and one of these patients was detected with a recurrence in the left lung 60 months after surgery (TAH + BSO). Although she underwent left upper lobectomy, there were repeated recurrences in the lung, pelvic cavity, and mediastinal lymph node. She eventually died of the primary disease, 108 months after initial surgery. One patient with deep stromal invasion received adjuvant treatment with pazopanib and had no recurrence for 17 months.

## Discussion

MA is a neoplasm with benign glandular and malignant stromal elements. Overall, 71% cases of adenocarcinoma occur in the uterine body, 15% in the ovaries, 12% within the pelvis, and only 2% cases occur in the cervix [2]. No large-scale, multicenter studies have been performed so far, and an optimal primary therapeutic approach to MA has not yet been determined.

Poor prognostic factors for MA are deep stromal invasion, SO, high mitotic rate, heterologous elements, necrosis, and extrauterine spread [3–5]; deep stromal invasion and SO are associated with the worst prognosis. Deep stromal invasion and SO are predictors of aggressive behavior and poor prognosis respectively [6,7]. SO is defined as the presence of pure sarcoma, usually of a high grade, without a glandular component, and occupying at least 25% of the tumor [8]. In the present study, two patients had MA with SO, and of these, one patient died of distant metastasis 108 months after surgery. Another patient with SO is alive, but the follow-up period was very short. Based on these observations, we believe that SO is a very strong prognostic factor.

Compared to endometrial MA, cervical MA tends to afflict younger women with average age at presentation being 37 years [3]. In our study, three of the six patients were of reproductive age, with a desire to preserve fertility. With the help of “mullerian adenocarcinoma” and “uterine cervix” as key words, we conducted a Medline search for articles on MA, published in English between 2000 and 2016, and extracted papers reporting data on patients less than 40 years of age. The literature provided information on a total of 15 patients including those in the present study [1,9–18]. Four out of these 15 patients (17%) underwent fertility-preservation surgery [10–12]. The clinical characteristics of these 15 patients are summarized in Table 2. Three of the four patients who underwent fertility preservation had no stromal invasion and SO, with no recurrence reported. In the previous studies, most authors have recommended hysterectomy usually accompanied by BSO for cervical MA of the cervix [19,20]. Seven nulliparous patients underwent hysterectomy with or without bilateral oophorectomy, and among them, one patient who had SO and heterologous elements died. Local excision has been curative in young patients with pedunculated cervical tumors and uninvolved stalks [19,21]. However, fertility preservation should not be recommended for all young women. Jones and Lefkowitz [3] reported that three of the

**Table 1**  
Clinicopathological characteristics of the 6 patients with mullerian adenocarcinoma of the uterine cervix.

Patient No.	Age (y)	Parity	Presenting symptoms	Growth form	Surgery	Cervical stromal invasion	Heterologous	SO	Adjuvant therapy	Status (months)
1	66	1	Vaginal bleeding	Exophytic	TAH + BSO	No	No	Yes	No	DOD (104)
2	74	3	Watery discharge	Exophytic	TAH + BSO	No	No	No	No	NED (106)
3	32	0	Vaginal bleeding	Exophytic	TAH + BS	No	No	No	No	NED (28)
4	34	0	Vaginal bleeding	Endophytic	MRH + BSO + PLD + LAR	$>1/2$	No	No	Pazopanib	NED (13)
5	17	0	Vaginal bleeding Introital mass	Exophytic	Conization	No	No	No	No	NED (62)
6	67	0	Watery discharge	Exophytic	MRH + BSO + PLD + PAND	No	No	Yes	No	NED (2)

SO = Sarcomatous overgrowth, TAH = Total abdominal hysterectomy, BSO = Bilateral Salpingo-oophorectomy, BS = Bilateral salpingectomy, MRH = Modified radical hysterectomy, PLD = Pelvic lymph node dissection, LAR = Low anterior resection, NED = no evidence of disease, DOD = dead of disease, PAND = para-aortic node dissection.

**Table 2**

Cases of Mullerian adenosarcoma of the cervix in patients aged less than 40 years: survey of the literature from 2000 to 2016.

