Hematometrocolpos in an Adolescent Female Treated for Pelvic Ewing Sarcoma

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Radiation therapy is often used to achieve local control of pelvic Ewing sarcoma in children. The effects of radiation on the female reproductive tract have been well documented in adults with gynecological malignancies, but the long-term consequences of pelvic radiation in prepubertal or adolescent girls are not as well described. We report a case of hematometrocolpos developing in an adolescent previously treated with chemotherapy and radiation therapy for pelvic Ewing sarcoma. We describe the clinical presentation, radiographic features, gross pathology, treatment strategies, outcome, as well as putative predisposing factors and preventative interventions. Pediatr Blood Cancer 2008;50:157–160.

Key words: Ewing sarcoma; hematometrocolpos; late effects of cancer therapy

INTRODUCTION

In children and adolescents with pelvic cancers like Ewing sarcoma, external beam radiotherapy is often used in an effort to avoid the morbidity of ablative surgical interventions like pelvic exenteration or hemipelvectomy. Although significant long-term effects have been well described following the application of external beam and intracavitary radiation for the management of adult gynecologic malignancies [1–6], little has been reported regarding the effects of pelvic radiation and intensive chemotherapy in prepubertal or adolescent females.

To highlight the potential significance of reproductive tract toxicity, we describe a case of hematometrocolpos, which is usually diagnosed in adolescents with primary amenorrhea due to imperforate hymen or other vaginal outlet obstruction [7]. In the present case, it developed in an adolescent following therapy for Ewing sarcoma of the pelvis. We discuss several aspects of her treatment that may have contributed to this complication and we present potential preventative and therapeutic interventions that might be considered in similar patients.

CASE PRESENTATION

At the age of 12 years the patient was diagnosed with non-metastatic Ewing sarcoma. CT scan of the abdomen and pelvis demonstrated an aggressive process, involving the left acetabulum and superior pubic ramus with an associated soft tissue component (Fig. 1A). The patient received 48 weeks of chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide according to the guidelines of the Pediatric Oncology Group study 9354. A prescribed radiation dose of 55.8 Gy was delivered to the left ischium and pelvis (Fig. 1B) from weeks 12 to 19 of therapy using conformal techniques. We subsequently verified chemotherapy and radiation dosing to have been correct.

Treatment was complicated by several episodes of fever and neutropenia and complaints of dysuria with an erythematous labial mucosa evident before beginning radiation therapy. Urine analysis and culture revealed minimal pyuria and hematuria without bacterial pathogens. Significant vaginal discharge was not observed and vaginal culture was not performed. During radiation therapy perineal and intralabial skin desquamation was observed becoming grade III (CTC 2.0) at 32.4 Gy, concurrent with an absolute neutrophil count of zero. The skin reaction improved to grade II following a 1-week treatment break and remained so through the completion of radiation. Management included topical creams and anesthetics. Over the next 4 months, vaginal pain recurred with chemotherapy-induced neutropenia.

Throughout therapy, menstrual bleeding was suppressed using intranasal nafarelin acetate (~11.5 month duration) because oral contraceptives were not tolerated. When amenorrhea persisted for 13 months after therapy, gynecological evaluation was sought. Serum FSH levels were elevated (71 mIU/ml). The patient was diagnosed with ovarian failure and treated with ethinyl estradiol and norethindrone, which induced regular menstrual bleeding. Approximately 6 months after beginning hormone supplements, she presented to a local emergency room with severe, left lower quadrant pain associated with perineal pressure. Similar pain had occurred over the past 2 months starting approximately 10 days prior to the onset of her menses. Evaluation was negative so she was treated with ketorolac and encouraged to follow up in our oncology clinic should symptoms recur. After transient relief with analgesics, the lower abdominal pain recurred. When the patient presented to our clinic 2 days later, she was unable to stand erect and found it difficult to lie supine. A pelvic ultrasound performed to rule out an ovarian cyst showed a vaginal diameter about twice that of the uterine diameter and debris within the vagina and to a lesser extent within the uterus (Fig. 2A), consistent with the diagnosis of hematometrocolpos. Retrospective review of pelvic MRI scan obtained 3 months prior to presentation of hematometrocolpos showed similar findings (Fig. 2B, top).

