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Osteochondromas After Radiation for Pediatric Malignancies: A Role for Expanded Counseling for Skeletal Side Effects

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Abstract

Background—A relationship has been reported between total body irradiation (TBI) and later development of osteochondromas in children who receive radiation therapy as conditioning before hematopoietic stem cell transplantation (HSCT). The goal of this study was to better characterize osteochondromas occurring in these children.

Methods—We identified all children (0 to 18 y) who received an allogeneic HSCT and TBI from 2000 to 2012 from a blood and marrow transplant (BMT) database. Thereafter, we identified those who developed osteochondromas through a chart review. In addition, we searched for diagnosis and operative codes from 1996 to 2012 in our pediatric orthopaedic clinical records, isolating osteochondroma patients with a history of radiation exposure.

Results—Four patients who underwent allogeneic HSCT and were later diagnosed with osteochondromas were identified from the BMT database (N=233 children); all 4 were among a group of 72 patients who received TBI. Three patients were identified from orthopaedic records. The cohort included 5 boys and 2 girls with acute lymphoblastic leukemia (N=5) or neuroblastoma (N=2), diagnosed at a median age of 2.0 years. Therapy for all patients included chemotherapy, radiation therapy (TBI, N=5; abdominal, N=2), and HSCT. A diagnosis of osteochondroma was made at a median age of 11.7 years (range, 5 to 16 y), on average 8.6 years after radiation therapy. Diagnosis was incidental in 2 patients and secondary to symptoms (pain or genu valgum) in 5. Locations of osteochondromas were the proximal tibia (N=3), distal tibia, distal femur, distal ulna, and the distal phalanx (N=1 each). Three patients underwent surgical resection.

Conclusions—Children may be more likely to develop osteochondromas after early exposure to radiation therapy, which may cause pain and require surgical resection. To the best of our knowledge, this is the first reported case of a radiation-induced osteochondroma causing lower extremity malalignment. Patients typically present to the pediatric orthopaedist's attention when symptomatic, but there may be an expanded role for counseling for potential for long-term skeletal effects in this group.

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Keywords

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Radiation therapy is frequently used in conditioning regimens before hematopoietic stem cell transplantation (HSCT), an important treatment modality for several childhood malignancies. Skeletal side effects of localized radiation therapy have been described, including growth retardation and formation of radiation-induced osteochondromas.^{1–3} Total body irradiation (TBI) has also been linked to the formation of osteochondromas, particularly in children who receive radiation therapy at a young age.^{4–8} The estimated incidence of osteochondromas in the general population is 1% to 3%,^{7,9,10} and this appears to be exceeded in children treated with radiation therapy. Prior observational studies have reported the estimated incidence of osteochondroma occurring in children who underwent HSCT to range from 6% to 24%.^{7,11–13}

Osteochondromas occurring in this population have primarily been described in the pediatric oncology literature, and there is not much evidence in the orthopaedic literature describing the incidence and behavior of osteochondromas in pediatric patients exposed to radiation. Our goal in this study was to better characterize osteochondromas occurring in children who received HSCTs and were exposed to radiation at an early age. In addition, we describe the first case, to the best of our knowledge, of radiation-induced osteochondromas resulting in lower extremity malalignment requiring surgical intervention. Expanding our knowledge about the behavior of these lesions can better inform counseling and long-term follow-up for children undergoing systemic treatment for childhood cancers.

METHODS

This was an Institutional Review Board–approved retrospective cohort study. We identified all children (0 to 18 y) who received allogeneic HSCTs and TBI from 2000 to 2012 from a blood and marrow transplant (BMT) database at our institution. We identified a group of 233 children who received an allogeneic HSCT, of whom 72 received TBI. We then searched these medical records using our Electronic Medical Record Search Engine (EMERSE) to identify patients who later developed osteochondromas.¹⁴ Other patients with a history of radiation therapy at other institutions presented to the orthopaedic clinics with osteochondromas. To identify these patients who presented through orthopaedic clinics, we searched the diagnosis and operative codes from 1996 to present for attending surgeons at our Pediatric Orthopaedic Surgery department to identify osteochondroma patients. Children with prior diagnosis of multiple hereditary exostoses were excluded. Within the identified group of children presenting to orthopaedic clinics with osteochondromas, we again used the EMERSE tool to review the medical records for those with a history of pediatric malignancies or radiation exposure.

Data collected from medical chart review included sex, cancer diagnosis, age at cancer diagnosis, age at HSCT, age at radiation exposure, age at osteochondroma diagnosis, and dose and site of radiation. Data were then analyzed to determine the mean age at diagnosis and radiation, as well as the latent time to osteochondroma development. We also recorded whether diagnosis of osteochondroma was incidental versus symptomatic, location of osteochondroma, and whether or not surgical intervention was required.

