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Osteonecrosis in Children After Therapy for Malignancy

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Abstract

OBJECTIVE—Osteonecrosis in the growing population of childhood cancer survivors results from disease and treatment. Imagers must be knowledgeable about patient groups at risk for its development, patterns of involvement and potential implications. This review will focus on implications of this potentially life-altering toxicity.

CONCLUSION—Childhood cancer survivors are at increased risk for developing osteonecrosis. Because osteonecrosis is often asymptomatic until late in the process, imaging is critical for its detection and characterization when interventions may be most effective to ameliorate its progression.

Keywords

acute lymphoblastic leukemia; bone mineral density; childhood cancer; osteonecrosis; pediatrics

Osteonecrosis is a significant long-term toxicity that can compromise joint functionality and quality of life in afflicted survivors of childhood cancer. The causes for its development are multifactorial and associated with adverse effects of disease and treatment. However, understanding of this process in pediatrics, particularly pediatric oncology, is limited.

In the United States, osteonecrosis is diagnosed in 10,000–20,000 individuals each year [1]. Osteonecrosis typically occurs in patients 20–50 years old and is rare in the pediatric population. Pediatric patients may develop osteonecrosis from chronic exposure to steroids. Preservation of joint function and control of pain are key factors in managing osteonecrosis. Unique to pediatric patients is concern about lifetime compromise of joint function; maintaining skeletal growth and development; and, when necessary, the potential need for multiple surgeries. The growing number of pediatric oncology patients represents an especially vulnerable population in which toxicities from the primary disease and treatment

compound surgical risk and skeletal integrity. This review will focus on implications of this potentially life-altering toxicity as seen in survivors of childhood cancer.

Early Diagnosis

Osteonecrosis often remains asymptomatic or associated with only minimal, nonspecific symptoms until it becomes advanced. Thus, early stage lesions need to be detected when implementation of interventions may ameliorate severity and preserve joint integrity [2–4]. The size of the osteonecrosis lesion inconsistently correlates with the severity of pain. Twenty-one percent of patients with stage III osteonecrosis of the hips classified according to the staging system of the Association Research Circulation Osseous (ARCO) [5] were asymptomatic whereas 28% with ARCO stage I osteonecrosis of the hips were symptomatic [3]. Similar findings have been reported in patients prospectively imaged for detection of osteonecrosis involving the knees [6]. Thus, the growing recognition of treatment-induced osteonecrosis has led to a high index of suspicion for osteonecrosis and prompted prospective monitoring of at-risk patient populations.

Longitudinal Outcomes of Osteonecrosis

The paucity of longitudinal studies and correlative standardized clinical assessment of joint function in pediatric cancer patients hampers understanding of the clinical ramifications of imaging findings. Symptoms may not occur until late in the evolution of osteonecrosis when most of the articular surface has been irreversibly destroyed. At this point, therapeutic options are limited, and patients usually require surgical intervention. Clinical symptoms are an unreliable indicator of the presence and severity of osteonecrosis [7]. Only lesions reaching and affecting more than 50% of the articular surface are consistently associated with symptoms. Large lesions may also be associated with no or only minor symptoms [3] (Fig. 1). Up to 21% of patients have remained asymptomatic after suffering subchondral collapse of hip osteonecrosis. In a meta-analysis series of adults, more than one half of asymptomatic cases progressed to symptomatic disease or collapse of the femoral head over 2–240 months [7]. Investigations into potential associations between metaphyseal and diaphyseal osteonecrosis, clinical symptoms, and joint function are currently lacking.

Few longitudinal studies investigating the outcome of MR findings are available for pediatric cohorts. Similar findings have been reported in adult populations [8, 9]. Osteonecrosis lesions involving at least 30% of the articular surface of the hips or the knees are associated with worse outcomes [3, 8]. Specifically, such lesions in the hips involving the capital femoral epiphysis, are predictive of progression to collapse of the articular surface in 80% of patients within 2 years of presentation, with 50% requiring arthroplasty [10]. Lesions involving < 30% of the articular surface commonly heal without collapse of the articular surface [10]; in some cases, large lesions also heal [10–12] (Fig. 1). As mentioned, osteonecrosis lesions of the hip with a large necrotic angle are also predicted to compromise joint function and ultimately to require arthroplasty [13, 14].

