MRI for Assessing Erosion and Joint Space Narrowing in Inflammatory Arthropathies

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The superior soft tissue contrast and multiplanar capability of magnetic resonance imaging has contributed to earlier diagnosis and implementation of effective treatment for a variety of arthropathies. Owing to overlapping clinical signs and symptoms, MRI plays a role in delineating the features and stages of these conditions. With the advent of disease-modifying therapies, it is important to diagnose inflammatory arthropathy as early as possible. In this chapter, we discuss the pathophysiology of bone erosion and joint space narrowing, as well as the role of MRI in the imaging of the seropositive and seronegative inflammatory arthropathies.

Key words: **erosion; joint space narrowing; magnetic resonance imaging**

Introduction

On the basis of epidemiological data,[1] rheumatoid arthritis affects 1% of the population. The disease demonstrates slow progression in some patients, whereas it rapidly destroys joint spaces and periarticular bone in others. The peak onset of symptoms is between the fourth and the sixth decades; however, juvenile rheumatoid arthritis is also well known. Before the development of MRI, clinicians had to rely on clinical examination, presenting symptoms, and radiographs to diagnose this disease. Unfortunately, radiographs demonstrate only the late changes owing to rheumatoid arthritis. MRI is able to detect early synovial changes before the development of erosions. Recent research also suggests that bone marrow edema detected by MRI may, in fact, be predictive of erosions.[2] Early diagnosis is of high priority in the initial workup of patients with suspected rheumatoid arthritis. Confirmation of the diagnosis allows clinicians to start disease-modifying therapy early, before severe secondary disability has occurred. Assessment of the severity of the disease on the baseline scans of individual patients may allow clinicians to tailor their drug regimens appropriately.

Pathophysiology for Joint Space Narrowing and Bone Erosion in Rheumatoid Arthritis

The chronic inflammatory arthritides are often associated with localized and generalized bone loss. Localized bone loss manifests as periarticular osteopenia and subchondral bone erosions and constitutes an important feature in diagnosing and directing treatment in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and juvenile idiopathic arthritis. MRI has now revealed that erosions occur early in these diseases. Furthermore, erosions tend to correlate with ongoing disease activity and joint destruction. Early intervention to alter the natural progression of joint destruction has been shown to substantially improve functional status. The revelation that erosions reflect ongoing disease activity and are thus associated with an unfavorable prognosis led to increased the efforts

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to identify the underlying mechanisms behind this pathologic process. Success of the antitumor necrosis factor- (anti-TNF-) therapy in retarding and, in some cases, possibly reversing early focal bone loss has been encouraging.

Osteoclasts (OCLs), cells that are uniquely capable of bone degradation, are consistently detected at erosion sites in all animal models of destructive arthritis as well as human RA.[2] Synovial inflammation generates tumor necrosis factor (TNF)-alpha, macrophage colony-stimulating factor (M-CSF), and receptor activator of nuclear factor-κB ligand (RANKL)—cytokines that fuel osteoclastogenesis and arthritic bone destruction. The targeted removal of OCLs by TNF blockers, RANKL antagonism, or genetic manipulation in animal models potently blocks this bone destruction.[3–6.]

Role of Osteoclasts in Bone Erosion

Osteoclasts are multinucleated cells derived from the mononuclear cell precursors of the monocyte/macrophage lineage that resorbs bone matrix. Bone destruction in RA is mainly attributable to the abnormal activation of OCLs. Bone is a dynamic tissue that is constantly remodeled by bone-resorbing osteoclasts and bone-forming osteoblasts. Dysfunction or imbalance in these cells is seen in RA. The discovery of RANK ligand highlighted the central role of OCLs in the pathogenesis of bone destruction in RA.[7]

OPG

The discovery of osteoprotegerin (OPG) in 1997 was a major advance in the field of bone biology. OPG is released in soluble form by stromal cells/osteoblasts. In addition to bone, OPG mRNA is expressed by a number of other tissues, including lung, heart, kidney, liver, stomach, intestine, thyroid gland, brain, and spinal cord. OPG inhibits the differentiation and activity of osteoclasts by acting as a decoy receptor for the receptor activator of nuclear factor κB ligand (RANKL), thereby downregulating the RANKL signaling through receptor activator of nuclear factor κB (RANK). In this manner it inhibits osteoclast differentiation, suppresses mature osteoclast activation, and induces OCL apoptosis.

RANK

RANK is a transmembrane protein that belongs to the tumor necrosis factor receptor (TNFR) superfamily. It is expressed primarily in the cells of the monocytes/macrophage lineage, including osteoclastic precursors, B and T cells, dendritic cells, and fibroblasts. RANK is also present on the surface of mature osteoclasts.

RANKL

The discovery of OPG was soon followed by the identification of its ligand, initially termed "osteoprotegerin ligand" (OPG-L), which turned out to be identical with two previously described members of the TNF superfamily. RANKL is a 317 amino acid peptide that also belongs to the TNF-superfamily. It exists in two forms, soluble and membrane bound. RANKL has been detected in synovial fibroblasts, osteoblasts, and activated T cells from peripheral blood as well as tissue near the pannus–bone interface. TNF-α induces RANKL and M-CSF in stromal cells and also stimulates osteoclast precursor cells to synergize with RANKL signaling.[8,9] It is also reported that anti-TNF drugs induce apoptosis in synovial macrophages, suggesting a complex action mechanism.

