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Embryonal Rhabdomyosarcoma of the Uterine Corpus In A 22-Year-Old Woman: A Case Report And Review Of The Literature

Gertraud Heinz[1*], Nicol Bolletta[1], Alexandra Ökrösi[1], Lukas Lomoschitz[1], Susanne Schubert[2], Melitta Kitzwögerer[3]

[1]Department of diagnostic and interventional Radiology, University Hospital of St. Pölten, Austria

[2]Department of Gynaecology and Obstetrics, University Hospital of St. Pölten, Austria

[3]Department of clinical and molecular Pathology, University Hospital of St. Pölten, Austria

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[*]**Corresponding author:** Gertraud Heinz, Department of diagnostic and interventional Radiology, University Hospital of St. Pölten, Austria

ABSTRACT

Background: Embryonal rhabdomyosarcoma (ERMS) is a major histological subtype of Rhabdomyosarcoma which may have a polypoid variant called Sarcoma botryoides or botryoid RMS arising from embryonal rhabdomyoblasts. Botryoid RMS is the most prevalent rhabdomyosarcoma subtype in female genital tract and occurs predominantly in the vagina during infancy and early childhood. Uterine ERMS in adults occur most commonly in the cervix, followed by the corpus uteri. The pathogenesis of ERMS is unclear. DICER1 somatic and/or germ-line mutation may play a role. Patients usually present with a polypoid mass in the vagina, urinary and bowel symptoms, and they may have severe vaginal bleeding. Due to its rare occurrence treatment remains challenging as finally the preservation of hormonal, sexual and reproductive function should also be a goal. However, there has been an increasing tendency towards conservative therapy in recent years consisting of limited surgery and multidrug therapy.

Case Presentation: We report a case of a 22-year-old Austrian young female adult presenting with severe abdominal-pelvic pain and vaginal bleeding three months after resection of a benign cervical/uterine polyp. Clinical and MRI examination showed a large polypoid-like mass with a stalk-like structure in the uterine cavity protruding into the vagina.

The patient subsequently underwent an emergency excisional surgery of the polypoid mass, hysteroscopy, and curettage of the uterine cavity. There was no evidence of residual disease. Histopathology revealed an ERMS of the botryoid variant. The patient was referred to a specific sarcoma center. Since the patient decided for preservation of the reproductive system, the tumor board of this center recommended ovarian tissue conservation surgery (OTC) and adjuvant radiation and multidrug chemotherapy with IVA. During laparoscopic OTC an additional large right sided ovarian cyst was removed which was unremarkable on histology. Follow-up MRI after 4 cycles of IVA was suspicious

of recurrent disease which was confirmed by diagnostic hysteroscopy and fractional curettage revealing sarcomatous tissue. The patient finally underwent radical hysterectomy and further adjuvant chemotherapy. On close clinical and imaging follow-up there has not been evidence of recurrent disease up to now.

Conclusions: This very rare case of uterine cavity botryoid rhabdosarcoma in a 22-year-old young female adult shows that the presence of a cervical polyp in a young adult may be a gynecologic oddity and needs careful evaluation and histopathologic work-up. Although treatment strategies changed towards more conservative approaches a fertility sparing treatment still remains challenging. Further research must be done to evaluate the most appropriate chemotherapy regimen including the number and sequence of the chemotherapy agents. In addition, the value of a neoadjuvant concept according to treatment outcome and fertility preservation should be studied.

Keywords: Rhabdomyosarcoma; Uterine Cavity; Young Female Adult; Case Report; Chemotherapy; Ovarian tissue conservation.

Diagnosis: Physical examination, Biopsy, Surgery, MRI, Histopathology, Oncomine Childhood Panel Test

INTRODUCTION

Rhabdomyosarcoma (RMS), which originates from embryonal mesenchyme, is the most common soft tissue sarcoma in childhood and young adults, accounting for 4-6% of all malignancies in this age group [1-8].

