MRI for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis - a study of patients receiving combined anakinra and methotrexate therapy

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ABSTRACT

Objectives: By MRI to assess the efficacy of addition of anakinra for controlling synovitis and stopping erosive progression in RA patients with high clinical activity despite methotrexate, and to determine the predictive value of MRI for subsequent radiographic erosive progression.

***Methods*:** In 17 patients with clinically active RA on methotrexate (median 15 mg/week), 100 mg anakinra s.c./day were added. Contrast-enhanced MRI of the non-dominant wrist and 2nd-5th metacarpophalangeal (MCP) joints (OMERACT-evaluation) at weeks 0, 12 and 36 were performed, as were radiography of both hands and wrists (modified Sharp-evaluation) at weeks 0 and 36.

Results: MRI synovitis scores (medians at baseline/week 12/week 36: 11/13/14) were not significantly changed during the study. Unilateral wrist and MCP-joint MRI after 12 weeks (OMERACT score, standardised response mean (SRM)=0.77) had a similar sensitivity for detection of progression of bone erosion (10 patients) as bilateral hand and wrist radiography (modified Sharp score, SRM=0.6) after 36 weeks (11 patients). 9 of the 10 patients with MRI progression at 12 weeks had X-ray progression at 36 weeks. Baseline MRI synovitis and erosion scores, but no clinical/biochemical parameters, were significantly correlated with subsequent erosive progression on bilateral hand and wrist radiographs.

Conclusion: Addition of anakinra did not significantly reduce MRI signs of synovitis, and the majority of patients experienced progressive joint destruction. Baseline MRI findings were predictive of subsequent radiographic erosive progression. Unilateral wrist and MCP-joint MRI already after 12 weeks had a similar sensitivity for detection of progression of bone erosion as bilateral hand and wrist radiography after 36 weeks.

KEYWORDS:

Rheumatoid arthritis; magnetic resonance imaging; anakinra; radiography; synovitis; erosion.

INTRODUCTION

Anakinra (Kineret®, Amgen Inc., Thousand Oaks, USA), a recombinant human interleukin-1 receptor antagonist (IL-1Ra), has been shown to reduce joint inflammation and destruction in rheumatoid arthritis (RA) patients, as assessed by the conventional outcome measures, i.e. clinical, biochemical and radiographical examinations [1-3].

Magnetic resonance imaging (MRI) is more sensitive for the detection of both inflammatory (synovitis) and destructive (erosive) joint changes than clinical examination and radiography [4-6]. Thus, MRI offers improved opportunities for investigating the course of joint inflammation and destruction during new therapeutic approaches, as in this case interleukin-1 blockade.

The aim of the present study was, by means of MRI, to describe the course of inflammation and destruction of RA joints during combined anakinra and methotrexate (MTX) therapy in RA patients with high clinical activity despite MTX, and to compare the MRI-findings with findings obtained by conventional clinical, biochemical and radiographical methods. Furthermore, the predictive value of pre-treatment MRI with respect to subsequent erosive progression on radiographs was investigated.

PATIENTS AND METHODS

Seventeen rheumatoid arthritis RA patients (fulfilling American College of Rheumatology 1987-criteria for RA [7]) at the Departments of Rheumatology at the Copenhagen University hospitals at Herlev and Rigshospitalet, Denmark, enrolled in an open label, single-arm 36-weeks follow-up study (Amgen Protocol Number 20000258), were included in this supplementary investigator initiated amendment, involving repeated MRI and X-ray examinations.

All patients (13 women and 4 men; median age 55 years (range 33-73 years), disease duration 13 (2-37) years, number of previous disease-modifying anti-rheumatic drugs 3 (1-7)), received 100 mg anakinra s.c. daily and concomitant MTX (median 15 (5-20) mg/week, initiated ≥ 3 months before baseline). These doses were kept stable during the trial, as were doses of oral prednisolone (median 0 (0-10)) and NSAIDs. No intramuscular or intraarticular steroid were administered.

All patients signed a separate informed consent for inclusion in this amendment. The study and the amendment were approved by the local Independent Ethics Committee, and conducted according to the principles of the Declaration of Helsinki. Amgen Inc. had no influence on or involvement in the planning of this investigator-initiated study, the data analysis or the preparation of the manuscript.

Standard clinical assessments were performed at baseline and after 2, 4, 12, 24 and 36 weeks (Table).

Conventional radiographs (X-ray), including posterior-anterior (PA) projections of hands and wrists, lateral projection of wrists and oblique projection of hands [8], were obtained on single emulsion films at baseline and after 36 weeks and assessed according to the modified Sharp method [9]. Furthermore, the number of wrist- and MCP-joint bones with erosions was counted.

MRI of the non-dominant wrist and 2^{nd}-5^{th} MCP joint was performed at baseline and after 12 and 36 weeks. A 0.23 T MR system (Panorama 0.23T, Philips, Best, the Netherlands), equipped with a receive-only solenoid coil and localised at the Department of Radiology, the Copenhagen University Hospital at Herlev, was used. Coronal and axial T1-weighted 3D fast field echo sequences (slice thickness (ST) 1.5 mm; matrix 328x420, field of view (FOV) 140 mm (coronal) or 120 mm (axial)) and a coronal T2-weighted STIR sequence (TSHIRT, ST 3.5, FOV 180, matrix 216x256) were performed. The T1-weighted sequences were repeated after intravenous injection of 0.2 ml/kg of the contrast agent Omniscan® (GE Healthcare, Amersham,United Kingdom).