Bone Erosion Provides Further Evidence of a Link between Immune System Activation and Bone Resorption

Once the function of OPG/RANK/RANKL in bone remodeling was recognized, it was hypothesized that RANKL may be of major pathophysiological importance in the bone and joint destruction observed in inflammatory

arthritides such as RA. Studies by Goldring and Gravallese[45], provided initial insights into the role of RANKL in the pathogenesis of focal bone erosions. Other studies have provided compelling evidence that both activated T cells from the RA synovium and synovial fibroblasts produce RANKL. Indeed it is now assumed that activated T cells, which play a central role in the pathogenesis of RA, may contribute to the osteoclast-mediated bone resorption via RANKL expression. Although the role of RANKL in other inflammatory diseases is not yet known, Ritchlin *et al.*,[10] using immunohistochemistry, revealed striking spatial regulation of RANK, RANKL, and OPG expression in the PsA joints.

The severity of bone erosion correlated with higher circulating mononuclear OCL precursor (OcP) numbers, which revealed a novel mechanism for osteoclastogenesis in PsA.[10]

The Role of T Cells in Osteoclastogenesis

As RANKL is expressed in activated T cells, it is of vital importance to determine whether T cells have the capacity to induce osteoclast differentiation. Indeed, Kong *et al.*[11] showed that RANKL expressed on activated T cells directly induces osteoclastogenesis.

Helper T (Th) cells are divided into two main subsets according to the cytokines they produce, Th1 and Th2.[12] Th1 cells produce mainly interferon-γ and IL-2 and are involved in cellular immunity, whereas Th2 cells produce mainly IL-4, IL-5, and IL-10 and are involved in humoral immunity. Interferon-γ and IL-2 are the key cytokines produced by Th1 cells. Interferon-γ strongly inhibits osteoclastogenesis, suggesting that normal Th1 cells inhibit osteoclastogenesis and do not induce bone loss.

T cells in RA joints are defective in suppressive effect owing to the lack of interferon-γ, but they have a strong capacity to induce inflammatory cytokines, which stimulate the expression of RANKL on synovial cells. Interestingly, IL-4[13,14] and IL-10,[15] both of which are classic Th2-type cytokines, also inhibit osteoclastogenesis,[16] so the positive effect of T cells on osteoclastogenesis can only be observed under strictly limited conditions. Thus, the actual role of T cells in osteoclastogenesis is highly complex and may depend on the type of prevailing cytokines.[17] Under some conditions, T cells may not drive osteoclastogenesis, even if RANKL is expressed. In the presence of high levels of TNF, subosteoclastogenic ("permissive") amounts of RANKL may be sufficient for TNF to drive RANKL-mediated osteoclastogenesis.[18]

MRI-Observed Erosion and Joint Space Narrowing in Inflammatory Arthritis

Magnetic resonance imaging is a sensitive modality for the detection of erosions, and it does so more often and at an earlier stage than radiography.[19]

Fast spin-echo T1-weighted sequences, fat-saturated T2 fast spin-echo sequences, and postcontrast T1-weighted sequences with fat saturation are performed in axial, coronal, and sagittal orthogonal planes. If fat-saturated T2-weighted sequences are not available, a short-tau inversion recovery (STIR) sequence can be obtained. Good fat saturation and contrast enhancement are important for the evaluation of bone marrow edema and synovial hyperemia, respectively.

In many cases, bone erosions are seen on MRI scans when radiographs do not indicate abnormalities (Fig. 1).[20] In one recent study, for example, only 41% of the erosions seen on MRIs were subsequently detected on radiographs (Fig. 2).[21] Only focal lesions that demonstrate contrast enhancement are eligible to be classified as erosions. Before the development of contrast-enhanced MRI, the term erosion was applied to juxta-articular lesions in patients who demonstrated distribution of

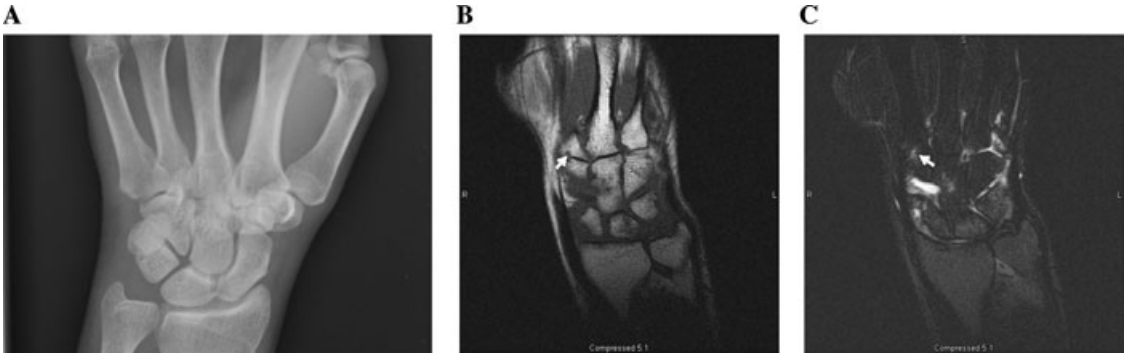

Figure 1. Postero-anterior (PA) view of the left wrist of a 43-year-old woman with rheumatoid arthritis: (**A**) The bone mineralization is normal and no joint space narrowing or erosive changes is seen in the wrist. Coronal T1- (**B**) and coronal T2-weighted fast spin-echo fat-saturated (**C**) MRI scans of the left wrist were performed approximately 1 month later. There is proliferative synovitis with a high T2 signal in the joints on T2-weighted images (white arrow in **C**) and bone marrow edema with scattered erosions (white arrow in **B**) are present throughout the wrist. The most visible erosion on these images is at the base of the 2nd metacarpal.

