# Causes of Pain in Early and Advanced Stage Osteonecrosis

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## 21.1 Introduction

The natural history, pathophysiology, and etiology of pain in nontraumatic osteonecrosis (ON) are poorly understood. In most clinical scenarios, a patient presents with pain which then leads to imaging examinations that identify the ON. Therefore, it is difficult to determine the frequency of asymptomatic disease. Nonetheless, it is clear that asymptomatic disease occurs as it is often identified incidentally, either in a contralateral site or when imaging is performed for unrelated reasons.

A better understanding of both when symptoms occur and how they are temporally related to the onset of disease is important as pain may be erroneously attributed to ON that is seen on imaging when the true etiology of pain lies elsewhere. In addition, the causes of pain are important to identify in order to provide treatment that effectively resolves the pain. There are numerous potential causes for pain that vary with the stage of ON.

## 21.2 Natural History

Prospective, longitudinal, observational studies are rare in ON. Nonetheless, several screening studies using magnetic resonance imaging (MRI) have revealed that findings of ON usually precede pain [1–6]. Pain rarely occurs at the time of disease onset. The best predictor of disease progression is the extent of involvement, regardless of how this is quantified. Plain radiographs are not as sensitive as MRI for the detection of ON; therefore, MRI imaging is essential for detecting this disease in an asymptomatic patient. In many scenarios, a patient may not have pain until subchondral collapse occurs. As any intervention attempting to salvage the native femoral head is more successful prior to subchondral collapse, understanding the natural history and relationship between pain and disease onset is crucial.

## 21.3 Possible Causes of Pain

### 21.3.1 Increased Marrow Pressure and Edema

There are several aspects of the pathophysiology of ON that may result in increased marrow pressure. These are related to (1) mechanical blockage of the microvasculature as seen in sickle cell disease, Gaucher's disease, hyperlipidemia syndromes, as well as thromboembolic disorders; (2) disruption of the blood supply to the bone marrow due to any of the above diseases; (3) bone marrow infarct and cellular necrosis secondary to the disruption of the blood supply that eventually leads to bone marrow edema and intraosseous compartment syndrome (normal pressure is 20–30 mm of Hg); (4) localized osteopenia and osteoporosis; and (5) direct cellular toxicity possibly secondary to medications or abnormal metabolites [7].

The most striking example of pain from bone marrow edema is the entity bone marrow edema syndrome (BMES) in which patients have marked, severe groin pain demonstrated with increased tracer uptake in the femoral head on Tc-99 bone scan and MRI findings of diffuse, regional marrow edema (Figs. 21.1, 21.2) [2].

In ON, edema at the hyperintense T2 band on the edge of necrosis may also potentially cause pain as opposed to the diffuse, regional marrow edema seen in BMES. However, in ON, this pain may or may not correlate with the stage or extent of anatomic involvement of the bone [1]. Patients with these symptoms typically have diffuse, polyostotic ON involving both subchondral and large metaphyseal infarcts and present with diffuse bone pain, analogous to sickle cell

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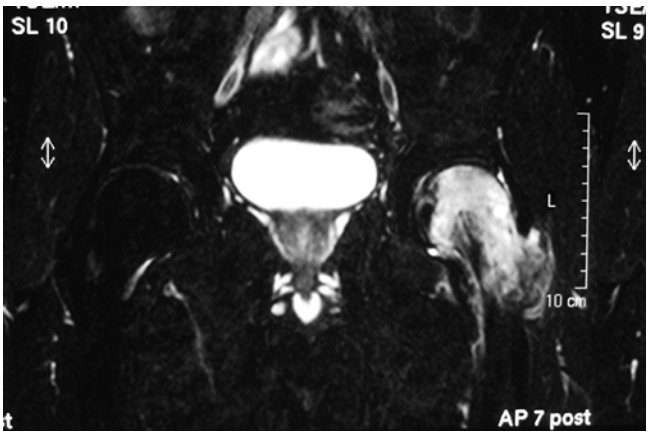



**Fig. 21.1** MRI findings (fat suppression, fluid sensitive sequence) of bone marrow edema syndrome showing marked, bright, hyperintense signal in left femoral head and neck