The MR images were scored for synovitis, bone oedema and bone erosions according to the latest "Outcome Measures in Rheumatology Clinical Trials" (OMERACT) recommendations [10].

Radiographs were read by an experienced musculoskeletal radiologist and MRIs by a rheumatologist trained in evaluation of MR images of RA joints. Readers were unaware of the chronological order of the images and of clinical, biochemical and other imaging data

Statistical analysis

The Wilcoxon-Pratt test was used to analyse changes within the patient. Spearman's test of rank correlation was used for correlation analyses. The standardized response mean (SRM) was calculated for changes in MRI and radiographic scores. P-values <0.05 were considered statistically significant.

RESULTS

Clinical and imaging findings

At baseline, all patients had clinically active RA (median DAS28 score 5.6, range 3.9-7.2) (Table). Clinical disease activity parameters were significantly reduced at week 12 and 36 (Wilcoxon-Pratt, $p<0.001$ to $p<0.05$) (Table). At week 36, 5, 6 and 6 patients showed good, moderate and no EULAR response[11]. 5 patients fulfilled the EULAR criteria for low disease activity (DAS28 < 3.2) while no patients had clinical remission (DAS28 < 2.6)[12].

Radiography of both hands and wrists, assessed by the modified Sharp method, revealed progression in bone erosions in 11 of 17 patients during the 36 weeks treatment period, while the median total Sharp score increased from 50 (range 1–233) at baseline to 59 (range 2-243) at week 36 ($p<0.05$) (Table). Particularly, the erosion component of the score increased ($p<0.01$), while the JSN component showed no significant change.

MRI scores of synovitis, bone oedema and bone erosions are given in the Table. The MRI-synovitis scores and bone oedema scores did not change significantly during the study. The MRI-erosion score at baseline ranged from 0-116 (median 17). A significant increase was observed at week 12 (median 19, $p<0.01$) and at week 36 (median 21, $p<0.05$) (Table). The MRI erosion score revealed progression in 12 of 17 patients during the 36 weeks follow-up period. The standardised response mean for the X-ray modified Sharp score change from week 0 to 36 was 0.60, while for the OMERACT MRI erosion score 0.77 (week 0-12) and 0.79 (week 0-36). At 12 weeks, MRI revealed progression in 10 patients. In other words, unilateral MRI of wrist and MCP-joints after 12 weeks detected erosion progression in a similar number of patients as bilateral X-ray of MCP, PIP and wrist joints after 36 weeks (11 patients). 9 of the 10 patients with MRI progression at 12 weeks had X-ray progression at 36 weeks.

Baseline findings versus erosive progression on radiographs

As the only baseline parameter, the MRI erosion score was correlated with the change in the radiographic total Sharp score during the 36 weeks of follow-up (rho=0.55, $p<0.05$).

Furthermore, the baseline MRI-synovitis score was highly correlated with the increase in the total number of radiographic eroded bones in the wrist, MCP-joints and PIP-joints from baseline to week 36 (rho=0.70; $p<0.01$) and with the total Sharp score at week 36 (rho=0.61; $p<0.05$).

The change in MRI-erosion score from baseline to week 12 correlated with the change in total Sharp score from week 0 to week 36 (rho=0.55, $p<0.05$).

MRI-scores were not correlated with clinical, biochemical or composite disease activity markers, which were, furthermore, not significantly correlated with radiographic progression.

DISCUSSION

In this study of patients with severe RA with high clinical disease activity and advanced erosive joint damage, MRI-scores of synovitis were not significantly reduced by adding anakinra to methotrexate therapy. Thus, MRI directly visualized that anakinra did not efficiently suppress joint inflammation.

The majority of RA patients showed erosive progression during anakinra therapy, on radiographs as well as on MRI. This is in accordance with the fact that presence of synovitis is linked to erosive progression [4 6 13], and supports the clinical significance of the observed MRI-signs of inflammation. As no control group was incorporated, the study design did not allow detection of a potential beneficial effect of anakinra on bone destruction, if present. However, it can with certainty be concluded that erosive progression was not eliminated by combined anakinra and methotrexate therapy.

Radiography of both hands and wrists, incorporating assessment of both bone erosions and joint space narrowing, found increased damage scores in 13 out of 17 patients at 36 weeks. Eleven patients progressed if only the bone erosion component of the modified Sharp method was considered. In contrast, MRI already at 12 weeks demonstrated erosive progression compared to baseline in 10 patients. Nine of these 10 patients displayed radiographic progression after 36 weeks. The SRM of the 12 weeks MRI erosion score change was higher than of the 36 weeks X-ray score. These findings illustrate the capacity of MRI to visualize erosive progression in insufficiently treated RA patients over a very short time period. This makes MRI very promising for RA clinical trials, because studies as short as 3-4 months may be able to demonstrate significant differences in erosive joint damage.

In the present study the baseline MRI findings were highly correlated with subsequent radiographic progressive joint destruction. This finding is in accordance with previous findings of a predictive value of MRI findings in early [4 14] and established [13 15] RA during conventional DMARD therapy. A predictive value of MRI has, to our knowledge, not previously been demonstrated in patients undergoing treatment with anakinra or other biological therapies.

The present study strongly supports a value of MRI for accelerated assessment of drug effect on structural joint damage and for predicting subsequent radiographic progression.

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TABLES

Table. Clinical, biochemical and imaging parameters before and during anakinra and methotrexate combination therapy.

