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Susanne E. M. Gruessner · Charles O. A. Omwandho
Thomas Dreyer · Renate Blütters-Sawatzki
Alfred Reiter · Hans R. Tinneberg · Rainer M. Bohle

Management of stage I cervical sarcoma botryoides in childhood and adolescence

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Abstract Rhabdomyosarcomas are the most common soft tissue sarcomas in childhood. The botryoid variant arises in infancy from the vagina or urinary bladder and extremely rarely from the uterine cervix. Treatment regimes range from local excision of the tumour to radical hysterectomy with adjuvant multidrug therapy and/or radiotherapy. In cases of minimal cervical invasion, the less invasive local excision in combination with adjuvant chemotherapy has resulted in excellent survival rates with complete functional preservation of the bladder, rectum, vagina, and ovaries. We present here a 30-year literature review and a case report of a cervical sarcoma botryoides in a 5-year-old girl. *Conclusion*: Based on the literature review and our own observation, we recommend minor surgical approaches in combination with chemotherapy as the treatment of choice for early stage I cervical rhabdomyosarcoma.

Keywords Cervix · Chemotherapy · Conservative surgery · Embryonal rhabdomyosarcoma · Sarcoma botryoides

S. E. M. Gruessner (✉) · H. R. Tinneberg
Department of Obstetrics and Gynaecology,
Justus-Liebig-University Giessen, Klinikstrasse 32,
35392 Giessen, Germany
E-mail: susanne.gruessner@gyn.med.uni-giessen.de
Tel.: +49-641-9945280
Fax: +49-641-9945289

C. O. A. Omwandho
Department of Biochemistry, University of Nairobi,
Nairobi, Kenya

T. Dreyer · R. M. Bohle
Institute of Pathology, Justus-Liebig-University,
Giessen, Germany

R. Blütters-Sawatzki · A. Reiter
Department of Paediatric Oncology,
Justus-Liebig-University, Giessen,
Germany

Abbreviations IRS: Intergroup Rhabdomyosarcoma Study Group · RMS: rhabdomyosarcoma · VAC: vincristine, adriamycin, cyclophosphamide · VAI: vincristine, adriamycin, ifosfamide

Introduction

In early childhood and young adolescence, embryonal rhabdomyosarcoma (RMS) is the most common neoplasm of the lower female genital tract, particularly of the vagina [2, 6, 15, 27,32]. It accounts for 4% to 6% of all malignancies in this age group. Cervical location of these malignancies is extremely rare (usually five times less common than in the vagina), its peak incidence being in the second decade of adolescence [17,20]. Of note, vaginal lesions have a better prognosis than cervical lesions with survival rates of 96% and 60% respectively [2, 4, 16,23]. Two paediatric study groups, the Intergroup Rhabdomyosarcoma Study Group (IRS) and the International Society of Pediatric Oncology have classified RMS into three major histologic subtypes: (1) embryonal, (2) alveolar, and (3) undifferentiated [20, 22,31]. The current IRS clinical classification is shown in Table 1. Sarcoma botryoides is a variant of embryonal RMS, usually demonstrating a submucosal lesion with a typical grape-like appearance [1, 17,20]. Microscopic pathology is characterised by a submucosal cellular zone of primitive rhabdomyoblasts. Early diagnosis is possible if irregular bleeding is the first symptom. Outcome depends on tumour size and extent at the time of presentation as well as on the histological subtype. Usually, if the tumour shows an alveolar pattern, the prognosis is poor [1, 6, 7, 10,30].

Since the 1987 report on 73 cases of cervical sarcoma botryoides [6], 20 more cases of cervical RMS stage I in patients aged ≤ 18 years have been published. We present here a 30-year literature review and our own observation of a cervical sarcoma botryoides in a 5-year-old girl.