Suspecting a partial or complete vaginal obstruction, she underwent evaluation under anesthesia (EUA) which demonstrated

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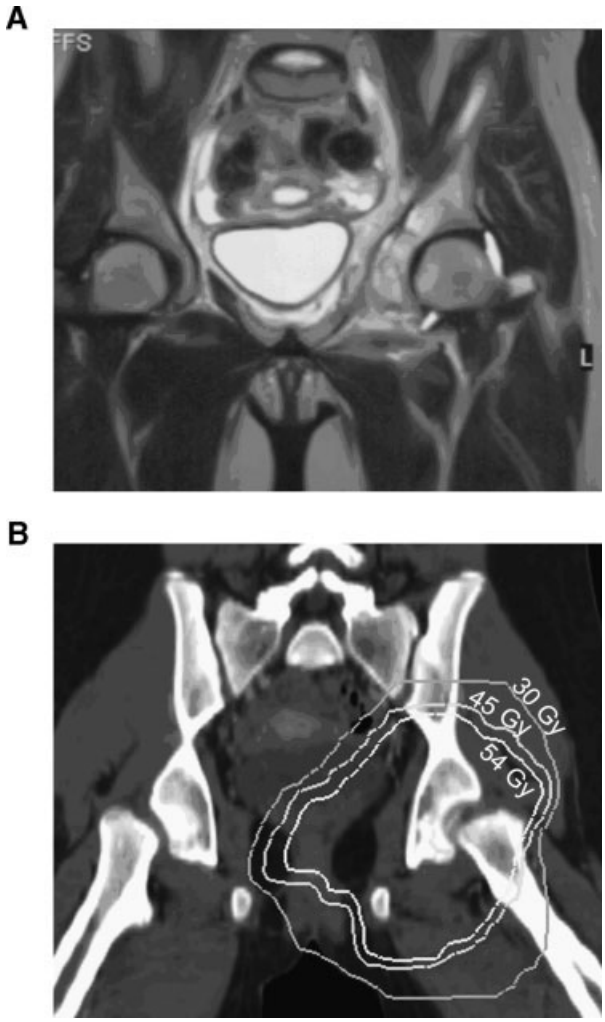

Fig. 1. Representative radiographs at diagnosis and treatment planning. **A**: Abnormalities of the left acetabulum and a soft tissue mass are seen on coronal T2 MR obtained at diagnosis. **B**: Isodose lines of 30, 45, and 54 Gy depict planned radiation dose on coronal CT obtained prior to radiation.

circumferential vaginal narrowing and obstruction. She was taken to the operating room where vaginal adhesions were lysed. Several months later, she again presented with similar complaints. MRI of the pelvis showed re-accumulation of the hematometrocolpos (Fig. 2B, bottom). At this time, EUA demonstrated a normal distal vagina, marked fibrous scarring in the mid-vagina, and a fibrous sheet obstructing the upper vagina. The upper vagina was distended with blood and the cervix was not visible; adhesions were again lysed. She was re-examined 10 days post-operatively and proceeded to undergo monthly vaginal dilation. Beginning with the second dilation, a NuvaRing was placed for local hormone delivery. Despite daily application of intravaginal estrogen cream with the ring in place, she had some additional vaginal agglutination. Over approximately 6 months, vaginal scarring gradually improved and the cervix could be visualized on exam. She has resumed regular menses, which are light, and the ring is being replaced monthly.

DISCUSSION

Blood-filled dilation of the vagina (hematocolpos) or the vagina and uterus (hematometrocolpos) generally occurs in pubertal girls with primary amenorrhea due to an imperforate hymen or other cause of vaginal obstruction (reviewed in [7]). It has rarely been reported in childhood cancer survivors. This case highlights several aspects of disease pathogenesis, factors contributing to delayed diagnosis, and potential preventive strategies that might be considered in children and adolescents who survive treatment for pelvic cancers.

Most of the relevant literature addressing vaginal complications of cancer treatment relates to women treated for cervical or endometrial malignancies. One quarter to one half of women treated with external beam or intracavitary ionizing radiation for cervical or endometrial cancer had subsequent problems including vaginal stenosis, narrowing, or shortening; vaginal adhesions; mucosal atrophy and dryness; or sexual dysfunction [1–6]. Very few data are available in children treated with chemotherapy and radiation for primary tumors of the pelvis. In a 1993 report, Kaste et al. [8] reported the occurrence of vaginal occlusion in two post-pubertal children treated with intensive chemotherapy and radiation for pelvic rhabdomyosarcoma and Ewing sarcoma. A more recent retrospective analysis of late effects in 26 female patients treated for pelvic rhabdomyosarcoma at St. Jude Children's Research Hospital showed that endocrine (77%), gastrointestinal (69%), musculoskeletal (69%), and renal (54%) late effects were common [9]. In this series, 58% of patients developed gynecologic late effects. Moderate to severe vaginal stenosis requiring dilation or surgical correction was observed in 7 of the 26 patients. Because adult women report finding it difficult to approach physicians about these issues [5] and pediatricians often hesitate to ask about adolescent sexuality [10], the true incidence of gynecologic complications in pediatric patients treated for pelvic tumors may be even higher.

