

Osteoarthritis and Cartilage



Imaging atlas for eligibility and on-study safety of potential knee adverse events in anti-NGF studies (Part 1)



F.W. Roemer † ‡ *, C.W. Hayes §, C.G. Miller ||, K. Hoover §, A. Guermazi †

† Quantitative Imaging Center (QIC), Department of Radiology, Boston University School of Medicine, Boston, MA, USA

‡ Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany

§ Department of Radiology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

|| Medical Affairs, BioClinica, Newtown, PA, USA

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SUMMARY

Monoclonal antibodies that bind and inhibit nerve growth factor (NGF) have demonstrated both, good analgesic efficacy and improvement in function in patients with osteoarthritis (OA). Despite initial promising data, trials in OA had been suspended by the Federal Food and Drug Administration (FDA) due to concerns over accelerated rates of OA progression. Imaging will play a crucial role in future clinical trials to define eligibility of potential participants and to monitor safety during the course of these studies. This will require baseline and frequent follow-up radiographs of both, the index joints and other large weight bearing joints to identify subjects at risk prior inclusion and on study so treatment can be discontinued.

This imaging overview in the form of an atlas describes and illustrates potential exclusionary joint imaging findings at eligibility and potential adverse joint events on radiography and magnetic resonance imaging (MRI) in studies investigating a-NGF compounds. The overarching goal of this atlas is to facilitate trial design and to promote a common language and understanding between potential expert readers. This first section of the atlas will focus on knee joint specific findings that are relevant to a-NGF studies.

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Introduction

Monoclonal antibodies that bind and inhibit nerve growth factor (NGF) have demonstrated both, good analgesic efficacy and improvement in function in patients with osteoarthritis (OA) and low back pain^{1–5}. Despite initial promising data, trials in OA had been suspended in 2010 by the Federal Food and Drug Administration (FDA) due to concerns over accelerated rates of OA progression (i.e., rapid progressive osteoarthritis – RPOA) to total joint replacement particularly in the large joints of the lower limb^{6,7}. The observations about adverse events in tanezumab studies, one of the a-NGF compounds under investigation, lead to a report on the process and results of the adjudication of these events⁸. These adverse events were observed in patients using NGF-inhibitors alone, and more commonly in combination with non-steroidal

anti-inflammatory drugs (NSAIDs) suggesting that the cumulative analgesic effect of two separate classes of drugs prompted patients to permit increased joint loading lacking the usual pain that would limit such pathologic stress on an already damaged joint^{5,8}. The authors further reported a significant dose–response relationship between incident RPOA and increasing doses of tanezumab, which was greater when tanezumab was given in combination with NSAIDs⁸.

Since anti(a)-NGF therapies offer potential as the first new class of analgesics for many years, future studies of a-NGF compounds will require rigorous safety criteria. Imaging will play a crucial role in future clinical trials to define eligibility of potential participants and to monitor safety during the course of these studies. This will require baseline and frequent follow-up radiographs of both, the index joints and other large weight bearing joints to identify subjects at risk for RPOA and identify subjects on study with adverse events such as RPOA Type I or II so treatment can be discontinued. Additional magnetic resonance imaging (MRI) examinations will be important during the course of a study in cases of unexpected joint pain or swelling or in cases of discrepancy between clinical symptoms, mainly pain and radiographic findings⁶.

* Address correspondence and reprint requests to: F.W. Roemer, Department of Radiology, Boston University School of Medicine, FGH Building, 3rd Floor, 820 Harrison Ave, Boston, MA 02118, USA. Tel: 1-617-414-4954; Fax: 1-617-638-6616.

E-mail addresses: froemer@bu.edu, frank.roemer@uk-erlangen.de, frank.roemer@klinikum-augsburg.de (F.W. Roemer).

Thus, the aim of this imaging overview in the form of an atlas is to describe and illustrate potential exclusionary joint imaging findings at eligibility and potential adverse joint events on radiography and MRI in studies investigating a-NGF compounds. The overarching goal of this atlas is to facilitate trial design and to promote a common language and understanding between potential expert readers. This first section of the atlas will focus on knee joint specific findings that are relevant to a-NGF studies.

Methods

This atlas is based on eight in-person and 20+ teleconference meetings of four experienced musculoskeletal radiologists (FWR, CH, KH, AG) and a senior imaging expert (CGM) representing a contract research organization (CRO) active in a-NGF studies to define potential eligibility and safety findings relevant for a-NGF clinical trials. 400+ baseline and follow-up radiographic and MRI image examples of knee joints were reviewed in consensus to define the most relevant and characteristic imaging findings of entities that may be encountered during a-NGF studies at screening or during the course of a study. Images for this atlas were derived from personal teaching and training files of these radiologists and partly from a Pfizer library of knee radiographs obtained during the course of the tanezumab program. As the terminology for several of the potentially encountered findings is not uniform, the following section will briefly define those pathologic conditions for the purpose of this atlas.

The term osteonecrosis in the context of this atlas is used for a focal circumscribed or extended region of infarcted bone. “Avascular necrosis” and “bone infarct” are commonly used in synonymous fashion. Any focus of infarcted bone regardless of its location within the bone will be defined as osteonecrosis. The term “spontaneous osteonecrosis of the knee” (also called SONK or SPONK) will be summarized under subchondral insufficiency fracture (SIF), reflecting current etio-pathologic understanding^{9,10}.

RPOA Type 1 is defined as rapid loss of joint space width (which is defined as ≥ 2 mm or other protocol-specific cut-off) within approximately 1 year without evidence of bone loss or destruction. The diagnosis can only be established whenever prior images are available to allow longitudinal assessment¹¹.

RPOA Type 2 is used for a condition of abnormal bone loss or destruction in a short period of time, including limited or total collapse of at least one subchondral surface that is not a feature of conventional advanced OA¹².

A SIF may stabilize or heal with minor deformity or no deformity, or may progress to complete subchondral collapse. The latter is often referred to as SONK or SPONK in the knee joint¹³. For the purposes of this atlas, the term “SONK” will not be used as it is considered to be part of the spectrum of SIF and not a separate condition. SIF may be seen on radiography as a focal area of subchondral osteopenia and once articular surface deformities are present. MRI is more sensitive to detect early manifestations of SIF, once these are still potentially reversible and is able to define prognosis¹⁴.

Atrophic osteoarthritis is characterized by joint space narrowing (JSN) without relevant osteophyte formation and absence of erosions or other radiographic signs of inflammatory arthritis^{15,16}. In some cases, RPOA Type I is preceded by an atrophic OA appearance; therefore subjects exhibiting radiographic atrophic OA at the screening visit are commonly excluded from entering any study.

Severe malalignment may be a marker of more rapid OA progression and thus, may be an additional diagnosis of exclusion at eligibility. Cut-off values of severe malalignment are not defined in the literature and may vary. Commonly used cut-offs are between 6 or 10° varus or valgus in the anterior–posterior direction¹⁷.

Large areas of bone marrow edema without fracture line as visualized on fluid-sensitive fat-suppressed MRI are usually painful conditions and will explain incident or worsening of pain in a number of subjects^{18,19}. These can be part of the OA disease process especially if they are observed in a subchondral location²⁰. They may also be the result of more acute overloading leading to a stress reaction that manifests itself as a large area of bone marrow edema, but does not show a characteristic hypointense fracture line²¹. “Idiopathic transient bone marrow edema” will present in identical fashion^{22,23}.

Diagnoses of exclusion for **eligibility** are those that potentially increase the risk of RPOA Type I or II. These are pre-existing atrophic OA and RPOA, SIF and potentially severe malalignment of the knee. Additional diagnoses of exclusion for eligibility may be severe chondrocalcinosis, which may be observed in association with OA²⁴. However, the threshold definition for “severe” may vary between studies and the literature is not unequivocal in regard of rates of progression²⁵. Other arthropathies, e.g., rheumatoid arthritis, gout, systemic metabolic bone or joint diseases are reasons for excluding subjects from entering a trial and if detected while on-study, a reason to recommend discontinuation of treatment but may vary between studies. These also include primary or metastatic malignant tumors consistent with grades 2 and 3 of the Lodwick classification^{26,27}. In addition, fractures (stress, traumatic, pathologic) detected by either radiography or MRI are reason to exclude a subject from entering a trial regardless of cause of fracture. Fractures are defined by a visible fracture line.

Diagnoses relevant for safety after enrollment (i.e., joint safety findings) are RPOA Types I and II, SIFs, osteonecrosis and pathologic fractures plus incidental findings of the entities described above. Several of these diagnoses have non-specific findings on the radiograph or cannot be detected radiographically in early stages. Thus, in cases of inconclusive or suspicious radiography an additional MRI examination will commonly be acquired to rule out or confirm some of these diagnoses especially in early stages and thus, MRI findings will be presented in addition.

The image acquisition process being defined in this atlas is that potential participants will be screened by radiography for eligibility criteria, using a conservative approach to allow subjects being included into the study. Once included into a study, radiography will still be the first line imaging approach, but MRI scans of any or all joints may be requested if needed (i.e., “for cause”, commonly requested due to equivocal radiographic findings or discrepancies between radiography and clinical symptoms).

The term “adverse event(s)” is used throughout this atlas in relationship to clinical trials as defined by the FDA: “Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.”²⁸ No causality or level of whether this is a “serious” adverse event is being attributed in this atlas.

