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Vaginal tumors in childhood: the experience of St. Jude Children's Research Hospital

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Abstract

Background/Purpose—To retrospectively analyze the clinical presentation, histology, treatment and outcomes of children with vaginal tumors who were treated at a single institution.

Methods—A retrospective review was conducted of medical records and pathologic materials of all children with vaginal tumors treated at St Jude Children's Research Hospital between 1970 and 2009.

Results—Eighteen patients (median age 3.7 years, range 0.1–15) were identified. Three different histologies were found: rhabdomyosarcoma (RMS) (N=13), germ cell tumor (GCT) (N=3) and clear cell adenocarcinoma (CCA) (N=2). Bleeding or blood-tinged discharge was the most common clinical presentation (66%) followed by a protruding mass (39%). Vaginal and uterine salvage was 44.4% (8 of 18 patients). Thirteen patients (72.2%) remain disease-free with a median follow-up of 23.2 years (range, 2–39). Four patients (22.2%) died of disease progression (1 RMS, 2 GCT and 1 CCA) and 1 RMS patient died of colon cancer 12 years after the primary diagnosis had been made.

Conclusions—Vaginal tumors are extremely rare in the pediatric population. Early recognition of symptoms like bleeding and a protruding vaginal mass may prevent morbidity and mortality. Our findings confirm the good prognosis of vaginal RMS.

Keywords

vaginal tumors; rhabdomyosarcoma; germ cell tumor; adenocarcinoma

Introduction

Gynecologic tumors in children are rare and represent less than 5% of all pediatric neoplasms (1). Vaginal tumors may have a variable clinical presentation, including

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abdominal pain, abdominal mass, chronic genital ulcer, bloody discharge or tissue protruding from the vagina (Figure 1) (1,2). Rhabdomyosarcoma (RMS) is the most common malignant neoplasm of the vagina followed by germ cell tumor (GCT) and clear cell adenocarcinoma (CCA) (2). The management of pediatric vaginal tumors has evolved from radical surgery in the 1970s and early 1980s to neoadjuvant chemotherapy followed by local control with surgery or radiotherapy (3) in the last decades. We reviewed our institutional experience over a 39-year period to more completely characterize the clinical presentation, treatment, and outcome of vaginal tumors in pediatric patients.

Material and methods

A review of the St. Jude Solid Tumor database identified 18 patients diagnosed with vaginal tumors among the 4485 patients under 21 years of age evaluated for malignant solid tumors (excluding brain tumors) between 1970 and 2009. The following information was collected retrospectively: patient age at diagnosis, symptoms, stage of disease, histological findings, therapy, clinical course, and outcome. This study was approved by the St. Jude Institutional Review Board.

Rhabdomyosarcoma was classified according to the international classification as botryoid, embryonal or alveolar (4) and was staged according to the tumor, lymph node, metastasis (TNM) system of the International Union Against Cancer (UICC) and the Intergroup Rhabdomyosarcoma Study (IRS) clinical grouping system (4,5), which assigns group I for localized tumor that is completely removed with pathologically clear margins and no regional lymph node involvement, group II for localized tumor that is grossly removed with microscopic disease at the margin, involved and grossly removed regional lymph nodes or both, group III for localized tumor with gross residual disease after incomplete removal or biopsy only and group IV for metastatic disease.

Results

Table 1 lists the clinical characteristics, treatment and outcomes of the 18 patients.

Rhabdomyosarcoma

Thirteen of the 18 children with malignant vaginal tumors had RMS, 10 botryoid subtype and 3 embryonal subtype. They presented at a median age of 3.7 years (range 0.16–15). Bleeding or blood-tinged discharge from the vagina was the most common clinical presentation (61%), followed by a protruding mass (39%). According to the IRS postsurgical grouping system there were three patients in group I, eight patients in group II, one patient in group III and one patient in group IV. As initial therapy, eleven of thirteen patients received chemotherapy (Table 1). The most common chemotherapy agents used were vincristine, dactinomycin, cyclophosphamide, doxorubicin and more recently ifosfamide and etoposide. The surgical approach was variable. Six patients underwent hysterectomy and vaginectomy (1 at initial diagnosis, 5 later during therapy), 2 underwent anterior pelvic exenteration, and 5 had only a biopsy. Five patients received external beam radiation therapy (EBRT) with a median dose of 39.5 Gy (range 12.8–47.1) and two patients received 54 and 52.4 Gy of brachytherapy. Only one patient experienced local tumor recurrence. This patient had undergone conservative surgery for tumor excision and received no adjuvant therapy. She was successfully salvaged with chemotherapy and hysterectomy/vaginectomy. Eleven patients of thirteen (84%) remain disease-free with a median follow-up of 21.4 years (range, 3–37). Two patients died, one of them who underwent anterior pelvic exenteration and ileal conduit reconstruction without radiation therapy succumbed to colon cancer 12 years after vaginal RMS diagnosis. The other patient did not receive planned postsurgical chemotherapy due to parental refusal and died of progressive metastatic

disease. The remaining 11 patients have no evidence of disease. Two patients were cured without local treatment except for initial biopsy. Uterine salvage was 30% (4 of 13 patients), but most of the patients undergoing hysterectomy were treated in the 1970s and early 1980s. Only 2 of the 6 patients treated in the last 25 years have required extensive surgical resection, either during treatment or for long-term complications.

