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## Uterine cavity embryonal rhabdomyosarcoma

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### ABSTRACT

Rhabdomyosarcoma (RMS) is a rare solid tumor in childhood and adolescence. The higher incidence is predominant during the first two decades of life. According to the Intergroup RMS Study Group, the embryonal RMS (ERMS), botryoidal variant, constitutes a histological subtype characterized as a “grape-like” lesion of 2.0 cm to 9.5 cm. The treatment involves chemotherapy, surgery, and/or radiotherapy. We present the case of a 14-year-old female patient diagnosed with ERMS, botryoidal variant, which originated in the uterine cervix with vaginal externalization. The initial therapeutic approach comprised an initial prolapsed mass excision followed by Wertheim–Meigs surgery due to the tumor extension. No consensual protocol to ERMS treatment is found in the medical literature; however, a combined approach seems to offer a better result. The postoperative time period was uneventful and the patient followed an adjuvant therapy with vincristine, d-actinomycin, and cyclophosphamide. A comprehensive evaluation of the therapeutic options preserving the reproductive function—unfortunately not always possible—is part of a multi-disciplined care team concerning the pediatric patients.

### Keywords

Rhabdomyosarcoma, Embryonal; Uterine Cervical Neoplasms; Cervix Uteri.

### INTRODUCTION

Soft tissue sarcomas constitute the fifth most common solid tumor type in childhood and rhabdomyosarcoma (RMS) is the most common type found in the first two decades of life. This entity can occur anywhere in the body, except the bones.<sup>1</sup> RMS occurs mostly in the genitourinary tract, with the head and neck as the second most

common site.<sup>2,3</sup> RMS can be associated with specific gene changes, such as the activation of *KRAS* or the inactivation of *p53*. In particular, most embryonal rhabdomyosarcomas show a point mutation in exon 6 of the *p53* gene located on chromosome 17.<sup>4</sup> The Intergroup Rhabdomyosarcoma Study Group (IRSG) subdivide the rhabdomyosarcoma into three

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histological subtypes: (i) embryonal RMS (ERMS), botryoid and fusiform variants; (ii) alveolar RMS (ARMS), including the solid variant; and (iii) undifferentiated RMS.<sup>5,6</sup> RMS may metastasize to any tissue or organ in the body.<sup>1</sup> The EMRS botryoid variant presents as a submucosal “grape-like” lesion,<sup>7</sup> with a polypoid aspect measuring from 2.0 cm to 9.5 cm.<sup>8</sup> The multimodal treatment includes systemic chemotherapy, surgery, and/or radiotherapy for local control. Currently, the overall 5-year survival is 82%.<sup>9</sup> However, the therapeutic side effects include infertility and/or sexual dysfunction.<sup>10</sup> Polypectomy and cervical conization have been performed in cases of localized and purely embryonal RMS of the uterine cervix, as an alternative to radical hysterectomy.<sup>11,12</sup> A radical abdominal trachelectomy, with a technique that preserves the fertility, was applied as a treatment for embryonal rhabdomyosarcoma of the cervix for the first and only time in 2009, according to a literature review.<sup>10</sup>

## CASE REPORT

A 14-year-old female patient attended the gynecology department reporting discomfort in the vaginal introitus for 3 months due to a small bulging tumor. Her menarche was at the age of 12 and she was nulliparous. She reported two regular menstrual cycles every 30 days in this time period. However, during the last 3 days, she noticed a worsening discomfort in the vaginal introitus through which a bulging mass emerged. Although no colic pain was referred, a large fleshy mass followed by high-volume mucosanguinolent secretion was finally expelled from her vagina. The physical examination showed a large, foul-smelling, lobed-shaped vaginal exophytic lesion of 14 × 10 × 8 cm attached to the uterine cervix by a pedicle (Figure 1).

After the ligation of the pedicle, the mass was excised. The histological report rendered the diagnosis of the botryoid type ERMS. The immunohistochemistry was positive for desmin, myogenin, CD34, smooth muscle actin, and S-100, and negative for AE1/AE3 and EMA. The patient was staged as group III and stage 3 according to the Intergroup Rhabdomyosarcoma Study Group (IRSG).