The radiographic imaging acquisition protocol that is being recommended for the knee in aNGF studies is the posterior–anterior view in a modified Lyon-Schuss technique^{29–31}. This technique has been shown to provide the best precision for evaluating JSN in clinical trials^{32,33}. The MRI protocol should be a standard clinical protocol or an abbreviated protocol consisting of at least a sagittal and coronal proton density or T2-weighted fat suppressed sequence and a coronal or sagittal T1-weighted non-fat suppressed sequence. The use of 1.5 T or 3 T large bore MRI is recommended for assessment of joints in aNGF studies. 1.0 T or 1.5 T extremity scanners may be used alternatively but are only applicable to image the knee joint and not other joints commonly assessed in aNGF studies such as the hip or shoulder.

Results

The radiographic appearance of atrophic osteoarthritis, one of the diagnoses of exclusion at eligibility is depicted in Fig. 1. Figure 2 exemplifies a case of RPOA Type 1 over the course of 18 months. The catastrophic events of two cases of RPOA Type II are illustrated in Fig. 3. Several examples of the spectrum of SIFs with or without focal areas of necrosis are illustrated in Figs. 4–8. Characteristic MRI findings of osteonecrosis (or bone infarcts) are shown in Fig. 9. Examples of large areas of subchondral bone marrow edema in the context of OA or due to mechanical overload (i.e., stress reaction) without a fracture are shown in Fig. 10. Figure 11 represents an example of transitory migrating bone marrow edema syndrome, a self-limiting entity that may affect

several joints over time. Other arthropathies may be potential diagnoses for exclusion at screening and include severe chondrocalcinosis (Fig. 12), inflammatory arthritis, pigmented villonodular synovitis (PVNS), or fracture, which may also be safety endpoint on study (Figs. 13 and 14). Primary or secondary malignant bone tumors are a diagnosis of exclusion while some tumor-like entities such as enchondroma, non-ossifying fibroma or ganglion cysts may not. Some of these entities are shown in Figs. 15 and 16. Finally, severe malalignment may be considered a risk factor for more rapid progression and thus, may be an exclusionary diagnosis at eligibility. An example of severe varus and valgus malalignment is shown in Fig. 16. This atlas is not illustrating all potential diagnoses that might be relevant for eligibility or safety but covers the large majority of these.

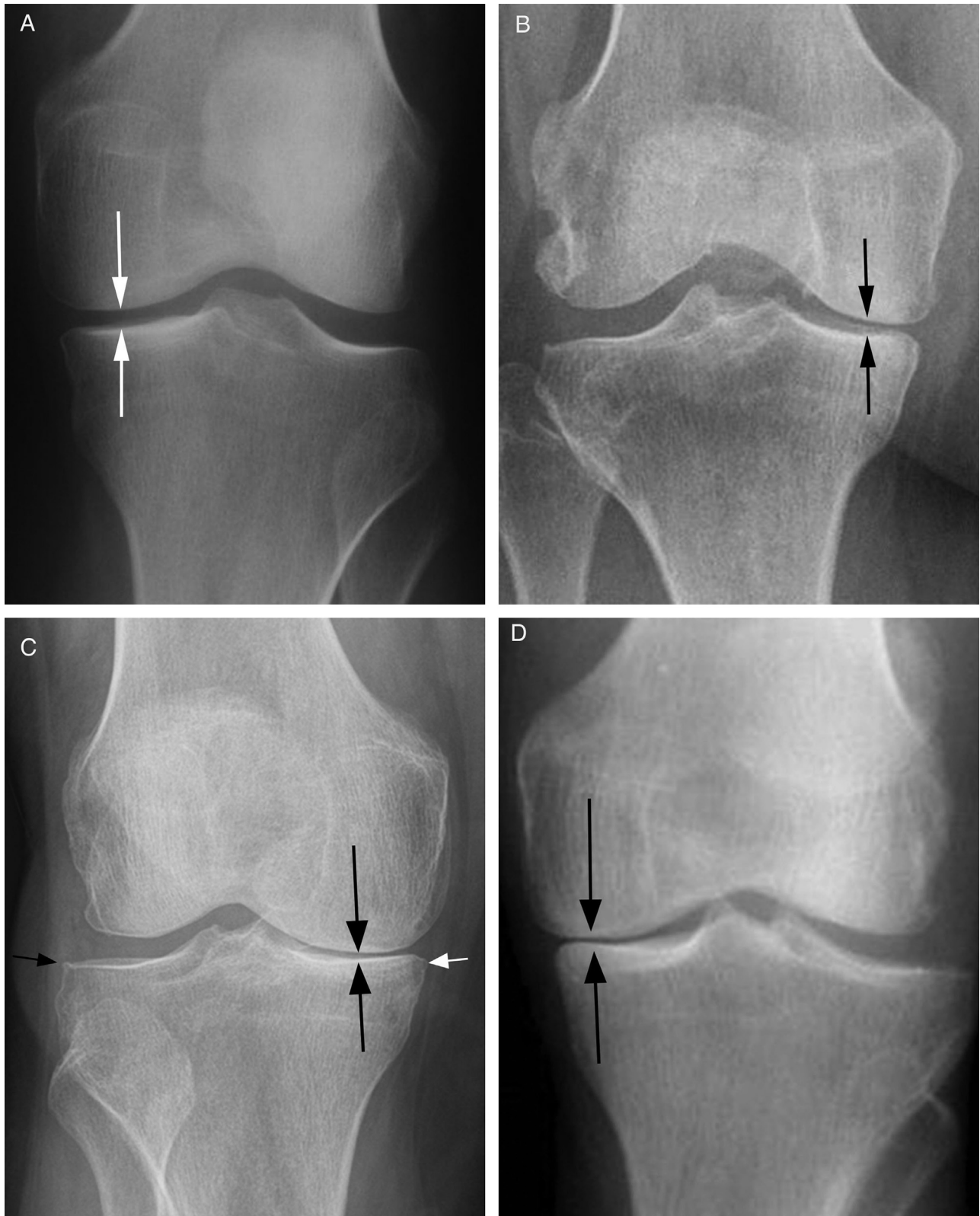


Fig. 1. Different examples of atrophic osteoarthritis. A. Anterior–posterior (a.p.) radiograph shows definite (grade 1 according to the Osteoarthritis Research Society International (OARSI) atlas) JSN at the medial tibio-femoral compartment (arrows) without osteophyte formation. B. Moderate JSN is depicted (arrows – grade 2 according to the OARSI atlas) with only minimal osteophyte formation at the lateral tibia. C. Severe JSN is shown in this example (large arrows) with presence of only a small osteophyte at the lateral tibia (small black arrow) and another very small osteophyte at the medial tibial margin (short white arrow). As some remaining joint space is still present, this knee qualifies for a grade 2 according to OARSI. D. Another example of advanced grade 2 JSN is shown in this radiograph (arrows). No osteophytes are observed. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage*. 2007;15 Suppl A:A1-56.