Surgical complications included recto-vaginal fistula, vesico-vaginal fistula and urinary incontinence in one patient who required hysterectomy, vaginectomy and cystectomy 15 years after diagnosis.

Germ Cell Tumor

Germ cell tumor was found in 3 patients, endodermal sinus tumor subtype in two cases and embryonal carcinoma in one case. They presented at a median age of 0.9 years (range 0.6–1.2). Bleeding or blood-tinged discharge from the vagina was seen in two patients and a protruding mass in one patient. Serum alpha-fetoprotein (AFP) was markedly elevated in all these patients at diagnosis. Two patients received neoadjuvant chemotherapy (carboplatin/etoposide/bleomycin and VAC regimen, respectively) and the other patient had primary hysterectomy and vaginectomy. Two patients had postoperative external radiotherapy with doses ranging from 44 to 49 Gy. Two of the 3 patients developed local recurrences in rectum and vagina, 8 and 26 months after diagnosis, respectively, and both died of disease progression. The only survivor received carboplatin/etoposide/bleomycin and did not require surgical resection. A postchemotherapy biopsy was negative for tumor. She is alive 2 years after diagnosis without complications.

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma was found in 2 of 18 patients. They presented at a median age of 10.2 years (range 7.4–13). Bleeding from the vagina was observed in both patients. One patient underwent a marginal resection via partial vaginectomy and received adjuvant cisplatin/paclitaxel chemotherapy and 54 Gy brachytherapy. She is alive 11 years after diagnosis. The other patient had neoadjuvant chemotherapy (vincristine, actinomycin-D, cyclophosphamide) to which a partial response was achieved, followed by hysterectomy and vaginectomy. Microscopic residual disease was present after surgery and she received additional postoperative chemotherapy with the same preoperative regimen and 50 Gy brachytherapy. She presented with vaginal and rectal recurrence 24 months after diagnosis and died of rectal bleeding from the tumor. Neither of these patients had documented prenatal exposure to diethylstilbestrol (DES).

Discussion

Vaginal tumors are uncommon in adults, comprising 1% to 2% of gynecologic malignancies and mainly represented by squamous cell carcinoma and adenocarcinoma, two distinct diseases with a different pathogenesis and natural history (1,2). The 18 pediatric patients with vaginal tumors treated at St. Jude Children's Research Hospital over a 39-year period illustrate the rarity of this malignancy in childhood. In our patient cohort, the most common neoplasm of the vagina was rhabdomyosarcoma followed by germ cell tumor and clear cell adenocarcinoma. Bleeding or blood-tinged discharge was the most common clinical presentation; a protruding vaginal mass was the second most common presentation.

Rhabdomyosarcoma is the most common malignancy of the pediatric female genital tract and it generally presents in the first few years of life, with vaginal bleeding, discharge, and/or a vaginal mass (1–3). RMS is a small, round, blue-cell neoplasm with malignant skeletal muscle differentiation (4). The botryoid subtype, which is frequently 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).

Pelvic exenteration was the accepted surgical approach for vaginal RMS before 1972 (6,12). Since then, the management has progressed from radical surgery to neoadjuvant chemotherapy followed by surgery or radiotherapy after the IRS Group began to enter patients on prospective clinical trials (7,8). Hays *et al.* (9) reported 22 cases of nonmetastatic vaginal RMS treated on the IRS I and II protocols between 1972 and 1984. This included six patients who underwent biopsy only without extensive surgical resection. The response rate to chemotherapy was greater than 90% and when combined with a subsequent excision the results relative to survival were equally good. Andrassy *et al.* (10) reviewed 25 years of publications in vulvovaginal RMS and confirmed the role of organ-preserving approach. The rate of radical surgery decreased from 100% in 1972–78 to 13% in 1988–96. The prognosis was excellent; 25 of 27 girls with vulvovaginal tumors survived >5 years, with an 88% preservation rate for the uterus. All patients were treated with chemotherapy and 11 received additional radiotherapy. Recently, Arndt *et al.* (3) evaluated the factors affecting outcome in 151 patients with RMS of the female genital tract treated on IRS protocols I–IV. The rate of hysterectomy decreased from 48% in IRS-I/II to 22% in IRS-III/IV and the overall 5-year survival was 82%. Analysis of prognostic factors revealed that an age of 1–9 years at the time of diagnosis, noninvasive tumors, and the use of IRS-II or IRS-IV treatments (based on VAC regimen, a conservative surgical approach, and the use of radiation therapy for selected patients) were associated significantly with better outcome. Martelli *et al.* (11) reported the results of a conservative multimodal approach in 38 girls with nonmetastatic RMS of the genital tract (vulva, vagina, uterus), treated between 1984 and 1994 in the International Society of Pediatric Oncology (SIOP) protocol. Twenty-seven patients presented with a vulvovaginal RMS and 25 of them survived with a uterine salvage rate of 88%.

