REVIEW ARTICLE

MRI and ultrasound of the hands and wrists in rheumatoid arthritis. I. Imaging findings

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Abstract

The management of patients with rheumatoid arthritis (RA) has rapidly evolved with the development of newer disease-modifying drugs and the recognition that long-term damage can be mitigated by an earlier and more-informed use of these medications. Historically, radiographs were the mainstay of imaging in RA patients, but radiographic joint narrowing and erosions are late and insensitive findings in the disease. MRI (with intravenous contrast agent) and ultrasound (with power Doppler interrogation) of the hands and wrists are able to demonstrate erosions earlier and with greater sensitivity than radiographs. More importantly, these imaging studies also depict synovitis and active soft-tissue inflammation, which represents a precursor to structural damage. Additionally, MRI can show inflammation within the bones (osteitis), which is proving to be the most important prognosticator of an aggressive disease course. Part I of this review discusses the imaging techniques, pitfalls, definitions, and comparative studies of MRI and ultrasound for identifying and quantifying erosions, synovitis, and osteitis. Part II will demonstrate how these imaging findings influence the clinical management of RA patients throughout their disease course, from presentation through clinical remission.

Keywords Rheumatoid arthritis · Synovitis · Tenosynovitis · Erosions · Osteitis · Magnetic resonance imaging · Ultrasound

Abbreviations

JSN	Joint space narrowing
MCP	Metacarpophalangeal
OMERACT	Outcome Measures in Rheumatology
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis MRI Scoring

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder that targets synovium and affects multiple organ systems. Advanced disease results in irreversible structural damage to joints, which is associated with disability, decreased quality of life, and early mortality [1, 2]. The prevalence in different populations and ethnic groups varies from 0.1% to 5% [3], with worldwide estimates of 1 in 400 people affected [4].

In Part I of this series I review the specifics of performing and interpreting magnetic resonance imaging (MRI) and ultrasound in the hands and wrists of arthritis patients, addressing pitfalls and controversies along the way. The discussion emphasizes three findings: erosions, osteitis, and synovitis. The review also compares and contrasts the accuracy and relative advantages and disadvantages of each modality. Arthritis in large joints, conditions in the axial skeleton, or juvenile-onset disease are not specifically covered, although some of the same concepts apply in those conditions. Part II will illustrate how MRI and ultrasound findings can influence the clinical management of RA at several time points in the disease course: at presentation, during treatment, and at remission.

A fair question is why limit this discussion to imaging of the hands and wrists, given that RA is a systemic disease affecting many joints and organs. First, the hands and wrists are a common high-yield target region in RA with many joints, bones, and synovial surfaces in one region. Although identifying and quantifying cartilage loss is easier in large joints such as the knee [5], erosions are easier to detect in small

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bones compared with large ones. Synovitis identified in the hands seems to be a reasonable surrogate for the total synovitis burden shown by whole-body MRI examinations [6]. Historically, when radiographs were the primary imaging modality in RA patients, investigators noted more involvement of the foot compared with hand joints in the first 3 years of disease [7], with erosions often appearing earlier in the feet [8]. However, an MRI study of RA patients with symptoms for a mean of 5 months found only rare instances of synovitis or erosions in the feet without these features in the hand or wrist; conversely, 20% of patients had erosions in the wrist or metacarpophalangeal (MCP) joints without erosions in the metatarsophalangeal joints [9]. Overall then, the hand and wrist provide a window into the workings of RA throughout the body; working from this assumption, researchers have created and validated scoring systems and atlases of disease based on imaging of the hand and wrist.

One final question is why a review like the current one is relevant for radiologists. Currently, an overwhelming amount of research being done on the impact of advanced imaging in RA is conducted outside of the USA (primarily in Western Europe, Scandinavia, Japan, and Oceania.) Furthermore, as can be appreciated by scanning the references in this review, most research in this field is published in the rheumatology, not the radiology, literature. The result is that many practicing radiologists have not been exposed to the most up-to-date information on this topic. Thus, a comprehensive review of imaging findings and their implications will help the radiologist performing MRI or ultrasound to provide relevant information that improves the management of RA patients.

Imaging techniques

Ultrasound should be performed using a linear transducer with the highest possible frequency to obtain high-resolution images of the relatively superficial bones and joints. For each joint, the examiner should evaluate each of the bone surfaces (radial, ulnar, dorsal, and volar) that are accessible, recognizing that the visibility of the radial and ulnar portions of the mid-carpal bones and central MCP joints are blocked by the adjacent bones. The synovial membranes and joint contents should be insonated from both the volar and dorsal sides. Graded compression allows distinction of joint fluid from non-compressible synovitis. Power Doppler examination needs to be able to show low levels of flow using a 9-MHz or higher transducer [10]. For the power Doppler examination, the filter should be set for low velocity flow and then the color gain adjusted until noise appears. The gain is then slowly turned down until only flow signal (if present) is shown [11].

The biggest question regarding ultrasound is how many joints to examine. Evidence does not point to an ideal number. Investigations have included as many as 78 separate joints in single patients to evaluate response to drug treatment. Although the ultrasound scores obtained with this method correlate with clinical and laboratory measures of disease activity, the average time for each ultrasound examination is greater than 1 h [12]. Clearly, such a comprehensive approach is not practical for routine clinical use. Others have suggested more limited examinations [13, 14], with as few as seven joints (the dominant wrist, second and third MCP, index and long finger proximal interphalangeal, and unilateral second and fifth metatarsophalangeal joints) constituting a complete study [15].

An MRI examination can be done unilaterally (typically of the dominant or most symptomatic limb) or can include both sides [16]. In either case, the radiofrequency coil diameter should closely match the size of the scanned limb to maximize the signal-to-noise ratio, while at the same time providing the necessary coverage and patient comfort. Typical, commercially available dedicated wrist coils can cover from the distal radio-ulnar joints through the carpometacarpal joints, or from the carpometacarpal joints through the MCP joints, but not both. Flexible surface coils 160–200 mm in length can be wrapped around the limb and provide coverage from the distal radio-ulnar joint through the MCP joints. Alternatively, a whole-volume knee coil can be used, as described in the following paragraph, to provide the equivalent coverage for scanning both sides simultaneously. If one side is imaged, supine positioning with the arm at the side is usually comfortable, but it places the hand near the periphery of the bore where the static field is relatively heterogeneous, and requires a coil that can be positioned next to the patient's body. Alternatively, the arm can be elevated above the head (usually with the patient prone) allowing the hand and wrist to be placed in a whole volume coil near the magnet isocenter. Sometimes called the "superman" position, in reality lying with the shoulder straight overhead (like the caped crusader) quickly causes severe pain in the shoulder in almost all patients [17], but especially those who may have arthritis in multiple joints. I find that placing as many pillows as possible under the chest to elevate the upper body permits the patient to forward flex at the shoulder and is much more tolerable.

The evaluation of certain findings, such as the progression of erosions, is equivalent if based on MRI examination of one or both sides [18]. However, symmetric synovitis—one of the cardinal features of RA that influences both early diagnosis and prognosis—requires bilateral, contrast-enhanced examination [19–23]. Contrast-enhanced MRI of each side can be performed on separate days [21]; however, this approach is logistically awkward. Alternatively, both hands and wrists can be imaged simultaneously in a supine or prone patient, with both arms raised and immobilized above the head [24], but patients

find this position quite uncomfortable [9]. My preferred technique is to allow the patient to lay decubitus, with the shoulders, elbows, hips, and knees comfortably flexed (Fig. 1). The palms are opposed in front and slightly cranial to the patient's face within a knee coil. Padding and pillows between the patient's back and the side of the bore, between the knees, and around the hands in the coil allows even patients with multiple painful joints to comfortably remain motionless for the duration of the 20- to 25-min examination. At my institution, we have imaged several hundred RA patients using this "fetal-praying" position with success.