The chest computed tomography was within the normal standards and the magnetic resonance imaging

(MRI) of the abdomen and pelvis—undertaken 5 days after the ligation of the pedicle and 36 days before surgery—showed normal uterine retrocervical regions, a rectovaginal septum, and an anterior rectosigmoid wall also normal, which were different from the surgical findings.

A retrospective review of the MRI of the pelvis was performed with the surgical and postoperative pathological findings. T2-weighted images (axial cut T2 and its correspondence in sagittal cut T2) showed a uterus with normal dimensions, diffuse thickening of the endometrium—more significant in the posterior region of the uterine cervix, where there are small cysts up to 6 mm in length—and irregular contour of the adjacent myometrium, possibly corresponding to neoplastic infiltration (Figure 2).



**Figure 1.** Large, foul-smelling, lobed-shaped vaginal exophytic lesion of 14 × 10 × 8 cm attached to the uterine cervix by a pedicle.

A review of the images was extremely important for a better understanding of the surgical technique adopted during the procedure due to the presence of residual tumor. The retrospective analysis may have been facilitated by surgical and pathological findings; therefore, the surgical decision was adequate in the face of the physical examination of the patient's cervical isthmus transition.

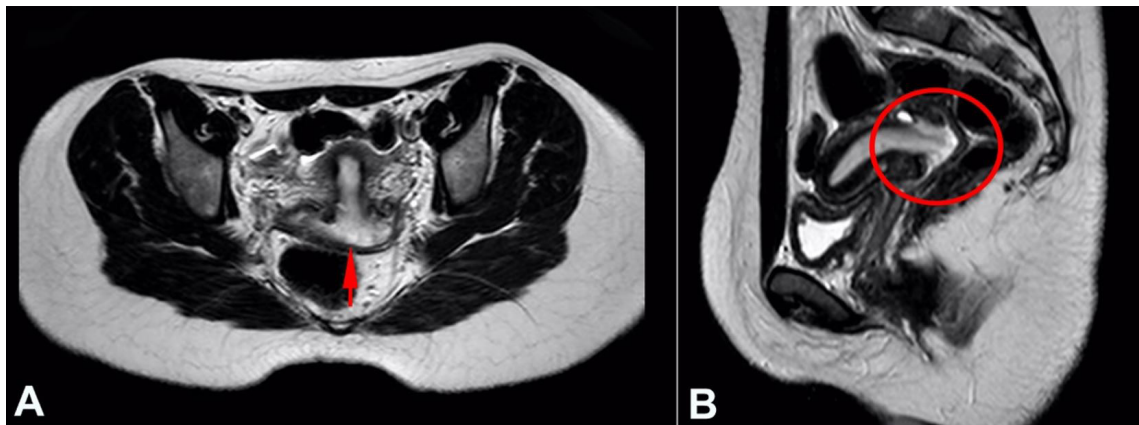
Surgery was performed 36 days after the MRI. A video laparoscopic radical abdominal trachelectomy and pelvic lymphadenectomy were initially proposed; however, Wertheim–Meigs surgery was performed due to the tumor extension to the lower part of the uterine body. The postoperative anatomopathological report showed a locally advanced tumor compromising the

endocervix, as well as the isthmus and endometrium. There was no evidence of lymph node involvement, and the surgical margins were free of the disease, which corresponded to the post-surgical group I IRSG stage.

