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ORIGINAL ARTICLE

Bone scintigraphy in axial seronegative spondyloarthritis patients: role in detection of subclinical peripheral arthritis and disease activity

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Abstract

Aim: To detect subclinical peripheral arthritis and disease activity in axial seronegative spondyloarthritis (SpA) patients using bone scintigraphy.

Methods: Seronegative SpA patients with an established diagnosis and no clinically evident arthritis at the time of the study were included. After excluding symptomatic cases, 20 patients were recruited; 18 with ankylosing spondylitis (AS) and another two with psoriatic arthritis (PsA). Conventional bone scintigraphy was performed to detect the distribution of increased uptake, blood vascular pool (vascularity) and activity.

Results: The peripheral joints in all the patients were asymptomatic with no signs of arthritis on clinical examination. Disease activity was higher in those with hypervascularity and activity (75%) detected by scintigraphy. Scintigraphic activity of the sacroiliac joints was found in 10 patients (50%) with a mean sacroiliac joint index of 2.4 $\pm$ 0.6. Subclinical involvement of the hips, knees, shoulders, ankles, small joints of the hands, ankles and sternoclavicular joints, as well as the small joints of the feet were detected with descending frequencies (25%, 25%, 20%, 20%, 15%, 10% and 10%, respectively). Dorsal spine increased uptake was found in 35% and hypervascularity of the skull in two cases. Avascular necrosis of the hip was present in one case with hypovascularity.

Conclusion: The spectrum of joint involvement in seronegative SpAs should not be limited to sacroiliitis. Bone scintigraphy provides a cost-effective method for detecting the extent of involvement in this group of autoimmune systemic diseases (axial SpA) without clinical evidence of peripheral arthritis.

Key words: ankylosing spondylitis, bone scintigraphy, psoriatic arthritis, seronegative spondyloarthritis.

INTRODUCTION

The concept of spondyloarthritides (SpAs) comprises a group of interrelated disorders.[1] The clinical spectrum of SpAs comprises ankylosing spondylitis (AS) and psoriatic arthritis (PsA) and has been expanded to include even clinical disorders without any involvement of the axial skeleton.[2]

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Ankylosing spondylitis is a chronic inflammatory autoimmune disorder that predominantly affects the spine,[3] with prevalence between 0.1–0.9%.[4] Immune dysfunction is the hallmark of this condition and if untreated may cause significant morbidity.[3] At least 30% develop severe spinal restriction during the natural course of the disease.[5] In addition to the spine, large joint synovitis and enthesitis may develop. A proportion of patients respond well to non-steroidal anti-inflammatory drugs (NSAIDs) coupled with a structured exercise program. However, about half these patients need escalation to biologic therapy.[3] The field

of SpA has faced tremendous changes triggered by the development of several effective therapies for AS. Drug development and registration nowadays requires appropriate classification criteria to sharply delineate the trial population of interest as well as a validated toolset for measuring outcomes of clinical trials.[6]

Sacroiliitis is usually the first and main feature of seronegative SpA. In its early stages it is difficult for diagnostic imaging techniques to demonstrate and specificity is poor. At the same time, there may be few or even no symptoms at all. Therefore, the anatomical damage is quite often diagnosed at an advanced and irreversible stage.[7] New classification criteria for axial SpA validated in the Assessment of Spondyloarthritis International Society (ASAS) take into account sacroiliitis showing up on magnetic resonance imaging (MRI) being given as much weight as sacroiliitis on radiographs, thereby also identifying patients with early axial SpA.[1,3]

Bone scan has acquired a useful role in the evaluation of acute and chronic back pain. Spinal pain is also a characteristic of chronic AS.[8] On reviewing the bone scintiscans in AS patients with low back pain and indeterminate radiographs, the presence of typical uptake patterns, particularly costovertebral, were useful in suggesting the diagnosis. Selective application of bone scintigraphy aids the diagnosis of AS and its potential complications.[9]