RESULTS

Four patients who underwent allogeneic HSCT at our institution and were later diagnosed with osteochondromas were identified from the BMT database (N=233 children). All four were among a group of 72 patients who had received TBI. Three additional patients were identified from orthopaedic records with osteochondroma by a diagnosis code search and with a history of previous childhood malignancy and radiation treatment at other institutions. The cohort included 5 boys and 2 girls with a diagnosis of acute lymphoblastic leukemia (N=5) or neuroblastoma (N=2), which was diagnosed at a median age of 2.0 years (range, 3 wk to 4 y). Patient characteristics are summarized in Table 1. Therapy for all patients included chemotherapy, radiation therapy (TBI, N=5 and abdominal, N=2), and HSCT. Radiation dose for those at our institution ranged from 450 cGy to 13.2 Gy. The most common regimen was a 12 Gy radiation given in 6 fractions over 3 days as conditioning therapy before HSCT. Chemotherapy regimens varied with cancer diagnosis, although all 7 children did receive cyclophosphamide before HSCT. Two children received growth hormone therapy after completion of their treatment.

The diagnosis of osteochondroma was made at a median age of 11.7 years (range, 5 to 16 y), with an average latent period of 8.6 years after undergoing radiation therapy. Diagnosis was incidental in 2 patients and because of symptoms in 5 patients. Presenting symptoms included pain with activity (N=4) and genu valgum (N=1). The incidental diagnoses were both made on bone age radiographs of the hands and wrists. Locations of the osteochondromas were the proximal tibia (N=3), distal tibia (N=1), distal femur (N=2), distal ulna (N=1), and the distal phalanx of finger (N=1). One child presented with multiple osteochondromas in bilateral distal femurs and proximal tibias, which resulted in genu valgum deformity (Fig. 1A). To date, 3 patients have undergone surgical resection of symptomatic osteochondromas, and 1 patient underwent left distal femur and proximal tibia hemiepiphysiodesis for genu valgum (Fig. 1B). In the child with genu valgum, the osteochondromas were not excised at the time of the hemiepiphysiodesis, as they were painless and not increasing in size. One additional patient had been planning resection at an outside hospital at the time of his last visit to the oncologist, but we do not have documentation of that surgical resection.

DISCUSSION

Osteochondroma is the most common benign bony tumor, with the majority presenting as solitary lesions in children and adolescents, usually in the metaphyseal region of long bones.^{9,10} Radiation-induced osteochondromas have previously been described after local high-dose irradiation in pediatric patients with solid tumors, possibly related to growth arrest and damage to the epiphysis.^{1,5,7} More recently, radiation-induced osteochondromas have also been reported in children undergoing TBI as conditioning before HSCT.^{4,11–13} The incidence of osteochondroma occurring in this group ranges from 6% to 24%^{4,6,11} and is more likely to occur in children under the age of 5 years who underwent radiation therapy.⁴ This has largely been described in the pediatric oncology literature rather than in the orthopaedic literature.^{4,12,13,15}

This study describes osteochondromas occurring in children who were treated with radiation therapy and were identified either through a BMT database or through orthopaedic clinical records. This data collection method does not allow for calculation of incidence, although true incidence is often difficult to determine, given that many osteochondromas are asymptomatic and therefore many are likely undiagnosed. In our group of patients, the average time to development of osteochondroma was 8.6 years from radiation exposure, slightly longer than the 6-year average latent period described by Harper et al.¹¹ For 2

patients, diagnosis was incidental on bone age radiographs of the hands and wrists. These lesions were small and may never have become symptomatic. Patients were followed by their endocrinologist with repeat radiographs and were not referred to orthopaedic surgery. Five children presented with symptoms, most commonly pain with activity, leading to radiographic diagnosis of osteochondroma. Osteochondromas identified in the patients in our study were solitary lesions in 6 of the 7 patients. One patient presented with multiple osteochondromas in bilateral distal femurs and proximal tibias causing genu valgum. He was treated with left distal femur and proximal tibia medial hemiepiphysiodesis and has done well, with improvement in lower extremity alignment allowing for subsequent removal of hardware. To the best of our knowledge, this is the first reported case of radiation-induced osteochondromas resulting in lower extremity malalignment requiring surgical intervention. Malignant change to chondrosarcoma is rare¹⁶ and was not observed in our group of patients.