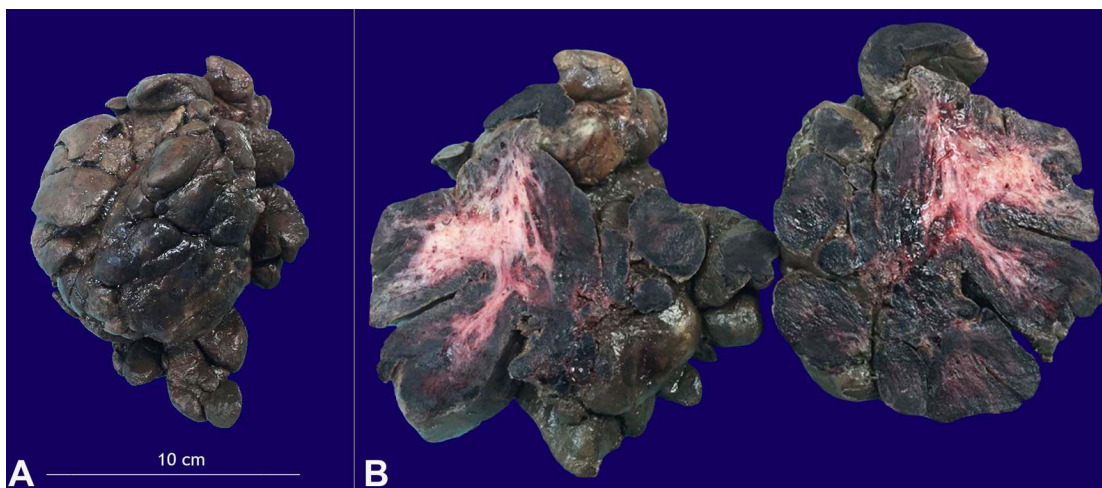
The postoperative time period was uneventful, and the patient was referred to the regional cancer center for chemotherapy.

## ANATOMOPATHOLOGICAL STUDY

The first surgical excision specimen was a blackish bunch-of-grapes-like mass of  $14.0 \times 10.0 \times 8.0$  cm weighing 0.468 kg (Figure 3A). The cut surface showed hardened tissue with necrosis and a fleshy pink center (Figure 3B).



**Figure 2.** **A** – Axial cut T2 and its correspondence in sagittal cut T2 (**B**) of the magnetic resonance imaging of the pelvis showing a uterus with normal dimensions, diffuse thickening of the endometrium (arrow and circled area)—more significant in the posterior region of the uterine cervix, and irregular contour of the adjacent myometrium, possibly corresponding to neoplastic infiltration.

