CASE REPORT

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Uterine embryonal rhabdomyosarcoma in adult women: a case report on the challenging diagnosis and treatment

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Abstract

Background: Uterine embryonal rhabdomyosarcoma (uERMS) in adult women is a very rare malignant entity. The study aim was to report a case of adult uERMS and to discuss the implications of histopathological diagnosis on the treatment and prognosis. *Case presentation*: We present here the clinicopathological features of a uERMS case in an adult woman. The study has been approved by the institutional Ethics Committee and an informed consent has been obtained (IJB/CE3005). A 45-year-old woman presented to her gynecologist with intermenstrual bleedings and polypoid cervical mass (initially interpreted as benign polyp). A second biopsy was sent to our Department of Pathology at the Jules Bordet Institute, Brussels, Belgium for revision and was reinterpreted as botryoid-type uERMS. The patient underwent a total hysterectomy. The final pathology confirms a 3 cm cervical ERMS, and a simple surveillance was decided by our multidisciplinary team. Six months later, pelvic magnetic resonance imaging control showed a recurrence in the right pelvic lymph nodes. Multi-drug chemotherapy and radiotherapy were done before surgical resection. Pathological examination of the resected pelvic mass confirmed uERMS recurrence of 60 mm, with large zones of necrosis and the presence of cartilaginous structures. The patient is free of disease 60 months after diagnosis. *Conclusions*: Adult uERMS is rare and the pathological examination is the main element for diagnosis and treatment. It is often confused with other benign entities, at least at the time of diagnosis. ERMS should be included in the differential diagnosis of cervical and uterine polyp of adult women. Long-term survival is possible with a multimodal therapy approach.

Keywords: rhabdomyosarcoma, embryonal rhabdomyosarcoma, uterine rhabdomyosarcoma, surgery, adult sarcoma.

Introduction

Rhabdomyosarcomas (RMS) are a unique group of sarcomas arising from embryonal mesenchyme, respectively from skeletal muscle stem cells with an inadequate final differentiation. RMS is exceedingly rare in adults, accounting for less than 5% of all soft tissue sarcomas (STS) [1–4] and can affect almost all organs of the body due to its embryonal mesenchymal origin. The main localizations of RMS in adults are the trunk (27%) and the extremities (26%) followed by the genital tract (17%) [3]. The *World Health Organization* (WHO) *Classification* system for RMS distinguishes four subtypes: embryonal (ERMS), alveolar (ARMS), pleomorphic (PRMS), and spindle cell/sclerosing RMS (SRMS) [4].

The majority of RMS arising in the female genital tract is ERMS (including botryoid type). ERMS usually occurs in the vagina during the first decade of life, with a mean age of three years [5, 6]. One of the least common sites for RMS in the female genitourinary tract is the uterus (corpus and/or cervix). The mean age at diagnosis of patients with uterine (u)RMS is the second decade [7–9]. uRMS very rarely occurs in adults, representing approximately 0.2–0.5% of all malignant tumors of the uterus [2, 10–15]. Almost all the current information regarding adult uERMS comes from case reports, and it remains an under-recognized neoplasm that is often confused with other benign or malignant entities, at least at the time of diagnosis [1, 6].

Since the *Intergroup Rhabdomyosarcoma Study Group* (IRSG) was formed in 1972, the management of female genital tract RMS in pediatric populations has been established and validated through large, randomized trials, and a multimodal treatment of surgery (S), chemotherapy (CHT) and radiotherapy (RT) significantly improves patient survival and decreases morbidity in children with locoregional disease [1, 3, 9]. Unfortunately, similar randomized prospective studies have not been conducted in the adult population, due to the rarity of the disease, and consequently there is no clear standard of treatment established. The current, accepted treatment strategies for uRMS are based on treatments for RMS at other sites and, in accordance with the *IRSG* trials, addressed mostly to the pediatric population [2, 3, 9, 12, 13].

Aim

The purpose of this study was to report a uterine cervix ERMS in an adult woman and to describe the challenges associated with its pathological diagnosis and therapeutic management.

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Case presentation

We present here the clinicopathological features of a cervical uterine ERMS (uERMS) case in a 46-year-old woman. The study has been approved by the institutional Ethics Committee and an informed consent has been obtained (IJB/CE3005).