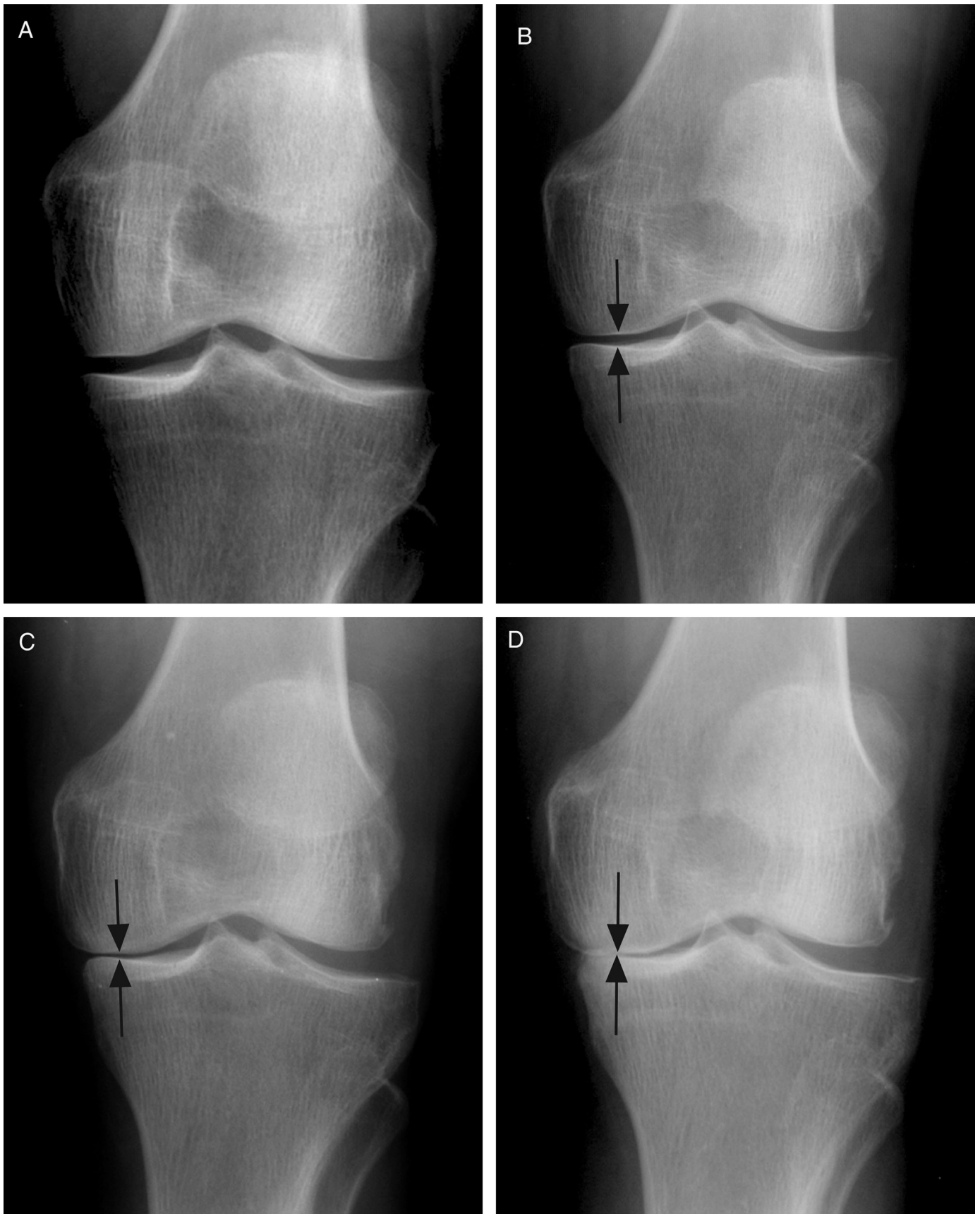


Fig. 2. RPOA Type 1 over the course of 18 months. A. Baseline radiograph shows normal medial and lateral joint space width. B. 6 months follow-up radiograph depicts definite medial JSN (arrows) with persistent absence of osteophytes medially. C. Radiograph acquired 8 months after image B shows progressive loss of joint space medially (arrows). D. 4 months later bone-to-bone appearance with complete obliteration of joint space at the medial compartment is observed (arrows).

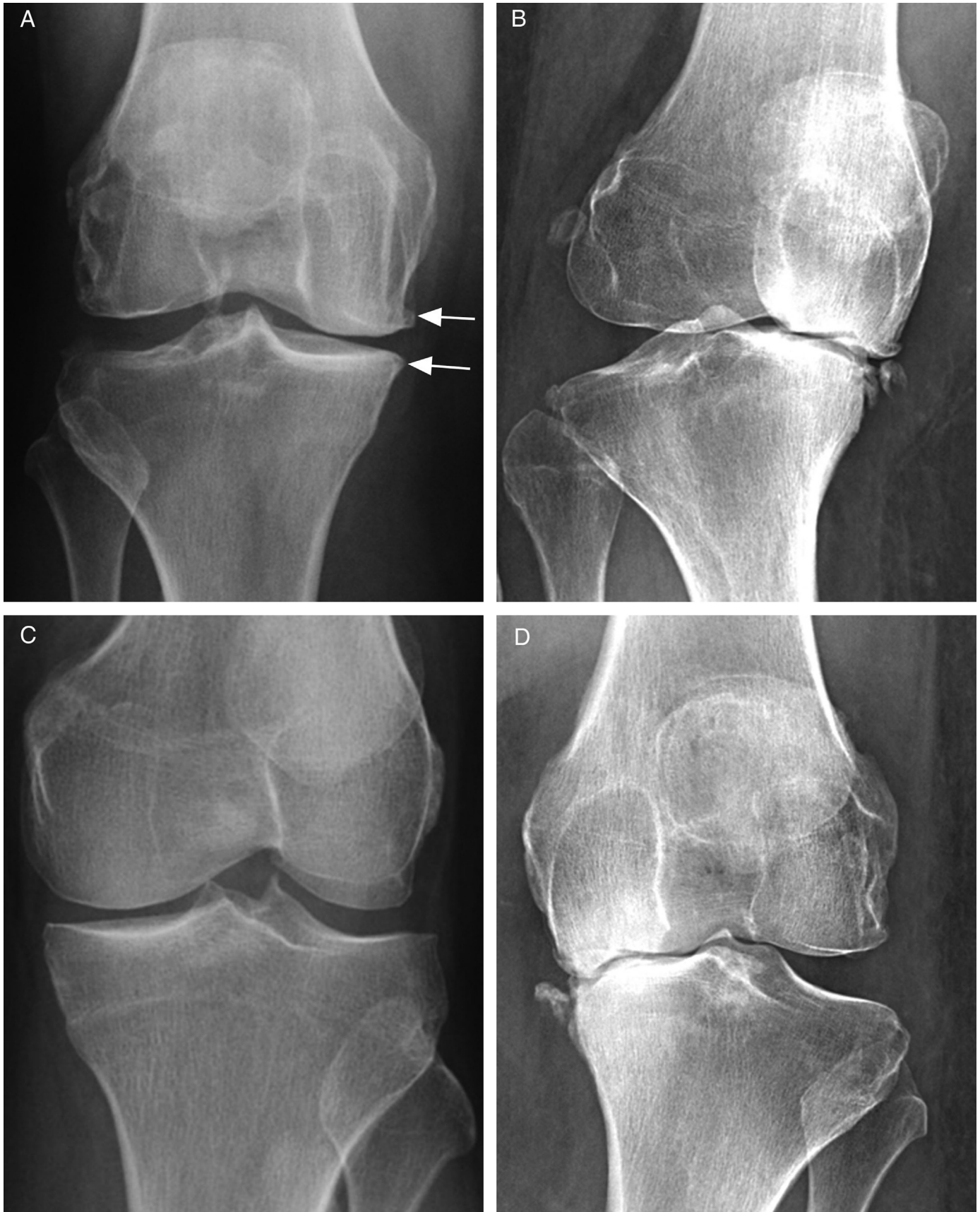


Fig. 3. RPOA Type II over a period of 9 months. A. Baseline radiograph shows definite osteophytes at the medial tibial and femoral margin (arrows) and a regular articular surface contour. B. 9 months later deformity of the medial femoral and tibial articular surface is noted. In addition there is collapse especially of the tibial plateau. Consequent varus deformity is observed. C. Another knee exhibits minimal medial joint space width at baseline without relevant osteophyte formation. D. Follow-up image 10 months later shows marked deformation of the medial compartment articular surface consistent with RPOA Type II.

