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Irreversible Primary Amenorrhea Secondary to Uterine Damage and Premature Ovarian Failure in 2 Patients with Ewing Sarcoma

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Abstract

Background: The long-term morbidity of childhood cancer survivors is an emerging field as more patients are now expected to live through adulthood.

Case: We describe 2 adolescent patients with permanent premature ovarian failure and failure of endometrium to respond to estrogen after they received a combination of chemotherapy and pelvic radiation for metastatic Ewing sarcoma. Both girls were prepubertal at diagnosis of Ewing sarcoma. Puberty was induced with high-dose estrogen and progesterone; however, none of the patients had withdrawal bleeding.

Summary and Conclusion: It is critical to counsel these patients that menstruation might not be possible even with hormone replacement therapy.

Keywords

Ewing sarcoma; Radiation therapy; Amenorrhea

Introduction

Current advances in multimodal cancer therapies have resulted in markedly improved cure and survival rates. Thus, there is an increasing need for studies that focus on the long-term morbidity of cancer survivors in adult life. It is well known that female cancer patients with a history of pelvic, abdominal, or total body irradiation, have a substantial risk for reproductive problems, including premature ovarian failure and damage to the uterus.^{1–3} Although there is extensive literature on the post-radiation ovarian function of cancer survivors, data on the resultant uterine damage have not been described fully in this patient

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population. Studies have shown that despite physiologic sex hormone replacement, the uterine volume is still reduced at an estimated 40% of the average adult size.³

We describe 2 adolescent patients with permanent premature ovarian failure and failure of the endometrium to respond to estrogen after they received a combination of chemotherapy and pelvic radiation for metastatic Ewing sarcoma. As her treating endocrinologists, we were ill-prepared to counsel the patients on the likelihood that they would not experience withdrawal bleeding. In addition, similar cases have not been reported in the literature.

Cases

Demographic Characteristics and Initial Presentation

Patient 1 was 7 years old when she was diagnosed with Ewing sarcoma of the left sacrum after she had presented with persistent back and upper leg pain for several months. She was found to have bilateral lung metastases on diagnosis. Patient 2 was 10 years old when she was diagnosed with Ewing sarcoma of the right ilium after she had presented with progressive leg pain and weight loss. Her disease course was complicated by lung and multiple bone metastases despite intensive treatment.

Treatment History

Patient 1 initially received vincristine, ifosfamide, doxorubicin, etoposide, and actinomycin (protocol AEWS-0331, with doses of ifosfamide of 102 g/m², total dose of doxorubicin of 360 mg/m², and total dose for etoposide 2700 mg/m²). Subsequently she was treated with radiation of the sacrum for 6 weeks at for a total dose of 5580 cGy, followed by whole-lung radiation for a total of 1500 cGy. She achieved longstanding remission and is cancer-free 11 years after her initial presentation.

Patient 2 was initially treated with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (Children's Oncology Group protocol AEWS-0031 regimen B with doses of doxorubicin of 75 mg/m², and cyclophosphamide 1.2 g/m² alternating with ifosfamide 9 g/m² and etoposide 500 mg/m² for 14 cycles) followed by radiation to the site of the primary tumor at 5400 cGy with an additional dose of 6760 cGy. She required a total of 6 additional cycles of chemotherapy for multiple metastases and eventually died 8 years after her diagnosis, while receiving palliative care.

Diagnosis of Ovarian Failure and Treatment

Both patients were referred to endocrinology for concerns of delayed puberty and primary amenorrhea at the ages of 13.5 and 15 years, respectively. Laboratory evaluation revealed elevated follicle-stimulating hormone levels with low estradiol levels, consistent with a diagnosis of primary ovarian failure. Both patients were treated with slowly increasing doses of transdermal estrogen to induce puberty and subsequent additional use of progesterone. Patient 1 was treated with oral estradiol (Estrace; Allergan) 0.5 mg every other day with gradual increase of the dose to 1.5 mg daily and subsequent additional use of progesterone (medroxyprogesterone 10 mg for days 1-10). Although puberty progressed normally and she eventually developed Tanner 5 breast and pubic hair, she never experienced withdrawal

bleeding. Ultrasound of the pelvis showed an infantile uterus (3.3 cm × 1.1 cm × 1.8 cm), with absence of endometrial stripe. She was switched to oral contraceptive tablets (JUNEL Fe 1 mg/20 µg; Teva Pharmaceuticals), which she continues to take at the age of 18 years without ever achieving menarche.

Patient 2 started using an estradiol patch 50 µg uptitrating to the full replacement dose of 100 µg. Progesterone pills were eventually used in addition (medroxyprogesterone 10 mg for days 1-10), however she never experienced withdrawal bleeding. At her last endocrine visit at the age of 16 years and 4 months, her puberty status had progressed to Tanner 3 for breast tissue and Tanner 2 for pubic hair. A pelvic ultrasound revealed an infantile uterus (2.7 cm × 1.1 cm × 1.6 cm with uterine volume of 2.2 mL) without endometrial stripe despite estrogen and progesterone treatment. She still did not reach menarche despite increasing the estrogen dose to 50 µg of oral ethinyl estradiol combined with progestin.

A summary of patient characteristics, laboratory values, and disease course is shown in Table 1.