	Baseline	Week 12	Week 36	Change form baseline to week 36 (No. of patients)		
				Increase	No change	Decrease
Clinical/biochemical parameters						
Erythrocyte sedimentation rate (ESR) (mm/h)	28 (14-54)	20 (5-46); p<0.01	17 (4-84); p=0.06 (NS)	3	2	12
Swollen joint count (0-28)	7 (0-22)	5 (0-10); p<0.05	3 (0-8); p<0.01	4	0	13
Tender joint count (0-28)	10 (3-24)	3 (0-15); p<0.01	2 (0-12); p<0.001	2	0	15
Patient´s global assessment of pain (VAS; 0-100)	69 (30-85)	44 (4-84); p<0.01	44 (6-80); p<0.01	1	0	16
Patient´s global assessment of disease activity (VAS; 0-100)	70 (45-93)	37 (3-87); p<0.05	41 (9-84); p<0.001	2	0	15
Health assessment questionnaire (HAQ)(0-3)	1.75 (0.63-2.75)	1.62 (0-2.38); p<0.01	1.50 (0.25-2.50); p<0.05	1	1	15
DAS28 (ESR-based)	5.6 (3.9-7.2)	4.3 (2.4-6.4); p<0.01	3.8 (2.6-6.6); p<0.01	2	0	15
MRI parameters (non-dominant wrist and 2nd-5th MCP joints)						
Synovitis score (0-21)	11 (3-21)	13 (2-21); p=0.90(NS)	14 (3-21); p=0.22(NS)	4	4	9
Bone edema score (0-69)	5 (0-45)	5 (0-28); p=0.08(NS)	4 (0-27); p=0.06(NS)	1	7	9
Erosion score (0-230)	17 (0-116)	19 (0-124); p<0.01	21 (1-122); p<0.01	12	3	2
No. of bones with erosion (0-23)	10 (0-18)	10 (0-17); p=0.09(NS)	11 (1-18); p<0.05	10	4	3
X-ray parameters (bilateral wrist, MCP and PIP joints)						
Modified Sharp score – total (0-314)	50 (1-233)	Not done	59 (2-243); p<0.03	13	0	4
Modified Sharp score – erosions (0-170)	26 (0-125)	Not done	29 (0-140); p=0.01	11	4	2
Modified Sharp score - joint space narrowing (0-144)	34 (0-108)	Not done	36 (2-103); p=0.86(NS)	9	2	6

Except when otherwise stated, values are medians (ranges). p-values denote changes compared to baseline values (Wilcoxon-Pratt test).
DAS = Disease activity score; VAS = Visual analogue scale; NS = Not statistically significant.

FIGURE LEGENDS

Figure 1. Synovitis, bone oedema and development of new bone erosion in RA finger joint.

MRI of the 2nd MCP joint of a RA patient at baseline (A-E), and MRI (F-J) and conventional PA-radiograph (K) after 36 weeks of anakinra therapy.

Baseline axial and coronal pre- (A&C) and post (B&D)- contrast T1-weighted images show post-contrast enhancement, indicating synovitis, and a STIR image (E) shows high signal intensity in the metacarpal head, indicating bone oedema. No erosions are seen. Corresponding MR images after 36 weeks of anakinra therapy (F-J) show persistent synovitis and bone oedema, and a new MRI bone erosion in the 2nd metacarpal head (arrow). The erosion is seen in 2 perpendicular planes, as required by the OMERACT definition. The corresponding conventional PA radiograph after 36 weeks of anakinra therapy (K) did not visualize any bone erosions.