Table 1 IRS clinical classification in groups

Group	Clinical findings
I	Localised disease, completely resected, no regional nodes involved
Ia	Confined to organ or muscle of origin
Ib	Infiltration outside organ or muscle of origin
II	Regional disease
IIa	Microscopic residual disease, no regional nodes involved
IIb	Regional disease, completely resected, nodes may be involved and/or extension of tumour into adjacent organ
IIc	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residues
III	Incomplete resection or biopsy with gross residual disease
IV	Distant metastases present at onset

Case report

A 5-year-old girl, initially treated with antibiotics by her paediatrician for foul vaginal discharge, was referred 8 weeks later to the Department of Gynaecology at the University of Giessen, Germany in December 1999. The patient had abnormal vaginal bleeding and a partially protruding polyp-like tumour in the vaginal introitus. Gynaecological speculum examination showed a large polypoid mass, measuring 5×3×1.5 cm, originating from the anterior cervical lip. Physical and gynaecological examination as well as sonography revealed no other uterine or adnexal abnormalities. A polypectomy was performed and the specimen was sent for pathological examination. By light microscopy (formalin fixed, paraffin-embedded and haematoxylin-eosin stained tissue sections), a mesenchymal tumour with a myxoid stroma (Fig. 1a) containing small cells with hyperchromatic nuclei and an enhanced tumour cell density beneath the vaginal-cervical epithelium producing a cambium layer was detected. The tumour cells showed moderate polymorphism and immuno-histochemistry revealed positive staining for desmin (Fig. 1b) and vimentin with enhancement of the growth fraction (Ki67+). Keratin, CD34, CD68 and smooth muscle actin were not detected. Histopathological examination was consistent with botryoid embryonal RMS and the diagnosis was confirmed by Prof. Dr. D. Harms (Paediatric Tumour Registry, Department of Paidopathology, University of Kiel, Germany). Of note, microscopic examination showed that the tissue margins were still positive. For definitive surgical therapy, a small conisation of the cervix (1×0.9×0.8 cm), was performed 4 weeks after the initial polypectomy. In this specimen, histology and immuno-histochemistry showed no detectable tumour tissue. Final histopathological staging was consistent with group Ia embryonal RMS of the uterine cervix according to the IRS Clinical Grouping classification (Table 1). Subsequent abdominal sonography, chest X-ray film, CT scan of the abdomen and pelvis, skeletal scintigraphy, bone marrow biopsy, echocardiography, electro-encephalography and serological examination showed no evidence of tumour spread. Four days after surgery, adjuvant chemotherapy was started using the actinomycin-D, vincristine and ifosfamide regimen according to the CWS-protocol 96 (Kooperative Weichteil-Sarkom-Studie, Germany). Myelotoxicity (WHO grade 3), alopecia (grade 3), vomiting (grade 3) mucositis (grade 1) were the most conspicuous side-effects. Three months after conisation, local excision of three visible, 3 mm diameter large, polypoid structures

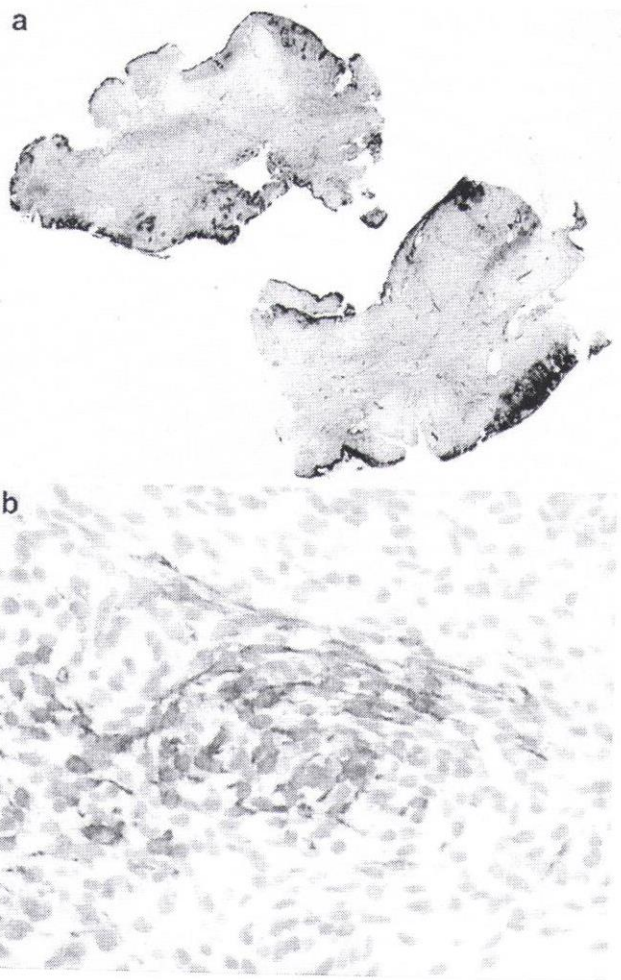

Fig. 1 **a** Low-power view of the polypoid mass originating from the cervix (H&E; scale bar 0.5 cm). **b** Cytoplasmic desmin immunoreactivity of rhabdomyosarcoma tumour cells (APAAP, original magnification ×40)

