Use of contrast enhanced magnetic resonance imaging to detect spinal inflammation in patients with spondyloarthritides

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ABSTRACT

Inflammation of spinal structures is a characteristic feature of the spondylo - arthritides (SpA). The term SpA covers patients with inflammatory back pain and/or peripheral arthritis who can be further categorized. Ankylosing spon - dylitis (AS), the prototype of the SpA, the most frequent inflammatory spinal disease in adults, usually starts in the sacroiliac joints. Pathologic spinal changes occurring in AS are spondyl - itis, spondylodiscitis and inflammation and ankylosis also at other sites in the axial skeleton. In the later stages of AS such changes can be well recognized by spinal x-rays. In the early disease stages it has been more difficult to ana - lyze the exact anatomic localization of spinal inflammation to date, because conventional imaging systems have only a limited capacity to demonstrate such changes early. There is some evi - dence that magnetic resonance imag - ing (MRI) with fat saturation and con - trast enhanced MRI are useful to visu - alize early and late inflammatory changes in the sacroiliac joints. In this paper we report that MRI is also useful to localize the site of inflammation to distinct regions of the spine in AS and other SpA.

Introduction

Inflammation of spinal structures is a characteristic feature of the spondyloarthritides (SpA). This heterogenic group of diseases has recently been shown to have a high prevalence (1), also in primary care settings (2). The term SpA covers patients with the leading symptoms of inflammatory back pain (IBP, 3) and/or peripheral arthritis, predominantly of the lower limbs (4), who can be further categorized as ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel diseases (IBD) and undifferentiated SpA (uSpA) (5). The pathogenesis of the SpA is not known; current hypotheses include the remarkable association with HLA B27, possibly triggering bacterial infections and autoimmunity (6).

AS, the prototype of the SpA, is the most frequent inflammtory spinal disease in adults (7). Frequently running a chronic course AS usually starts in the sacroiliac joints (SIJ) early in disease (8) and tends to involve other parts of the axial skeleton later on. Accordingly, IBP, most frequently located at the lower part of the back, partly as alternating buttock pain, may also diffusely spread to other locations in the spine, typically causing pain at night (4).

While recently developed biopsy techniques have allowed some new insights in the pathogenic changes occurring in the sacroiliac joints (9,10), our knowledge about the possibly involved spinal sites in AS comes mainly from histologic post mortem studies performed decades ago, where some evidence was accumulated to confine the early spinal lesions in AS to ligamentous and discal structures (11), which may give rise to discal and vertebral destruction and ankylosis later on (12).

These pathologic spinal changes are well known as spondylodiscitis (Andersson lesion, 13) and spondylitis anterior (Romanus lesion, 14). In later stages of AS such changes are well recognized by spinal x-rays (15), but also by computed tomography and MR imaging (reviewed in 16, 17).

In early disease stages it has been more difficult to analyze the exact anatomic localization of spinal inflammation to date, because clinical examination and the available imaging systems such as conventional x-rays, computed tomography and nuclear devices have only limited capacity to demonstrate such changes early (18). There is some evidence that magnetic resonance imaging (MRI, 19) and, as recently described, contrast enhanced MRI (20-23) are

useful to visualize early and late inflammatory changes in the sacroiliac joints. Here we present our cumulative experiences with MRI from 1994-1998 used to localize the site of inflammation to distinct regions of the spine.

Patients and methods

All together 335 patients with spondyloarthritis (SpA) who presented to the outpatient clinic of the University hospital complaining about inflammtory back pain localized to the vertebral column were examined by contrast enhanced MRI. History, clinical examination and measurement of C-reactive protein levels (CRP, normal < 6 mg/l) MRI of the sacroiliac joints were determined in all patients; these data have already been published elsewhere (21, 22). The patients' characteristics are given in Table I.

Contrast enhanced MRI of the lower lumbar spine was performed in all patients. Conventional x-ray films of the spine were obtained in parallel in all 25 patients with MR imaging proven spondylitic and spondylodiscitic lesions and were evaluated together by three radiologists (M.B., C.E., M.T.) blinded to the clinical data and to the MRI findings.

In addition, in 30/100 AS patients with spinal pain received conventional x-ray and MR imaging of the whole spine.

The following diagnostic criteria were applied: for patients with ankylosing spondylitis (AS) the modified New York criteria (24), for patients with undifferentiated spondyloarthritis (uSpA), inflammatory bowel disease (IBD), reactive arthritis (ReA) and for patients with psoriatic arthritis (PsA), in the presence of typical skin lesions, the ESSG criteria (4).