Although the pathogenesis of vaginal stenosis/adhesions following cancer therapy is not clear, radiation likely plays a role. Acute vulval and vaginal erythema, desquamation, and ulceration occur following ionizing radiation. Subsequently, tissue atrophy, loss of sweat and sebaceous glands, and firm induration and fibrosis can occur. In adult patients with gynecological malignancy, combined intracavitary and external beam irradiation are given at a high dose rate (Gy/hr) and yield vaginal surface doses in excess of 100 Gy—much higher than that received by the patient in this report. Other factors may compound the effects of radiation. For example, hematometrocolpos was reported in a bone marrow transplant patient treated with only 10.5 Gy of total body irradiation [11]. In this case, inflammation from chronic graft versus host disease was thought to contribute. In principle, effects of cytotoxic chemotherapy on the vulval or vaginal mucosa may be similar to those of ionizing radiation and chemotherapy can potentiate the effects of prior radiation on vaginal mucosa [12]. This could have played an important role in the presented case in which perineal symptoms episodically worsened with chemotherapy following radiation therapy.

Because vaginal mucosal integrity depends on estrogen, we considered whether a prolonged low-estrogen state—initially induced by a gonadotropin releasing hormone agonist for menses suppression and later by ovarian failure—contributed to the late effects. Estrogen deficiency is certainly not requisite for hematometrocolpos after cancer therapy: two previous cases occurred in adolescents taking exogenous estrogen [8]. Prolonged nafarelin

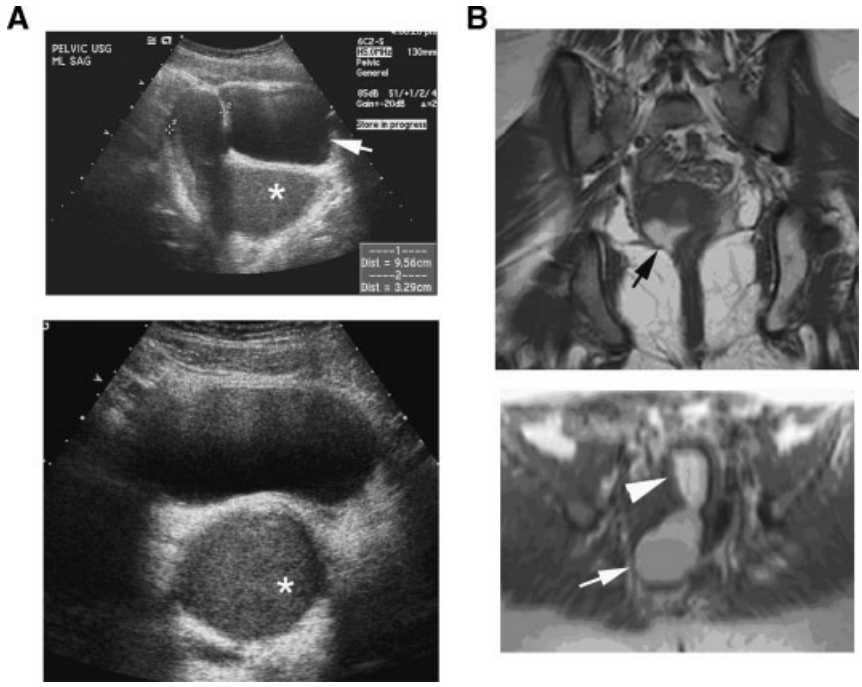

Fig. 2. Radiographs document hematometrocolpos in the reported patient. **A**: Hematometrocolpos (*) posterior to the bladder (arrow, top) is evident in sagittal (top) and axial (bottom) images from pelvic ultrasound. **B**: Coronal T1 weighted MR (top) obtained 3 months prior to sonogram (A) shows a collection of blood, (arrow), in the vagina as asymptomatic hematocolpos. Coronal oblique T1 weighted MR obtained approximately 6 months after the sonogram (A) demonstrates blood in the uterus (arrowhead) and vagina (arrow).

acetate has been used in children with gonadotropin-dependent precocious puberty [13] and in women with endometriosis (reviewed in reference [14]) without significant vaginal complications. Similarly, central suppression of menses using leuprolide acetate was reported to be safe and effective in post-menarcheal women undergoing bone marrow transplant [15].