RMS can arise in many different sites throughout the body. It consists of three major histological subtypes: pleomorphic rhabdomyosarcoma (PRMS), embryonal rhabdomyosarcoma (ERMS), and alveolar rhabdomyosarcoma (ARMS). Sarcoma botryoides or botryoid RMS is a polypoid variant of ERMS, arising from embryonal rhabdomyoblasts and constituting approximately 3% of all RMSs [2].

Embryonal rhabdomyosarcoma (ERMS) is the most prevalent rhabdomyosarcoma subtype in female genital tract and occurs predominantly in the vagina during infancy and early childhood. Uterine ERMS in adults occur most commonly in the cervix, followed by the corpus uteri [3]. In cases of ERMS of the uterus, adenosarcoma with sarcomatous overgrowth and malignant mixed Mullerian tumor or carcinosarcoma may also be in the differential diagnosis [4]. The latter can grow in an exophytic manner from the uterine wall or cervix and have a grossly and microscopically sarcomatous appearance. However, unlike ERMS, malignant mixed Mullerian tumor usually occurs in older women, and has histologically a malignant epithelial component in addition to the malignant mesenchymal component [4].

Due to the paucity of literature on this topic, the pathogenesis of ERMS is unclear. Some studies have shown that DICER1 somatic and/or germ-line mutation plays an important role in developing late-onset rhabdomyosarcoma [5]. The management of this tumor is challenging as it presents at a younger age where the preservation of hormonal, sexual and reproductive function is essential. Over the past few decades, there has been a change in management strategy, from radical surgeries to a more conservative approach with adjuvant chemotherapy [2].

Here, we describe a rare case of a 22-year-old woman with an embryonal rhabdo-myosarcoma of the uterine corpus (ucERMS) in whom resection of a small cervical tumor most likely was misinterpreted as a benign polyp and a recurrent severe bleeding polypoid mass protruding into the vagina necessitated an emergency resection three months

after initial surgery. The concept of a fertility sparing approach failed when discovering recurrent malignant disease after OTC and neo-adjuvant chemotherapy.

CASE PRESENTATION

A 22-year-old young adult female patient presented with unclear small pelvis pain at the gynecologic department of our University Hospital in April 2022. Her gynecological history included repeated cervical cytologic abnormalities (two times CIN 3) and positivity for HPV 53 and 66. She completed the HPV vaccination. Since June 2021 she had a Copper T intrauterine device (IUDs).

She had no additional prior medical or surgical history, and there was no family history of cancer in general, and not specifically of the Li-Fraumeni syndrome, neurofibromatosis 1, and pleuropulmonary blastoma.

Physical examination of her pelvis revealed a polypoid, spherical, reddish mass protruding from the cervical canal. During the colposcopy the transformation zone was not sufficiently visible due to the large polypoid structure, however three biopsies at the cervical edge and two at the red polypoid structure were taken and histological results showed a granulation tissue polyp. In addition, an ecto- and endocervical PAP test as well as an HPV test were taken. The results showed a high grade squamous intraepithelial lesion, chronic granulomatous cervicitis, and positivity for HPV 53, 66 and 42. Ultrasound examination showed a regular uterine corpus. The patient underwent a polypectomy in May 2022; the histological result showed a benign cervical/uterine polyp, and a follow-up was planned.

In August 2022 the patient presented unexpectedly to our emergency department complaining of abdominal pain and severe vaginal bleeding. Blood tests showed a hemoglobin of 8.1 g/dl, hematocrit of 23.5 %, neutrophile of 82.3 % but not leukocytosis and normal renal and liver function parameters. The tumor markers such as cancer antigen (CA-125, CA 15-3, CA 72-4, and CA 19-9) and carcinoembryonic antigen (CEA) were all within normal range. Although the patient completed the anti-COVID 19 vaccination with three immunizations, she was tested SARS-Co-2 positive with a CT-value of 29.7.

