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CONCISE REPORT

Whole-body MRI of patients with polymyalgia rheumatica identifies a distinct subset with complete patient-reported response to glucocorticoids

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2015-207395>).

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Received 2 February 2015

Revised 22 June 2015

Accepted 14 July 2015

Published Online First

16 September 2015



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To cite: Mackie SL, Pease CT, Fukuba E, et al. *Ann Rheum Dis* 2015;**74**:2188–2192.

ABSTRACT

Objectives To determine whether whole-body MRI defines clinically relevant subgroups within polymyalgia rheumatica (PMR) including glucocorticoid responsiveness.

Methods 22 patients with PMR and 16 with rheumatoid arthritis (RA), untreated and diagnosed by consultant rheumatologists, underwent whole-body, multiple-joint MRI, scored by two experts. Patients with PMR reported whether they felt 'back to normal' on glucocorticoid therapy and were followed for a median of 2 years.

Results All patients with PMR were deemed to respond to glucocorticoids clinically. A characteristic pattern of symmetrical, extracapsular inflammation, adjacent to greater trochanter, acetabulum, ischial tuberosity and/or symphysis pubis, was observed in 14/22 of the PMR cases. In PMR, this pattern was associated with complete glucocorticoid response ($p=0.01$), higher pretreatment C-reactive protein (CRP) and serum interleukin-6 (IL-6), and better post-treatment fatigue and function. Only 1/14 in the extracapsular group could stop glucocorticoids within 1 year, compared with 4/7 of the others. A score derived from the five sites discriminating best between PMR and RA correlated with IL-6 ($p<0.002$). IL-6 levels ≥ 16.8 pg/mL had 86% sensitivity and 86% specificity for the extracapsular MRI pattern.

Conclusions A subset of patients with rheumatologist-diagnosed PMR had a characteristic, extracapsular pattern of MRI inflammation, associated with elevated IL-6/CRP and with complete patient-reported glucocorticoid responsiveness.

INTRODUCTION

Polymyalgia rheumatica (PMR) is a clinically diagnosed cause of glucocorticoid-responsive pain and stiffness at the shoulders and hips, with great variation in the duration of glucocorticoid treatment required.^{1,2} Previous MRI and 18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) studies have suggested distinct extracapsular^{3,4} or capsular-based⁵ inflammation in PMR. Elevated pretreatment interleukin-6 (IL-6) levels (>10 pg/mL) with good symptomatic response to 20 mg prednisone was associated with requirement for >1 year of therapy.⁶ Given the superior resolution of MRI compared with 18-FDG-PET, we sought to determine an anatomical explanation for these findings.

Rheumatologists have traditionally been concerned not to miss rheumatoid arthritis (RA) in patients with PMR, although the anti-citrullinated peptide (anti-CCP) antibody test has made this easier.^{7,8} We designed this study to identify patterns of inflammation on whole-body, multiple-joint, 3-Tesla MRI⁹ that distinguished PMR from RA but during follow-up we were struck by the prognostic heterogeneity within the PMR group. Given a known association of ultrasound-defined inflammation with glucocorticoid responsiveness in PMR,¹⁰ we hypothesised that an extracapsular pattern of inflammation in PMR predicts glucocorticoid response.

METHODS

Ethical approval was obtained (09/H1307/98, approved by Leeds West Research Ethics Committee 15.1.10; 05/Q1108.28, York Research Ethics Committee). All patients gave written, informed consent.

Cases

Twenty-two consecutive patients with untreated PMR fulfilling Bird criteria¹¹ were identified by two rheumatologists. All had an elevation of at least one acute-phase marker (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) plasma viscosity (PV)), were negative for rheumatoid factor and anti-CCP antibody and were commenced on prednisolone 15 mg after their MRI scan, increasing to 20 mg at 1-month follow-up if clinically indicated.

Patients recorded pain/stiffness location using mannequins, and graded symptom severity using visual analogue scores (VAS) and Stanford Health Assessment Questionnaire - Disability Index (HAQ-DI).¹² Patients were asked whether they felt 'back to normal since taking steroids', on a five-point Likert scale from 'strongly agree' to 'strongly disagree'. 'Strongly agree' and 'agree' were classified as 'yes', others 'no'. Standardised glucocorticoid taper was adjusted to maintain symptom control until glucocorticoid cessation.² Median follow-up was 2 years.

Imaging controls

To minimise MRI scorer bias, 16 control MRI scans were chosen from patients with seropositive or seronegative RA.