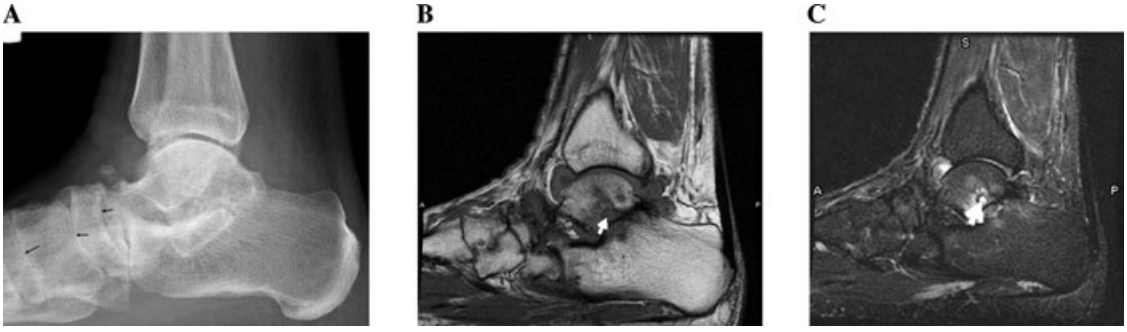

Figure 2. Lateral X ray (**A**) of the ankle of a 62-year-old man with RA. There is joint space narrowing at multiple joints (black arrows) with relative sparing of the tibiotalar joint, but there is soft tissue prominence at the tibiotalar joint, suggesting an effusion or synovitis. Erosions are not seen clearly on the X ray but are obvious on the ankle MRI performed approximately $1\frac{1}{2}$ years earlier. Sagittal T1 (**B**) and sagittal STIR (**C**) MRI scans were performed. Synovial proliferation in the ankle is intermediate in signal on the T1-weighted images and bright on the STIR images. There is a large erosion (white arrow in **B**) at the posterior subtalar joint with surrounding bone marrow edema (white arrow in **C**). These findings are bright on the STIR images. Multiple erosions in other joints were also visible on the MRI.

the lesions in a pattern characteristic of RA. With the advent of contrast-enhanced MRI, the definition of the term erosion became more precise. According to the outcome measures in rheumatoid arthritis clinical trials scoring system (OMERACT),[22] erosion is defined as a sharply marginated bone lesion with correct juxta-articular localization and typical signal characteristics. According to OMERACT, to be labeled erosion the cortical break should be seen in at least two planes.

Focal lesions that show increased T2 signal without contrast enhancement can represent subchondral cysts. Such a distinction becomes particularly important in cases where RA has to be differentiated from degenerative OA (osteoarthritis). MRI allows for early detection of erosions and correct classification of osseous lesions as erosive in cases where abnormality is located far from the joint. In some cases, even large erosions are occult on radiographs but are clearly demonstrated on MRIs (Fig. 3).[23]

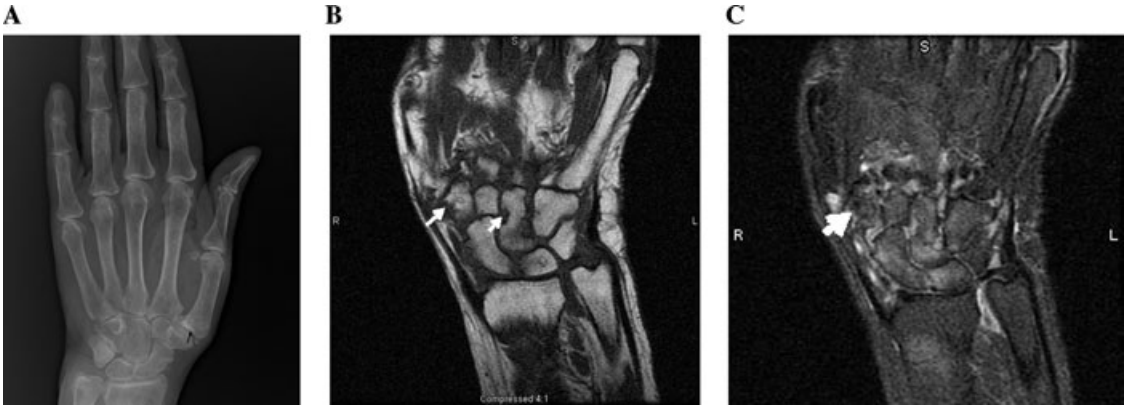

Figure 3. Postero-anterior (PA) (**A**) views of the left hand of a 76-year-old woman with RA. The bones are diffusely osteopenic. Some erosions show in the PA view at the 1st CMC joint. Coronal T1 (**B**) and coronal T2-weighted fast spin-echo with fat saturation (**C**) images of the left wrist of the same woman. The MRIs better demonstrate findings of RA with multiple low-signal erosions (white arrows in **B**) seen in the wrist on the T1-weighted images. Proliferative synovitis is seen as a bright signal within the joint spaces on the T2-weighted images. Bone marrow edema is also seen on the T2 images as a bright signal within the bone.