In September 2017, a 45-year-old woman presented to her gynecologist with intermenstrual bleedings which led to the diagnosis of a polypoid uterine cervical mass, for which initial excisional biopsy revealed a benign polyp. Three months later, she returned with recurrent uterine bleeding and cervical mass. A second biopsy was sent to our Department of Pathology at the Jules Bordet Institute, Brussels, Belgium for revision and was reinterpreted as botryoid-type uERMS. The patient was referred to our Department of Surgical Oncology. There was no significant past medical history. Pelvic magnetic resonance imaging (MRI) demonstrated a 4 cm fibromyoma of the uterine corpus and multiple Naboth cysts, without mass or abnormal uptake of contrast in the cervix. Positron emission tomography/computed tomography (PET/CT) did not show significant ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) uptake in the uterine cervix and no other foci of ^{18}F-FDG avidity in the rest of the whole-body scan (Figure 1, A and B). The patient underwent a C1-type hysterectomy (HRT). Intraoperatively, there was no obvious intraperitoneal disease visible.

The final pathology report described a polypoid cervical lesion (30×7 mm), which exhibits the classical appearance of "bunch of grapes" associated with several Naboth cysts. This lesion prolapsed from the cervix ostium (Figure 2, A and B). Additionally, the myometrium contained multiple leiomyomas, the largest of 5 cm. Microscopically, the samples of the cervix and the isthmus showed a polypoid lesion composed of fusiform cells with oval nuclei. The surface was delimited by a squamous epithelium above a densification of stromal cells (cambium layer) beneath the surface (Figure 2C). The tumor stroma was myxoid with pronounced edema. In depth, the tumor infiltration becomes denser and tumor cells more basophilic. Cartilaginous foci have not been demonstrated. The vaginal collar and the parameters are healthy. The immunohistochemistry (IHC) was positive for myogenin (Ventana BenchMark ULTRA, Sanbio, anti-mouse antibody MYF4, clone F5D, 1/1 dilution) and desmin (Ventana BenchMark ULTRA, Agilent, anti-mouse antibody, clone D33, 1/1 dilution) (Figure 2, D and E). The histology and the immunohistochemical profile were in favor of a cervical ERMS (botryoid subtype). The tumor cervical stromal infiltration was less than 50% and the pathological tumor, node, metastasis (TNM) staging was IA1. According to the *IRSG* clinical classification, the patient was grouped as IA, and it was decided by our multi-disciplinary teams of gynecological oncology and sarcomas to carry out a simple surveillance.

Six months later, pelvic MRI control showed a recurrence in the right pelvic lymph nodes (LNs), with a necrotic mass of 40 mm. The mass had intense metabolic activity [maximum standardized uptake value (SUV_{max}) 11.3] on ^{18}F-FDG PET/CT scan (Figure 1, C and D) without any evidence of metastatic disease. A multi-drug VIDE CHT regimen with Vincristine (1.5 mg/m^2, D1), Ifosfamide (3 g/m^2/day, D1–D3), Doxorubicin (20 mg/m^2/day, D1–D3) and Etoposide (150 mg/m^2/day, D1–D3) was started. The ^{18}F-FDG PET/CT scan after two cycles showed a partial metabolic response of this known right pelvic necrotic mass (SUV_{max} 4.1; ΔSUV_{max} -65%) but with an increase in size (6 cm) on CT scan images (Figure 1, E and F). Due to the discrepancy between the two imaging techniques, it was decided to complete the CHT (for five cycles in total, then stopped for toxicity) and to do an external RT (50 Gy) before surgical resection. Pathological examination of the resected pelvic mass confirmed uERMS recurrence of 60 mm, with large zones of necrosis and the presence of cartilaginous structures. At present, the patient is free of disease 60 months after diagnosis.

Discussions

Diagnostic and staging imaging

RMS represents the sarcoma for which their evolution, treatment strategy, and prognosis vary widely according to age at diagnosis, primary site, and histological type [9, 14, 15]. The etiology of RMS, and therefore also of uERMS, is not yet fully understood, but it is almost certain that the tumors arise from dysontogenetic mesenchymal tissue of the urogenital ridge [4–6, 16, 17]. The occurrence of RMS at sites without the presence of striated muscles, such as the uterus, remains unexplained [16–20].

In a recent mouse model, Hatley *et al.* showed that ERMS can develop from an adipocyte lineage by restricted activation of an oncogenic smoothened allele. This model may explain the ERMS development at sites that do not normally have skeletal muscle and suggests that ERMS may occur through trans-differentiation of mesenchymal, non-skeletal muscle precursors [20].

