Osteonecrosis of the femoral head in childhood malignancy

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Abstract

Purpose Children undergoing chemotherapeutic treatment of malignancies have up to a 9 % incidence of osteonecrosis. The purpose of this article is to determine the time from initiation of chemotherapy to the onset of symptoms and the diagnosis of osteonecrosis of the femoral head in this patient population.

Methods A retrospective review of the records of 18 patients (29 hips) under 21 years of age with both a diagnosis of osteonecrosis of the femoral head and childhood onset malignancy was undertaken to determine the time from initiation of chemotherapy to the onset of symptoms and diagnosis of osteonecrosis of the femoral head.

Results Mean time from initiation of chemotherapy to the onset of pain was 18.8 months (8.0–49.1). The mean time from development of pain to diagnosis of osteonecrosis was 3.9 months (–13.1 to 25). The mean overall time from initiation of chemotherapy to diagnosis of osteonecrosis was 22.7 months (9.0–54.1). 11/18 patients had bilateral disease. 16/18 patients (21/29 hips) had already progressed to stage 4 osteonecrosis at the time of diagnosis.

Conclusions There was a high incidence of stage 4 or greater osteonecrosis at the time of diagnosis. Providers caring for these patients should be aware of the potential for osteonecrosis, and the need for prompt diagnosis and

referral to an orthopedic surgeon. Screening with advanced imaging studies may be warranted for children undergoing chemotherapeutic regimens for childhood malignancy to prevent delay in the diagnosis and management of this process so that joint preservation therapies remain an option.

Keywords Osteonecrosis of the femoral head · Malignancy · Chemotherapy · Avascular necrosis of the femoral head

Introduction

Osteonecrosis (ON), also called avascular necrosis (AVN) or aseptic necrosis, of the femoral head is a condition in which bone within the femoral head incurs an insult which causes the osteocytes to die [1–3]. There are a variety of conditions associated with osteonecrosis of the femoral head, including trauma, pyarthrosis of the hip, Legg–Calvé–Perthes disease, slipped capital femoral epiphysis, developmental dysplasia of the hip, Gaucher disease, sickle cell hemoglobinopathies, renal osteodystrophy, and iatrogenic complications [1–5]. During early stages of the condition, the patient may be asymptomatic, but the natural history includes progression to pain associated with weight-bearing, limited range of motion, and limping, which can become debilitating [1–3]. In addition to the causative factors named above, children and adolescents who undergo chemotherapeutic treatment for malignancies have also shown a high incidence of the development of ON (up to 9 %), with the femoral head being one of the most common sites of involvement [1, 2, 6, 7, 10–14]. The pathogenesis has been called multifactorial, with possible etiologies including direct toxicity and apoptosis of

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osteocytes, intramedullary lipoblast proliferation or tumor burden leading to compressive ischemia, and vascular endothelial and smooth muscle cell modulation leading to intravascular stasis, thrombus formation and ischemia, as well as insufficiency fractures due to osteoporosis [1, 3, 6–15].

Given the potentially severe pain, loss of function, and overall poor quality of life seen in untreated ON of the femoral head, early diagnosis gives the treating physician an opportunity to intervene prior to late stages of the disease when irreversible changes may have occurred, necessitating total hip arthroplasty [2]. The presenting signs and symptoms of hip pain, thigh pain, and difficulty with weight-bearing are well known [1–21]. However, there are less data on the time frame from diagnosis of malignancy and initiation of chemotherapy to presentation with hip pain and diagnosis of ON of the femoral head [1, 2, 5, 7, 10, 11, 13, 14]. Accurate data on this time frame may improve awareness on the part of pediatricians and pediatric oncologists who primarily manage these patients, such that they may obtain radiographic studies in a timely manner and alter medication regimens if appropriate or consult an orthopedic surgeon for further evaluation. Earlier detection of femoral head ON at a less advanced stage may in turn leave an option for conservative treatment or hip preservation surgery (such as core decompression or free vascularized fibular grafting) rather than total hip arthroplasty to prevent long-term complications [9, 16–21]. The purpose of the study described in the present paper was to retrospectively review these children who developed ON of the femoral head in the setting of chemotherapeutic treatment for childhood malignancies, and to determine the time from initiation of chemotherapy to the beginning of symptoms of ON such as hip or knee pain as well as to the diagnosis of ON. In addition, the time from onset of symptoms to diagnosis of ON was reviewed. The stage of the disease at presentation as well as demographic data were also reviewed and are discussed below.

