REVIEW ARTICLE

MR and ultrasound of the hands and wrists in rheumatoid arthritis. Part II. Added clinical value

David A. Rubin [1] ⓘD

Abstract

Advanced imaging has become just as vital for diagnosing, staging, and monitoring disease in rheumatoid arthritis (RA) patients as it is for cancer patients. Part 1 of this review discussed synovitis, tenosynovitis, erosions, and osteitis—key imaging findings that occur in patients with RA. Part 2 will now show how these features, in combination with clinical and serologic data, can assist clinical decision-making at various stages of a patient's disease course. Specifically, assessing current disease activity and prognosticating future aggressiveness inform treatment decisions at initial presentation, during medical treatment, and at clinical remission. In addition to summarizing the current literature on advanced imaging in RA, clinical examples from different stages throughout the disease course will illustrate practical approaches for applying these research results. Last, this review will describe potential future roles of imaging in RA patients.

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

Abbreviations

CCP	Cyclic citrullinated peptide
CRP	C-reactive protein
DMARD	Disease-modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
MCP	Metacarpophalangeal
MR	Magnetic resonance
PPV	Positive predictive value
RA	Rheumatoid arthritis
RAMRIS	Rheumatoid Arthritis MRI Scoring system
RF	Rheumatoid factor
TNFα	Tumor necrosis factor alpha
UA	Undifferentiated arthritis
US	Ultrasound

✉ David A. Rubin
    rubinda@wustl.edu

[1]   Department of Radiology, Washington University School of
    Medicine, 510 South Kingshighway Blvd., St. Louis, MO 63110,
    USA

Introduction

This review is the second of a two-part series. Part 1 covered magnetic resonance (MR) and ultrasound (US) techniques for examining the hands and wrists of rheumatoid arthritis (RA) patients, together with the definitions of key findings (erosions, osteitis, and synovitis/tenosynovitis). Some pitfalls and quantification methods were also discussed. Part 2 will now explore how these imaging features impact patient management. Specific topics will include how MR and US imaging findings can facilitate an earlier and more specific diagnosis than is possible with just clinical and serologic markers, can help prognosticate the aggressiveness of the disease course, can assess disease activity at both symptom onset and during medical treatment, and can contribute to identifying remission. Lastly, this review will discuss potential future roles of imaging in preclinical disease (when risk factors are present without symptoms), and for directing personalized medicine (selecting drugs that are more likely to be effective in specific patients). In addition to presenting the relevant scientific data, a practical approach to interpreting MR and US examinations at different junctures in the disease course, which assists the referring rheumatologist in his or her decision-making, will be illustrated through a series of clinical examples.

Imaging at symptom onset

When a patient first presents with polyarticular arthralgia, the immediate clinical goals are to establish a diagnosis that is as specific as possible, and to initiate nonpharmacological and drug treatment that is appropriately aggressive based on the likely clinical course, without exposing patients to unnecessary costs and toxicities. Findings on advanced imaging can and should impact these decisions.

There are no pathognomonic histologic findings or independent "gold standard" for RA, so rheumatologists establish a diagnosis based on a set of clinical features. In 1987, the American College of Rheumatology endorsed a classification criteria (Table 1) defined as patients 18 years or older showing at least four of seven features (five clinical, one radiographic, one serologic) [1]. It is important to recognize that classification criteria are not the same as diagnostic criteria: the former are designed to identify relatively homogeneous patient groups for the purposes of standardizing research populations, while the latter are used to establish a diagnosis in a particular patient [3, 4]. Because they focus on populations with established disease, the 1987 classification criteria are insensitive for early diagnosis [5].

Until recently, the main goal of treatment was symptom control using a stepwise "pyramid" approach. Thus, a typical patient might initially be treated with nonsteroidal anti-inflammatory agents and oral or parenteral glucocorticoids, then later first level disease-modifying anti-rheumatic drugs (DMARDs) like hydroxychloroquine, oral and parenteral gold, and penicillamine. If these fail, more effective DMARDs such as sulfasalazine, leflunomide, and methotrexate, and eventually combination drug therapy might be tried. The problem with this approach is that while the initial agents (including steroids) might reduce inflammation and temporarily improve symptoms, they have no effect on achieving remission or preventing joint destruction [6]. Historically, introducing DMARDs like methotrexate, which can slow or arrest
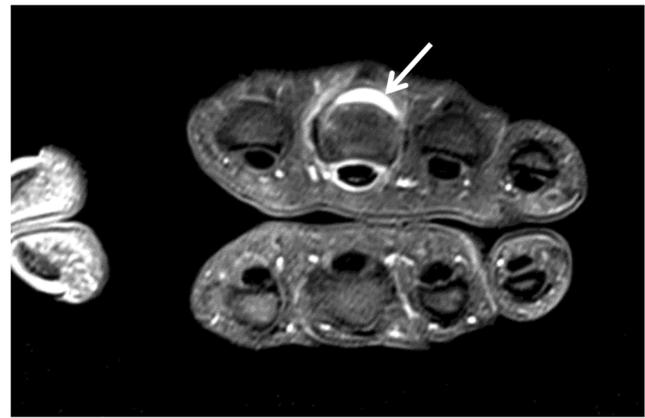

Fig. 1 Twenty-three-year-old man with recent onset joint pain. Intravenous contrast-enhanced, transverse, fat-suppressed T1-weighted image of both hands (right hand on top) shows moderate synovitis of the right third MCP joint (*arrow*) with associated tenosynovitis of the long finger flexor tendon sheath. No findings are present in the left hand. Asymmetric synovitis in early arthritis strongly suggests a diagnosis other than RA. He later developed skin psoriasis and met established criteria for peripheral seronegative spondyloarthropathy

the disease progression [7], would be delayed until the patient failed other drugs and met the 1987 classification criteria for RA (which may not occur until several years after presentation), at which time structural damage and its associated morbidity had already occurred [1, 8].

In this historic model, conventional radiography was adequate to document joint damage and progression in established RA; there was little need for imaging in early disease. Indeed, radiographic findings in the first 6 months of symptoms are unable to predict whether the disease course will be aggressive or indolent, and thus are not useful to guide initial treatment decisions [9].

A paradigm shift began with the recognition that a delay of even 9 months in starting DMARD therapy negatively affects long-term radiologic and clinical outcomes [10, 11]. The current management goal is now disease control through early DMARD therapy based on this early window of opportunity.

Table 1 Classification criteria for rheumatoid arthritis. * = observed by a physician and present at least 6 weeks

1987 Revised American College of Rheumatology [1] At least 4 of the following 7 for definitive diagnosis	2010 American College of Rheumatology/EULAR [2]	
	Category	Points (≥ 6 for definitive diagnosis)
Morning stiffness > 1 h*	Number/size of joints involved	0–5
≥ 3 simultaneously swollen joints*	RF and/or anti-CCP titers	0–3
≥ 1 swollen wrist or hand joint*	Elevated CRP and/or ESR	0–1
Symmetric swelling of ≥1 joint area*	Symptom duration	0–1
Rheumatoid nodules		
Elevated RF		
Radiographic erosions		

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; RF, rheumatoid factor

Additionally newer, more potent biologic DMARDs—including anti-tumor necrosis-factor alpha (TNFα) antagonists, interleukin-6 antagonists, and T cell and B cell modifying drugs—further enhance the rheumatologist's armamentarium, albeit at a higher cost and with more potential toxicity [5, 12]. DMARD therapy is now started in patients with *early arthritis*, defined as atraumatic swelling or pain in at least one joint of ≤ 3 months' duration plus serologic evidence of either inflammation (such as an elevated C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) or circulating autoantibodies (rheumatoid factor [RF] or anti-cyclic citrullinated peptide [CCP]) [13]. At this stage, most patients will be diagnosed with *undifferentiated arthritis (UA)*, because they do not meet the classification criteria of RA or another specific rheumatologic condition [13–16].

