Recurrence of low-risk vaginal embryonal rhabdomyosarcoma: A case report and literature review

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Abstract

Background Low-risk vaginal embryonal rhabdomyosarcoma (ERMS) requires no radiotherapy (RT) for local control.

Case summary A 32-month-old girl presented with an exophytic vaginal botryoid mass, which was confirmed of be ERMS. She was given two courses of vincristine, topotecan, and cyclophosphamide (VAC) as neoadjuvant therapy, after which she underwent a hysteroscopy and conservative resection of the vaginal lesion with a negative margin. She was diagnosed with low-risk ERMS (stage I, subgroup A and Group I) and was discharged after another four courses of VAS. However, twenty-eight months after the last treatment, she presented with a giant mass protruding through the vaginal introitus, which was confirmed to be a recurrence of ERMS. Despite multiple rounds of therapy, the patient died 39 months after her diagnosis, at 5 years of age.

Conclusion When making the decision to eliminate RT for low-risk vaginal ERMS patients, the risk of local recurrence should be considered and emphasized.

Introduction

Gynecologic neoplasms are rare in children and represent less than 5% of all childhood tumors. Rhabdomyosarcoma (RMS) of the female genital tract in children is the most common pediatric malignancy.\[1, 2\] RMS is a malignant heterologous mesenchymal tumor with skeletal muscle differentiation. The most common sites are the uterine cervix and corpus. Pleomorphic and embryonal subtypes are most frequent, while spindled and alveolar subtypes are exceedingly rare. Both embryonal and pleomorphic RMS could form poorly defined polypoid, submucosal or intramural masses.\[3\] Embryonal RMS (ERMS) is the most frequently observed RMS in children, accounting for approximately 60–70% of childhood RMS, and botryoid tumors represent approximately 10% of all ERMS cases.\[4\] The botryoid subtype seen in vaginal primary tumors has a typical “grape-like” appearance due to a layer of spindle cells pushing up beneath the mucosa in polypoid masses.\[5\] Vaginal botryoid ERMS usually arises from the anterior vaginal wall.\[6\] The Intergroup Rhabdomyosarcoma Study (IRS) group conducted four consecutive trials.\[7–10\] Low-risk RMS was defined as follows: RMS with favorable pathology, stage I disease, any localization without
involvement of the lymph nodes, tumor size ≤ 5.0 cm, and patient age ≤ 10 years.[11] Low-risk ERMS had a favorable survival prognosis in IRSs III-IV after systematic chemotherapy with local treatment. [9, 10] However, the optimal locoregional treatment approach for patients with vaginal RMS remains controversial since the tumor usually cannot be surgically resected if organ integrity is to be preserved. Furthermore, most patients presented before the age of 2 years, making them especially susceptible to long-term complications of radiotherapy (RT).[12–15]

Here, we report a recurrence in a 32-month-old girl with low-risk ERMS after chemotherapy and conservative resection of vaginal lesions but without RT. Local rapid progression occurred 26 months after the last treatment. A discussion is also presented about the definitive treatment for low-risk RMS.

Case Presentation
The Institutional Review Board of study center had approved this study. The parents of the patient provided consent for publication.