MRI

Whole-body multiple-joint MRI was performed⁹ (see online supplementary methods). Gadolinium was used except where contraindicated. The four non-contrast MRI image files were evaluated (by DM, SLM and EF) to determine presence/absence of extracapsular PMR pattern as previously described.³ All 34 whole-body, multiple-joint, contrast-enhanced MRI image files were anonymised. Axial images were systematically scored in ImageJ in the following order: spine, shoulders, hips, hands, knees, feet. Each defined site was semiquantitatively scored by the two experts (DM and EF), scoring 0, 1, 2 or 3, for no inflammation, mild, moderate or severe inflammation respectively (figure 1). Each MRI was also classified as 'extracapsular pattern' or 'non-extracapsular pattern'. The anonymisation code was not broken until the MRI scoring datasheet (including overall classification) had been locked down.

IL-6 measurement

IL-6 was measured by ELISA (IL-6 Quantikine, R+D Systems) using serum taken from consenting patients before MRI.

Analysis

We tested the hypothesis that an extracapsular pattern of disease was associated with glucocorticoid responsiveness. Statistical analyses were performed in SPSS V.21 (IBM).

RESULTS

Demographics and disease characteristics

At screening, all 22 patients with PMR fulfilled Bird criteria¹¹ and (retrospectively) the provisional ACR/EULAR classification criteria,⁸ including elevation of at least one acute-phase marker; in two PMR cases, however, acute-phase markers normalised by the time the MRI scan was done. At follow-up, PMR was confirmed as the most likely diagnosis. All 22 patients were recorded by the treating rheumatologist as responding to prednisolone; in three cases an increase in dose was required for complete response. No alternative explanation for patients' musculoskeletal symptoms was found.

Training set (non-contrast) MRIs in PMR

Extracapsular inflammation³ was seen in 2/4 non-contrast MRI scans of patients with PMR. Oedema was seen around the

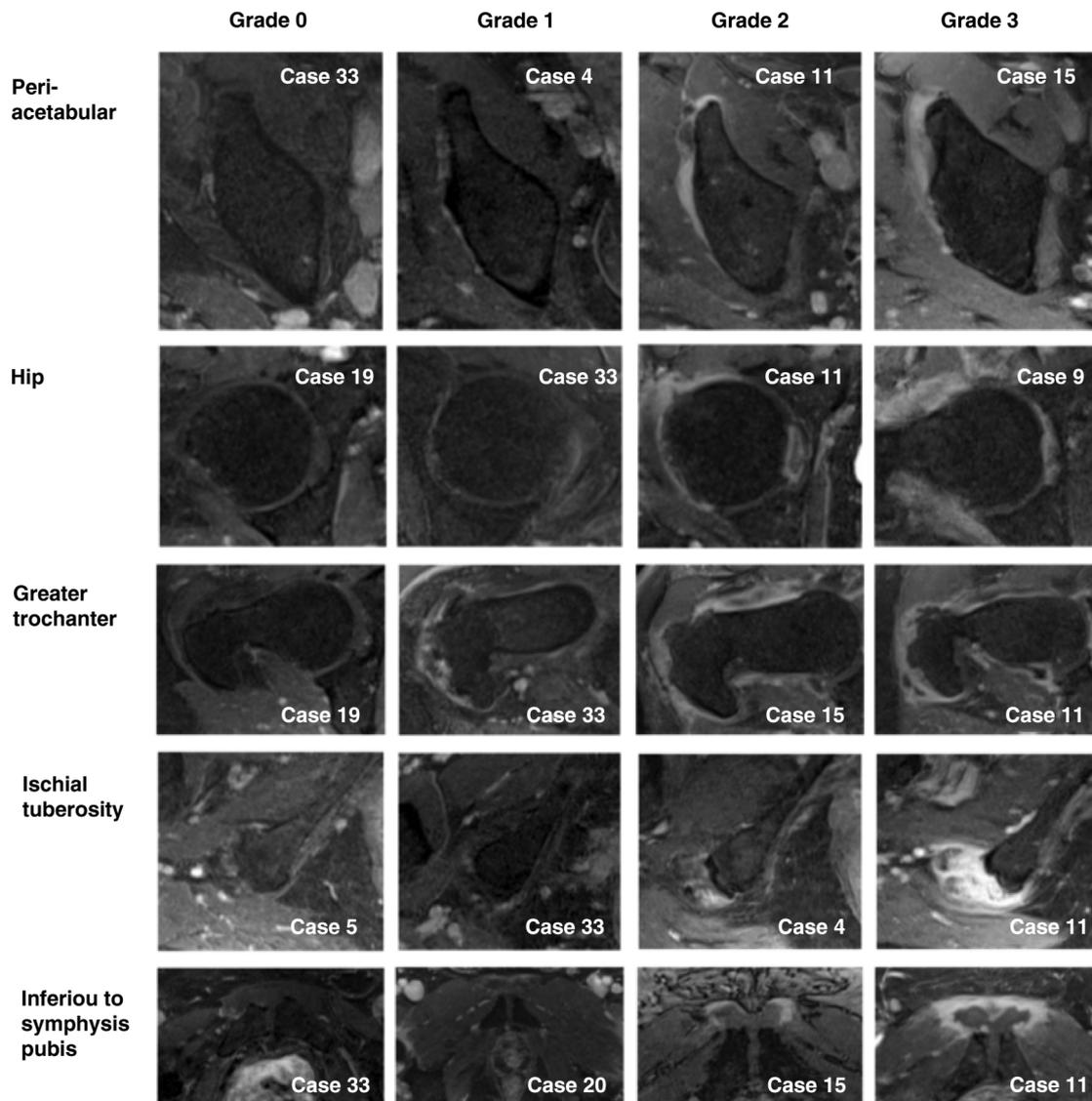


Figure 1 Exemplar images of semiquantitative scoring system.