In 20–60% of cases, UA is self-limited and will resolve with no treatment [7]. Of those patients who develop persistent UA, only some will have an aggressive course with later development of radiologic erosions. Another 6–55% will eventually meet the 1987 classification criteria for RA, and as a group, these patients are at higher risk for structural damage [8, 15]. The issue is deciding whom to treat and how aggressively, without risking overtreatment of patients destined for an indolent or self-limited course. To address this concern, in 2010 the American College of Rheumatology together with the European League Against Rheumatism (EULAR) devised an approach that identifies risk factors for persistent and erosive disease in UA [2]. A score of 0 to 10 points is assigned based on the number and type of joints involved, serum titers of RF and anti-CCP autoantibodies, elevated ESR and CRP, and the duration of symptoms (Table). A multicenter trial found that 68% of patients who are assigned scores of at least 6 would meet the 1987 classification criteria for RA within 1 year, and 70% of those with high scores who did not progress to typical RA nonetheless developed persistent arthritis [17]. Based on these findings, DMARD therapy is now offered to patients with American College of Rheumatology/EULAR scores of 6 or higher. Patients with low disease activity begin with one drug; those with high activity start with two drugs, one of which is typically methotrexate. A biologic agent is added for patients whose disease activity remains moderate or high despite initial drug therapy [18]. Somewhat analogous to the way cancer such as acute leukemia might be managed, the goal of this aggressive early treatment is to quickly establish a clinical remission. Progress is reassessed in 3 months and modified if remission is not achieved, or if deterioration or side effects occur.

Certain patients are at high risk for an aggressive disease course. Randomized controlled studies support the idea that more rapid remission and better outcomes are achieved in these poor-prognosis patients if they are begun on monotherapy or two-drug therapy that includes an anti-TNFα drug rather than methotrexate alone [19–21]. Subsequent drug therapy is then based on disease activity [12]. The ultimate goal in this treat-to-target approach is to maintain a clinical remission with an acceptably low level of disease activity [12, 22, 23], defined as a degree of inflammation that will not lead to further radiologic progression [24].

In this current context, what then is the role of advanced imaging in UA? There are at least three important contributions of imaging at symptom onset. The first is relatively straightforward: documenting the amount of structural damage already present. Cartilage loss (radiologic joint space narrowing) and erosions (for which MR and US are much more sensitive than radiographs – See Part 1) represent the interaction of previous disease severity and duration [25, 26]. Ideally, most patients will have little-to-no structural damage at presentation, but there will still be those who have not sought evaluation, who have been mismanaged, or who had relatively few symptoms despite early development of erosions. Nevertheless, identifying structural damage as early as possible plays a non-trivial purpose in some clinical scenarios; for example, there are countries where the public health system will not pay for advanced DMARD medications without identification of erosions or progressive erosions [27]. The second two roles of imaging—allowing an earlier and more specific diagnosis, and guiding the initiation of treatment—are more nuanced.

Establishing a specific diagnosis

Some UA cases will be self-limited, resolving spontaneously without medical therapy. Other patients will eventually meet the diagnostic criteria for alternate conditions including peripheral spondyloarthropathy, gout, Sjögren's syndrome, or a collagen-vascular disease; still others will progress to RA. It is tempting to assume that simply identifying positive imaging findings can separate these groups. While erosions on US or MR studies, and osteitis on MR images, are more common in patients with early RA compared to those with other diagnoses, the imaging findings are not specific and cannot be used alone to distinguish among the conditions [28, 29]. However, distinguishing symmetric from asymmetric synovitis is useful. Here *symmetric synovitis* is defined as any involvement of the wrists, metacarpophalangeal (MCP), or proximal interphalangeal compartments bilaterally, though absolute joint-by-joint, right–left symmetry is not required [30]. Obviously, to apply this definition, an MR examination that allows simultaneous contrast administration for both sides is desirable (See Part 1). Asymmetric synovitis in a UA patient without erosions strongly suggests a diagnosis other than RA (Fig. 1), whereas symmetric enhancing synovitis has 96% sensitivity and 86% specificity for predicting a future RA diagnosis in this group [31]. Indeed, simply substituting symmetric synovitis on MR for clinical swelling
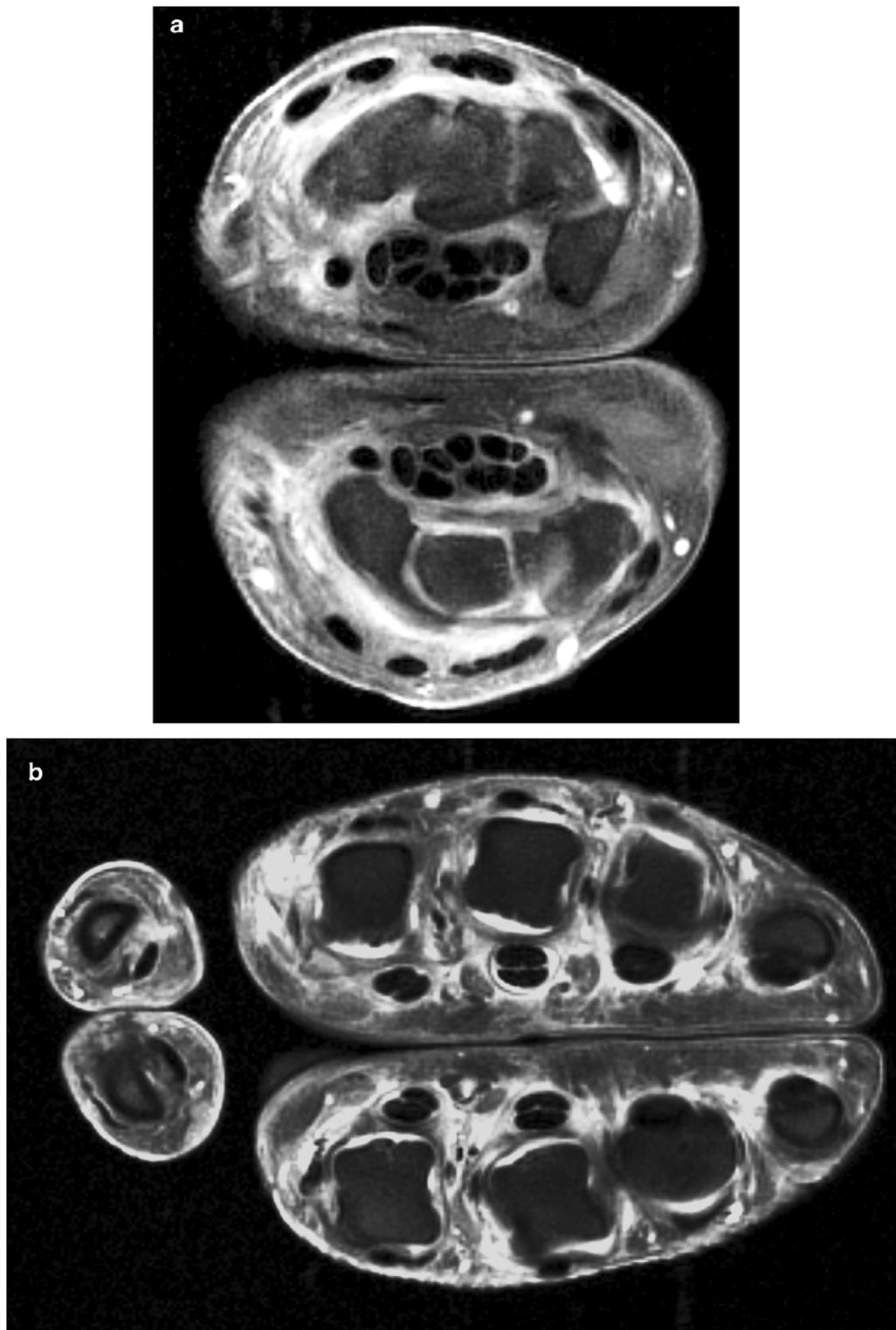
Fig. 2 Fifty-seven-year-old man with 3 months of polyarticular joint pain, and elevated ESR. Transverse, intravenous contrast-enhanced, fat-suppressed, T1-weighted images of (**a**) both wrists and (**b**) both hands (right side up) demonstrate symmetric enhancing synovitis, severe in the wrists and moderate in the MCP joints, with flexor tenosynovitis of the index and long fingers. The distribution and symmetry allowed an early clinical diagnosis of RA. Tenosynovitis in early disease is more common in flexor compared to extensor compartments. Lack of erosions and osteitis put him in a "high-activity, low-risk" category. Rapid improvement followed initiation of low-dose methotrexate
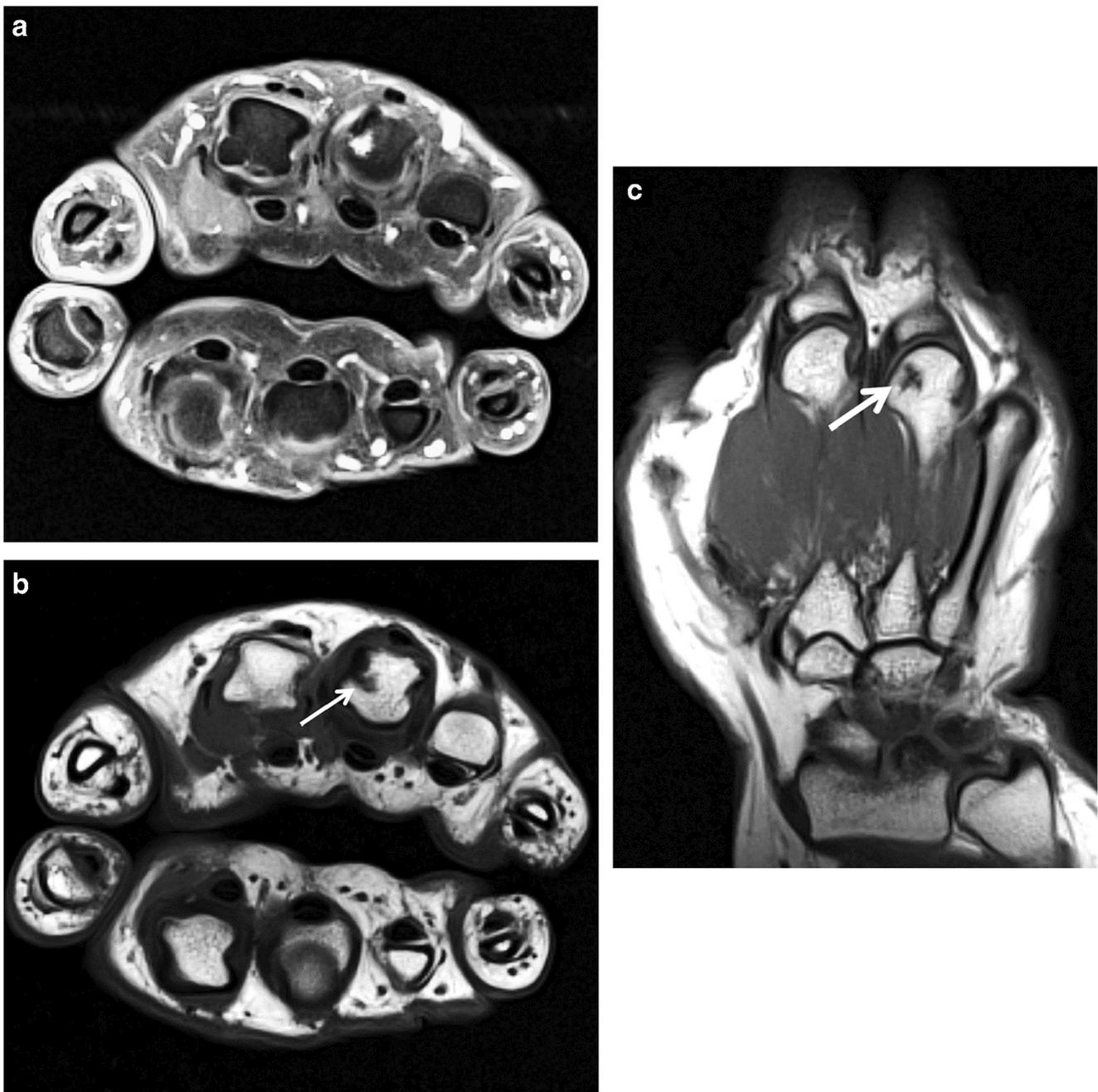
Fig. 3 Thirty-year-old woman with UA and negative serologies. **a** Intravenous contrast-enhanced, transverse, fat-suppressed T1-weighted image (right side up) shows mild, symmetric enhancing synovitis in the second and third MCP joints. T1-weighted **b** transverse and **c** coronal images additionally show an erosion in the right third metacarpal head (*arrows*). The combination of symmetric synovitis with erosions involving the second and/or third MCP joints strongly predicts later progression to classic RA