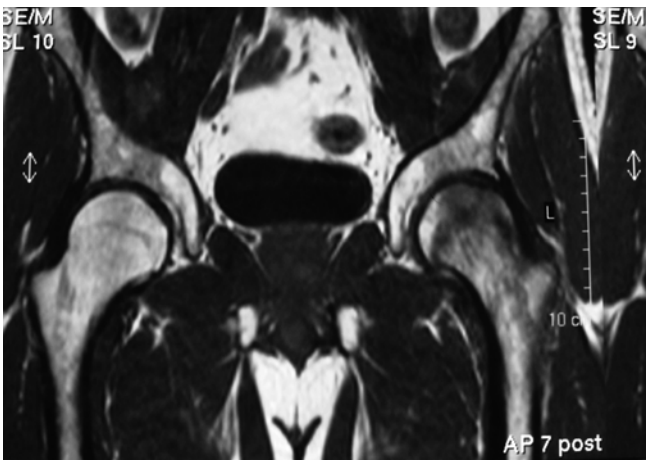



**Fig. 21.2** MRI findings (T1 sequence) of bone marrow edema syndrome showing dark, hypointense signal in left femoral head and neck

disease patients. Commonly, this will occur in ON related to steroid usage for either bone marrow transplantation or treatment of acute lymphoblastic leukemia (Fig. 21.3).

### 21.3.2 Subchondral Fractures

These are the fractures through the necrotic subchondral bone which most often occurs in the superolateral aspect of the femoral head [8]. This classical finding is seen as a "crescent sign" on radiographs in ARCO stage 3 disease and is responsible for increasing pain with activity in stage 3 of the disease process. These fractures may also lead to instability of the overlying articular cartilage with loss of fixation to the subchondral bone occurring (Fig. 21.4a, b). At times a gap may develop between the subchondral bone and overlying cartilage leading to a joint effusion (Fig. 21.5).

### 21.3.3 Degenerative Joint Disease

The unstable articular cartilage eventually will fracture at the margin of the subchondral bone depression resulting in a loose flap of cartilage. This is associated with flattening of the femoral head and the loss of contour initiates the early degenerative cascade with subsequent advanced degenerative changes responsible for pain either at rest or with minimal activity [2]. The etiology of persistent disabling pain in late stages of ON involves degenerative joint disease that is a combination of joint effusion, synovitis, osteochondral fragments, and a bone-on-bone erosive process that is similar to the end-stage osteoarthritis from any other cause.

## 21.4 Causes of Pain in Different Stages of Disease

As there are multiple causes for pain in ON, they may vary depending upon the specific stage of disease (ARCO staging Table 21.1) [9].

### 21.4.1 ARCO Stage 1

By definition, there is no subchondral fracture. Most of the patients are asymptomatic. If a patient has pain, it is likely due to the onset of intraosseous hypertension because of abnormally high content of fluid in the bone marrow secondary to acute bone marrow ischemia. In this stage mild pain can also be perceived as severe by some patients [5].

### 21.4.2 ARCO Stage 2

Localized osteopenia, marrow necrosis, and bone infarcts are possibly responsible for the dull aching pain in this stage [2]. Patients that have polyostotic disease with large metaphyseal infarcts typically have diffuse poorly localized, vague, non-activity-related pain. This likely is due to elevated intraosseous pressure and/or marrow edema accentuated by the large infarcts. In some patients, a synovial effusion is present despite the absence of a demonstrable subchondral fracture (Fig. 21.3). As is typical for any synovial effusion, the distended joint capsule is symptomatic. Some patients with ARCO stage 2 ONFH may be asymptomatic as well. During this stage, in the absence of a synovial effusion, determining whether or not a patient's pain is due to ON or some other etiology can be challenging (Fig. 21.6a–c).