This time the gynecological inspection showed a large polypoid mass protruding into the vagina. The patient underwent an emergency MRI of the small pelvis confirming a huge rather well circumscribed polypoid lesion of 7.5 x 8 x 6 cm in the proximal vagina with a stalk-like structure in the widened uterine cavity. There were no signs of myometrial infiltration, and the cervical stroma was intact without any sign of parametrial infiltration Figure 1a and 1b. There were no abnormalities according to the urinary bladder and the rectum and there was no evidence of pelvic lymphadenopathy.

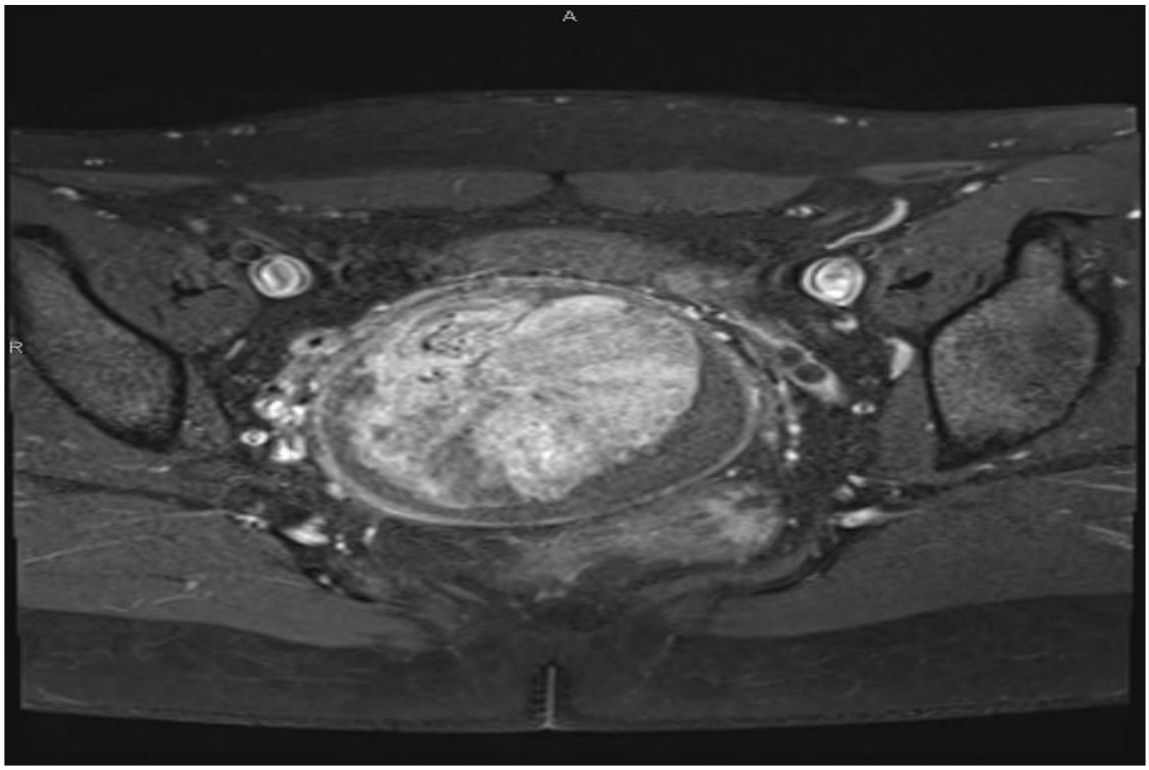
The patient subsequently underwent an emergency excisional surgery of the polypoid mass, hysteroscopy, and curettage of the uterine cavity. Intraoperatively, there was no obvious extrauterine disease and no evidence of residual disease. The patient's postoperative course was unremarkable.

Histopathology examination revealed an embryonal rhabdomyosarcoma of the Uterus-botryoid variant, IRSG (Intergroup Rhabdomyosarcoma Study Group) stage Ib. A postoperative pelvic/abdominal CT scan with iv. contrast media was negative for metastases.