Our findings confirm the excellent prognosis of RMS arising in the vagina and emphasize the efficacy of a conservative approach to local therapy that leads to a high rate of cure. In the present study, 11 of 13 girls with vaginal RMS survived without evidence of disease at follow up of 3–39 years.

Although the overall survival of patients with vaginal RMS has improved, little is known about the late effects of treatment in long-term survivors. Spunt *et al.* (24) reviewed the spectrum and severity of late effects in female survivors of pelvic RMS treated at our institution and found significant late effects that reduced the quality of life and the functional capacity. These included vaginal stenosis, fistulas, gastrointestinal strictures, and bladder dysfunction.

From review of our patients, we conclude that biopsy and primary chemotherapy constitute the current initial treatment of choice for vaginal RMS, reserving surgical resection for truly persistent or recurrent disease. Radiotherapy, which is associated with significant long-term sequelae, should be avoided whenever possible.

Malignant GCT represent less than 3% of all pediatric malignancies, with endodermal sinus tumor being the most commonly observed histological subtype (13–18). The vagina is an extremely rare primary location, ranging from 3% to 8% of GCT. Clinical presentation is usually vaginal bleeding in girls under the age of 3 years. Our patient series supports this observation since all of our patients were under 2 years of age. Alpha-fetoprotein (AFP) is considered a reliable marker for diagnosis, evaluation of treatment response and remission status (14). Before 1965, surgery and/or irradiation were the usual treatment. Copeland *et al.* (15) reported 6 cases with a total of 4 survivors, all with tumor resection at diagnosis and

VAC chemotherapy. Only one with a small tumor had preservation of the vagina. Hwang *et al.* (16) reported 2 children with small tumors treated with excision at diagnosis with organ preservation and VAC. The introduction of cisplatin-based chemotherapy in the 1980s has significantly improved the survival in children with malignant GCT at all anatomic sites (17). Platinum and bleomycin containing chemotherapy regimens replaced the historical VAC regimen due to the excellent response rate and tolerable toxicity (18). Both of our GCT patients who died were treated before the development of cisplatin-based chemotherapy. Current survival rate at 2 years for vaginal malignant GCT has been reported to be 70% (18). Initial biopsy followed by cisplatin-based chemotherapy and organ preservation in patients showing a complete tumor response including AFP normalization is the current approach for vaginal malignant GCT.

Clear cell adenocarcinoma is very rare before adolescence, and often has a very aggressive pattern in young children (19–23). Larger masses generally present as polypoidal and nodular or sometimes as flat and ulcerated tumors. Histology is characterized by solid sheets of clear cells due to dissolution of glycogen. The most common symptom of pediatric patients at presentation is vaginal bleeding. The development of this tumor in the vagina of young females has been historically linked to prenatal exposure to diethylstilbestrol. The age of the DES-exposed patients has varied from 7 to 34 years. Disease characteristics in young girls seem to be similar to older patients, except that young patients had a slightly higher incidence of advanced-stage disease. Surgical resection and lymph node dissection have an important role in the treatment of CCA (19). McNall *et al.* (20) reported one case and reviewed 37 published cases of vaginal and cervical mesonephric adenocarcinoma or CCA in patients under the age of 18 years. Overall survival was higher for patients who underwent complete tumor resection. The role of neoadjuvant chemotherapy in the treatment of vaginal CCA is unclear and combinations of platinum compounds and paclitaxel have been used (21,22). Tumor excision rather than radical hysterectomy or exenteration is preferred when feasible. Pelvic and para-aortic lymph node dissections are recommended even in patients with early stage disease (20). The 2-year event-free survival estimate is 90% for patients with Stage I disease, 71% for patients with Stage II disease, and 29% for those with Stage III/IV disease (20,22). Radiotherapy in children with vaginal CCA should be reserved for the treatment of microscopic residual disease or lymphatic metastasis and bilateral oophorectomy is recommended if postoperative EBRT is considered (20).