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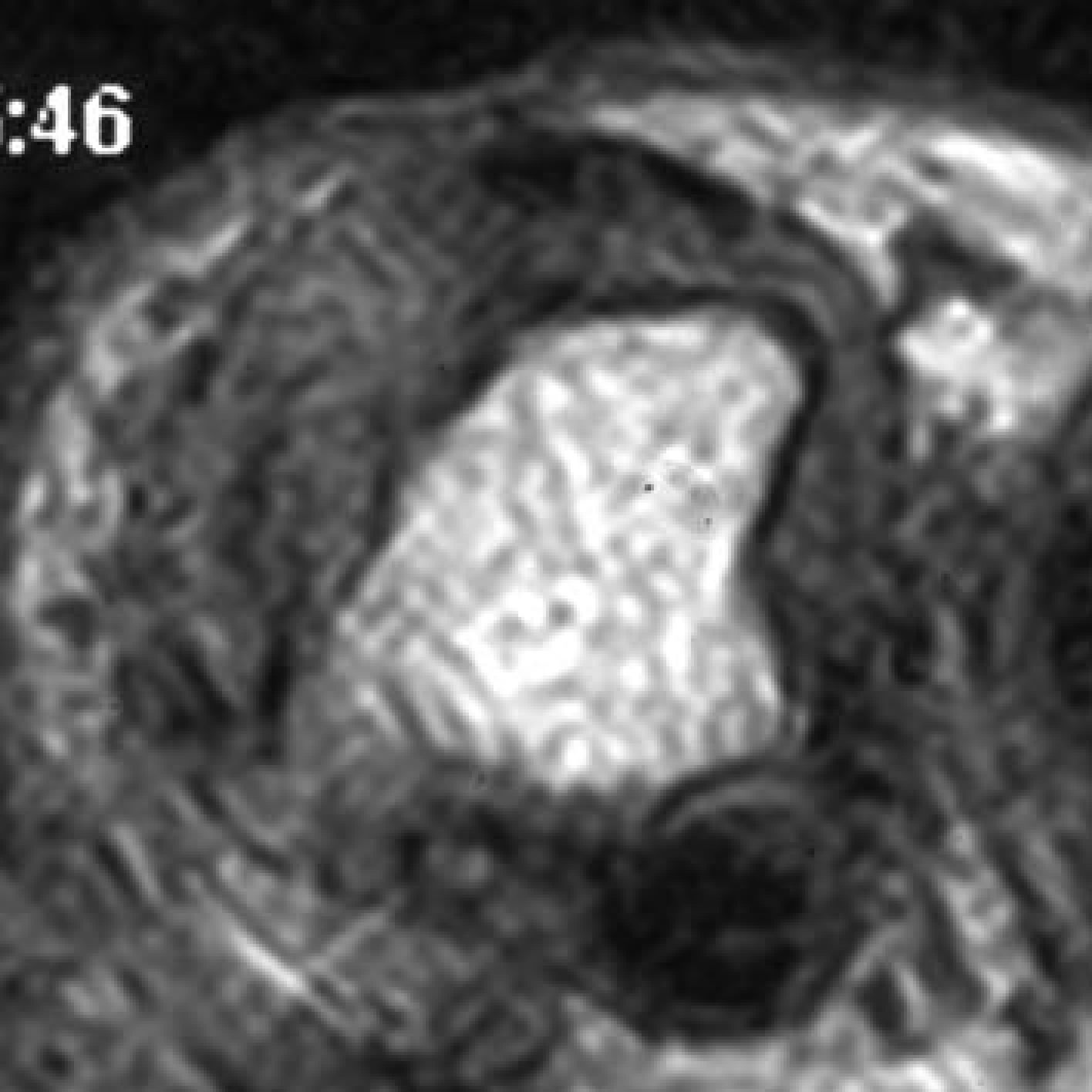
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