Erosions detectable by MRI are likely to progress to radiograph-detectable erosions in patients with high baseline disease activity. Moreover, before the advent of MRI, it was not possible to evaluate osseous structures for the presence of bone marrow edema. Increased T2 signal on MRIs results from increased water content in the bone marrow, which is probably related to an inflammatory response. Bone marrow edema is a strong predictor of future erosions. Bone marrow edema has been shown to be associated with a sixfold increase in risk of developing erosions at the same site at 1 year of follow-up.[24] A more recent study also demonstrated that bone marrow edema predicts erosive progression in early RA during the first 2 years of the disease.

Contrast-Enhanced Imaging in Rheumatoid Arthritis

Whereas T2-weighted imaging allows for detection of edematous tissues and joint effusions, administration of intravenous contrast enables detection of inflamed hypervascular tissues. Intravenous contrast can be used to differentiate inflamed synovium from adjacent bone marrow edema and joint effusion (Figs. 4 and 5). Several factors contribute to good contrast between the inflamed synovium and adjacent tissues, including the amount of injected contrast, the amount of joint effusion, and the vascularity of the adjacent tissues.[25,26]

If a significant amount of time is allowed to pass between contrast injection and the acquisition of the magnetic resonance images, contrast will diffuse into the joint. This phenomenon has been studied in healthy volunteers, and there is no reason to think that the same process would not occur in patients with inflammatory arthritis. If the images are not acquired in a timely fashion, it may not be possible to differentiate between synovium and joint fluid. Hence, accurate timing of the scan is very important when imaging patients with suspected RA. In the wrist, the peak steady state of contrast enhancement is reached at 60 to 120 s.[27] The initial period of 10 min after administration of contrast has been suggested as the optimal time for imaging of the knee joint, but other reports counter that the optimal timing may be as early as 5 to 6 min after administration.[28,29]

The use of contrast-enhanced MRI in evaluation of RA is supported by several studies. Moreover, it has been shown to detect

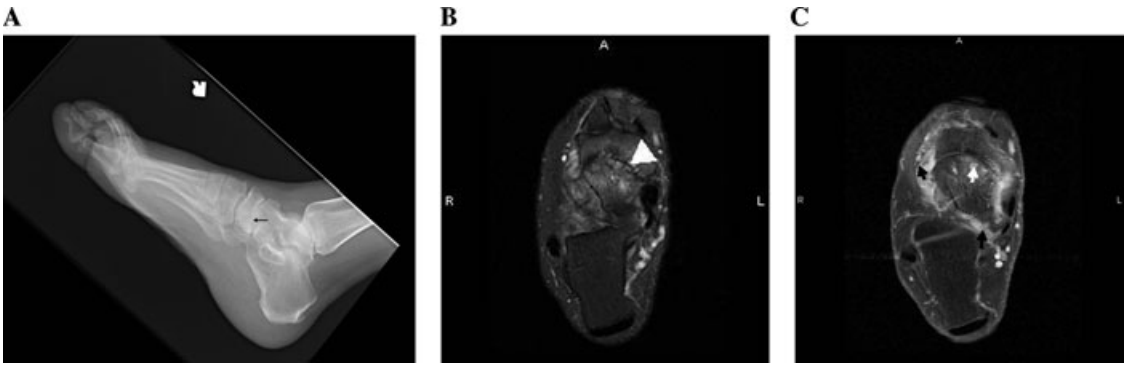

Figure 4. Lateral view (**A**) of the right foot of a 53-year-old woman with RA. The bones are osteopenic and there is joint space narrowing at the talonavicular joint (black arrows) without evidence of erosions. Axial T2 fast spin-echo images with fat saturation (**B**) and axial T1-weighted images with fat saturation and gadolinium contrast administration (**C**) were taken of the right ankle/hindfoot. Erosions are easily visualized at the talonavicular joint as focal areas of bright T2 signal (white arrowhead in **B**), and they enhance after contrast administration (white arrow in **C**). There is also enhancing rheumatoid pannus (black arrow in **C**).

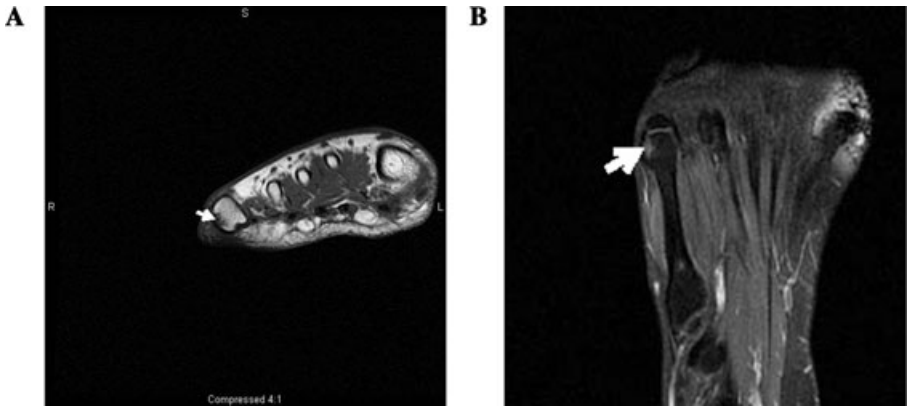

Figure 5. MRI was performed on a woman with a diagnosis of RA and pain in her 3rd through 5th toes. Coronal T1 (**A**) and axial T1-weighted images with fat saturation and gadolinium contrast administration (**B**) were taken. These images reveal an erosion at the lateral aspect of the 5th metatarsal head that is low signal on the T1-weighted images and enhances after gadolinium administration (white arrows).

more periarticular bone abnormalities than T2-weighted imaging. Figure 6 illustrates an example of erosions that are better depicted on a contrast-enhanced image than on T2-weighted fat-saturated image.