Conclusion

Our small group of patients with vaginal tumors illustrates the rarity of malignancies at this anatomic site in childhood. Abnormal vaginal bleeding in girls should be promptly investigated through the use of pelvic examination, appropriate imaging and tumor markers evaluation (AFP, HCG). Over time, the management of pediatric vaginal tumors has progressed from radical surgery in the 1970s and early 1980s to biopsy followed by neoadjuvant chemotherapy, particularly with the VAC regimen for RMS and cisplatin-based chemotherapy for malignant GCT, in the last decades. A higher incidence of advanced-stage disease is noticed in younger patients with CCA, in which surgical resection and lymph node dissection have an important role.

Our retrospective study has several limitations that should be considered in the interpretation of our findings, including the small number of patients in the study cohort and the referral bias inherent in our status as a tertiary referral center. Prospective studies are needed to define the best systemic therapies for these tumors and to determine when radical surgery and/or radiation therapy are warranted. Further studies are also needed to define the relationship between treatment exposures and long-term outcomes, including fertility and

sexual function. There is a great need for interventions to support survivors who may have long-term anatomic and functional abnormalities.

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Figure 1.
Clinical presentation with a mass protruding from the vagina

Table 1
Clinical Characteristics, Treatment, and Outcome of 18 Pediatric Patients With Vaginal Tumors

Patient	Age at diagnosis (years)	Clinical symptoms	Histology	IRS group	Initial therapy	Surgery	Postsurgery therapy	Outcome
1	0.5	Vaginal bleeding	B-RMS	I	V,D,C	APE	V,D,C	Died of colon cancer 12 yrs
2	0.5	Vaginal bleeding	B-RMS	II	V,A,C,E	APE	V,C,D,I,E EBRT 46 Gy	NED 8 yrs
3	0.7	Vaginal mass	B-RMS	III	V,A,C	-	V,A,C	NED 4 yrs
4	2.8	Bloody discharge	B-RMS	II	V,A	-	V,A	NED 3 yrs
5	0.1	Vaginal bleeding	B-RMS	IV	V,A,C,I,E EBRT 12.8 Gy	H/V	V,A,C,I,E EBRT 27.1 Gy	NED 39 yrs
6	11.5	Vaginal mass	B-RMS	I	V,D,C	H/V	V,D,C	NED 37 yrs
7	0.5	Vaginal bleeding	B-RMS	I	V,A,C EBRT 25 Gy	H/V	V,A,C	NED 34 yrs
8	12.5	Vaginal mass	E-RMS	II	V,D,C	H/V	V,D,C EBRT 39.6 Gy	NED 28 yrs
9	4.2	Vaginal mass	B-RMS	II	H/V	-	V,A,C EBRT 47.1 Gy	DOD 0.7 yrs
10	0.6	Vaginal bleeding	E-RMS	II	V,D,C	H/V	V,D,C	NED 27 yrs
11	1.5	Vaginal bleeding	B-RMS	II	V,A,C,D	-	V,A,C,D BT 54Gy	NED 24 yrs
12	1.7	Bloody discharge	E-RMS	II	V,A,C,D	-	V,A,C,D BT 52.4 Gy	NED 24 yrs
13	2.5	Vaginal mass	B-RMS	II	Mass resection	-	V,A	NED 8 yrs
14	0.6	Vaginal bleeding	GCT-EST	-	CB,E,B	-	CB,E,B	NED 2 yrs
15	1	Bloody discharge	GCT-EC	-	V,A,C	Mass resection	V,A,C EBRT 44 Gy	DOD 3 yrs
16	1.2	Vaginal mass	GCT-EST	-	-	H/V	E,I EBRT 49Gy	DOD 2.8 yrs
17	13	Vaginal bleeding	CCA	-	Partial vaginectomy	-	CP, PT, CB EBRT 54 Gy	NED 10 yrs
18	7.4	Bloody discharge	CCA	-	V,D,C	H/V	V,D,C EBRT 50Gy	DOD 3.5 yrs

B-RMS: botryoid rhabdomyosarcoma, E-RMS: embryonal rhabdomyosarcoma, GCT-EST: germ cell tumor-endodermal sinus tumor, GCT-EC: germ cell tumor-embryonal carcinoma, CCA: clear cell adenocarcinoma, IRS: International Rhabdomyosarcoma Study, V: vincristine, A: actinomycin, C: cyclophosphamide, D: doxorubicin, I: ifosfamide, E: etoposide, CB: carboplatin, CP: cisplatin, PT: paclitaxel, B: bleomycin, APE: anterior pelvic exenteration, H/V: hysterectomy and vaginectomy, EBRT: external beam radiotherapy, BT: brachytherapy, NED: no evidence of disease, DOD: died of disease.