In contrast to skeletally mature adults, the potential for alteration of growth and development of a joint affected by osteonecrosis is a concern in pediatric patients. Merrow and Laor [15] reported a single case of preserved longitudinal bone growth in a patient who

developed symptomatic osteonecrosis of the distal tibial epiphysis, metaphysis, and diaphysis during treatment of leukemia. In the reported case, the area of osteonecrosis migrated proximally as unossified physeal cartilage. More recent anecdotal experience supports this case report (Fig. 1), but published longitudinal experience is lacking.

Prevalence of Osteonecrosis in Pediatric Patients Treated for Cancer

The reported incidence of osteonecrosis varies from about 1–72% [16–19] depending on study design, primary diagnosis, symptomatic versus asymptomatic cases, and osteonecrosis definition used. Reports based on symptomatic cases [16–19] and those using radiographic evaluation typically report a lower incidence of osteonecrosis than those prospectively monitoring its development with contemporary MR techniques [19]. In the Childhood Cancer Survivor Study consisting of 9261 patients and a random sample of 2872 siblings, 52 (0.56%) survivors of childhood cancer self-reported osteonecrosis developing in 78 joints; 60% reported multiple joint involvement [18]. Thus, prospective MR monitoring for osteonecrosis is now incorporated into some standard pediatric oncology treatment protocols.

Two populations of childhood cancer survivors at risk for osteonecrosis warrant special mention: acute lymphoblastic leukemia (ALL) and patients who have undergone allogeneic bone marrow transplantation. ALL is the most common pediatric cancer, with survival now exceeding 90% [20]. The reported incidence of symptomatic cases ranges from 1.8% 5-year cumulative incidence [17] to a 3-year life-table incidence of 9.3% [16]. These reported frequencies underestimate the overall prevalence of osteonecrosis. Kawedia et al. [19] reported a cumulative incidence of osteonecrosis involvement in hips or knees in 72% of prospectively monitored patients with ALL while on therapy, irrespective of symptoms.

In patients who have undergone allogeneic bone marrow transplantation, the reported incidence of osteonecrosis of any joint ranges from 3.9% to 44.2% [21–24]. Recently, nearly 22% of prospectively monitored pediatric patients, irrespective of clinical symptoms, were found to have MR-documented osteonecrosis of the hips or knees. Nearly one half of those with osteonecrosis had at least 30% epiphyseal involvement [24].

Risk Factors for the Development of Osteonecrosis in Pediatric Oncology Patients

Development of osteonecrosis is multifactorial. Older patient age at the time of oncologic therapy has been consistently identified as a risk factor for its development [10, 12, 18, 23–28]. Adolescents are at greater risk than younger patients [2, 3, 15–17, 23]. The surge in sex hormones and rapid skeletal maturation during puberty may contribute to the development of osteonecrosis [29, 30]. Increased intraosseous pressures related to growth plate fusion may also contribute to increased risk [16, 31]. Osteonecrosis of the hip in patients older than 16 years treated for hematologic malignancies may be more extensive and progress to end-stage collapse more readily than those lesions in younger patients [3].

Exposure to glucocorticoids (particularly dexamethasone) has consistently been associated with development of osteonecrosis [12, 16, 18]. Glucocorticoid-induced osteonecrosis results from complex interactions of several pathways [32]. One proposed mechanism describes early apoptosis of osteocytes with concurrent increase in intramedullary adipocytosis, contributing to increased intraosseous pressure that subsequently compromises vascular perfusion of the epiphysis and adjacent bone [33]. Glucocorticoid-induced hypoperfusion may result from down-regulation of vascular endothelial growth factor [34]. Investigations into genetic [35–38] and pharmacogenetic factors contributing to osteonecrosis are ongoing [26, 38].

Inconsistent results have been reported from investigations into the association between osteonecrosis and other risk factors, such as patient sex [22, 24, 34], obesity, and body mass index [22, 24, 39].