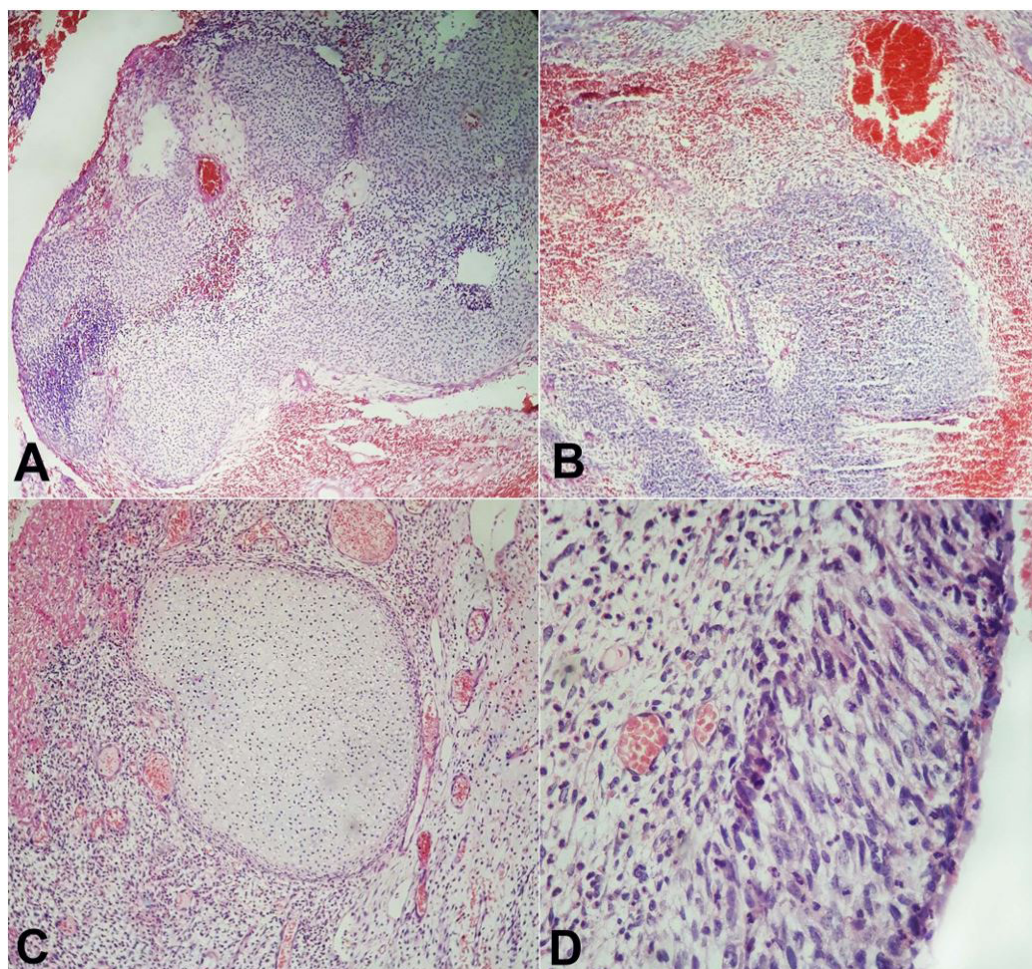


**Figure 3.** **A** – Surgical excision specimen was a blackish bunch-of-grapes-like mass of  $14.0 \times 10.0 \times 8.0$  cm weighing 0.468 kg; **B** – Hardened tissue with necrosis and a fleshy pink center.

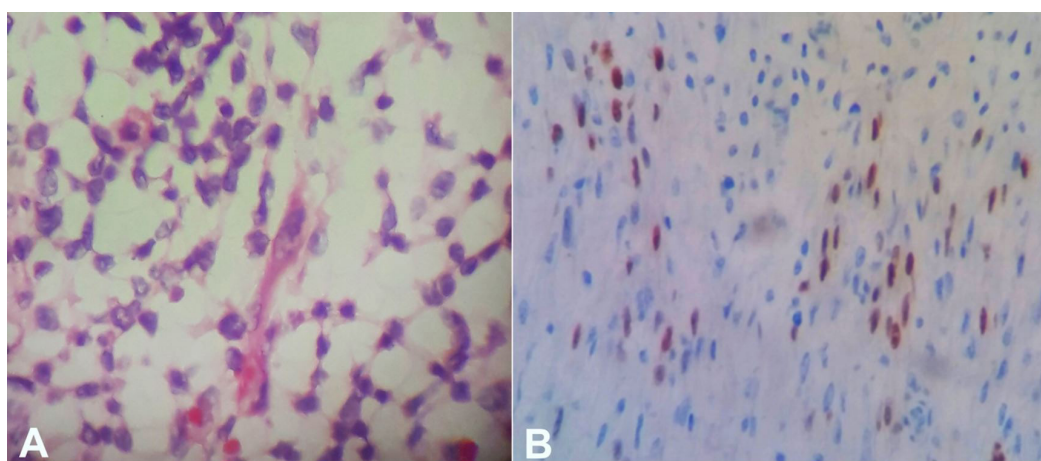


There were several histological aspects of an undifferentiated neoplasia of small, round, blue cells with extensive necrosis in the endocervical region, probably of embryonal cell origin with foci of cartilaginous metaplasia (Figure 4).

Rare elongated cells with eosinophilic cytoplasm, consistent with rhabdomyoblastic differentiation were also found (Figure 5A). Immunohistochemistry was positive for desmin, *myogenin* (Figure 5B), CD34, SMA, and S-100; and negative for AE1/AE3 and EMA.