Methods

After permission was obtained from our institutional review board, a retrospective review of an existing clinical database of patients identified those who presented to the orthopedic surgery clinic at one institution with a diagnosis of osteonecrosis of the femoral head over a ten-year period. Subjects up to 21 years of age with both a confirmed diagnosis of a childhood malignancy treated with a chemotherapeutic regimen and ON of the femoral head were included in the study. All of these patients were referred to our institution for consideration of free vascularized fibular grafting for hip preservation. Diagnosis had been made

based on symptoms, clinical exam findings, and radiographic studies, including plain radiographs and magnetic resonance imaging (MRI). Patients in whom ON resulted from a disorder other than a childhood malignancy, such as trauma, infection, slipped capital femoral epiphysis, or Legg–Calvé–Perthes disease, were excluded. Demographic data including age, sex, sidedness of ON, type of malignancy, and chemotherapeutic regimen were recorded (Table 1). Time from induction of chemotherapy to development of symptoms and time from onset of hip pain to diagnosis of ON were also documented (Table 1). Severity of ON at the time of diagnosis was graded using the Duke scoring system (Table 2), a modification of the Ficat and Steinberg radiographic staging systems [9].

Results

We identified 327 patients under 21 years of age who presented to the orthopedic clinic at our institution with radiographic evidence of osteonecrosis of the femoral head. Thirty-seven of these patients (11 %) carried a concurrent diagnosis of malignancy. Of these, eighteen patients, for a total of 29 hips, had complete clinical and radiographic data to analyze for this study (Table 1). The average age was 17.1 years (range 12–20 years). There were 12 females and 6 males. All study subjects were on a chemotherapeutic regimen. There was variation in the medications used to treat the patients, but all were treated with corticosteroids. The mean time from induction of chemotherapy to the development of symptoms (hip or knee pain) was 18.8 months (range 8.0–49.1 months). The mean time from initiation of chemotherapy to diagnosis of ON was 22.7 months (range 9.0–54.1 months). The average time from development of pain to the diagnosis of ON was 3.9 months (range –13.1 to 25 months) (Table 1). One patient who had a radiographic diagnosis of ON 13 months prior to becoming symptomatic was assigned a negative number of months between onset of pain and radiographic diagnosis. Four patients had isolated right-sided ON, and two had isolated left-sided ON. Eleven patients had bilateral disease. 16/18 patients and 21/29 hips were in stage 4 at the time of diagnosis. Fourteen patients went on to undergo a free vascularized fibular graft (Fig. 1).

Summary

Children and adolescents with malignant hematologic disorders and malignant solid tumors have a relatively high incidence of symptomatic osteonecrosis of the femoral head, ranging from 1 to 9 % in previous studies [1, 2, 6, 7, 10, 12–15]. When ten years of follow-up were performed, Patel et al.

Table 1 Demographic data

Patient	Diagnosis	Age	Gender	Months from chemo to symptoms	Months from chemo to ON diagnosis	Months from symptoms to ON diagnosis	Duke stage left hip	Duke stage right hip
1	ALL	20	F	12.0	14.0	2.0	2A	4B2
2	ALL	15	F	14.0	25.0	11.0	4C2	5C4
3	ALL	18	M	18.1	27.1	9.0	4B0	5B2
4	ALL	14	F	8.0	9.0	1.0		4C2
5	ALL	17	F	28.1	30.1	2.0	4B1	
6	ALL	16	F	19.0	20.0	1.0	5B2	2B
7	ALL	20	F	14.3	39.4	25.1	2A0	2A0
8	ALL	12	F	17.0	19.0	2.0	4B2	
9	ALL	16	F	13.9	21.0	7.0		4C2
10	AML	18	M	18.0	25.0	7.1	4C1	5C1
11	Astrocytoma	15	M	49.1	54.1	5.0	4A1	
12	Astrocytoma	20	F	9.0	10.0	1.0	4B1	4B1
13	CLL	19	M	13.0	13.0	0.0	4B2	2B1
14	CML	16	M	37.0	24.0	−13.0 ^a	4A2	4B3
15	Hodgkin's	19	F	11.1	17.1	6.0		4C2
16	Hodgkin's	17	F	13.0	16.0	3.0	4B1	2A0
17	Pre-B cell lymphoma	18	F	22.0	22.0	0.0	4B0	3B0
18	T cell lymphoma	18	M	21.1	22.1	1.0		2C0
Median				15.65	21.5	2		
Mean				18.8	22.7	3.9		
SD				10.3	10.8	7.3		

