Rhabdomyosarcoma of the uterus in an adult patient with osteopetrosis: a case report

Soheila Aminimoghaddam¹, Ali Rahbari² and Roghayeh Pourali³*

Abstract
Background: Uterine sarcoma accounts for 3–7% of uterine malignant neoplasms. It is more aggressive than epithelial neoplasms, and patients have a poor prognosis. Rhabdomyosarcoma is classified as a heterologous uterine sarcoma. It is the most common soft tissue malignancy in children while rare in adults. In young patients, the majority of genital tract rhabdomyosarcomas occur in vagina; however, the most common site of gynecologic rhabdomyosarcoma is cervix followed by uterine corpus, in adults. Uterine corpus rhabdomyosarcoma is rare in adults. Diagnosis of pure rhabdomyosarcoma in uterus involves widespread and perfect sampling as well as precise histopathological evaluation to uncover any epithelial component.

Case presentation: Here we report a case of pure rhabdomyosarcoma of uterine corpus in a 60-year-old Iranian postmenopausal female who had osteopetrosis, presenting with 8-month heavy vaginal bleeding and a protruding cervical mass. She is alive on 18-month follow-up after treatment.

Conclusions: Rhabdomyosarcoma of uterine corpus is rare in adults. Diagnosis of pure rhabdomyosarcoma in uterus involves widespread and perfect sampling as well as precise histopathological evaluation to uncover any epithelial component. Treatment options in adult gynecological rhabdomyosarcoma are based on studies in younger patients, and more studies may help us choose the best approach for improving outcome.

Keywords: Rhabdomyosarcoma, Uterus, Sarcoma

Introduction
Rhabdomyosarcoma (RMS) is an aggressive tumor that tends to develop in children and younger patients [1]. A large majority of genital tract RMSs occurs in infants’ and adolescents’ vagina [2]. RMS of uterine corpus either occurs as a component of biphasic uterine tumor (adenosarcoma or carcinosarcoma) or can be a pure heterologous tumor [3, 4]. Pure uterine RMS is rare in adult patients and difficult to diagnose. Accurate diagnosis of these tumors depends on precise histopathological evaluation [5]. We hereby report a case of pure RMS of uterine corpus in a 60-year-old postmenopausal female who had osteopetrosis. There is limited experience with RMS management in adults. Older age, widespread disease at the time of diagnosis, and unfavorable histologic variants such as pleomorphic and alveolar led to poor outcomes in adult patients despite multidisciplinary approach. Reviewing rare cases can result in more rapid diagnosis and improved treatment and, consequently, best possible survival rate.

Case report
A 60-year-old Iranian female patient attended our emergency department with complaints of heavy vaginal bleeding during last 8 months. In her medical history, she...
had three vaginal deliveries, diabetes mellitus, depression, and osteopetrosis. Her menopause started at 50 years of age. She did not report any history of sexually transmitted infection or receiving hormonal medications. Her medications included metformin (500 mg twice a day), sertraline (50 mg daily), vitamin D (1000 mg daily), and calcium (500 mg daily). She had undergone surgery twice over the last 10 years, due to fracture of lower extremities. Her family history was unremarkable.

She was admitted to our hospital. Hemoglobin level was 6 g/dl at the time of admission. The other hematologic and biochemistry tests revealed no significant problems. On pelvic examination, which was performed under anesthesia, we found a remarkably enlarged uterus and a 10-cm soft hemorrhagic mass originating from posterior part of cervix and protruded into vagina.

Excisional biopsy was performed. Abdominopelvic computerized tomography (CT) scans revealed a large uterus, a 15-cm pelvic mass in posterior wall of uterus (Fig. 1), and enlarged pelvic lymph nodes. Chest CT scan and whole-body bone scan were normal. Pathology reported the cervical mass as a high-grade sarcoma in favor of pleomorphic rhabdomyosarcoma.