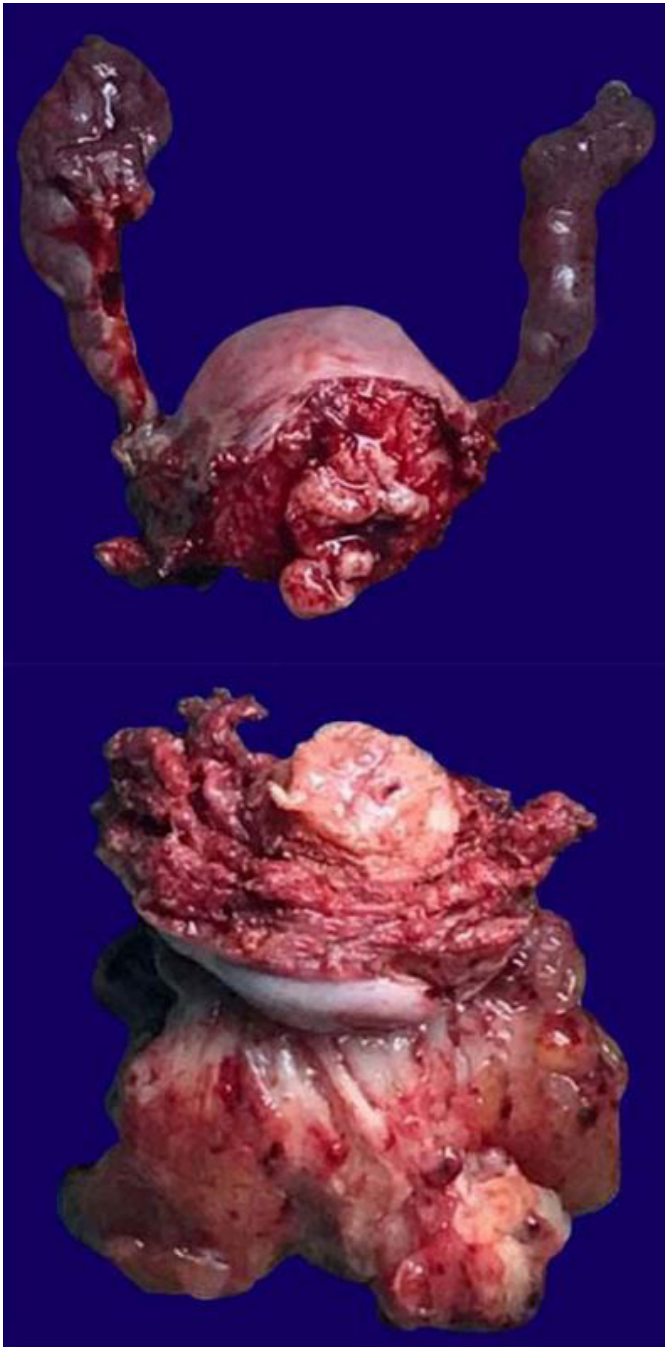


**Figure 4.** Photomicrographs of the undifferentiated neoplasia: **A** – Subepithelial hypercellular areas (H&E, 40X); **B** – Extensive necro hemorrhagic component of neoplasia (H&E, 40X); **C** – Foci of cartilaginous metaplasia (H&E, 40X); **D** – Prevalence of small, round, blue cells, characterizing a probable neoplasm of embryonal cells (H&E, 100X).



**Figure 5.** Photomicrographs of the tumor. **A** – Rare elongated cells with eosinophilic cytoplasm, suggesting rhabdomyoblastic differentiation (H&E, 400X); **B** – Immunohistochemistry positivity for myogenin.





**Figure 6.** Gross view of the surgical specimen after the Wertheim-Meigs surgery showing residual “grape-like” gelatinous tumor mass within the uterine cavity (edited picture).

The patient was classified with group III and stage 3, according to the IRSG.

The anatomopathological study of the second surgical specimen showed a locally advanced “grape-like” gelatinous tumor involving the endocervix, the isthmus, and the endometrium (Figure 6). There was no evidence of lymph node involvement and the surgical margins were free of the disease.

## DISCUSSION

Botryoid sarcoma of the uterine cervix is rare and accounts for about 10% of all cases of RMS.<sup>13</sup> It is mostly found in the first two decades of life.<sup>1</sup> RMS cases usually occur sporadically, with no recognizable predisposing or risk factors. However, some cases show an association with genetic changes, such as the activation of *KRAS* or the inactivation of *p53*. In particular, most of the ERMS show a point mutation in exon 6 of the *p53* gene located on chromosome 17.<sup>4</sup> The Li-Fraumeni cancer susceptibility syndrome, evident by a cluster of soft tissue malignancies (including sarcomas), was discovered in a family as being caused by a heterozygous germline mutation of *p53*. Dehner et al.<sup>14</sup> also found a relationship between the family of blastoma, pleuropulmonary tumors and confirmed *DICER1* mutations and suggests that RMS in children should be managed in a broader context to include the possibility of pleuropulmonary blastoma familial tumor predisposition syndrome.<sup>14</sup> Our patient could not be tested for a genetic study due to financial constraints.