Table 1 Description of features of patients with polymyalgia rheumatica (PMR) with and without characteristic extracapsular pattern of inflammation

	Extracapsular pattern (n=14)	Non-extracapsular pattern (n=8)	p Value
Demographics			
Age, median (range)	75 (55, 85)	78 (70, 84)	0.22
Male, n (%)	8 (57%)	0 (0%)	0.02
Acute-phase markers			
ESR, median (range), mm/h	46 (9, 119)	38 (4, 81)	0.63
CRP, median (range), mg/L	36 (5, 118)	5.25 (5, 76)	0.03
PV, median (range), mPa s	1.93 (1.78, 2.12)	1.81 (1.57, 2.04)	0.36
IL-6, median (range), pg/mL	25.8 (0.3, 87.6)	6.0 (0.2, 131.5)*	0.04
Composite disease activity scores			
PMR-AS (median, IQR)	78.6 (53.8, 103.0)	70.2 (34.4, 106.1)	0.73
Pretreatment patient-reported outcomes			
Pain VAS (median, IQR)	7.7 (5.0, 8.1)	7.9 (4.3, 8.7)	0.63
Stiffness VAS (median, IQR)	6.3 (4.5, 8.0)	8.2 (5.2, 8.9)	0.29
Fatigue VAS (median, IQR)	7.1 (5.2, 7.6)	8.4 (7.0, 9.7)	0.03
HAQ-DI (median, IQR)	1.25 (1.09, 1.50)	1.56 (1.28, 2.09)	0.07
Assessment of glucocorticoid responsiveness at first follow-up			
'I feel back to normal since taking steroids'. n (%)	11/13 (85%)	1/6 (17%)	0.01
'I feel [or felt] back to normal since taking steroids'. n (%)	12/14 (86%)	1/8 (13%)	0.001
Fatigue VAS at follow-up (median, IQR)	1.3 (0.2, 3.8)	7.1 (3.6, 9.8)	0.02
HAQ-DI at follow-up (median, IQR)	0 (0, 0.625)	1.0 (0.76, 2.07)	0.003
Prognosis			
Stopped glucocorticoids permanently after <1 year†	1/14	4/7	0.03
Relapse-free†	7/14	2/8	1.00
Relapsed when on 5 mg or more†	3/14	3/7	0.35
Required initial dose increase >15 mg	2/14	1/8	1.00

The PMR-AS is the PMR Activity Score as described by Bird and Leeb. Either Mann-Whitney U test or Fisher's exact test was used for non-normally distributed values; unpaired t test for normally distributed variables. All tests were two-tailed. Apart from glucocorticoid responsiveness (the a priori hypothesis), p values should be interpreted in the light of multiple testing. Bonferroni correction for all the variables reported here (likely over-stringent because of strong correlation between ESR/CRP/PV/IL-6 and between patient-reported VAS scores) would require a threshold of 0.05/19, or p<0.0026.

*Excludes one patient who did not have IL-6 measured.

†Excludes one patient who was lost to follow-up at 4 months.

CRP, C-reactive protein; IL-6, interleukin-6; PV, plasma viscosity; VAS, visual analogue score.

The two patients with PMR extracapsular pattern who were not complete glucocorticoid responders by self-report (figure 2) had the highest IL-6 and CRP, and both required escalation of prednisolone dose for full response. Another patient with extracapsular pattern later developed biopsy-proven giant cell arteritis.

Association of IL-6 with MRI inflammation

The top five MRI features (mean of left and right) were summed to provide a composite score. This was significantly associated with IL-6 (p<0.001) (see online supplementary figure S2) but not with CRP (p=0.055). The most discriminatory IL-6 cut-off for the extracapsular pattern was ≥ 16.8 pg/mL (sensitivity 86%, specificity 86%).

DISCUSSION

All our patients were diagnosed with PMR by rheumatologists; we sought to determine whether this could be further stratified based on the pattern and extent of inflammation on whole-body MRI. We identified a subset, with characteristic, extracapsular pattern of inflammation on MRI that was more likely to feel 'back to normal' after glucocorticoids. MRI allowed good resolution of pelvic inflammation. In addition, despite having more males (male gender in PMR generally predicts shorter glucocorticoid duration¹⁴), our 'extracapsular' group was also more

likely to require glucocorticoid treatment for >1 year. IL-6 correlated with pelvic MRI inflammation; a cut-off of ≥ 16.8 pg/mL IL-6 had 86% sensitivity and 86% specificity for the extracapsular pattern. Our data support an extra-articular model of the primary inflammatory change in PMR.³ A recent report describes focal 18-FDG-PET uptake anterior to the hip joint in PMR¹⁵ similar to our 'periacetabular' pattern.