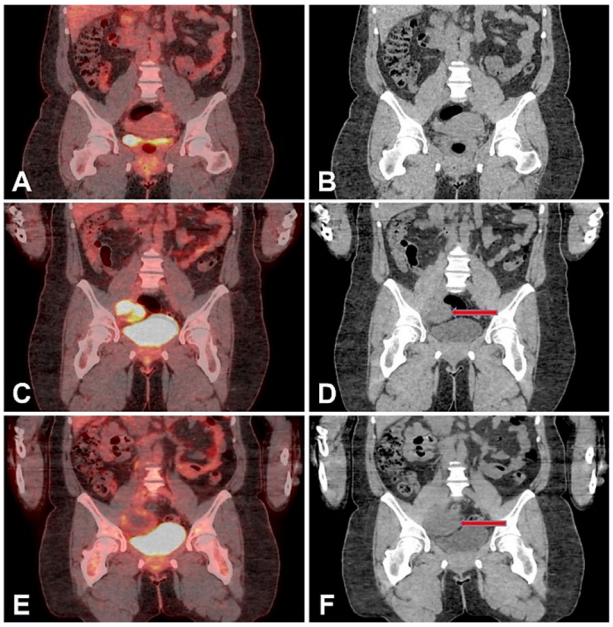

Figure 1 – ***Coronal and CT images of ^{18}F-FDG PET/CT scans at three different time points: initial diagnosis (A and B), at the time of local recurrence (C and D) showing an intense hypermetabolic right pelvic lymph node mass, and after two cycles of CHT (E and F) showing a partial metabolic response (ΔSUV_{max} -65%), but with an increase in volume of the right pelvic mass on CT images probably due to necrotic tissue (red arrow on D and F images). ^{18}F-FDG: ^{18}Fluorine-fluoro-deoxyglucose; CHT: Chemotherapy; CT: Computed tomography; PET: Positron emission tomography; SUV_{max}: Maximum standardized uptake value.***

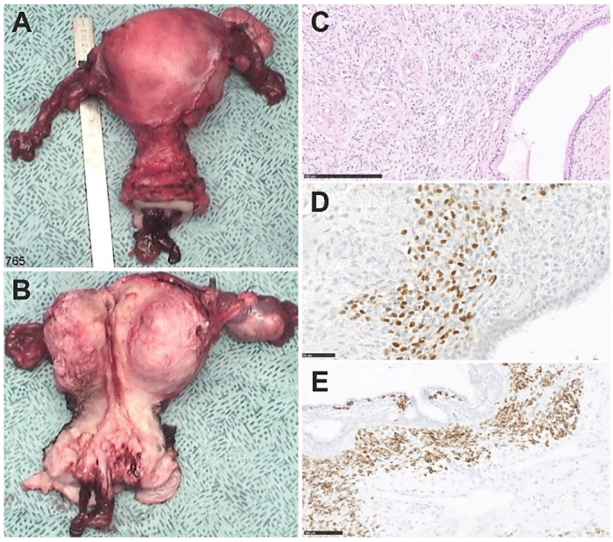

Figure 2 – ***Macroscopic (A and B) and microscopic (C–E) views of the polypoid uterine cervical mass. Hematoxylin–Eosin staining (C) showing the fusiform cells with oval nuclei in a myxoid stroma associated with a densification of these stromal cells (cambium layer) beneath the surface, highlighted better after immunohistochemistry (D and E). The tumor had nuclear myogenin immunostaining (D) and diffuse cytoplasmic desmin immunostaining (E). Scale bar: (C) 250 µm; (D) 50 µm; (E) 100 µm.***

uERMS appears initially as a cervical/endometrial polyp and is always associated with vaginal bleeding. The peak age of female genital tract ERMS is 1–5 years (2/3 of cases) with a second peak seen at 15–19 years [1, 5]. The median age of adult women with gynecological RMS, in a literature review, was 32 years and nearly 1/3 of cases were diagnosed after 50 years of age [21].

There is no specific technique for diagnosis and staging of uERMS. The most common imaging used is MRI with a tumor detection rate of 83% [13, 15, 22–26]. In fact, the main advantage of MRI is its ability to evaluate tumor depth invasion preoperatively, as is already the case for endometrial and cervical cancer [22–26].