ALL acute lymphoblastic leukemia, AML acute myelogenous leukemia, CLL chronic lymphocytic leukemia, CML chronic myelogenous leukemia

^a Negative number indicates a patient with ON diagnoses prior to symptoms

Table 2 Duke staging criteria for osteonecrosis/avascular necrosis of the femoral head

Stage	Criteria	Suffix qualifiers
1	Normal plain films; abnormal MRI findings	A. <25 % B. 25–50 % C. >50 %
2	Plain film changes (cysts and/or increased density)	A. <25 % B. 25–50 % C. >50 %
3	Subchondral collapse (crescent sign); no flattening of femoral head	A. <25 % B. 25–50 % C. >50 %
4	Flattening of femoral head	A, B, C grading as above and 0. No step-off 1. 1 mm step-off 2. 2 mm step-off 3. 3 mm step-off
5	Joint space narrowing ± acetabular changes	Same as for stage 4

[14] found that up to 29 % of the patients who were treated initially at ages 15–20 years old eventually developed ON in any bone, with approximately half of these involving the femoral head. The radiographic detection rate of ON of the femoral head specifically has been reported to be 6.25 % (2/32) in one MRI-based study, which was performed on both asymptomatic and symptomatic patients being treated for childhood malignancy, with one of the two patients symptomatic at the time of the study [6].

There are published data on the time from diagnosis of cancer to the diagnosis of ON [1, 2, 5, 7, 11, 13, 14]. However, only two of these articles focus specifically on ON of the femoral head [2, 13]. Time between diagnosis of malignancy or initiation of chemotherapy and onset of symptoms (rather than diagnosis) is not quantified in these reports. Karimova et al. [13] found a mean of 1.7 years (0.1–17.5 years) between diagnosis of malignancy and diagnosis of ON. In another small study of the natural history of osteonecrosis of the femoral head in children with acute lymphoblastic leukemia, there was a median of 20 months (10–91 months) between the diagnosis of ALL and the diagnosis of ON [2]. In a radiographic diagnostic

Fig. 1 Postoperative radiograph of a patient who underwent free vascularized fibular grafting for osteonecrosis of the right femoral head

study of ON (of both the knees and hips), a diagnosis was made in children with ALL and non-Hodgkins lymphoma at an average of three years following the diagnosis of malignancy [5]. The femoral head was involved in 9/17 of these children, and 7/9 were symptomatic at the time of radiographic diagnosis [5].

There is little information available on the time from initiation of chemotherapy to the onset of symptoms or the diagnosis of femoral head osteonecrosis [10, 11]. It has been reported that ON can occur during any phase of the chemotherapeutic regimen, from the induction phase to onset after the cessation of therapy [1, 2, 5, 7, 10, 11, 14]. Some authors suggest that osteonecrosis develops earlier in the chemotherapeutic regimen in children and adolescents than in adults [14]. The present study is the first to quantify the mean time from induction of chemotherapy to the development of symptoms and the onset of symptoms to the diagnosis of ON as well as the mean time from chemotherapy to the diagnosis of femoral head osteonecrosis. We found the mean time to the development of symptoms (hip or knee pain) was 18.8 months (range 8.0–49.1 months), and that to diagnosis of ON of the femoral head was 22.7 months (range 9.0–54.1 months) following the initiation of chemotherapy. One previous cohort was described in which the mean time from initiation of chemotherapy (which was equated to a diagnosis of ALL) to the diagnosis of osteonecrosis at any site including the hip was 30 months [11]. In the high-risk ALL group, the time

was reduced to only 18.5 months, versus 64.5 in the low-risk ALL group [11]. Our data indicate that a subset of children (2/18) will develop symptoms of ON less than one year after initiating chemotherapy. Burger et al. [7] reported that 35 % of children in their study had less than 12 months between the diagnosis of ALL and ON of the hip or knee. All of these children were symptomatic at the time of radiographic diagnosis, meaning that symptoms also began prior to 12 months post ALL diagnosis and presumably the initiation of treatment. One child in our cohort developed ON prior to the initiation of chemotherapy, suggesting that the malignancy itself could have been a factor in osteonecrosis in this case, although whether there had been prior use of corticosteroids for other reasons in this case is not known.

