Published in final edited form as:

J Pediatr Orthop. 2019 February ; 39(2): 104–110. doi:10.1097/BPO.0000000000000900.

Osteonecrosis of the Shoulders in Pediatric Patients Treated for Leukemia or Lymphoma: Single-Institutional Experience

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Abstract

BACKGROUND—Osteonecrosis of the hips and knees is an often debilitating adverse event in children treated with glucocorticoids for leukemia and lymphoma but the impact of shoulder involvement has been understudied. Thus, we investigated the severity and functional impairment of shoulder osteonecrosis in a well-characterized population of pediatric patients treated for acute lymphoblastic leukemia or lymphoma.

METHODS—We retrospectively reviewed orthopedic clinic and physical therapy evaluations to determine range of motion (ROM), pain, and impact of MR-defined osteonecrosis (ON) on activities of daily living (ADLs). Adverse events (AE) were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

RESULTS—We identified 35 patients (22 female), median age at cancer diagnosis 14.2 (range, 4.3 to 19) years; median age at osteonecrosis diagnosis 16.7 (range, 5.5 to 28) years. Median time to last follow-up from diagnosis of primary malignancy was 6.4 (range, 0 to 12.7) years and from diagnosis of osteonecrosis was 4.0 (range, 0 to 8.9) years. Twenty-two patients had MR-evidence of osteonecrosis; 43 shoulders involved at least 30% of the articular surface of the capital humeral epiphyses.

CTCAE mean scores for initial assessments of 55 shoulders (29 patients) showed moderate negative impact of ON on activity of daily living (1.94), decreased ROM limiting athletic activity (0.98), and mild to moderate levels of pain (1.38). Analysis of this group's most recent assessment

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All authors have fulfilled the criteria for authorship.

Level of evidence: Level IV, case series

showed improvement in pain and osteonecrosis over time, with an average pain grade of 0.58 indicating no pain to mild pain, and 1.37 for ON grade, indicating asymptomatic to mildly symptomatic impact on ADL. We also found minimal worsening average ROM grades (1.11).

CONCLUSIONS—Shoulder ON is an underappreciated adverse late effect of therapy in children treated for leukemia/lymphoma which can limit quality of life and functionality. In most cases, pain and disability can be improved with treatment.

Introduction

Glucocorticoid-induced osteonecrosis is a known toxicity in pediatric and young adult patients treated for acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Most reports focus on osteonecrosis of the hips and/or knees, as impairments in these joints impart significant functional morbidity both during therapy and years following successful cure. [1–4]. Despite the fact that glucocorticoid therapy is a systemic exposure in these patients, little literature exists on the prevalence, extent, interventions or long-term outcomes of patients who have developed osteonecrosis of the shoulders.

In contrast to the hips, knees, and ankles, shoulders are normally non-weight bearing joints. However, in the presence of lower extremity osteonecrosis, the upper extremity joints may become ‘weight bearing’ in patients for whom crutches or other ambulatory assistive devices are prescribed to assist with management of lower extremity osteonecrosis. Whether such weight-bearing stresses contribute to development or progression of osteonecrosis in the shoulders is not known.

Early identification of osteonecrotic lesions may allow for implementation of interventions to preserve progression of involvement and ameliorate or minimize functional limitations [5]. As little is known about the prevalence or clinical impact of shoulder osteonecrosis, we describe our single-institutional experience in a population of young patients treated for acute lymphoblastic leukemia and non-Hodgkin’s lymphoma and report the severity, interventions and long-term outcome of affected shoulders.

Materials and Methods

With approval from the Institutional Review Board, we retrospectively searched institutional databases from January 1996 through October 2014 for patients under active treatment or with a history of treatment that included dexamethasone, who presented with shoulder pain and who underwent shoulder imaging to evaluate for osteonecrosis. We abstracted demographic information, primary diagnosis, physical function data, and type (if any) of surgical intervention.

Imaging

If there was obvious radiographic evidence of osteonecrosis and/or flattening of the articular surface of the capital humeral epiphysis/humeral head, MRI was considered versus following the patient with radiographs. If radiographs were normal, an MRI was performed. MRIs comprised non-contrast short tau inversion recovery (STIR) and T1-weighted sequences in the coronal plane and sagittal fast low angle shot (FLASH) images. All

imaging was reviewed by a single senior pediatric radiologist who recorded presence or absence of osteonecrosis involving the proximal humerus, estimated the degree of involvement (or < 30% of the humeral head articular surface), patency of the proximal humeral physis (as an indicator of skeletal maturity), and distribution of involvement of osteonecrosis (epiphysis, metaphysis, diaphysis).