On February 8th, 2015, a 32-month-old girl presented to our hospital with an exophytic vaginal botryoid mass noted by her mother. Her condition was good, and she had no vaginal bleeding or pain. The pregnancy history of her mother and family history of her parents were unremarkable. Physical examination revealed a 2 × 2-cm red mass with a botryoid appearance that protruded through the vaginal introitus. No enlarged inguinal lymph nodes were palpated. Digital rectal examination revealed a mobile, non-tender mass originating in the right vaginal wall. A positron emission tomography-computed tomography study revealed a single vaginal lesion without metastasis. A hysteroscopy with biopsy confirmed the diagnosis of ERMS, which was the botryoid variant (Fig. 1 and Fig. 2). Microscopic findings were characterized by the proliferation of small primitive cells with scant cytoplasm and oval nuclei (Fig. 1). The cells tended to condense under the surface epithelium and around entrapped endometrial glands (“cambium layer”, Fig. 1A, 1B and 1C). There were alternating hypo- and hypercellular areas (Fig. 1B and 1C). The former typically have an edematous or myxoid background, while the latter are typically formed by small aggregates of cells that may show focal rhabdomyoblastic differentiation with cross-striations. The immunohistochemical (IHC) tests revealed
positive findings for Ki67 (approximately 75%), desmin and myogenin, and partially positive smooth muscle actin (SMA), but negative findings for MyoD1 and myoglobin (Fig. 2). Other reported IHC results included positive synaptophysin, chromogranin A, protein S-100, neuron-specific enolase and vimentin but negative human melanoma black 45 (HMB-45) and cytokeratin.

After discussion with her parents, the girl was given two courses of vincristine, topotecan, and cyclophosphamide (VAC) chemotherapy. The vaginal lesion shrank well. The pelvic MRI study on March 10, 2015, showed a vaginal mass of approximately 2.4·1.9·1.0 cm in size (Fig. 3). The next day, hysteroscopy using a bipolar electrode was performed to completely resect the vaginal lesion with the pedicle. Partial vaginal mucosa was also resected without repair. Pathological evaluation revealed uninvolvement of the margin. Her recovery was uneventful. The patient underwent another 4 cycles of VAS, and the final course ended on June 1, 2015. The grade 3/4 adverse events included neutropenia, febrile neutropenia, and alopecia. We suggested meticulous follow-up, but the patient was lost to follow-up one year after the last treatment.

On July 6, 2017, at five years old, the patient was brought to our outpatient clinic for a vaginal mass found one month before. Physical examination revealed a firm and lobulated 8.0·6.0·6.0-cm mass that protruded through the vaginal introitus. Multiple enlarged lymph nodes could be touched in both groins. A pelvic MRI study suggested vaginal malignancy with enlarged lymph nodes in the bilateral inguinal region (Fig. 4). A biopsy of the prolapsed mass confirmed recurrent ERMS. Treatment of the patient with multiple lines of chemotherapy and RT failed, and she died on May 5, 2018, due to severe damage to liver function caused by medicine toxicity and to the ileus caused by disease progression.

The failure-free survival (FFS) and overall survival (OS) rates were 28 and 39 months, respectively.

Discussion
We report a recurrence of ERMS in a 36-month-old girl with stage I, low-risk, vaginal ERMS, even after standard treatment with chemotherapy and complete surgery. She had FFS and OS rates of only 28 and 39 months. The management of pediatric genitourinary RMS has evolved from pelvic exenteration in the 1970s and early 1980s to a multimodal treatment involving conservative surgery, chemotherapy, and RT in an effort to preserve genitourinary organs and reduce treatment morbidity.
The rate of hysterectomy decreased from 48% in IRS-I/II to 22% in IRS-III/IV, with an increase in the use of RT from 23% in IRS-II to 45% in IRS-IV. Approximately half of RMSs in the female genital tract arise in the vagina, and a majority is of the embryonal subtype, all of which have a favorable prognosis.[1, 9, 12, 13] With the goals of limiting late effects resulting from treatment and preserving organ function, the approach to local treatment has changed radically over the last 30 years. However, local therapy in children and adolescents with vaginal RMS remains a challenge. The predominant context of treatment failure in patients with initially localized RMS has been local recurrence. In IRS-II, of patients who achieved complete remission with chemotherapy and surgery, almost 20% of patients with Group I to III disease had local or regional relapses, and 30% of patients with Group IV disease had local or regional relapses.[8] Local or regional relapses accounted for 70-80% of all relapses among children with Group I to III disease and 46% of all relapses among patients with Group IV disease.[8]