Table 2 Cervical sarcoma botryoides (patients age ≤ 18 years). Cases reported from 1988 to 2003. (*A and NR* alive and no recurrence, *ACD* actinomycin-D, *CPM* cyclophosphamide, *D and C* dilatation and curettage, *PND* pelvic node dissection, *TAH* total abdominal hysterectomy, *VCN* vincristine)

Reference/patients	Age (years)	Symptoms	IRS Group	Histology	Surgery	Radiotherapy	Chemotherapy	Delayed therapy (w/o relapse), therapy for relapse	Outcome
[10] 4 patients	<1	Genitourinary	I	RMS	Organ-preserving surgery	None	Chemotherapy (body weight) reduced by 33%–50%		A and NR, 76 months
[29] 1 patient	15	Protrusis vaginal mass	Ia	Embryonal botryoid	First: biopsy; second: polypectomy + uterine biopsy	None	Epidoxorubicin 75 mg/qm g l 2 l, 6 courses		A and NR, 60 months
[21] 7 patients	Median 15	Bleeding	I	Embryonal botryoid	Partial cervixectomy (n =3) + partial vaginectomy (n =1); biopsy (n =3)	External beam radiotherapy (n =3), after biopsy + chemotherapy (n =1), after vaginectomy + chemotherapy	After vaginectomy (n =1): ifosfamide, vincristine, -and actinomycin D, 2 courses (n =3), after biopsy: 2 courses: vincristine + actinomycin D		A and NR, 122 months
[13] 1 patient	14	Bleeding	Ib	Embryonal botryoid	TAH + PND	None		Sertoli-Leydig cell tumour; right oophorectomy	A and NR, 16 years
[5] 1 patient	12	Bleeding	Ia	Embryonal botryoid	TAH	None	Ante op: chemotherapy-VAC; post-op: chemotherapy-VAC		A and NR, 192 months
[14] 1 patient	18	Bleeding	I	Embryonal botryoid	Local excision	None	VCN (2 mg/day) on day 1, ACD (0.5 mg/day), days 1–5, CPM (8 mg/kg) days 1–5, three cycles	Cervical conisation (neg) (14 weeks) Chemotherapy-VAC, 9 cycles	A and NR, 31 months
[16] 5 patients	15	Not indicated	I	Embryonal botryoid	Polypectomy	None	VCN (2 mg/m^2) i.v. every week x 12, ACD (0.015 mg/kg/day) i.v. x 5 repeat x 4		A and NR, 78 months
	15	Not indicated	I	Embryonal botryoid	Radical hysterectomy + PND	None	VCN (2 mg/m^2) i.v. every week x 12, ACD (0.015 mg/kg/day) i.v. x 5 repeat x 4		A and NR, 72 months
	14	Not indicated	I	Embryonal botryoid	Polypectomy + D and C	None	VCN (2 mg/m^2) i.v. every week x 12, ACD (0.015 mg/kg/day) i.v. x 5 repeat x 4	Simple hysterectomy, oophoropexy, PND (4 weeks)	A and NR, 66 months
	14	Not indicated	I	Embryonal botryoid	Polypectomy D and C	None	VCN (2 mg/m^2) i.v. every week x 12, ACD (0.015 mg/kg/day) i.v. x 5 repeat x 4	No relapse	A and NR, 66 months
	14	Not indicated	I	Embryonal botryoid	Polypectomy D and C	None	Pulse VAC for 24 months	Hysteroscopy D & C (neg.) (16 and 44 weeks)	A and NR, 33 months

on the endocervical conisation bed was performed. Histologically, no recurrence of sarcoma botryoides was found. Abdominal ultrasound, chest X-ray film, skeletal scintigraphy, and gynaecological examination follow-up studies every 3 months (1st year) or 6 months (2nd and 3rd year) after the initial diagnosis revealed no local or distant evidence of tumour recurrence or spread. Punch biopsies of the anterior and posterior cervical lips taken 43 months after primary diagnosis were histologically and immunohistologically negative for botryoid rhabdomyosarcoma. Thus, the patient has remained tumour-free for 45 months after initial diagnosis and 39 months after completion of chemotherapy (Fig. 1a,b).