in the 1987 classification criteria increases the predictive value for diagnosing RA (Fig. 2) [32].

Similarly, when synovitis is present on US, a diagnosis of RA can be made earlier and with more confidence than is possible based solely on clinical and laboratory findings. In patients with early arthritis who do not meet the 2010 classification criteria for RA, the presence of moderate or severe synovitis in any hand or wrist joint on a power Doppler examination accurately predicts patients who will later be classified as having RA [33]. US results also increase the diagnostic certainty of rheumatologists for clinically diagnosing RA in new patients [34, 35].

Other features can also predict conversion of UA to RA well before patients meet the classification criteria for RA. The first is the presence of circulating anti-CCP autoantibodies. UA patients who are anti-CCP-positive have a 38
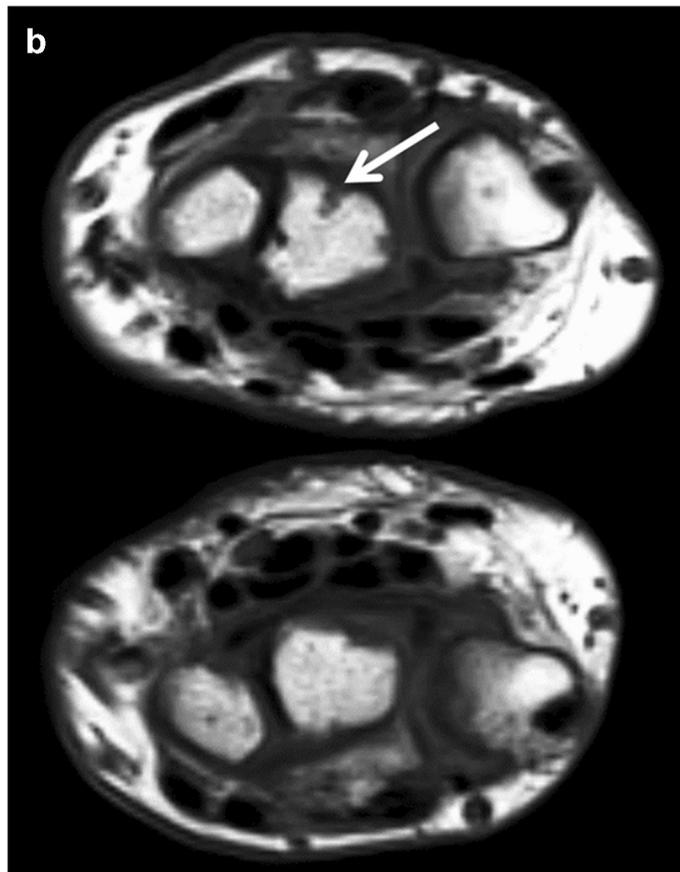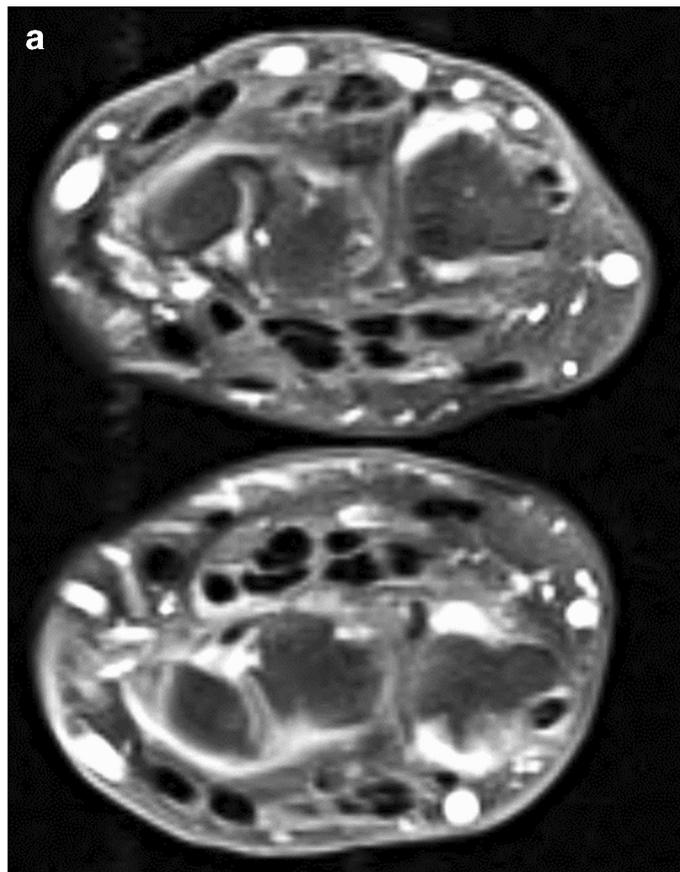
Fig. 4 Forty-nine-year-old woman with new diagnosis of RA. **a** Intravenous contrast-enhanced, transverse, fat-suppressed, T1-weighted image of both wrists (right side up) shows moderate-to-severe bilateral enhancing synovitis. **b** Transverse T1-weighted image demonstrates minimal erosions that were confined to the right lunate (*arrow*). **c** Coronal STIR image of the right hand and wrist shows no osteitis. Active synovitis with minimal erosions and no osteitis places the patient in a "high-activity, low-risk" category. Treatment with sulfasalazine and leflunomide initially controlled symptoms with no new erosions 6 years later

times higher conversion rate to RA within 3 years [36], and have more severe radiologic structural damage at 4 years [37] compared to those who are serologically negative. When anti-CCP status is combined with imaging findings, the predictive value is even higher. For example, positive serology (anti-CCP or RF IgM) combined with symmetric synovitis on MR has a 80% positive predictive value (PPV) for meeting the 1987 RA classification criteria at 1 year; the PPV increases to 100% when osteitis in one or both hands is also present on MR in a patient with anti-CCP autoantibodies [38].