After a multidisciplinary meeting, the patient was treated with multiagent neoadjuvant chemotherapy. We prescribed intravenous vincristine (2 mg), actinomycin-D (1 g), and cyclophosphamide (1200 mg) (VAC) every 3 weeks for six cycles. Delayed radical hysterectomy, bilateral salpingoophorectomy (BSO), and pelvic lymph node dissection (PLND) were performed due to large bulky tumor and partial response to initial chemotherapy. Her postoperative condition was appropriate, and she was discharged 3 days after surgery. Following discharge, external pelvic irradiation (total dose of 5040 cGy in 28 fractions) was performed in 6 weeks. No complications, such as radiation cystitis or proctitis, occurred. She signed an informed consent form and gave us permission to report her disease. She was followed up every 3 months and was free of disease 18 months after treatment (Figure 2).

**Pathology report**

Grossly, the tumor was cream-colored and fleshy, measuring 10 × 8 × 6 cm, filling entire endometrial cavity, and protruding into endocervical canal (Fig. 3). Microscopically, the tumor was placed in endometrium with infiltrative border, and the myometrial invasion was less than 50%. In high-power microscopic field, rhabdoid cells were present with abundant bright eosinophilic cytoplasm and atypical enlarged nucleus (Fig. 4a). The tumor displayed variable degrees of necrosis, and tumor giant cells were present. Neither epithelial nor other heterologous component were seen. Numerous mitotic figures, including atypical forms and solid sheets of cells separated with fibrotic bands, were present (Fig. 4b).
These histologic patterns and cytological features describe the solid variant of alveolar subtypes of RMS. There was no lymphovascular space invasion. All 14 pelvic lymph nodes, cervix, vaginal margins, adnexa parameters, and peritoneal washing fluid were free of tumor. Immunohistochemistry (IHC) test showed positive desmin (Fig. 5a), MyoD1 (Fig. 5b), and myogenin (Fig. 5c) cytoplasmic staining.

**Discussion**

Uterine sarcoma accounts for 3–7% of uterine malignant neoplasms and is more aggressive in comparison with epithelial neoplasms [4, 6]. Uterine sarcomas are classified as homologous, including elements that are normally found in the uterus (endometrial stromal sarcoma, undifferentiated sarcoma, fibrosarcoma, leiomyosarcoma) or heterologous, including sarcomatous components that are not usually found in the uterus (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, liposarcoma). RMS is the most common soft tissue malignancy in children, and a remarkable majority of genital tract RMSs occur in vagina in infants and adolescents [2]. Pure heterologous RMS of uterine corpus is rare in adults. Prognosis and survival rate of RMS is disappointing in adult patients.

We hereby presented a case of uterine alveolar RMS in a 60-year-old postmenopausal female patient. We searched PubMed and Scopus for English original articles, letters, and short communications with keywords: “Rhabdomyosarcoma” AND “Uterus” since 1972. Articles that reported rhabdomyosarcoma in corpus of uterus in adults were reviewed if their full text was available. Table 1 summarizes a series of these cases from medical literature. These articles reported 41 patients between 22 and 90 years of age of which 21 patients (51.2%) had pleomorphic type, 9 patients (21.9%) had embryonal type, and 6 patients (14.6%) had alveolar type RMS. The tumor size ranged from 5 to 20 cm. Different management approaches were considered for each patient, including surgery and adjuvant and/or neoadjuvant chemotherapies. Thirty-one patients (75.6%) had undergone total hysterectomy (TH) + bilateral salpingoophorectomy (BSO) (2 subtotal hysterectomy), and 19 patients (46.3%) had received adjuvant and/or neoadjuvant treatment with chemotherapy and/or irradiation. Also, 21 patients (53%) died within a mean duration of 12.9 months after initial diagnosis or therapy.

Previous pelvic irradiation and long-term use of tamoxifen are among the risk factors for developing uterine RMS [7]. Our patient did not have these risk factors, but she had history of fracture in lower extremities due to osteopetrosis twice, while none of these cases had similar comorbidity and no correlation was found between RMS and osteopetrosis.

