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CASE REPORT

Cervical embryonal rhabdomyosarcoma: a case series from a single-institution

Rabdomiosarcoma embrionario de cuello uterino: serie de casos de una sola institución

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ABSTRACT

Rhabdomyosarcoma is an aggressive malignant neoplasm that originates in the mesenchyme. It is the most frequent type of sarcoma in infants and children. Its localization in the uterus is extremely rare, and its incidence increase from 20 years-old onwards. Prognosis typically depends on the histological type, age, and the absence of metastasis. We present 5 cases of young females with a history of bleeding, a cervical tumor, whose biopsy was positive for embryonal rhabdomyosarcoma, botryoid variant. All patients received chemotherapy and surgery. Since rhabdomyosarcoma has a high rate of incidence in young women and its diagnosis in the cervix is less aggressive, conservative management of these cases is recommended fertility preservation. Post-surgical management should always consist of chemotherapy, as advances in this type of therapy have been shown to improve general survival rates. Hence, it is essential to report on rare tumors, as it helps in acquiring experience and appropriate knowledge for their clinical management and raises the need for further studies on this disease.

Keywords
Rhabdomyosarcoma; Adolescent, Young adult; Cervix (source: MeSH NLM).

RESUMEN

El rabdomiosarcoma es un neoplasma maligno agresivo que se origina en el tejido mesenquimal. Es el tipo más frecuente de sarcoma en la edad pediátrica. Su localización en el útero es extremadamente rara y su incidencia incrementa desde los veinte años de edad en adelante. El pronóstico generalmente depende del tipo histológico, la edad y la ausencia de metástasis. Presentamos 5 casos de mujeres jóvenes con antecedente de sangrado, tumor uterino, cuya biopsia fue positiva para rabdomiosarcoma embrionario, variante botrioide. Todas las pacientes recibieron quimioterapia y cirugía. Dado que el rabdomiosarcoma tiene una alta tasa de incidencia en mujeres jóvenes y su diagnóstico en el cuello uterino es menos agresivo, se recomienda un manejo conservador de estos casos para asegurar la preservación de la fertilidad. El manejo posquirúrgico siempre debe consistir en quimioterapia, ya que se ha demostrado que los avances en este tipo de terapia mejoran las tasas generales de supervivencia.

Es fundamental reportar los tumores raros, ya que ayuda a adquirir experiencia y conocimientos adecuados para su manejo clínico y plantea la necesidad de realizar más estudios sobre esta enfermedad.

Palabras clave

Rabdomiosarcoma; Adolescente, Adulto joven; Cervix (fuente: DeCS BIREME).

INTRODUCTION

Rhabdomyosarcoma (RMS) is an aggressive malignant neoplasm that originates in the mesenchyme. It is the third most frequent solid tumor in the pediatric population and the most common type affecting infants and children [1]. It is usually located in the head and neck areas; however, the second most commonly affected location for this type of cancer is the genitourinary tract (bladder and prostate in men and the vagina for women). Cervical RMS is extremely rare, but its incidence increases towards the second decade of life. Prognosis typically depends on the histological type, patients' age and the absence of metastasis [2].

Due to its low incidence and prevalence, there is a scarcity of global epidemiological data on this disease. Based on the information available in the SEER (Surveillance, Epidemiology, and End Results) repository, 144 RMS patients with lower female reproductive tract origin (cervix, vagina and vulva) were detected between 1973 and 2013. The median age in patients was sixteen years old. Only around 10 patients had distant metastases and 76% were embryonal RMS [3].

Five young females diagnosed with cervical RMS are presented in this report. These female patients had a history of vaginal bleeding, discharge of vaginal tissue, and a cervix tumor, whose biopsy was positive for embryonal RMS–botryoid variant. All patients received chemotherapy and surgery. In this case series, we discuss the challenges of multidisciplinary management of this disease.

CASES REPORT

Our report includes five cases of RMS. All patients presented a history of bleeding with no significant clinical symptoms before the first physician consultation. In 2 of the cases, an endocervical polyp was found during clinical examination, and one patient expelled a small piece of tumor through the vaginal conduct. There were no signs of fever, pain, palpable mass, or systemic symptoms. Patients' clinical features are presented in Table 1. The overall median age was 16.5 years (range, 5-21) and the median tumor size was 5 cm (range, 4-10) (Figure 1). Represents an endocervical polypoid tumor similar to a bunch of grapes. All patients underwent a biopsy of the

Table 1. Clinical characteristics of patients diagnosed with cervical rhabdomyosarcoma

ID (year of diagnosis)	Age (years)	Clinical presentation	Location (size in cm)	Type of surgery	Therapy	Status (follow-up in years)
1 (2010)	18	Bleeding and tumor	Cervix (3x2)	Conization, polypectomy TAH	CT (IMEV) RT	NED (9)
2 (2016)	21	Postcoital bleeding and tumor	Cervix (6x5)	RH	Delayed CT (IVA)	DOD (1)
3 (2017)	14	Bleeding, tissue discharge and tumor	Cervix (6x5) uterus Pelvic recurrence (7x6)	Polypectomy TAH Pelvic tumor removal	Delayed CT (IMEV), RT CT	NED (2)
4 (2018)	13	Bleeding, tissue discharge	Cervix (4x3)	Vaginoscopy Trachelectomy	CT (VAC) + RT	NED (1)
5 (2018)	6	Bleeding, tissue discharge	Cervix (1.5x1.5)	Vaginoscopy Microcone	CT (VAC)	NED (2)