	Age (y)	Parity	Presenting symptoms	Growth form	Surgery	Cervical stromal invasion	Heterologous	SO	Adjuvant therapy	Status (months)	Status
Ramos et al. (2002) [18]	25	0	Metrorrhagia	Exophytic	TAH + BSO	>1/2	Cartilage	NM	No	NED (24)	NED 24 m
Park et al. (2004) [16]	37	NM	Irregular vaginal spotting	Exophytic	TAH + BSO + PLD	No	No	Yes	No	NED (9)	NED 9 m
Manoharan et al. (2007) [1]	28	0	Postcoital bleeding	NM	RH	NM	None	Yes	Chemotherapy (ifosfamide + doxorubicin) + radiotherapy	NED (48)	NED 48 m
Manoharan et al. (2007) [1]	26	2	Intermenstrual and postcoital bleeding	NM	Vaginal hysterectomy + laparoscopic retroperitoneal PAND	NM	NM	No	Radiotherapy	NED (36)	NED 36 m
Bagga et al. (2009) [9]	15	0	Vaginal bleeding	NM	TAH + BSO + PLB + partial omentectomy	NM	Rhabdomyosarcoma	Negative	None	NED (9)	NED 9 m
Fleming et al. (2009) [14]	10	0	Vaginal bleeding	NM	RH + BS + PLD + upper vaginectomy	NM	NM	NM	None	NED (NM)	NED
Buyukkurt et al. (2010) [10]	14	0	Mass	Exophytic	Excisional biopsy	No	No	NM	None	NED (15)	NED 15 m
Duggal et al. (2010) [13]	15	0	Foul smelling menstrual bleeding	NM	TAH + BSO + omentectomy	NM	Chondrosarcoma, myxoidliposarcoma, leiomyosarcoma, rhabdomyosarcoma	Yes	Chemotherapy + radiotherapy	DOD (12)	DOD 12 m
Charfi et al. (2012) [11]	26	NM	Mass	Exophytic	Excisional biopsy	NM	Rhabdomyosarcoma	Yes	None	Lost	Lost follow up
Chin et al. (2013) [12]	17	0	Vaginal bleeding	Exophytic	Cervical wedge resection	No	Heterologous	No	No	NED (204)	NED (204)
Podduturi et al. (2016) [17]	38	3	Introital mass	NM	NAC (cyclophosphamide + vincristine + actinomycin D) + RH + BSO + PLD	NM	Rhabdomyosarcoma	Yes	None	NED (10)	NED 10 m
Morales et al. (2016) [15]	39	NM	Pelvic pain + vaginal bleeding	NM	RH + PLD	NM	Cartilage and Rhabdomyosarcoma	Yes	None (patient rejection)	AWD (21)	AWD 21 m
Present study	32	0	Vaginal bleeding	Exophytic	TAH + BS	No	No	No	No	NED (28)	NED (28)
	34	0	Vaginal bleeding	Endophytic	MRH + BSO + PLD + LAR	>1/2	No	No	Pazopanib	NED (13)	NED
	17	0	Vaginal bleeding	Exophytic	Conization	No	No	No	No	NED (62)	NED (62)
			Introital mass								

SO = sarcomatous overgrowth, TAH = Total abdominal hysterectomy, BSO = Bilateral Salpingo-oophorectomy, NM = Not mentioned, NED = no evidence of disease, PLD = Pelvic lymph node dissection, RH = Radical hysterectomy; PAND = para-aortic node dissection; PLB = Pelvic lymph node biopsy, BS = Bilateral salpingectomy, DOD = dead of disease, NAC = Neoadjuvant chemotherapy, AWD = alive with disease, MRH = modified radical hysterectomy, LAR = Low anterior resection.

twelve women had excisional biopsy while the others underwent a hysterectomy. Their study indicated that deep stromal invasion is an important prognostic determinant and that MA usually exhibits a favorable prognosis [3]. We suggest that patients with SO, heterologous elements and deep stromal invasion must be excluded from fertility preservation surgeries. In our study, three patients hoped to preserve fertility. Two patients could not preserve their uterus since one of them had the tumor in the endocervix, as detected by magnetic resonance imaging. Another patient underwent modified radical hysterectomy, BSO, pelvic lymph node dissection, and lower anterior resection because she had an endophytic cervical mass that had spread to the rectum serosa through the posterior vaginal wall. Another 17-year-old patient, with an exophytic cervical polyp with absence of SO, heterologous elements, and deep stromal invasion, underwent fertility-preservation surgery by conization of the cervix. No tumor recurrence was reported at the end of a 62-month follow-up period.

In summary, although deep stromal invasion was not evident in the patient who died in our study, research suggests that the presence of stromal invasion and SO is associated with poor prognosis. Along with adequate counseling, fertility-preservation surgery may be acceptable in cases presenting with exophytic cervical MA, provided there are no indications of SO, heterologous elements, and deep stromal invasion. Long-term follow-up is required in these patients.

#### Conflict of interest statement

The authors declare that there are no conflicts of interest.