Imaging of Osteonecrosis

The imaging appearance of osteonecrosis in childhood cancer survivors parallels that seen in the general and other high-risk populations. Many excellent publications are available for review of osteonecrosis imaging characteristics. Thus, the imaging findings discussed here focus on reports targeting pediatric patients receiving or having received therapy for a malignancy.

Radiography

Although readily available and inexpensive, radiographic evaluation for detection of osteonecrosis is insensitive to the early stages of osteonecrosis when intervention may be most effective in preventing progression to collapse of the articular surface [40]. Its use is primarily limited to advanced disease, orthopedic surgical planning, and longitudinal postoperative monitoring. Even in the presence of extensive MR-proven osteonecrosis, involved joints are often radiographically normal [3, 22, 41].

MRI

MRI is the most sensitive and specific method for detection and monitoring of osteonecrosis [41–43]. Minimal MRI comprising coronal unenhanced T1-weighted and STIR sequences exquisitely delineates osteonecrosis lesions (Figs. 1–7). The addition of sagittal or axial sequences may add to volumetric assessment of osteonecrosis involvement. A cartilage-specific sequence, such as FLASH 2D may be useful for assessing secondary changes related to osteonecrosis.

The administration of IV contrast material did not contribute to the detection and characterization of osteonecrosis in a single adult series [44]. However, preliminary experience with diffusion- and perfusion-weighted sequences suggests such techniques may identify development of osteonecrosis at an earlier stage and better depict regional vascularity than that shown by unenhanced studies [45–48]. A recent experimental animal study showed that functional perfusion MRI may predict development of steroid-associated osteonecrosis [49]. Whole-body MR techniques show promise for detecting osteonecrosis lesions, but clinical use is currently limited [50, 51].

CT

CT has the distinct advantage of being able to better detect subchondral collapse and even subtle depression of the articular surface [52]. Yeh et al. [52] compared MRI with CT detection of subchondral fractures related to osteonecrosis as interpreted by two blinded readers, a musculoskeletal radiologist and a general radiologist. These investigators found only 58% (16/28) agreement in identifying subchondral collapse by MRI. However, current efforts in pediatric oncology are focusing on early detection of osteonecrosis at stages when intervention may preserve joint integrity. Furthermore, patient exposure to ionizing radiation limits the utility of CT in pediatric patients for assessment of joint integrity.

Functional Imaging

Skeletal scintigraphy has long been advocated as a sensitive diagnostic tool to detect osteonecrosis; it is fairly available and can provide whole-body assessment [53–55]. However, MRI has largely superseded skeletal scintigraphy because of superior anatomic detail, lack of exposure to ionizing radiation, and improved specificity [54].

Metabolic activity in sites of osteonecrosis has been detected during ^{18}F -FDG PET or PET/CT performed for disease staging; these sites of osteonecrosis may mimic metastatic lesions [56]. Preliminary investigations in adults have found FDG PET to be a sensitive imaging method for detecting osteonecrosis [57–59] and in assessing perfusion of the femoral head [57, 58]. However, prospective reports in pediatric cases are lacking.

Coexisting Lesions

The sensitivity of MRI to signal changes in bone marrow can present a challenge when providing a differential diagnosis. Distinguishing osteonecrosis from recurrent leukemia (Fig. 2), metastatic disease, and nonspecific transient signal abnormalities is of utmost importance in providing an appropriate differential diagnosis.

On MRI, areas of osteonecrosis are typically described as being geographic in distribution and well-margined by a thin sclerotic line with fat signal emanating from the lesions themselves. These are often irregular in outline. Recurrent leukemia is typically manifested by well-defined smoothly margined intramedullary foci of decreased signal on T1-weighted sequences and bright signal on STIR [60, 61] (Fig. 2). The sclerotic line has low intensity on all sequences; a high-intensity line lies adjacent to the sclerotic margin on STIR. T2-weighted images reveal a double line sign formed from high-intensity (inner) and low-intensity (outer) lines.