### 21.4.3 ARCO Stage 3

Onset of subchondral collapse, flattening of the articular surface, and bone impaction resulting in increased intraosseous pressure are the main causes of pain with activity [2, 10]. In

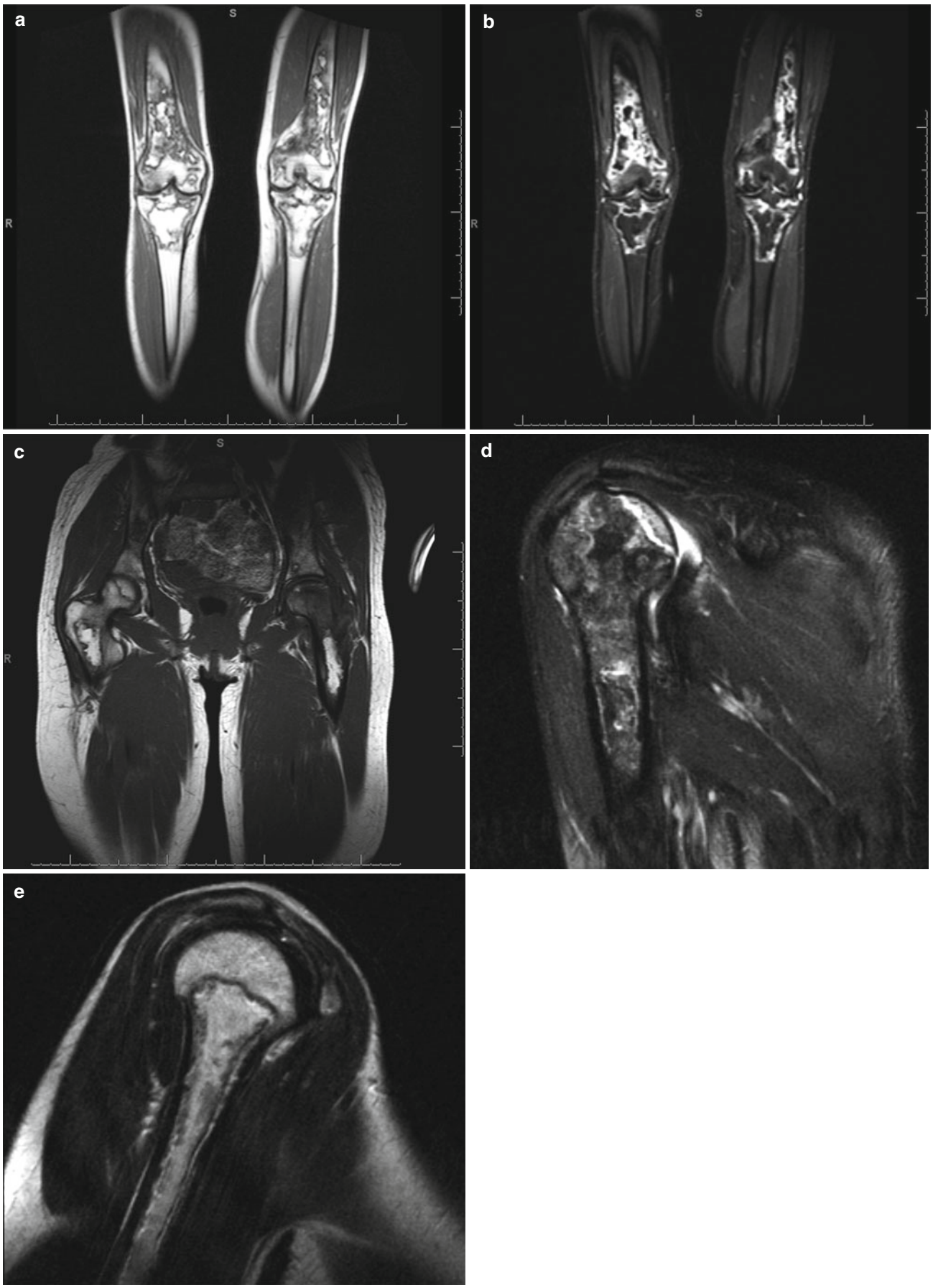



**Fig. 21.3** A case example of polyostotic ON involving bilateral distal femur and proximal tibia (**a**, **b**), femoral head and proximal femora (**c**), and proximal humerus (**d**, **e**) as seen on MR