Function

Patients were evaluated in orthopedic clinic to determine upper extremity osteonecrosis, range of motion, pain level and overall function. We used these results to classify function according to the Musculoskeletal and Connective Tissue Disorders category of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [6, 7] (Table 1); higher grades indicate greater impairment. Patients without the adverse event were given a score of 0. Grades were assigned for the initial functional assessment for all patients, for the post procedure functional assessment for those who required surgical intervention and for the date of last contact.

Medical management

Patients diagnosed with osteonecrosis who had a full range of motion and were asymptomatic were closely monitored with radiographic and clinical follow-up. Physical therapy was initiated for patients with limited range of motion. Patients who complained of mild to moderate pain received anti-inflammatory agents at the discretion of the medical oncologist. Patients who developed progressively worsening pain and/or loss of motion underwent intra-articular administration of anesthetic and DepoMedrol and physical therapy as the first intervention. Patients failing conservative treatment (anti-inflammatory agents where appropriate, cortisone injections, and physical therapy) underwent surgical intervention.

Surgical management

Initial surgical management consisted of arthroscopic evaluation. If the cartilage was intact, core decompression was performed. Using fluoroscopic guidance to locate the area of osteonecrosis previously mapped with MR, stab incisions were made to access the necrotic area of the proximal humerus. A 3.2 drill bit was advanced through the incision into the necrotic section; multiple perforations with the bit were made until a thorough decompression was achieved. No bone grafting was utilized.

If a significant cartilage defect was found, an attempt was made at pick arthroplasty, debridement, or chondroplasty of the area up to a size of 1–2 cm. For lesions larger than 2 cm or if there was complete loss of cartilage and bone was exposed, conservative measures were implemented with plans to perform a resurfacing hemiarthroplasty at a later date. For patients with significant collapse and pain and who were not candidates for arthroscopy, we proceeded directly to resurfacing once the patient's pain and/or motion failed conservative treatment.

Patients who progressed radiographically with further collapse, who developed significant pain and loss of function, or who failed core decompression underwent hemiarthroplasty.

The resurfacing technique utilized a standard anterior approach through the deltopectoral complex, reflecting the subscapularis muscle off of the anterior shoulder to allow access into the shoulder joint. Once the shoulder was dislocated, the area of cartilaginous defect was identified, sized and then the appropriate resurfacing hemiarthroplasty was either press-fit or cemented into place based on the patient's bone quality.

Results

Thirty-five patients underwent shoulder MRs between January 1996 and October 2014 and had imaging available on the picture archiving computer system (PACs). Imaging was prompted in 24 patients by the onset of shoulder pain. In two patients, the initial MR was protocol-specified.

Patient demographics

The study cohort included 22 females and was a median age at cancer diagnosis of 14.2 (range, 4.3 to 19) years. Median age at osteonecrosis diagnosis was 16.7 (range, 5.5 to 28) years. Median time to last follow-up from diagnosis of primary malignancy was 6.4 (range, 0 to 12.7) years and from the diagnosis of osteonecrosis, 4.0 (range, 0 to 8.9) years.

All patients had been or were receiving glucocorticoid-based therapy for ALL or NHL, according to contemporary IRB-approved institutional Total Therapy protocols [8–12]. Twelve patients were treated on Total Therapy XVI, nine on Total Therapy XV [13], one on Total Therapy XIV [10, 11], and eight on Total Therapy XIII [9, 11, 12], one on HLHR13 [14], one on NHL13 [15], two on NHL16 [16] and one on ALL-R16 protocol [17]. All patients are alive a median of 6.8 (range, 0.6 – 21.9) years from diagnosis of ALL/NHL and a median of 4.9 (range, 4.9 to 18.8) years from demonstration of osteonecrosis. Thus, the 35 patients included in our study, represent approximately 2.4% of the cumulative enrolled 1478 patients from the treatment protocols listed above. Twenty-six had a documented history of crutch use for lower extremity osteonecrosis; nine patients had no record of crutch use.