Nonspecific appearance of bone marrow signal has been reported around the knee in children with leukemia [62–64] and is composed of punctuate foci (dotlike abnormalities with 1- to 3-mm diameters with no discernible interior fatlike areas) (Fig. 3), bone marrow edema (Fig. 5), and diffuse marrow heterogeneity [65] (Fig. 4). The distinguishing characteristic of the latter two abnormalities from osteonecrosis or metastatic disease is the lack of sharply defined borders. Diffuse marrow heterogeneity lacks the interior zone of fatlike signal, which is especially evident on STIR. These findings typically resolve over time [65] and may represent red marrow conversion [66]. Varying degrees of edema or

edemalike signal changes [66] (Figs. 4 and 5) may be seen in association with osteonecrosis but may also exist transiently and independent of osteonecrosis [64]; possible reported causes include bone marrow contusion, ischemia, and micro-fractures [66]. Areas of edema may be painful whether or not they are associated with developing osteonecrosis [67].

Patterns of Osteonecrosis

The joints most often reported to be involved with osteonecrosis vary between reports of symptomatic and asymptomatic cases. Typically, the hips and knees are most often reported although any joint may be involved [18]. In pediatric patients treated for malignancies, osteonecrosis lesions are typically bilateral in distribution [3, 7, 8, 12] unless there has been local radiation therapy, surgery, or other focal insult that would unilaterally predispose a joint to this toxicity. Multijoint involvement is common [3, 18, 24].

Distribution osteonecrosis among the epiphysis, metaphysis, and diaphysis varies by patient as does the extent of such lesions. Several investigators have described the extent of epiphyseal involvement to be predictive of joint destruction [10, 13, 15, 68, 69] (Figs. 1 and 6). Extension of epiphyseal lesions to the articular surface [3, 64] and estimated percentage involvement of the articular surface are important MR findings to describe the extent of osteonecrosis involvement [3, 64, 68]. These aspects are important for predicting the eventual outcome of joint function and risk of arthroplasty [8, 10, 65, 70–72]. Epiphyseal lesions involving at least 900 mm² [69], large lesions involving more than one third of the femoral condyle on a midcoronal image or more than one of three zones on a midsagittal image [70], and those with a combined epiphyseal necrotic angle of at least 250° [13] are all characteristics reported as predictive of joint destruction and the need for arthroplasty.

The correlation between clinical symptoms and functional impairment of one anatomic site over another is limited and currently inconclusive [73]. Because epiphyseal involvement leads to the most significant morbidity, investigative initiatives have been directed toward detection and evolution of these lesions, with little attention paid to the significance and evolution of metaphyseal and diaphyseal lesions.

In the knees, osteonecrosis typically occurs on both the femoral and the tibial sides of the joint. When MR monitoring is prospectively performed, regardless of the presence or absence of clinical symptoms, involvement of the knees is the most common site of osteonecrosis, superseding involvement of the hips [24]. The knees may be the only joints involved. When the hips are involved, the knees are also commonly involved but the reverse less commonly occurs [3, 24].

Monitoring Recommendations for Asymptomatic Patients

To our knowledge, no published recommendations exist regarding monitoring of asymptomatic patients for osteonecrosis in the hips or knees. However, because of the less common development and a lower rate of complications [3, 4, 10] of osteonecrosis in patients younger than 10 or 11 years [3, 20], routine monitoring may not be indicated. For older patients, our current recommendations, supported by preliminary analysis of ongoing unpublished investigations and based on prior publications, seem to indicate a need to

monitor asymptomatic patients exposed to glucocorticoids [3, 16] or those who undergo bone marrow transplantation [24]. We have found few instances of new sites of osteonecrosis or progression of existing osteonecrosis beyond 3 years of follow-up [6]. Patients with subtle MR changes in the hips or knees or those who develop symptoms, regardless of the presence or absence of MR changes, warrant an individualized approach to imaging. Further analyses may warrant revision of our current recommendations.

