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The Impact on Survival of an Extensive Sex Cord-Like Component in Mullerian Adenosarcomas: A Study Comprising 6 Cases

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Summary

Mullerian adenosarcomas are uncommon tumors of the female genital tract characterized by a synchronous proliferation of benign glands and sarcomatous stroma. In general, uterine Mullerian adenosarcomas are associated with a low risk of recurrence. The presence of “stromal overgrowth” (SO), historically defined by an estimate of the volume of sarcoma growing independently of epithelium, is associated with deep myometrial invasion, presence of heterologous elements, and poor outcomes. Very rarely, the stromal component can harbor foci resembling ovarian sex cord tumors (FROSCT). The aim of this study was to determine whether the presence of an extensive FROSCT component in Mullerian adenosarcomas has an impact on survival, akin to more typical types of SO. Six patients were included in this study. Age ranged from 39-71 years. Five patients presented with uterine lesions (4 intracavitary, 1 isthmic), and one was located in the ovary. Tumors ranging in size from 2.5 to 19 cm were all diagnosed as stage I. Morphologically, all had prominent FROSCT-like components that comprised 60-90% of tumor volume. Immunohistochemically, the FROSCT component was positive for CAM 5.2, Vimentin, WT1, CD56, α -inhibin, calretinin, androgen and progesterone receptors, α -actin, and desmin. All patients are alive without disease at 26-102 months. Compared to adenosarcomas with typical forms of SO, FROSCT overgrowth is low grade and not associated with recurrence or metastasis in this small series. Therefore, Mullerian adenosarcoma with extensive FROSCT should not be equated with SO.

Keywords

adenosarcoma; sex-cord like component; stromal overgrowth; survival

Introduction

Mullerian adenosarcomas are uncommon but not rare tumors of the female genital tract. They are characterized by a synchronous proliferation of sarcoma, usually histologically low-grade, and benign-appearing, mostly endometrioid epithelium (1). Most uterine adenosarcomas are clinically low-grade, with low rates of recurrence and mortality. Occasionally, mullerian adenosarcomas may be overgrown by various types of an aggressive, high-grade sarcomatous component (2). There is consensus that the presence of sarcomatous stromal overgrowth (SO) is an adverse prognostic finding, even though definitions for SO are not yet standardized. Most cases with SO are also histologically high-grade, myoinvasive, and may show heterologous differentiation, but rare Mullerian adenosarcomas may contain histologically high-grade and/or heterologous stroma and/or myometrial invasion in the absence of SO. It is therefore difficult to determine the most important drivers of adverse outcome: volume of stroma; sarcoma grade; presence and depth of myometrial invasion; and/or sarcoma type. Very rarely, Mullerian adenosarcomas at various locations in the female genital tract can harbor foci resembling ovarian sex cord tumors (FROSCT) (3,4,5). When this component predominates over the epithelial component, it is uncertain whether to categorize the tumor as adenosarcoma with SO and whether this component is associated with survival.

The aim of this study was to determine whether the presence of FROSCT component, and its volume, have an impact on survival and, secondarily, whether this pattern should be considered SO. We report a series of 6 cases of Mullerian adenosarcomas with extensive FROSCT components, leading to the impression of a stromal component that has overgrown the epithelial component.

Material and Methods

Six patients were included in this study. The clinical and pathological information, together with paraffin blocks for slide review, were selected from the databases of the Department of Pathology, University of Medicine Targu Mures, Romania (SS), the Department of Pathology, University of Granada, Spain (FFN), and the Department of Pathology, Memorial Sloan Kettering Cancer Center New York, USA (RS). In each case, the original slides were reviewed by the authors of this paper. The average number of slides per case was 18 (range, 10-28). For the immunohistochemical examination, a panel of markers was used. These markers are listed in Table 1.