MR findings

Of the 35 patients, 22 had MR-defined osteonecrosis in 43 shoulders that involved at least 30% of the articular surface of the capital humeral epiphyses/humeral heads. Nineteen shoulders had less than 30% involvement of the articular surfaces, six shoulders were normal and two shoulders were not imaged. Twenty-nine patients had osteonecrosis involving both shoulders. All patients had documented multifocal osteonecrosis of lower extremity joints. The diagnosis of shoulder osteonecrosis preceded that of lower extremity joints in four patients by a median of 5.5 years (range, 1.8 – 7.8 years). The demonstration of shoulder osteonecrosis was made simultaneously with that of the lower extremities in six patients; for the remaining patients, shoulder osteonecrosis was demonstrated a median of 1.2 years after that of lower extremities (range, 0 – 7.4 years). Fifteen patients (28 shoulders) had no subchondral crescent formation or humeral head collapse.

Surgical interventions

Eleven patients underwent intra-articular injections for shoulder pain. Of these, seven shoulders were relieved of symptoms and no further treatment was performed (Table 2). Seven patients (12 shoulders) underwent core decompression; three after failing injection, seven as a primary treatment modality. Nine shoulders received no further treatment after the core decompression. Six patients (eight shoulders) underwent hemiarthroplasty following failure of either injections (three shoulders) or core decompression (three shoulders; Figure 1). Two patients (two shoulders) underwent hemiarthroplasty as a primary treatment without prior injection or core decompression. None underwent total shoulder arthroplasty. Four patients were receiving therapy at the time of the orthopedic intervention; two patients received intra-articular steroid injection and two underwent core decompression. All other procedures were performed after completion of therapy.

Joint functional outcomes

CTCAE mean scores for initial assessments of 55 shoulders (29 patients) showed moderate negative impact of osteonecrosis on activity of daily living (1.94), decreased ROM limiting athletic activity (0.98), and mild to moderate levels of pain (1.38) (Table 2). Analysis of this group's most recent assessment showed improvement in pain and osteonecrosis over time, with an average pain grade of 0.58 indicating no pain to mild pain, and 1.37 for osteonecrosis grade, indicating asymptomatic to mildly symptomatic impact on ADL. Results also showed minimally worse average ROM grades (1.11). An overall similar pattern of assessments was seen in patients not undergoing orthopedic intervention (Table 4).

Ten patients (13 shoulders) underwent intra-articular injection and presented with mean grades indicating moderate to severe grades of osteonecrosis impact (2.61), ROM (2.15) and pain (2.69). Post-injection results indicated improvements in pain (1.23), ROM limitations (1.69), and impact of osteonecrosis (1.76) grades. Seven patients (12 shoulders) underwent core decompression and presented with mean grades of moderate to severe pain (2.75) and impact of osteonecrosis (2.91), and ROM limitations of 25–50% (2.00). Following core decompression, improvements were demonstrated for pain (1.00) and impact of osteonecrosis (1.66), but not for ROM (2.08). Six patients (8 shoulders) underwent hemiarthroplasty and presented with mean grades of moderate to severe pain (2.87), osteonecrosis (2.75), and ROM limitations of 25–50% (2.37). Post-operative averages showed improvements in all three outcomes: impact of osteonecrosis (1.75), pain (0.75), and ROM (1.87).

The median interval between first and last functional assessment was 6.2 (range, 0.9 – 8.9) years; seven patients had only a single assessment. At the time of initial diagnosis, osteonecrosis-related ADL limitation had the highest grade; pain had the next highest grade. Pain and function improved over time with the described medical and surgical management plans (Table 2). Since lower scores indicate better outcomes, a negative change is favorable. Results showed that the greatest change occurred in average decrease in pain (–0.80) from initial to final assessment, followed by improvement in the average osteonecrosis grade (–0.57) over time. Range of motion grades changed only slightly (+0.13).

Discussion

Previous investigations of skeletal sequelae in pediatric cancer survivors whose treatment included glucocorticoids have largely focused on the development of symptomatic osteonecrosis of the femoral head [18]. Physical limitations and impact on quality of life in such cases are well-reported [19]. However, since oncologic chemotherapy has systemic effects, the prevalence and related clinical impact of glucocorticoid exposure on other joints is also warranted. We document the functional status, medical management and joint outcomes among survivors who developed osteonecrosis of the shoulder(s) as a result of therapy. We found that the diagnosis of osteonecrosis may be delayed likely because the shoulders are non-weight bearing with even advanced involvement tolerated compared with similar extent of involvement in femoral heads [20, 21].

