Update on imaging in rheumatology – recent advances

King Kenneth Cheung

Margaret A Hall-Craggs

Abstract

Imaging plays a vital role in the diagnosis and management of rheumatological disorders. Traditionally, plain film radiography was widely used in arthropathies to assess periarticular bony changes; these often reflect established changes in the late stage of disease and thus have limited value in early diagnosis and disease monitoring. Magnetic resonance imaging (MRI) has become an important imaging modality in rheumatological disorders because it can assess both morphological and functional changes. It plays a substantial role in early diagnosis, monitoring of disease evolution, assessment of treatment responses and prognostication. More recently, advances in hardware and novel imaging sequences have aided the development of new MRI techniques: whole-body MRI, for example, is gaining in popularity and allows an assessment of overall inflammatory status in arthritis. Quantitative MRI shows promise in allowing more objective evaluation and standardization of imaging-based assessment of inflammatory arthritis. This article also discusses other emerging imaging techniques. These include high-resolution peripheral quantitative computed tomography in early detection and monitoring of periarticular bone damage, fluorescence optical imaging in visualizing active inflammation, and molecular imaging in investigating pathogenesis and disease evaluation on a cellular level.

Keywords Arthritides; arthritis; arthropathy; imaging; inflammatory; magnetic resonance imaging; positron emission tomography; rheumatoid; rheumatological

Key points

- Structural bony changes seen on radiographs reflect late disease, and thus have a limited role in early diagnosis and disease monitoring
- Magnetic resonance imaging (MRI) is highly sensitive for detecting early bony changes and synovial inflammation, and is becoming more routinely used for early diagnosis, disease/treatment monitoring and prognostication of arthropathies
- Novel magnetic resonance techniques provide new avenues for disease evaluation: whole-body MRI facilitates detection of inflammation at multiple sites; diffusion-weighted imaging, dynamic contrast enhancement and chemical-shift-encoded MRI provide quantitative and objective assessment of periarticular damage and can aid in standardization and automation
- Other developments include fluorescence optical imaging, which provides a quick and non-invasive overview of active inflammation of the extremities, and receptor-specific molecular imaging, which shows potential for monitoring of pathogenesis, disease evolution and treatment selection/response

Introduction

Plain radiography has in the past been the primary imaging tool for investigating arthropathies. Radiographic features of the various types of arthritis have been extensively described in the literature and previously in this journal. However, structural bony changes, such as sclerosis and erosions, seen on radiographs, occur late in the course of disease, and early changes are not apparent. The sensitivity of plain films is low, and disease activity cannot be adequately assessed. Pelvic and lumbar spine radiography incurs a relatively high dose of ionizing radiation; for example, the dose from an anteroposterior radiograph of the pelvis is 35 times that from a chest X-ray. It should therefore be avoided where possible, particularly in children and adolescents. Magnetic resonance imaging (MRI) and ultrasonography are being increasingly used to aid early diagnosis of arthropathies, and this facilitates early treatment that may prevent progression to irreversible structural damage.

Here we describe recent advances in the imaging of rheumatological diseases. For a more in-depth review of the role of ultrasound, the interested reader is referred to the dedicated ultrasound chapter (10.1016/j.mpmed.2017.12.010) in this publication.

Magnetic resonance imaging

MRI has emerged as the most sensitive imaging modality for detecting arthritis and discriminating between acute and chronic inflammation. In recent years, substantial technical advances have been made in software and hardware, such as phased-array coils, higher performance gradients, parallel imaging and advanced post-processing techniques. This has led to reduced scan times and improved image quality.

Other advances include isotropic three-dimensional (3D) imaging techniques, which reduce partial volume artefacts and allow reformatting in multiple planes for improved visualization of anatomy and pathology. High-field strength systems (e.g. 3T MRI) are increasingly used in clinical practice, providing better spatial resolution and signal-to-noise ratio.