Radionuclide joint imaging (RJI) of the peripheral and axial skeleton detects early articular inflammation and has proven useful in establishing the extent and pattern of involvement. It is more sensitive than clinical examination in detecting inflammatory peripheral joints. Results obtained by RJI must be supplemented by the clinical findings and conventional investigations to establish a specific diagnosis.[10] Sacroiliac scintigraphy may detect AS prior to the development of radiological change. The clinical circumstances must be taken into account, as scintigraphic abnormalities are not diagnostic of any specific disease entity.[11] Radionuclide bone scans provide a sensitive, no-risk diagnostic technique for the detection and evaluation of a wide variety of diseases of the spine. Bone scans and radiographs provide complementary diagnostic information, and should both be considered in the medical imaging portion of the diagnostic plan.[12] Bone scintigraphy together with other imaging modalities have improved the capabilities of detecting early disease and became useful adjuncts to plain films. In addition, bone scan also enables more accurate detection of pathology at various anatomic sites of the musculoskeletal system predominantly involved in SpA.[13]

The aim of the present study was to detect subclinical peripheral arthritis and disease activity in axial seronegative SpA patients using bone scintigraphy.

PATIENTS AND METHODS

Axial seronegative SpA patients without peripheral arthritis were selected. Twenty SpA patients were recruited, including 18 with AS diagnosed according to the modified New York criteria[14] and two with PsA fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR).[15] All patients with AS or PsA fulfilled the Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis.[16] Those with peripheral arthritis at the time of the study or during the preceding month were excluded. The study was approved by the local ethics committee and written consent was obtained according to the Declaration of Helsinki.

All patients underwent rheumatologic examination with special consideration of the assessment of lumbar spine mobility according to the modified Schöbers test[17] (normal ≥ 5 cm), chest expansion (normal ≥ 5 cm), lateral bending (normal ≥ 5 cm) and the occiput to wall distance (≥ 2 cm).

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was assessed in both AS and PsA patients.[18] Active axial disease was defined as a BASDAI score of > 4 (scale 0–10, 0 meaning no activity and 10 high disease activity). The BASDAI is also able to discriminate between high and low disease activity states in axial PsA.[19]

Plain X-ray of the spine and sacroiliac joints (SIJ) was performed on the patients and MRI of the SIJ was carried out for those with clinical suspicion. For radiological assessment in the patients, the Bath Ankylosing Spondylitis Radiology Index (BASRI) was used.[20] The BASRI radiologic scoring system is a valid instrument for use also in axial PsA.[21]

Bone scintigraphy

Patient preparation

Patients were issued with the appropriate preparation instructions and radiation protection measures in advance and all married females within the child-bearing period were asked to do a pregnancy test prior to the study.

Method

Intravenous injection of 20 mCi (740 MBq) 99mTc-MDP was given via a cannula. Site of injection was selected to avoid known or suspected pathological conditions. Anterior and posterior whole body views of the entire skeleton were taken at 5 min post-injection as blood pool images and at 3 h post-injection as delayed images. Planar static images for 250–300 K-counts using 256 × 256 matrix size of the pelvis included the sacroiliac joints in posterior projections and for other regions when indicated. A rectangular region of interest (ROI) was drawn covering the entire left sacroiliac joint and a mirror ROI over the right sacroiliac joint was copied. A third ROI was drawn over the sacrum between the two ROIs. Counts per pixel were estimated for the three ROIs to calculate the sacroiliac to sacrum (SIJ/S) ratios or SIJ index.

Image interpretation

Any spot of abnormal enhanced radiotracer uptake at delayed bone scan images including joints was considered abnormal. The presence of hyperemia at these spots on early blood pool images was indicative for disease activity. SIJ index higher than 1.34 was considered positive for the presence of sacroiliitis even in clinically asymptomatic cases.[22]

Table 1 Demographic, clinical and laboratory features of axial spondyloarthritis patients

