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Mullerian adenosarcomas of the uterine cervix with sarcomatous overgrowth

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ABSTRACT

Mullerian adenosarcoma with sarcomatous overgrowth (MASO) of the uterine cervix is an extremely rare variant of adenosarcoma of the genital tract associated with aggressive clinical course. We searched the PubMed and Medline databases for MASO of the cervix and we identified and reviewed eleven cases published between years 2004 and 2017. The most common clinical picture includes abnormal vaginal bleeding, postcoital bleeding, pelvic pain and foul-smelling vaginal discharge. Therapeutic options for MASO are still undefined. Radical hysterectomy with sufficient tumour-free margins combined with adjuvant chemotherapy and radiotherapy should serve as an effective treatment tool with favourable outcome.

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Introduction

Adenosarcoma is an extremely rare gynecological tumor whose term was introduced by Clement and Scully in 1974. The most common localization is the uterus (71%) and ovary (15%) with very few cases originating from the uterine cervix (2%).[1,2] It is characterized by a combination of low-grade stromal sarcoma, benign glandular component, presence of myometrial invasion and ≥2 mitotic figures per 10 HPF. Unfavorable prognostic factors include: sarcomatous overgrowth, high mitotic rate, myometrial invasion, necrosis, and extrauterine metastases.[3] There are 2 types of adenosarcoma associated with poorer prognoses: Mullerian adenosarcoma (MA) with sarcomatous overgrowth (MASO) and MA with heterologous elements like skeletal muscle, bone or cartilage that are found in 10%-15 % of case.[4] Sarcomatous overgrowth is diagnosed, when the pure sarcomatous component represents more than 25 % of the primary tumor.

Molecular background is still under investigation. Adenosarcomas are genetically heterogenous. A consistent finding is a rate of 26%-28 % of amplifications affecting MDM2/CDK4.[5] Additional alterations include mutations affecting PI3K/AKT/PTEN pathway, Wnt/β-catenin pathway, ATRX, FGFR2, KMT2C, TP53 and amplifications of TERT and MYLB1. MYLB1 and ATRX mutation was present in 50% of MASO.[6,7] MYLB1 is a transcriptional factor regulating cell proliferation whereas ATRX regulates DNA methylation and chromatin remodeling. There were reported also numerical abnormalities of chromosomes 2,8,10,13,19,21 and hyperdiploid karyotype.[7] Higher level of gene copy number alterations is associated with aggressive futures of adenosarcomas.[5]

MASO of the uterine cervix

MASO was first described in 1989 and is associated with multiple recurrences, metastases even diagnosed in initial stage.[2,8] In our work we focused on extremely rare cases of MASO originating from uterine cervix. We searched the PubMed and Medline databases for MASO of the cervix and we identified and reviewed 11 cases between years 2004 and 2017. The exact etiologic factors remain unknown but at least 3 risk factors are discussed: pelvic irradiation, hyperestrogenism (long-term contraceptive use, unbalanced oestrogen stimulation) and treatment with tamoxifen.[9,10] In contrast to squamocellular carcinoma of the cervix no high-risk human papillomaviruses were detected by polymerase chain reaction or hybridization method in the published literature.

Differential diagnosis includes benign lesions as adenofibroma, atypical endocervical polyp, and adenomyomas. Atypical endocervical polyp is characterized by unusual stroma and irregular gland outlines lacking biphasic pattern. There are only focal changes and absent mitotic activity compared to adenosarcoma. Embryonal rhabdomysoarcoma should be also included in differential diagnosis although it is very rarely presented in cervix. Immunohistochemical findings in MASO are similar to findings in carcinosarcoma.[11] In uterine location immunoreactions for 2 markers of cell proliferation Ki-67 and p53 were stronger compared to typical MA. In contrast the expression level of cell differentiation markers CD10 and PR was higher in typical adenosarcoma. MA shows phyllodes like architecture and intraglandular stromal projections.[11]