Strengths of this study include the standardised assessments and the blinded MRI scoring. PMR diagnoses were all made by a consultant rheumatologist, and all patients were treated as PMR without any alternative diagnosis supervening.

The limitations of this study were its descriptive and exploratory nature, small numbers, slightly younger age of the RA group, and the subjectivity inherent in clinical diagnosis of PMR even following diagnostic guidelines.^{8 16} We hypothesise the 'non-extracapsular' patients with PMR may be a pathogenetically heterogeneous group, analogous to 'autoantibody-negative RA'. Whether they ought to be labelled PMR is a philosophical question beyond the scope of this investigation.

This novel, pathoanatomical description of the clinical spectrum of PMR adds weight to the idea of PMR as a clinically heterogeneous disorder.¹ MRI may help to identify a more homogeneous subset, with potential value for defining eligibility for early clinical trials of targeted therapies. Our data suggest that in the specialist setting CRP and IL-6 may be more

prognostically useful tests than ESR or PV. An MRI might be useful in cases of diagnostic doubt. The diagnostic importance of glucocorticoid responsiveness is still debated in PMR⁸ especially since the best way to measure response remains unclear: the limitations of previously proposed disease activity scores, including the physician global assessment and the PMR-AS, have been well-discussed elsewhere.¹⁰ Although most disease activity scores focus on pain and stiffness, we identified residual fatigue and functional impairment after glucocorticoid treatment in our non-extracapsular group; this is of interest since fatigue¹⁸ and disability¹⁹ have been identified from recent qualitative studies as being important to patients. We found that MRI yielded additional valuable information to the clinical assessment, particularly in the pelvic region where an extracapsular pattern was clearly seen in a distinct subset of patients. Further research is required to determine the clinical utility of MRI, symptom location (eg, buttock pain) or CRP/IL-6 as diagnostic, prognostic or treatment stratification features in PMR.

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Acknowledgements Thanks to Ged Connolly-Thompson for anonymising the case-control MRIs, allocating random anonymisation codes and keeping the decode sheet until the scoring sheet had been locked down. Rob Evans and Carole Burnett performed the MRI scans, and Tracey Hulland provided administrative support and welcomed the patients. Thanks to Farah Mohamad Idris for carefully going through the pain and stiffness mannequins, digitally superimposing the images to give combined pain/stiffness images, and comparing with the MRI scoring data. Thanks to Agata Burska for assistance with ELISAs and Professor Ann Morgan for advice on earlier versions of the manuscript. Permission has been obtained from all persons named in the acknowledgement. SLM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors SLM helped design the study, conducted research visits, organised MRI scoring, analysed data, and drafted the paper; CTP recruited patients, collected clinical data; EF helped devise the scoring system and scored MRIs; EH carried out the IL-6 ELISAs; PE and JF led the Disease Continuum study, and provided clinical data on the patients with RA; RH developed the MRI protocol; DM helped design the study, recruited patients and scored the MRIs. All authors contributed to design and/or data interpretation, revised the manuscript for important intellectual content, and approved the final version.

Funding SLM was funded by a National Institute for Health Research Academic Clinical Lecturer Award during the data collection and is currently funded by a National Institute for Health Research Clinician Scientist Award. MRI scans were funded by the NIHR Leeds Musculoskeletal Biomedical Research Unit. Biomarker analyses were funded by a grant to SLM from the Leeds Teaching Hospitals Charitable Trustees. This article presents independent research supported by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. An earlier version of this work was presented in poster form at the American College of Rheumatology Annual Meeting in November 2014.

Competing interests None declared.

Ethics approval Leeds West Research Ethics Committee and York Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Further data including anonymised MRI images available to bona fide researchers by request to the corresponding author. Any data that could identify individual patients will not be available, for ethical reasons.

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Online-Only Supplement – Contents and Legends

Supplementary Methods. Sequence parameters for 3-Tesla, whole-body, multiple-joint magnetic resonance imaging scans.

Supplementary Table 1. Clinical and demographic features of cases and controls at recruitment.

Supplementary Table 2. Discrimination between PMR and RA of individual scores at 13 regions in the shoulder or hip.

Supplementary Figure 1. Trios of images from a single case (no. 11) illustrating some of the characteristic features of the extracapsular inflammation pattern. Coloured lines represent the three intersecting orthogonal planes (axial, sagittal or coronal) used to generate each trio of images. (a) Cross sections through femoral head showing peri-acetabular enhancement (b) Cross sections through pubic bone showing enhancement below the symphysis pubis; also showing inflammation of anterior superior iliac spine.