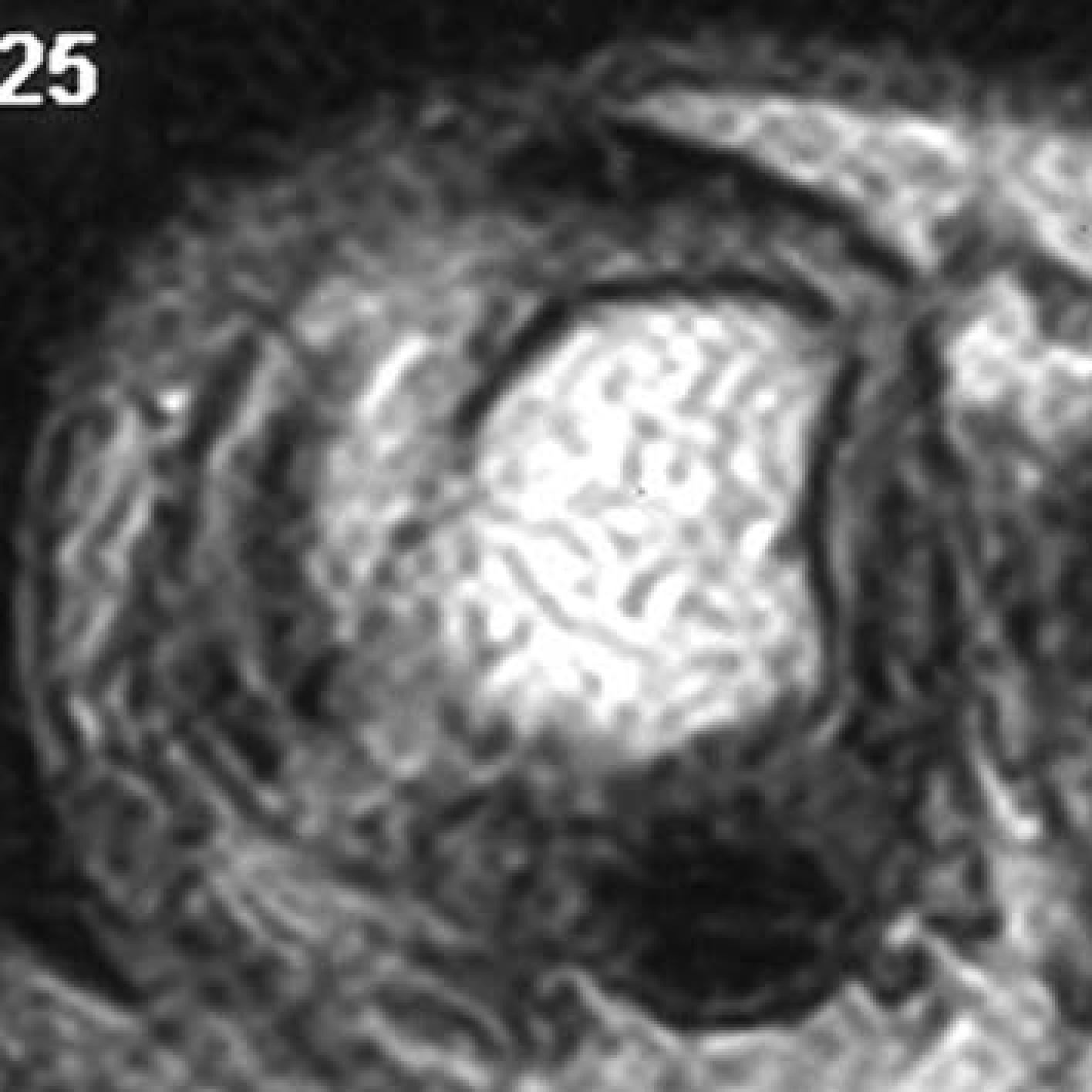
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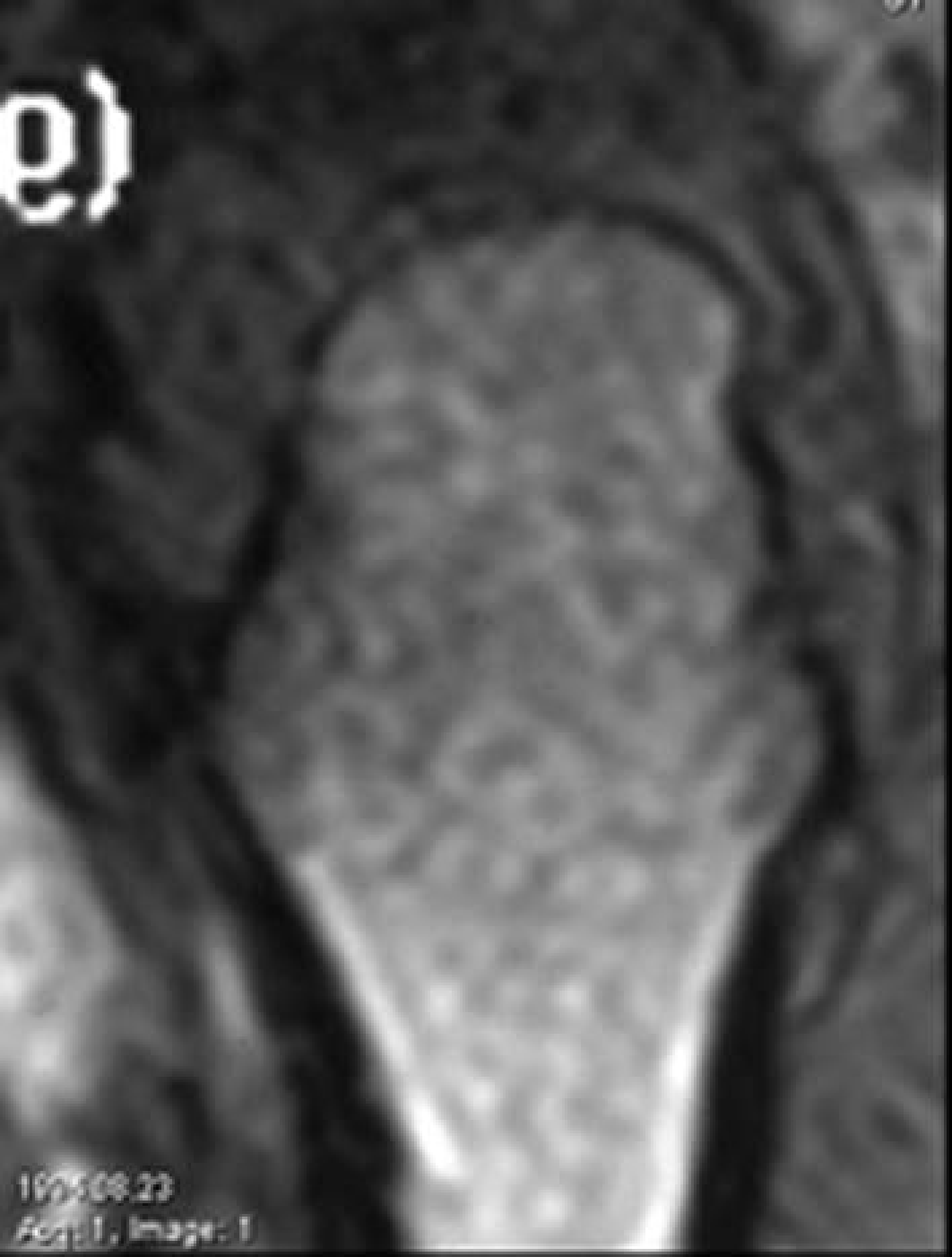