New Challenges

Oncotherapy regimens continue to evolve to improve outcomes and now also to minimize toxicities. Currently incorporated into phase I, II, and III clinical studies are new agents—antiangiogenesis and targeted molecular agents—that have been shown in pre-clinical trials to adversely affect skeletal development. These agents, particularly the antiangiogenesis agents, alter vascularization of chondrocytes, which in turn compromises endochondral ossification of the long bones. Coupled with early apoptosis of chondrocytes, decreased longitudinal growth of the long bones from early physal fusion has been shown in preclinical models [74–76]. Experience with these agents is preliminary, but similar alteration of skeletogenesis is of concern in growing children.

Conclusion

Children and adolescents treated for malignancies represent a unique and growing population at significant risk for developing osteonecrosis that may limit joint functionality; require surgical intervention at a young age; and, overall, compromise quality of life. Longitudinal outcomes studies are currently limited, and a standardized approach to interventions has not been defined. Imaging plays a key role in identifying and staging osteonecrosis lesions because symptoms are unreliable for identifying affected patients and determining the severity of osteonecrosis and the risk of progression.

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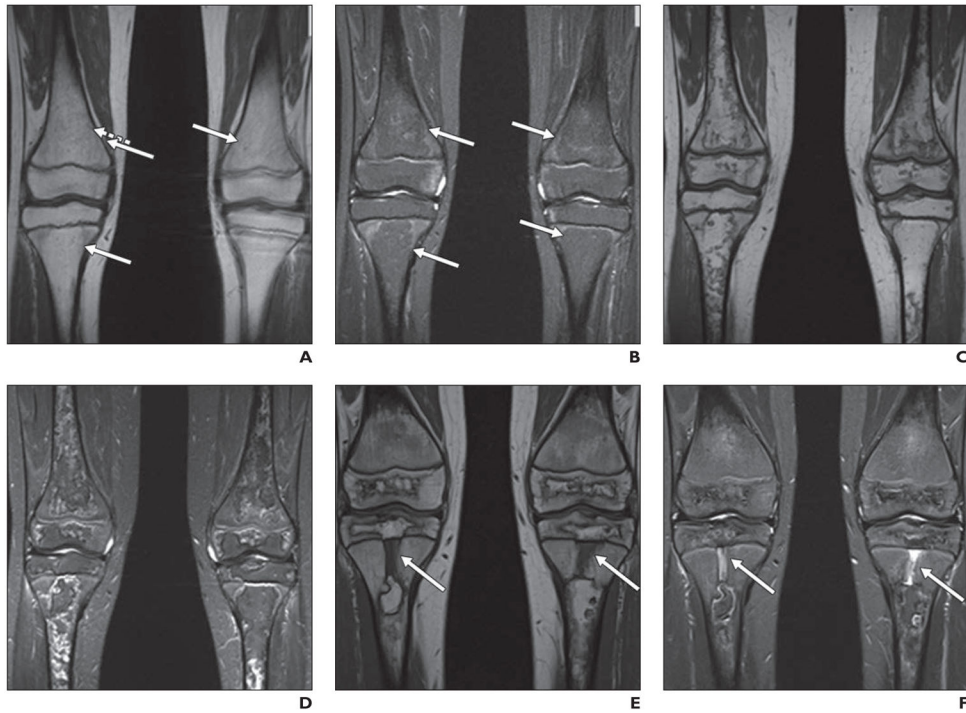


Fig. 1. 9-year-old girl being treated for standard-risk acute lymphoblastic leukemia who underwent routine MR screening for osteonecrosis

A and B, Coronal unenhanced T1-weighted (**A**) and STIR (**B**) images of knees show very subtle geographic signal changes (*arrows*) in distal femoral and proximal tibial diametaphyses bilaterally. These signal changes are less well defined than those described in literature for osteonecrosis.

C and D, MR images show that over course of 3 months, these changes evolved into typical geographic signal changes of osteonecrosis.

E and F, Annual follow-up examinations (not shown) revealed progressive definition of these extensive lesions, with overall decrease in extent. Note rectangular foci of abnormal centrally located metaphyseal signal in proximal tibias (*arrows*), dark on T1-weighted image (**E**) and bright on STIR image (**F**). Over course of 3 years, these abnormalities narrowed transversely and elongated, coincident with longitudinal growth of patient. These findings represent cartilaginous ingrowths from arrested enchondral ossification.