Feature	Axial SpA patients (20) (AS [18] + PsA [2])
Age (years)	37.5 ± 7.7 (31–57)
Sex M : F	13 : 7
Disease duration (years)	10.2 ± 7.1 (2–20)
BASDAI	1.6 ± 1.1 (0–3.2)
IBP	20 (100)
Psoriasis	2 (10)
Uveitis	2 (10)
Dyspnea (exertional)	1 (5)
SNHL	1 (5)
Fatigue	18 (90)
Clinical examination	
Sacroiliitis	13 (65)
Enthesitis	5 (25)
Modified Schöbers test (cm)	3.9 ± 1.1 (1–5)
Chest expansion (cm)	4 ± 1.25 (1–5)
Lateral bending (cm)	3.5 ± 1.2 (1–5)
Occiput to wall (cm)	0.6 ± 0.6 (0–2)

Results are expressed as mean ± SD (range) or number (percentage). AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IBP, inflammatory back pain; PsA, psoriatic arthritis; SNHL, sensorineural hearing loss; SpA, spondyloarthritis.

Statistical analysis

Results were expressed as mean ± SD and median (min–max) and number (percentage). Nonparametric Mann–Whittney tests were used to compare two inde-

Table 2 Plain radiographic and bone scan features of axial spondyloarthritis patients

Feature	Axial SpA patients (20) (AS [18] + PsA [2])
Plain radiography	
Bilateral sacroiliitis	20 (100)
Hip joint space narrowing	4 (20)
Dorsal kyphosis	2 (10)
Lumbar vertebra squaring	4 (20)
Bamboo spine	2 (10)
Facet joint ankylosis	6 (30)
BASRI-Hip	0.93 ± 1.52 (0–4)
BASRI-Spine	2.76 ± 1.44 (2–7)
BASRI-Total	3.66 ± 2.58 (2–10)
Bone scan	
Sites of hypervascularity	
Sacroilliacs	10 (50)
Enthesitis	3 (15)
Dorsal spine	7 (35)
Hip joint	5 (25)
Knee joint	5 (25)
Ankle joint	4 (20)
Lateral condyle of tibia	1 (5)
Small joint of the feet	2 (10)
Maxillae	1 (5)
Parietal skull	1 (5)
Sternoclavicular J	2 (10)
Shoulder/acromioclavicular joint	4 (20)
Small joint of the hands	3 (15)
Sites of normal vascularity	
Mid-clavicle lesion	1 (5)
Degenerative dorsolumbar spine	1 (5)
Blood vascular pool (vascularity)	
Hypervascularity	15 (75)
Hypovascularity of right hip (AVN)	1 (5)
Normal	5 (25)
Activity	
Active	15 (75)
Inactive	3 (15)
Normal	2 (10)

Results are expressed as mean ± SD (range) or number (percentage). AS, ankylosing spondylitis; AVN, avascular necrosis; BASRI, Bath Ankylosing Spondylitis Radiology Index; PsA, psoriatic arthritis; SpA, spondyloarthritis.