Supplementary Figure 2. Relationship of serum IL-6 to MRI score. Spearman $\rho=0.754$, $p<0.001$, $n=17$.

Supplementary Figure 3. Pain (red) overlaid with stiffness (green) mannequins, for each of the patients who underwent contrast-enhanced MRI scans.

Supplementary Methods.

Sequence parameters for 3-Tesla, whole-body, multiple-joint magnetic resonance imaging scans.

	TR/TE/FA	Resolution (mm)	Time (mins)	
Spine x3	3100/105	1.2 x 0.9 x 3	1:15	2D FSE
Sacro-iliac joints	4580/107	1.1 x 0.9 x 3	1:33	SPAIR
Shoulders	11/2.5, 3.7/15	1.0 x 1.0 x 0.6	3:02	3D VIBE
Hips, hands	6.4/2.5, 3.7/15	0.8 x 0.8 x 0.6	3:02	Dixon post gadolinium
Knees	10/2.4, 3.7/20	0.8 x 0.8 x 0.6	2:59	
Feet	6.4/2.5, 3.7/15	0.8 x 0.8 x 0.6	3:16	

Whole-body multiple-joint MRI was performed using a 3T Siemens Verio scanner with multiple radiofrequency coils. T2-weighted, fat-suppressed images of the spine and sacroiliac joints were acquired, followed by images of the joints and entheses (regions: shoulders, hips and hands, knees, feet) using VIBE (volumetric interpolated breath hold examination) Dixon sequences post intravenous gadolinium contrast. If gadolinium was contra-indicated, a non-contrast scan covering equivalent anatomical areas was performed.

Supplementary Table 1. Clinical and demographic features of cases and controls at recruitment.

	PMR cases having MRI	PMR cases having contrast MRI	RA controls having contrast MRI
Total number	22	18	16
Males (n, %)	8 (36.4%)	7 (38.9%)	6 (37.5%)
Age (median, range)	75.5 (55, 85)	75.5 (55, 85)	52.5 (23, 66)
C-reactive protein, mg/L (median, interquartile range)	30 (5.4, 55)	30 (<5.0, 43.8)	13 (<5.0, 21.1)
ESR, mm/hour (median, interquartile range)	46 (22.25, 54.5)	42 (17, 54.5)	23.5 (6, 37.5)
Plasma viscosity, mPa s (median, interquartile range)*	1.84 (1.79, 1.98)	1.84 (1.79, 1.98)	1.82 (1.69, 1.89)
IL-6, pg/mL (median, interquartile range)	21.1 (5.2, 31.4)	21.1 (2.9, 31.0)	-
Seropositive***, n (%)	0	0	10 (62.5%)
Radiographic erosions present, n (%)	0	0	8 (50%)
Pain VAS, (median, interquartile range)	7.7 (5.0, 8.5)	7.7 (5.0, 8.5)	-
Stiffness VAS, (median, interquartile range)	6.9 (4.9, 8.75)	6.9 (4.9, 8.75)	-
Fatigue VAS, (median, interquartile range)	7.3 (6.1, 8.3)	7.3 (5.7, 8.5)	-
HAQ-DI, (median, interquartile range)	1.375 (1.125, 1.719)	1.312 (1.125, 2.00)	-

*Reference range for plasma viscosity in our laboratory: 1.50 to 1.72.

**Excludes one PMR patient who did not have IL-6 measured.

***Seropositivity defined as rheumatoid factor titres and/or anti-cyclic citrullinated peptide antibody levels outside the quoted laboratory reference range.

Supplementary Table 2. Discrimination between PMR and RA of individual scores at 13 regions in the shoulder or hip.