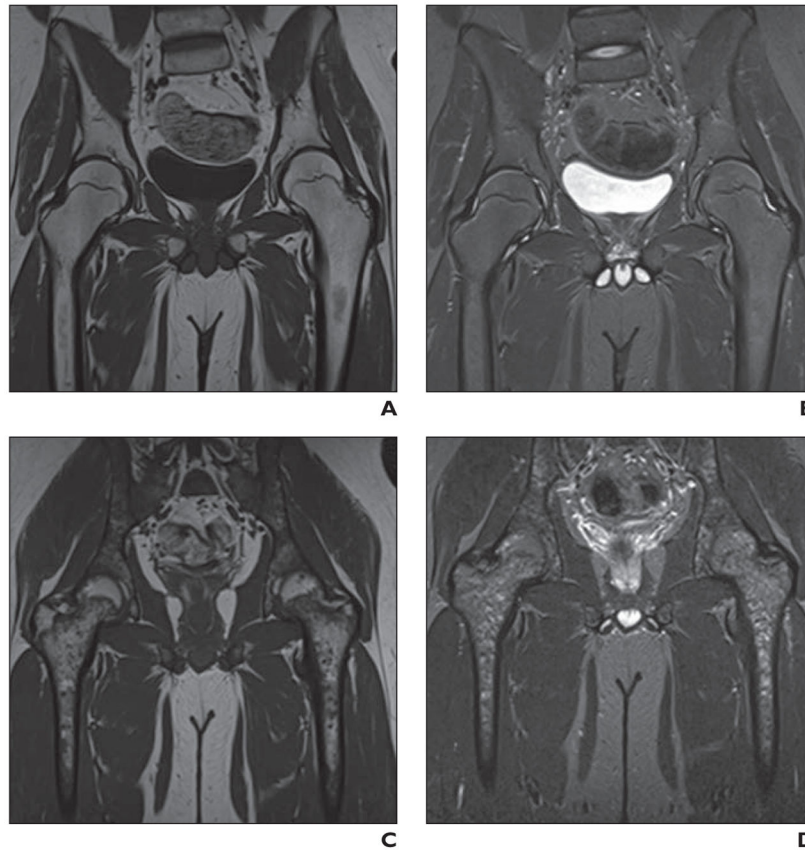


Fig. 2. Relapse of acute lymphoblastic leukemia in 14-year-old boy who underwent stem cell transplantation for acute lymphoblastic leukemia

A and B, MR images of hips obtained as part of pretransplantation assessment reveal no evidence of osteonecrosis or other abnormality of bones and soft tissues.

C and D, MR images obtained 1 year after bone marrow transplantation reveal numerous foci of decreased signal on T1-weighted and increased signal on STIR sequences indicative of relapsed leukemia.

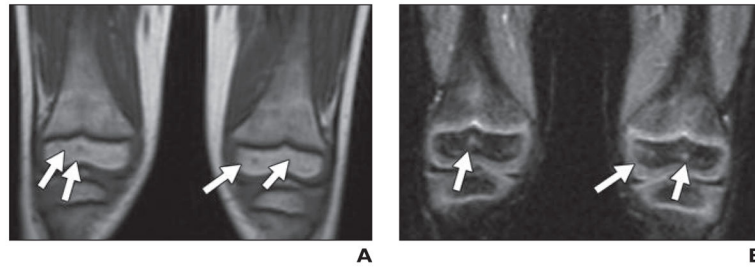


Fig. 3. Nonspecific punctuate lesions that can be confused with tiny areas of osteonecrosis in 4-year-old boy

A and B, T1-weighted image (**A**) shows tiny foci of decreased signal (*arrows, A*) and STIR image (**B**) shows bright signal (*arrows, B*). These may be confused with tiny foci of osteonecrosis.