The recommended MRI protocol for routine evaluation of an RA patient consists of fat-suppressed T2-weighted (or short tau inversion recovery [STIR]) sequences and T1-weighted pre- and post-intravenous contrast-enhanced sequences (typically using fat suppression after contrast agent administration) in the coronal and transverse planes. A 2D spin-echo or fast-spin-echo sequence in each plane can be used for the T1-weighted images, or a near-isotropic, 3D spoiled gradient-echo-recalled acquisition in one plane can be reconstructed into the other plane [25]. The result should be three sets of images that, interpreted together, can distinguish erosions, osteitis, effusion, synovitis, and tenosynovitis (Fig. 2).

Much has been written and debated about the specific requirements for an adequate MRI examination in RA patients. Specific issues include whether intravenous contrast agent is necessary (and if so, is there value in altering the dose, or in scanning during dynamic contrast agent administration), whether T2-weighted or STIR images are necessary in addition to T1-weighted and post-contrast images, and whether low-field scanners can provide the same information as high-field systems. I will address all these questions below (see Additional imaging issues). But the answers are nuanced and largely depend on what specific findings are most important in a given scenario. Therefore, I want to fully describe each imaging finding before returning to these technique questions.

Structural damage, bone inflammation, and soft-tissue inflammation are the critical imaging findings that influence diagnosis, management, prognosis, and follow-up in RA patients. The radiologist needs a reliable way of identifying and rating the extent and severity of each finding for meaningful comparisons over time. In the literature, methods used for scoring radiographic, MRI, and ultrasound findings are primarily used for clinical and drug trials; although these have importance in large populations, they are seldom invoked in the management of an individual patient [26]. Outcome Measures in Rheumatology (OMERACT), a multi-institution study group, is tasked with developing and testing evaluation systems for use in MRI and ultrasound. The OMERACT Rheumatoid Arthritis MRI Scoring (RAMRIS) system is a semiquantitative method that assigns points for various MRI findings [25]. Although the actual assigning of scores is impractical for routine clinical use (see Part II of this review), I find the RAMRIS definitions useful to apply when clinically interpreting a study (without assigning scores), and I discuss them below. The OMERACT working group has developed an analogous scoring system for ultrasound, to which I also refer.

Fig. 1 Decubitus patient positioning allowing simultaneous MRI of both hands and wrists. a-c Photographs of a volunteer lying on her side, with shoulders, elbows, hips, and knees flexed. The palms are placed together slightly cranial to the head in an extremity coil (top of the coil removed for demonstration purposes). Note padding and pillows between limbs, and between patient and scanner. d Sagittal scout gradient-echo-recalled image shows uniform signal reception from the distal radio-ulnar through the metacarpophalangeal joints bilaterally. Vitamin E capsule (arrow) is used to denote the right side
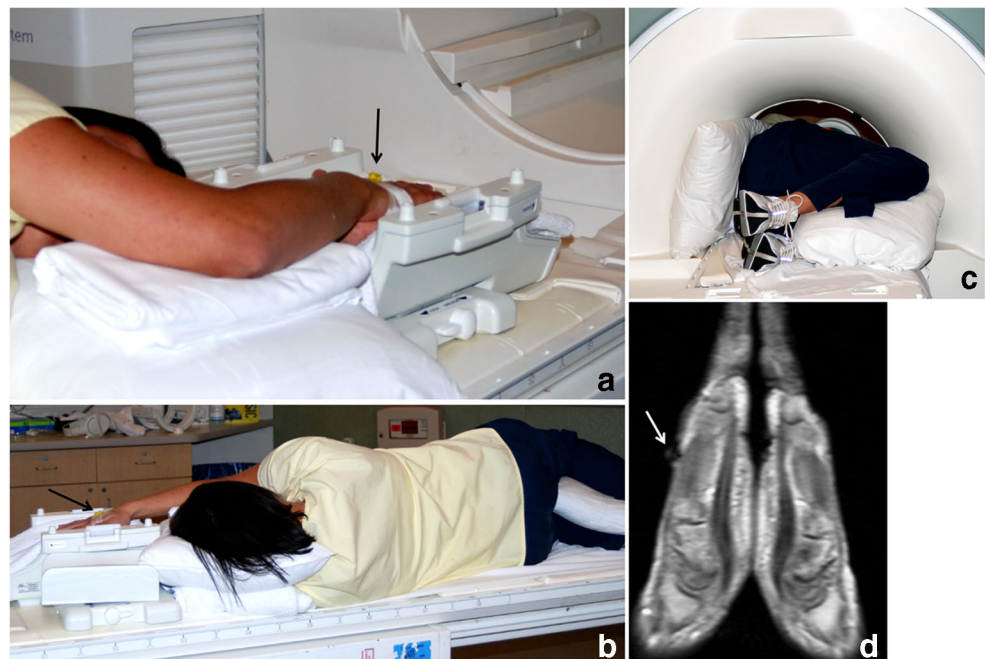
Fig. 2 Typical MRI examination in a 56-year-old woman who had had seropositive rheumatoid arthritis for 3 years. A tryptic of transverse series: **a** T1-weighted, **b** fat-suppressed T2-weighted, and **c** intravenous contrast-enhanced fat-suppressed T1-weighted images through the metacarpophalangeal joints showing third metacarpal head erosions (*black arrows*), metacarpophalangeal synovitis (*long white arrows*), and flexor tenosynovitis (*short white arrows*). The left side is displayed inferiorly. **d** Coronal contrast-enhanced fat-suppressed T1-weighted image of the left side shows additional severe synovitis (*long arrow*) and erosions in the carpus (*short arrows*). **e** Postero-anterior radiograph of the left wrist confirms erosions in the third metacarpal head and the first metacarpal base (*arrows*), but underestimates the extent of erosions in the wrist. There is no joint space narrowing
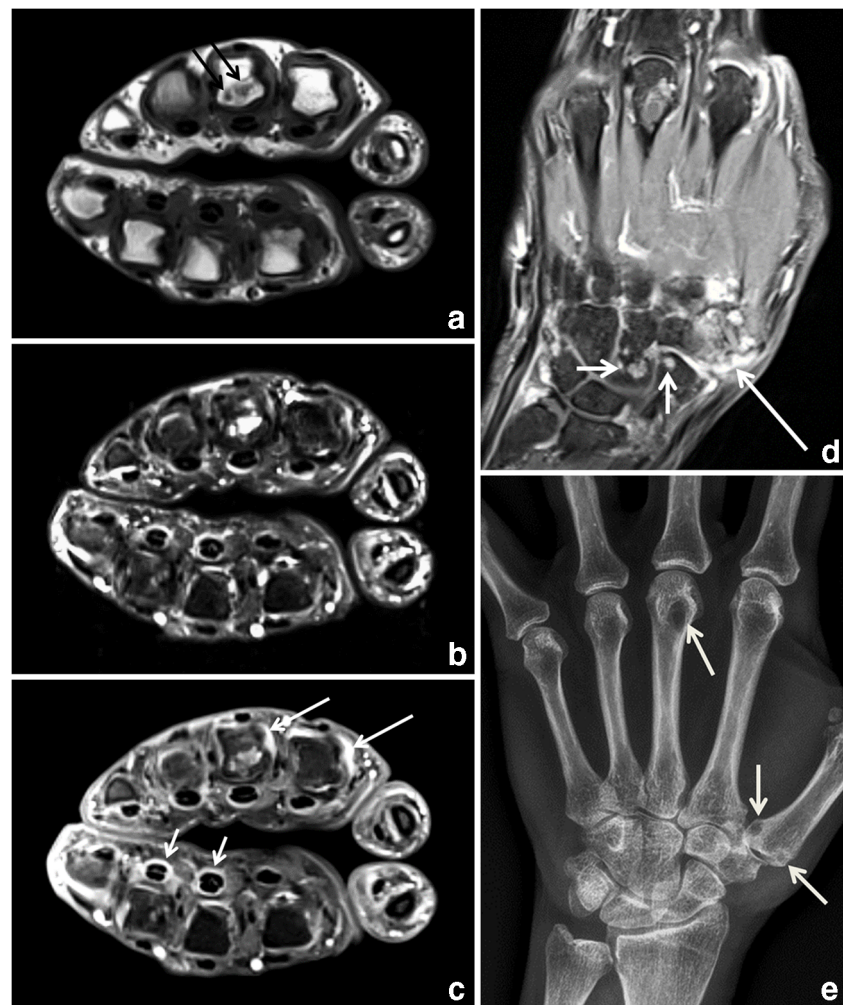
Structural damage

