Pleomorphic Rhabdomyosarcoma of the Uterus – Case Report and a Systematic Review of the Literature

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Abstract. *Background: Pleomorphic rhabdomyosarcomas of the uterus, mainly occurring in postmenopausal women with leading symptoms of vaginal bleeding and abdominal pain, are very rare malignant tumors of the female genital tract. Due to the inefficiency of the adjuvant therapy, the outcome remains poor in the majority of the reported cases. Patient and Methods: We present a case of a 73-year-old patient diagnosed with pleomorphic rhabdomyosarcoma of the uterus. Together with the case report, a systematic review of the literature is presented focusing on different treatment strategies and their outcome. The 95% confidence interval (CI) of the overall mean survival and the respective mean survival of each different treatment strategy was calculated using SAS Studio. Results: In the presented case, the patient showed no symptoms and was admitted into hospital due to abnormal uterine findings during a routine gynecological examination. Vaginal ultrasound scans showed a severely enlarged and intracavitary filled uterus. The patient underwent hysterectomy, as well as bilateral salpingo-oophorectomy. Regarding the systematic review of the literature, patients with adjuvant chemotherapy show the best outcome with a mean survival rate of 15.8±7.3 months (one patient excluded), whereas with a mean survival rate of 4.1±5.2 months, patients with sole surgical treatment show the shortest survival after diagnosis. Conclusion: Although there is no standardized approach in the treatment of this rare disease, we present a differentiated overview.*

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With an estimated incidence of less than 0.5/100,000, pleomorphic rhabdomyosarcoma of the uterus is a very rare and poorly investigated disease (1, 2). Mainly occurring in postmenopausal women, the leading symptoms are vaginal bleeding and abdominal pain (1-14). Due to the high malignancy of the tumor and the inefficiency of the adjuvant therapy, the outcome remains poor in the majority of the reported cases (1-14).

Materials and Methods

A review of the English-language literature since 1980 for “pleomorphic rhabdomyosarcoma of the uterus” was performed. Depending on the treatment received, the cases were organized in different groups (Tables I and II). The 95% confidence interval (CI) of the overall mean survival and the respective mean survival of each treatment group was calculated using SAS Studio (https://www.sas.com/en_us/software/foundation/studio.html).

Results

Case Report. A 73-year-old patient was admitted to the hospital due to abnormal uterine findings during a routine gynecological examination. The patient’s medical history included breast cancer with breast-conserving surgical treatment followed by irradiation and tamoxifen therapy over a period of three years, as well as a total thyroidectomy.

A hysteroscopy, dilatation and curettage of the uterus were performed. The histopathological results showed a poorly differentiated (G3) pleomorphic rhabdomyosarcoma of the uterus with a weak expression of progesterone receptor and negative expression of estrogen receptor.

The patient was then referred to our hospital for a second opinion and further treatment. Pelvic examination and vaginal ultrasound scan showed a severely enlarged and intracavitary filled uterus. In the interview, the patient reported no symptoms, especially no vaginal bleeding or abdominal pains. A subsequent computerized tomography (CT) of the pelvis revealed an inhomogeneous contrast-

Table I. Literature overview with particular emphasis on adjuvant treatment.