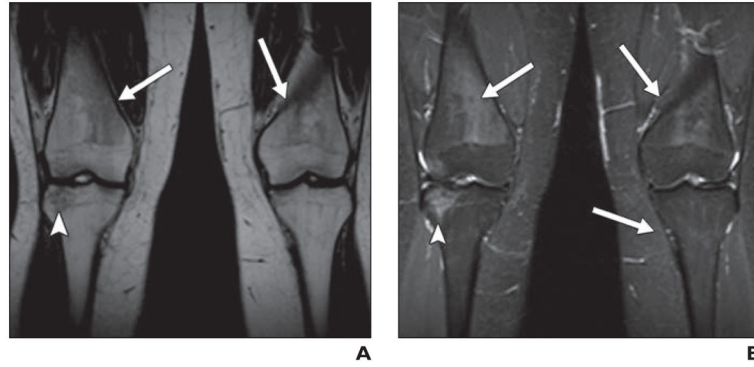


Fig. 4. Mottled marrow pattern in 18-year-old man previously treated for acute lymphoblastic leukemia who underwent MRI for complaint of chronic knee pain

A and B, Coronal unenhanced T1-weighted (**A**) and STIR (**B**) images of knees show bilateral heterogeneous marrow signal (*arrows*) in distal femoral and proximal tibial metaphyses, which is mildly dark on T1-weighted and bright on STIR images. These changes became less apparent over course of 2 years (not shown). Also note area of nonspecific edema (*arrowheads*) in right lateral tibial epiphysis, which completely resolved over 2 years.

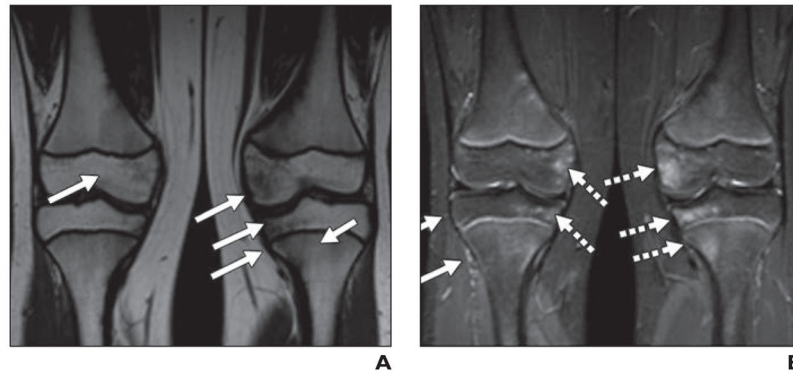


Fig. 5. Nonspecific patchy edema in knees in 13-year-old boy who had completed treatment for leukemia and underwent MRI surveillance for development of osteonecrosis to evaluate knee pain

A and B, Coronal unenhanced T1-weighted (**A**) and STIR (**B**) images of knees show poorly defined decreased signal on T1-weighted and increased signal on STIR images, indicative of edema involving distal femoral and proximal tibial epiphyses and proximal left tibial epiphysis and metaphysis (*arrows*). These changes resolved at time of follow-up MRI 8 months later.

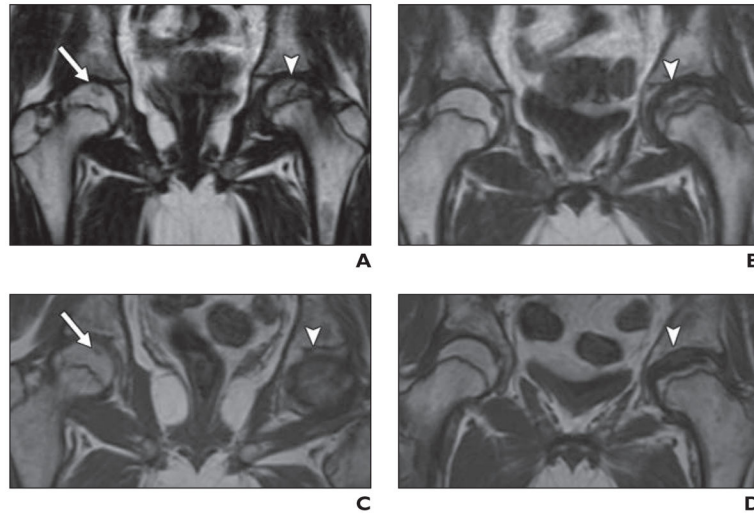


Fig. 6. 15-year-old boy treated for acute lymphoblastic leukemia and asymmetric osteonecrosis of hips

A and B, Coronal unenhanced T1-weighted MR images of hips show small focus of osteonecrosis in right femoral head (*arrow*, **A**) and large (involving greater than 30% of articular surface) focus in left femoral head (*arrowhead*).