Structural damage represents (mostly) irreversible damage done by the rheumatoid inflammatory process. The main target areas are bone (manifest as erosions), articular cartilage (joint space narrowing), and tendon (rupture). Long-term loss of function seems to be correlated with structural damage [27]. Historically, erosions and joint narrowing were often lumped together, because both are visible on radiographs. MRI and ultrasound are much more sensitive than radiographs for erosions, which are the most relevant feature of structural damage in the hands and wrists.

Erosions

Erosions indicate focal bone destruction, reflecting cumulative damage in RA. Development of erosions is associated with premature mortality, disability, and decreased quality of life [28]. Although less than half of patients have erosions at presentation, erosions develop in most RA patients over time. Less than 2% of patients who meet the 1987 American

College of Rheumatology classification criteria for RA (covered in depth in Part II) for 5 or more years truly have non-erosive disease (no erosions visible even by CT, which is considered the most sensitive test and de facto gold standard) [29]. There are two proposed mechanisms of erosion development. The commonly accepted explanation is that activated synovitis (pannus) interacts with articular cartilage producing collagenase, leading to direct destruction of cortical bone, which exposes the underlying marrow to invasion by B-cells and plasma cells, and which also activates osteoblasts inducing new bone formation [26, 30]. This "outside-in" model is supported by data showing that synovitis demonstrated by MRI or ultrasound is associated with future development and progression of erosions [31–36]. A second theory suggests that some erosions develop from inflammation inside the bone working outward, in keeping with the observation that even some large bone erosions do not communicate with the articular surface [37]; this model finds support in the research done on osteitis (described below), which reveals that osteitis is the strongest prognosticator of erosive disease in all clinical phases of RA.

Although most patients do not have radiographic erosions at the time of initial diagnosis, almost half do by 1 year and the rate of progression is fastest in the first 2 years of the disease [38, 39]. Radiographically, erosions appear as focal disconti- nuities in the subchondral bone plate or articular cortex, with or without destruction visible in the underlying trabeculae. The cortical disruption is easiest to recognize when seen in profile; *en face* erosions appear as focal radiolucent lytic le- sions. The traditional way of quantifying radiographic ero- sions is to grade their subjective visibility or size for a given articular surface and then to total the observations over the number of affected bones as a composite score [40, 41], a method that has high inter- and intra-observer agreement [42]. Computer-aided detection has been suggested to im- prove recognition and quantification of erosions [43], but is not in widespread use.

Early researchers noted that MRI images of the hands and wrists in patients with RA frequently showed erosions that were not visible radiographically [44, 45]. The reasons for this increased sensitivity are two-fold. Like all tomographic exam- inations, MRI is free from superimposition of out-of-plane structures. Additionally, MRI uses contrast agent differences in the bone marrow to identify disease, and so is not reliant solely on spatial resolution to identify erosions [46]. The RAMRIS definition of an erosion—a sharply-defined juxta- articular bone lesion that is visible in two orthogonal planes, and which disrupts the bone cortex in at least one (Fig. 3)— shows moderate inter-observer correlation (intraclass correla- tion coefficients of 0.46–0.85, better for MCP than for wrist joints) with smallest detectable differences of 24–42% [25, 47]. The two-plane criterion is important to ensure that normal contour variations—foramina, nutrient vessels, and ligament attachments that are present in normal, asymptomatic subjects [48, 49]—are not misinterpreted as pathological. Lesion en- hancement with intravenous contrast agent is not part of the definition. For OMERACT/RAMRIS grading, individual ero- sions are assigned a score from 0 to 10 by estimating in 10% increments (0 = no erosion, 1 = 1–10%, 2 = 11–20%, through 10 = 91–100%, with a score of 10 also assigned if joint fusion

is present) how large the erosion is compared with a standard assessed bone volume. This comparison volume is defined for long bones such as metacarpals and phalanges as the distal or proximal 1 cm; for carpal bones, it is the entire bone [25, 50]. Compared with CT, MRI is slightly less sensitive, but 87% of erosions seen in the wrist, and 82% of the erosions seen in the MCP joints with the two modalities are concordant and com- parable in size [51, 52]. Conversely, MRI is much more sen- sitive than radiographs (Fig. 2), showing up to seven times more erosions in early arthritis [53, 54]. Fewer than half of the erosions detected by baseline MRI ever become visible radio- graphically. Estimates range from 21% at 1 year [55] to 41% at 7 years [56], with a median lag of 2 years for those that even- tually appear on radiographs [57]. In the MCP joints, erosions on MRI that destroy less than 20% of the bone area are con- sistently invisible on radiographs [58], but even erosions 1 cm in diameter visible on MRI may be radiographically occult [37].

It is important to recognize that erosions are not specific to RA, nor are they even pathognomonic of arthritis. MRI exam- ination may demonstrate small erosions in the hands and wrists of some healthy controls (in approximately 2% of the bones) [59] and erosions in normal subjects increase in prev- alence with advancing age [60].

The OMERACT consensus ultrasound definition of an erosion has high inter- and intra-observer agreement, and is similar to that for MRI: discontinuity of the intra- articular bone cortex visible in orthogonal planes (Fig. 4) [61, 62]. Compared with CT as the gold standard, ultrasound has a 44% sensitivity for erosions in the MCP joints in RA patients, but detects 95% of the lesions with more than 20% bone loss on CT [63]. The sensitivity of ultrasound is decreased in areas where bone surfaces are not easily accessible, including the radial and ulnar sur- faces of the central carpal bones and metacarpal heads [63, 64]. False-positives are 29% with ultrasound com- pared with micro-CT [65]. One common pitfall is mistak- ing the normal depression on the dorsal metacarpal head for an erosion [64]. Nevertheless, ultrasound is much
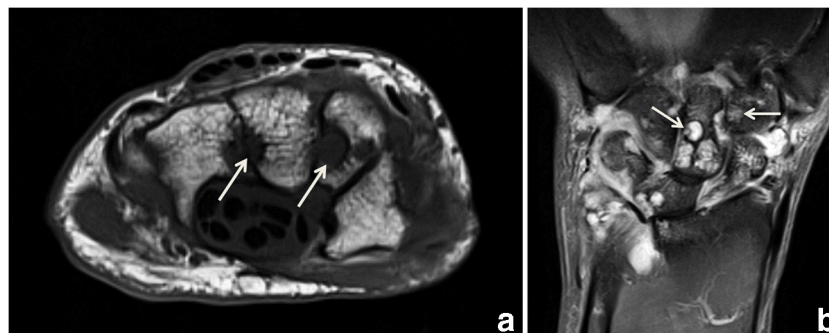
Fig. 3 Wrist erosions in a 51-year-old woman with seropositive rheuma- toid arthritis. **a** Transverse T1-weighted and **b** coronal fat-suppressed T2- weighted images show subchondral marrow-replacing bone lesions in the trapezoid and capitate (*arrows*), visible in orthogonal planes and destroying the cortex in at least one. Additional erosions are present in other carpal bones and the distal ulna