Symptoms and diagnostics

The average age at the diagnosis is 41 years, whereas 4 patients were diagnosed with MASO in their menopause.[4,12,13,14] The most common clinical picture includes abnormal vaginal bleeding, postcoital bleeding, pelvic pain, and foul smelling vaginal discharge. During examination cervical polyp with tendency to recur or enlarged uterus and pelvic mass are detected.[2] According to the published literature the fleshy fragile polypoid mass is relatively big measuring between 2.0. and 12.5 cm. None of the reviewed article used the colposcopy examination and the HPV virus detection for the presenting lesion. Tumor markers are not useful in diagnostics. In the study of Patrelli et al. cancer markers CEA AFP, CA19-9, CA 125, HE4, CA 15-3 were within

Table 1
MASO of the uterine cervix according to their histopathological features.

	Size	Stage	SO (%)	Mitoses/ 10HPF	Heterologous components	Immunohistochemistry
[3]	2.0	IB1	n.a.	20	none	Positive: vimentin Negative: cytokeratin, HMB-45, CD34, CD99, S-100 protein, desmin
[18]	6.0	IB2	n.a.	>10	Striated muscle	n.a.
[12]	12.5	IB2	40	10	none	Positive: vimentin, PR, ER, SMA, desmin in sarcomatous cells Negative: CD34, HMB-45, cytokeratin, S-100
[4]	n.a.	IB	n.a.	6	n.a.	n.a.
[19]	7.0	IV	70	24	Chondrosarcoma, myxoid liposarcoma, leiomyosarcoma, rhabdomyosarcoma	Positive: vimentin, CD10, S-100 Negative: PR, ER
[13]	8.0	IB2	70	10	rhabdomyosarcoma	Positive: vimentin, desmin Negative: MNF116 keratin
[11]	2.0	IB1	50	25	rhabdomyosarcoma	Positive: vimentin, desmin
[14]	9.5	IB2	n.a.	n.a.	Cartilage rhabdomyosarcoma	Positive: SMA, MSA, ER, PR, desmin, CKAE1/3, CAM5.2 Negative: myogenin, EMA, CD10, caldesmon, HMB-45, CD31, CD34, inhibin, S100
[16]	7.5	IB2	25	52	Cartilage rhabdomyosarcoma	Positive: CD10, S100, myogenin, cytokeratin, ER, Ki-67 60 %
[27]	2.3	IB2	n.a.	n.a.	Rhabdomyosarcoma, cartilage	Positive: ER, PR, myogenin, desmin Negative: WT1
[17]	3.0	IV	80	4	Benign cartilage	Positive: vimentin, desmin Negative: actin, S-100,

SO, sarcomatous overgrowth; HPF, high power field.

the norm.[13] On the contrary Seagle et al. showed increased values of CA125 and CA19-9.[14] The primary diagnosis is based on the biopsy and histopathological evaluation with the focus on differential diagnosis. A pathology review of national expert is advised in the diagnostic process. The exact immunohistochemical findings published in the English literature are summarized in Table 1.

Surgery, implications of molecular profiling and outcome of MASO of the uterine cervix

Therapeutic options for MA and/or MASO are still undefined. Most authors recommend total abdominal hysterectomy with bilateral salpingoophorectomy. Staging by pelvic lymphadenectomy during primary surgery is also discussed.[15] Morales et al. recommend radical hysterectomy aimed at obtaining sufficient tumor-free margins, because most clinically evident lesions are FIGO stage IB1 and IB2.[16] Radical hysterectomy is a standard surgery technique in case reports since 2014. Total abdominal hysterectomy with bilateral salpingoophorectomy was performed in 7 cases. On the contrary only one case report showed positive lymph nodes (Morales et al.

Table 2
MASO of the uterine cervix – treatment modalities and survival.