Magnetic resonance imaging

MR imaging examinations of the sacroiliac joints and the lower lumbar spine were performed with a 1.5 Tesla Magnetom Vision (Siemens Erlangen, Germany) using the body-array-coil. Using the standard protocol for detecting sacroiliitis recently described (20-23) an evaluation of the caudal lumbar segments L4/5 and L5/S1 was performed.

Additional in 30 AS patients the whole spine was examined using the spine-coil. The sequences used in sagittal orientation were as follows, possible advantages of each sequence are given in short form in brackets.

- T1-weighted spin echo (SE) sequence: repetiton time (TR) / echo time (TE) 500/14 ms, slice thickness (SL) 3-4 mm, 2 acquisitions (Ac) (standard T1-weighted spin echo MR images provide good anatomic detail and high contrast between hypointense disk cartilage and hyperintense subchondral bone marrow. Inflammatory changes show hypointens signal intensity)
- T1-weighted turbo(T)-SE-sequence: TR/TE: 640/12 ms, SL 3-4 mm, 4 Ac (faster imaging and higher resolution compared to conventional spin echo techniques. Using fat-suppression technique in postcontrast examinations better contrast between dark bone marrow and enhancing regions of bone marrow edema or inflammation reveals)
- T2-weighted TSE-sequence: TR/TE: 4000/120 ms, SL 3-4 mm, 4 Ac (Fast imaging and high resolution. Hyperintense signal intensity imaging of liquor, gelatinous nucleus pulposus of the disks and of inflammatory tissues)
- short-tau-inversion-recovery-sequence (STIR): TR/TI/TE: 4000/150/60 ms, SL 3-4 mm, 1 Ac (excellent imaging of edematous and/or inflammatory tissues: a short inversion time {TI} is used to create an image where the net longitudinal magnetization of fat is a minimum; therefore, the STIR sequence nullifies the signal from fat: normal fatty bony marrow appears dark. The T1 and T2 contrast of other tissues is additive; therefore, contrast between areas with high concentrations of free water {like inflammation, edema or tumor} and normal tissues is greatly enhanced (25).
  After application of Gadolinium-DTPA 0.1 mmol/kg body weight the previously used T1-weighted TSE-sequence was repeated.

The MRIs were evaluated together by three experienced radiologists (M.B., C.E., M.T.), blinded to the clinical data and to the x-ray results.

Results

Definite signs of actual inflammatory involvement of spinal regions as visualized by contrast enhanced MR imaging were obtained in altogether 25/341 SpA patients and 67 acute inflamed discovertebral levels were identified (Table II).

The spondylodiscitic lesions in 25 SpA patients were characterized by hyperintense discovertebral end-plate changes in T2- and STIR-weighted images and by hypointense discovertebral end-plate changes in noncontrast T1-weighted images. Greater lesions showed demarcation by adjacent low signal rims corresponding to sclerotic changes (Figures 2 and 3). Significant enhancement of the contrast agent gadolinium-DTPA was demonstrated in the disc

Table I. Patient characteristics.

Diagnosis	n	m/f	Mean age years (range)	Disease duration years (range)		HLA B27+ %	
uSpA	111	1.1	38.7	(21-57)	5.3	(0.3-16)	68.2
ReA	15	1.1	42.3	(29-51)	4.3	(0.8-10)	67.6
PsA	52	0.8	49.1	(23-71)	10.4	(0.4-41)	46.3
IBD	63	1.4	43.1	(16-73)	10.2	(0.3-35)	19.7

Diagnosis	n	Sacroiliitis (n) MRI findings	%	Spondylitis (n) MRI findings	%
uSpA	111	87	78.4	8	9.2
AS	94	94	100	12	12.8
ReA	15	67.6	7	46.7	0
PsA	52	19	36.5	2	10.5
IBD	63	13	20.6	0	0

Table II. Inflammatory spinal regions (n = 67) as visualized by contrast enhanced MR imaging were obtained in 25/335 SpA patients.