Series	Age	Extrauterine spread	Treatment	Outcome
Surgical treatment				
Ordi <i>et al.</i> , 1997 (6)	87	Yes	HE	DOD, 1 month
Mccluggage <i>et al.</i> , 2002 (4)	67	Yes	Tumordebulking, BSO	DOD, 0.1 month
Fadare <i>et al.</i> , 2010 (5)	51	Yes	HE, BSO, LNE, OE	DOD, 0.5 month
Fadare <i>et al.</i> , 2010 (5)	74	Yes	HE, BSO, LNE, OE	Loss of FU
Leung <i>et al.</i> , 2009 (8)	68	No	HE, BSO	NED, 12 months
Jaworski <i>et al.</i> , 1984 (14)	71	No	HE, BSO	NED, 7 months
Surgical treatment with adjuvant pelvic radiation				
Ferguson <i>et al.</i> , 2007 (9)	69	Yes	HE, BSO + PR	DOD, 5 months
Fadare <i>et al.</i> , 2010 (5)	79	Yes	HE, BSO, LNE, OE + PR	DOD, 6.3 months
Siegal <i>et al.</i> , 1983 (10)	69	No	HE, LNE + PR	NED, 3 months
Holcomb <i>et al.</i> , 1999 (2)	63	No	HE, BSO + PR	DOD, 24 months
Podczaski <i>et al.</i> , 1990 (12)	73	No	HE, LS, BO, LNE, OE + PR	DOD, 3 months
Present case	73	No	HE, BSO + PR	NED, 3 months
Surgical treatment with adjuvant chemotherapy				
Vakiani <i>et al.</i> , 1982 (11)	68	Yes	HE, BSO+ChT (AM, AD, VI, CY)	DOD, 14 months
Ordi <i>et al.</i> , 1997 (6)	67	Yes	HE + ChT (VI, AD, CY)	DOD, 15 months
Ordi <i>et al.</i> , 1997 (6)	60	Yes	HE + ChT (CIs, DO)	DOD, 72 months (probably of OD)
Borka <i>et al.</i> , 2006 (3)	67	Yes	HE, BSO, LNE, pCE + ChT (DO)	NED, 12 months
Ordi <i>et al.</i> , 1997 (6)	35	No	HE + ChT	DOD, 15 months
Ordi <i>et al.</i> , 1997 (6)	80	No	HE + ChT (VI, AD)	DOD, 9 months
Chmaj-Wierzchowska <i>et al.</i> , 2010 (1)	66	No	HE, BSO + ChT (CY, VI, DO, DA)	DOD, 30 months
Surgical treatment with adjuvant chemotherapy and pelvic radiation				
Ordi <i>et al.</i> , 1997 (6)	61	Yes	HE + ChT (DO, DA, CIs) + PR	DOD, 15 months
Okada <i>et al.</i> , 1999 (13)	53	Yes	HE, BSO, LNE+ChT (5-FU)+ PR	RD, 2 months
Yeasmin <i>et al.</i> , 2008 (7)	60	Yes	HE, BSO, LNE, OE+ChT + PR	DOD, 20 months
Fadare <i>et al.</i> , 2010 (5)	68	Yes	HE, BSO, LNE, OE+ChT (VI, AD, CY)+PR	DOD, 19 months
Ordi <i>et al.</i> , 1997 (6)	69	No	HE+ChT+PR	DOD, 6 months

AD, Actinomycin D; AM, adiramycin; BSO, bilateral salpingo-oophorectomy; ChT, chemotherapy; CIs, cisplatin; CY, cyclophosphamide; DA, dacarbazine; DO, doxorubicine; DOD, death of disease; FU, follow-up; HE, hysterectomy; LNE, lymphonodectomy; NED, no evidence of disease; OD, other disease; OE, omentectomy; PR, pelvic radiation; pCE, partial colectomy; VI, vincristine.

enhancing tumor of the corpus uteri with invasion of the cervix uteri, adjacent to bladder and rectum (Figure 1). While an infiltration of the rectum could not be safely excluded, the CT scan showed no involvement of other organs or lymph nodes. Except an elevated lactate dehydrogenase (LDH) level of 264 U/l, all other blood counts were without pathological findings.

An inferior medium laparotomy, hysterectomy, as well as bilateral salpingo-oophorectomy, were performed. Intraoperatively, the peritoneum was smooth and no signs of further tumor spread could be detected.

The case was discussed in our interdisciplinary online tumor conference (15). Due to the lack of evidence-based profit of adjuvant chemotherapy, a recommendation for

pelvic radiation was made. The patient rejected any further treatment and shows currently no evidence of disease.

Pathology findings. Macroscopically, the tumor (65×60×50 mm) was whitish-/yellowish-colored and showed, in some parts, an infiltration of the myometrium, while an intracavitary location as a polypoid lesion in other parts (Figure 2).

Microscopical findings were a mesenchymal tumor containing spindle-shaped, partly interlaced, partly polygonal and size-variable cells with an eosinophilic, in some extend fibrillic, cytoplasm and pleomorphic nuclei, often with prominent nucleoli (Figure 3B). Furthermore, polynuclear cells and cells with bizarrely enlarged nuclei could be detected (Figure 3A).