	Age	Treatment	Adjuvant therapy	Follow-up
[3]	37	TAH + BSO + pelvic LAE	none	9 m DFS
[18]	28	Radical hysterectomy without BSO	CHT – iphosphamide, doxorubicin RT + BRT	4 y DFS
[12]	60	TAH + BSO	None	14 m DFS
[4]	52	TAH	None	Death after 35 m
[19]	15	TAH + BSO + omentectomy, peritoneal washing	RT + CHT	Death after 14 m
[13]	72	TAH + BSO + pelvic LAE + omental biopsy + appendectomy	RT + CHT	3m DFS
[11]	26	TAH	none	Recurrence after 6 m
[14] [	54	Radical hysterectomy + BSO + pelvic LAE	Brachytherapy 25 Gy CHT – 6 cycles of doxorubycine 40mg/m2	66 m DFS
[16]	39	Radical hysterectomy + pelvic LAE	RT + BRT, CHT iphosphamide	Recurrence after 8 m
[27]	38	Radical hysterectomy + BSO, pelvic LAE	Neoadjuvant CHT cyclophosphamide, vincristine, actinomycine D (3 cycles)	n.a.
[17]	32	TAH + BSO	CHT iphosphamide + doxorubicin, RT+ BRT	n.a.

TAH, total abdominal hysterectomy; BSO, bilateral salpingoophorectomy; LAE, lymphadenectomy; RT, radiotherapy; BRT, brachytherapy; CHT, chemotherapy; DFS, disease free survival; y, year; m, month.

2015), lymphovascular space invasion was detected in 3 cases (Morales et al. 2015[17,18]). Most of the patients were in stage IB with the possibility of curative surgical treatment. Koyouncoglu even reported ovarian metastases[17] and Duggal a peritoneal nodulus during the primary surgical procedure.[19] It is rather surprising that the metastases even in relatively big tumors were absent in lymph nodes or in small pelvis. The exact surgical and adjuvant treatment is summarized in Table 2.

No standard of care exists for radio and chemotherapy of uterine and cervical MASO due to their extreme rarity. MASO are often treated according to guidelines for high-grade undifferentiated endometrial sarcoma.[20] Because of unpredictable clinical behavior long-term strict follow-up is essential. Adenosarcomas rarely have distant metastases, but they have a propensity for local recurrence.[16] Local recurrence rate of 24% and distant recurrence rate of 2% after hysterectomy were reported between 0.5 and 9.5 years.[1] A recent small series of uterine MASO reported a 20% 2-year survival.[21] Most studied adjuvant chemotherapy includes iphosphamide and doxorubicine or platinum combined with pelvic radiotherapy and brachytherapy (Morales et al. 2015).[14]

There was no specific gene therapy used in the published literature as far as MASO of the uterine cervix is concerned. On the other hand, molecular profiling is very promising in the development of targeted therapies. Genomic background of high-grade and low-grade adenosarcomas is similar with the exception of p53 pathway alterations. The strong association between high-grade morphology and TP53 pathway abnormalities has important implications. p53 immunohistochemical staining cannot only be used as a confirmation tool of the presence of a high-grade component, but also serve as a predictor of the clinical behavior.[6] Targeting mutant p53 through restoration of its wildtype tumor suppressive function or induction of its degradation has the potential to selectively kill cancer cells.[22]

Molecular treatment strategies have been limited and the available data include targeting mTOR pathway and angiogenic pathways. mTOR inhibition is a promising therapeutic option to impede PI3K/AKT/mTOR signalling contributing to cell survival and has demonstrated effective growth inhibition in the panel of sarcoma cell lines. Multiple studies have demonstrated the potent antiproliferative effects of mTOR inhibitors and their ability to down-regulate the PI3K/AKT/mTOR pathway (Hui et al., 2016[23,24]). Finally, multitargeted tyrosine kinase inhibitors, with activity against angiogenic, stromal (VEGFR1–3, TIE2, FGFR1, and PDGFR-β), oncogenic (KIT and RET), and intracellular signalling (RAF1 and B-RAF) kinases among others are currently in phase II trials for soft tissue sarcomas.[25,26]

Conclusion

In summary MASO of the uterine cervix is an extremely rare variant of adenosarcoma of the genital tract associated with aggressive clinical course and postoperative recurrence. Due to its unpredictable clinical behavior and lack of clinical experience the appropriate treatment is questionable. Therefore, further studies are needed to evaluate the efficient treatment strategies.

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