Early tenosynovitis identified on MR also independently prognosticates conversion of UA to RA [39]. The presence of flexor (but not extensor) tenosynovitis strongly predicts later development of RA over other diagnoses, especially with positive serologies [40, 41], and in one study was a stronger predictor compared to synovitis or erosions [41]. Another study of patients with UA of less than 3 months duration found that enhancing tenosynovitis on MR in the second flexor tendon sheath (Fig. 2) increased the rate of meeting the 1987 classification criteria for RA 1 year later by 14 times, compared to wrist synovitis (eight times) or extensor carpi ulnaris tenosynovitis (3x) [42].

What about the role of imaging in seronegative UA patients? In this population, while tenosynovitis and erosions in the wrist do not have a predictive role, the presence of either symmetric wrist synovitis or erosions in the second or third MCP joints on MR portend conversion of UA to RA within 1–2 years (Fig. 3) [43, 44]. Thus, in both seronegative and sero-positive early arthritis patients, MCP erosions and symmetric synovitis seem to have the highest predictive value for an eventual diagnosis of RA [38, 44, 45]. Being able to accurately predict which UA patients will convert to RA – before they meet the American College of Rheumatology classification criteria – allows initiation of early aggressive treatment in this high-risk subgroup, without exposing patients who may have a more indolent disease course to the potential toxicities of DMARDs.

A bigger question is whether incorporating MR or US for the diagnosis of early RA has actual added value or is cost-effective. Here, the jury is still out. A cohort study of early arthritis patients found that incorporating US findings into a clinically based prediction tool did not improve the ability to predict an outcome diagnosis of RA [46]. On the other hand,

adding MR criteria (symmetric synovitis, osteitis, or erosions) to the clinically based 2010 American College of Rheumatology/EULAR classification criteria (Table) does increase sensitivity for predicting conversion from UA to RA (defined as meeting the 1987 classification criteria or the initiation of DMARD therapy based on clinical judgment) by 1 year, but at a cost of decreased specificity and slightly decreased PPV [47, 48]. Including MR does not appear to be cost-effective compared to strategies that use only laboratory assays as a test for the early diagnosis of RA [49, 50]. However, considering the costs of many of the newer biologic agents, incorporating MR as part of a global strategy (beyond just early diagnosis) to prognosticate, monitor disease activity, and assess treatment response may be cost-effective, although this specific question has not been investigated systematically.

Stratifying risk and guiding initial drug treatment

Selecting which agents, what doses, and how many drugs are initially best for a given patient relies on the treating physician's estimates of both current disease severity and future aggressiveness. While composite indices of multiple clinical factors are often used in randomized clinical trials as predictors of long-term outcomes [51], the practicing rheumatologist must weigh the literature results against clinical judgements, costs, and risks of any regimen. Similarly, despite strong data showing how baseline imaging findings influence the likely disease course (not just the diagnosis, as discussed above), there is no cookbook way to apply these results to an individual patient. One approach is to try to convey both current disease activity (high or low, based on the amount of synovitis and tenosynovitis) and the risk of future structural damage (high or low, based on the literature discussed below) when interpreting an imaging study on a new arthritis patient. For example, the radiologist can have a conversation with the rheumatologist telling them that a particular patient appears to have "severe active disease currently, but no imaging findings associated with an aggressive clinical course," where a relatively low-cost and low-risk single drug might constitute initial management. Figures 2 and 4 illustrate patients whose imaging findings suggest "high-activity, low-risk" disease. Conversely, the radiologist can express to the rheumatologist that a patient like the one shown in Fig. 5 has evidence of "high disease activity and high risk for new and progressive erosive disease," which, together with the clinical findings, might prompt the rheumatologist to initiate combination therapy that includes a biologic agent to both lessen current activity and decrease the risk of progression. A similar tactic can be applied when interpreting follow-up studies once therapy is started or at the time of apparent remission (see below).

In RA, *high risk* means the propensity for radiographic new or progressive erosions or joint space narrowing in the future. Not surprisingly then, patients whose radiographs already

Fig. 5 Fifty-three-year-old woman with RA, 2 months following initiation of DMARD therapy. Transverse images of both wrists with right side up. **a** Intravenous contrast-enhanced, fat-suppressed T1-weighted image shows persistent synovitis bilaterally (*arrows*). **b** Fat-suppressed, T2-weighted image reveals osteitis of the left first metacarpal base and trapezium (*arrows*). Despite treatment, she remains "high-activity, high-risk" and an additional biologic agent was added to her regimen. **c** An initial posteroanterior left wrist radiograph showed focal erosions primarily in the ulnar head (*arrow*). **d** Five-year follow-up radiograph shows an enlarged ulnar erosion and new erosions in the distal radius and carpal bones (*arrows*) representing progressive structural damage, despite aggressive medical treatment

show erosions at presentation will have more structural damage over the course of their disease compared to those without baseline erosions on radiographs, independent of their serologic status, clinical exams, or disease durations [52]. Similarly, the presence of erosions on US or MR at baseline predicts that erosions will become radiographically evident at 1–2 years [53, 54].

While a positive titer of either RF or anti-CCP in very early RA is the best non-imaging predictor of future erosions and radiologic progression [55], baseline synovitis on MR has even higher predictive value for future erosions identified radiologically or by MR [56–58]. Nevertheless, imaging evidence of synovitis is a weaker prognosticator than osteitis [59, 60], likely because the vast majority (90%) of RA patients will demonstrate synovitis on MR within the first 6 months of disease onset [61]. Similarly, evidence of synovitis on a power Doppler examination of an MCP joint has an odds ratio of approximately eight times for progressive radiologic erosions or joint space narrowing of that joint at 1 year [62]. Even when baseline synovitis is present on one test (US or clinical exam) but not the other, the risk of progressive structural damage at 2 years increases by 2–3.5 times [63].

For future joint deterioration, the predictive value of osteitis on MR exceeds that of clinical and immunologic markers [56, 64, 65], including for patients treated aggressively with conventional DMARDs [65, 66]. Baseline osteitis is by far the best independent prognosticator of radiographic erosions and joint space narrowing [35, 60, 67], and is also an independent marker for rapid radiologic progression at 1 year [68], making it the most important marker for high-risk disease. In early, untreated RA, osteitis is present in 8% of MCP joints and 48% of wrists [69]. Osteitis in a given bone has an odds ratio of 6.5 times for subsequent appearance of an erosion in that bone [60], endorsing the "inside-out" mechanism of erosions development (see Part 1). Lastly, baseline osteitis is associated with cartilage loss in the same joints on MR, although it does not necessarily correlate with progressive cartilage loss as judged by MR [70].

Long-term morbidity in RA comes not just from cartilage loss and erosions but is also associated with loss of tendon function. Little data exist correlating early imaging characteristics with future tendon disease. One MR study did find that baseline composite scores within a tendon compartment (including changes in tendon size, signal, and effusions or tenosynovitis) were a risk factor (odds ratio = 1.5 times) for extensor tendon rupture at 6 years [71], but this investigation did not separate influences of tenosynovitis and tendinitis. Osteitis at initial presentation of RA does strongly predict clinical dysfunction of flexor and extensor tendons at 8 years [72], but it is unclear whether it is an independent predictor, because osteitis is a marker for severe disease activity, which in turn is a risk factor for tendon rupture. Nevertheless, initial osteitis scores predict overall physical function 6 years later in RA patients [73].