Fig. 4 Long finger proximal interphalangeal joint erosions in a 66-year-old woman with both rheumatoid arthritis and gout. **a** Sagittal and **b** transverse ultrasound images show disruption of the highly echogenic bone cortex of the proximal phalanx head in two planes (*long arrows*). A smaller erosion is present in the middle phalanx base (*short arrow*). **c** Sagittal Doppler examination shows associated hyperemia
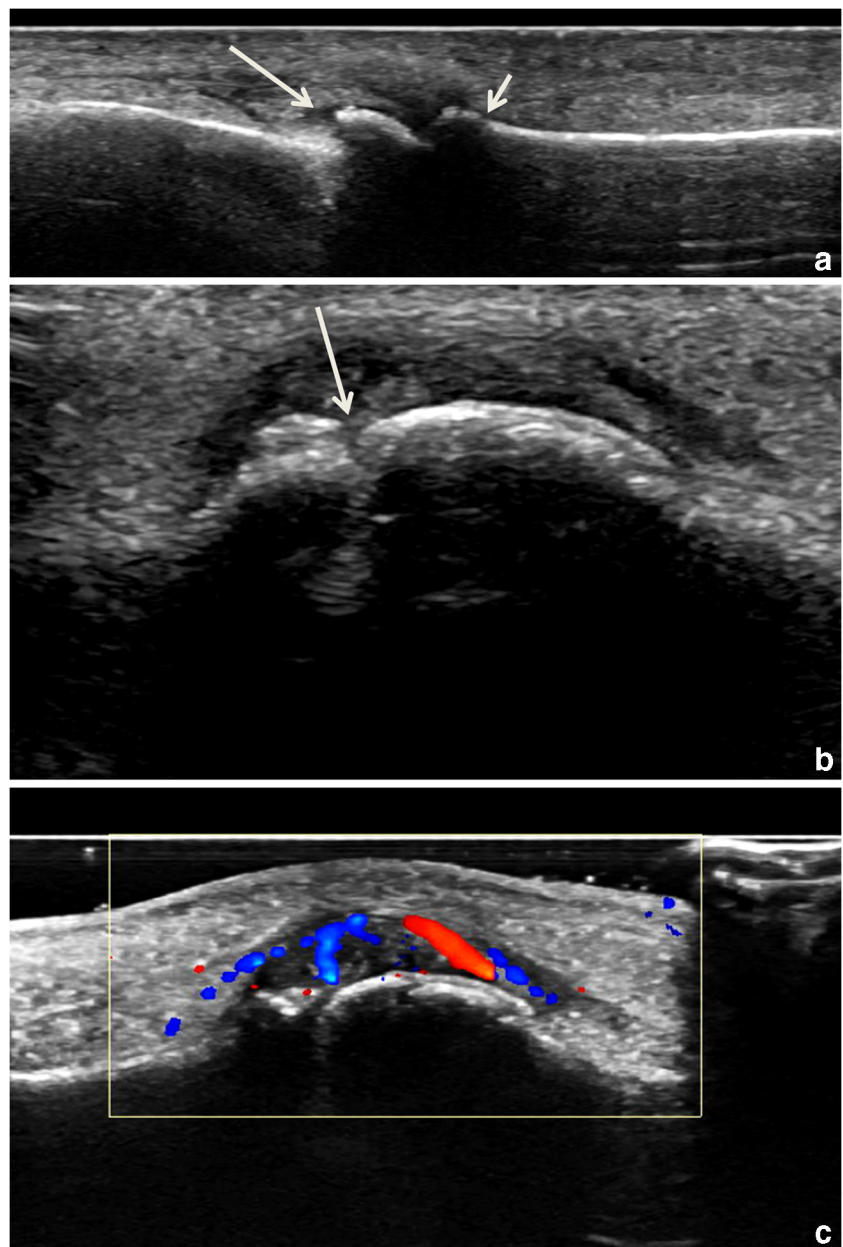
more sensitive than radiography for erosion detection, showing approximately 6.5 times as many MCP lesions in early RA, and 3 times as many in established RA [62]. Most studies have found that ultrasound reveals fewer erosions in both baseline and follow-up studies of RA patients compared with MRI [66, 67], although one study of a small number of RA patients found no significant difference in the detection of wrist erosions, and an advantage of ultrasound over MRI for MCP erosions [68].

In general, the natural history of erosive disease is that it either remains stable or progresses; thus, it is not surprising that more and larger erosions are found in patient groups with longer-standing disease [29, 69]. The typical RA patient experiences the fastest progression of erosions in the initial 2 years after diagnosis [39] and then their evolution will slow or stop. There is general agreement among experts that repair of erosions can occur [70, 71], albeit rarely. Radiographically, erosion healing in RA patients treated with disease-modifying anti-rheumatic drugs (especially biologic agents) occurs in 7–11% of patients [72, 73] and in approximately 4% of affected joints [74]. MRI studies demonstrate decreased size in a minority (17%) of erosions in RA patients managed with these agents at 1 year, with partial repopulation of the affected bone by marrow fat at 6 years [75, 76]. However, in individual patients, if there is any partial erosion repair, progression and development of new erosions typically occur simultaneously [73].

Joint space narrowing

Joint space narrowing (JSN) is a hold-over term from radiographs indicating that the distance between the visible subchondral bone plate of two articulating bones is less than normal, reflecting loss of the radiolucent articular cartilage. Some linguistic purists object to the phrase, arguing that there is no empty "space" in the gap between the bones. Nevertheless, other anatomical regions in the body—from the space of Retzius to the space of Poirier—are similarly named, despite having tissue contents, and JSN is an accepted descriptor in rheumatological practice. In research studies on RA patients, erosions and JSN in a set number of hand and wrist joints are often tabulated together on radiographs to assign a single (modified Sharp) score [40, 41]. Although useful as one measure of the total visible burden of structural damage, these scores are not used in clinical practice. Furthermore, JSN and erosions represent different unique pathophysiology, cartilage and bone destruction respectively, and data suggest that investigating each component separately may benefit both patients and research. Indeed, clinically, irreversible disability seems to correlate more strongly with JSN than with erosions for patients in remission [77].

In larger joints like the knees, the normal articular cartilage is several millimeters thick and can be assessed relatively easily with morphological cross-sectional imaging techniques. However, in the hands and wrists, the thinness and highly curved contour of the cartilage makes direct visualization and assessment more difficult with MRI and ultrasound compared with high-quality radiographs. Several investigators have demonstrated that it is possible to semiquantitatively assess the thickness of the hyaline cartilage in the hands and wrists with relatively high inter-observer agreement (at least using 3-T MRI scanners with a multichannel receiver coil and 1 mm thick, 3D acquisitions) and that these assessments correlate with radiographic JSN [78–81]. An MRI scoring system for direct cartilage loss has been validated [82, 83], but has not been formally incorporated into RAMRIS, and is not currently used clinically. Investigational techniques such as delayed gadolinium-enhanced MRI imaging of cartilage and T2 mapping, which reflect the loss of cartilage proteoglycans, have been applied to the MCP joints in RA patients. Interestingly, these studies seem to show that proteoglycan loss is strongly associated with bone inflammation (osteitis), less strongly associated with synovitis, and not necessarily correlated with erosions [84, 85]. This observation supports the notion that bone and cartilage destruction may reflect different pathophysiologies, and that more than one pathway may lead to articular cartilage loss.