King Kenneth Cheung *BSc MB BS PhD FRCR is a Specialist Registrar in Radiology at University College London Hospital, UK. Competing interests: none declared.*

Margaret A Hall-Craggs *BA MRCP FRCR MD is a Consultant Radiologist at University College London Hospital, and Professor in Medical Imaging, University College London, UK. Competing interests: none declared.*

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Cheung KK, Hall-Craggs MA, Update on imaging in rheumatology – recent advances, Medicine (2018), https://doi.org/10.1016/j.mpmed.2017.12.004

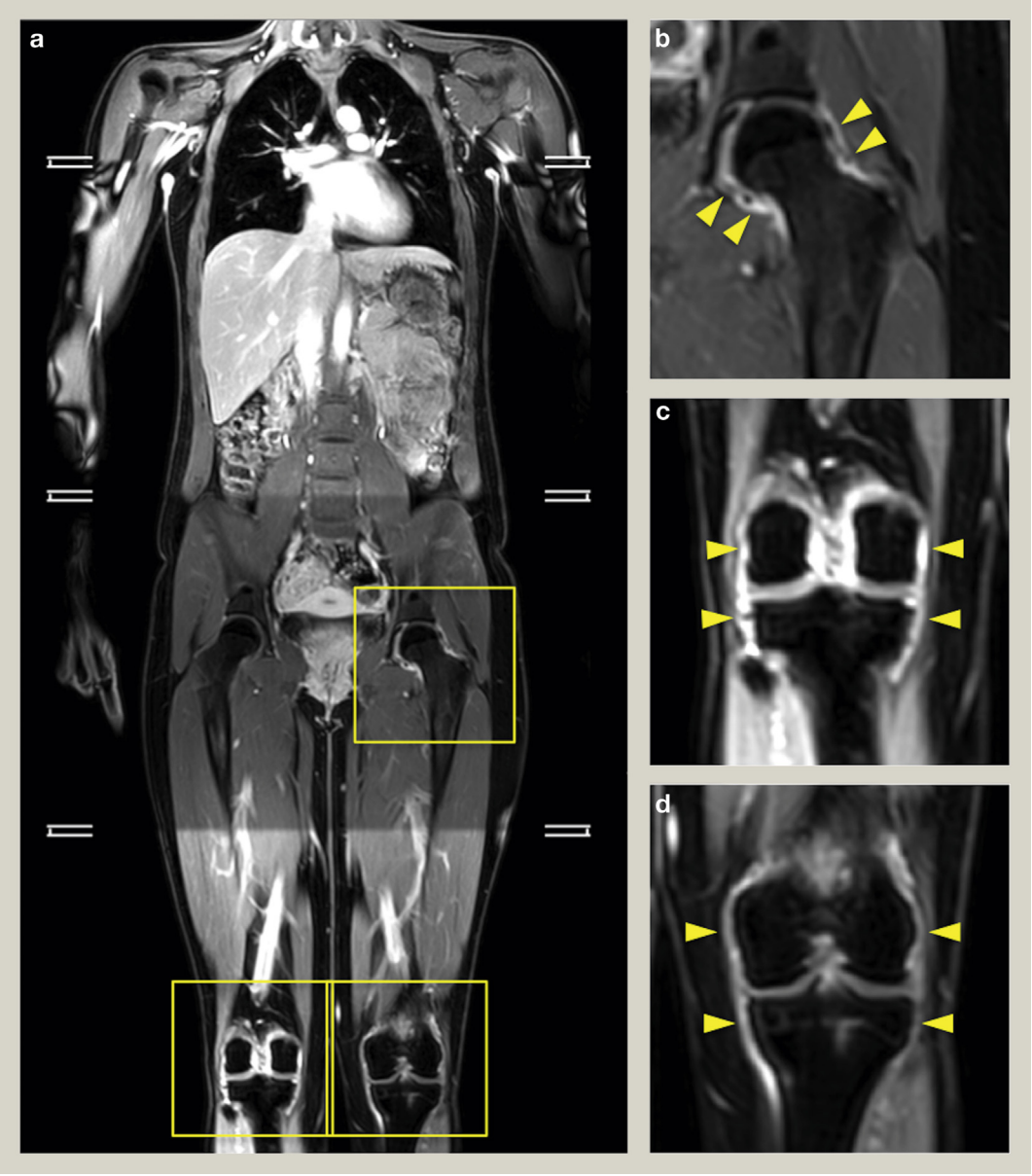

Figure 1 Whole-body MRI (WB-MRI) of a 22-year-old patient with polyarticular juvenile inflammatory arthritis. WB-MRI can image multiple joints, facilitating assessment of the distribution and severity of joint inflammation. (**a**) Large field of view image showing enhancing active synovitis in the left hip and right knee. Note the asymmetry of the hips, with lack of synovial enhancement of the right hip. Magnified views of the diseased left hip (**b**) and right knee (**c**) (compare with a normal left knee, seen in (**d**)), with arrowheads depicting the enhancing synovium.