Subsequently, the patient was referred to a dedicated Sarcoma center for further evaluation and treatment strategies. Analysis of various genes with next generation sequencing using an Oncomine Childhood Cancer Research Assay showed a DICER 1 variant in Exon 26. In addition, a variant of unclear significance was found for CCR5 in Exon 3. There was no germline TP53 gene mutation.

Since the patient decided for a fertility-sparing approach and as there was no evidence of residual disease, the MDTB recommended ovarian tissue conservation surgery followed by adjuvant chemotherapy and additional brachytherapy since the tumor originated from the uterine cavity. During laparoscopic OTC surgery on September 16, 2022, also, a large right ovarian cyst was removed which proved to be a benign ovarian cyst at histological work up. Afterwards the patient received 4 cycles of adjuvant chemotherapy with IVA (ifosfamide 3g/m2 given as a 3-hours intravenous infusion on day 1 and 2, vincristine 1.5 mg/m2 weekly during the first 7 weeks and then only on day1 of each cycle given as a single intravenous injection, and actinomycin D 1.5 mg/m2 on day 1 given as a single injection).

Follow-up MRI Figure 2a and 2b after 4 cycles of multidrug chemotherapy was suspicious of recurrent disease which was confirmed by diagnostic hysteroscopy and fractional curettage on January 12, 2023. The fertility sparing approach was obviously unsuccessful and thus, considering this high- risk situation, the MDTB together with the patient finally decided for radical hysterectomy and proceeding with multi-agent adjuvant chemotherapy. On February 2, 2023, the patient underwent successfully laparoscopic hysterectomy and bilateral adnexectomy. Afterwards she regularly finished adjuvant chemotherapy consisting of another 5 cycles of IVA at the same dose. The patient is still under close clinical and imaging follow-up since then. On a clinical and imaging follow-up (PET scan) in August 2024, there was no evidence of recurrent disease. Since then, no further follow-up examinations are available.