Results

Six patients, 39-71 years of age, 2 of them on Tamoxifen (20 mg daily for 4-5 years) for a previously diagnosed breast carcinoma, were admitted for vaginal bleeding. Four patients presented with intracavitary polypoid tumors at ultrasound examination; one superficially infiltrated the myometrium, and another originated in the isthmus and secondarily involved the endocervical canal. Another patient was admitted for abdominal pain and ultrasound examination revealed a tumor mass located in the ovary. Total hysterectomy with bilateral

salpingo-oophorectomy was performed for all 6 patients. No adjuvant treatment was delivered in 5 cases, while the one patient with a superficially myoinvasive tumor underwent biopsy of a sentinel lymph node (which was negative) and vaginal brachytherapy (Table 2).

Macroscopically, tumors ranging in size from 2.5 to 19 cm diameter were all diagnosed as Stage I. The uterine corpus and isthmus tumors were polypoid in appearance and obliterated the uterine cavity/endocervical canal. On cut section they were soft, gelatinous, yellow to tan in color, and had multiple small cystic formations. The ovarian tumor was predominantly cystic. Morphologically, all tumors were composed of an admixture of epithelial and mesenchymal components (Figs. 1-4). The former consisted of cystically dilated tubular glands that often showed intraglandular blunt papillary projections (very characteristic at low power for a phyllodes-like architecture) lined by benign endometrioid or mucinous epithelium frequently showing squamous, eosinophilic and ciliated metaplasia. Glands were surrounded by thin cuffs of a stromal condensation of histologically low-grade sarcomatous stroma with mildly atypical oval-to-spindled nuclei and low mitotic index (2-5 mitoses/10 HPF). This component was highlighted on examination at low microscopic power by strong CD10 positivity. Each case also contained a second stromal component, representing 60-90% of the tumor volume. This component featured polygonal tumor cells with eosinophilic or foamy cytoplasm resembling ovarian lutein cells; these cells were arranged in sheets, cords, and tubules, and lacked nuclear atypia. The cells were diffusely positive for CAM 5.2, Vimentin, WT1, CD56, α -inhibin, and calretinin (Fig. 5 A-C). They were variably positive for androgen and progesterone receptors, α -actin, and desmin. Other myoid markers such as calponin and h-caldesmon, as well as CK7, CK20, CD99, CD10, p53, Synaptophysin, Chromogranin, HMB45, Podoplanin, TTF1, and Thyroglobulin were negative (Table 3). This second component was designated *foci resembling ovarian sex cord tumors* (FROSCT).

None of the tumors were associated with intravascular tumor emboli. One tumor had superficial myometrial involvement of 1-2mm in depth. All patients are alive without disease at 26-102 months after initial diagnosis. One patient (number 1) had a lung nodule which has not changed in size and is now thought to represent bronchiectasis (Table 2).

Discussion

Mullerian adenosarcoma of the female genital tract is a biphasic tumor that commonly occurs in the uterine corpus but can also develop in the cervix, ovary, and, rarely, in the fallopian tube and vagina (6,7). The stromal component is usually morphologically of low-grade endometrial stromal or fibroblastic type and immunohistochemically positive for CD10. However, in rare instances the stroma can be overgrown by various types of high-grade sarcomas (stromal overgrowth [SO]), resembling or representing fibrosarcoma, rhabdomyosarcoma, leiomyosarcoma, angiosarcoma, and undifferentiated sarcoma (2). The presence of SO, historically defined by an estimate of the volume of sarcoma growing independently of epithelium, is frequently associated with deep myometrial invasion, presence of heterologous elements, and poor outcomes (8,9). However, SO is defined differently by different sources. The most recent World Health Organization classification book (2014) requires high-grade sarcoma but does not include a volume criterion. The

Gynecologic Cancer InterGroup (GCIG) consensus recommends a diagnosis of SO when more than 25% of the tumor is composed of pure high-grade sarcoma. The 2003 WHO book and the College of American Pathologists (CAP) defined SO as sarcoma, “usually high grade,” comprising 25% or more of the total tumor volume. Histologically “low-grade SO” has also been reported (10,11,12).

Additional features can sometimes be present, e.g., sex cord-like differentiation. Areas resembling ovarian sex cord tumors have been previously reported in adenosarcomas of the cervix and endometrium, and rarely in the ovary (3,4,6). Usually these areas represent less than 25% of the tumor. However, massive involvement by areas resembling sex cord-like components has been reported previously, 2 endometrial examples of which are included in this manuscript as well (5). We suggest that a massive component of sex cord-like growth should not be considered SO, but rather a differentiation phenomenon with no impact on prognosis because of event-free survivals of 3 and 5 years. Data provided in the current study validate this idea using 4 additional cases with sex cord-like differentiation representing 60-90% of the tumor volume. All 6 patients in this series are alive without recurrence at 26-102 months of follow-up.