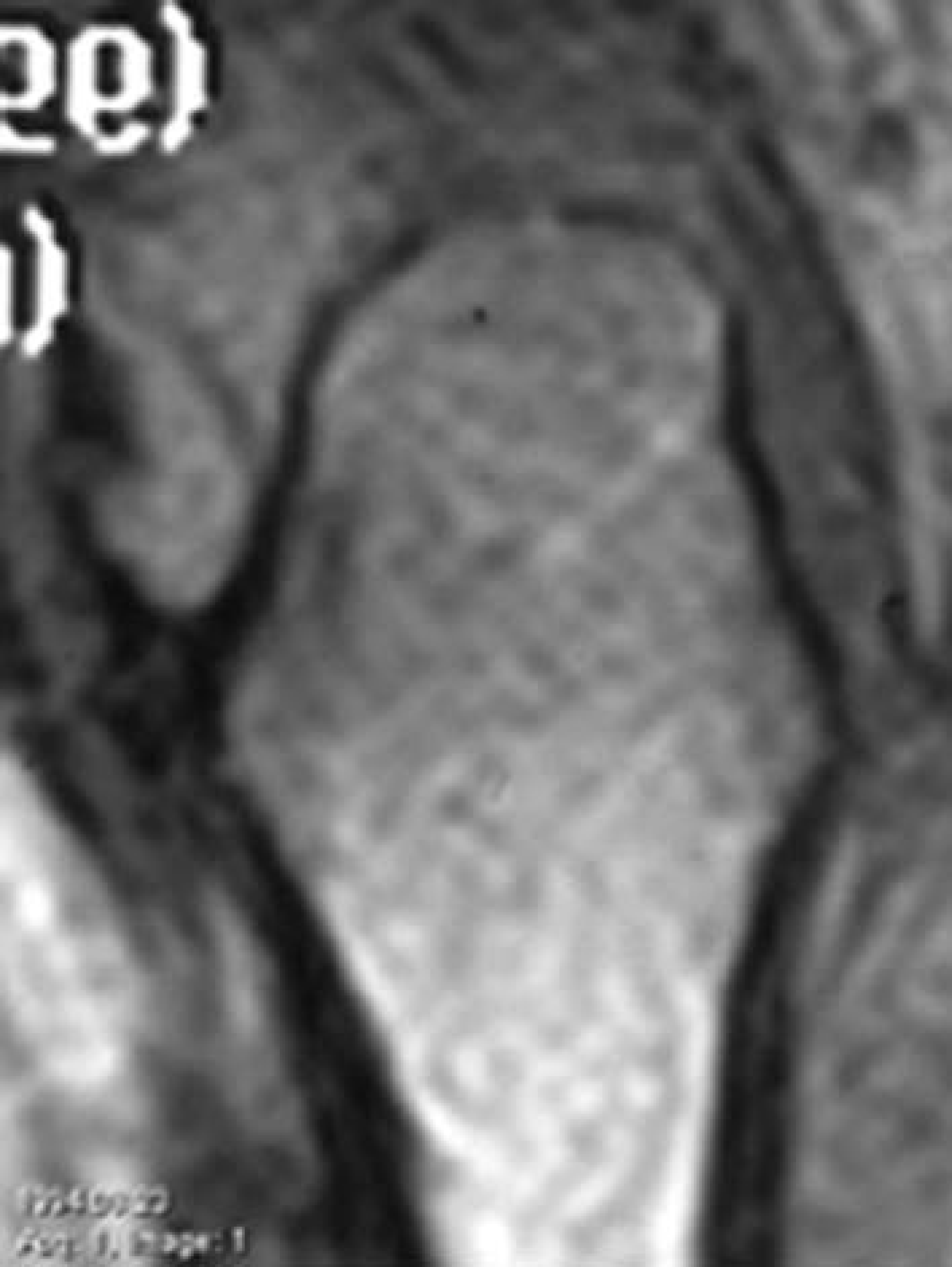

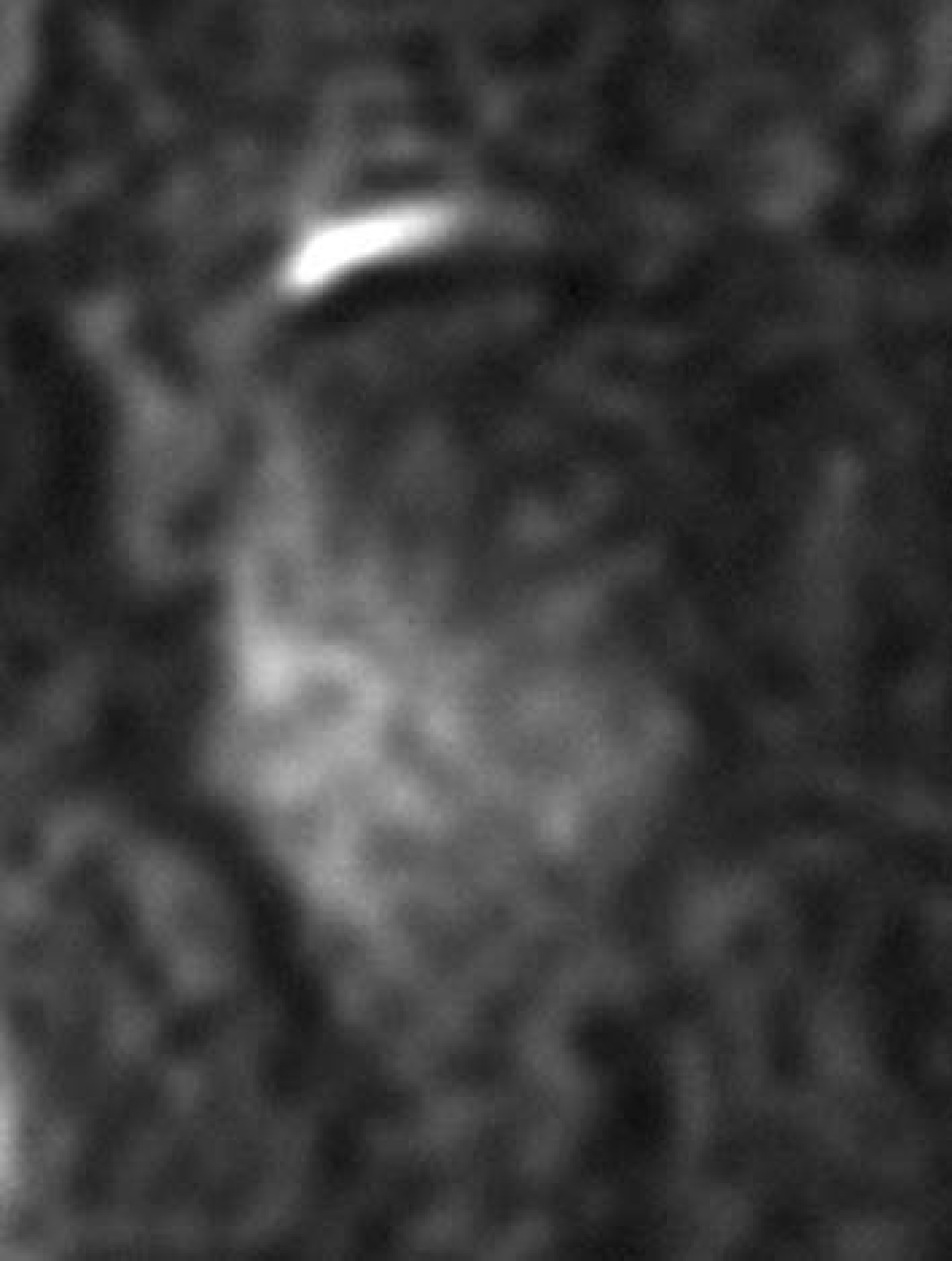