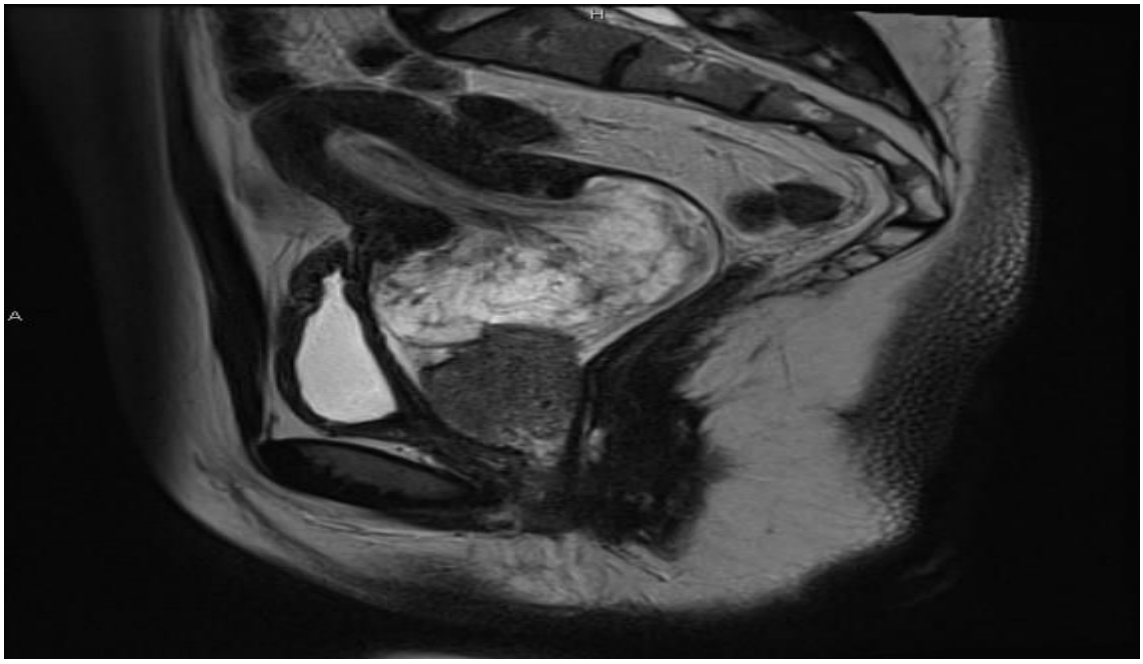
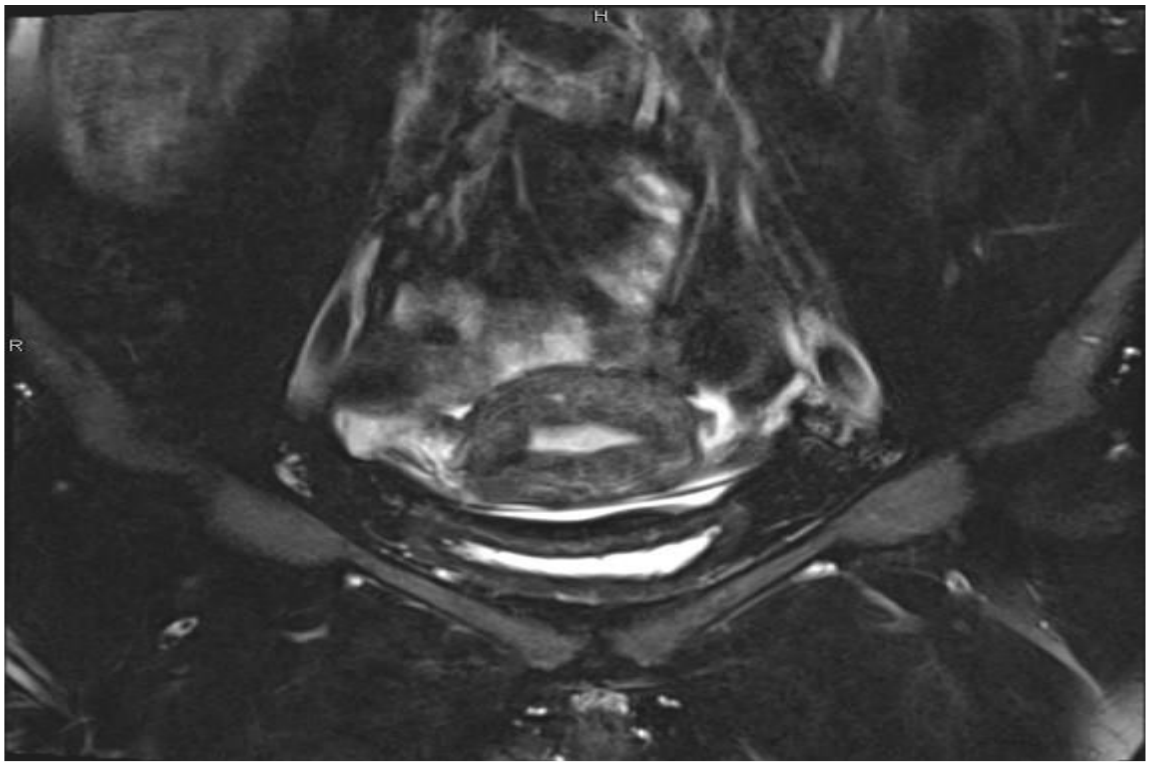


Figure 1a and b: MRI of the pelvis (axial CE-T1weighted and sagittal T2-weighted images) showing a heterogeneously enhanced well-circumscribed hyper vascularized lesion (7.5 x 8 x 6 cm) in the proximal vagina with a stalk-like structure within the uterine cavity. There are no signs of myometrial or parametrial infiltration and there is no evidence of pelvic lymphadenopathy. Vaginal tamponade distant to polypoid mass.