Table II. Summary and patient's characteristics of the literature overview.

Characteristics	Value
Total number of patients	n=24 (100%)
Median age in years	66.6±10.4
Extrauterine spread at diagnosis [yes/no]	14 (58%)/10 (42%)
Overall mean survival after diagnosis in months	12.8±15.2 (CI=6.2-19.6)
Mean survival without extrauterine spread in months	11.2±11.1 (CI=4.5-17.9)
Mean survival with extrauterine spread in months	14.0±15.8 (CI=2.6-25.4)
Patients with sole surgical treatment	n=6 (25%)
Extrauterine spread at diagnosis [yes/no]	4/2
Mean survival after diagnosis in months	4.1±5.2 (CI=-2.4-10.6)
Patients with surgical treatment and adjuvant pelvic radiation	n=6 (25%)
Extrauterine spread at diagnosis [yes/no]	2/4
Mean survival after diagnosis in months	7.4±8.3 (CI=-1.3-16)
Patients with surgical treatment and adjuvant chemotherapy	n=7 (29%)
Extrauterine spread at diagnosis [yes/no]	4/3
Mean survival after diagnosis in months	23.9±22.3 (CI=3.3-44.4)
(One patient excluded)	(15.8±7.3)
Patients with surgical treatment and adjuvant pelvic radiation and chemotherapy	n=5 (21%)
Extrauterine spread at diagnosis [yes/no]	4/1
Mean survival after diagnosis in months	12.4±8 (CI=2.4-22.6)

CI, Confidence interval.

Figure 1. Computed tomography images revealing an inhomogeneous contrast-enhancing tumor of the corpus uteri with invasion of the cervix uteri, adjacent to bladder and rectum.

MyoD1 (Dako–Agilent Pathology Solution, Santa Clara, CA, USA) shows moderate cytoplasmic staining in morphologically-appearing rhabdomyoblasts (Figure 4A). Desmin (Dako–Agilent Pathology Solution) (Figure 4B) and CD10 (Leica Biosystems, Nussloch, Germany) were partly positive. Ki-67 (Dako–Agilent Pathology Solution) was approximately 70%. An epithelial component was not detectable, either with conventional histomorphology or with immunohistochemistry for pan cytokeratin (Dako–Agilent Pathology Solution) (Figure 4C).

In conclusion, the presented case shows the typical features described for rhabdomyosarcoma: the polypoid or invasive expansion macroscopically, histologically identifiable rhabdomyoblasts and the background of sarcomatoid-looking cells of round, polygonal or spindle-shaped morphology (6). Immunohistochemically, the mesenchymal origin of the

Figure 2. Macroscopic appearance of rhabdomyosarcoma.

Figure 3. A. Sarcoma with intermingled bizarre enlarged and multinucleated nuclei. B. Histological detection of rhabdomyoblasts.

Figure 4. A. Moderate cytoplasmic staining for MyoD1 in morphological rhabdomyoblasts. B. Some desmin-positive cells are detected. C. Immunohistochemistry for pan cytokeratin is negative.

neoplastic cells is shown (6). In the presented case, the immunohistochemical myogenic marker shows only moderate cytoplasmic staining for MyoD1 and partial desmin positivity.

Discussion

We present the case of a 73-year-old woman with pleomorphic rhabdomyosarcoma of the uterus with no symptoms and an elevated LDH level at initial examination and complete remission following surgery.

Pleomorphic rhabdomyosarcoma of the uterus is a rare disease. More frequent sarcomas of the uterus are leiomyosarcomas, stromal sarcomas and undifferentiated sarcomas (4). Frequently, like in the presented case, overlaps of rhabdomyosarcoma and undifferentiated sarcoma exist. This might be due to a dedifferentiation process of the rhabdomyosarcoma associated with subsequent loss of the immunohistochemical myogenic markers.