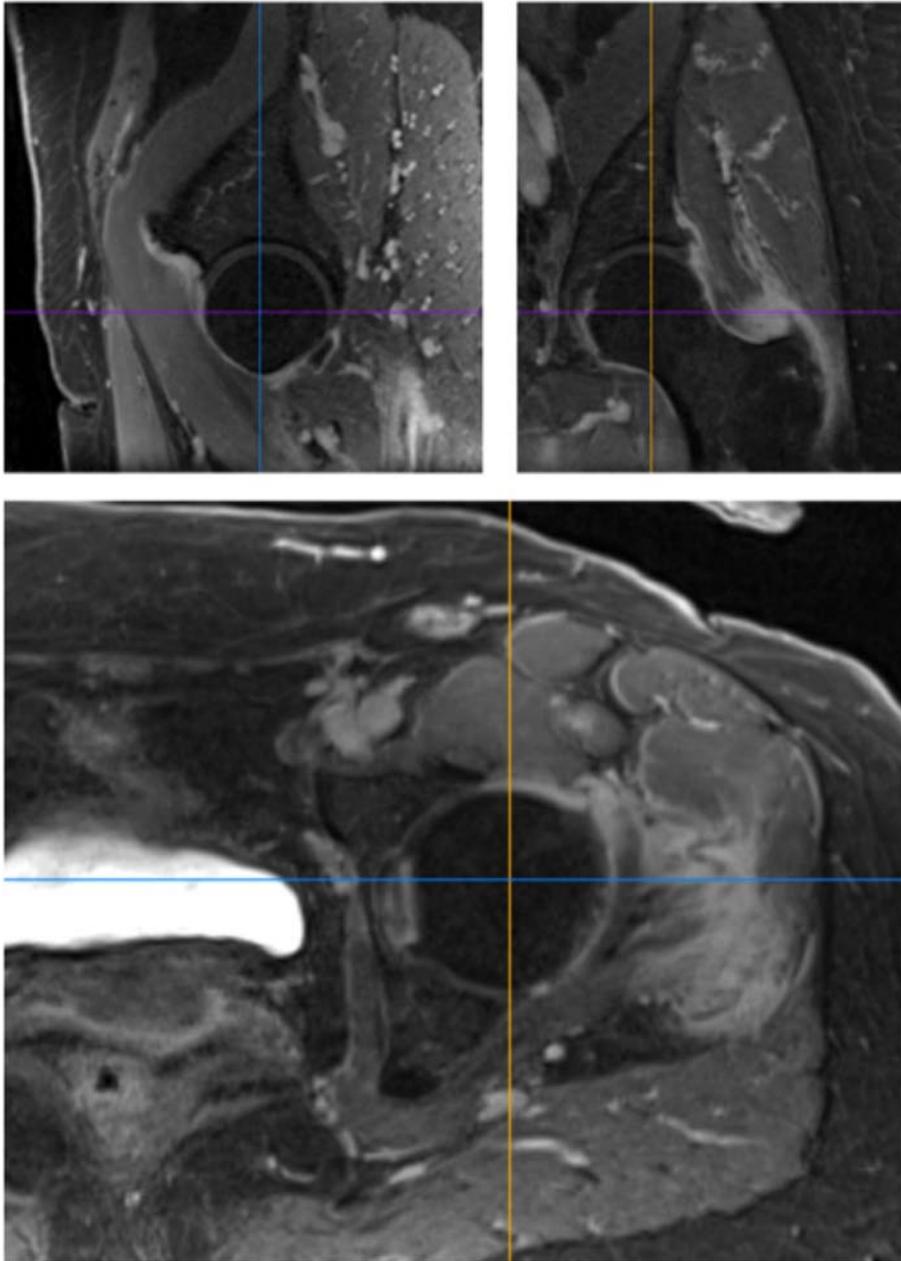
Site	Region	c-statistic	95 % CI of c-statistic
Ischial tuberosity	Pelvic	0.833	0.689, 0.977
Hip joint	Pelvic	0.785	0.628, 0.941
Greater trochanter	Pelvic	0.780	0.617, 0.942
Peri-acetabular	Pelvic	0.771	0.609, 0.933
Symphysis pubis	Pelvic	0.689	0.510, 0.869
Subcoracoid bursitis	Shoulder	0.684	0.503, 0.865
Subacromial bursitis	Shoulder	0.663	0.478, 0.848
Obturator tendon	Pelvic	0.661	0.477, 0.846
Long head of biceps tendon	Shoulder	0.658	0.469, 0.847
Glenohumeral joint synovitis	Shoulder	0.656	0.457, 0.855
Subdeltoid bursitis	Shoulder	0.573	0.378, 0.768
Iliopsoas bursitis	Pelvic	0.557	0.362, 0.752
Subscapularis tendon	Shoulder	0.530	0.727, 0.332

For bilateral structures the mean of the scores from the right and left are taken. The value of the c-statistic, equivalent to the area under the ROC curve, is defined as 0.500 for a non-discriminatory test (no better than chance) and 1.000 for a perfectly discriminatory test. Sites of inflammation are ranked in descending order of the c-statistic.