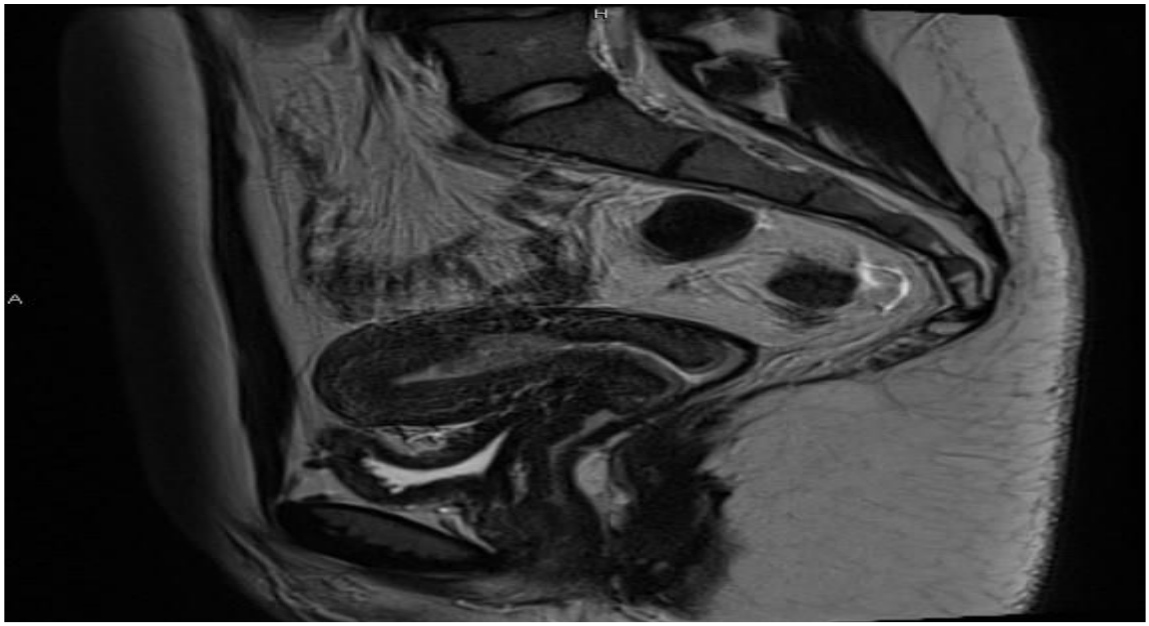


Figure 2a and b: Follow-up MRI of the pelvis (coronal (a) and sagittal (b) T2-weighted images) after adjuvant chemotherapy showing a small solid lesion in the uterine cavity (arrow heads) suspicious for recurrent disease which was histologically proven.

DISCUSSION

Primary rhabdomyosarcoma of the uterus is exceedingly rare [3], and there is limited information about is clinicopathological features in the literature as compared to most other gynecologic malignancies. Review of the literature discloses 115 patients with uterine corpus or cervical ERMS, ranging in age from 5 months to 90 years; fifty-two cases reported in women aged 20 years or older [9].

Due to the paucity of literature on this topic, the pathogenesis of ERMS is unclear. Risk factors that increase the likelihood of this cancer include inherited disorders such as Li-Fraumeni syndrome, Neurofibromatosis type 1, Beckwith-Wiedemann syndrome, Costello syndrome, Noonan syndrome, and DICER1 syndrome [10].

Some studies have shown that DICER1 somatic and/or germ-line mutation, which is considered to being the key in microRNA silencing pathway, may play an important role on developing late-onset cervical rhabdomyosarcoma [11]. Bennett et al. studied 21 embryonal rhabdomyosarcoma of the uterine corpus and identified somatic DICER1 mutation in 67% of ucERMS. Germline DICER1 mutation was first identified in pediatric patients with familiar pleuropulmonary blastoma (12) but as the disease spectrum markedly expanded, it was renamed DICER1 syndrome. Outside of the gynecological tract, DICER1 mutations are exceedingly rare in ERMS, and a recurring mutation or fusion has not been identified for this group of tumors. No difference in outcomes were seen between DICER1 mutations and DICER1-independent ucERMS [5]. Analysis of various genes with next generation sequencing using an Oncomine Childhood Cancer Research Assay in our patient showed a DICER 1 variant in Exon 26. In addition, a variant of unclear significance was found for CCR5 in Exon 3. There was no germline TP53 gene mutation.