The histologic differential diagnosis of uterine RMS is endometrial stromal sarcoma, leiomyosarcoma, adenosarcoma/carcinosarcoma. As we mentioned earlier,
diagnosis of pure RMS in uterus involves precise histopathological evaluation. Widespread and perfect sampling is necessary to uncover any epithelial component. IHC test can help us to evaluate any suspected areas [5]. IHC staining identifies muscle-specific proteins such as actin, myosin, myoglobin, desmin, and MyoD1. Rhabdomyosarcoma is classified into four main subtypes: embryonal, alveolar, spindle cell/sclerosing, and pleomorphic. Myoglobin and desmin are positive in most RMS cases, while epithelial markers are not detectable [8]. Fluorescent in situ hybridization (FISH) and reverse-transcription polymerase chain reaction (RT-PCR) methods can detect fusion genes such as PAX3_FOXO 1 and PAX7_FOXO1 that are found in alveolar RMS [9]. IHC staining was positive for cytoplasmic desmin, MyoD1, and myoglobin in this patient, but cytogenetic tests were not available.

Ferguson et al. studied 15 women with gynecologic RMS and showed that the most prevalent site of the gynecologic RMS is uterine cervix, followed by uterine corpus. In this study, the 5-year disease-specific survival (DSS) was 29%, and older age, widespread disease at the time of diagnosis, and unfavorable histologic variants such as pleomorphic and alveolar led to poor outcomes in adults [10].

Enzo Ricciardi et al. studied 15 patients with primary cervical RMS. Vaginal bleeding and pelvic mass were the most common symptoms, and Intergroup Rhabdomyosarcoma Study Group (IRS) clinical staging was the best predictor of prognosis [11]. This case presented with heavy vaginal bleeding and a large protruding cervical mass.

There is limited experience with RMS treatment in adults, and a combined modality is considered based on IRS group studies in younger patients [12]. Complete excision of localized tumor, if feasible, followed by chemotherapy or radiotherapy is a common approach.

Maha et al. evaluated 137 patients with nonmetastatic gynecologic RMS, in a systematic review. Surgery was the main approach for local control of tumor in all patients [13]. According to the suggested scheme in this study, our patient was in the high-risk group owing to a large bulky pelvic mass, heavy vaginal bleeding, and alveolar variant of RMS. Therefore, we chose neoadjuvant chemotherapy (NACT) followed by definitive surgery.

In a retrospective analysis of 171 patients (older than 18 years of age), Ferrari et al. concluded that RMS responds to chemotherapy in adults exactly as it does in children, and there is no reason to select different approaches [14].

Luca Bergamaschi et al. reported 95 adult patients with RMS in a prospective single-center case series. The treatment recommendation was a multidisciplinary approach that included surgery, chemotherapy, and radiotherapy. Chemotherapy was recommended for all patients. It consisted of a multidrug treatment, alternating the ifosfamide, vincristine, and actinomycin-D (IVA) regimen with ifosfamide, vincristine, and adriamycin (IvAd) or ifosfamide, vincristine, and etoposide (IVE). Delayed surgery was performed after three to four courses of chemotherapy. Radiotherapy (with a conventional fractionation and doses ranging from 50 to 60 Gy) was suggested in all cases of alveolar, not otherwise specified (NOS) RMS, and embryonal RMSs that were incompletely resected at diagnosis. In this study, the 5-year event-free and overall survival rates were 33.6% and 40.3%, respectively [15].