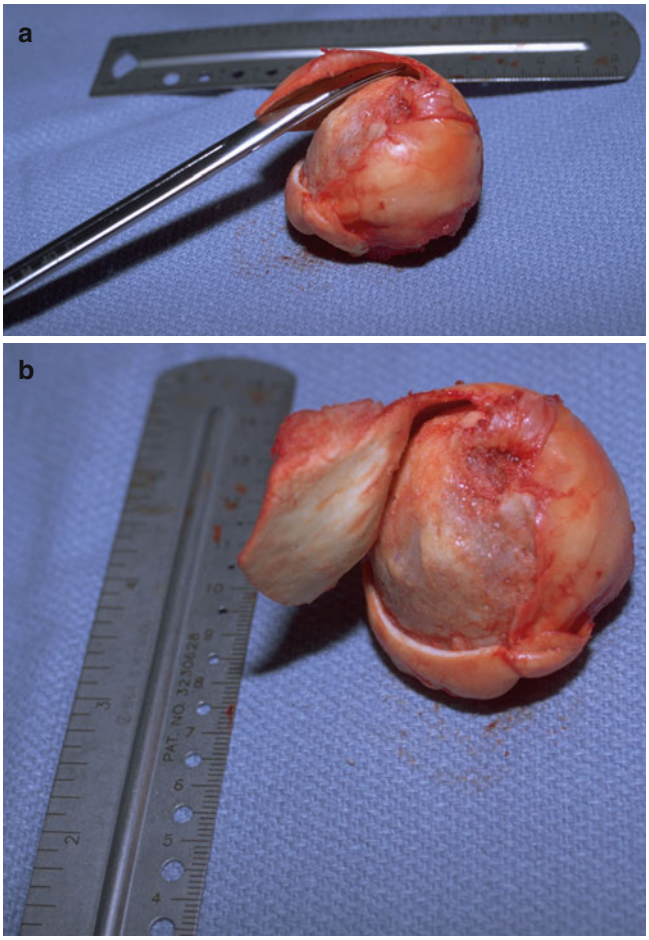



**Fig. 21.4** (**a**, **b**) A case example of underlying detachment of the cartilage from the bone in the femoral head seen during hip replacement surgery

addition, a synovial effusion is usually present when a joint incongruity is present.

### 21.4.4 ARCO Stage 4

The irregularity of the articular surface initiates fissures in the cartilage, subsequently followed by onset of advanced degenerative joint disease with corresponding changes on both sides of a joint (e.g., acetabulum) and worsening pain both at rest and with activity [2].

## 21.5 Clinical Features and Presentation

The most accurate clinic-radiological data comes from prospective screening studies performed in high-risk patient groups [1, 11–14].

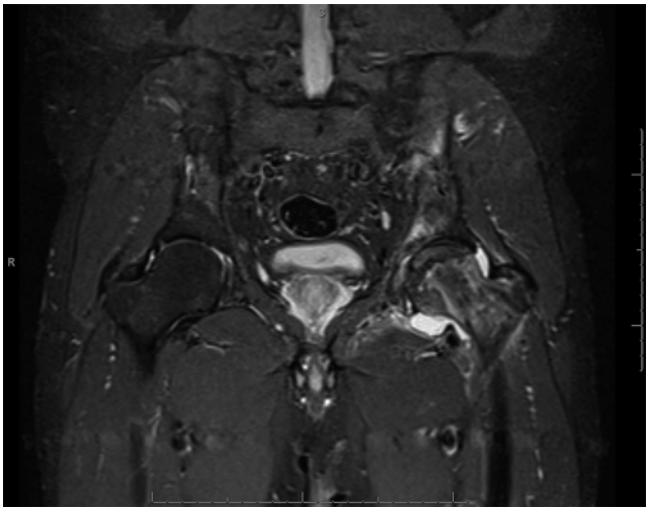


**Fig. 21.5** MRI STIR sequence with contrast showing ON with subchondral fracture in the pre-collapse stage. Note the unilateral synovial effusion in the left symptomatic hip and absence of effusion in the right asymptomatic hip