Between 1982 and 2015, twenty-four cases of pleomorphic rhabdomyosarcoma of the uterus have been described in the

English-language literature, including the present case (1-14). The median age of the patients was 66.6 ± 10.4 years with a range between 35 and 87 years. Fourteen (58%) out of all twenty-four patients presented with extrauterine spread at the time of diagnosis. While the overall mean survival rate was 12.8 ± 15.2 months (CI=6.2-19.6), the mean survival rate of patients without extrauterine spread at the time of diagnosis was 11.2 ± 11.1 months (CI=4.5-17.9) and the mean survival rate of patients with extrauterine spread at the time of diagnosis was 14.0 ± 15.8 months (CI=2.6-25.4). Seventeen patients (71%) died due to consequences of the disease, eight (33%) of them within the first year. Regarding the surgical treatment in all cases (100%), a hysterectomy was performed. Additionally, fifteen (63%) patients underwent bilateral salpingo-oophorectomy, nine (38%) patients lymphonodectomy and six (25%) patients either partial or complete omentectomy.

Sole surgical treatment was carried-out in six patients (25%). From this patient collective, three out of four patients with extrauterine spread at the time of diagnosis died within

the first month and one refused further follow-up. While the mean survival rate was 4.1 ± 5.2 months (CI=-2.4-10.6), the two patients with no initial spread showed no evidence of disease seven and twelve month after diagnosis. Further six patients (25%) received adjuvant pelvic radiation after surgical tumor resection. Two out of this patient collective presented with extrauterine spread; for the other four patients, the disease was limited to the uterus. The mean survival rate was 7.4 ± 8.3 months (CI=-1.3-16) after diagnosis. In seven patients (29%), surgical treatment and adjuvant chemotherapy was performed, with four of them initially presenting with extrauterine spread. The mean survival rate was 23.9 ± 22.3 months (CI=3.3-44.4). The survival rate of one patient, being 72 months after diagnosis, seems to fall out of the series. This value was excluded as the median survival rate was 15.8 ± 7.3 months. The final group of five patients (21%) received adjuvant pelvic radiation, as well as chemotherapy. Four of these five patients presented with extrauterine spread at the time of diagnosis. The mean survival rate was 12 ± 8 (CI=2.4-22.6) months.

In consideration of the small number of patients, one can see a slight tendency towards surgical treatment with adjuvant pelvic radiation in patients with initially limited disease, while surgical treatment with adjuvant pelvic radiation, as well as chemotherapy, was mainly the management of patients with extrauterine spread at the time of diagnosis. Patients with adjuvant chemotherapy showed the best outcome with a mean survival rate of 15.8 ± 7.3 months (one patient excluded), whereas, with a mean survival rate of 4.1 ± 5.2 months, patients with sole surgical treatment showed the shortest survival after diagnosis.

In children, the multimodal treatment protocols for rhabdomyosarcoma are well-defined and led to an improved survival rate, especially in those with non-metastatic disease (16-18). In adults, however, the same protocols showed much less response (19, 20). Due to the rareness of the disease in adults, the use of a variety of chemotherapeutic agents in studies involving an adult patient collective and a standardized chemotherapy regime have yet to be established (19-22).

As it is known, in patients with malignant tumors, an elevated level of LDH can frequently be observed. This applies especially in advanced metastatic stages of the disease (23, 24). In the present case, the patient presented an elevated LDH level of 264 U/l prior to surgery. Similar to this case, Yeasmin *et al.* (7) presented a case of a patient with pure pleomorphic rhabdomyosarcoma of the uterus with elevated LDH level, where, furthermore, the degree of elevation showed a correlation to the progression of the disease. These findings are in line with the result of Nagai *et al.* (25) presenting significantly elevated LDH levels in patients with uterine sarcomas, whereby no patients with uterine rhabdomyosarcomas were in the investigated patient collective.

In comparison, Nelson *et al.* (26) found normal or near normal LDH isoenzyme patterns in patients with uterine sarcomas with rhabdomyosarcomatous differentiation.

All in all, due to the presence of an initial elevation of LDH level and lack of other prognostic markers, the fluctuation of the elevation may be used as tumor marker for further follow-ups and an early detection of possible recurrence of the disease. Based on this case report we initiated a register for gynecological sarcomas called REGSA.

Conflicts of Interest

None.

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