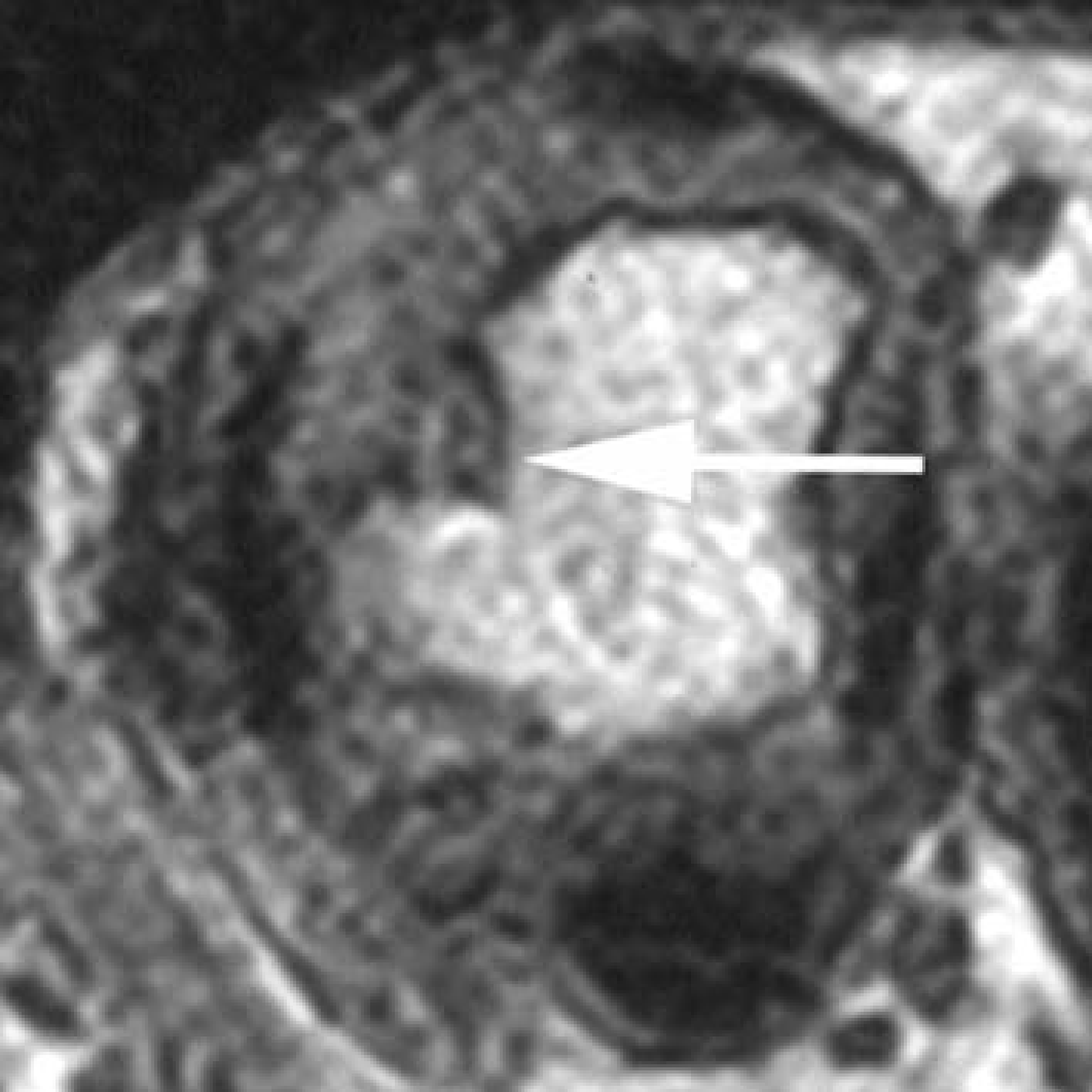

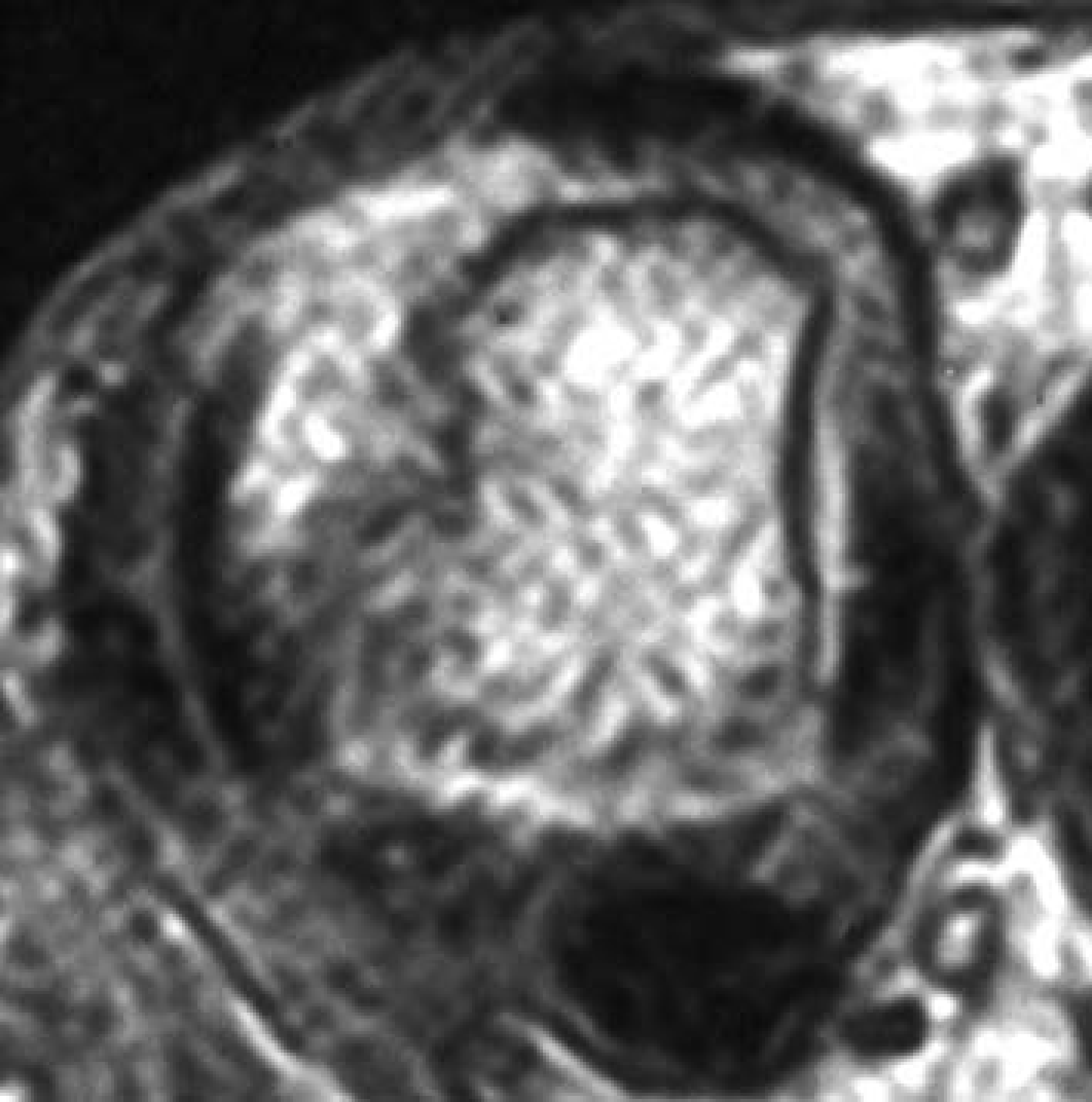