Patient initials	Sex (m/f)	Age years	Diag-nosis	HLA B27 (+/-)	DD years	CRP mg/l	phytes: X-ray findings (+/-)	Syndesmo-Sacroiliitis MRI grading	Spinal MRI findings acute inflammation	n: pathologic levels
1. IP	f	39	AS	+	19	35	-	IVx/IVx	spondylitis ant./post. spondylodiscitis	21: from C7/TH1 up to S3/4: 4: TH6/7, L1/2, L2/3, L3/4
2. CW	m	24	AS	+	7	6	+	IIIb/IIIb	sponylitis anterior spondylodiscitis	3: L2/3, L3/4, L5/S1 2: TH12/S1, L1/2
3. MA	m	37	AS	+	7	29	+	IVx/IVx	spondylitis anterior spondylodiscitis	2: TH7/8, L2/3 2: TH11/12, L5/S1
4. CU	f	46	AS	+	11	12	-	IIIb/IIIb	spondylitis anterior spondylodiscitis	2: TH10/11, L1/2 1: L4/5
5. KR	m	39	AS	+	10	11	-	IIIa/IIIb	spondylitis anterior	1: L1/2
6. LL	m	52	AS	+	15	18	+	IVx/IVx	spondylodiscitis	2: L4/5, L5/S1
7. MQ	f	47	AS	+	16	6	+	IVb/IVa	spondylodiscitis	2: L4/5, L5/S1
8. HK	m	64	AS	+	12	35	+	IVa/IVx	spondylodiscitis	2: L4/5, L5/S1
9. SJ	f	25	AS	+	6	6	-	IIIa/IIIb	spondylodiscitis	1: L4/5
10. AR	m	38	AS	+	10	21	+	IVx/IIIb	spondylodiscitis	1: L5/S1
11. PP	m	58	AS	+	25	16	+	IIIb/IIIa	spondylodiscitis	1: L5/S1
12. JS	m	25	AS	+	8	6	+	IVa/IVx	spondylodiscitis	3: TH11/12, TH12/L1, L1/2
13. WT	m	55	AS	+	25	20	+	IVx/IVx	spondylitis posterior spondylodiscitis	1: TH 1/2 1: TH 1/2
14. BB	m	27	AS	+	5	6	-	IIIb/IIIb	spondylitis anterior	2: L1/2,TH12/L1
15. NR	w	27	AS	+	8	16	-	IIIb/IIIb	spondylitis anterior	2: TH10/11, TH12/L1
16. GR	m	46	uSpA	+	6	8	-	Ib/IIx	spondylodiscitis	1: L5/S1
17. AS	m	28	uSpA	+	3	9	-	Ib/0x	spondylodiscitis	1: L5/S1
18. PH	m	39	uSpA	+	2	13	-	0x/0b	spondylodiscitis	1: L5/S1
19. EP	f	42	uSpA	+	1	12	-	0b/0b	spondylodiscitis	1: L5/S1
20. JD	f	47	uSpA	+	1	17	-	0a/0b	spondylodiscitis	1: L5/S1
21. KS	f	26	uSpA	+	4	40	-	Ib/Ia	spondylodiscitis	1: L5/S1
22. NG	m	47	uSpA	-	1	34	-	IIb/0x	spondylodiscitis	1: L4/L5
23. CM	f	48	uSpA	-	2	24	-	IIx/Ib	spondylodiscitis	1: L5/S1
24. SW	f	35	PsA	+	7	18	-	Ib/Ib	spondylodiscitis	1: L5/S1
25. LM	m	34	PsA	+	6	33	-	0a/0b	spondylodiscitis	2: L4/5, L5/S1

pat.: patient, DD: disease duration, AS: ankylosing spondylitis, uSpA: undifferentiated spondyloarthropathy, PsA: psoriatic arthritis
MRI: magnetic resonance imaging. ant.: anterior, post.: posterior.

and the adjacent vertebral plates at the level L4/5 and/or L5/S1 in 18/25 patients (Table II). MR imaging revealed 33 active spondylodiscitic lesions corresponding to inflammatory Andersson lesions only in those 22 SpA patients, who also had MR imaging evidence of sacroiliitis: 18/100 AS patients (18%), 8/87 uSpA patients (9.2%), 2/19 PsA patients (10.5%), none of 13 patients with IBD, and none of 7 patients with ReA. 8/25 patients showed normal x-ray appearance of the spine, 7/25 showed indicative disc space narrowing and 10/25 revealed significant chronic x-ray changes like syndesmophytes and/or segmental ankylosis.

Inflammations of the entire anterior and posterior ligaments, combined with spondylitis anterior and posterior at 21 discovertebral lesions, partly evolving into early syndesmophytes were seen in one AS patient presented in Figure 1. Circumscribed contrast enhancing inflammations of the anterior ligaments corresponding to 13 spondylitic anterior lesions (Romanus lesions) revealed in further 7 AS patients (Table II), four of whom had normal x-rays.