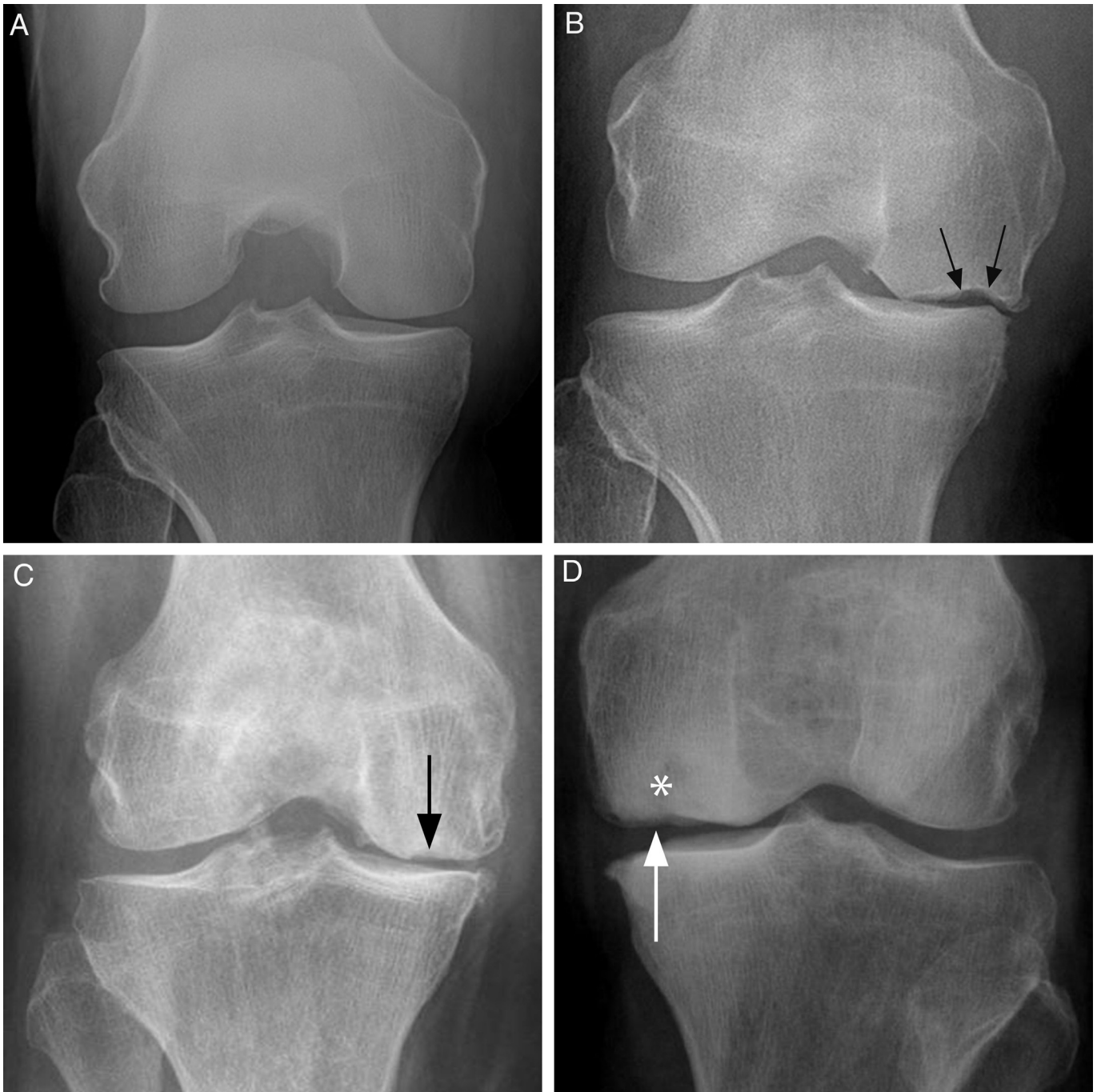


Fig. 4. SIF and subchondral collapse (also known as SPONK). A. Baseline image shows mild medial JSN on the a.p. knee radiograph without signs of osteophyte presence. B. Follow-up image 10 months later reveals femoral surface deformity (arrows) as a sequela of SIF. A corresponding MRI at baseline (not shown) exhibited diffuse bone marrow edema, which cannot be visualized by radiography. C. Another example shows medial femoral subchondral collapse as the result of SIF with mild depression of the femoral surface (arrow). D. Radiograph of advanced subchondral collapse secondary to SIF with deformity of the medial femoral surface (arrow). Note marked subchondral sclerosis (asterisk) reflecting structural remodeling in the subchondral bone due to altered local biomechanical loading.

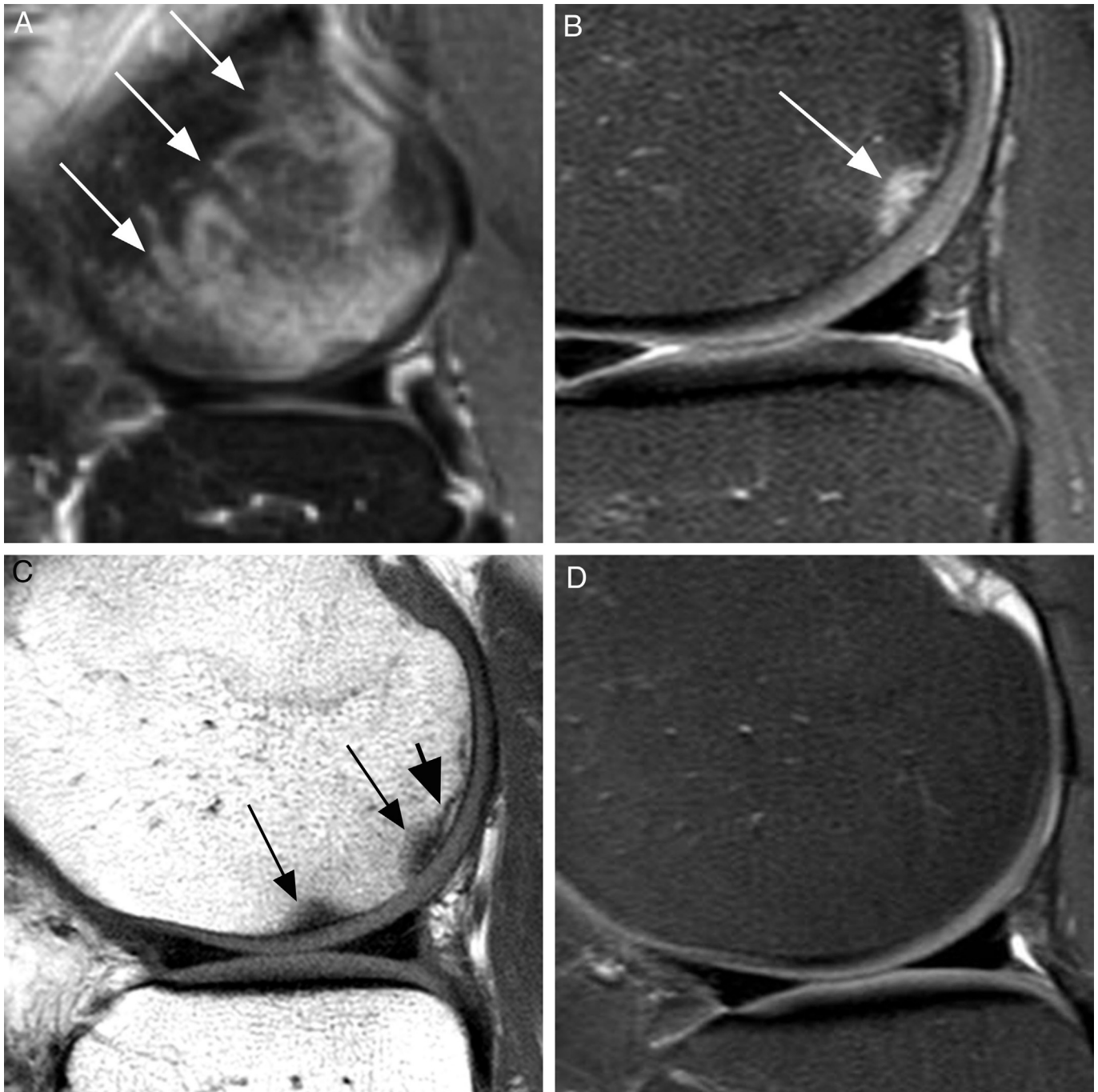


Fig. 5. Resolution of SIF over time. A. Baseline sagittal fat suppressed T2-weighted MR image shows an extensive area of diffuse bone marrow edema in the lateral femoral condyle (arrows). B. Follow-up proton density-weighted fat suppressed image 4 months later depicts marked regression of bone marrow edema but a persistent focus of subchondral hyperintensity (arrow). C. Corresponding T1-weighted image exhibits edema-like changes as hypointensities (long arrows). In addition, there is a subchondral fracture line (short arrow). Note intact articular chondral surface. D. Follow up proton density-weighted fat suppressed image another 8 months later shows complete resolution of signal changes and fracture. All of these changes visualized on MRI were occult on radiography.

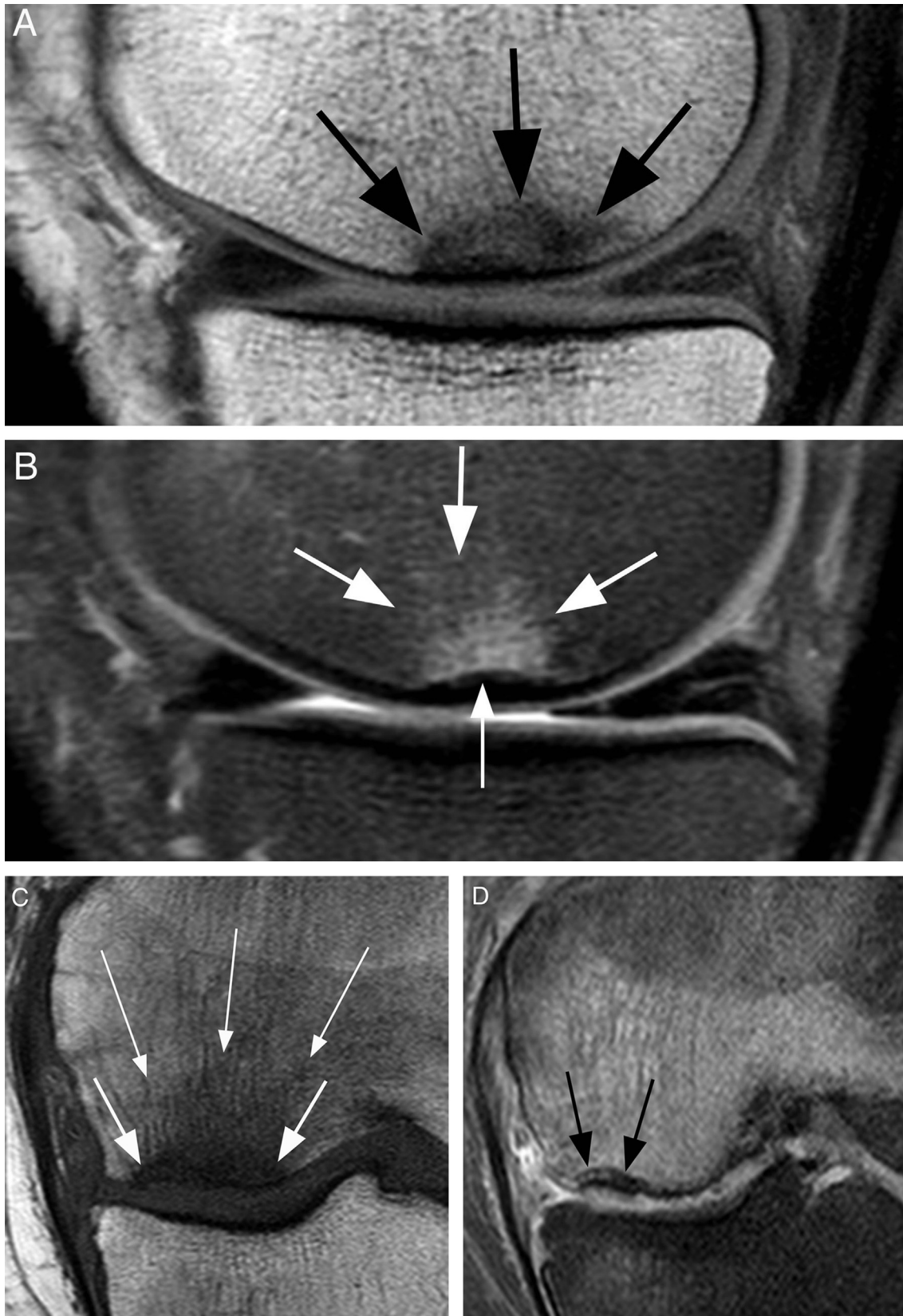


Fig. 6. SIF with necrosis and unfavorable outcome. A. Coronal T1-weighted MR image shows an area of subchondral ill-defined hypointensity consistent with bone marrow edema (arrows). B. Corresponding proton density-weighted fat suppressed image depicts edema-like signal as diffuse hyperintensity (large arrows). In addition there is a focal area of hypointensity directly adjacent to the subchondral plate representing subchondral necrosis (small arrow). Articular surface is at risk for collapse. C. Another knee shows a more advanced stage of SIF with a large area of subchondral necrosis (thick arrows) and surrounding diffuse bone marrow edema-like alterations (thin arrows). D. Corresponding coronal proton density-weighted fat suppressed image depicts focal collapse of articular surface (arrows) and extensive edema-like signal in the medial femoral condyle.