RH: radical hysterectomy; PLD: pelvic lymphatic dissection; TAH: total abdominal hysterectomy; SOB, salpingo oophorectomy bilateral; NED: no evidence of disease; DOD: dead of disease; CT: chemotherapy; VAC: Ifosfamide-Vincristine-Dactinomicin; IMEV: ifosfamide-mesna-vincristine and etoposide; VAC: vincristine-dactinomycin- cyclophosphamide; RT: radiotherapy.

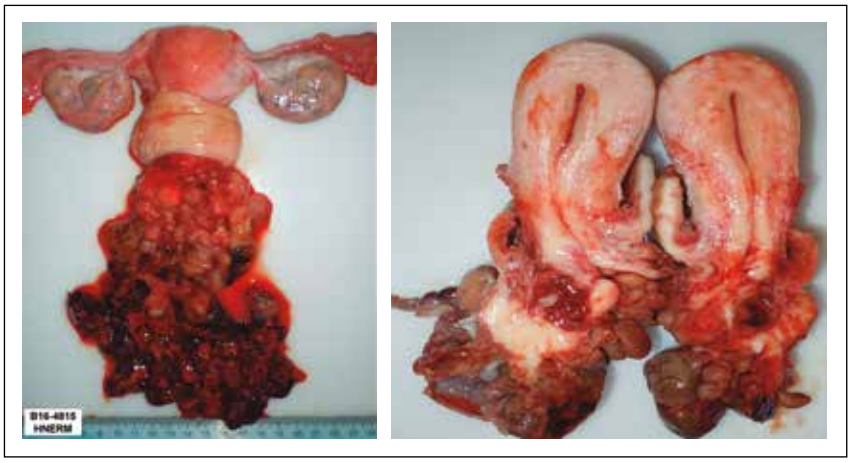

Figure 1. Hysterectomy specimens with endocervical polypoid tumor resembling a bunch of grapes.

lesion, and the pathology report was coherent with the botryoid variant of embryonal RMS (Figure 2).

Regarding the diagnosis of the 5 patients studied, two of them had an initial diagnosis different from that of RMS and were treated in other hospitals; however, the evaluation of the surgical specimens by pathologists at the Rebagliati Hospital in Lima, Peru confirmed the diagnosis of RMS. All patients underwent surgery. In case 2, type III radical hysterectomy was performed in addition to pelvic lymphadenectomy with appendectomy. Case 3 presented with an exophytic polyp, thereby polypectomy was performed with cervical conization, followed by a total abdominal hysterectomy with bilateral salpingectomy. Myomectomy was performed by considering the tumor as a uterine fibroid in case 4. Subsequently, case 4 underwent surgery twice for the resection of the tumor. Case 5 was misdiagnosed with an ovarian tumor, but after the confirmation of an RMS diagnosis, a primary cytoreduction was performed with a pelvic tumor resection. Chemotherapy was the treatment of choice in all cases (vincristine, D-actinomycin and cyclophosphamide) for high-risk RMS. Only one patient received second-line chemotherapy, but her prognosis was dismal.

With a median of 15 months of follow-up, there were distinct signs of relapse in 3 patients, leading to performing a radical hysterectomy and pelvic lymphadenectomy. One patient died of the disease and 4 remained alive with no evidence of the disease.

Ethical considerations

Informed consent and assent were obtained from the patients and parents. The confidentiality of the data obtained from the medical records was maintained.

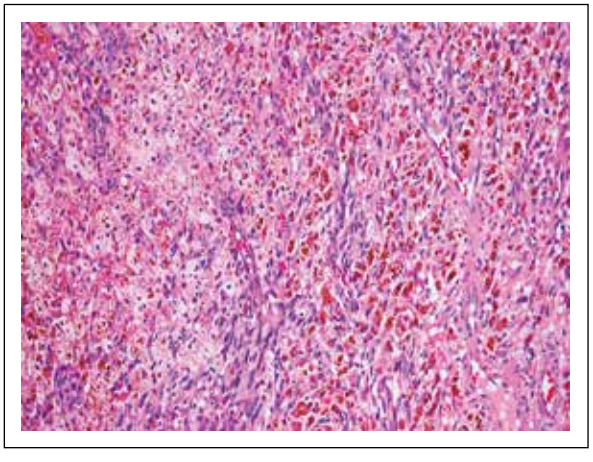

Figure 2. Haematoxylin and eosin stain shows embryonal RMS of the uterine cervix.

DISCUSSION

This report describes five cases of young women with cervical embryonal RMS (cERMS) of lower reproductive tract. RMS is a rare malignant neoplasia, primarily diagnosed in areas without striated muscle [4]. It is a soft-tissue tumor, relatively frequent during the second decade of life, and its incidence radically decreases with age until it becomes a rare entity among the adult population (less than 1%) [5]. The vagina is the most commonly affected organ by an embryonal RMS affecting the urogenital tract. The cervical uterine compromise is only found in 0.5% of RMS female cases [6] and are often presented with early signs of vaginal bleeding.