The patients shown in Figures 2 and 3 had the most impressive findings of spondylodiscitis in MR imaging. Both had had severe IBP for months despite treatment with high doses of indomethacine (>200 mg/day). They were two of five patients, who were treated with a combined CT- and fluoroscopy-guided intradiscal steroid injection and underwent MR follow-up 5-11 months after intervention. The five patients reported significant improvement of back pain, starting after 2 days at the

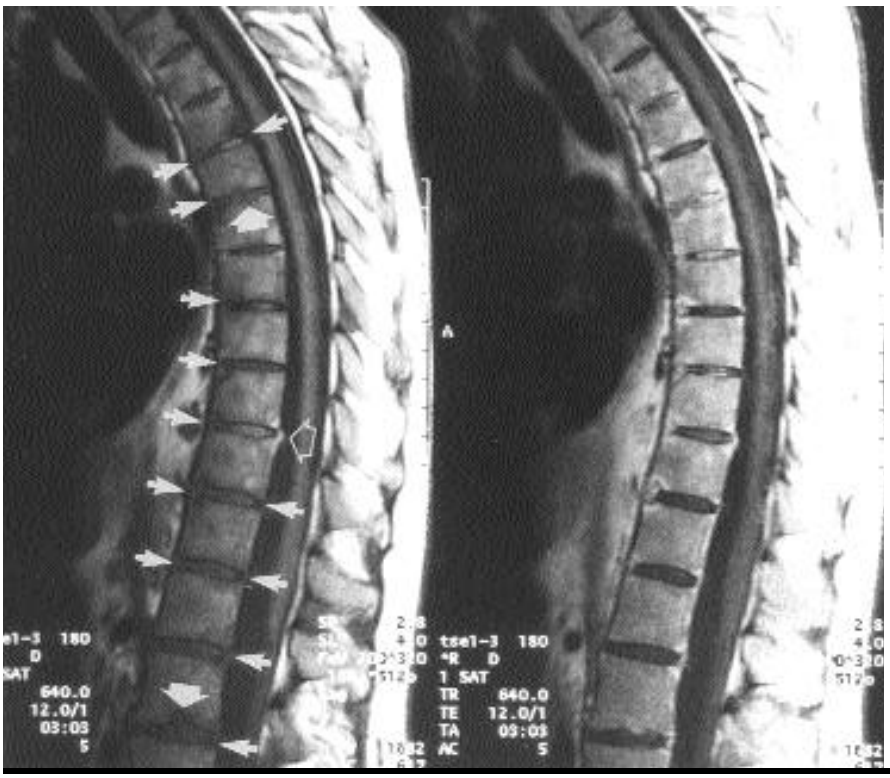


Fig. 1. Patient I.P., female, 39 years-old, ankylosing spondylitis, disease duration 19 years, severe inflammatory back pain located over the whole spine. Severe spondylitis anterior and posterior (spondylitis marginalis) of the thoracic, lumbar and sacral spine and spondylodiscitis in discovertebral segments TH6/7, L1/2, L2/3 and L3/4.
(a) (left) In this noncontrast T1-weighted turbo-SE-sequence (TR/TE: 640/12 ms) several rims and edges of the thoracic spine vertebral bodies show low signal intensity (arrows) not only in the ventral (spondylitis anterior) but also in the dorsal parts (spondylitis posterior) in proximity of the longitudinal ligaments.
(b) (right) After Gd-DTPA-application the multiple spondylitic lesions show significant enhancement. In the dorsal part of segment TH 10/11 bony proliferations to be interpreted as early syndesmophytes show high signal intensity but no contrast enhancement (open arrow). The closed arrows mark spondylodiscitic lesions with contrast enhancement of the discovertebral levels TH6/7 and L2/3. The spondylodiscs of the discovertebral segment L1/2 is not shown in this slice position.