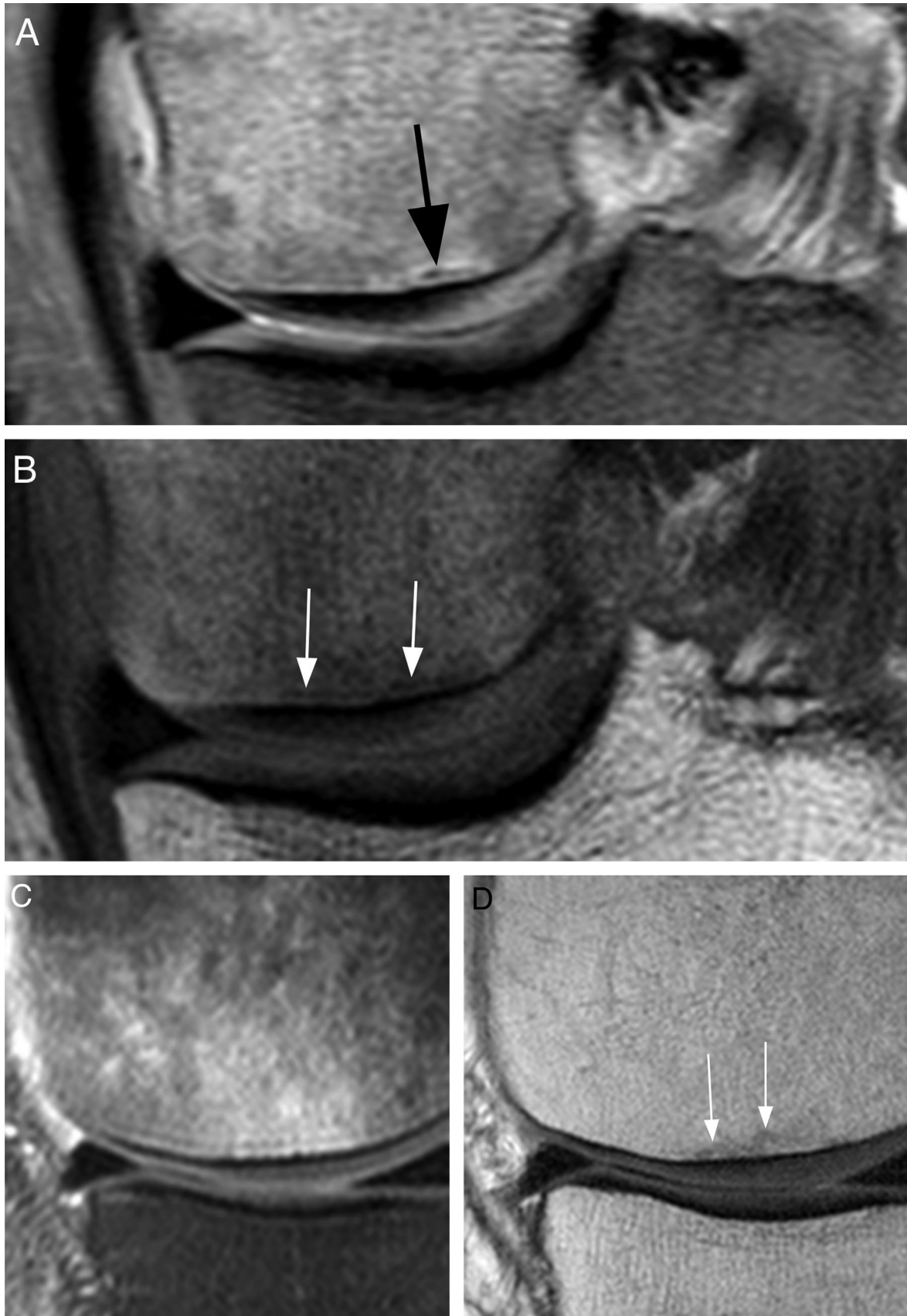


Fig. 7. SIF without necrosis and favorable outcome. A. Proton density-weighted fat suppressed image shows diffuse subchondral bone marrow edema and a small fracture line (arrow) directly adjacent to the subchondral plate. No area of focal hypointensity representing possible necrosis is seen. B. T1-weighted image of same patient depicts fracture line in superior fashion (arrows). C. Another case shows diffuse bone marrow edema on this fat suppressed proton density-weighted image but no fracture line. D. Corresponding T1-weighted image shows discrete but definite subchondral fracture (arrows) in the subchondral bone reflecting the higher sensitivity of T1-weighted imaging for the detection of fractures on MRI.