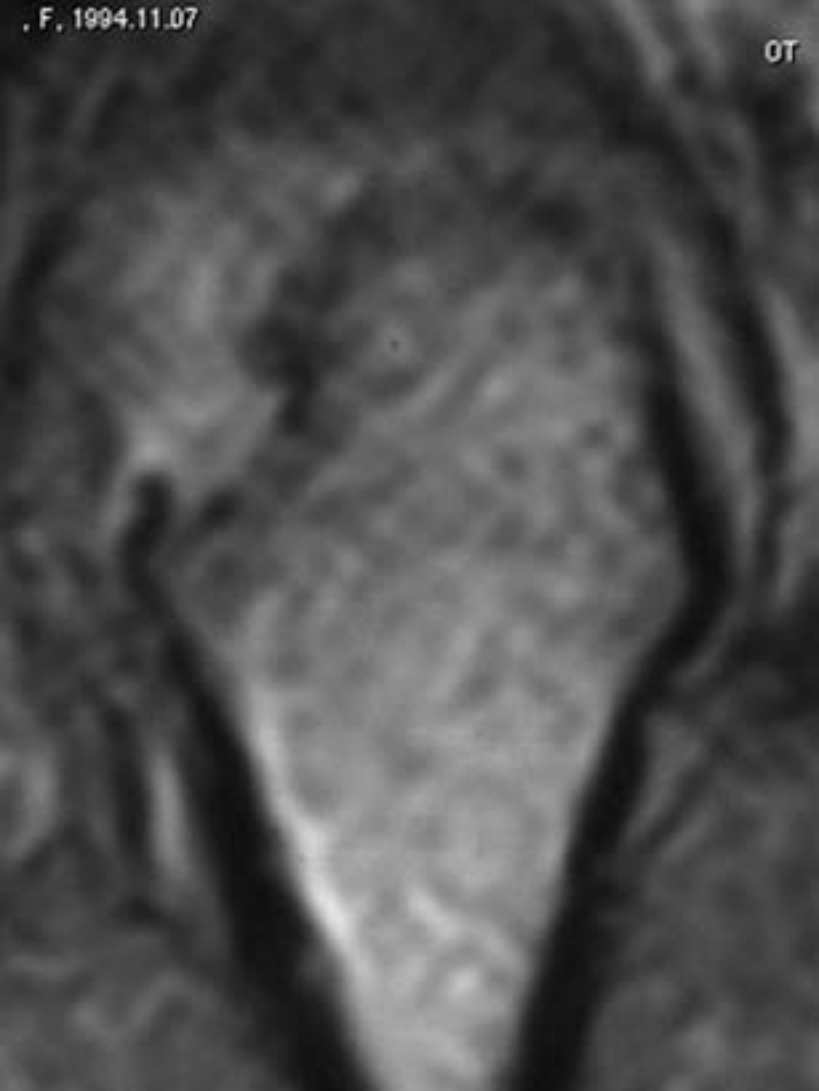
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