Applications of morphological MRI and common findings

Conventionally, morphological and contrast-enhanced MRI are used to assess inflammatory arthritis. In general, short tau inversion recovery (STIR) and contrast-enhanced T1-weighted images are useful for assessing active inflammation.

In rheumatoid arthritis, the diseased joints show proliferative synovitis on MRI. This inflammation leads to bone erosions, which in the acute phase demonstrate loss of cortical definition and presence of subcortical bone marrow oedema (osteitis). These are seen as high signal on STIR (which is fluid-sensitive) and contrast-enhanced images. Mature erosions show sharply marginated areas of trabecular bone loss with cortical defects. Tenosynovitis, a common finding, is seen as synovial sheath thickening with marked enhancement on post-contrast images.

In axial and peripheral spondyloarthropathies, sacroiliitis is a common feature; it is seen on MRI as subchondral bone marrow oedema, synovitis, capsulitis and enthesitis. In the new Assessment of Spondyloarthritis International Society criteria for axial spondyloarthritis,[1] the presence of subchondral bone marrow oedema is mandatory for the diagnosis of acute sacroiliitis. In chronic sacroiliitis, periarticular fat metaplasia, sclerosis and erosions are seen, followed by ankylosis in some patients. Active spondylitis is seen as facet and costovertebral joint synovitis, enthesitis of spinal ligaments and corner inflammatory lesions resulting from bone marrow oedema of the vertebral entheses.

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Cheung KK, Hall-Craggs MA, Update on imaging in rheumatology – recent advances, Medicine (2018), https://doi.org/10.1016/j.mpmed.2017.12.004