Exposure to radiation at an early age has been shown to induce skeletal changes, including growth retardation and osteochondroma formation.^{1,4,6,17,18} One proposed mechanism is that exposure to radiation causes epiphyses to remain open longer, allowing more time for osteochondromas to develop and leading to disorganization in the growth plate.^{5,7} It has also been suggested that the pattern of multiple osteochondromas occurring after TBI resembles the hereditary form of the disease, that is, multiple hereditary exostoses, because of the multiple nature of lesions and their distribution. Multiple hereditary exostoses is caused by mutations in either of the 2 genes, exostosis-1 (*EXT1*) or exostosis-2 (*EXT2*). Reduction in functions of these genes results in defective endochondral ossification.⁹ Exposure to radiation may cause mutations in these genes leading to development of multiple exostoses in patients who have undergone TBI.¹¹ In the future, attempting to characterize the gene mutations in radiation-induced osteochondromas could be helpful. From the group presented here, no relationship was observed between the location of the radiated field and the location of osteochondromas.

The potential effect of chemotherapy regimens on development of osteochondromas is not known. In our group, chemotherapy regimens varied, although all children received cyclophosphamide, which has been shown to induce apoptosis in the proliferative zone of the growth plate in rabbit studies¹⁹ but has not been linked to osteochondroma in pediatric patients. Two patients in our group received growth hormone therapy; however, a previous study found that receiving growth hormone therapy did not influence the natural history of osteochondromas.¹¹

It is important to recognize that although osteochondromas are benign and frequently do not require resection if asymptomatic, discovery of a new tumor causes significant anxiety for this group of patients and their parents. These children typically present to the pediatric orthopaedist's attention when symptomatic, either with activity-related pain, a mass, or, as we describe here, lower extremity malalignment. Within the population of pediatric patients with malignancies, advances in therapeutic interventions leading to longer survivorship will increase the need for long-term oncologic follow-up and surveillance for secondary malignancies. Routine surveillance for osteochondromas is not typically recommended and likely would not be cost-effective. However, it may be wise to expand counseling for families and the discussion of long-term skeletal effects of radiation therapy to include possible development of osteochondromas, which may require surgical resection or realignment procedures in some cases. Continued maintenance of databases of patients who have received radiation treatment in childhood will allow for better estimation of the rates of osteochondromas in this group.

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FIGURE 1.

Patient 3, with a history of precursor B-cell acute lymphoblastic leukemia who underwent total body irradiation at the age of 4 years. A, Standing long-leg radiographs at the age 12 years showing left genu valgum deformity and osteochondromas about bilateral knees. B, Radiographs, 7 months after left distal femur and proximal tibia medial hemiepiphyodesis, showing partial correction of the left genu valgum deformity.

TABLE 1

Patient Characteristics

ID	Sex	Cancer Diagnosis	Age at				Cancer Diagnosis	Site of Irradiation	Radiation Dose	Location of Osteochondroma	Incidental vs. Symptomatic	Surgical Intervention Required for Osteochondroma
			Stem Cell Transplantation	Radiation Therapy	Osteochondroma Diagnosis							
1	M	7 wk	17mo	17mo	7 y	Precursor B-cell ALL	TBI, testicular boost	12 Gy	Left distal ulnar metaphysis	Incidental on bone age radiographs	No	
2	M	21mo	6 y	6 y	15 y	Precursor B-cell ALL	TBI, whole brain boost	12Gy (TBI), 6Gy (brain)	Left proximal tibia	Pain with activity, bony prominence	Considering	
3	M	4 y	4 y	4 y	12 y	Precursor B-cell ALL	TBI	12 Gy	Bilateral distal femurs, proximal tibia	Genu valgum	No	
4	F	2 y	31mo	31mo	6 y 7mo	Precursor T-cell ALL	TBI	13.2Gy	Left middle finger distal phalanx	Incidental on bone age radiographs	No	
5	F	22mo	2 y	2 y	12 y	Stage IV neuroblastoma	Abdominal	12 Gy	Right proximal tibia	Pain with activity	Yes	
6	M	4 y	6 y	6 y	16 y 9mo	T-cell ALL, CNS relapse	TBI, brain boost	12 Gy	Right distal tibia	Pain with activity	Yes	
7	M	3 wk	9mo	5mo	13 y	Neuroblastoma	Abdominal	450 cGy	Right distal femur	Pain with activity, bony prominence	Yes	

Patients 1 to 4 were identified from the Blood and Marrow Transplant Database, and patients 5 to 7 presented through pediatric orthopaedic clinics. ALL indicates acute lymphoblastic leukemia; CNS, central nervous system; F, female; M, male; TBI, total body irradiation.