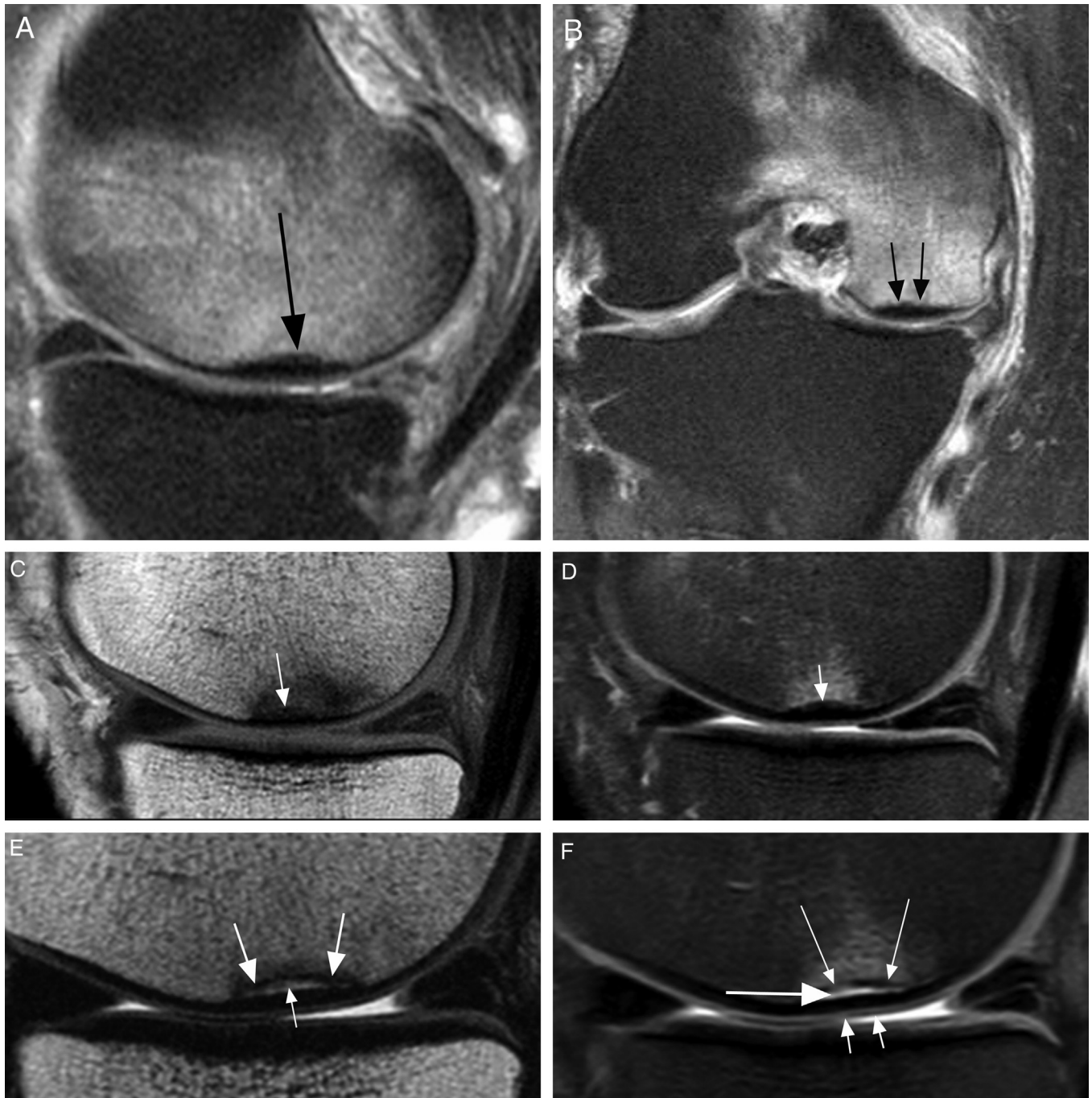


Fig. 8. SIF with necrosis and beginning collapse of articular surface. A. Sagittal proton density-weighted fat suppressed MR image shows diffuse bone marrow edema in the medial femoral condyle and a focal area of subchondral hypointensity representing necrosis (arrow). Articular surface is at risk of collapse. B. Corresponding coronal proton density-weighted fat suppressed image shows extent of the lesion in the medial–lateral direction (arrows). C. Another case (T1-weighted image) exhibits less diffuse edematous changes but a subchondral hypointense impaction representing necrosis (arrow). D. Corresponding fat suppressed proton density-weighted image superiorly exhibits edema and also visualizes subchondral area of necrosis (arrow). E. T2-weighted follow-up image 3 months later shows beginning demarcation of necrotic area (arrows) with fluid-like signal beneath the fracture line (small arrow). F. Corresponding fluid sensitive fat suppressed image confirms this finding showing the fracture line (long, thin arrows) and fluid beneath the fracture (large arrow). In addition, note beginning articular surface deformity (short arrows).



Fig. 9. Osteonecrosis. A. Coronal proton density-weighted fat suppressed MR image shows areas of osteonecrosis in the medial femur (thick arrows) and in the metaphyseal tibia (thin arrows). These are usually incidental findings on MR imaging. Note characteristic serpiginous hyperintense demarcation and central areas of fat equivalent signal. B. Another case of large epiphyseal osteonecrosis in the lateral femur (arrows). Note fat equivalent signal in the center of lesions (asterisk). Osteonecrosis can be a source of pain, may weaken bone and lead to articular surface collapse, especially when located epiphyseally. C. Coronal T1-weighted image shows typical metaphyseal osteonecrosis (arrows) with central fat-like signal (asterisk). D. Another case of tibial osteonecrosis (white arrow) and concomitant finding of insufficiency fracture (black arrow).

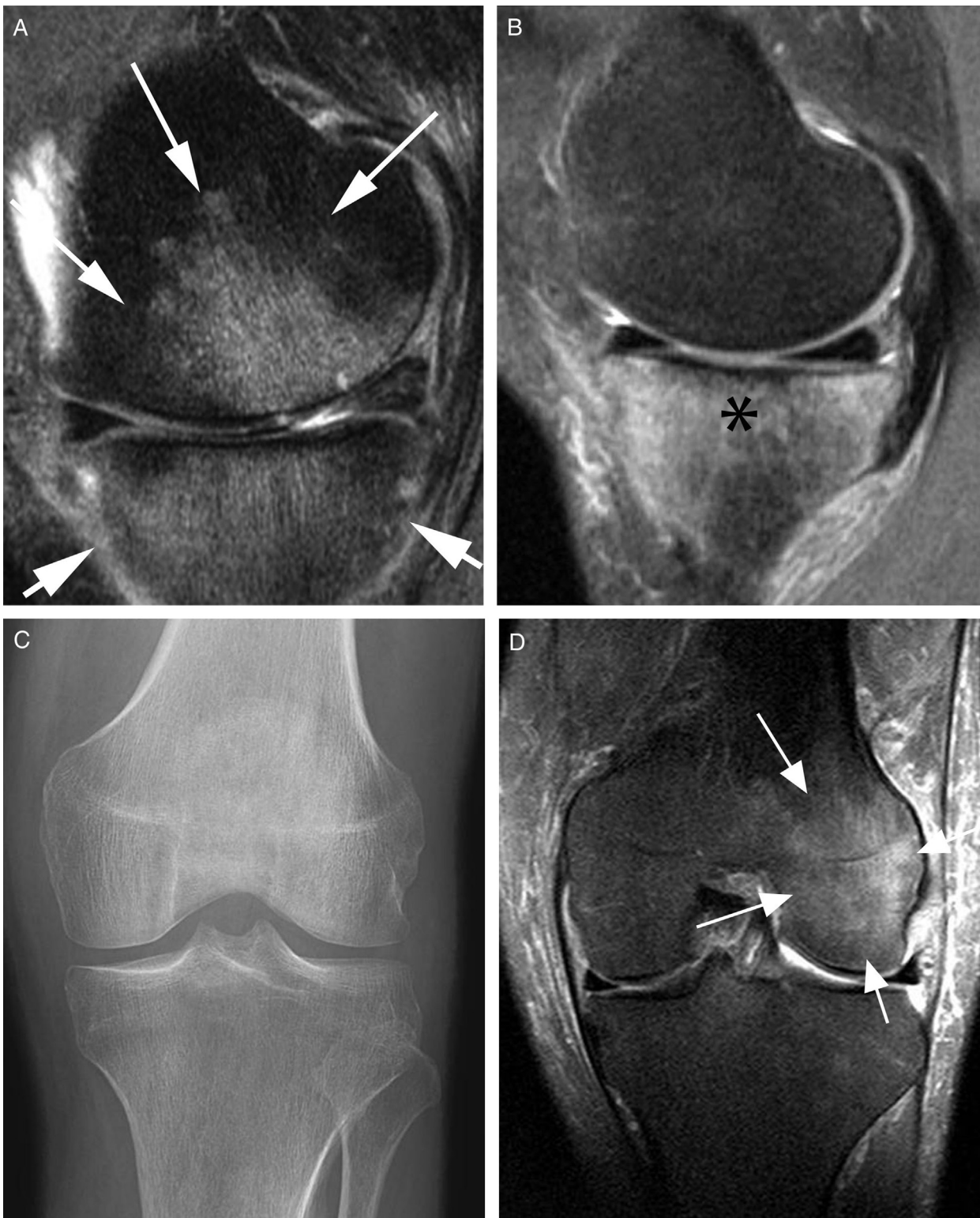


Fig. 10. Large areas of bone marrow edema. A. Subchondral bone marrow lesions (BMLs) are a common finding in OA knees and are associated with pain and more rapid structural progression. Sagittal proton density-weighted fat suppressed image depicts large subchondral areas of diffuse hyperintensity in the medial femur (long arrows) and tibia (short arrows) representing BMLs. B. Large diffuse subchondral hyperintensity changes may also be observed as a consequence of mechanical overload as seen in this case in the medial tibia (asterisk) after extensive running. Continued loading may potentially lead to SIF. C. Unexplained pain with no explanatory finding on X-ray may be caused by transient bone marrow edema syndrome. D. Corresponding coronal fat suppressed proton density-weighted MRI shows large area of diffuse bone marrow edema in the medial femoral condyle (arrows). This is commonly a self-limiting condition that may potentially progress to SIF if loading continues.