Tendon rupture

Tendon rupture in the hand and wrist occurs spontaneously in at least 1% of patients with long-standing RA, although the incidence is likely underestimated [86]. Nevertheless, loss of tendon function has a profound negative impact on hand function, and is difficult to manage surgically once rupture has occurred, especially if multiple tendons are affected. Finger extensor tendons are more commonly torn compared with flexors [87, 88]. The cause can be attritional, owing to the tendons rubbing along the rough surfaces of the eroded carpal bones or distal ulna. Alternatively, proliferative tenosynovitis can directly invade or compress tendons in their sheaths leading to ischemia in addition to ultrastructural changes in the tendon collagen [88–90]. Whether de novo inflammation within a tendon occurs in RA is uncertain; if tenosynovitis need not precede tendinitis, it would represent another potential "inside-out" mechanism of damage in RA.

Surprisingly, clinical evaluation for tendon tears in rheumatoid wrists and hands is relatively poor because rupture is insidious and often painless, and the physical signs may be masked by more profound limitations from the joint disease and malalignments. The MRI signs of tendon rupture are the same throughout the body, whether in the hands, rotator cuff, or Achilles' tendon: disruption of some or all of the fibers, with variable fibrotic tissue and fluid in the tendon gap. The OMERACT group is currently working on consensus ultrasound definitions and an ultrasound scoring system for tendon disease in the hands of rheumatoid patients, and there is relatively high inter- and intra-observer agreement of the ultrasound findings within the wrist and finger tendons [91, 92]. Compared with findings at surgery, the reported sensitivity of MRI for full-thickness extensor tendon tears in patients with longstanding RA varies from 17 to 90% and for ultrasound is 67%, but both imaging techniques have a lower sensitivity for partial tears [86, 89].

Bone inflammation

Osteitis is defined as a region within bone marrow that shows ill-defined MRI signal intensity that is "edematous," i.e., hypointense on short TR/TE sequences and hyperintense on T2-weighted and STIR sequences, compared with skeletal muscle (Fig. 5) [25]. For research purposes, a score of 1–3 is assigned based on what percentage of the bone (0–100%, in 33% increments) shows the signal changes. Osteitis can coexist with sharply marginated erosions in the same bone, or can manifest in bones without erosions. Although some authors still refer to this finding as "bone marrow edema," in RA it does not represent simply increased fluid in the marrow. Rather the abnormal bone marrow enhances after intravenous contrast agent administration, and histological studies
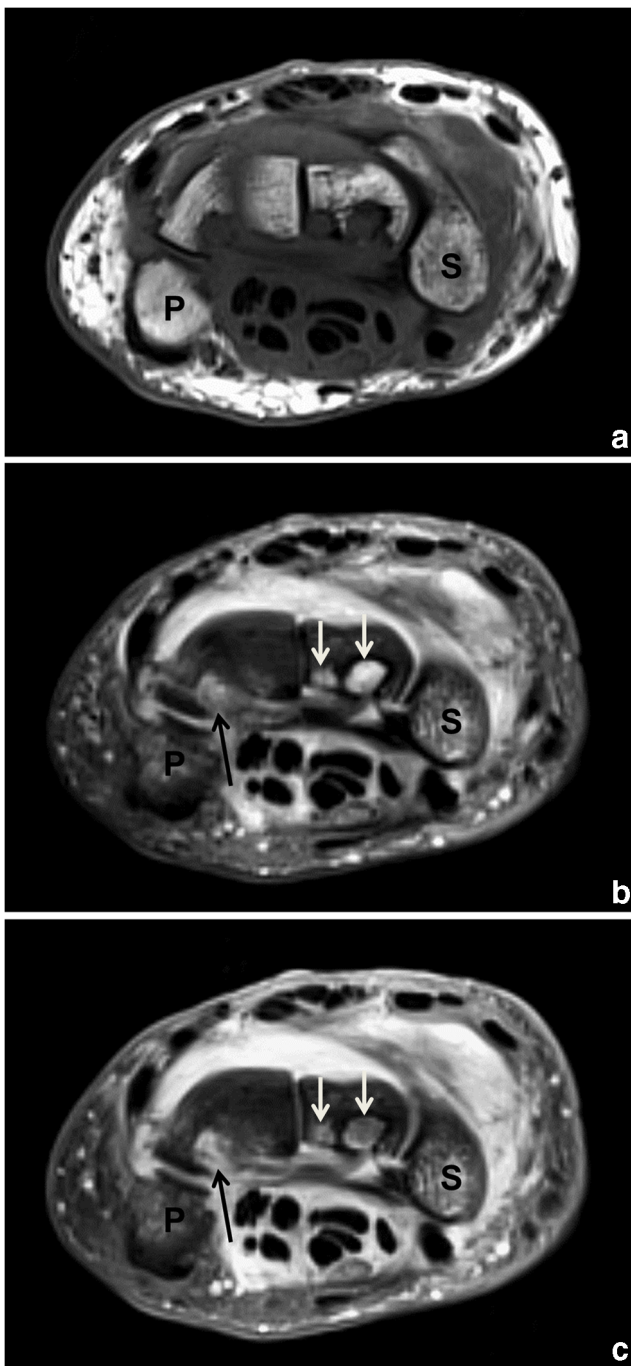
Fig. 5 Wrist osteitis, synovitis, and tenosynovitis in RA. Same patient as Fig. 3. Transverse **a** T1-weighted, **b** fat-suppressed T2-weighted, and **c** contrast-enhanced fat-suppressed T1-weighted images show an ill-defined reticulated marrow "edema" pattern with contrast enhancement, preserving the trabeculae in the scaphoid (*S*) and pisiform (*P*) bones, representing osteitis. The dorsal synovium and flexor tenosynovium in the carpal tunnel are severely thickened and enhancing. Note that the erosion in the triquetrum (*black arrow*) enhances, whereas those in the lunate (*white arrows*) do not; enhancement is not part of the definition of erosions

demonstrate inflammatory cellular infiltrates consisting of macrophages, plasma cells, T-cells, and B-cells [93–95].

Thus, the term osteitis, meaning true bone inflammation, is more correct. Of the common imaging modalities, only MRI is able to show osteitis. Radiographs and ultrasound cannot show alterations within the marrow elements, which is a major limitation of ultrasound in the evaluation of RA patients. Likewise, standard CT is insensitive to marrow edema or inflammation, although in the future, dual-energy CT may be able to detect and potentially quantify osteitis. Preliminary pilot studies have investigated this application in patients with gout [96] and RA [97].

At least three associations make osteitis one of the most important clinical findings in RA. First, unlike erosions (and as will be seen, synovitis) osteitis is fairly specific for inflammatory arthritis: with the exception of one small nonblinded study [48], osteitis is not found in healthy, asymptomatic control subjects [59]. Second, osteitis is a marker for patients who manifest a particularly aggressive, severe disease phenotype. In early RA (less than 2 years' duration), patients with osteitis in the hand or wrist have higher degrees of positivity in all other imaging, serological, and genetic indicators of disease, and are more likely to have positive serological markers compared with those without the MRI finding [98, 99]. Third, because it does portend an aggressive course, osteitis is the single strongest independent predictor (of all imaging, immunological, and clinical variables) of future negative outcomes—especially the development and progression of structural disease [100–103]. Interestingly, future erosions often develop in the same bones that previously showed osteitis [100], supporting osteitis as a precursor lesion for at least some erosions [95]. One mechanism for this "inside-out" development of erosions is the release of cytokines by the intraosseous inflammatory cells, which then stimulate osteoclasts to resorb bone [101, 104].

Soft-tissue inflammation

Synovitis

Synovitis, defined as inflammation of the lining of the joints, is one of the hallmark findings in RA. Although very early in the disease (in the first 2 months of symptoms), synovitis is more common in the foot metatarsophalangeal joints than in the MCP joints, by 6 months 90% of RA patients have MRI evidence of synovitis in the MCP and/or wrist joints [105]. The clinical assessment of synovitis is relatively insensitive, both at presentation and especially when assessing for remission [106–109]. The examiner palpates individual joints and records whether each is subjectively swollen, tender, or both. A clinical disease activity score is then assigned by counting the number of affected joints [110, 111].