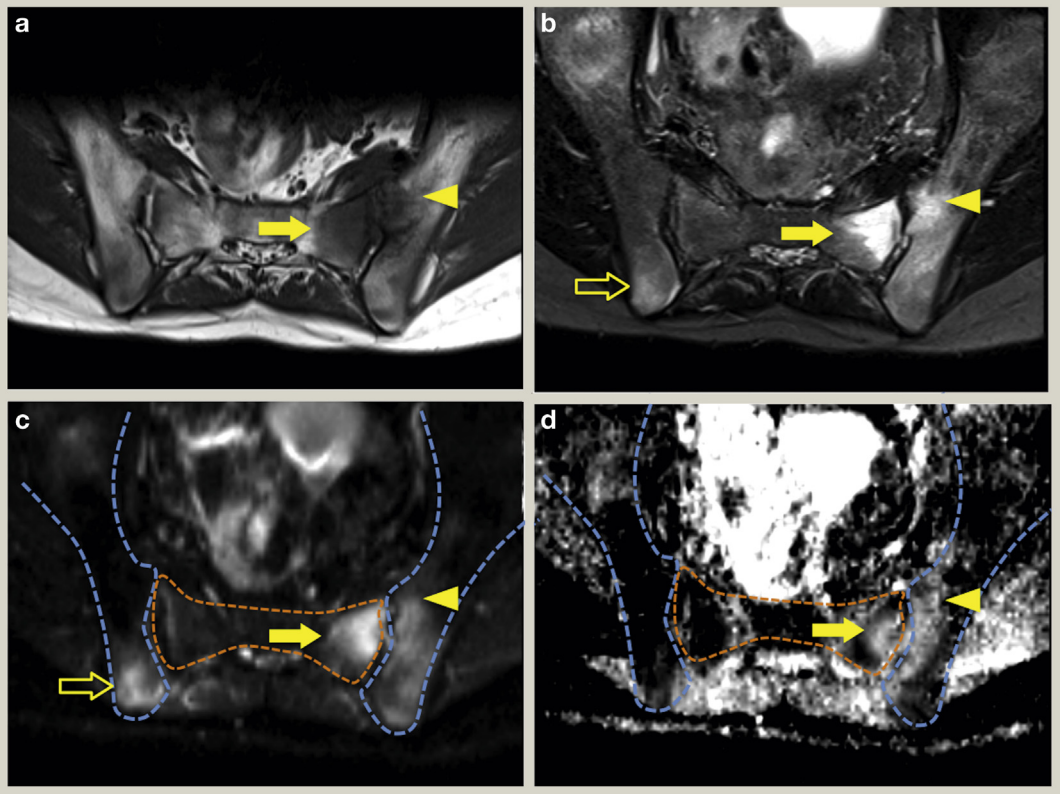

Figure 2 MRI of the sacroiliac joints of a 20-year-old patient with enthesitis-related arthritis and sacroiliitis. There is marked disease of the left joint (arrowhead, iliac side; filled arrow, sacral side), with less extensive involvement on the right (open arrow). (**a**) T1-weighted image showing subchondral bone marrow oedema/osteitis as low signal intensity, compared with the normal adjacent fatty marrow, which is high signal on T1. (**b**) Fluid-sensitive STIR sequence demonstrating the corresponding foci of osteitis as high-signal regions. (**c**) Diffusion-weighted image (DWI) and (**d**) apparent diffusion coefficient (ADC) map. Areas of active osteitis are hyperintense on both the DWI and ADC images, reflecting unrestricted diffusion (arrowed in (**c**) and (**d**)). Blue line, outline of ilium; orange line, outline of sacrum.

Fatty deposition at the vertebral corners (fatty Romanus lesions) is highly specific for axial spondyloarthropathy.

New magnetic resonance techniques and clinical applications

Whole-body (WB) MRI: in recent years, WB-MRI has been used to assess rheumatological diseases with multifocal and systemic involvement. It can detect inflammation, some of which may be subclinical, at multiple sites, allowing estimation of total disease load and activity. WB-MRI also facilitates visualization of enthesitis at multiple sites (Figure 1). A standardized scoring system based on WB-MRI is under development.[2]

Quantitative MRI: conventional analysis of MRI studies is subjective and relies on the experience and expertise of the reading radiologist. Quantitative methods provide objective evaluation, have the potential for automation and standardization, and have been explored in randomized clinical trials to evaluate treatment response.[3] Novel quantitative MRI techniques include diffusion-weighted imaging (DWI), dynamic contrast enhancement (DCE) and chemical-shift-encoded (CSE) MRI.

DWI-MRI measures the mobility of free water in living tissue; areas of active inflammation have increased free water content that results in increased diffusivity. Apparent diffusion coefficient values in these regions are higher than in non-inflamed tissue (Figure 2), and have been used to evaluate sacroiliitis and as a biomarker for measuring treatment response.[4]

DCE-MRI uses serial imaging at short intervals (typically a few seconds) during intravenous contrast administration. The dynamic enhancement profiles (time versus signal intensity) of the diseased region differ from those of normal tissue because of the presence of inflammation and neoangiogenesis; they have been shown to correlate with disease activity and predict progression of erosive disease.[5] It is also possible to derive quantitative physiological parameters by fitting dynamic enhancement data to pharmacokinetic models, which reflect exchanges between plasma and extracellular extravascular space. Such absolute parameters have the advantage of being independent of MRI hardware and parameters, and have shown promise for detecting synovial inflammation in early arthritis and assessment of tissue microcirculation.

CSE-MRI uses the small difference between the precession frequencies of water and fat protons when exposed to a strong external magnetic field (i.e. inside an MRI scanner). This phenomenon allows quantitative measurement of water and fat composition, and by the same token bone marrow oedema and fat metaplasia, which reflect active inflammation and structural damage, respectively, in inflammatory arthritis (Figure 3). This technique has been successfully applied in a cohort of adolescent patients with sacroiliitis to quantify bone inflammation and healing.