MRI as a Follow-Up Tool

With the advent of disease-modifying therapy, MRI became an important tool for the evaluation of patient responses to therapy. As the disease is now being treated early, before significant bone and joint destruction has occurred, MRI can be used to evaluate the response of synovium to therapy and accurately document the stability or progression of erosions. Tam *et al.*,[46] for example, used dynamic contrast-enhanced MRI to document changes in synovitis severity, volume of the synovium, and synovial perfusion indices after patients were treated with a combination of methotrexate and infliximab. Quantification of hand synovitis by measuring the volume of enhanced inflammatory tissue has also been used to evaluate the effectiveness of new medications in

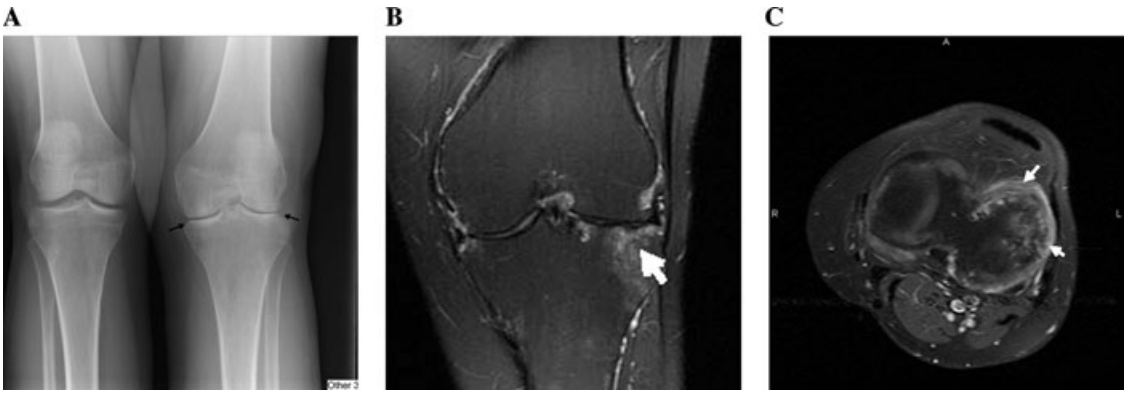

Figure 6. Antero-posterior (AP) view of both knees (**A**) of a 46-year-old woman. Although the joint spaces are maintained in the right knee, there is diffuse joint space narrowing in the left knee with erosive changes (black arrows) and no significant osteophyte formation. Despite the asymmetry, the findings in the left knee are compatible with RA. The findings are confirmed on MRIs of the knee. Coronal T2 fast spin-echo images with fat saturation (**B**) and axial T1-weighted images with fat saturation after the intravenous administration of gadolinium contrast (**C**) were taken. Erosive changes with edema, both bright on the T2-weighted images, are greatest at the lateral compartment of the knee, where they involve predominantly the tibial plateau. The erosions enhance after contrast administration.

the treatment of refractory arthritis.[30,31] Other researchers have used MRI to evaluate bone marrow edema and the progression or development of erosions to compare a new drug regimen with a placebo.

MRI can also be used to predict functional outcome in patients with early inflammatory arthritis. Benton *et al.*[32] demonstrated that MRI of patients with early RA can predict functional outcome at 6 years of follow-up. Another report based on the same cohort also demonstrated that areas of bone marrow edema at baseline evolved into erosions at follow-up. Evidence of tendinopathy on MRIs in early RA can also predict tendon rupture at 6 years.

MRI in Psoriatic Arthritis

Magnetic resonance imaging has advanced our understanding of many types of arthritis, with respect to both inflammatory processes and articular damage. Psoriatic arthritis (PsA) has been the subject of less research scrutiny than RA in many areas, including imaging, but this is likely to change because there is an increasing use of MRI outcome measures in clinical trials of new therapeutic agents such as biologics.[33]

Although the work conducted by Ritchlin and co-workers[34] recently focused attention on activated osteoclasts in PsA and raised the possibility that a disorder of bone remodeling may underlie this disease, evidence from MRI studies conducted thus far suggests that PsA erosions are rather similar to those of RA. There are differences in terms of distribution, but the erosions themselves consist of a break in cortical bone overlying a region of altered signal intensity with definite margins, as described in RA (Fig. 7). Furthermore, as those in RA, PsA erosions can be large and are frequently not visualized in conventional radiography. The study conducted by Savnik and co-workers[35] in patients with inflammatory arthritis suggested that MRI erosions in PsA patients did not progress over time to the same extent as those in patients with early RA, raising the possibility that PsA bone disease may sometimes be less aggressive. Backhaus and colleagues[36] included 15 PsA patients in their study of MRI, ultrasound, and scintigraphy of the finger joints, nine of whom were described as having MRI-observed erosions. Some of these erosions were