Our data describing the variability in the severity of osteonecrosis at the time of diagnosis is in line with other published reports that focused on femoral head ON in malignancy [2, 13]. In a report of seven patients with ON of the femoral head diagnosed radiographically, 1/7 had Ficat grade 3 changes and 6/7 had grade 4 changes [2]. Additionally, 29/36 patients followed in a long-term study of patients treated for leukemia or lymphoma had collapse of the articular surface at the time of femoral head ON diagnosis [13]. In our study, we found that 72.4 % of the hips had advanced to at least Duke stage 4 osteonecrosis at the time of diagnosis and referral to our institution, meaning that there was already collapse and flattening of the femoral head when the patient was referred for orthopedic management. 88.8 % of patients had at least one stage 4 hip at diagnosis. Dean et al. have described an 84 % success rate of free vascularized fibular grafting in the treatment of ON in children and adolescents [21]. Their data, however, also show diminishing operative survival rates with advancing stage of the disease.

Other risk factors previously identified for the development of osteonecrosis of the femoral head in the setting of chemotherapeutic treatment of malignancy included female gender [1, 2, 4, 6, 7, 10–14], age >9 years [1, 2, 4, 6, 7, 10–14], white race [1, 2, 4, 6, 7, 10–14], and in one study high body mass index [15]. In addition, Wei et al. [11] reported their series of AVN in children with acute lymphoblastic leukemia, and pointed out the differences between the poor-prognosis/high-risk ALL population and the general ALL population with regards to earlier onset of AVN, more advanced degeneration of the femoral head at diagnosis, and more rapid progression of AVN in these children. Awareness of these risk factors should allow physicians to make prompt referrals for radiographic studies in these children.

Given the overall high incidence of femoral head osteonecrosis in this patient population in other reports, our data on the timing of disease onset, and the large

proportion of patients with stage 4 or greater AVN at presentation, children who undergo chemotherapeutic treatment for a malignancy may warrant screening studies such as plain radiographs or MRI of the pelvis at regular intervals once chemotherapy is initiated in order to achieve the diagnosis of AVN at an earlier stage. Prompt detection of AVN could lead to earlier medical intervention or timely referral to the orthopedist for consideration of treatment options with higher success. This would also allow for consideration of modifying steroid dosage in the chemotherapeutic regimen or consideration of medical management with bisphosphonates. Several small series have shown improvement of clinical symptoms and radiographic parameters of capital femoral epiphyseal AVN after treatment with bisphosphonates in both pediatric and adult patients [17–20]. Earlier surgical intervention such as a core decompression, osteotomy, or free vascularized fibular graft for joint preservation could also be considered, and may be more successful if undertaken at earlier stages [9, 16, 21].

Our study is limited by the retrospective nature of our investigation. There were also only a small number of subjects who met all inclusion criteria: many potential subjects had limited follow-up at our institution, so long-term results were not available. As our institution is one of just a few that perform a high volume of free vascularized fibular grafts, many patients in our database were referred to us with late stages of disease for evaluation of joint preservation or salvage procedures rather than observation and nonsurgical management with bisphosphonates or non-weight-bearing rest. Bias towards patients with late-stage AVN was likely in this situation. Our data also include patients with a variety of diagnoses and a variety of chemotherapeutic regimens. Corticosteroid use, however, was universal among our patients. It is difficult to draw conclusions regarding specific medical regimens due to the heterogeneity of our patients' therapies. Despite these limitations, this report should bring about awareness that children being treated with chemotherapy, especially those with high-grade malignancies, have a high incidence of osteonecrosis of the femoral head, which may not be detected until an advanced stage when joint preservation strategies are not feasible. Further prospective data on the effect of pre-symptom detection of ON with radiographic screening on eventual outcome in these patients would be useful to determine the most effective protocol. It would also be useful to determine which chemotherapeutic regimens have the highest incidence or quickest onset of ON. Given that 11.1 % of our study population was symptomatic by 9 months, 22.2 % by 12 months, and 61.1 % by 18 months, we propose that radiographic screening should begin 6–12 months following the initiation of chemotherapy and every 6–12 months thereafter. The ultimate goal

will be to avoid the devastating long-term complications of delayed diagnosis of osteonecrosis of the femoral head in children treated for malignancy.

Conflict of interest None.

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