In a recently published study of adult patients (mean age 39 years, range 25–55 years), diagnosed with symptomatic glucocorticoid-induced osteonecrosis and followed for an average of 15 years, the shoulder was found to be the second most commonly involved joint (140/200 patients; 70%), second only to hip osteonecrosis (100%) [22]. Our results were similar, with all patients demonstrating multifocal involvement of the lower extremities [23]. Mieuttunen et al reported on a small (n=11) pediatric cohort with ALL who underwent whole body MR for musculoskeletal pain persisting for at least 4 weeks. Nine of the 11 patients were found to have multifocal osteonecrosis; eight with epiphyseal lesions. All of the proximal humeral epiphyseal lesions involved more than one-third of the articular surface and none were symptomatic [23].

At the time of imaging, most patients in our study had moderate to severe shoulder osteonecrosis with moderate to severe pain and limitations in range of motion. For patients who underwent orthopedic intervention – intraarticular injection, core decompression or hemiarthroplasty – we found a decrease (improvement) in grade of impact of osteonecrosis, range of motion limitations, and severity of pain for all procedures except for range of motion in patients who underwent core decompression. We found that the greatest improvement was in pain grades across all three interventions post-procedurally. Impact of osteonecrosis grades improved to a lesser degree across all three types of procedures. Range of motion grades improved in the shoulder resurfacing and injection groups, but not in the group receiving core decompression.

Although we found improvement in symptoms related to shoulder osteonecrosis in most patients who underwent orthopedic intervention, we also found that some patients complained of persistent moderate to severe pain as a result of their osteonecrosis, and over 60% complained of at least minimal pain following orthopedic intervention. Continued pain is an important finding as chronic pain significantly impacts health related quality of life, and opioid use for the treatment of chronic pain is associated with even lower quality of life scores (SF-36) and higher occurrence of depression [24]. We also found that some patients had moderate to severe ROM limitations that persisted after intervention. This is important as range of motion limitations directly impact ability to perform daily activities like personal hygiene, eating, drinking, and dressing [25].

Prospective screening for the detection of osteonecrosis, especially screening beyond that of the hips has not been routinely performed, precluding accurate determination of the prevalence and severity of shoulder involvement. Since glucocorticoid-induced osteonecrosis results from systemic exposure to the drug, MR imaging of all joints may be warranted, at least in high risk patients, in those who are symptomatic, and in those with documented involvement of at least one other joint. We recently reported our results of prospectively screening hips and knees of nearly 500 pediatric patients undergoing therapy for acute lymphoblastic leukemia with MR, regardless of the presence or absence of symptoms. The cumulative incidence of osteonecrosis involving the epiphysis or metaphysis of at least one hip in these patients was 17.1% + 1.8% after 1 year of therapy and 21.7% + 1.9% after completion of therapy [3]. The estimated incidence of 2.4% shoulder involvement reported herein likely underestimates the true prevalence of shoulder involvement as most of these cases were imaged either because of symptoms or because of involvement of other joints.

Our data support the fact that chemotherapy induced osteonecrosis is multifocal, likely impacting not only the hips, knees, and/or ankles, but also the shoulders. Functional limitations in both lower and upper extremities have the potential to result in significant disability. Loss of shoulder function likely interferes with rehabilitation following surgical intervention for lower extremity osteonecrosis, such as hip or knee replacement, when patients must depend on upper extremity strength to use an assistive device for mobility. Patients with shoulders limited by decreased function or pain may have a more difficult rehabilitation process, which could lead to exacerbated shoulder symptoms, and/or poor rehabilitation outcomes following lower extremity surgery. More research into the relationship between upper and lower extremity disease is merited.

Strengths of this study stem from the standardized method of clinical grading of osteonecrosis using the established assessment of CTCAE 4.0, range of motion and severity of pain. Though the management of osteonecrosis varied and was designed on a case-by-case basis, patient management by a single clinical team allowed for excellent characterization of patient status and follow-up.

The results of our report must be considered within the limitations of the retrospective nature of our study which curtailed standardization of patient selection and outcome measures. In addition, the clinical management and surgical interventions evolved over nearly 9 years and likely contributed to non-standardized surgical techniques. Similarly, therapeutic protocols evolved and glucocorticoid doses varied over the course of the study. Most patients included in this report underwent evaluation of shoulder functionality and imaging due to symptoms that suggested the development of osteonecrosis of the shoulders. Thus, determination of the true prevalence of shoulder osteonecrosis in pediatric patients treated for ALL and NHL is precluded but is part of ongoing clinical research initiatives at our institution. Despite these limitations, we believe our report is clinically valuable and contributes to the understanding of this under-studied complication of therapy in pediatric patients.