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Cheung KK, Hall-Craggs MA, Update on imaging in rheumatology – recent advances, Medicine (2018), https://doi.org/10.1016/j.mpmed.2017.12.004

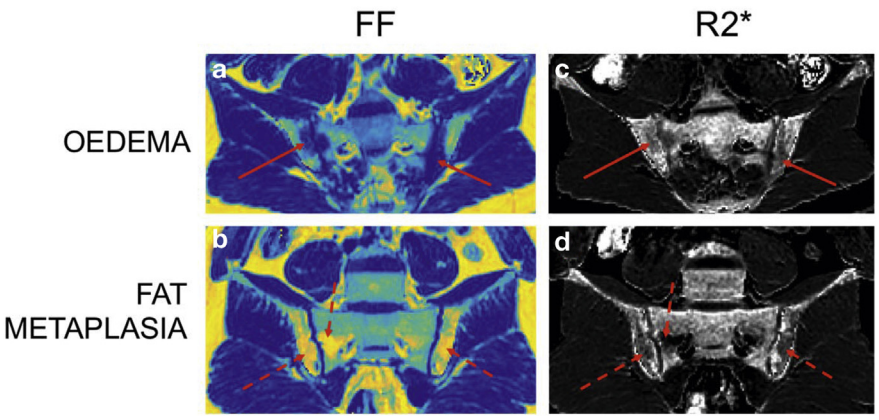

Figure 3 Chemical-shift encoding MRI in spondyloarthritis: fat fraction (FF) and R2* images showing areas of bone marrow oedema (solid arrows) versus fat metaplasia (dash arrows). R2* represents the rate of transverse magnetization decay, and has been proposed as a marker for bone mineral loss/osteoporosis. FF values are reduced in areas of bone marrow oedema (**a**), but increased in areas of fat metaplasia (**b**). R2* measurements are slightly reduced in areas of bone marrow oedema (**c**) and markedly reduced in areas of fat metaplasia (**d**), which may be due to local osteoporosis. Image courtesy of Dr TJP Bray, UCLH, London.

Other novel imaging modalities

Outside MRI, a number of novel imaging modalities for evaluating rheumatological disorders have emerged in recent years, including the following.

Fluorescence optical imaging (FOI): this involves intravenous administration of a non-specific fluorophore (typically indocyanine green), which is excited by light at the dark red spectrum. The emitting fluorescence is detected by an optical camera sensor and imaged serially every second over a few minutes. Active inflammation is seen as increased fluorescence intensity caused by increased neovascularity. FOI allows a quick overview of active inflammation, and has the potential to detect subclinical inflammation that is not apparent on clinical examination or ultrasound. Unlike ultrasound, it has the advantage of being operator-independent, but it is currently limited to evaluating the hand and wrist, and does not provide morphological information.

High-resolution peripheral quantitative computed tomography (HR-pQCT): HR-pQCT offers extremely high-resolution 3D imaging (typically 82-micrometre isotropic voxel size) of bone structure with a low radiation dose. The high resolution and quantitative nature of this technique enable assessment of periarticular bone marrow density and cortical/trabecular microarchitecture for detecting early erosive damage.

Molecular imaging: the imaging modalities discussed so far – albeit with great promises and advances – rely on the detection of anatomical and structural changes related to the disease, and are insensitive to the preceding molecular and cellular changes in the very early stages of pathogenesis. 'Molecular imaging' is a collective term used to describe techniques that employ molecular probes to allow visualization of the underlying biochemical processes driving the disease.

Probes are designed to target various disease processes such as inflammation, T/B cell activation, activated macrophages, activated vascular endothelium and apoptosis. To visualize these processes, probes are bound to imaging tracers (typically radiolabelled, which facilitate detection through tissue penetration) that are detected using modalities such as positron-emission tomography CT and single photon emission CT.

Molecular imaging has also shown great potential in the development of personalized therapy; for example, the use radiolabelled biologicals such as anti-tumour necrosis factor-α and anti-CD20 allows confirmation of the presence of these targets in a patient; this may help in predicting and selecting the most efficacious treatment. ◆

KEY REFERENCES

1 Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; **68**(suppl 2)**:** ii1–44.