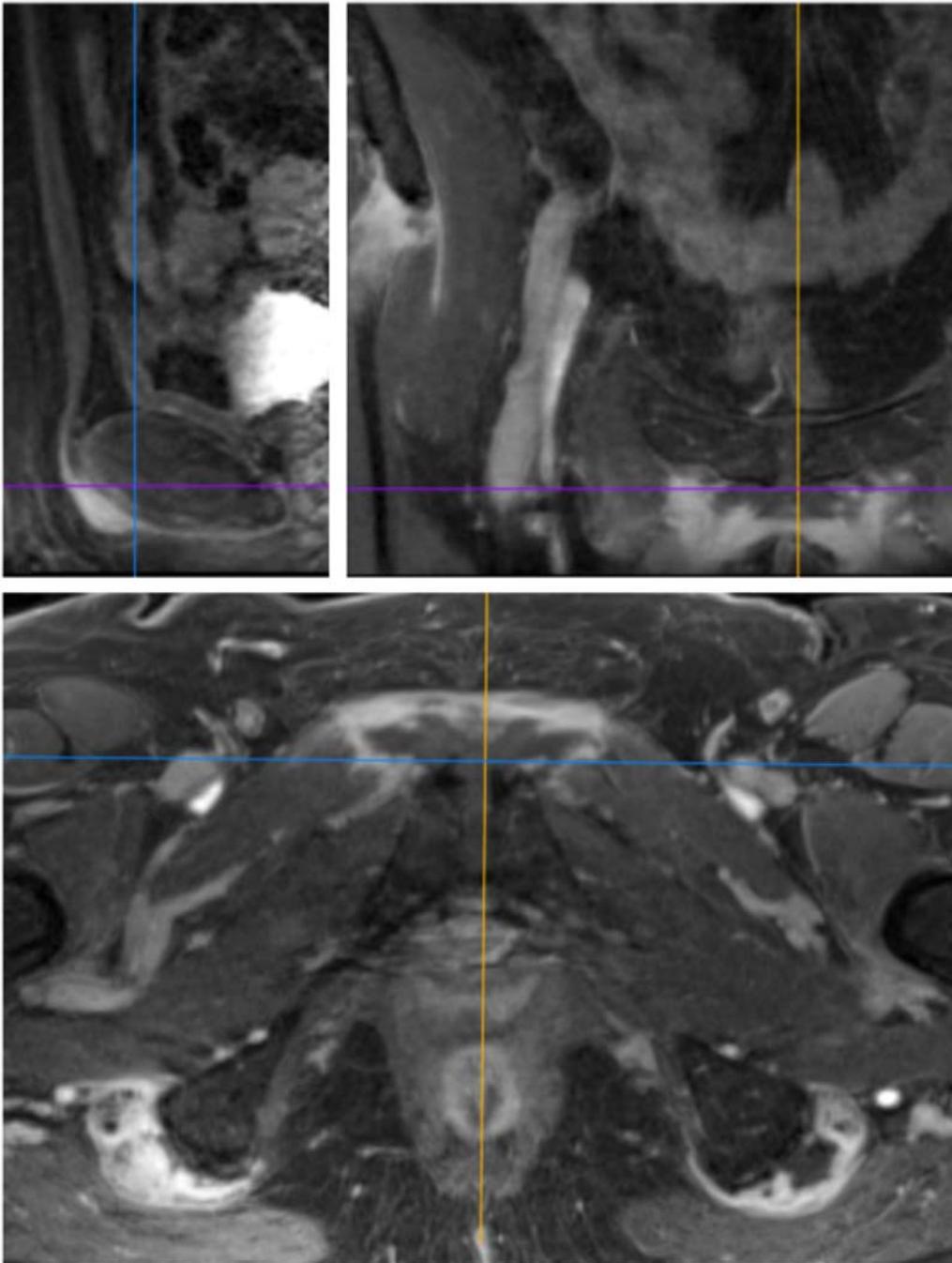
Supplementary Figure 1a,b. Trios of images from a single case (no. 11)

illustrating some of the characteristic features of the extracapsular inflammation pattern. Coloured lines represent the three intersecting orthogonal planes (axial, sagittal or coronal) used to generate each trio of images.

(a) Cross sections through femoral head showing peri-acetabular enhancement

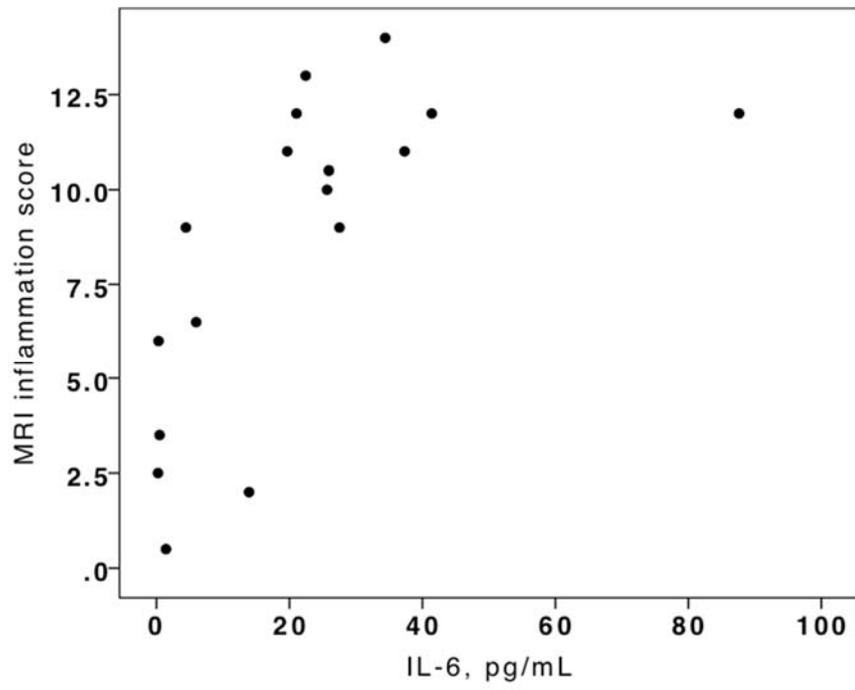


(b) Cross sections through pubic bone showing enhancement below the symphysis pubis; also showing inflammation of anterior superior iliac spine.