Early studies with intravenous contrast-enhanced MRI in patients with established RA showed that both focal and

diffuse enhancement occurs in the synovium [112]. Furthermore, in patients with early arthritis, dynamic contrast-enhanced MRI shows early synovial enhancement compared with control subjects [113]. The OMERACT definition of synovitis is the presence of synovium that is both thicker than normal (the normal synovial membrane is barely perceptible) and that shows "above normal enhancement" after intravenous contrast agent administration (Figs. 2, 5) [25]. The phrase denoting enhancement greater than normal implies that the normal synovial membrane shows some enhancement. One study of healthy control subjects found minimal enhancement confined only to the prestyloid recess in nonthickened synovium [114], which would not meet the consensus definition of synovitis. A second study depicted only minimal early synovial enhancement on dynamic, contrast-enhanced MRI images in less than 10% of MCP and wrist joints in control subjects [59]. Of note, most of the patients who showed enhancing synovium in this study actually had elevated C-reactive protein levels, suggesting systemic inflammation, despite their "healthy" label. The degree of enhancement in both of these studies would be scored as 0–1 in the semiquantitative RAMRIS system, where the amount of synovitis is subjectively assigned a rating from 0 (none) to 3 (severe) [25]; in my experience, most RA patients with active synovitis show enhancing synovium that is unequivocally brighter and thicker than normal in multiple compartments. Additionally, the cut-off for the presence/absence of synovitis

in most published research studies is a RAMRIS score of 2 or higher.

Magnetic resonance imaging and clinical evidence for synovitis are strongly correlated and concordant in approximately 60% of joints [106, 107]. However, MRI appears to be much more sensitive. In a cohort of RA patients with a median disease duration of 5 months, 64% of the patients whose MRI studies showed bilateral synovitis without erosions or osteitis had no tender or swollen joints on physical examination [107]. Another study showed that MRI revealed ten times the number of MCP joints with synovitis in patients with active RA compared with clinical examination. In 105 total wrist and hand joints, synovitis was found on MRI, but not by clinical examination; the converse (clinical examination positive, MRI negative) was true for only two joints [106].

The consensus ultrasound definition of synovitis is intra-articular tissue that is typically (but not always) hypoechoic compared with subcutaneous fat, and that is nondisplaceable and poorly compressible (Fig. 6) [61]. Lack of compressibility is important to distinguish synovitis from simple joint fluid. Synovitis may or may not exhibit signal with power Doppler interrogation, and in research studies the incidence of synovitis on grayscale and Doppler images is often analyzed separately. Experimentally, administration of an intravascular ultrasound contrast agent that contains micro-air bubbles may enhance the Doppler signal in inflamed synovium [115]. Although it is tempting to consider Doppler signal as an

Fig. 6 Second MCP synovitis in a 58-year-old woman with RA. **a** Sagittal grayscale ultrasound shows tissue with medium echogenicity in the dorsal recess of the MCP (*asterisk*). This material was not compressible. **b** Power Doppler image shows severe hyperemia of the tissue. The apparent Doppler signals that map to the bone cortex and subchondral bone are artefactual
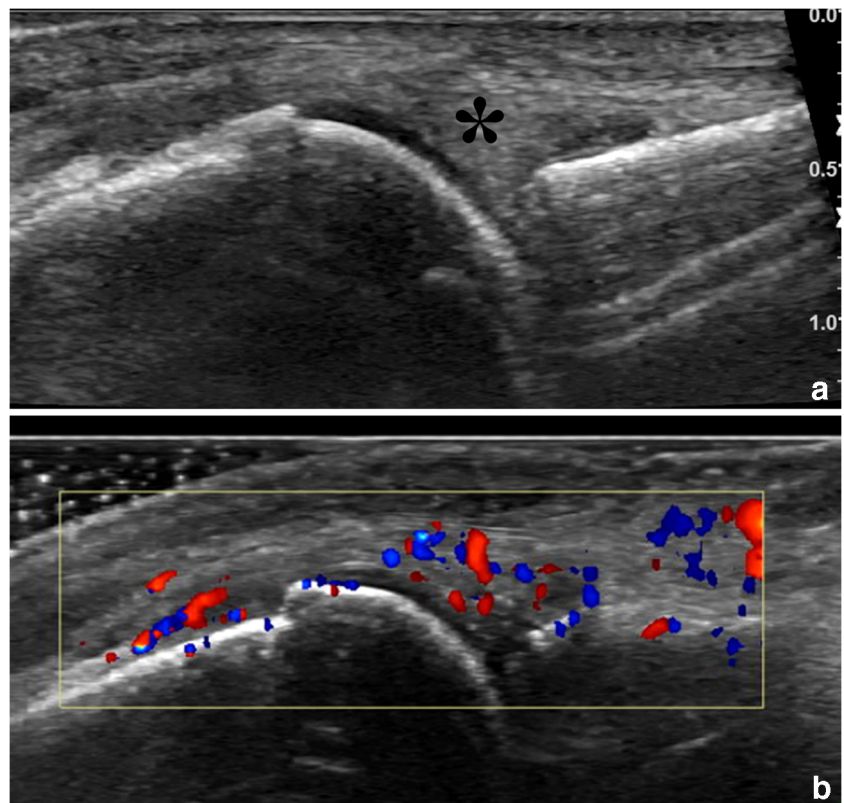
indication of active disease, the sensitivity of this finding is uncertain. Biopsies of Doppler-positive synovium in patients with mainly long-standing RA have shown histological evidence for synovitis and immunohistochemical staining for increased vascularity [116]. However, in the same study, biopsy of Doppler-negative areas also often showed pathological synovitis (i.e., a negative Doppler examination does not rule out active synovitis). Power Doppler ultrasound is more sensitive and specific than physical examination for detecting synovitis in the MCP joints (with contrast-enhanced MRI as the standard) [11], and a systematic review of 23 peer-reviewed articles confirms high inter- and intra-observer agreement among highly trained operators for interpretation of the Doppler images [117]. But at least in patients with early arthritis, baseline examination with MRI detects more synovitis than Doppler ultrasound, especially in the wrist and MCP joints [16]. Unlike on MRI, it may be difficult at times to distinguish synovium from adjacent cartilage sonographically. Other ultrasound pitfalls include motion and electronic noise, which can result in spurious Doppler signals, and over-compression, which can obscure them [64].

As synovitis is a measure of disease activity, a reliable and reproducible method of quantifying it is highly desirable to apply to follow-up examinations. Essentially, there are three possible ways of accomplishing this task using MRI. The current de facto standard is the semiquantitative method of rating the synovitis in each joint on a subjective 0–3 scale, and adding the scores for multiple joints [25]. When observers apply this method after intense training and with the use of a standardized atlas [50], interobserver reliability is good-to-moderate (though worse than that reported for erosions and osteitis); the smallest detectable change is estimated to be 26–35%, which may not be sensitive enough for all patients [118–121]. Experimental studies frequently use two observers for each examination because of the inherent variability [105]. The training requirements, interpretation time, and need for double reading make the RAMRIS synovitis score impractical for routine clinical use [122–124]. One proposed way to decrease observer times for semiquantitative rating is to create coronal, maximum intensity projections from dynamic or static contrast-enhanced images that provide a visual overview of the involved joints (and tendon sheaths) [125, 126]. Although this technique usually involves first subtracting precontrast images, it can also be done without subtraction, allowing a time saving by eliminating the need to acquire a matching precontrast sequence (Fig. 7).