A recent paper from McCluggage's group (13) describes two ovarian adenosarcomas containing extensive sex cord components resembling juvenile granulosa cell tumor; one tumor displayed local extension to extra-ovarian structures. It remains uncertain whether extra-ovarian extension was related to the presence of extensive sex cord-like components or the natural history of ovarian adenosarcomas, which are known to be more clinically aggressive than uterine counterparts (6).

Immunohistochemistry was performed in the reported cases to confirm the morphological impression of sex cord-like differentiation, although immunohistochemical staining was not absolutely necessary for diagnostic purposes. If one is uncertain whether an extensive non-epithelial component of adenosarcoma represents sarcoma or sex cords, it is certainly worthwhile to perform markers of sex cord-like differentiation, a partial list of which includes inhibin, calretinin, FOXL2, which are most sensitive, as well as CD10, CD99, and WT1. It should be noted that a variety of gynecologic tumors may contain sex cords and sex cord-like differentiation. Uterine tumors resembling ovarian sex cord tumors (UTROSCT) and selected endometrial stromal neoplasms display immunophenotypic evidence of sex cord differentiation, although both tumors may contain polyphenotypic proliferations that not only express sex cord markers, but also display epithelial- and mesenchymal-related differentiation. Four of 5 tumors tested with multiple markers in this study were, in fact, polyphenotypic (Table 3). Both endometrioid carcinomas and epithelioid leiomyosarcomas may contain areas resembling sex cords, but immunophenotypic evidence of sex cord differentiation in these latter tumors is lacking. Given the presence of extensive sex cord-like differentiation, a diagnosis of adenosarcoma can only be established when the typical features of adenosarcoma (i.e., phyllodes-like appearance with peripheral stromal condensation) are present at least focally within a well sampled tumor.

Although we cannot determine from this dataset whether volume or grade should take equal importance prognostically, we can assert that based on studying limited numbers of cases,

Mullerian adenosarcomas with extensive FROSCT infrequently invade myometrium and are clinically indolent. Thus, they should specifically not be considered SO, despite their volume.

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Figure 1.
Adenosarcoma with an extensive sex cord-like component.

Figure 2. Adenosarcoma with an extensive sex cord-like component. Microscopy features a gland with a blunt stromal papillary projection surrounded by stroma rich in sex cord-like elements.

Figure 3. Adenosarcoma with an extensive sex cord-like component. Microscopy features a gland with peripheral stromal condensation surrounded by stroma rich in sex cord-like elements.

Figure 4.
Adenosarcoma with an extensive sex cord-like component. High power microscopy demonstrates features that recall lipid-rich Sertoliiform tubules.

Figure 5.
Immunohistochemical features of extensive sex cord-like components. **A.** Inhibin; **B.** Calretinin; **C.** CD56.