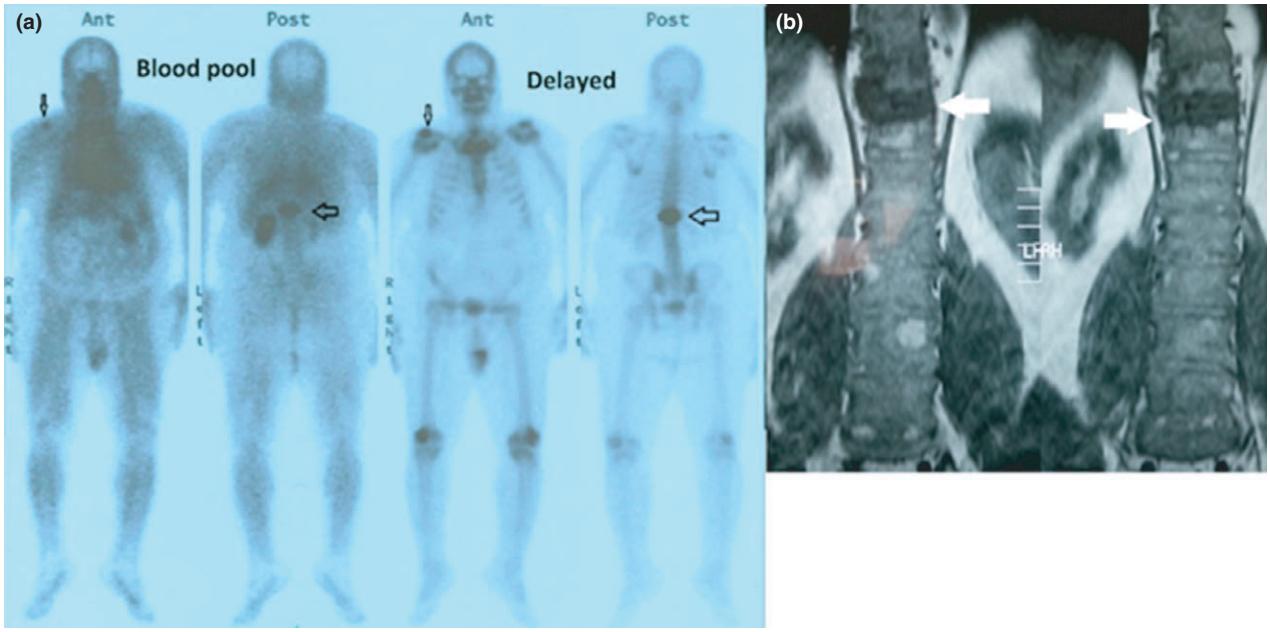

Figure 1 99mTc bone scan in a male patient, 57 years old with axial SpA (ankylosing spondylitis) showing (a) an expanding active lesion at dorsal vertebrae (D11, D12) (wide arrows) and at the right acromio-clavicular (AC) joint (narrow arrows). The AC joint was asymptomatic and more likely to be inflammatory. These lesions show hypervascularity in the blood pool images. (b) T1-weighted sagittal magnetic resonance imaging shows D11 and D12 spondylitis and diskitis with characteristically reduced signal intensity (white arrows).

pendent variables with significance considered at $P < 0.05$ (two-tailed). Spearman's correlation was performed and considered significant at $P < 0.05$. All tests were analyzed using the SPSS version 15 program (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 20 axial seronegative SpA patients with established diagnoses. Demographic and clinical features of the axial SpA patients are shown in Table 1. None of the patients had peripheral arthritis at the time of the study or during the preceding month. There was history of peripheral arthritis involving the hips in four patients, knees in 13, ankles in five and small joints of the feet in nine. Joints involved in the upper extremity included the shoulders in 10, wrists in nine and small joints of the hands in six. None of the patients had elbow involvement.

All patients had a negative rheumatoid factor. Human leukocyte antigen (HLA)-B27 was not performed as all patients fulfilled the classification criteria. Only one AS patient gave a history of bilateral acute anterior uveitis which was inactive during the period of the study. All the patients were inactive (having a BASDAI score of < 4).

Radiological features of the patients included sacroiliitis in all patients and plain X-ray findings in the axial spine, sacroiliac joints and hips which were unremarkable for other joints involved. The bone scans detected subclinical peripheral arthritis and other lesions that were not detected on clinical examination as shown in Table 2 and Figures 1 and 2. Plain radiographic and bone scan features of the patients are shown in Table 2.

The SIJ index for the 10 patients with clinically inactive and scintigraphically active sacroiliits was 2.43 ± 0.61. The plain X-ray could not assess activity of the SIJ and the MRI was useful in detection of sacroiliitis in three asymptomatic and clinically suspicious cases. Comparing the studied parameters and scores between those with hypervascularity and activity (15/20) as detected by bone scan and those without (5/15), there was a significantly increased BASDAI and reduced modified Schöber test (2.25 ± 1.4 and 3.63 ± 1.45 *vs.* 0.33 ± 0.14 and 5; $P = 0.02$ and $P = 0.03$, respectively). The BASRI showed a tendency to increase in those with hypervascularity (4.46 ± 3.02) compared to those without (2.57 ± 0.52) ($P = 0.1$). The blood pool