A second approach to quantifying synovitis on MRI is to sum the volume of enhancing synovium in a given joint or region. The volume of MR-determined synovitis does correlate with later progression rates of erosions, but volume determination requires manual outlining of regions on dozens of transverse images [32], which is again not practical for clinical use. The procedure can be simplified by only analyzing three

transverse images and using computer-assisted manual segmentation; volumes calculated in this way show good inter-observer agreement and strong correlation with RAMRIS synovitis scores, but even for three images, the manual outlining still takes longer than assigning semiquantitative scores [127]. Automated software algorithms have also been developed to estimate synovitis volumes on MRI. Although these result in measurements that also correlate with RAMRIS scores [81], the programs are currently proprietary and not available for individual patient assessment.

A final approach is to administer intravenous contrast agent dynamically and analyze the enhancement kinetics (e.g., the time to enhancement onset, the rate of early enhancement, or the relative amounts of enhancement). In the knee joint, the overall enhancement rate 30–60 s after contrast agent administration does correlate with histological findings of active synovitis, but extensive regional variation and heterogeneity of inflammation limit correlations of smaller synovial sections [128]. This spatial variation affects the use of dynamic contrast analysis in the hands and wrists, where results vary depending on the precise placement of regions of interest [129, 130]. Again, automated software that analyzes the

Fig. 7 Polyarticular synovitis in a 29-year-old woman with seronegative RA. Coronal maximum intensity projection made from a set of contrast-enhanced fat-suppressed T1-weighted images gives an overview of the amount, distribution, and severity of the synovitis in the intercarpal, MCP, and thumb's interphalangeal joints

enhancement kinetics of every voxel has been developed to reduce this variability [131, 132], but in reality, results derived from dynamic contrast analysis do not seem to have an advantage over those that are based on static images made 2–5 min after contrast agent administration [124].

Quantifying synovitis for temporal comparison in individual patients is even more challenging with ultrasound. Reproducibly calculating synovial volumes is not possible on ultrasound images and it is difficult to compare the degree of synovitis during scanning. These factors make ultrasound less well suited compared with MRI for sequential examinations in RA patients. Currently, the only way to quantify the synovitis burden in a patient using ultrasound is to assign a subjective severity rating to each joint based on its gray-scale or power Doppler appearance and then sum these ratings over a standard number of joints [133]. The ideal number of joints to evaluate is not clear—various studies have investigated from 6 to 44 separate joints in single patients [108, 134]. Assessing more joints has the potential to detect smaller changes over time (although this has not been proved), but increases the examination time to a point where it would be prohibitive to perform for clinical purposes.

Tenosynovitis

Tenosynovitis, inflammation in the lining of the tendon sheaths, is an important ancillary finding in RA, and may appear before synovitis [135]. A small amount of fluid in the tendon sheaths can occur in healthy subjects. An abnormal amount of fluid in the hands or wrist is typically defined by either distension of a sheath greater than 1 mm or fluid diameter greater than the tendon diameter in a sheath on a T2-weighted MRI sequence [89]. As is the case for synovitis in a joint, intravenous contrast agent enhancement is needed to distinguish a tendon sheath effusion from tenosynovitis (Fig. 8). The same MRI criteria apply: tenosynovitis is tissue thicker than the normal tenosynovial membrane [136, 137]. The ultrasound criteria for tenosynovitis are also analogous to the consensus definition of synovitis. Tenosynovitis is characterized by hypoechoic or anechoic thickened tissue within a tendon sheath, visible in two perpendicular planes, with or without fluid in the sheath, and with or without Doppler signal [61]. Applying this definition results in good-to-excellent inter- and intra-observer agreement with trained examiners [92]. MRI appears to be more sensitive than ultrasound for detecting tenosynovitis, at least in patients presenting early in the course of disease [16].

The prevalence of tenosynovitis varies at different stages of disease. Overall, approximately 20% of a heterogeneous group of RA patients with different disease duration had evidence of tenosynovitis on ultrasound [92]. The extensor carpi ulnaris tendon sheath is most frequently involved at 1 and 6 years' disease duration [75]. But in early arthritis, flexor

tenosynovitis is more common than extensor tenosynovitis [138]. The reason for this discrepancy is unclear. It may be that flexor tendon sheath disease is transient by nature, or perhaps that flexor tenosynovitis has a better response to treatment than other inflamed sites.

Additional imaging issues

Before proceeding to explain how the imaging findings can influence clinical management over the disease course of RA, it is useful to address some common imaging questions and controversies.

Is intravenous contrast necessary for MRI?

In a word, yes. Injecting (gadolinium-based) intravenous contrast agent does add cost, time, and discomfort to the
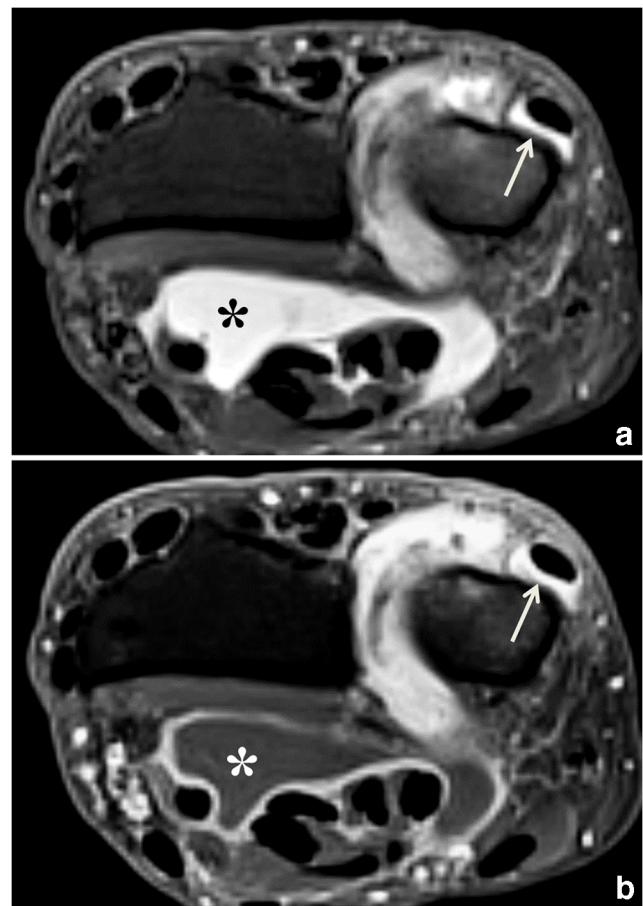
Fig. 8 Tenosynovitis in a 50-year-old man with RA. **a** Transverse fat-suppressed T2-weighted image shows high signal material in the carpal tunnel (*asterisk*) and extensor carpi ulnaris tendon sheath (*arrow*). **b** Contrast-enhanced fat-suppressed T1-weighted image shows enhancing tenosynovitis in the extensor carpi ulnaris sheath (*arrow*). In the flexor tendon compartment, the synovium is of normal thickness and the contents of the tendon sheaths do not enhance (*asterisk*), representing a simple effusion. Active synovitis is present in the distal radio-ulnar joint

examination, may pose a logistic challenge in some practices, and carries a small risk of allergic reactions and nephrogenic systemic sclerosis. But it greatly enhances the assessment of disease activity. In patients with early arthritis, the sensitivity and specificity for identifying synovitis and tenosynovitis are lower when using T2-weighted sequences alone compared with contrast-enhanced images, although the same is not true for detecting erosions or osteitis [139–142]. Using T2-weighted images alone tends to overestimate synovitis and tenosynovitis, because simple effusions may not be distinguishable from inflamed tissues (Fig. 8) [17]. And unenhanced T1-weighted images cannot distinguish active synovitis from fibrotic pannus in burned-out disease [105]. In one study, synovitis was evident in 50% more of the early arthritis patients who eventually developed RA on contrast-enhanced MRI studies compared with unenhanced scans (even on a 3-T scanner), with contrast-enhanced images identifying nearly twice as many patients with tenosynovitis [143]. There is one caveat, however: although not in widespread use clinically or part of the OMERACT methodology, preliminary data suggest that diffusion-weighted sequences might be able to distinguish fluid from synovitis without the need for intravenous contrast agent. Specifically, the measured apparent diffusion coefficient is lower in joint contents corresponding to enhancing synovitis compared with regions where unenhanced effusions are present [144, 145].