Imaging after treatment initiation

Monitoring disease activity

A current issue in rheumatology is how best to judge whether a particular drug regimen is working. When a side effect develops or a patient reports subjective worsening of symptoms, the answer is straightforward: a change in dosage or drugs is needed. However, if symptoms improve, does that mean that the disease course has been altered, or that symptom improvement is masking continued joint destruction? And for successful therapy, when is it safe to taper or discontinue medications?

Clinically, disease activity is usually assessed by adding the number of swollen and tender joints, and combining those counts in a formula together with ESR or CRP and the patient's self-reported global assessment. Such scores (the Disease Activity Score 28 is a common example) can then be compared over time once treatment is begun [74, 75]. While these measures have been validated and can reasonably discriminate between responders and nonresponders in clinical drug trials [76], there are limitations to their routine use in clinical practice. For example, patients with disease most severe in their feet may be underscored, while scores in patients with persistently discrepant joint exams and ESR levels may be misleadingly elevated. Additionally, physical examination of joint findings underestimates true disease activity, especially early in the course of disease: of joints with MR evidence of synovitis, tenosynovitis, or osteitis, 50–60% are not swollen and 48–56% are nontender [77]. For these reasons, imaging findings are frequently used to supplement or supplant clinical estimates of disease activity.

US can be used in a fashion similar to physical examination to total the number of joints that demonstrate a given level of synovitis, and then to compare those counts over time. The reliability of US-based joint scores has been established; however, studies have shown similar or worse sensitivity to change over time compared to clinically based scores [78–80]. Discordance between clinical and US scores [80] and a lack of consensus for how many joints to count during US [81] also limit the application of US for global disease activity assessment. One suggestion to make US more practical is to perform serial US of one sentinel joint (say the most severely affected MCP) as a surrogate for overall disease activity [82], but this idea has not been scientifically tested. Reproducibly estimating synovitis volume using US is difficult to perform and currently not used clinically.

Changes in the number and size of erosions occur very slowly radiographically, so trials using radiologic outcomes typically take years. In contrast, MR—even using portable, low-field scanners—is able to detect small differences in erosions [83]. For example, one study demonstrated changes in size and number of erosions in the wrist and second and third
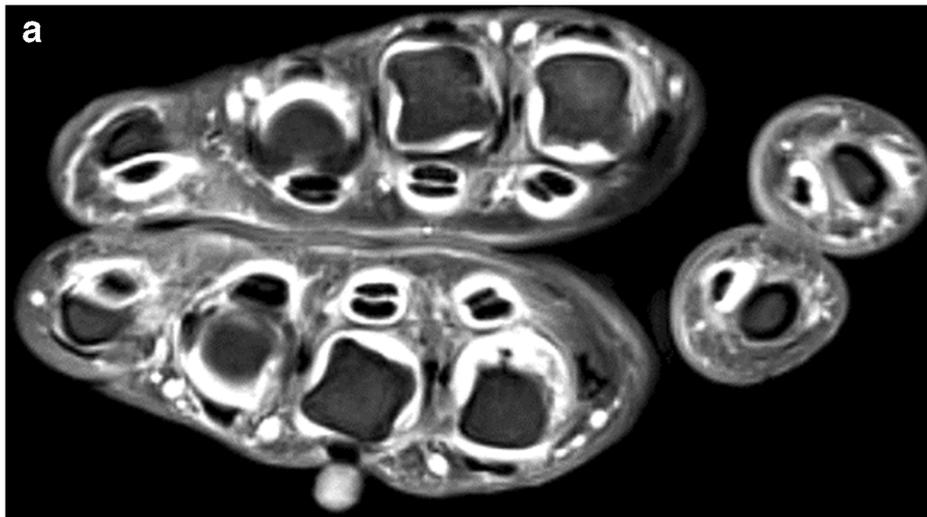
Fig. 6 Twenty-nine-year-old seronegative RA patient who stopped all her medications due to side effects. She has minimal symptoms and is asking whether she needs drug therapy. **a** Intravenous contrast-enhanced, transverse, fat-suppressed T1-weighted image of both hands (*marker on right side*) demonstrates severe, symmetric, enhancing synovitis in all MCP joints and tenosynovitis of each flexor tendon sheath. **b** Coronal T1-weighted image of the right wrist shows both a well-defined erosion (*arrow*) and ill-defined osteitis (*arrowheads*) involving the fourth metacarpal base. Based on the severe disease activity (synovitis and tenosynovitis), evidence of structural damage (erosion), and high-risk factor (osteitis), her rheumatologist convinced her to try a different drug regimen

MCP joints in 50% of patients with MR, compared to 1% with radiographs, at a mean follow-up of 8 months [84].

Measuring changes in synovitis on sequential MR examinations has become the imaging biomarker most frequently used to gauge treatment effectiveness [61]. Quantitative and semiquantitative measures of synovitis respond rapidly, often showing statistically significant improvements as early as 14 weeks following initiation of DMARD therapy [19, 85]. However, equating lessened synovitis with clinical success is not automatic. For example, in one drug study, non-responders actually had greater absolute decreases in synovitis compared to responders, likely because the first group started off with higher volumes of synovitis [85]. Another study found that the measured volume of synovial enhancement on MR correlated with uptake on FDG-PET uptake, but was not associated with treatment success or failure [86], and improved synovitis does not necessarily mean that disease progression has stopped, with no further potential for progressive structural damage. However, for routine clinical purposes, the biggest limitation to using changes in MR synovitis as evidence of treatment failure or success is lack of a practical, easily applied, analysis technique.

Methods for quantifying synovitis on MR—volume measurements, dynamic enhancement analysis, and semiquantitative scoring using the Rheumatoid Arthritis MRI Scoring (RAMRIS) system—were discussed in depth in Part 1. The RAMRIS approach assigns points for the presence and severity of MR findings (erosions and osteitis in addition to synovitis) in up to 46 joints and 14 compartments if bilateral scoring is performed [87]. While the tool has been validated in the hands and wrists with discriminant value after treatment [88], scoring requires anywhere from 13 to 43 min per case, depending on the level of detail employed [89–91]. A simplified system (scoring fewer target areas) that takes less time has been tested and proposed as a clinically feasible alternative [90], but the sensitivity of this method to detect changes over time has not been investigated. Similarly, reproducibly quantifying synovial volumes or enhancement dynamics require defining relevant regions of interest (manually, or with computer assistance) and often specialized software for motion correction and analysis [57, 89, 92, 93]. In short, methods used in research studies to quantify synovitis on MR are impractical for routine clinical purposes [94, 95], and little data exists on the reproducibility and sensitivity to change for sequential US estimates of synovitis [95].

One practical approach to interpreting follow-up examinations in patients who have begun treatment is relatively straightforward and does not require any quantification or scoring. The assumption is that a minimum goal of therapy is objective improvement. Thus, any progression of findings (either enlarging erosions or increased synovitis in an involved joint, or either finding in a new location) indicates failure and the need to adjust dosages and/or drugs. Frankly, the same applies when findings are persistent or unchanged, given the expected rapid response to successful DMARD therapy. In these cases, the radiologist can assess disease activity and future risk in the same way as on a baseline exam (Fig. 5). The imaging interpretation should also note any persistent osteitis, which (compared to residual synovitis) is even more highly associated with progression of erosive disease [96, 97]. When imaging findings have improved, the radiologist can simply report that without trying to quantify the amount— the assumption is that the treating rheumatologist will continue the same regimen with this information (if there were clinical progression or side effects, the physician would not have needed the follow-up study to know that a therapeutic change was needed, so these follow-up studies are only requested when the patient is unchanged or better clinically). In cases where medical treatment has been stopped by the physician or patient, imaging studies can be interpreted in the same way as for a newly diagnosed patient. For example, Fig. 6 shows a patient who stopped her medications due to side effects and now has minimal symptoms. Nevertheless, the MR images show features of "high-activity, high-risk" disease, which the rheumatologist used to suggest an alternate drug regimen.