In this age group, most cases present occasional genital bleeding and some present tumor growth infiltrating the vagina and protruding from the introitus. The tumor is presented as a polyploid morphology in the

shape of a bleeding bunch of grapes. The most distinct histological findings include hypercellularity around epithelial components and nuclear atypia. The skeletal muscle antibodies staining positivity enables the accurate confirmation of the diagnosis [2]. Differential diagnoses of this entity comprehend benign and malignant conditions, such as a prolapsed endometrial polyp, fibroepithelial polyp, endometriosis, leiomyoma, endometrial stromal neoplasm, fibroadenoma, and adenosarcoma [7].

Most cases occur sporadically without any recognizable predisposed risk factors; however, a low percentage is linked to genetic factors. Most common RMS cases are linked to specific genetic variations, such as those involved in K-ras activation or p53 inactivation. Particularly, the embryonal variant is accompanied by a mutation in exon 6 of the Tp53 gene, located in chromosome 17, whereas links of cervical embryonal RMS with DICER1 germline mutations were first established in three families by Foulkes in 2011 [8]. These mutations were later reported by Dehner et al., who found a connection between RMS and pleuropulmonary blastoma familial syndrome with confirmed DICER1 mutations [9,10].

In 2013, the World Health Organization classified RMS into four histologic subtypes: embryonal RMS (including botryoid subtype), solid anaplastic alveolar RMS, pleomorphic RMS and spindle cell/sclerosing RMS [11]. Previously published research has shown adult cases of botryoid RMS, which have demonstrated a slower growth rate, higher chemosensitivity, and lower metastatic capacity [12].

This pathology is rare in adulthood, with universal literature limited to only 115 cases [2], posing constraints onto physicians in terms of planning for appropriate treatments according to protocols used to treat infants with this disorder, or based on experiences accumulated by centers where the number of patients over 40 years old. Since the beginning of the 1980s, combined chemotherapy (Vincristine, Ifosfamide, Actinomycin, Adriamycin, cyclophosphamide, and doxorubicin in prolonged treatment regimens) had become the predominant treatment for patients of all ages. Higher progression-free survival (PFS) rates are associated with optimal surgery and radiotherapy. Globally observed 5-year PFS is 70% and about 90% for non-metastatic diseases in high-income countries. These rates were more variable and less optimistic among adult women, ranging approximately from 60 to 70% in patients with Group 1 and embryonal subtype, and slightly lower, about 30%, in bulky, disseminated, or histologically more aggressive disease [13].

The following subtypes have been identified to have a poor prognosis: alveolar and pleomorphic RMS, tumor size larger than 5 cm, age older than 20, tumor location in the body and cervix, myometrial infiltration, disease progression during chemotherapy, presence of metastasis and macroscopic residual disease (≥ group III) [14]. According to the data published in the literature, the progression of this disease in cases with poor prognosis occurs between 9 and 15 months.

The conventional treatment for cERMS has been a fertility-compromising surgery [14]. Nevertheless, considering that the highest incidence of this neoplasm occurs among young women, patients usually wish for fertility preservation. Current literature suggests that botryoid cERMS has a less aggressive behavior than botryoid sarcoma of the vagina and the uterus, enabling the evolution of cERMS management towards the preservation of genitourinary organs (oncofertility) [14]. A specific chemotherapy regimen is chosen based on risk stratification, which often requires a more conservative surgical approach, enabling complete tumor resection. Nowadays, radiotherapy is reserved as salvage therapy for unfit patients that would not be able to stand intensive chemotherapy regimens [10].

According to the RMS study group, fertility-preserving surgery followed by chemotherapy is an adequate treatment for patients with localized disease. Nonetheless, cases with unfavorable results have been reported despite adequate surgical treatment and chemotherapy, emphasizing the necessity of consistent and close clinical follow-up. Fertility-preserving surgery must be contemplated in cases of extensive uterine compromise and/or metastasis, deep myometrial invasion, and lymphovascular invasion. Alveolar subtype foci should receive aggressive surgical treatment [15].

Prognosis depends on tumor localization, type (better prognosis for embryonal RMS and worst prognosis for pleomorphic RMS), and age, with younger patients experiencing the highest mortality rates. Yet, it is important to note that RMS located in the genital region have a better prognosis than those located in other areas. Nowadays, physicians prefer the approach of surgery and adjuvant therapy, combined with chemotherapy and radiotherapy in selected patients, which has led to a significant increase in survival rates [1].

Since RMS has a high rate of incidence in young women and its diagnosis in the cervix is less aggressive, conservative management of these cases is recommended to ensure the preservation of fertility. Post-surgical management should always consist of chemotherapy, as advances in this type of therapy have been shown to improve general survival rates. Hence, it is essential to report on rare tumors, as it helps in acquiring experience

and appropriate knowledge for their clinical management and raises the need for further studies on this disease.

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