### 21.5.1 Temporal Relationship Between Diagnosis and Pain

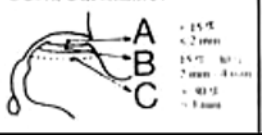
The majority of patients have no pain in the early stages of ON. Marston and Cheng prospectively followed 103 asymptomatic hips in solid organ transplant patients with serial MR imaging, and at 1 year after transplant, life table analysis revealed that 11 % of hips developed ON. Overall, 7 of the 8 hips in patients that developed ON were asymptomatic at the time of diagnosis. Kopecky et al. also prospectively followed 64 renal transplant patients for at least 1 year with serial MR imaging and seven hips had ON that eventually became symptomatic. In each of these hips, the MRI demonstrated ON before the onset of symptoms by a minimum of 3 months (range 3–10). In a mixed population of patients with ethanol- and steroid-related ON, Kang et al. in 2013 found that 38/68 (56 %) hips that were diagnosed initially with asymptomatic disease became painful at a mean of 2.27 years (range 0.5–6.5 years). Therefore, these prospective studies clearly show that ON usually develops in an occult manner and patients are usually asymptomatic at disease onset.

### 21.5.2 Temporal Relationship Between Pain and Collapse

Several studies have shown that pain precedes collapse. Min et al. in 2008 prospectively followed 81 asymptomatic hips

**Table 21.1** Schematic modified outline of the five-stage Association Research Circulation Osseous (ARCO) international classification for osteonecrosis of the femoral head (Reproduced with permissions ARCO [9])

**ARCO INTERNATIONAL CLASSIFICATION OF OSTEONECROSIS**

| STAGE | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| FINDINGS | All present techniques normal or non-diagnostic | X-ray and CT are normal at least ONE of the below mentioned is positive | NO CRESCENT SIGN! X-RAY ABNORMAL: sclerosis, osteolysis, focal porosis | CRESCENT SIGN! on the X-ray and/or flattening of articular surface of femoral head | OSTEOARTHRITIS! joint space narrowing, acetabular changes, joint destruction |
| TECHNIQUES | X-ray, CT Scintigraph MRI | Scintigraph MRI *QUANTITATE on MRI | X-ray, CT Scintigraph MRI *QUANTITATE MRI & X-ray | X-ray, CT ONLY * QUANTITATE on X-ray | X-ray ONLY |
| SUBCLASSIFICATION | NO | LOCATION   | | | NO |
| QUANTITATION | NO | QUANTITATION % AREA INVOLVEMENT minimal A < 15 % moderate B 15 % - 30 % extensive C > 30 % LENGTH of CRESCENT A < 15 % B 15 % - 30 % C > 30 % % SURFACE COLLAPSE & DOME DEPRESSION   | | | NO |

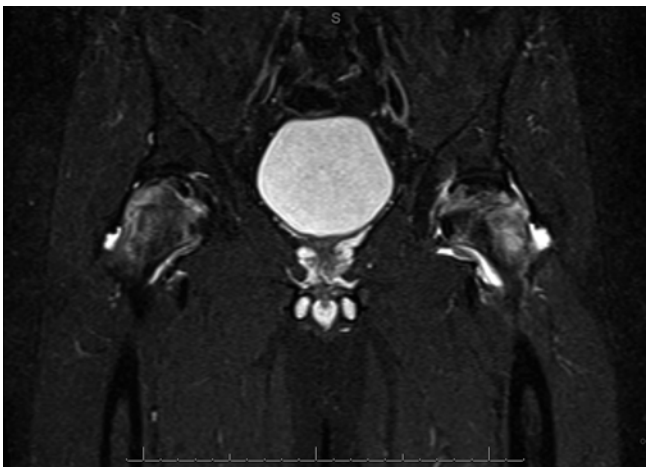


**Fig. 21.6** ARCO stage 2 bilateral disease of femoral head that with bilateral small effusions on MR but symptomatic on only one side

for a minimum of 5 years. The mean interval from diagnosis to onset of pain was 3.4 years (range 0.7–8.9) and 31/81 (38 %) of hips became symptomatic. The mean interval from diagnosis to collapse was 4.1 years (range 1.2–11.9) and pain always preceded collapse by a mean of 8 months (range 1–36). Hernigou et al. analyzed 121 asymptomatic hips in patients with sickle cell disease using radiographs. They found that 110 hips (91 %) became painful and collapse occurred in 93 (77 %). In all cases, pain preceded collapse. Although the study populations are different in these two studies, the finding that pain precedes collapse is consistent.