More difficult is providing added value in the assessment of tendon disease based on imaging studies in RA patients undergoing treatment. Tendon rupture severely impacts patient well-being, but is notoriously difficult to predict. Recognized risk factors for extensor tendon rupture include tenosynovitis that has persisted greater than 12 months despite medical treatment, dorsal subluxation of the distal ulna, prolonged disease duration (> 8 years), and prior extensor tendon rupture [98–100]. Current recommendations are for prophylactic tenosynovectomy to prevent subsequent tendon rupture if there is persistent tenosynovitis longer than 6 months despite medical management [98, 100], although there are little outcome data supporting this recommendation and a large discrepancy between the perceived success of this procedure between rheumatologists and hand surgeons [101]. Extensor tenosynovectomy does appear to be successful in reducing pain, however [102]. Risk factors for flexor tendon rupture are less well characterized, but include long disease duration, advanced bone destruction, and high disease activity [103, 104]. In clinical cases, the radiologist can emphasize MR or US evidence of residual or increasing
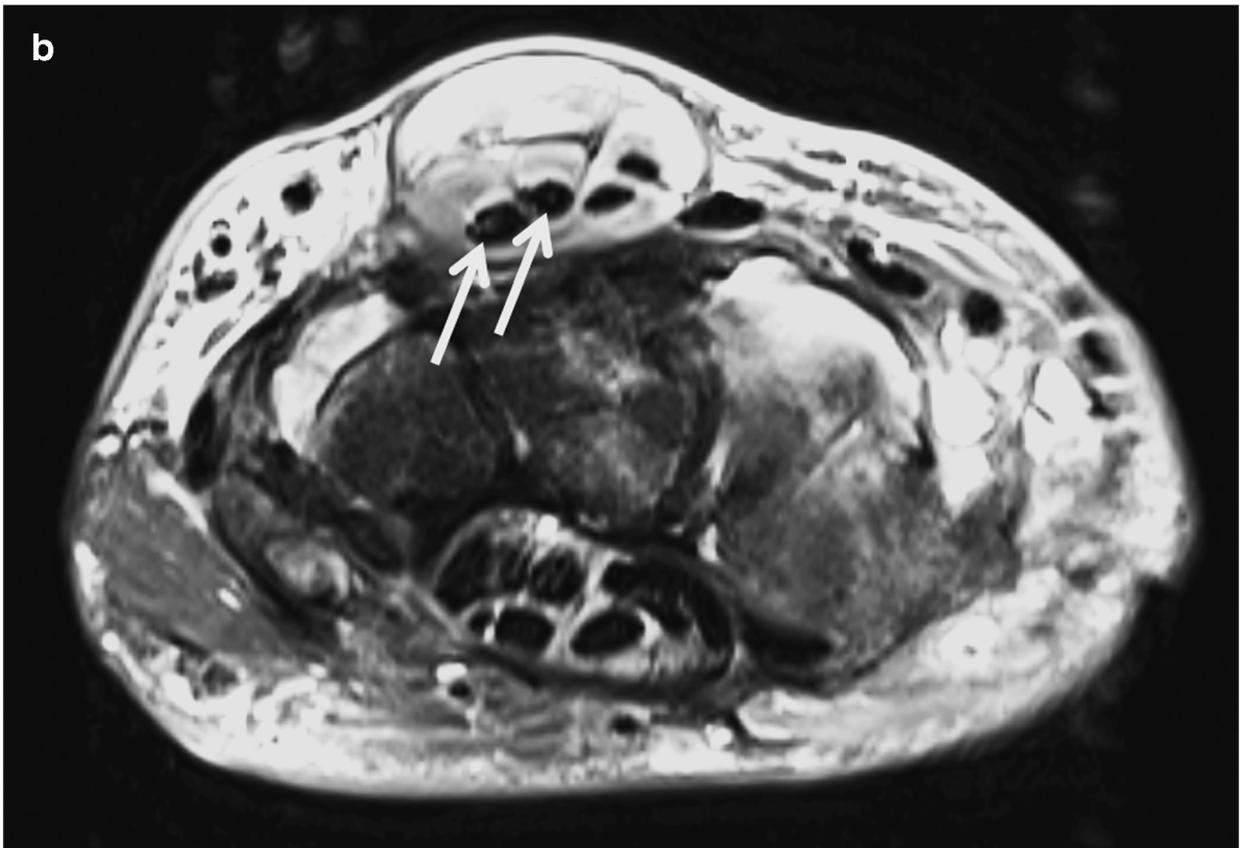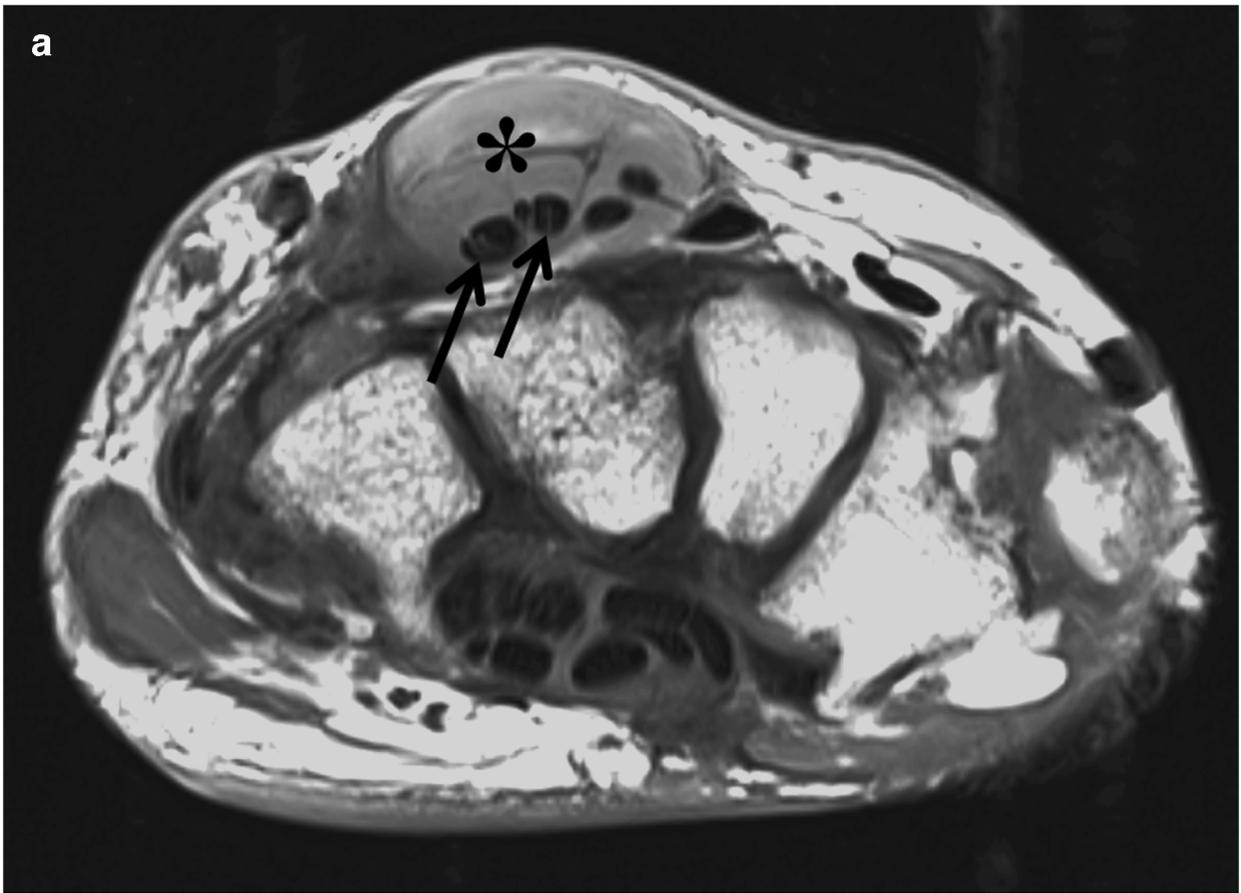
◀ **Fig. 7** Sixty-two-year-old woman with seronegative RA and impending tendon rupture. Transverse **a** T1-weighted and **b** fat-suppressed T2-weighted images of the left wrist show severe distention of and tenosynovitis (*asterisk*) within the fourth extensor tendon compartment. The extensor digiti minimi and extensor digitorum communis tendons of the small finger are absent due to prior ruptures. Mild intratendinous signal (*arrows*) is present in the extensor digitorum communis tendons for the ring and long fingers. With refractory tenosynovitis and previous atraumatic tendon tears, inflammation within a tendon may be a harbinger of future rupture. Despite prophylactic tenosynovectomy performed 1 week following the MR examination and methotrexate treatment, the ring and long finger extensor tendons spontaneously ruptured approximately 2 months later

tenosynovitis, especially in the face of prior tendon tears, as a potential risk factor for subsequent rupture. For example, Fig. 7 illustrates a patient with RA and prior tendon ruptures whose MR images shows severe persistent tenosynovitis surrounding the extensor digitorum communis tendons in whom even a prophylactic tenosynovectomy could not prevent subsequent additional tendon ruptures. However, as Fig. 8 shows, even when tenosynovitis has progressed to actual intra-tendinous inflammation, accurately prognosticating future tendon rupture is far from perfect.