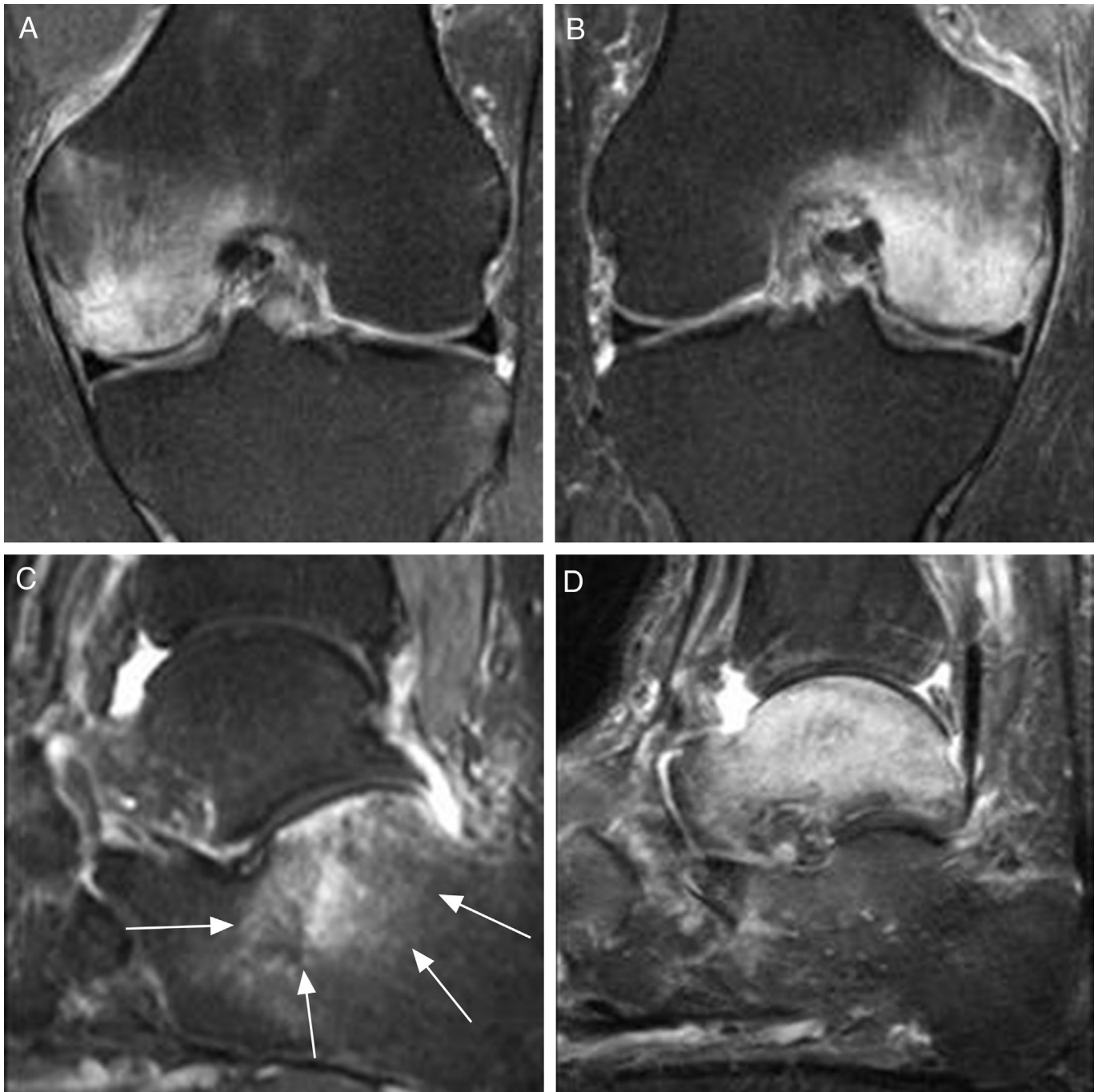


Fig. 11. Transient migratory bone marrow edema syndrome. A. At initial presentation this patient complained about diffuse pain in the left knee. A large area of bone marrow edema without fracture was observed in the medial femur. B. While pain receded on the left, incident pain in the right knee was reported 7 months later. A large area of bone marrow edema was seen in the medial femoral condyle of the right knee. C. After complete resolution of symptoms, 12 months later incident pain was reported in the left hindfoot. Now bone marrow edema was seen in the calcaneus (arrows). D. After 30 months of initial complaints in the left knee, a diagnosis of bone marrow edema (BME) was established in the left talus. Such a course is rare but not unusual. Complete resolution of all symptoms was observed after 3 years.

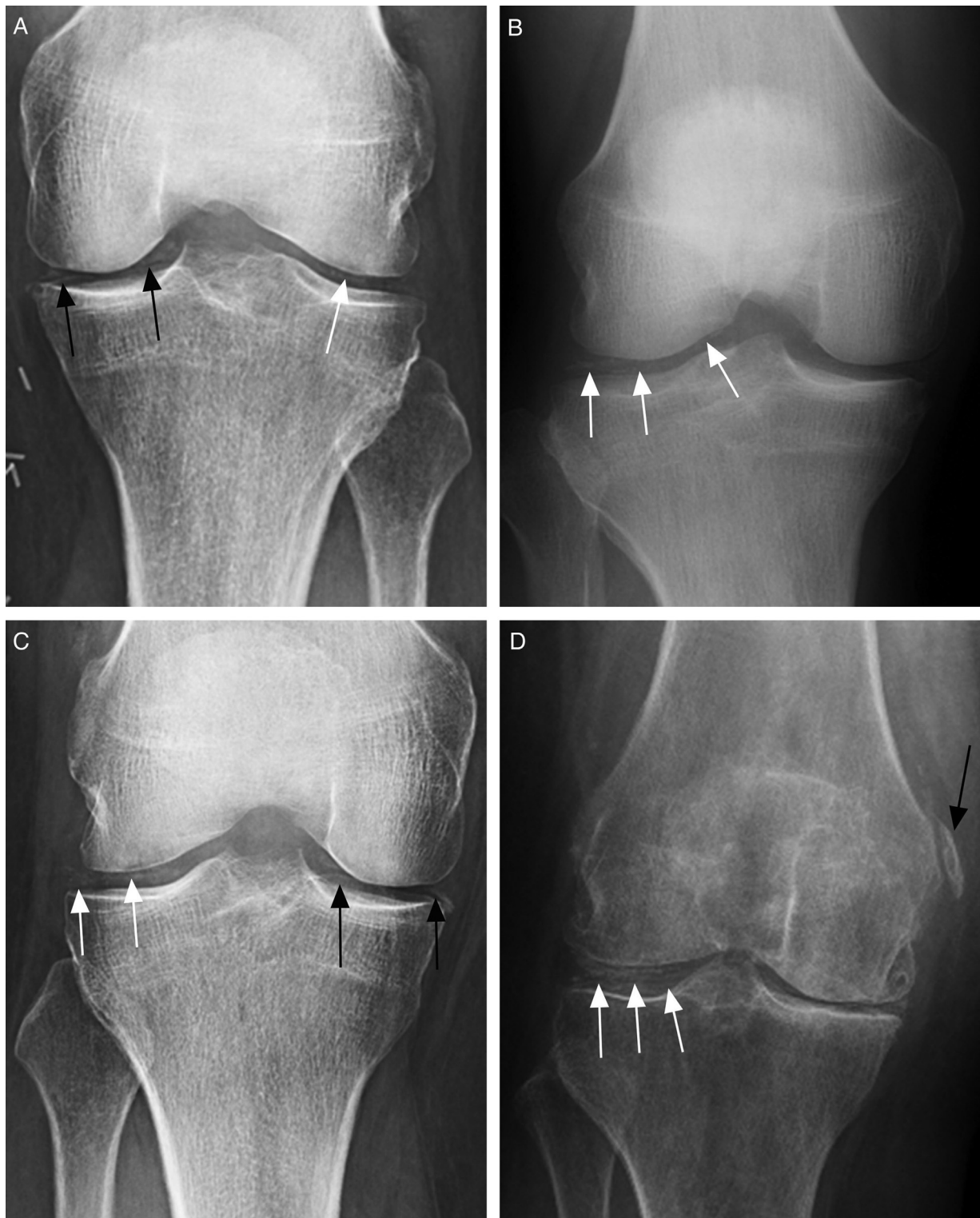


Fig. 12. Chondrocalcinosis is common in patients with OA and is a finding commonly to be expected in a-NGF patients. In some aNGF programs under development, severe chondrocalcinosis may be a reason for exclusion at eligibility due to potentially increased risk for on-study adverse events. A. Anterior–posterior radiograph shows mild chondrocalcinosis in the medial (black arrows) and lateral (white arrow) tibiofemoral joint. B. Another knee exhibits mild chondrocalcinosis in the lateral tibiofemoral joint only (arrows). C. Mild to moderate intraarticular calcifications representing chondrocalcinosis are seen in this example medially (white arrows) and laterally (black arrows). D. Example of severe chondrocalcinosis with marked calcifications in the lateral tibiofemoral joint space (white arrows). In addition there is a so-called Stieda-Pellegrini fragment at the medial femoral condyle reflecting remote trauma to the medial collateral ligament (black arrow).



Fig. 13. Other arthropathies may be reasons for exclusion at eligibility and during the course of a study. These may include inflammatory arthritis and fractures. A. Radiograph shows typical bone erosion at the medial tibial plateau (arrow) consistent with rheumatoid arthritis. Note incidental finding of an area of partially sclerotic bone reflecting a metaphyseal femoral bone infarct (white arrows). B. Soft tissue opacities consistent with typical gout tophi are seen in the periarticular region of this knee (large arrows). In addition minor bony erosions are detected (small white arrows). C. Separate patellar ossicle (arrows) represents bipartite patella, an anatomical variant not to be mistaken for a fracture. D. In contrast, a sclerotic band in the metaphysal tibia of this knee joint represents healing response at the fracture site (arrows).