An unexpected finding of our case report, for the first time reported in adult uERMS, was the discovery of a pelvic LN recurrence with intense metabolic activity on ^{18}F-FDG PET/CT, while the exam was negative at the time of diagnosis (Figure 2, A1 and B1). This ^{18}F-FDG PET/CT avidity in a recurrent tumor could be at least partially explained in our case by tumor heterogeneity and selection of clones since, for instance, we were able to observe a maturation of some cell populations (cartilage) after CHT in the pelvic LN that was absent in the primary tumor. Furthermore, ^{18}F-FDG PET/CT reevaluation after two cycles of CHT showed a partial metabolic response while the lesion was increasing in size on CT images. Current data do not suggest a role of ^{18}F-FDG PET/CT for initial staging in RMS [18, 27]. However, in uERMS, the ^{18}F-FDG PET/CT use has been reported only in six cases including our case and the tumors exhibited hypermetabolic activity in four cases and no metabolic activity in two of them [8, 19, 28–30].

Histopathological assessment

Pathological examination is one of the most important aspects of management of uERMS. Due to its rarity, RMS is often not considered in the differential diagnosis of cervical and uterine corpus neoplasms in adult women [1, 4–6, 31–34]. Clinicians should keep this disease in mind and send biopsy material to a reference gynecological pathologist in cases where there is any suspicion of uERMS because, as shown in our case and in a large pathology series from Ferguson *et al.* [1] and Li *et al.* [5], for one-quarter of women, the initial diagnosis was mistaken, and the final diagnosis was made upon recurrence [1, 5].

The frequency of uRMS subtypes in adult women is unknown, the reports of gynecological RMS concluded that the most common RMS subtypes involving the uterus are uERMS, followed by PRMS, and ARMS [2–6, 34–36].

The final diagnosis is made on histological evaluation of the biopsy or operative specimen, in combination with an IHC examination [1, 4–6, 12, 37, 38]. ERMS tumor cells are characterized by a small and fusiform nucleus. One of the microscopic features useful for diagnosis is the presence of highly cellular areas with abundant blood vessels, alternating with poor cellular regions that show abundant mucoid intercellular material. A specific characteristic feature is the presence of Nicholson's cambium layer, that is characterized by a dense zone of undifferentiated tumor cells, situated immediately under the glandular epithelium, which was also present in our case (Figure 2C). Cross striations may or may not be present. On the histological examination, attention should also be paid to the differential diagnosis between the uRMS and adenosarcoma, carcinosarcoma, endometrial stromal sarcoma, or leiomyosarcoma because some of these entities can occasionally reveal skeletal muscle differentiation [1, 5, 6]. In accordance with the large case series from Ferguson *et al.* [1] and Li *et al.* [5], our case and nearly all tumors identified in the published case reports with histopathological (HP) detail, are positive for myogenin (93.8%) and desmin (98%), and negative for hormone receptors [1, 5–8, 10–19, 24–26, 31–38]. The Ki-67 index or the mitotic index, is usually high, but was only evaluated in 20% of patients and we cannot draw any conclusions related to clinical aggressiveness of the tumor [5, 11, 15, 16, 37, 38]. The microscopic findings of published uERMS with HP detail are summarized in Table 1.

Table 1 – ***The most frequently reported microscopy findings in uERMS (cases series since 1970)***

Characteristic*	No. and percent of uERMS cases with	
	Available findings	*Positive findings*
	n (%)	*n (%)*
Cambium layer	47 (39.8)	44 (93.6)
Edema	31 (26.2)	27 (87)
Entrapped glands	31 (26.2)	20 (64.5)
Heterologous elements	39 (33)	18 (46.1)
Immunohistochemistry		
▪ Desmin	50 (42.3)	49 (98)
▪ Myogenin	49 (41.5)	46 (93.8)
▪ Vimentin	14 (11.8)	14 (100)
▪ ER	10 (8.4)	3 (30)**
▪ Ki-67 index	16 (13.4)	16 (100)***

ER: Estrogen receptor; *n*: No. of cases; uERMS: Uterine embryonal rhabdomyosarcoma; *Available for 58 cases in 27 studies [1, 5–8, 10–19, 24–26, 31–38]; **Focal positive; ***In seven additional cases, a high number of mitoses were reported by microscopic field.