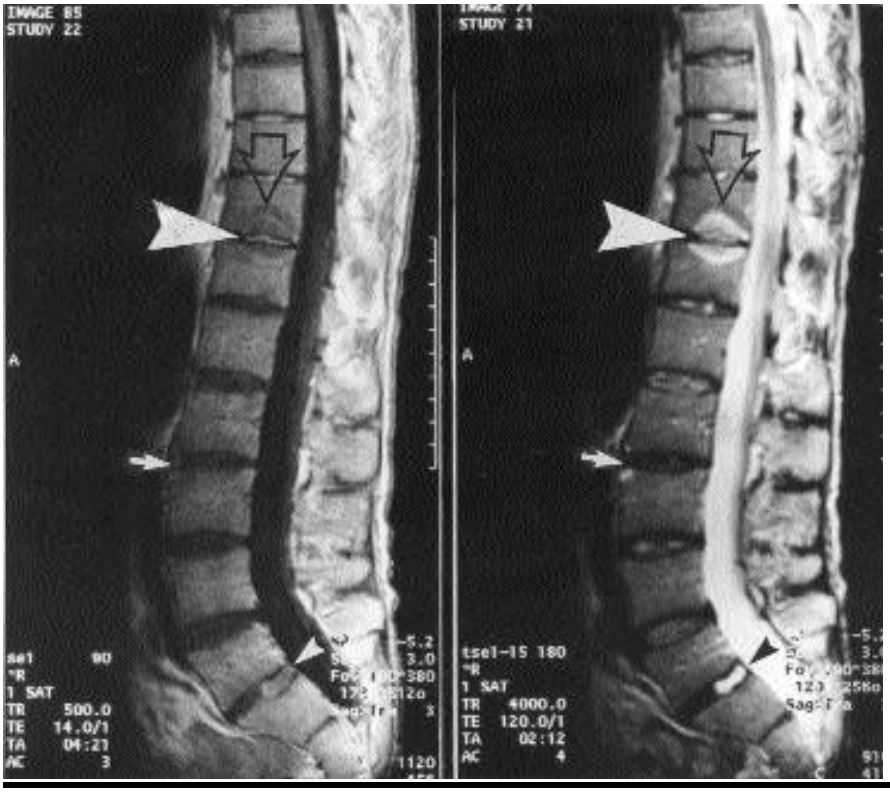
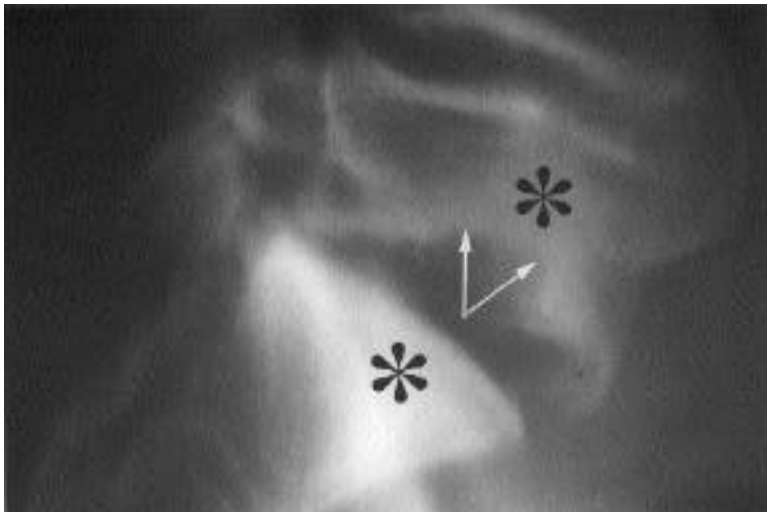


Fig. 2. Patient M.A., male, 37 years-old, ankylosing spondylitis, disease duration 7 years, severe inflammatory back pain, mainly in the thoracolumbar transition. Severe spondylodiscitis at TH11/12 and at L5/S1. Spondylitis anterior at L2/3
Noncontrast T1-weighted SE-sequence (TR/TE: 500/14 ms) **Fig. 2a (left)** and T2-weighted turbo-SE-sequence (TR/TE: 4000/120 ms) **Fig. 2b (right)** in sagittal orientation and 3 mm slice thickness: hemispheric changes of the discovertebral complex of TH 11/12 (**large arrowhead**) and of the dorsal part of the intervertebral disk L5/S1 (**small arrowhead**) with respectively hypointense to intermediate signal intensities and homogen enhancement after contrast agent (not shown) using T1-weighted images and hyperintens signal intensities using T2-weighted images. Important findings are the low signal rims in the T1-weighted images as well as in the T2-weighted images adjacent to the lesion at the level TH11/12 corresponding to sclerotic changes (**black open arrows**). Detection of contrast enhancing (not shown). Opposite ventral edges (Romanus lesion) of the vertebral bodies of L2 and L3 showing low signal intensities in the noncontrast T1-weighted image (**arrow in fig. 2a**) and high signal intensities in the T2-weighted image (**arrow in fig. 2b**).