We used neoadjuvant chemotherapy, including VAC regimen, for the patient, and she received external pelvic irradiation with a total dose of 5040 cGy within 6 weeks after surgery.
| References | RMS type | Age | Tumor size | Treatment | Outcome |
|------------|----------|-----|------------|-----------|---------|
| 1 Oluwole et al. | Pleomorphic | 51 years | 7 × 5.8 × 3.4 cm | TH + BSO + PPLND + resection of gross tumors | Death due to disease 0.5 months |
| Fadare et al. [16] | Pleomorphic | 74 years | 14 × 6.5 × 5.1 cm | TH + BSO + PPLND + resection of gross tumors | Death due to disease 40 week F/U |
| | Pleomorphic | 79 | 10 × 6 × 4 cm | TH + BSO + PPLND + resection of gross tumors + adj pelvic RT | Death due to disease 6.3 months |
| 2 Sohsuke Yamada et al. | Embryonal | 55 years | 11 × 7 cm | TH + BSO | 6 month F/U free of disease |
| 3 Garrett La et al. | Embryonal | 28 years | 5.6 cm | TH + BSO | 40 week F/U during chemo |
| 4 Masaharu Fukunaga | Alveolar | 72 years | 6 cm | TH + BSO + PLND + resection of gross tumors + adj chemotherapy | Death due to disease 12 months |
| 5 Masashi Takano et al. | Embryonal | 76 years | 15 × 17 cm | TH + BSO + adj chemotherapy | 10 months F/U after surgery |
| 6 Carolina Chmaj et al. | Pleomrophic | 66 years | 8.2 × 6.4 cm | TH + BSO + adj chemotherapy | Death 2.5 y/s after surgery |
| 7 Donkers et al. | Embryonal | 90 years | 450 gram uterus | TH + BSO | Death 7 months after surgery probably due to CHF |
| 8 Roberto Chiarle | Alveolar | 80 years | 9 cm | TH + BSO | Death 6.5 y/s after surgery |
| 9 Hideo Teshima et al. | Embryonal | 52 | 320 gruterus | TH + BSO + PLND + adj chemotherapy | 30 month F/U after surgery |
| 10 Fabrice Leung et al. | Pleomrophic | 68 years | 5 × 5 × 2 cm | TH + BSO | 12 month F/U after surgery |
| 11 Reynolds et al. | Embryonal | 65 years | 27 × 17 × 15 cm | TH + BSO + partial cystectomy + omentectomy + PLND | Death 10 days after surgery |
| 12 Siegal et al. | Unavailable | 69 years | 6.1 × 5 × 4.9 cm | TH + BSO + PPLND + resection of gross tumors + adj pelvic RT | F/U 3 months after surgery |
| 13 Pinto et al. [5] | Alveolar | 40 years | 12 cm | Chemotherapy | 18 month F/U after surgery |
| | Pleomorphic | 68 years | 13.6 cm | Chemotherapy | 18 month F/U after surgery |
| | Pleomorphic | 65 years | Unavailable | Chemotherapy | 26 month F/U after surgery |
| | Pleomorphic | 62 years | 15.2 cm | Hospice care | 4 month F/U after surgery |
| | Pleomorphic | 70 years | 13 cm | Chemotherapy | 9 month F/U after surgery |
| | Alveolar | 64 years | 14.5 cm | Hospice care | Death 6 weeks after surgery |
| 14 Sara Alavi et al. | Pleomorphic | 73 years | 6.5 × 6 × 5 cm | TH + BSO | Unavailable |
| 15 Norio Motoda et al. | Alveolar | 50 years | 10 cm | Partial resection | Death 19 days after surgery |
| 16 Afshan Ambreen et al. | Embryonal | 22 | 8 × 10 cm | TH + BSO + adj chemoradiation | Death 14 months after surgery |
| 17 Aljehani et al. | Embryonal | 54 years | 10 cm | Palliative pelvic radiotherapy | Unavailable/new case |
| 18 Goldstein et al. | Unavailable | 73 years | Unavailable | TH + BSO + adj chemotherapy | 11 month F/U post surgery |
| 19 Ashley S. Case et al. | Alveolar | 21 | 10.2 × 8.2 cm | TH + BSO + neoadjuvants and adj chemotherapy | 20 month F/U after surgery |
| 20 Podczaski et al. | Pleomorphic | 73 years | 10 × 7 × 5 cm | TH + BSO + omentectomy + PPLND + adj pelvic radiation | Death 3 months after surgery |
| 21 Dae Woon Kim et al. | Spindle cell | 76 years | 20 × 15 × 7 cm | Subtotal hysterectomy + BSO | Death 3 months after diagnosis |
| 22 Mutsumi Kuroki et al. | Unavailable | 36 years | Unavailable | Chemotherapy | Death 5 months after diagnosis |
| 23 Okada et al. [7] | Pleomorphic | 53 years | 15 cm | Radical hysterectomy + adj radiation | Recurrence 2 months after surgery |
| 24 McIlugage et al. | Spindle cell | 28 years | 12 cm | Modified radical hysterectomy + PLND + adj chemotherapy | F/U 2 years after surgery |
| | Pleomorphic | 67 years | 5 cm | Subtotal hysterectomy + BSO | Death 3 days after surgery |
| 25 Hart et al. [17] | Embryonal | 22 years | 100 gruterus | Radical hysterectomy + and neoadjuvant chemotherapy VAC | F/U 4.4 years after surgery |
| | Pleomorphic | 70 years | 450 gruterus | TH + BSO | Death 4 months after surgery |
| | Pleomorphic | 56 years | Unavailable | Palliative chemotherapy | Death 6 weeks after diagnosis |
Table 1  (continued)