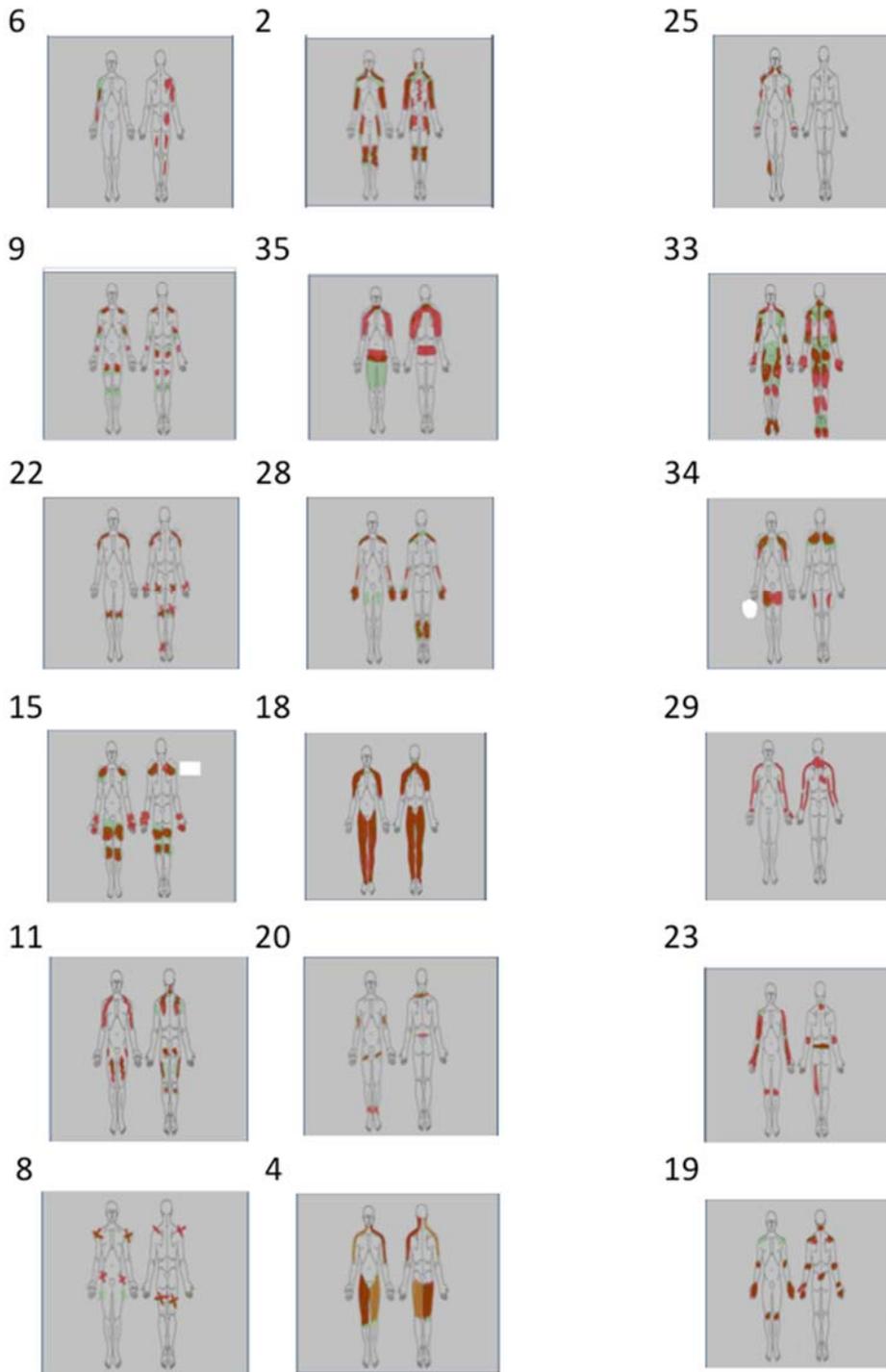


Supplementary Figure 2. Relationship of serum IL-6 to MRI score. Spearman

$\rho=0.754$, $p<0.001$, $n=17$



Supplementary Figure 3. Pain (red) overlaid with stiffness (green) mannequins, for each of the patients who underwent contrast-enhanced MRI scans.



Extracapsular MRI pattern

Non-extracapsular MRI pattern