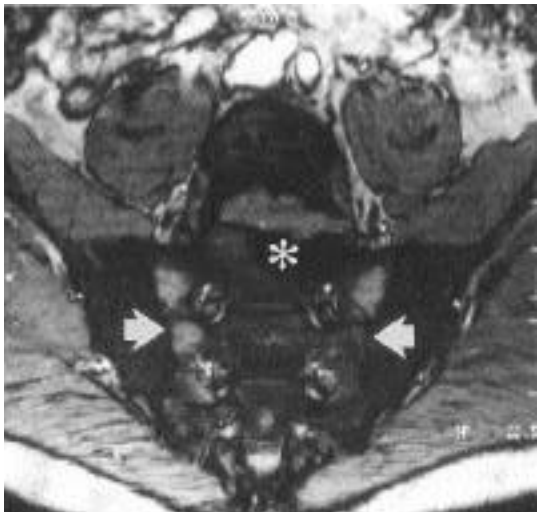
latest; no side effects of the spinal interventions were observed.

Discussion

This study provides evidence that contrast enhanced MR imaging of spinal sites is useful to localize spinal inflammation in SpA patients, even in early disease stages. The here presented examples of spinal MR images document the capacity of this method to visualize spondylodiscitis and spondylitis anterior and/or posterior: the inflammatory changes have been observed by a decreased signal on T1-weighted and increased signal on T2-weighted and STIR sequences and clear-cut enhancement was demonstrated in 25 SpA-patients. Altogether 33 acute spondylodiscitic lesions in 22 SpA patients and 34 acute spondylitic lesions (both,



(a)



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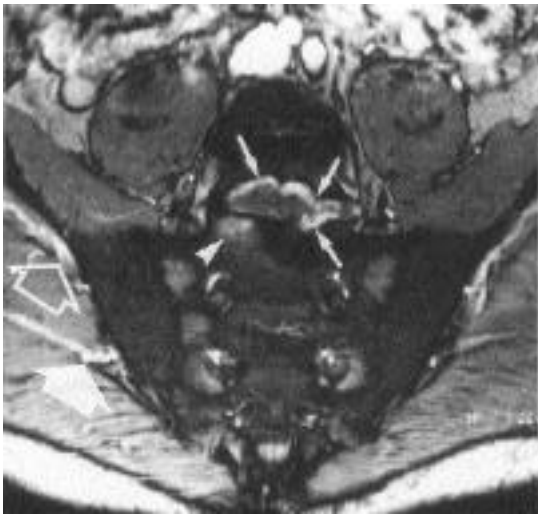
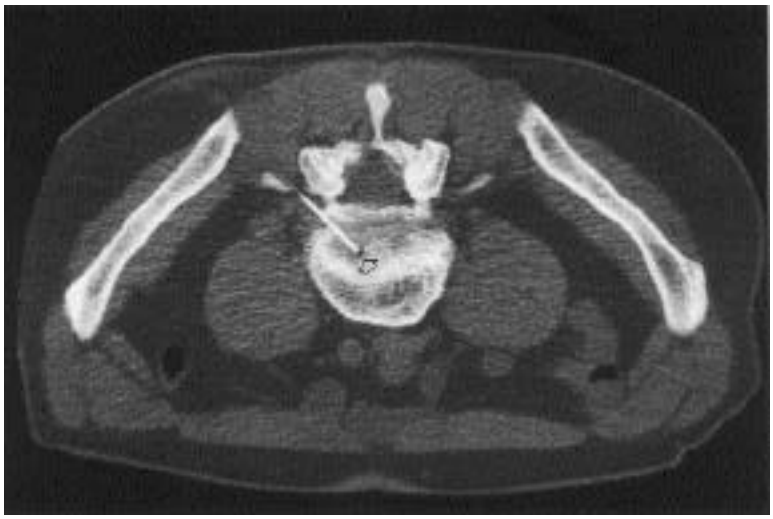
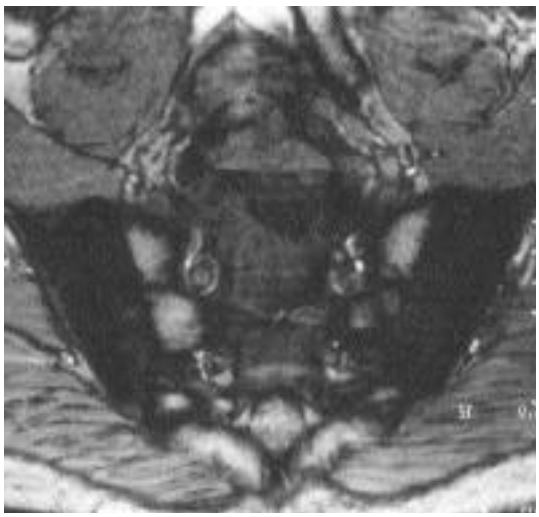