Determining disease remission

The ultimate goal of RA treatment is establishing and maintaining remission. Historically, remission meant eliminating subjective and objective evidence of the disease, including a patient's symptoms and physical exam findings. So clinical
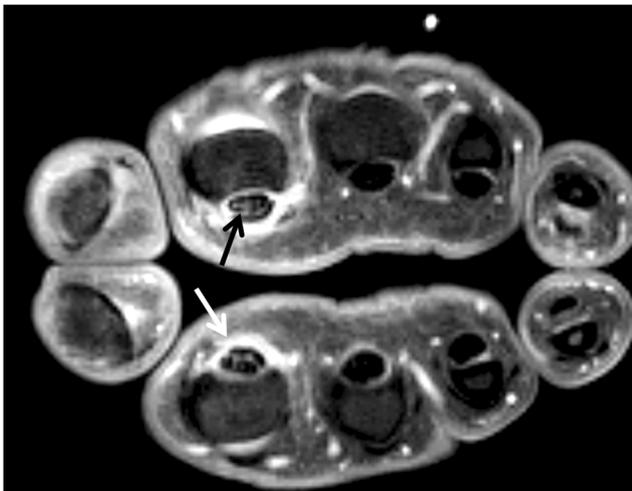
Fig. 8 Forty-two-year-old woman with long-standing RA, managed with etanercept and methotrexate with only fair control. Intravenous contrast-enhanced, fat-suppressed, T1-weighted image of both hands (right side up) shows persistent tenosynovitis (*white arrow*) and intratendinous inflammation (*black arrow*) involving the index finger flexor tendon compartments bilaterally. No surgery was performed and her tendons remain intact and functional 12 years later, despite continued symptoms. This case illustrates the difficulty in predicting impending tendon rupture

definitions of remission are based on physician counts of swollen and tender joints combined with patient-based global assessments and serum inflammatory markers [105–108]. However, just like a patient with lymphoma would not be declared "cured" simply because they no longer had palpable enlarged lymph nodes or subjective complaints following a round of chemotherapy, it has become evident that RA can still be active (with the predilection for future structural damage) without clinically overt disease activity [109]. Depending on the specific criteria applied, 19–30% of patients in clinical remission will progress radiologically [110].

A recent meta-analysis found that approximately 44% of patients in clinical remission have persistent evidence of synovitis on power Doppler US [111]. This subclinical synovitis does not necessarily correlate with serum inflammatory markers (ESR and CRP) [69]. The incidence is even higher on MR, where 87–96% of patients show persistent synovitis and 23–46% demonstrate continued osteitis despite clinical remission [112, 113]. The vast majority (> 99%) of joints with persistent synovitis or osteitis have no swelling that is detectable clinically [114].

Importantly in these remission patients, persistently positive imaging findings are also prognosticating [35]. The degree of residual synovitis on MR is an independent predictor of radiologic progression at 1 year (especially in patients with a positive RF) [24], while persistent osteitis is the strongest prognosticator for 1-year progression of erosions [112, 115]. On Doppler US, higher degrees of continued synovitis are associated with increased risk of structural damage at 1–2 years [113, 116, 117], despite clinical remission. Last, imaging findings at this stage also relate to the risk of relapse. Evidence of synovitis in even one joint on a Doppler US exam predicts clinical failure for attempted tapering of biologic DMARDs at 6 and 12 months in patients with sustained clinical remission [118]. The overall risk of relapse after clinical remission increases 3.6-13 times with a positive Doppler US examination [116, 119, 120].

What these studies make clear is that clinical activity scores overestimate true disease remission. Subclinical inflammation is the rule in patients meeting clinical definitions of remission, and persistent synovitis and osteitis contribute to progression of structural damage and clinical failure in a subset of these patients [121]. Stricter clinically based definitions of remission have been proposed for use in drug trials [122, 123]. While the presence of synovitis on MR is a commonly used biomarker for measuring responses in research, there are now proposals to incorporate MR assessment of synovitis into future definitions of remission applied in clinical practice [124, 125]. Attaining complete absence of any evidence of inflammation may not be a reasonable or attainable goal for most patients [106], so researchers now are trying to determine what might be an acceptably low level of disease activity demonstrated by MR that would be associated with little risk
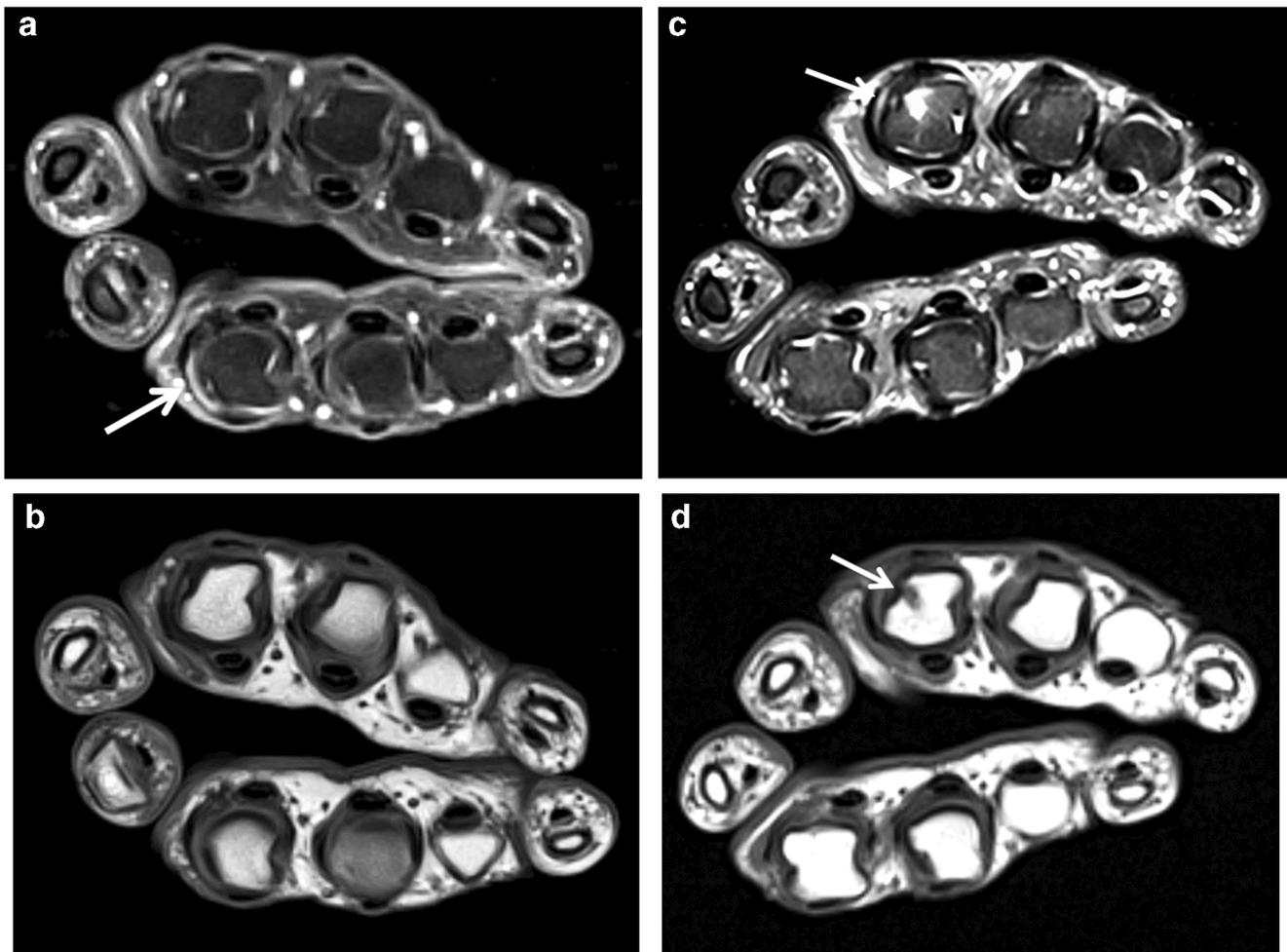
Fig. 9 Forty-eight-year-old woman with seropositive RA and disease progression despite clinical remission. Transverse (right side up) images of both hands 5 years after initial diagnosis. **a** Intravenous contrast-enhanced, fat-suppressed, T1-weighted and **b** T1-weighted images show mild synovitis, most conspicuous in the left second MCP joint (*arrow*) and no structural damage. Mild symmetric synovitis was also present in the wrists (not shown). Her classification was "low-activity, low-risk" and she was managed with sulfasalazine and hydroxychloroquine. Two-years later, she is in complete clinical remission with no symptomatic joints but a repeat **(c)** intravenous contrast-enhanced, transverse, fat-suppressed T1-weighted image shows persistent synovitis in the left second MCP, development of mild new synovitis in multiple additional MCP joints (*arrow* indicates right second MCP joint), and new flexor tenosynovitis (*arrowhead*). **d** T1-weighted image also shows a new erosion in the right second metacarpal head (*arrow*). Rather than tapering her medication, a new DMARD was begun after the MR examination