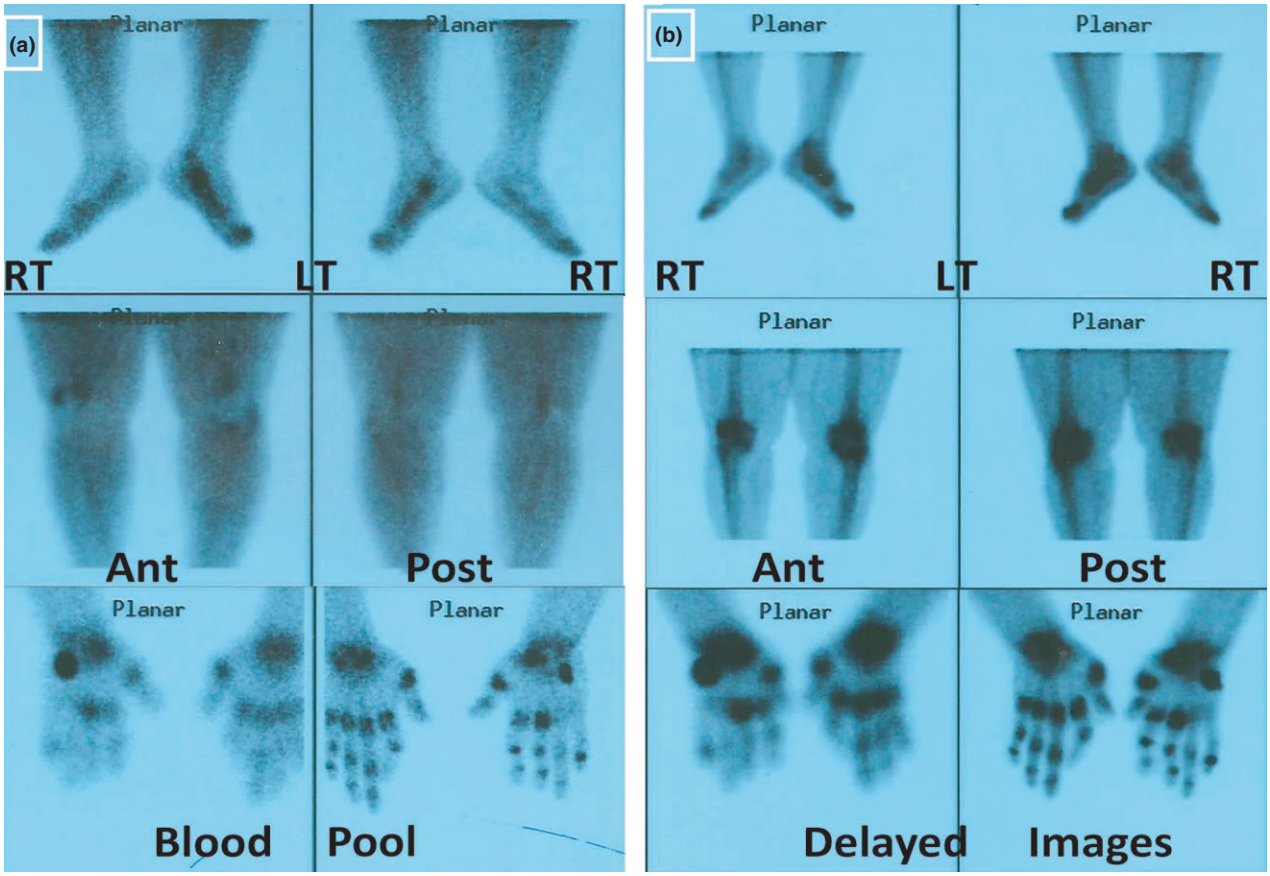

Figure 2 99mTc bone scan in a female patient, 43 years old with axial SpA (psoriatic arthritis). (a) Early blood pool images show significant hyperemia (b) pronounced active tracer localization at delayed images involving knees, ankles, wrists and small joints of hand. Active lesion of the left tendoachillis is present and characteristic of enthesitis.

scanning was also able to detect clinically hidden avascular necrosis of the hip (hypovascularity) in one patient. In view of gender, there were comparable results between males and females.