We know of no preventative measures to protect patients from developing osteonecrosis at this time. However, efforts are being made to identify patients at increased risk for developing ON as early as possible, to allow for possible modifications of therapy to

minimize toxicity but without compromising cure. However, understanding the prevalence, severity and distribution of osteonecrosis in children treated for cancer should contribute to developing interventions to minimize and ameliorate this skeletal toxicity.

Acknowledgments

This work was supported in part by grant number P30 CA-21765 from the National Institutes of Health, a Center of Excellence grant from the State of Tennessee, and the American Lebanese Syrian Associated Charities (ALSAC).

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Figure 1.

18 year-old girl treated for acute lymphoblastic leukemia (ALL). Asymptomatic osteonecrosis of her hips and knees was identified 6 months into therapy by routine screening MR; involvement of her right elbow was diagnosed 8 years after diagnosis of leukemia.

A. (right) and B. (left) Initial shoulder radiographs obtained 23 months after diagnosis of ALL show changes bilaterally of ON, worse on left (B) where a large subchondral crescent is apparent (arrows). Central sclerosis is seen in the right (A) humeral head (arrow).

C. and D. Coronal non-contrast T1 and STIR (short tau inversion recovery) MR obtained 2 months later shoulder extensive bilateral changes of ON associated with joint effusions. Her CTCAE functional code (See Table 1) was 3-2-3. She underwent bilateral core decompressions 2 months following the imaging. One month post-operatively, her CTCAE functional code was 2-2-1 bilaterally.

E. (right) and F. (left) Forty-one months after the core decompression, the patient's functional score had deteriorated to 3-2-3. She underwent right-sided hemiarthroplasty 2 months later. Five months after the hemiarthroplasty, her functional scores were 1-1-0, bilaterally.

Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) for Musculoskeletal and Connective Tissue Disorders

CTCAE v4.0					
Musculoskeletal and Connective Tissue Disorders					
Grade					
Adverse Event	1	2	3	4	5
Osteonecrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL*	Severe symptoms; limiting self-care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Joint Range of Motion (ROM) Decreased	25% loss of ROM; decreased ROM limiting athletic activity	> 25% – 50% decrease in ROM; limiting instrumental ADL	> 50% decrease in ROM; limiting self-care ADL; disabling	–	–
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–	–

* ADL – Activities of Daily Living; Cancer Therapy Evaluation Program (CTEP), National Cancer Institute website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40.

Pre- and post-procedure coding of osteonecrosis grade, range of motion and upper extremity pain.

Table 2

Adverse Event Grade Averages Over Time (average follow-up, 6.2 years)						
Osteonecrosis n=55 shoulders at diagnosis n=53 shoulders – most recent		Range of motion n=55 shoulders at diagnosis n=51 shoulders - recent		Pain n=55 shoulders at diagnosis n=53 shoulders – recent		
Time of Assessment	Diagnosis	Most Recent	Diagnosis	Most Recent	Diagnosis	Most Recent
Grade	1.94	1.37	0.98	1.11	1.38	0.58
Injection: 10 patients (13 shoulders)						
Adverse Event	Pre-Procedure (mean)		Post-procedure (mean)			
Osteonecrosis	2.61		1.76			
Range of motion	2.15		1.69			
Pain	2.69		1.23			
Core Decompressions: 7 Patients (12 shoulders)						
Adverse Event	Pre-Procedure (mean)		Post-procedure (mean)			
Osteonecrosis grade	2.91		1.66			
Range of motion	2.00		2.08			
Pain	2.75		1.00			
Shoulder Resurfacing: 6 Patients (8 shoulders)						
Adverse Event	Pre-Procedure (mean)		Post-procedure (mean)			
Osteonecrosis grade	2.75		1.75			
Range of motion	2.37		1.87			
Pain	2.87		0.75			

Table 3

Demographic information for patients who underwent orthopedic intervention.

Intervention Group	Average age at time of intervention in years (range)	Average time from osteonecrosis diagnosis to intervention
Injection	16.9 (15–20)	1 day – 3 years
Core Decompression	17.7 (14–21)	12 months
Hemiarthroplasty	20.6 (15–24)	24.6 months

Coding of osteonecrosis grade, range of motion and upper extremity pain for those who received no orthopedic intervention.

Table 4

Osteonecrosis n=27 shoulders at diagnosis n=25 shoulders – most recent		Range of motion n=27 shoulders at diagnosis n=25 shoulders - most recent		Pain n=27 shoulders at diagnosis n=25 shoulders – most recent	
Time of Assessment		Diagnosis	Most Recent	Diagnosis	Most Recent
Grade		1.44	1.32	0.29	0.68
				0.70	0.56