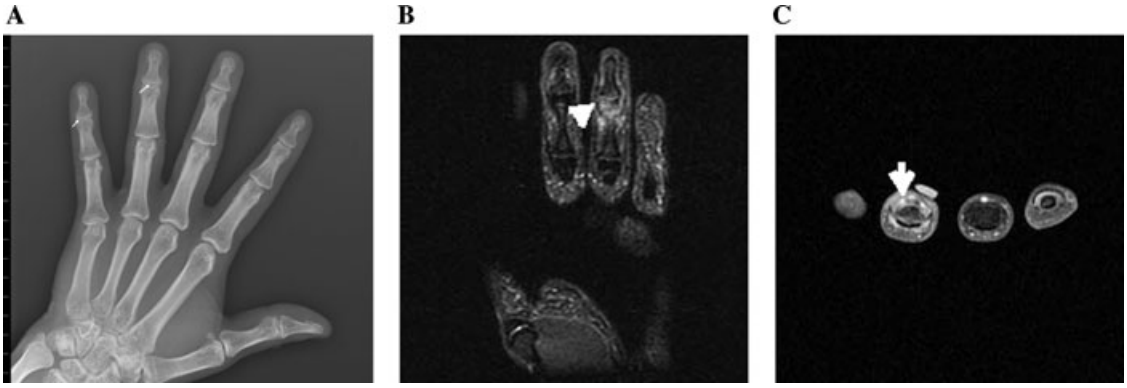

Figure 7. Postero-anterior view (**A**) of the left hand in a 50-year-old man. There is mild juxta-articular osteopenia and soft tissue swelling at the 4th DIP joint. The joints of the 4th and 5th fingers appear narrowed but on MRI only the 4th DIP joint is abnormal. Coronal STIR image (**B**) and axial T1-weighted image with fat saturation after gadolinium contrast administration (**C**) in the same patient. Imaging is focused on the 4th finger. On the STIR image there is bone marrow edema with a high signal in the distal aspect of the middle phalanx in the 4th DIP joint. A bright signal is also seen along the periosteum. (white arrow in **B**) Contrast-enhanced T1-weighted image demonstrates synovial enhancement (white arrow in **C**). The DIP joint and periosteal involvement is suggestive of PsA.

"nonenhancing" following contrast injection, suggesting that they might contain fibrous tissue rather than inflammatory pannus and therefore be relatively "inactive," but there was no clear description of these lesions.

As in RA, the histopathological correlate of MRI-observed bone edema has not been defined in PsA, but Bollow and co-workers[37] found some evidence of osteitis in subcortical bone in their biopsy study of sacroiliac joints in spondyloarthropathy patients (including two with PsA). Bone edema has been described in PsA, reactive arthritis, ankylosing spondylitis, and RA and is recognized as an ill-defined area in the subcortical bone with increased signal on STIR, T2-weighted with fat saturation (FS), and postcontrast T1-weighted with FS sequences.

Savnik and colleagues[38] found MRI-observed bone edema in PsA patients included in their cohort with early inflammatory arthritis, and noted that the total number of bones affected did not change over 1 year (compared with the RA patients, in whom it increased). They found examples in PsA of bone edema involving distal, middle, and proximal phalanges of the fingers as well as carpal bones, radius, and ulna, and found that in various cases it either appeared or disappeared between the baseline and 1 year MRI examinations. Bone edema was a strong predictor of bone erosions in their RA group (as was described elsewhere[39]), but this was not specifically demonstrated in PsA joints, and further studies are needed to clarify this point.

In their series comparing MRIs of the hand in 28 PsA and 18 RA patients, Giovagnoni and co-workers[40] also noted signal changes in subchondral bone (bone edema) in 43% of their patients, associated with pronounced periarticular edema of the soft tissues, spreading to the subcutis, and suggested that this might constitute a "psoriatic pattern" on an MRI.

Comparing MRI Findings in Rheumatoid Arthritis and Psoriatic Arthritis

In RA and PsA, the finger joints are usually the first joints affected. Although the diagnosis is based primarily on clinical findings, it is sometimes difficult even for a trained rheumatologist to differentiate between them. This is

especially true in cases of PsA *sine psoriase*. Radiographic changes in PsA are specific and differ from those in RA, but a conventional radiograph may also be normal in acute arthritis. A study done by Schoellnast and Hannes[41] compared MRI findings of the wrist and the hand in patients with PsA and RA. Using contrast-enhanced MRI, they found that erosions were statistically more frequent in patients with RA and that periostitis was statistically seen more frequently in patients with PsA. No statistically significant difference was found in the frequency of synovitis, bone marrow edema, bone cysts, or tenosynovitis between the two groups. The radiocarpal joint, the midcarpal joints, the carpometacarpal joints, and the metacarpophalangeal joints were significantly affected more frequently in patients with RA than in patients with PsA, whereas the proximal interphalangeal joints were significantly more frequently affected in patients with PsA ($p < 0.05$).

Offidani *et al.* showed that joints were frequently affected in patients with psoriasis but without clinically evident arthritis,. They reported periarticular effusion and synovitis/intra-articular effusion as the two most frequent findings (36 and 44%, respectively).[41]

Pitfalls

Several pitfalls should be considered during interpretation of MRI studies in the context of RA. Partial volume artifacts can mimic erosive changes, synovitis, and tenosynovitis. Insertion sites of interosseous ligaments can mimic erosions.[42] Close proximity of anatomical structures in the wrist can lead to confusion among bone marrow edema, synovitis, and tenosynovitis on fluid-sensitive sequences. Furthermore, bone edema, erosions, and tenosynovitis have been reported in healthy volunteers.[43] Small amounts of fluid are commonly identified in the extensor tendons, particularly extensor carpi radialis brevis and longus.[44] The cause of this finding is unknown and, in some cases, it may be confused with tenosynovitis. Inhomogeneous fat suppression may mimic bone marrow edema. In some cases, bone marrow edema may be found surrounding focal erosions. In others, a small focal area of edema may mimic a focal erosion, especially on images obtained without contrast. Differentiation between an erosion and edema would be difficult in such cases. Focal bone changes, such as the development of small bone islands, can also mimic erosions on T1-weighted images. However, evaluation of all available sequences, including fat-suppressed contrast-enhanced T1-weighted images, should solve most challenging cases.