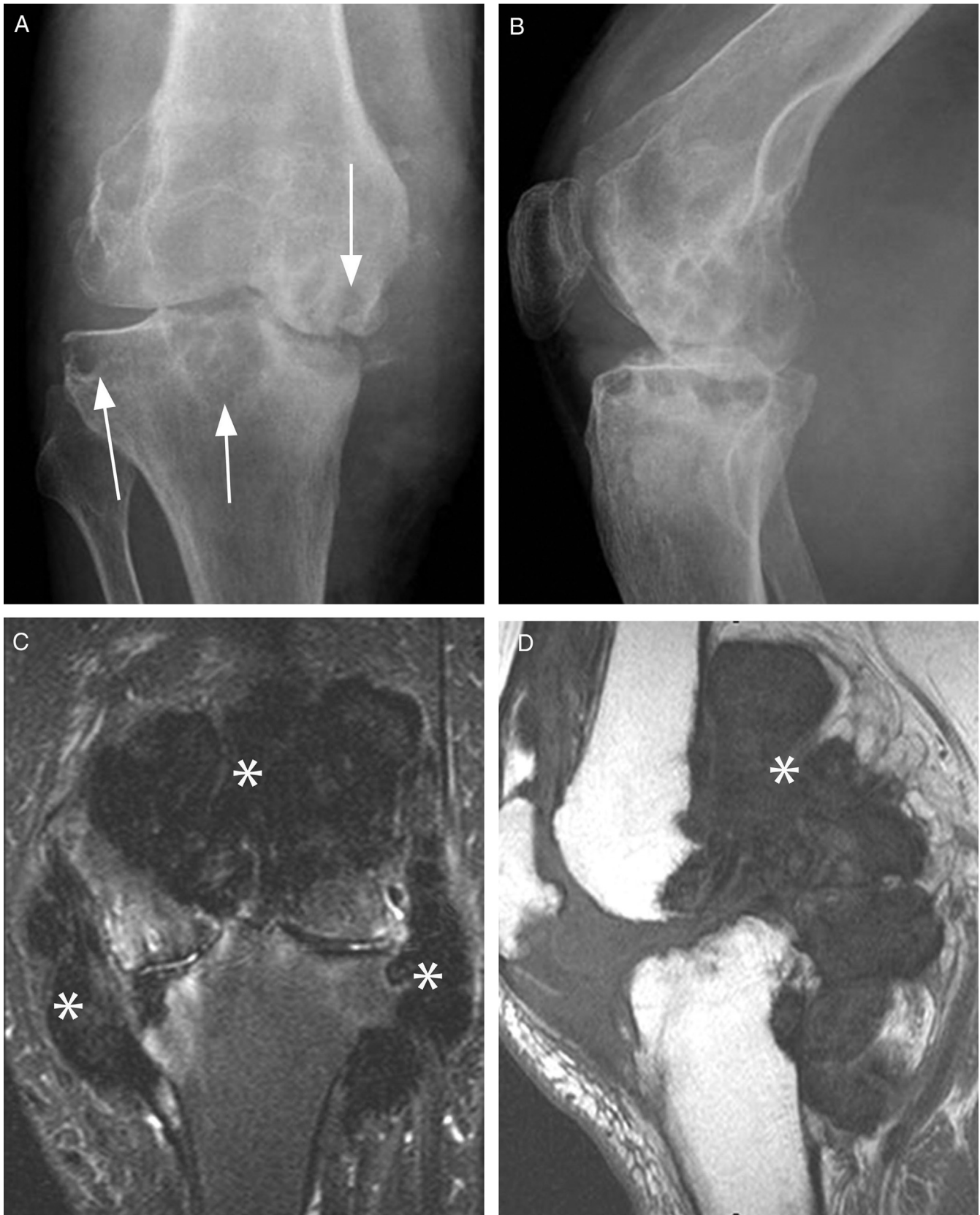


Fig. 14. Other arthropathies. A. Anterior–posterior radiograph shows a markedly deformed knee joint with collapse of the medial tibial plateau. Note large subchondral cystic areas in the periarticular femur and tibia (arrows). B. Lateral radiograph confirms severe osteoarthritic changes with joint deformity. A definite diagnosis cannot be established based on radiograph alone, but joint deformity is consistent with RPOA Type II and thus, a diagnosis of exclusion. C. The additional coronal fat suppressed T2-weighted MRI shows a large mass of diffuse hypointensity reflecting susceptibility artifacts (asterisks). D. Corresponding sagittal T1-weighted MRI confirms hypointense mass-like lesion within the joint cavity (asterisk). This is the typical appearance of PVNS characterized by hemosiderin deposits.

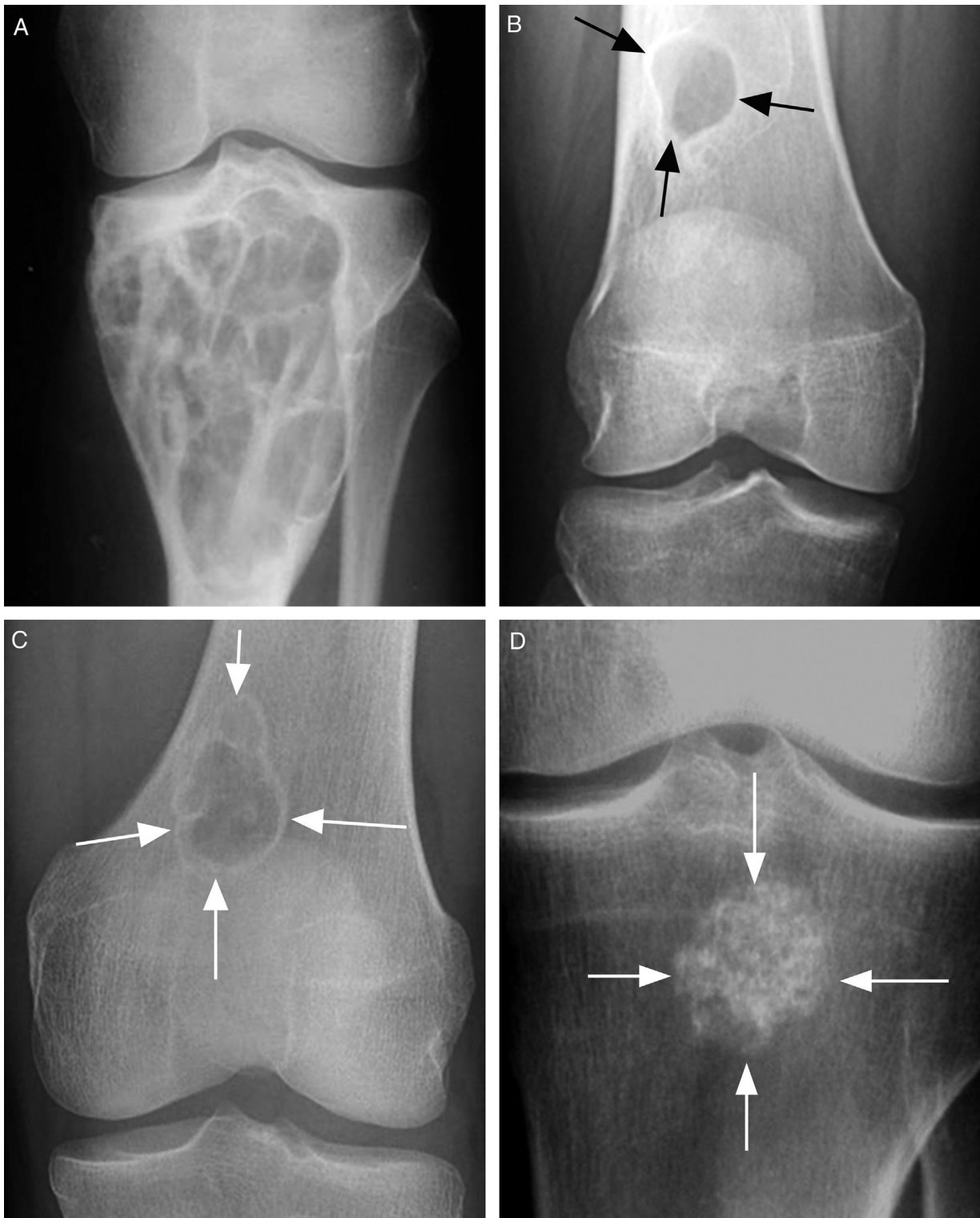


Fig. 15. Tumor-like and cystic lesions may or may not be a diagnosis of exclusion depending on size, benign or malignant appearance and particularly based on potential risk of fracture. A. Radiograph shows typical multilobulated and expansive appearance of fibrous dysplasia, a benign condition. As lesion occupies a large proportion of tibia this represents a finding of exclusion. B. Metaphyseal cystic lesion with sclerotic rim (arrows). No definite diagnosis can be established based on X-ray alone but lesion appears to be definitely benign. However, as lesion in its entirety occupies more than 1/3 of bone in both views, the a.p. and lateral, this would be considered a lesion of exclusion due to increased fracture risk. C. Typical finding of a non-ossifying fibroma of the metaphyseal femur. Lesion is well-demarcated and shows a sclerotic rim (arrows). The lateral radiograph showed that lesion only occupied the posterior quarter of the femur, and thus, this would not be a diagnosis of exclusion. D. Typical finding of a tibial metaphyseal enchondroma with multilobulated popcorn-like appearance (arrows). Benign incidental finding and no diagnosis for exclusion.



Fig. 16. A. Typical finding of a malignant bone tumor with spiculated cortex and partly lytic, partly sclerotic appearance. Finding represents an osteosarcoma, a definite diagnosis for exclusion. B. Systemic disease may be a reason for exclusion. This example shows severe joint destruction due to repetitive intraarticular hemorrhage in a hemophilic patient. C. Severe malalignment is not uniformly defined but may be a diagnosis for patient exclusion at eligibility. Example shows 10° varus malalignment as measured using the anatomical axis. D. Severe valgus malalignment of 11° is shown in this example, which may be reason for ineligibility.

Authors contributions

- (1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
- (2) All authors contributed to drafting the article or revising it critically for important intellectual content.
- (3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions

- Analysis and interpretation of the data: FWR, CWH, CGM, KH, AG
- Drafting of the article: FWR, CWH, CGM, KH, AG
- Provision of study materials or patients: FWR, CWH, CGM, KH, AG
- Statistical expertise: N/A
- Obtaining of funding: FWR, CGM, AG
- Collection and assembly of data: FWR, CWH, CGM, KH, AG

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; froemer@bu.edu).

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Competing interests

Dr Guermazi has received consultancies, speaking fees, and/or honoraria from Sanofi-Aventis, Merck Serono, and TissuGene and is President and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services. Dr Roemer is Chief Medical Officer, Director of Research and shareholder of BICL, LLC. Dr Colin Miller is a full time employee of BioClinica. Dr Curtis Hayes and Dr Kevin Hoover are consultants to BioClinica.

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