Summary and Conclusion

In this report, we describe 2 adolescent patients with a history of pelvic radiation and chemotherapy for metastatic Ewing sarcoma who presented with primary amenorrhea. Both girls developed secondary sexual characteristics in response to exogenous estrogen and progesterone, however, endometrial stripe did not form secondary to uterine radiation. Both patients showed evidence of puberty progression, however none had withdrawal bleeding. Although patient 1 progressed through puberty and reached full maturation (Tanner 5 breast and pubic hair), patient 2 failed to progress beyond Tanner stage 3. Although it is difficult to predict progression through puberty, the disease burden of patient 2, complicated by multiple metastases and additional chemotherapy cycles, likely contributed to the failure to progress through puberty stages.

As in every patient with amenorrhea, it is critical for the treating physician to consider the clinical and psychological implications of amenorrhea. Hypoestrogenic status has a negative effect on various organ systems, including bone, cardiovascular, reproductive, and mental health. Patients might be at risk for decreased bone mass density, which might predispose them to fractures. Endothelial dysfunction and abnormal lipid profiles is a known complication of hypoestrogenism.⁴ Finally, failure to achieve menstruation is often emotionally difficult for patients to experience. Ideally, pretreatment counseling should include a detailed discussion about the clinical implications of hypoestrogenism and amenorrhea. Treating providers should be well prepared to counsel patients on the likelihood that they might not experience withdrawal bleeding despite hormonal therapy.

Another important consideration when assessing an amenorrheic patient with a history of pelvic radiation is the possibility of radiation-induced vaginal stenosis. This is defined as the formation of fibrosis leading to abnormal vaginal shortening and represents a commonly observed side effect of pelvic radiation.⁵ Vaginal stenosis might lead to hematometra or hematocolpos as a result of the failure to achieve withdrawal bleeding. Furthermore, these

patients often experience dyspareunia and sexual dysfunction leading to a significant negative effect on their psychosexual and emotional well-being. Every effort should be made to minimize the radiation burden on the pelvic organ-s—ovaries, uterus, and vagina—in close communication with the treating radiation oncologist.

It is well established that cancer treatment in childhood can result in primary gonadal injury, particularly if the patient was treated with a combination of an alkylating agent and abdominal radiation therapy.^{1,6} Contrary to the ovarian damage after pelvic radiation, the effect of radiation to the uterus is not as extensively studied. The risk of uterine damage is mainly associated with the total irradiation dose and the age of the patient at the time of the radiotherapy. Doses between 14 and 30 Gy are more likely to result in uterine dysfunction.^{7,8} Interestingly, although the prepubertal ovary is thought to be less affected by radiation because of the larger number of primordial follicles,^{1,2} limited evidence suggests that the prepubertal uterus seems to be more vulnerable to the toxic effects of radiation.^{8,9}

In searching the pediatric literature for case reports of patients who failed to achieve menarche despite estrogen and progesterone supplementation, the existing data are limited. Larsen et al⁹ described 3 patients who failed to achieve menarche after they had received high-dose pelvic or abdominal radiation (30-54 Gy). Despite uterine stimulation with high-dose estrogen (150 µg/d for 3 cycles), no improvement was noted in uterine size, blood flow, or endometrial thickness. Compared with this study, our patients were older at the time of diagnosis (8-10 years old vs 1.3-8.2 years old) and the radiation dose was significantly less (5.5-12 Gy vs 30-54 Gy). Our patients, as in the study by Larsen et al, were also treated with high-dose estrogen (100-150 µg/d for at least 3 cycles).

Critchley et al⁷ reported 3 women with premature ovarian failure and a history of whole abdominal irradiation in childhood, who were followed-up with serial ultrasound examinations after 1 cycle of exogenous sex steroid replacement; no increase in endometrial thickness was noted, suggesting likely irreversible uterine damage. In this study, the patients underwent only 1 cycle of estrogen therapy compared with our patients, who were treated for at least 3 cycles of estrogens.

Taking these data together, it seems that although physiological sex steroid replacement has the potential to improve uterine characteristics in some patients, there is a subgroup of radiation-treated patients in whom the uterine damage is irreversible. The reproductive outcome of such treatments along with the clinical implications of amenorrhea should be considered and discussed with the families in advance, to avoid unrealistic expectations. Strategies for fertility preservation should be implemented when possible. The menstrual cycle is often viewed as a “vital sign”¹⁰ in women and it is associated with being “normal.” It is therefore crucial for the treating physicians to assess the psychological effect of not being able to achieve menstruation despite hormonal therapy and counsel their patients regarding this possibility.

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Table 1

Summary of Patient Characteristics, Laboratory Values, and Disease Course

Characteristic	Patient 1	Patient 2
Age at diagnosis, years	7	10
Primary site	Left sacrum	Right ileum
Metastases	Lungs	Multiple bone sites and lungs
Pelvic radiation	5580 cGy	5400 cGy + 6760 cGy boost
FSH	78.8 U/L	164 U/L
LH	25.8 U/L	37.9 U/L
Estradiol	<20 pg/mL	<20 pg/mL
Puberty progression after sex hormone replacement	Adequate—full maturation of secondary sex characteristics	Did not reach full maturation
Menarche	No	No

FSH, follicle-stimulating hormone; LH, luteinizing hormone.