Additionally, there was no family history regarding the Li-Fraumeni syndrome, neurofibromatosis 1, and pleuropulmonary blastoma in our patient.

When embryonal rhabdomyosarcoma involves mucosal sites, like does in the endometrium, it tends to grow in a characteristic exophytic, grapelike configuration, garnering the term sarcoma botryoides; therefore, in essence, sarcoma botryoides simply represents a macroscopically distinct subset of EMRS with a characteristic clinical appearance, presumably the result of unrestricted growth into a cavitary space [13]. Vaginal bleeding which is the most common presentation was reported in our case as well. Most patients present with vaginal bleeding or a sensation of a mass in the introits [9]. At pathological examination the tumor mass was mostly composed of firm to soft red-yellowish tissue with areas of hemorrhage. The histological findings of sarcoma botryoides of the uterine corpus are similar like the ones which occur in other organs [11]. In our experience these finding consisted also of rhabdomyoblasts of varying differentiation dispersed within myxoid stroma and a distinct "cambium layer" beneath the epithelium that is characteristic of sarcoma botryoides. Immunohistochemical analysis in our patient showed positivity for desmin, myogenin and the Ki-67 index was 73%.

Pinto et al. [8] reported a cases tumor size range from 6.0 cm to 15.2 cm in largest dimension in a description of eight primary uterine RMS. The masses were mostly centered in the myometrium (6/8), but focally extended into the cervix in three cases. Two tumors arose in the cervix. Our patient presented with an up to 8 cm diameter tumor arising most likely within the uterine cavity and protruding into the vagina with a large stalk remaining in the uterine cavity.

Due to is rarity, ERMS is often not considered in the differential diagnosis of uterine corpus and cervical spindle cell tumors in adult women and may be initially misdiagnosed as a benign cervical or endometrial polyp, a low-grade tumor, or a variety of other neoplasms. Furthermore, recognition can be rendered difficult by hemorrhage, which can obscure the characteristic hypercellular foci [9].

In our case the patient was diagnosed with a benign granulation tissue cervical polyp three months before presenting with a huge sarcoma botryoides. Retrospectively, it is likely that initially there was misinterpretation of a seemingly benign polyp. Thus, a brief mention is merited of the well-known peculiar property of botryoid ERS to form polypoid extrusions which are covered by an epithelial layer covering a loose stroma [14]. Thus, it is conceivable that the initial biopsy of our patient captured only such an extrusion which was, for lack of typical malignant tissue, misinterpreted as a benign polyp. Garrett et al. [14] also reported a case where the lesion was interpreted as benign endocervical or endometrial polyp. However, polyps lack the cambium layer, mitotic activity, and rhabdomyoblasts. As in our case the clinical course of recurrent episodes of abnormal bleeding of the patient should have also perhaps signaled a more worrisome entity in such a young healthy woman.

Due to the rare occurrence of uterine ERMS, there is limited literature on the evaluation of optimal therapy and a lack of level 1 evidence. It seems that there is no uniform approach to these tumors. However, over the decades a paradigm shift took place, moving from ultra-radical surgery like pelvic exenteration in the late 1960s to more limited surgery with adjuvant chemotherapy and/or adjuvant irradiation in the 1970s [15]. There is still a wide spectrum of surgical therapy including radical hysterectomies, hysterectomies, vaginectomies, cervicectomies, polypectomies, local excisions, and diathermy loop excisions [15]. In earlier reports radiotherapy was used as a treatment modality [15].

Now there is a general agreement that these tumors are less radiosensitive. It is hence generally reserved for residual and recurrent tumors [15].