### 21.5.3 Duration of the Asymptomatic Period

The exact duration of the asymptomatic period in nontraumatic ON is variable. Studies to date have revealed that the time from MR diagnosis to onset of pain varies from 3 months to over 3 years (Table 21.2). This variance is probably due to differences in the cohort population, lesion size, and timing of diagnosis.

### 21.5.4 Risk Factors for Developing Pain

Pain characteristics are based mainly on the size and location of the lesion with larger size and lateral location being at

**Table 21.2** Studies showing the timing of the onset of pain from the initial MRI diagnosis

| Study author | Mean time to onset of pain from initial radiological diagnosis (in months) | Maximum range (in months) |
|---|---|---|
| Hernigou et al. | 64 | 20–204 |
| Min et al. | 40 | 7–99 |
| Kopecky et al. | 3 | 3–10 |

greatest risk for becoming symptomatic [13]. Kang et al. studied 68 patients with asymptomatic osteonecrosis of the femoral head and found out that the lesion size and location were significantly associated with symptom development. In their study of 20 hips with small lesions, 10 % became symptomatic; out of 29 hips with medium lesion, 69 % became symptomatic; and out of 19 hips with large lesion, 84.2 % became symptomatic. Also symptoms developed in 76.3 % of their hips with lateral location of the lesion on the femoral head, in 38.1 % of hips with central lesion, and in 10 % of hips with medial lesion.

### 21.5.5 Time from Risk Factor Insult to MR Diagnosis of Osteonecrosis

The time to development of disease cannot be assessed for risk factors such as sickle cell disease or ethanol usage or coagulopathies. However, the date of administration of steroids related to chemotherapy or immunosuppression can be identified and provide some information about the time to onset of disease. Kubo et al. studied 51 renal allograft recipients and detected abnormal MRI findings in 18 femoral heads of 10 patients at 6–16 weeks (average 10 weeks) from transplantation [15]. Sakaia et al. in their study on rabbit serum sickness model also concluded that ON could be detected very early within 1–12 weeks (average 6 weeks) on conventional MRI [16].

### 21.5.6 Characteristics of Pain in the Hip in Early, Precollapse Stages of ON (ARCO 1 and 2)

As patients with early precollapse ON may or may not have pain, it is a challenge to know whether or not to attribute pain to the presence of ON on imaging. In the absence of pathology or a pain-generating entity elsewhere, ON demonstrated on imaging is usually identified as the etiology for pain. The onset is usually insidious and sporadic in majority of the patients. The quality of the pain is typically similar to intra-articular pain of the affected joint that might be due to any other cause. If a joint effusion is present with imaging findings of ON, one can be confident that the ON is the cause of the symptoms.

In patients with polyostotic ON involving metaphyseal and subchondral sites, patient may complain of diffuse bone pain in all extremities. The quality of the pain is dull, aching, and mild or at times may seem out of proportion to findings on plain radiographs; however, the MR imaging usually shows bilateral, diffuse skeletal involvement (Fig. 21.4). Management of the pain in these patients is problematic due to the chronicity and severity of the symptoms that usually require narcotic analgesia.

### 21.5.7 Characteristics of Pain in the Hip in Late, Post-collapse Stages of ON (ARCO 3 and 4)

Pain at this stage is usually typical of degenerative arthritis. It is aggravated by joint motion and activities. In the lower extremity, an abnormal gait is present. Patients have difficulty sleeping and performing daily activities. In patients with bilateral joint involvement, their function may be severely curtailed.

## 21.6 Summary

Patients diagnosed with nontraumatic ON are usually asymptomatic initially. The duration of asymptomatic disease is variable [1]. In many cases, pain ensues and probably is related to elevation in the intraosseous pressure. The risk factors for developing pain are mainly the extent of disease and, when in the femoral head, the lateral location within the head. Pain usually precedes a subchondral fracture. The most likely pathophysiologies that cause pain are related to increased intraosseous pressure (from marrow edema and/or large infarcts), synovial effusion, or degenerative arthritis after joint incongruity from subchondral collapse. An accurate assessment of the etiology of pain in the setting of osteonecrosis is challenging but essential in order to optimize the successful resolution of pain after any treatment intervention.

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