2 Østergaard M, Eshed I, Althoff CE, et al. Whole-body magnetic resonance imaging in inflammatory arthritis: systematic literature review and first steps toward standardization and an OMERACT scoring system. *J Rheumatol*, 2017; https://doi.org/10.3899/jrheum.161114. pii: jrheum.161114, [Epub ahead of print].

3 Conaghan PG, Østergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. *Ann Rheum Dis* 2016; **75:** 1024–33.

4 Bray TJP, Vendhan K, Ambrose N, et al. Diffusion-weighted imaging is a sensitive biomarker of response to biologic therapy in enthesitis-related arthritis. *Rheumato (Oxford)* 2017; **56:** 399–407.

5 Huang J, Stewart N, Crabbe J, et al. A 1-year follow-up study of dynamic magnetic resonance imaging in early rheumatoid arthritis reveals synovitis to be increased in shared epitope-positive

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Cheung KK, Hall-Craggs MA, Update on imaging in rheumatology – recent advances, Medicine (2018), https://doi.org/10.1016/j.mpmed.2017.12.004

patients and predictive of erosions at 1 year. *Rheumato (Oxford)* 2000; **39:** 407–16.

FURTHER READING

Bray TJP, Bainbridge A, Punwani S, Ioannou Y, Hall-Craggs MA. Simultaneous quantification of bone edema/adiposity and structure in inflamed bone using chemical shift-encoded MRI in spondyloarthritis. *Magn Reson Med*, 2017; https://doi.org/10.1002/mrm.26729 [Epub ahead of print].

Klein A, Just GW, Werner SG, et al. Fluorescence optical imaging and musculoskeletal ultrasonography in juvenile idiopathic polyarticular disease before and during antirheumatic treatment – a multicenter non-interventional diagnostic evaluation. *Arthritis Res Ther* 2017; **19:** 147.

Maijer KI, Van der leij C, De hair MJ, et al. Dynamic contrast-enhanced magnetic resonance imaging using pharmacokinetic modeling: initial experience in patients with early arthritis. *Arthritis Rheumatol* 2016; **68:** 587–96.

Put S, Westhovens R, Lahoutte T, Matthys P. Molecular imaging of rheumatoid arthritis: emerging markers, tools, and techniques. *Arthritis Res Ther* 2014; **16:** 208.

Tam LS. The role of high-resolution peripheral quantitative computed tomography as a biomarker for joint damage in inflammatory arthritis. *J Rheumatol* 2016; **43:** 1911–3.

Acknowledgement

This work was undertaken at University College London Hospital/University College London, which receives funding from the Department of Health's National Institute for Health Research Biomedical Research Centre funding scheme. The views expressed here are those of the authors and not necessarily those of the UK Department of Health

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here

Question 1

A 28-year-old woman presented with pain and stiffness in the wrist and metacarpophalangeal joints of both hands.
On clinical examination, there was warmth, tenderness and evidence of thickening of the synovium in these joints.

Which conventional MRI sequence is the most sensitive and specific to image these changes?

A. T1
B. Contrast-enhanced T1
C. T2
D. Proton density
E. STIR

Question 2

A 13-year-old girl presented with asymmetrical pain and swelling of the small joints of the hands and feet.

Investigations

- Rheumatoid factor negative

Which imaging modality is the most appropriate to determine the distribution and extent of joint involvement?

A. Radiography (X-ray)
B. Ultrasound
C. Molecular imaging with SPECT
D. Fluorescence optical imaging
E. Whole-body magnetic resonance imaging

Question 3

A patient is interested in participating in a clinical trial that uses molecular imaging to access early detection and disease monitoring in inflammatory arthritis. She is keen to understand more about this new imaging technique.

What is the main potential advantage of molecular imaging over other imaging techniques in the evaluation of rheumatological disorders?

A. Its lack of ionizing radiation
B. Its ability to target pathogenetic pathways
C. Its ability to assess structural changes
D. Its low cost and availability
E. Its non-invasive nature

© 2017 Published by Elsevier Ltd.
Please cite this article in press as: Cheung KK, Hall-Craggs MA, Update on imaging in rheumatology – recent advances, Medicine (2018), https://doi.org/10.1016/j.mpmed.2017.12.004