Embryonal rhabdomyosarcoma arises from the unsegmented and undifferentiated mesoderm. Microscopically, the tumor cells are small and spindle-shaped, and have a deeply acidophilic cytoplasm. A highly characteristic feature of botryoid tumors is the presence of a dense zone of undifferentiated tumor cells immediately beneath the epithelium, a formation known as Nicholson’s cambium layer.<sup>15</sup>

Clinically, a botryoid sarcoma may present as abnormal vaginal bleeding, a vaginal mass prolapse, or an abdominal–pelvic mass. The immunohistopathology is crucial for the diagnosis. The IRSG stages this entity by (i) the primary site; (ii) the tumor size; (iii) the involvement of lymph nodes; (iv) adjacent tissues infiltration; and (v) the presence of metastases.<sup>1</sup>

Nuclear MRI is the gold standard for distinguishing the origin of the tumor (whether the endometrium, myometrium, or cervix) and is useful in demonstrating the dissemination and involvement of the adjacent structures.<sup>16</sup> However, in this case, the MRI was done 36 days before the surgical procedure and showed normal uterine retrocervical regions, rectovaginal septum, and anterior rectosigmoid wall, which differed from the surgical findings. A retrospective review of the MRI of the pelvis, performed with the surgical and

postoperative pathological findings, was extremely important for a better understanding of the surgical technique, and was therefore adequate in the face of the physical examination of the patient's cervical isthmus transition.

Girls and young women with RMS of the genital tract have an overall 5-year survival of 82%.<sup>9</sup>

According to the current knowledge, the treatment options for botryoid sarcoma of the uterine cervix include radical surgery, fertility-sparing surgery, chemotherapy, and a combined approach. The ideal management of these tumors is not yet established; however, the combined therapy seems to result in a better outcome.<sup>17</sup>

The risk of relapse, the neoplastic infiltration of the uterine body detected during the video laparoscopic trachelectomy, and the previous consent of the patient to an extensive procedure led the surgical team to the Wertheim–Meigs approach, hopefully with an excellent outcome.

With regard to the ideal adjuvant treatment regimen, there is still no robust evidence available. Notwithstanding, vincristine, d-actinomycin, and cyclophosphamide (VAC), is the chemo regimen mostly used with a better prognosis. Pelvic irradiation could be proposed as an alternative to adjuvant chemotherapy. However, this modality of treatment may interfere with the patient's ovarian function.<sup>18</sup>

A comprehensive evaluation of the impact of various therapeutic measures on the health (general, sexual, and reproductive) of the patient relies on a multidisciplinary study in cases of RMS of the uterine cervix of pediatric patients. In properly selected cases where the uterine involvement is not present, radical trachelectomy could be an attractive therapeutic option. In the present case, it was not possible to assure an ideal local control of the disease preserving the future fertility of the patient. The chosen treatment prioritized better prognosis and patient survival time.

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**Author contributions:** Nogueira Junior RC and Ramajo FM conceived the study as the main surgeons of the patient. Sardinha MGP, Marques CF, Bittencourt CMF, Caldano FG, Moço JMFL, Yano OL, Reis PMR and Malaguti VS collected the data. Sardinha MGP, Yano OL, Sousa CTRG analyzed and interpreted the patient data regarding the uterine cervix disease and the surgery. Marques CF, Bittencourt CMF, Caldano FG, Moço JMFL, Yano OL, Malaguti VS, Souza CTRG and Ponce CC contributed to the interpretation of the results. Nogueira Junior RC and Ramajo FM performed the surgery and biopsy. Ramajo FM, Sardinha MGP and Souza CTRG recorded and edited the surgery film. Ponce CC performed the histological examination of the uterus, lymph nodes, ovaries and fallopian tubes; Sardinha MGP was a major contributor in writing the manuscript. Ponce CC, Nogueira Junior RC, Ramajo FM revised the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

In addition to approval by the ethics committee in research with human beings—CEPSH/UNILUS - CAAE: 04683418 6 0000 5436—a consent declaration was signed by the patient and her mother.

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