Conclusions

Magnetic resonance imaging is an excellent modality for evaluation of patients with early inflammatory arthritis. In addition to demonstrating excellent sensitivity for detection of erosions, MRI can show even earlier changes, such as synovitis and tenosynovitis. Secondary manifestations of RA, such as carpal tunnel syndrome, can also be well evaluated by means of MRI. Fat-suppressed and contrast-enhanced sequences are an important part of the MRI protocols for evaluation of RA. In addition to early detection, MRI can also be used to evaluate the effectiveness of therapies.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Goldring, S. 2003. Osteoporosis and rheumatic diseases. In *Primer of the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 5th ed.: 379–382. Lippincott Williams & Wilkins. Philadelphia.
2. Gough, A.K., J. Lilley, S. Eyre, *et al*. 1994. Generalised bone loss in patients with early rheumatoid arthritis. *Lancet* **344:** 23–27.
3. Redlich, K., S. Hayer, A. Maier, *et al*. 2002. Tumor necrosis factor alpha-mediated joint destruction

is inhibited by targeting osteoclasts with osteoprotegerin. *Arthritis Rheum.* **46:** 785–792.
4. Redlich, K., S. Hayer, R. Ricci, *et al*. 2002. Osteoclasts are essential for TNF-alpha-mediated joint destruction. *J. Clin. Invest.* **110:** 1419–1427.
5. Schett, G., K. Redlich, S. Hayer, *et al*. 2003. Osteoprotegerin protects against generalized bone loss in tumor necrosis factor-transgenic mice. *Arthritis Rheum.* **48:** 2042–2051.
6. Zwerina, J., S. Hayer, M. Tohidast-Akrad, *et al*. 2004. Single and combined inhibition of tumor necrosis factor, interleukin-1, and RANKL pathways in tumor necrosis factor-induced arthritis: Effects on synovial inflammation, bone erosion, and cartilage destruction. *Arthritis Rheum.* **50:** 277–290.
7. Anandarajah, A.P. 2006. Anti-RANKL therapy for inflammatory bone disorder: Mechanism and potential clinical applications. *J. Cell. Biochem.* **97:** 226–232.
8. Takayanagi, H., S. Kim, K. Matsuo, *et al*. 2002. RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-beta. *Nature* **416:** 744–749.
9. Wyzga, N., S. Varghese, S. Wikel, *et al*. 2004. Effects of activated T cells on osteoclastogenesis depend on how they are activated. *Bone* **35:** 614–620.
10. Ritchlin, C.T., S.A. Haas-Smith, P. Li, *et al*. 2003. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J. Clin. Invest.* **111:** 821–831.
11. Kong, Y.Y., U. Feige, I. Sarosi, *et al*. 1999. Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. *Nature* **402:** 304–309.
12. Sato, K. & H. Takayanagi. 2006. Osteoclasts, rheumatoid arthritis, and osteoimmunology. *Curr. Opin. Rheumatol.* **18:** 419–426.
13. Kasono, K., K. Sato, Y. Sato, *et al*. 1993. Inhibitory effect of interleukin-4 on osteoclast-like cell formation in mouse bone marrow culture. *Bone Miner.* **21:** 179–188.
14. Abu-Amer, Y. 2001. IL-4 abrogates osteoclastogenesis through STAT6-dependent inhibition of NF-κB. *J. Clin. Invest.* **107:** 1375–1385.
15. Hong, M.H., H. Williams, C.H. Jin, *et al*. 2000. The inhibitory effect of interleukin-10 on mouse osteoclast formation involves novel tyrosine-phosphorylated proteins. *J. Bone Miner. Res.* **15:** 911–918.
16. Takahashi, N., G.R. Mundy & G.D. Roodman. 1986. Recombinant human interferon-γ inhibits formation of human osteoclast-like cells. *J. Immunol.* **137:** 3544–3549.
17. Nanes, M.S. 2003. Tumor necrosis factor-α: Molecular and cellular mechanisms in skeletal pathology. *Gene* **321:** 1–15.
18. Catrina, A.I., C. Trollmo, E. af Klint, *et al*. 2005. Evidence that anti-tumor necrosis factor therapy with both etanercept and infliximab induces apoptosis in macrophages, but not lymphocytes, in rheumatoid arthritis joints: Extended report. *Arthritis Rheum.* **52:** 61–72.
19. Klarlund, M., M. Østergaard & K.E. Jensen. 2000. Magnetic resonance imaging, radiography, and scintigraphy of the finger joints. *Ann. Rheum. Dis.* **59:** 521–528.
20. Scheel, A.K. & K.G. Hermann. 2006. Prospective 7 year follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis finger joints. *Ann. Rheum. Dis.* **65:** 595–600.
21. Ashikyan, O. 2007. The role of magnetic resonance imaging in the early diagnosis of rheumatoid arthritis. *Top. Magn. Reson. Imaging* **18:** 169–176.
22. Østergaard, M. & C. Peterfy. 2003. OMERACT rheumatoid arthritis magnetic in resonance imaging studies. *J. Rheumatol.* **30:** 1385–1386.
23. Tehranzadeh, J., O. Ashikyan, J. Dascalos & C. Dennehey. 2004. MRI of large intraosseous lesions in patients with inflammatory arthritis. *AJR Am. J. Roentgenol.* **183:** 1453–1456.
24. McQueen, F.M. & N. Benton. 2001. What is the fate of erosions in early rheumatoid arthritis? *Ann. Rheum. Dis.* **60:** 859–868.
25. Oliver, C. & S. Speake. 1996. Advantages of an increased dose of MRI contrast agent for enhancing inflammatory synovium. *Clin. Radiol.* **51:** 487–493.
26. Konig, H., J. Sieper & K.J. Wolf. 1990. Rheumatoid arthritis: Evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with Gd-DTPA. *Radiology* **176:** 473–477.
27. Cimmino, M.A., S. Innocenti, F. Livrone, *et al*. 2003. Dynamic gadolinium-enhanced magnetic resonance imaging of the wrist in patients with rheumatoid arthritis can discriminate active from inactive disease. *Arthritis Rheum.* **48:** 1207–1213.
28. Yamato, M., K. Tamai, T. Yamaguchi, *et al*. 1993. MRI of the knee in rheumatoid arthritis: Gd-DTPA perfusion dynamics. *J. Comput. Assist. Tomogr.* **17:** 781–785.
29. Sugimoto, H., A. Takeda & K. Hyodoh. 2001. MR imaging for evaluation of early rheumatoid arthritis. *Sem. Musculoskeletal Radiol.* **5:** 159–165.
30. Zikou, A.K., M.I. Argyropoulou, P.V. Voulgari, *et al*. 2006. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab. *J. Rheumatol.* **33:** 219–223.
31. Argyropoulou, M.I., A. Glatzouni, P.V. Voulgari, *et al*. 2005. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. *Joint Bone Spine* **72:** 557–561.