Because so little is known about the frequency or severity of this complication in children, optimal preventative or therapeutic strategies for reproductive tract toxicity are not well defined. Prior to initiating hormone replacement in adolescents with ovarian failure secondary to pelvic radiation, a gynecologic evaluation is imperative to evaluate for potential outlet obstruction. In adults with gynecological cancer, serial vaginal dilation and topical estrogen to the vagina is recommended to promote healing following radiation; low-dose systemic estrogen alone is likely not sufficient (reviewed in reference [12]). Compliance with this type of program in adults was significantly improved by a psychoeducational program focused on providing adequate information, enhancing motivation for participation, and teaching behavioral skills for proper use of vaginal dilators and lubricants [16]. However, whether these interventions influence ultimate reproductive tract health and sexual function is not established. Although the psychological and anatomic development of pediatric patients must be considered, similar prevention and treatment strategies might be applicable to children and adolescents as well.

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Outcome of Retinoblastoma in East Africa

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We estimated the proportion of patients reaching a pediatric ophthalmology unit (Comprehensive Community Based Rehabilitation for Tanzania Disability Hospital, CCBRT) or an oncology unit (ORCI) in east Africa and investigated presentation, histology, and treatment outcomes of patients with retinoblastoma. A 5-year retrospective study identified 91 patients, representing approximately 18% of the nationwide total. Mean lag time was 10 months (standard deviation (SD) = 17) and mean follow-up was 8 months (SD = 11, range 0–40, n = 91). Thirty months disease-free survival probability was 0.23 (standard error = 0.07). Outcomes for retinoblastoma in Africa remain poor. The data presented here suggest strategies for improving the outcomes, including encouraging earlier presentation and establishment of multi-disciplinary treatment centers. Pediatr Blood Cancer 2008;50:160–162. © 2006 Wiley-Liss, Inc.

Key words: Africa; outcome; presentation; retinoblastoma

INTRODUCTION

The annual incidence of retinoblastoma in Africa exceeds that of Western countries [1] probably due to poorly understood environmental factors [1,2]. Incidence estimates from Africa include 20 cases per million children under 5 in Malawi [3], 9.3 per million (age standardized) in Guinea Conakry) [4], and recent evidence from Zambia suggests incidence is increasing for unknown reasons [5]. The US incidence is reported to be 3.8 cases per million [6]. In addition, high birth rates in Africa and poorer access to health services create challenges for patients with cancer. In affluent countries, treatment has advanced considerably in recent years [7], but there are few data from Africa.

Dar es Salaam, the commercial capital of Tanzania has a high volume pediatric ophthalmology center (Comprehensive Community Based Rehabilitation for Tanzania Disability Hospital, CCBRT) with regular community outreach and liaison with community health workers and organizations to facilitate early referral. It also has an oncology center where chemotherapy and external beam radiotherapy are available (Ocean Road Cancer Institute, ORCI). Both are tertiary centers which are internationally subsidized and receive referrals from across the country, which has a population of 35 million. If there were a trend toward improved outcome in Africa, it might be expected to be detectable early in a city such as Dar es Salaam. This study investigated the number of patients with retinoblastoma, their clinical presentation, histology, and treatment outcomes.

METHODS

A retrospective study was conducted using computerized and paper records to identify all children treated for retinoblastoma at two units in Dar es Salaam between 1999 and 2004. Incidence values from Malawi [3] and Tanzanian census data [8] were used to estimate the annual incidence of retinoblastoma in Tanzania. Demographic details, clinical and histological features, management and, where possible, outcome of treatment were recorded and analyzed using SPSS for windows. Histological specimens from CCBRT are analyzed and reported at the Institute of Ophthalmology in London. Staging categories were according to established criteria (Table I) but, in some cases, distinction between intra-ocular and orbital disease was made clinically in the absence of histopathology results. Reese-Ellsworth (R-E) classification for intra-ocular disease was used for second eyes undergoing eye laser or cryotherapy. At both centers, staging was mainly clinical and investigations such as imaging, bone marrow, and cerebrospinal fluid analysis were not performed routinely. The radiotherapy regimen for retinoblastoma was: 4,500 r Eq given as 3,000 rad. in 10 fractions over 2 weeks and calculated to mid socket, and to include optic nerve and chiasm routinely. This was followed by a similar dose to the ispilateral preauricular nodes. Therapy was given within a 4 week post-operative window whenever possible. Because of frequent late or absent histopathology, post-operative adjuvant radiotherapy was given whenever there is clinical or histological suspicion of extra-ocular disease. Chemotherapy was not part of the routine regimen but given on a palliative basis in cases of advanced recurrent disease. Patients were asked to return for follow-up every 3–4 months. Loss to

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