#### Acknowledgment

None.

#### References

- [1] Manoharan M, Azmi MA, Soosay G, Mould T, Weekes AR. Mullerian adenocarcinoma of uterine cervix: report of three cases and review of literature. *Gynecol Oncol* 2007;105:256–60.
- [2] Arend R, Bagaria M, Lewin SN, Sun X, Deutsch I, Burke WM, et al. Long-term outcome and natural history of uterine adenosarcomas. *Gynecol Oncol* 2010;119:305–8.
- [3] Jones MW, Lefkowitz M. Adenosarcoma of the uterine cervix: a clinicopathological study of 12 cases. *Int J Gynecol Pathol* 1995;14:223–9.
- [4] Kaku T, Silverberg SG, Major FJ, Miller A, Fetter B, Brady MF. Adenosarcoma of the uterus: a gynecologic oncology group clinicopathologic study of 31 cases. *Int J Gynecol Pathol* 1992;11:75–88.
- [5] Kerner H, Lichtig C. Mullerian adenosarcoma presenting as cervical polyps: a report of seven cases and review of the literature. *Obstet Gynecol* 1993;81:655–9.
- [6] McCluggage WG. Mullerian adenosarcoma of the female genital tract. *Adv Anat Pathol* 2010;17:122–9.
- [7] Zaloudek CJ, Norris HJ. Adenofibroma and adenosarcoma of the uterus: a clinicopathologic study of 35 cases. *Cancer* 1981;48:354–66.
- [8] D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol* 2010;116:131–9.
- [9] Bagga R, Keepanasseril A, Srinivasan R, Dey P, Gainer S, Saha SC, et al. Adenosarcoma of the uterine cervix with heterologous elements: a case report and review of literature. *Arch Gynecol Obstet* 2010;281:669–75.
- [10] Buyukkurt S, Guzel AB, Gumurdulu D, Vardar MA, Zeren H, Sucu M. Mullerian adenosarcoma of the uterine cervix in an adolescent girl. *J Pediatr Adolesc Gynecol* 2010;23:e13–15.
- [11] Charfi S, Kallel R, Mnif H, Ellouze S, Dhoubi M, Guermazi M, et al. Mullerian adenosarcoma of the cervix with heterologous elements: a case report and review of literature. *Case Rep Obstet Gynecol* 2012;2012:358302.
- [12] Chin PS, Chia YN, Lim YK, Yam KL. Diagnosis and management of Mullerian adenosarcoma of the uterine cervix. *Int J Gynaecol Obstet* 2013;121:229–32.
- [13] Duggal R, Nijhawan R, Aggarwal N, Sikka P. Mullerian adenosarcoma (heterologous) of the cervix with sarcomatous overgrowth: a case report with review of literature. *J Gynecol Oncol* 2010;21:125–8.
- [14] Fleming NA, Hopkins L, de Nanassy J, Senterman M, Black AY. Mullerian adenosarcoma of the cervix in a 10-year-old girl: case report and review of the literature. *J Pediatr Adolesc Gynecol* 2009;22:e45–51.
- [15] Morales FD, Medina RM, Trujillo LM, Beltran MI, Dulcey IC. Mullerian adenosarcoma of the uterine cervix with sarcomatous overgrowth: a case report of aggressive disease in a young patient. *Int J Surg Case Rep* 2016;27:155–61.
- [16] Park HM, Park MH, Kim YJ, Chun SH, Ahn JJ, Kim CI, et al. Mullerian adenosarcoma with sarcomatous overgrowth of the cervix presenting as cervical polyp: a case report and review of the literature. *Int J Gynecol Cancer* 2004;14:1024–9.
- [17] Podduturi V, Pinto KR. Mullerian adenosarcoma of the cervix with heterologous elements and sarcomatous overgrowth. *Proc (Bayl Univ Med Cent)* 2016;29:65–7.
- [18] Ramos P, Ruiz A, Carabias E, Pinero I, Garzon A, Alvarez I. Mullerian adenosarcoma of the cervix with heterologous elements: report of a case and review of the literature. *Gynecol Oncol* 2002;84:161–6.
- [19] Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol* 1990;21:363–81.
- [20] Gast MJ, Radkins LV, Jacobs AJ, Gersell D. Mullerian adenosarcoma of the cervix with heterologous elements: diagnostic and therapeutic approach. *Gynecol Oncol* 1989;32:381–4.
- [21] Chen KT. Rhabdomyosarcomatous uterine adenosarcoma. *Int J Gynecol Pathol* 1985;4:146–52.