In a large part of published case reports, there is a lack of a complete pathological description, particularly, the depth of invasion, which has been observed as an unfavorable prognostic factor in the literature [1, 2, 5, 6, 21]. A regular assessment of in-depth tumor invasion should be part of the final pathological report in uERMS, because this relationship between deeply invasive disease and poor survival outcomes was seen both in the pediatric population and the adult women with gynecological RMS [1, 4–13]. Another problem related to pathological evaluation is the absence of tumor staging in most cases of uERMS reported, making interpretation of survival outcomes relatively difficult. We believe that staging the tumor through the two available systems, *Fédération Internationale de Gynécologie et d'Obstétrique* (FIGO – *International Federation of Gynecology and Obstetrics*) and TNM (for RMS) along with *IRSG* classification, and depth of tumor invasion should be part of a standardized pathological report which would facilitate information on survival and prognosis [1–6, 10, 19, 33].

Recently, the uERMS has been shown to be associated with the autosomal dominant pleuropulmonary blastoma familial tumor predisposition syndrome (DICER1 syndrome) [39]. The name relates to a germline mutation in the *DICER1* gene, a ribonuclease III (RNase III) enzyme that cleaves micro-ribonucleic acids (miRNAs). These mutations are unique among tumor suppressor genes, as they will produce a mutant non-functional protein instead of a protein loss. To detect any *DICER1* alterations/mutations a deoxy-ribonucleic acid (DNA) sequencing is needed. Among the gynecological cancers that have been reported to be associated with DICER1 syndrome include ovarian Sertoli–Leydig cell tumor and cervical RMS. This associated *DICER1* gene mutation was also detected in our patient, but for instance we do not know if there is a real RMS-associated familial syndrome for the adult population with uERMS [6, 39].

General overview of management

Treatment has evolved significantly over the past 50 years, with the implementation of multi-modal therapy. Complete surgical resection (R0 surgery) remains the cornerstone of treatment for all localized adult sarcomas, RMS included [3, 9, 40]. The surgical aggressiveness of the management of uRMS in adult women decreased progressively from pelvic exenteration to radical HRT, and now often involves a more conservative approach [2, 9–13, 22, 37, 40]. In a recent review of gynecological RMS, which suggested that patients with *IRSG* type I tumors at any gynecological site (n=68) can be treated with fertility-sparing surgery without a negative impact on outcomes [5-year overall survival (OS) 79% for radical surgery *versus* 90% for conservative surgery, p=0.229] [21]. Lymphadenectomy is an important step of R0 surgery in most gynecological malignancies, but in uterine sarcoma is still a matter of debate, except maybe carcinosarcoma [9, 39, 40]. On the other hand, LN involvement at diagnosis in adult uRMS was stated in 13.3% of patients in a recent multi-institutional series and were associated with a poor prognosis of this subgroup of patients [39]. Considering this data, and the rapid LN recurrence seen in our case, we believe that lymphadenectomy appears to be important in uERMS (at least as a staging procedure) to identify patients with a worse prognosis and to guide the additional treatments. New and more solid evidence is needed before he can draw a definitive conclusion about the place of LN surgery in uERMS.

Furthermore, the risk of recurrence and metastatic spread is a concern [2, 12–16, 21, 37]. The effectiveness of adding an adjuvant CHT regimen for sterilizing minimal amounts of residual disease or distant micrometastases remains debatable, even in cases of localized disease [8, 10, 13, 16, 18, 37–40].

Due to the rarity of the tumor, the optimal choice of CHT remains controversial. Anthracycline-based CHT is the "gold standard" in adult STS while the systemic treatment containing Vincristine, Actinomycin-D, and Cyclophosphamide (VAC) is currently considered the standard regimen for pediatric RMS including uRMS [9, 21, 39, 40]. The role of postoperative RT as the third arm of multimodal treatment in uERMS, is very questionable. In pediatric RMS with R0 surgery, no RT is recommended according to *IRSG* studies, excepting the patients with non-ERMS, patients with positive LN and for patients whose tumors could not be completely resected [9, 21, 39, 40]. Further collaborative studies are needed to better establish the role and type of each of these treatments in adult patients with uERMS.

Conclusions

uERMS is a rare disease among adult women. The pathological examination is the main element for diagnosis and treatment and is based on histological evaluation including IHC examination. ERMS should be included in the differential diagnosis of cervical and uterine polyps in adult women. Surgery is the mainstay of treatment, and with multimodal therapy, patients could have relatively good survival outcomes. Further prospective collaborative studies and an international registry are needed to better establish the optimal treatment for adult women with uERMS.

Conflict of interests

The authors declare that they have no conflict of interests.

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