(c)



(d)



(e)

Fig. 3. Patient L.L., male, 52 years-old, ankylosing spondylitis, disease duration 15 years, severe back pain. Spondylodiscitis L4/5 and L5/S1.
(a) Conventional tomography of L5/S1,lateral view, in hypocycloidal blurring-technique, slice thickness 0.5 cm: Sclerotic changes in the end plates of the discovertebral segment L5/S1 (**asterisks**). Destructive erosions of the inferior rim of L5 (**arrows**) at the discovertebral transition; ventral fusion of L4/5 by pontificating syndesmophytes.
(b) The precontrast T1-weighted GE image (TR/TE: 50/12 ms, 70º) shows structural changes of low signal intensity in regions of the ankylosed sacroiliac joints (**arrows**) corresponding to calcified fibrous tissue. The regions of high signal intensity in the sacrum are periarticular fat accumulations. Regions of low signal intensity in the 1. sacral vertebra (**asterix**) and proximal to the basis of the 5. lumbar vetebra correspond to the known sclerosions. Irregular destructions of the disk space are visible at the discovertebral complex of L5/S1.
(c) The postcontrast image (T1-weighted GE-sequence:TR/TE 50/12 ms,70º; same slice position as Fig. 3b) 4 minutes after Gd-DTPA-bolus shows a strong marginal enhancement in the erosive discovertrebral transition zones (**small arrows**) and juxtaarticular in the sacrum (**arrowhead**). The big arrows mark the enhanced right-sided vasa glutaea superior (**open arrow**) and inferior (**closed arrow**).
(d) Combined CT- and fluoroscopy-guided punction of the intradiscal space of L5/S1 with a 0.8 mm coaxial-needle (**open arrow** = tip of the needle), followed by injection of 60 mg of triamcinolone acetonide into the disk.
(e) MR imaging follow-up 4 months after the intradiscal corticosteroid-injektion: In a postcontrast image (T1-weighted GE-sequence: TR/TE 50/12 ms, 70º) of a similar position as in Fig. 3c no enhancement appeares 4 minutes after the Gd-DTPA bolus.

anterior and posterior) were detected in 8 SpA patients. Although we have not compared our results to scintigraphy in parallel, we are not in doubt that contrast enhanced MR imaging provides superior imaging because the technique allows for almost anatomical visualization of the involved structures and, in parallel, similar to what we found in the scroiliac joints (20-23), demonstration of contrast enhancement allowing for differentiation of acute and chronic changes at one time. While the avoidance of ionizing radiation is a clear advantage, the timing and the costs of the procedure are still a problem in the era of retrenchment.

Our results confirm and exceed in some points of previous studies on AS patients (27, 28), and several other studies on spinal pathology of different origin such as Modic type I end plate changes assoziated with early degenerative disk disease (29), spondylodiscitis in the SpA-related SAPHO syndrome (30), hemodialysis associated destructive spinal disease (31), and especially in pyogenic disk space infection (32-35).

It is still not clear, what the histomorphologic equivalent of the contrast enhancement in inflamed spondylitic or spondylodiscitic structures is. One possible cause is hypervascularization occurring in pannus areas as shown in rheumatoid synovitis (36), in Modic type I end plate changes (29) and especially in erosive osteochondrosis (37) due to fissuring and disruption of the end plates due to vascularized fibrous tissue within the adjacent bone marrow and the degenerative disc spaces. However, these have not been histopathologically demonstrated in spinal inflammation of SpA patients to date.

