Ewing sarcoma of the 9th rib subsequent to pediatric leukemia: a case series

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Abstract

Ewing sarcoma is an aggressive malignancy of bone and soft tissue that accounts for approximately 2% of cases of childhood cancer. It has been rarely reported as a secondary neoplasm. Data from the Childhood Cancer Survivor Study has evaluated secondary sarcomas in 5-year survivors of childhood cancer. We report two pediatric patients in northeast Pennsylvania, who developed secondary Ewing Sarcoma of the 9th rib within 5 years of primary childhood leukemia diagnoses.

Introduction

Ewing sarcoma (EWS) is a high-grade sarcoma described as a small round cell tumor of bone and soft tissue.[1,2] EWS is an aggressive malignancy that accounts for approximately 2% of cases of childhood cancer, most commonly occurring in adolescent and young adult patients. The metastatic pattern is typically hematogenous, with lung, bone, and bone marrow being the most common sites of metastasis. Ewing sarcoma family of tumors (ESFT) have been rarely reported as a secondary malignant neoplasm after treatment of childhood cancer. Friedman et al studied subsequent neoplasms via the Childhood Cancer Survivor Study (CCSS) data and found that secondary neoplasms occur more frequently among females, patients older at time of cancer diagnosis, and those treated with radiation therapy.[3] With increasing awareness of adverse long-term sequalae in survivors of childhood cancer, the most feared complications include subsequent malignant neoplasms.[4] We describe two pediatric cases of secondary EWS of the 9^{th} rib that presented following surveillance visits for diagnoses of primary precursor B-acute lymphoblastic leukemia (pre B-ALL) and acute myeloid leukemia (AML) within northeast Pennsylvania. Further investigation regarding these cases of secondary EWS is warranted to identify potential risk factors and emphasize the importance of surveillance cancer screening.

Case Descriptions

Patient 1 was a previously healthy 9-year-old female who presented to her pediatrician with a fever and right-sided neck mass. Laboratory evaluation revealed pancytopenia with a platelet count of 13,000/uL, white blood count of 4,000/uL, and hemoglobin of 6.0 g/dL. Computed tomography (CT) of the neck, chest, and abdomen revealed cervical lymphadenopathy, right greater than left, and hepatosplenomegaly. Subsequent bone marrow aspiration revealed lymphoblast morphology (92% blasts) and flow cytometry consistent with pre B-ALL. Cytogenics were notable for hyperdiploid karyotype with 56 chromosomes and trisomy 4, 10, and 17 positive. Central nervous system classification was negative. The patient underwent treatment for standard risk pre B-ALL per the Children's Oncology Group (COG) protocol AALL0932 and achieved complete remission. She received a cumulative of 75 mg/m^2 of anthracyclines. Almost 46 months

after completing chemotherapy, the patient presented with complaints of right-sided chest pain and dyspnea. Chest x-ray was unrevealing for acute pathology. Three weeks later, she developed increasing pain and swelling of her chest. CT chest revealed a large lesion involving the right chest wall. The lesion was biopsied, and pathology demonstrated a small round blue cell tumor consistent with EWS. Flow cytometry was notable for EWSRI (22q12) gene rearrangement. Positron emission tomography (PET) scan revealed localized EWS of the right 9^{th} rib with regional lymphadenopathy (Fig. 1). The patient was treated via the COG protocol AEWS0031 (regimen B_2) with proton radiation (5580 cGy) to achieve remission; lifetime anthracycline total was 450 mg/m^2. Fourteen months later, she endorsed right-sided chest and wrist pain. Surveillance PET/CT revealed findings of a new metabolically active tumor within a 7.3x8.2x7cm soft tissue mass in the central and posterior aspects of the right lung. Her previous lesions remained stable and there were no other areas of radiotracer uptake. Biopsy confirmed relapsed EWS positive for EWSR1 rearrangement. Bone marrow evaluation at time of relapse was negative. She underwent 7 cycles of individualized salvage therapy with temozolomide and irinotecan with progression of her right lung mass. She was subsequently enrolled in the pediatric MATCH (Molecular Analysis for Therapy Choice) trial (COG APEC1621) with no match identified. She had significant progression and underwent palliative radiation with 60% decrease in tumor size. She is currently undergoing further chemotherapy at time of writing this document.