of radiologic progression [24]. Note that recent attempts to target US-defined remission have not shown benefit over current clinical methods [126, 127].

When evaluating imaging examinations in patients who are referred in clinical remission (typically when the rheumatologist is concerned about tapering medications), the radiologist can emphasize the amount of continued synovitis, especially if it has increased, which should act as a warning that stopping or tapering drug therapy risks disease progression. In Fig. 9, an RA patient who meets the clinical criteria for remission nevertheless has increased synovitis (and a new erosion) on her current MR examination. The rheumatologist used this information to justify beginning a new DMARD rather than the planned tapering of her current agents. Absence of any enhancing synovitis characterizes a complete imaging remission, a relatively rare outcome. Figure 10 shows a patient with RA whose MR images show complete remission with no enhancing synovitis (despite the presence of erosions, which signify prior active disease).

Future imaging applications

Personalized medicine

Personalized or precision medicine attempts to tailor management based on the likely disease course or predicted response to treatment in individual patients. While most research has evaluated using imaging for treatment response and not to guide therapeutic decisions [94], investigators are now asking

Fig. 10 Fifty-five-year-old man with seropositive RA in complete clinical and imaging remission. **a** Intravenous contrast-enhanced, transverse, fat-suppressed T1-weighted image (right side up) shows no residual enhancing synovitis in the wrists. **b** Coronal T1-weighted image of the right wrist shows erosions in multiple carpal bones (*arrows*). Complete absence of synovitis in patients with clinical remission is a rare but desired goal, which portends a good future prognosis. Recall that erosions do not indicate active disease, but rather represent evidence of cumulative structural damage that is largely irreversible
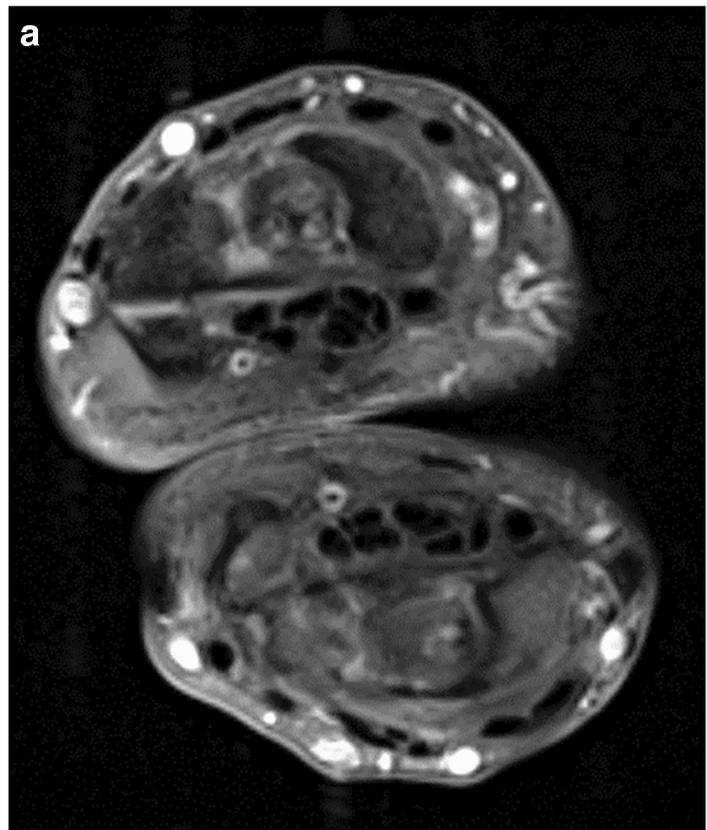
whether any MR findings might predict which patients will respond to specific RA drugs [85]. A recent study in seropositive RA patients undergoing initial drug therapy showed that RAMRIS erosion and global scores on baseline MR studies were lower in patients who responded to methotrexate at 3 months compared to non-responders [128].

Different pathophysiologic processes likely dominate in individual RA patients. For example, data support that the best predictor of cartilage loss at 1 and 3 years is the amount of baseline joint space narrowing, while future erosions are prognosticated by baseline erosions [70, 129], suggesting that these two forms of structural damage have different pathways and the disease course may preferentially follow one or the other in an individual. Additionally, biologic DMARDs have differing biologic effects dependent on their mechanisms of action [130]. Denosumab, an inhibitor of a receptor that regulates osteoclast activity, seems to preferentially slow the development of erosions rather than affecting joint narrowing or disease activity [131], while other anti-inflammatory agents reduce progression of both joint narrowing and erosions [129]. The hope is that MR findings might be a window into which pathways are relevant in a given patient and thus guide individual clinical treatment decisions. As one example, TNF-α as well as various interleukins are locally expressed within the bone marrow of anemic RA patients [132] and inhibit stromal cell differentiation into adipocytes (allowing replacement of fat by inflammatory cells in marrow) [133]; it is possible that patients with bone marrow abnormalities (osteitis) on MR would most likely benefit from agents that target these factors.

Preclinical RA

Disease exists for some period of time in the body before symptoms appear. Analogous to screening for certain types of cancer, one approach would be to identify persons at risk for RA (analogous to those with an elevated prostate specific antigen or who carry a known oncogene) through screening, and then select and proactively treat those who are most likely to develop overt disease. In people with a genetic predisposition for RA, environmental risks (including cigarette smoking) may induce circulating autoantibodies (anti-CCP or RF), with a subgroup later develop arthritis [134]. Studies of RA patients who had previously donated blood before disease onset reveal that 49% manifested RF or anti-CCP antibodies (compared to 1% of the general population) a median of 4.5 years before symptoms occurred [135]. Current investigations are searching for factors that may predict which subjects with circulating autoantibodies are most likely to progress to clinical arthritis.

In one study of anti-CCP-positive individuals without joint swelling (25% of whom developed clinical RA within 2 years), MR demonstrated synovitis in 65% and tenosynovitis in 80%

(compared to 0% of controls) [136], and in this population, the presence of synovitis or osteitis on MR is more common in those who have clinical complaints of arthralgia compared to those without joint pain [137]. Preclinical patients with anti-CCP antibodies and nonspecific musculoskeletal complaints have even higher risk for progression: In one study, 50% of that group developed inflammatory arthritis (86% of whom met the criteria for RA) in a median of 8 months. Among the risk factors for progression is a Doppler ultrasound examination showing synovitis [138]. However, preliminary studies investigating MR in seropositive pre-clinical groups have not shown that MR evidence of synovitis is associated with development of clinical arthritis [137, 139], while a small study in a similar cohort did find that MR evidence of tenosynovitis in at least two locations was associated with later clinically evident arthritis [136]. Future screening endeavors that incorporate both serologic testing and advanced imaging findings potentially may identify candidates for prophylactic treatment to diminish (or prevent) later clinical disease.

Conclusions

The imaging approach to patients with RA has evolved with continued understanding of the pathophysiology of the disease and the development of potent, disease-modifying drugs. In the past, radiographs were employed to offer a differential diagnosis and crudely assess progression after irreversible damage had already occurred. Now rheumatologists rely on MR and US to assess multiple parameters of the disease. Somewhat analogous to modern cancer management, advanced imaging is a vital contribution to the initial diagnosis, staging, treatment monitoring, and remission determination for RA patients. Future developments might expand the role to include preclinical screening and directing personalized medicine.

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