32. Benton, N., N. Stewart, J. Crabbe, *et al*. 2004. MRI of the wrist in early rheumatoid arthritis can be used to predict functional outcome at 6 years. *Ann. Rheum. Dis.* **63:** 555–561.
33. McQueen, F., M. Lassere & M. Østergaard. 2006. Magnetic resonance imaging in psoriatic arthritis: A review of the literature. *Arthritis Res. Ther.* **8:** 207.
34. Ritchlin, C.T., S.A. Haas-Smith, P. Li, D.G. Hicks & E.M. Schwartz. 2003. Mechanisms of TNFα and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J. Clin. Invest.* **111:** 821–831.
35. Savnik, A., H. Malmskov & H.S. Thomsen. 2002. MRI of the wrist and finger joints in inflammatory joint diseases at 1-year interval: MR features to predict bone erosions. *Eur. Radiol.* **12:** 1203–1210.
36. Backhaus, M., T. Kamradt & D. Sandrock. 1999. Arthritis of the finger joints. A comprehensive approach comparing conventional radiography, scintigraphy, ultrasound and contrast-enhanced MRI. *Arthritis Rheum.* **42:** 1232–1234.
37. Bollow, M., T. Fischer, H. Reißhauer & M. Backhaus. 2000. Quantitative analyses of sacroiliac biopsies in spondyloarthropathies: T cells and macrophages predominate in early and active sacroiliitis–cellularity correlates with the degree of enhancement detected by magnetic resonance imaging. *Ann. Rheum. Dis.* **59:** 135–140.
38. Savnik, A., H. Malmskov & H.S. Thomsen. 2001. Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases. *J. Rheumatol.* **28:** 2193–2200.
39. McQueen, F.M., N. Benton, D. Perry & J. Crabbe. 2003. Bone oedema scored on magnetic resonance scans of the dominant carpus at presentation predicts radiographic joint damage at the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum.* **48:** 1814–1827.
40. Giovagnoni, A., W. Grassi & F. Terilli. 1995. MRI of the hand in psoriatic and rheumatical arthritis. *Eur. Radiol.* **5:** 590–595.
41. Offidani, A., A. Cellini, G. Valeri & A. Giovagnoni. 1998. Subclinical joint involvement in psoriasis: Magnetic resonance imaging and X-ray findings. *Acta Derm. Venereol.* **78:** 463–465.
42. McQueen, F., M. Østergaard, C. Peterfy, *et al*. 2005. Pitfalls in scoring MR images of rheumatoid arthritis wrist and metacarpophalangeal joints. *Ann. Rheum. Dis.* **64**(Suppl. 1): i48–i55.
43. Parodi, M., E. Silvestri, G. Garlaschi, *et al*. 2006. How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging. *Clin. Exp. Rheumatol.* **24:** 134–141.
44. Timins, M.E., S.E. O'Connell, S.J. Erickson, *et al*. 1996. MR imaging of the wrist: Normal findings that may simulate disease. *Radiographics* **16:** 987–995.
45. Goldring, S.R. & E.M. Gravallese. 2004. Bisphosphonates: Environmental protection for the joint? *Arthritis Rheum.* **50:** 2044—2047.
46. Tam, L.-S., J.F. Griffith, A.B. Yu, *et al*. 2007. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: Clinical and magnetic resonance imaging evaluation. *Clin. Rheumatol.* **26:** 941–946.