How much contrast agent should be given?

Contrast enhancement is frequently less conspicuous on low-field magnets (0.2 T). Doubling the "typical" dose of gadolinium-based contrast agent (from 0.1 mmol/kg body weight to 0.2 mmol) can increase the assigned synovitis score on low-field scanners [146], but most studies performed with a standard dose of contrast agent show similar scores when compared with high-field MRI [147–149]. In fact, "half-dose" (0.05 mmol/kg of body weight) contrast agent results in diagnostically equivalent images for scoring synovitis and tenosynovitis compared with full dose at 0.2 T [150] and 3 T [151]. In short, it should not be necessary for most practices to change their contrast agent dosing schedules for RA patients, regardless of the equipment used, and a standard 0.1-mmol/kg dose of any gadolinium-based agent should suffice.

Is dynamic administration of contrast agent needed?

Without automated software capable of separately analyzing every synovial voxel, dynamic enhancement studies require the user to manually select a region of interest to investigate, which has been shown to be an important source of variation [129, 130]. Most objective measures of enhancement kinetics (such as the rate of early enhancement and the relative amount of overall enhancement) do correlate strongly with clinical

measures of disease activity in early arthritis; however, the same is true for RAMRIS synovitis scores, which are determined on static, post-contrast images [152]. Although calculating measures of enhancement kinetics has been suggested as a useful tool for following treated RA patients, the sensitivity to change appears to be similar to that for parameters based on static contrast enhancement [31, 153, 154]. For clinical assessment, simply administering contrast agent and immediately obtaining transverse and coronal sequences lasting 4–5 min each probably provides adequate information. Is there a delay that is too long? Although theoretically, contrast agent could "leak" from inflamed synovium into a joint effusion over time and falsely elevate the apparent amount of enhancing tissue, even in the knee joint, where synovitis and effusion often coexist, the border between the two remains defined for at least 11 min after intravenous contrast agent administration [155].

Are T2-weighted or STIR sequences necessary?

Here the answer is maybe. In early and established RA, contrast-enhanced images are equivalent to T2-weighted images for identifying osteitis [156]. However, eliminating T2-weighted images would result in missing unenhanced findings such as effusions, ganglia, and possibly rheumatoid nodules and burned-out fibrotic synovitis. Additionally, erosions need not enhance. In an RA cohort that incompletely responded to methotrexate, T2-weighted images demonstrated some erosions that were concordantly shown on CT images, but that were not always visible on contrast-enhanced images (although the converse was also true) [157]. Presumably, though, these erosions would be detected on T1-weighted images.

Is a low-field, dedicated extremity magnet sufficient?

This question is harder to answer, and the response probably depends on the indication for the study and what finding is most important in a given patient. Most studies looking at the predictive value of MRI findings have been based on high-field (1.5-T or greater) scanners [122]. There are several 0.2-T dedicated extremity machines available. Manufacturers are actively marketing these to rheumatologists, who can site them in the office or clinic and then offer limited MRI examinations as an adjunct to their clinical assessments. Advantages of these dedicated extremity scanners include reduced initial and operating costs, fewer issues with siting (including shielding, need for cryogens, space, and weight), less risk from projectiles and implanted devices, and better acceptance by some patients (because of the less painful and constrictive position, low noise, and eliminated claustrophobia concerns) [158]. Offsetting disadvantages include the lower signal-to-noise ratio (because of the lower static magnetic field),

a smaller useable field of view (typically limited to either a unilateral wrist or hand examination, but not both), and longer acquisition times (which may prohibit dynamic contrast enhancement studies). The lower magnet field (and higher heterogeneity) compared with high-field magnets means that chemical (frequency-selective) fat suppression is unreliable on these machines. Although STIR sequences can be used to suppress fat signal, STIR sequences have inherently lower signal-to-noise ratios and efficiency (number of slices obtainable per TR period) compared with fast spin-echo sequences, and cannot be used following contrast agent administration because gadolinium works by shortening T1, which decreases the signal on a STIR sequence.

Several studies have compared results using dedicated 0.2-T or 0.25-T scanners with systems using 1-T or higher magnetic fields. In general, when intravenous contrast agent is used, studies performed on low-field machines are able to identify approximately 90% of the synovitis seen on high-field examinations, with comparable estimates of synovial volume involved [137, 147, 148], although the low-field studies may require two separate scans for the same anatomical coverage [158]. Agreement between low- and high-field MRI examinations is lower when analyzing parameters of dynamic enhancement [148]. Additionally, when contrast agent is not used, sensitivity for synovitis is lower for examinations performed on low-field compared with high-field systems [139]. Erosion detection using low-field equipment that is optimized for spatial resolution is also similar to that achieved with high-field scanners [137, 147, 159], and erosions are detectable on a 0.2-T scanner even when contrast agent is not used or on scanners that can only image two MCP joints [160, 161]. However, disagreements are common between low- and high-field examinations investigating osteitis, with lower sensitivity for this finding at the lower field strengths [147, 159].

An American College of Rheumatology task force critically examined the literature on dedicated extremity MRI studies in RA patients, and found few data supporting their clinical utility. The small number of studies comparing different magnet systems often did not use optimized techniques, introducing potential bias that could falsely elevate the apparent accuracy of the extremity scanners [122]. There is one commercially available high-field dedicated extremity magnet. One study investigating patients with established RA found excellent agreement comparing contrast-enhanced examinations on this system compared with a whole-body, high-field system for RAMRIS scoring of synovitis, osteitis, and erosions. The extremity scanner studies used thinner sections (2 mm vs 3 mm for the whole-body scanner) and a STIR sequence in lieu of a fat-suppressed fast spin echo sequence. The examination times were longer but most patients found being positioned in a chair for the dedicated extremity scan more comfortable than being examined with the arm raised above the head. However, the field-of-view only allowed examination of either the MCP joints or the wrist, but not both, in a single scan [149].

Summary

Three major imaging findings in the hands and wrists—synovitis, osteitis, and erosions—have specific definitions, and together provide information that complements clinical evaluation and radiographs in the evaluation of rheumatoid arthritis patients. Synovitis indicates active disease. Both MRI (with intravenous contrast agent) and ultrasound (with power Doppler interrogation) are more sensitive than clinical examination for detecting synovitis. MRI is probably more sensitive than ultrasound, and there are more potential ways to reliably quantify the amount or severity of synovitis with MRI, making it an ideal candidate for sequentially evaluating patients during treatment and in clinical remission. Osteitis represents inflammation in bone and indicates high-risk disease with the potential for rapid, progressive structural damage. Osteitis can only be visualized by MRI (and evidence suggests that high-field systems might be more sensitive); it is occult on ultrasound, radiographs, and conventional CT studies. Erosions are a manifestation of cumulative damage by inflammation—potentially both from the synovium and from inside the bone. Both ultrasound and MRI are much more sensitive than radiographs for detecting erosions.

Part II of this review will discuss how these cardinal MRI and ultrasound findings, together with clinical and laboratory features, can influence the management of patients with RA. Scenarios discussed include the use of advanced imaging at initial presentation, during treatment to evaluate response and remission, and possibly to individualize management based on specific imaging findings.

Compliance with ethical standards

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