C and D, Over course of 18 months, small lesion remained stable (*arrow*, **C**) but eventually healed (images not shown). Lesion of left femoral head (*arrowhead*) rapidly progressed to collapse.

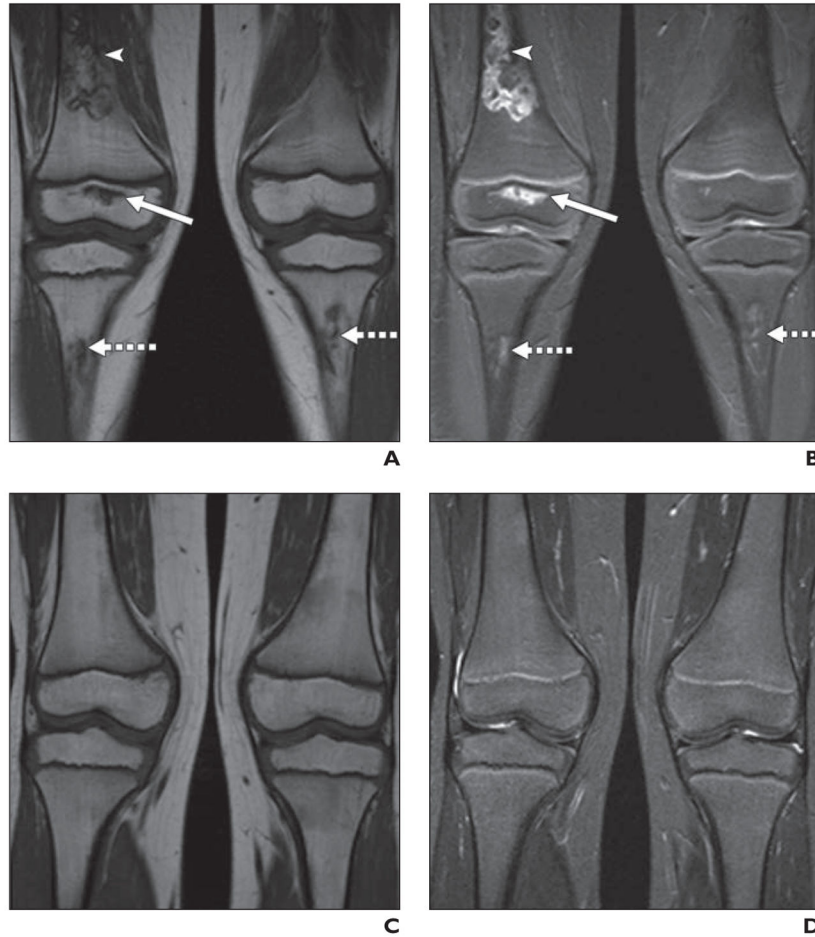


Fig. 7. Healing osteonecrosis of knees in 4-year-old girl undergoing treatment of acute lymphoblastic leukemia who was prospectively monitored annually for osteonecrosis of hips (normal throughout monitoring) and knees

A and B, Coronal unenhanced T1-weighted (**A**) and STIR (**B**) images of knees show small lesion of right distal femoral epiphysis (*solid arrows*), large lesion of distal right femoral diaphysis (*arrowheads*), and moderate-sized lesions of proximal tibial diaphyses bilaterally (*dotted arrows*).

C and D, Over course of 4 years, osteonecrotic lesions healed. Coronal unenhanced T1-weighted (**C**) and STIR (**D**) images of knees show no evidence of osteonecrosis.