Both surgery and RT are the primary measures taken to establish local control, but each has its risks and benefits. Surgical removal of the entire tumor should be considered initially, but only if functional and cosmetic impairment will not result.[16] RT is an effective method for achieving local control of the tumor in patients with microscopic or gross residual disease after biopsy, initial surgical resection, or chemotherapy. RT is recommended to enhance local control in all patients with RMS except those who had embryonal/fusion-negative clinical group I tumors. Brachytherapy, using either intracavitary or interstitial implants, is one method of local control and has been used in selected situations for children with ERMS, especially for patients with primary tumors at a vaginal site.[14, 17-19] The COG-STS recommended that RT be administered to patients with residual viable vaginal tumors beginning at week 12.[20] For patients aged 3 years and younger, reduced radiation doses may be appropriate if delayed surgery can provide negative margins. However, for patients who are unable to undergo surgical resection, higher doses of RT remain appropriate.[21] Many retrospective analyses have found that in patients with locally relapsed disease, not receiving RT was an important factor in tumor recurrence. However, these studies included intermediate- to high-risk RMS patients.[20, 22-24]. In a pooled analysis, fifty-one (51.5%) of the 99 survivors with known primary therapy and treatment for
relapse were cured with chemotherapy with or without conservative surgery.[25] When making the decision to eliminate RT, the risk of local recurrence must be considered.[24] Moreover, for girls with genitourinary primary tumors who will receive pelvic irradiation, ovarian transposition (oophoropexy) before radiation therapy should be considered unless dose estimations suggest that ovarian function is likely to be preserved. Alternatively, ovarian tissue preservation is under investigation and can be considered. When RT is indicated, modalities that limit sequelae, such as brachytherapy, should be considered.[25]

Surgery is the most common treatment option considered for children with vaginal RMS. For prepubertal girls and adolescents, radical surgery did not confer a survival benefit compared to local tumor excision.[26] Conservative surgical intervention for vaginal RMS, with primary chemotherapy and RT (external beam or brachytherapy) for residual disease (Group II or III), leads to excellent 5-year survival rates.[1, 24, 27] Complete excision for localized disease is recommended as long as functional and/or cosmetic results are acceptable. The principle of wide and complete resection of the primary tumor is less applicable to patients known to have metastatic disease at the initial operation, but it is an alternative approach if easily accomplished without loss of form or function. Children aged 3 years or younger who are diagnosed with RMS pose a therapeutic challenge because of their increased risk of surgery-related morbidity.[28]

If complete resection is not feasible, it is better to undergo an initial diagnostic biopsy followed by neoadjuvant chemotherapy and then definitive local therapy with either surgery or RT. Moreover, there is little evidence that debulking surgery improves outcomes compared with resection alone; therefore, debulking surgery is not recommended for patients with RMS.[29] In a retrospective study of 73 selected patients, second-look procedures (also called delayed primary excision) identified viable tumors that remained after initial chemotherapy; 65 of these patients had also received RT. Patients with viable tumors had shorter FFS rates than those without viable tumors, but there was no effect on OS.[28] Thus, delaying surgery until after chemotherapy is preferred.

Chemotherapy is the most common treatment modality for vaginal ERMS.[30, 31] The choice of regimen depends on the estimated risk of disease recurrence. Approximately 25% of newly diagnosed
patients are, by definition, low risk. Certain subgroups of low-risk patients have achieved survival rates higher than 90% when treated with a two-drug chemotherapy regimen that includes vincristine and dactinomycin (VA) plus RT for residual tumor.[32] In the report by Raney et al.,[33] the estimated 5-year FFS rate was 89% (95% CI, 84–92%) for low-risk RMS. In their study, Group I ERMS patients needed no RT. High-dose cyclophosphamide causes severe myelosuppression, infectious complications, and infertility in virtually all males and many females. In patients with Group I-III tumors, 43% of deaths are from toxicity.[1] The COG-ARST0331 trial evaluated the minimization of acute and long-term toxicities of therapy for two subsets of low-risk patients. The study enrolled 271 newly diagnosed patients with low-risk RMS, with a shorter duration chemotherapy regimen that included four cycles of VAC chemotherapy followed by 10 weeks of therapy with vincristine and dactinomycin.[34] The 3-year FFS rate was 89%, and the OS rate was 98%. These findings suggest that a shorter duration of therapy does not compromise the outcomes of these patients. The 5-year FFS outcome improved for these patients, from 70% for IRS-III patients with VA therapy to 84% for IRS-IV patients with the addition of intensive cyclophosphamide.[34] Neoadjuvant chemotherapy combined with radical surgery has achieved a favorable prognosis in cervical RMS[35] and vaginal RMS.[36, 37]