Nowadays a risk-specific approach to staging is recommended, based on the Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical categorization method and the TNM staging approach for rhabdomyosarcoma in order to determine the patient´s clinical risk group [16]. This will consequently stratify the risk group. However, the management of this tumor still poses a great challenge since it often occurs at young age, when the preservation of fertility may play a role. Local control of the tumor is essential in the treatment of these patients in addition with neoadjuvant or adjuvant multidrug chemotherapy [16]. In most case reports a combination of two or three chemotherapeutic agents were mentioned. Multidrug chemotherapy with VAC (vincristine, actinomycin D, cyclophosphamide) is a commonly used regimen, however ifosfamide, as a single agent, or even better in combination, was shown to be efficient in ERMS [4]. In our case the patient decided for a fertility-sparing approach. Thus, after complete resection of the tumor adjuvant chemotherapy with 4 cycles of IVA and adjuvant brachytherapy was planned. Unfortunately, imaging follow-up after chemotherapy was suspicious of recurrent disease which was histologically confirmed and necessitated a more aggressive management including hysterectomy and bilateral adnexectomy followed by another 5 cycles of adjuvant multidrug chemotherapy. Daya und Scully [17] reported that three of 13 patients with cervical ERMS treated with fertility-sparing surgery (polypectomy) followed by chemotherapy had comparable results to those treated with more radical surgery with or without chemotherapy. In our case, despite the more favorable location and the histological type of the tumor, the fertility-sparing approach failed.

Survival estimates for embryonal rhabdomyosarcoma of the uterus are extrapolated from pediatric literature based on experiences with vaginal and cervical tumor. Adults with rhabdomyosarcoma have a worse clinical outcome compared to pediatric cases [18]. Histological favorable subtype is of embryonal specification; unfavorable are alveolar, pleomorphic, and not otherwise specified [19].

The survival rates for vaginal and cervical lesions are 60% and 96% respectively, overall survival (OS) has been reported as 79% in patients treated with surgery and adjuvant chemotherapy [20]. Li et al. reported 25 cases of ERMS in woman 20 years of age or older. Tumors originated in the cervix in 20 cases and in the uterine corpus in 5 cases. Follow-up was available only for 7 patients. After 5 years six patients of the cervix tumor group and one of the uterine groups were alive without evidence of disease [9].

Also, Ferrari et al. [21] investigated the treatment outcomes in a large cohort of adult patients with RMS of all sites and the authors found the overall rate of response to chemotherapy was 85%, with a 5-years OS of 40%. The authors suggested that adults and children with RMS should receive similar therapeutic regimens as the response rate was comparable to that observed in children [21].

The study of Bennett et al. suggested that, in contrast to sarcoma botryoids occurring in other sites, cervical and uterine ERMS has a favorable outlook [5].

CONCLUSION

This very rare case of uterine embryonal rhabdomyosarcoma shows that care has to be taken in the differentiation from a benign cervical or uterine polyp due to the well- known propensity for the acellular areas of the botryoid form of EMS. Although there is general agreement for less aggressive treatment strategies the optimal approach proves challenging especially when fertility-sparing has to be taken into consideration. There is no uniformity in respect to the most appropriate multidrug chemotherapy regimen and according to the number and sequence of the chemotherapy. Further research must be done to evaluate the value of a neoadjuvant concept in respect to treatment outcome and fertility preservation.

Abbreviations: ACT: adjuvant chemotherapy; CE-MRI: contrast enhanced MRI; CT: computed tomography; ERMS: embryonal rhabdomyosarcoma; ucERMS: uterine/cervical embryonal rhabdomyosarcoma; HPV: human papilloma virus; IRSG: Intergroup Rhabdomyosarcoma Study Group; IUD: intrauterine device; IVA: multidrug chemotherapy with ifosfamide, vincristine, actinomycin D; MDTB: multidisciplinary tumor board; MRI: magnetic resonance imaging; OS: Overall survival; PET scan: positron emission tomography scan; RMS: rhabdomyosarcoma; VAC: multidrug chemotherapy with vincristine, actinomycin D, cyclophosphamide

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