Table 1

Immunohistochemical Markers

Antibody	Animal	CLONE	VENDOR	Ref #	DILUTION
CD 10	Mo	56C6	DAKO	M 7308	1:30
Calponin	Mo	CALP	DAKO	M 3556	1:50
H-Caldesmon	Mo	h-CD	DAKO	M 3557	1:50
CAM 5.2	Mo	CAM-52	DAKO	Z-0622	1:5000
CD 56	Mo	123C2	DAKO	M 7304	1:50
Inhibin	Mo	5A5	NEO MARKERS	MS-1110-S	1:100
Androgen Receptor	Mo	AR441	DAKO	M 3562	1:50
Progesteron Receptor	Rh	SP2	DAKO	A 0098	1:50
Vimentin	Mo Mo	V9	VENTANA	790-2917	RTU
WT1	Mo Mo	WT49	LEICA	PA0562	RTU
Inhibin	Mo Mo	R1	Ventana (Cell Marque)	760-2834	RTU
Calretinin	Rb Mo	SP65	VENTANA	790-4467	RTU
CK7	Mo Mo	OV-TL-12/30	DAKO	M7018	1:1600
CK20	Mo Mo	Ks20.8	DAKO	M7019	1:1600
CD99	Mo Mo	O13	COVANCE (BioLegend Antibodies)	SIG-3620-1000	1:800
CD10	Rb Mo	SP67	VENTANA	790-4506	RTU
p53	Mo Mo	D07	VENTANA	790-2912	RTU
Synaptophysin	Mo Mo	SNP88	BIO GENEX	MU363 UC	1:2K
Chromogranin	Mo Mo	LK2H10	VENTANA	760-2519	RTU
HMB45	Mo Mo	HMB45	DAKO	M0634	1:500
Podoplanin	Mo Mo	D240	Ventana (Cell Marque)	760-4395	RTU
TTF1	Mo Mo	Top of Form 8G7G3/1 Bottom of Form	VENTANA	790-4398	RTU
Thyroglobulin	Mo Mo	2H11+6E1	Ventana (Cell Marque)	760-2671	RTU
Desmin	Mo Mo	DE-R-11	VENTANA	760-2513	RTU
smooth muscle actin	Mo Mo	ASMI	VECTOR	VPS281	1:50
Caldesmon	Mo Mo	E89	Ventana (Cell Marque)	760-4375	RTU

Table 2

Clinical characteristics

Case	Age	HT	Clinical findings	Treatment (surgical and oncologic)	Original diagnosis	Survival (follow-up)
1#	59	Yes (tamoxifen)	Polypoid uterine tumor	TAHBSO	Endometrial polyp with cellular stroma/ FROSCT	Alive 58 months after diagnosis; NED
2#	39	No	Endometrial mass	TAHBSO and sentinel lymph node biopsy; intravaginal brachytherapy	Low-grade Mullerian adenocarcinoma with FROSCT, Stage 1	Alive, 26 month after the diagnosis; NED
3#	71	No	Intracavitary polypoid tumor	TAHBSO	Low-grade Mullerian adenocarcinoma	Alive, 102 month after initial diagnosis; NED
4#	64	Yes (tamoxifen)	Intracavitary polypoid tumor	TAHBSO	Endometrial polyp	Alive, 78 month after initial diagnosis; NED
5#	70	No	Polypoid tumor originating in the isthmus, involving the endocervical canal	TAHBSO	Endometrioid adenocarcinoma of endometrium	Alive, 28 month after diagnosis; NED
6#	48	No	Abdominal pain, Ovarian mass	TAHBSO	Low-grade Mullerian adenocarcinoma of the ovary	Alive, 102 month after diagnosis; NED

HT: hormonal treatment; NED: no evidence of disease; FROSCT: foci resembling ovarian sex cord tumors; TAHBSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Table 3

Morphological and IHC profile of cases

Case	Size of the lesion (cm)	Myometrial invasion	Mitoses/10HPF	Volume of the stroma occupied by the FROST (%)	IHC profile		Final diagnosis
					Positive	Negative	
1#	13cm (polyp) 0.2cm residual tumor in hysterectomy	No	2	90	Pan-Cytokeratin Vimentin WT1 α -inhibin Calretinin	CK7, CK20 CD99,CD10 P53,HMB45 Synapto, Chromo, Podoplanin TTF1, Thyroglobulin, Desmin, α - actin	Low-grade Mullerian adenosarcoma with extensive sex cord-like component, stage 1
2#	2.6	Yes	2	80-90	Desmin	CD10 Pan-Cytokeratin H-Caldesmon	
3#	2.5	No	1-2	80	CAM 5.2 CD56 α -inhibin Calretinin AR, PR α - actin	CD10 Calponin H-Caldesmon	
4#	8	No	4-5	80	CAM 5.2 CD56 α -inhibin Calretinin AR, PR α - actin	CD10 Calponin H-Caldesmon	
5#	3,5	No	1-2	60	CAM 5.2 CD56 α -inhibin		
6#	19 cm cyst with a foliaceous 6.5 cm	no	1-2	80	α -inhibin		

IHC, immunohistochemical