Numerous studies have discussed the molecular mechanism in ERMS to explore the pathogenesis of the disease, distinction of subtypes, and potential targeted therapies.[38] On the basis of methylation patterns, RMS is clustered into four distinct subtypes.[39] The IHC expression pattern of endogenous markers has emerged as a promising tool to predict the response to neoadjuvant chemotherapy for RMS. [40] A five-gene expression signature score shows a significant correlation with overall and FFS among cases from COG D9803.[41] However, these findings are awaiting further translation or validation in clinical trials. No available practical molecular testing or targeted therapy is officially used in RMS patients except for the association of alveolar RMS with translocations t(2;13)(q35;q14) and t(1;13)(p36;q14), which lead to the generation of fusion genes.

**Conclusion**

Localized vaginal ERMS is usually curable with combination chemotherapy and a conservative surgical
approach. When making the decision to eliminate RT for patients, the risk of local recurrence must be considered and emphasized with meticulous follow-up.

Declarations

Disclosure

All authors declare that they have no conflicts of interest to disclose.

Ethics approval

The Institutional Review Board of Peking Union Medical College Hospital approved this study.

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Availability of data and materials

All the data in this report have been presented in the manuscript.

Statement of submission

The paper is not under consideration by another journal, and the results presented in this work have not been previously presented or published.

Consent for publication

Consents for publication have been obtained from the patient’s parents.

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Figures
Pathology by hematoxylin-eosin staining. Abundant acidophilic granulates within the cytoplasm and round or oval nuclei are clearly visible (Figure 2A, x100-fold). The tumor cells are clustered in small nests or irregular trabecular structures demarcated by delicate fibrous stroma and capillaries in the Zellballen growth pattern (Figure 2B, x40-fold and Figure 2C, x100-fold). In the tumor stroma, a blood sinus, a blood capillary, and little fibrous tissue are evident (Figure 2D, x40-fold).
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Pathology by immunochemical staining (all x100-fold) reveals positive Ki67 (approximately 75%, A), myogenin (B), and desmin (C) but negative MyoD1 (D), and myoglobin (E) and partially positive smooth muscle actin (SMA) staining (F).
Figure 3

Magnetic resonance imaging on March 10, 2015. The arrows all indicate the vaginal lesion.

(A) Horizontal plane of short T1 and long T2 signals. (B) Horizontal plane of long T1 and short T2 enhanced signals. (C) Sagittal plane of long T1 and short T2 signals.
Figure 3

Magnetic resonance imaging on March 10, 2015. The arrows all indicate the vaginal lesion.

(A) Horizontal plane of short T1 and long T2 signals. (B) Horizontal plane of long T1 and short T2 enhanced signals. (C) Sagittal plane of long T1 and short T2 signals.
Figure 4

Magnetic resonance imaging with long T1 and short T2 signals of July 6, 2017. The arrows all indicate the vaginal lesion in the horizontal plane (A) and its protrusion out of the vagina in the horizontal (B), frontal (C), and sagittal planes (D). Multiple enlarged lymph nodes are also demonstrated in the bilateral inguinal region (asterisks).
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