Spondylodiscitis, originally described by Andersson in 1937 (13), was divided in two forms by Dihlmann and Delling in 1978 (38), who differentiated the inflammatory form, also described in this study, from a noninflammatory type due to osteoporotic fractures which are known to occur with an increased frequency in AS patients (39). According to a recent report (40) spondylodiscitis occurs in 15% of AS patients. This study suggests that spondylodiscitis might occur, in the presence and absence of spondylitis,more frequently than previously thought and that not only AS- but also uSpA patients, who might develop into AS later on (41), are prone to get it. The high frequency of unrecognized spondylodiscitis is interesting, since it it might suggest that the discs are a predominant origin of spinal inflammation in AS. Spondylodiscitis remains clinically often unrecognized, as also noticed in the above cited cross sectional study in which spinal x-rays were used for detection (40). However, the reason why most cases in this large series were asymptomatic seems quite obvious, since conventional radiography, as discussed above, can mainly detect definite structural changes of the vertebral bone and not early inflammation. The capacity of MR imaging to detect spondylodiscitis earlier than x-rays has also been described by others (27, 28). However, in these studies no contrast agent was used. As recently described, contrast enhanced MR imaging (20-23) are useful to visualize kindred inflammatory changes in the sacroiliac joints, the use of gadolinium-DTPA seems to be very useful to detect spinal inflammation, too.

Definite structural changes of the vertebral bone also occur as spondylitis anterior described by Romanus decades ago (14). Now, by MR imaging technology the state of activity of spondylitic lesions becomes accessible. This is of particular interest since it allows to learn more about the natural course and development of these lesions in the future. Mainly on the basis of J. Ball's histologic work (11) it can be assumed that the initial inflammatory lesion in the spinal stage of AS is the region where the disc, the anterior ligament and the edge of the vertebral body meet; this has been interpreted as a form of enthesopathy of the spine. Such early lesions may thereafter cause inflammation at the edge of the vertebral body, this has been referred to as spondylitis anterior. By conventional radiography these regions often show features of sclerosis and, less frequently, of erosions. Later on, syndesmophytes seem to start growing from these lesions and ossification of the anterior ligament develops. All these stages are present in the patients documented in this study. What was not so clearly known before is that posterior vertebral structures are involved in a similar way as the anterior ones: spondylitis posterior, inflammation and calcification of the posterior ligament and posterior syndesmophytes can be seen. Occurrence of the latter has also been recently described in a case report (42).

From these MR imaging data it seems that early spinal lesions in AS mainly involve discal structures and vertebral edges and rims, while involvement of cartilage and the subchondral bone occurs secondarily. This is less clear in the sacroiliac joints, where the subchondral bone might be involved earlier (43).

The MR images provide evidence that new bone formations occur in parallel to ongoing inflammations. The visualization of this crucial pathologic event in the pathogenesis of AS reminds us that the causal factors involved have not yet been characterized. Especially, the link between inflammation and ossification is poorly understood. We have proposed that TNF-α might play a role (8) in this debiliating scenario and there is reason (44) to believe that other growth factors of the TGF superfamily such as the bone morphogenetic proteins (45) are also involved.

In respect of the differential diagnosis of spondylitis and spondylodiscitis we have, similar to Kenny *et al.* (27), limited evidence to think that neither MR imaging nor CT are specific in their diagnosis of spondylitis / spondylodiscitis in early disease stages. However, it is possible to differentiate between spinal inflammation in SpA and spondylitis/ spondylodiscitis of infectious origin, if the bacterial infection has already spread to structures in the proximity (32-35). This non-confinement to anatomical borders does generally not occur in SpA.

What else is the clinical impact of the impressive capacity of MR imaging technology to visualize spinal inflammation? Mainly SpA patients with severe spinal pain lasting > 4 weeks seem to be candidates for MR imaging. Since the ability of conventional x-rays to show spinal changes in the thoracic spine is rather limited, MRI will proba-

bly emerge as the method of choice to detect spinal inflammation in that region, both in clinical practice and in clinical studies (46).

The new options of spinal imaging in AS described in this study have implications for the future search for innovative therapies in AS. So far we have treated 5 patients with painful spondylodiscitis with intradiscal corticosteroid injections with symptomatic success and with, so far, no side effects. Of interest, the MR imaging follow up also showed clear improvement of discal inflammation in all 5 patients. Due to the limited numbers no general recommendation for therapy can be given so far. However, a systematic randomized placebo controlled study will be difficult with this technique, but Maugars and colleagues recently managed to do this in patients with sacroiliitis (47), hereby confirming previous results obtained in open studies (23, 48).

Furthermore, there are now several studies indicating that anti-TNF therapy is very useful in SpA(49-53). In 3 of these MRI was used to detect spinal inflammation (49-52). Clearly MRI of the spine may also be useful to certify AS patients as candidates for anti-TNF therapy. This important question needs further study.

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