Discussion

As the results of pelvic exenteration as the treatment of choice for RMS in the 1960s were not satisfactory [7,18], combined treatment approaches were adopted in the 1970s. They included multidrug chemotherapy and/or radiotherapy with less invasive radical surgery [12, 19, 26]. Combined treatment options including radical hysterectomy continued to dominate much of the 1980s [13,16]; however, in the 1990s, there was a gradual shift towards less invasive and more organ-sparing procedures such as local excision, polypectomy, cervixectomy, or conisation, with or without adjunct chemotherapy [5, 14, 16,32]. Multimodal approaches have remarkably improved prognosis and decreased the need for radical surgery with its associated morbidity [1, 2, 4, 5, 11,31]. Consequently, the survival rate of children with RMS has improved dramatically from 25% before 1970 to over 65% in 1995 [8]. This is also attributed in part to early diagnosis and timely referral to specialised centres [24]. Also, a focus on bladder preservation has not adversely affected survival in most studies [3] and in cases where organ preservation is not possible, improvements in urinary diversion techniques still offer improved quality of life [1].

Although limited reports exist in the literature about the less invasive local excision, there is mounting evidence that combination of local excision with adjuvant chemotherapy give excellent outcomes with 2-year survival rates of $>96\%$ [4, 6,28]. The most common chemotherapy regimens use the combination of vincristine, actinomycin-D, and cyclophosphamide (VAC), or of vincristine, actinomycin-D and ifosfamide (VAI). These regimens are usually started preoperatively, particularly in patients with advanced tumour stages. The 5-year survival rates for patients in clinical groups I-IV were 83%, 70%, 52% and 25% respectively [9, 11, 22] and according to the IRS (Study-I), additional post-operative radiation therapy showed no further benefit in patients with stage Ia tumours.

Our current literature review (Table 2) also shows that in order to retain fertility, organ-preserving surgical procedures like polypectomy, cervixectomy, conisation, and local excision were undertaken in 13 of 20 cases [10, 14, 16, 21, 29]: all patients have remained tumour-free 31 to 122 months after the initial therapy. Similarly, our patient with stage Ia disease initially underwent local excision of the polyp followed later by conisation of the cervix uteri. After histological confirmation of residual tumour absence, polychemotherapy using the VAI regimen was initiated based on a multicentre study (CWS-96 protocol–Germany). The patient remains stable and without evidence of tumour recurrence 45 months after the initial diagnosis and 39 months after completion of chemotherapy.

Given that these cases involve young children and adolescents, functional preservation of the bladder and the reproductive organs is imperative [1, 29,31] to preserve long-term quality of life [25]. With less invasive surgical procedures being the therapy of choice for stage I tumours, the main post-surgical concern now is the adverse effects of chemo- and radiotherapy administered to these children. Although acute side-effects of cytotoxic chemotherapy (e.g. bone marrow suppression) can be managed effectively [24], certain risks remain. Exposure to anthracycline may lead to cardiac toxicity [10] and result in congestive cardiac failure. The IRS studies deal mainly with the VAC-chemotherapy regimens and eight deaths due to infection have been reported in genitourinary RMS [20, 21]. For this reason, cyclophosphamide, a chemotherapeutic agent with cardiotoxic side-effects, is often eliminated in those patients with favourable prognostic tumours [9, 20]. Ifosfamide, being an alkylating agent, can potentially cause a primary malignancy if radiotherapy [10, 25] is concurrently administered and has also been associated with renal tubular acidosis, chronic urinary electrolyte loss, and renal rickets with osteoporosis. Also, radiotherapy, when administered at a young age, may lead to primary tumour development and may result in substantial long-term soft tissue and vascular hypoplasia [24]. Nevertheless, these potential side-effects of multimodal therapy must be seen in the context of less invasive surgical therapy with its overall very low associated morbidity and good long-term outcome.

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