Patient 2 was a previously healthy 14-year-old male who presented with 3 weeks of right lower rib pain associated with night sweats, fatigue, and flu-like symptoms. Laboratory evaluation revealed leukocytosis (29,220/uL), severe thrombocytopenia (34,000/uL), and anemia (11.1g/dL). CT scan of the abdomen and pelvis revealed splenomegaly and no bony lesions. Peripheral blood flow cytometry showed 58% blasts with myeloid phenotype concerning for acute myeloid leukemia (AML). Subsequent bone marrow aspiration exhibited myeloblast morphology (75% blasts) and flow cytometry consistent with AML, non-M3 subtype. Cytogenetics revealed karyotype 45,X,-Y (loss of Y chromosome) and t(8;21)(q22;q22), positive for the RUNX1T1/RUNX1 fusion protein. Central nervous system classification was negative. The patient underwent standard chemotherapy per the COG AAML1031 protocol and achieved complete remission. He received a cumulative of 492 mg/m^2 of anthracyclines. Five months after completing treatment, he developed back pain. X-ray of the thoracic spine was unremarkable, however the pain intermittently persisted. Three months later, he presented to the emergency room for worsening back pain radiating to the right upper quadrant. CT scan showed an expansile permeative lesion with periosteal reaction involving the right posterior 9^{th} rib. Biopsy revealed a small round blue cell tumor and flow cytometry suspicious for a non-hematolymphoid tumor consistent with EWS. PET/CT showed localized disease (Fig. 2). Bilateral bone marrow aspirates were negative for disease. The patient was started on treatment per the COG AEWS0031 protocol. He underwent wide surgical excision of a 4.7x3.0x2.0cm tumor with negative margins, but viable tumor on the pleural margin. He was subsequently treated with radiotherapy and consolidation chemotherapy. He completed treatment without evidence of disease on follow-up imaging.

Discussion

Herein we presented two pediatric patients with findings of secondary EWS of the rib within 5 years of treatment completion for primary leukemia. Literature has suggested that ESFT are rare as a secondary neoplasm.[2] According to the CCSS, incidence of EWS after ALL was 1/49 (2%) and AML was 2/49 (4%) in 5-year survivors. Childhood cancer survivors have a nine-fold increased risk of developing secondary sarcoma compared to rates of sarcoma in the general population.[4] Spunt et al found that 4 of their 6 secondary ESFT developed in the bone, most commonly the rib.[2] Risk factors for subsequent bone sarcomas include younger age at time of cancer diagnosis (<4 years), radiation therapy, and exposure to both anthracyclines and alkylating agents.[4, 5] Both patients in our series were older at time of diagnosis and did not receive radiation therapy. Patient 2 did receive >300 mg/m^2 cumulative anthracycline dosage during treatment of AML – a level that has been associated with increased risk of secondary sarcomas.[3]There were common environmental factors in this case series to consider. Two months prior to diagnosis, Patient 1 was at the 92nd percentile for body mass index (BMI); and patient 2 was at the 93rd percentile for BMI. Limited literature exists regarding obesity and the risk of developing a second malignant neoplasm; Moke et al found a significantly increased risk among patients who were obese both at the time of diagnosis and at the end of treatment.[6] Both patients

resided in Northeast Pennsylvania, where there is an abundance of hydraulic fracturing (or "fracking") wells that have been linked to the release of carcinogens.[7] Others have reported locally increased incidence of rare EWS.[8] Further investigation is warranted to evaluate environmental factors that may increase the risk of EWS. This case series emphasizes the importance of continued surveillance and regular cancer screening for childhood cancer survivors.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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Legend List

Figure 1: PET/CT for Patient 1 showing radiotracer uptake in the right 9^{th} rib consistent with active malignancy.

Figure 2: PET/CT of Patient 2 also showing radiotracer uptake with similar location to Patient 1.