On follow-up after 2 months, five patients (25%) developed clinically evident and symptomatic peripheral arthritis, involving the knees in two patients, the ankles in another two and the hip in one. These patients subsequently developed overt arthritis in joints that had been identified by positive tracer uptake.

DISCUSSION

In the present study, 20 patients with axial SpA without clinically manifest peripheral arthritis were included. They were 13 males and seven females (1.86 : 1) and with a mean age of almost 37.5 years. In congruence, AS was found to be at least twice as common in men and most often manifesting in the third to fifth decades.[3] In the present study, the disease activity was significantly higher in those with hypervascularity and activity as detected by bone scan. However, the radiographic scores were comparable. Radiological changes are important hallmarks in AS because they reflect the cumulative process of destruction over time.[23] Because of its excellent agreement in the visualization of synovitis and lower cost, investigation of synovitis should be performed by blood pool scintigraphy. Synovitis is diagnosed according to increasing activity in the images compared to the surrounding tissues.[24] In accordance with the present results, plain radiographic changes correlated poorly with scintigraphic changes, scintigraphy detecting considerably more lesions than radiography.[25] Significantly increased uptakes on scintigraphy were found in SpA patients. The activity index was highest in the early periods of the disease making scintigraphy useful in early diagnosis of SpA.[26]

In the present study, increased uptake of the sacroiliac joints was present in 50% of the patients. The sensitivity and specificity of skeletal scintigraphy were significantly higher in detecting early sacroiliitis compared with plain radiography.[22,27] In agreement with our findings, increased bone scintigram activity in SIJ was present in 45% of AS cases with short disease duration.[25] The radionuclide uptake is markedly increased in patients with active AS or PsA.[28] Bone scintigraphy is a sensitive method of detecting sacroiliitis before radiologic evidence and in the evaluation of ongoing activity.[29]

In the present study, involvement of the sternoclavicular joint (SCJ) was present in two patients. On imaging of the SCJ in clinically manifesting SpA patients, bone scintigraphy showed an increased uptake in all patients compared to other imaging modalities; 23% showed cortical bone erosions on plain X-ray and 76% by computed tomography (CT) scan while effusion and synovitis were found in 81% by MRI.[30] Anterior chest wall involvement is difficult to evaluate in SpA patients and bone scan is highly sensitive in revealing subclinical involvement.[31]

In the studied patients, there was increased uptake in the dorsal spine in 35%, in the hips and knees in 25% of the patients. In AS patients complaining of axial back pain, bone scintigraphy revealed foci of markedly increased tracer accumulation.[32] Similarly, increased peripheral uptake was mainly in the hips and knees in advanced cases.[25] In AS, peripheral arthritis in the proximal joints is a common finding and increased uptake of radiotracer in the spine has also been found.[33]

Awareness of the scintigraphic appearances of AS may lead to a better estimation of disease activity and joint involvement before the development of radiographic changes and avoids confusion with other pathology.[25] Bone scan may show subclinical peripheral arthritis in axial SpA patients which may help in changing management regimens and could help in better patient selection on considering biologic agents. Even though single-photon emission computed tomography (SPECT) has an important role in contrast enhancement, its resolution is not better than planar scans. Furthermore, when the lesion under study is small, SPECT images displayed will contain limited anatomical information.[34] Combining SPECT with CT images could improve the specificity of radionuclide bone scans and the diagnosis of equivocal lesions on routine bone scans.[35] Inclusion of a SPECT study could be considered in future work on early-diagnosed cases.

In conclusion, bone scintigraphy is a reasonable, efficient and cost-effective radiographic modality in assessment of axial SpA patients, especially those without peripheral arthritis. It may detect subclinical cases not detected by plain X-rays. Advanced nuclear techniques are encouraged to be performed in this challenging and rare rheumatic disease in order to reach better criteria for changing the medications of those patients that will benefit from biologic therapy as a first-line treatment. A longitudinal study on a larger number of axial SpA patients is recommended in order to confirm the present results and detect the efficacy of bone scintigraphy in following up disease outcome, prognosis and therapeutic potential.

CONFLICT OF INTEREST

None.

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