| References                      | RMS type | Age     | Tumor size | Treatment                                 | Outcome               |
|---------------------------------|----------|---------|------------|------------------------------------------|-----------------------|
| 26 Kevin Holcomb et al.         | Pleomorphic | 63 years | 6 × 6 × 2 cm | TH + BSO                                 | Death 4 years after surgery |
| 27 S. Yeasmin et al.             | Pleomorphic | 60 years | Unavailable | TH + BSO + PPLND + adj chemotherapy       | Death 20 months after surgery |
| 28 Jaworski et al.               | Pleomorphic | 71 years | 1200 gram uterus | TH + BSO                                | F/U 7 months after surgery |
| 29 Katalin Borka et al.          | Pleomorphic | 67 years | 15 cm       | TH + BSO + PPLND + adj chemotherapy       | F/U 12 months after surgery |
| Aminimoghaddam et al.            | Alveolar  | 60 years | 10 × 8 × 6 cm | TH + BSO + PPLND + neo-adj chemotherapy + adj pelvic irradiation | Alive at 12 month F/U   |

$TH$ total hysterectomy, $BSO$ bilateral salpingo-oophorectomy, $PPLND$ pelvic lymph node dissection, $F/U$ follow-up, $CHF$ chronic heart failure

Conclusion
RMS of uterine corpus is rare in adults. It is an aggressive tumor with a poor outcome, despite multidisciplinary approach. Histopathological criteria, IHC staining, and molecular studies differentiate RMS from the other uterine sarcomas. More studies are needed on treatment options in adults.

Abbreviations
RMS: Rhabdomyosarcoma; CT Scan: Computed tomography; BSO: Bilateral salpingo-oophorectomy; PPLND: Pelvic lymph node dissection; IHC: Immunohistochemistry; TH: Total hysterectomy; FISH: Fluorescent in situ hybridization; RT-PCR: Reverse-transcription polymerase chain reaction; NACT: Neoadjuvant chemotherapy; RMS: Rhabdomyosarcoma; CT Scan: Computerized tomography; BSO: Bilateral salpingo-oophorectomy; PLND: Pelvic lymph node dissection; IHC: Immunohistochemistry; RT-PCR: Reverse-transcription polymerase chain reaction; NACT: Neoadjuvant chemotherapy; IVA: Ifosfamide, vincristine, actinomycin-D; IVA+d: Ifosfamide, vincristine, actriamycin; IVE: Ifosfamide, vincristine, etoposide; VAC: Vincristine, actinomycin-D, cyclophosphamide; DSS: Disease specific survival; IRS: Intergroup Rhabdomyosarcoma Study Group; $F/U$: Follow-up; CHF: Chronic heart failure.

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Authors’ contributions
SA performed management steps for the patient. AR interpreted the patient’s data. RP drafted the paper. All authors read and approved the final manuscript.

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Availability of data and materials
All the data of this case are available.

Ethics approval and consent to participate
The patient has signed an informed consent form for all the diagnostic and therapeutic plans.

Declarations
Consent for publication
The patient has signed an informed consent form for this publication. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that there is no conflict of interest.

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