Letters to the Editor

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High-resolution SPECT imaging of bony pathology in early arthritis of finger joints

Sir, We developed a multipinhole SPECT (MPH-SPECT) imaging system with up to 20 pinholes leading to a spatial resolution <1 mm and increased sensitivity by a factor of up to 50 compared with conventional bone scintigraphy (BS) [1]. Recently, we have demonstrated that MPH-SPECT represents a feasible tool for the study of osseous alterations in IL-1 receptor antagonist-deficient mice [2].

We report herein an initial clinical study with this newly developed method by imaging the clinically dominant hand of 13 early RA patients (ERA group, disease duration: <6 months), 9 early finger OA patients (EOA group, disease duration: <12 months, age <45 years) and 5 healthy controls (HCs). The study was approved by the local ethical committee and informed consent was obtained from all participating patients. All subjects received additional BS, and MRI was performed in the ERA patients. The number of affected joints, localization, pattern of tracer distribution and articulation involvement were semi-quantitatively scored in BS and MPH-SPECT images. In the latter, quantitative analysis was also achieved by region of interest (ROI) measurements. MRI examinations were assessed according to the RA-MRI scoring system (RAMRIS) [3] and image fusion of MPH-SPECT and MRI was performed in the ERA group.

We found that MPH-SPECT imaged osseous alterations early in the disease course, when other imaging modalities remained normal: 21/22 patients had pathological MPH-SPECT. In contrast, BS showed only in 13/22 patients’ pathological tracer uptake and could detect fewer joints (26 joints) with increased tracer uptake compared with MPH-SPECT (80 joints). The tracer uptake pattern on BS images was diffuse, with no distinguishing or localizing features. In contrast, improved local resolution of MPH-SPECT technique allows the definition of specific patterns and revealed significant differences between the two studied patient groups: ERA patients showed more often a central tracer distribution (10/13 ERA vs 2/9 EOA), whereas tracer uptake of EOA patients can be described as ‘hemispheric’, resembling more an eccentric pattern (7/9 EOA vs 2/13 ERA). The appearance of different uptake patterns in single finger joints with nuclear imaging is new. So far, an anatomic understanding of the earliest stages of ERA and EOA may have important implications for elucidating its pathogenesis, rather than for clinical diagnosing [4, 5]. The more centrally localized tracer uptake in our ERA patients probably reflects what happens in pre-erosive lesions: an osteoclastic activity combined with reactive attempts during bone repair and matches with MRI studies analysing osteoedema localization in arthritis [6, 7]. The eccentric tracer distribution in EOA might be interpreted as the beginning of very early osteophyctic reactions at the insertions of the collateral ligaments of the small finger joints, which was demonstrated in MRI analysis of other study groups in patients with early hand OA [5].

The quantitative analysis of activity accumulation in HCs and patients ranged from 4.50 to 222.70 normalized counts. In contrast, we found higher ROI values in affected joints in the patient group compared with HCs. The tracer uptake in the mainly affected joint was two to six times higher than in unaffected joints in a single patient. Comparing the individual joint uptake we found, on average, slightly higher values in the ERA group (3.58 times higher in EOA, 3.64 in ERA), but a distinction between EOA and ERA merely on the basis of the degree of increased bone metabolism was not possible (P < 0.59 using a two-tailed unpaired t-test). In contrast, the mean uptake values were slightly higher in the EOA patients than in ERA patients (78.75 vs 62.16). Within the ERA group, comparing affected and unaffected joints, significances were determined at P < 0.002 and in the EOA group at P < 0.024 using a two-tailed paired t-test.

The correlation of MRI and MPH-SPECT findings revealed that oedema and erosions matched with the localization of maximal tracer accumulation in 11/13 patients (Fig. 1). In 2/13 ERA patients, the signal of the cortical bone, as well as the bone marrow signal, appeared normal in all MRI sequences (RAMRIS score 0). In these joints (three MCP II joints and two MCP III joints), only soft tissue inflammation (synovitis) was evident in MRI. In contrast, MPH-SPECT revealed increased bone metabolism and the overlaid images of MRI and MPH-SPECT confirmed that the areas of increased bone metabolism were localized in bone matrix that appeared tomographically normal in MRI (Fig. 1), indicating that normal bone signal in MRI does not exclude the beginning of bony alterations.

In summary, MPH-SPECT provides increased sensitivity, high image resolution, accurate quantitation and compatibility with conventional SPECT cameras. MPH-SPECT allows the imaging very initial bony alterations in great detail in ERA and EOA, which could not be depicted by other imaging modalities, including MRI. These qualities make the technique optimal for researchers and clinicians who desire to bridge the gap between pre-clinical and clinical testing.

Rheumatology key message

- Revealing new insights and aspects of bony alterations in early arthritis, MPH-SPECT might be an important research tool in the future.
Low prevalence of ectopic germinal centre formation in patients with HTLV-I-associated Sjögren’s syndrome

Sir, We have proposed that HTLV-I infection can be a possible environmental factor for SS based on high prevalence of an anti-HTLV-I antibody in primary Sjögren’s syndrome (pSS) in Nagasaki [1–3], and recently confirmed that labial salivary glands (LSGs) of the HTLV-I-seropositive SS patients are less damaged in radiography [4]. Amft et al. [5] revealed the prominent expression of B cell-attracting chemokine 1 (BCA-1/CXCL13) on endothelial cells and lymphocytic aggregates in the ectopic germinal centre (GC) of LSGs in SS, speculating that ectopic GC is associated with the autoantibodies production as well as the salivary destruction [5].

We focused on the presence of ectopic GC formation in situ as well as the expression of CXCL12/CXCL13. Sixty-four pSS patients were registered and classification of pSS was determined by the revised criteria proposed by the American-European Consensus group [6]. LSGs from a control subject who was obtained. The presence of anti-HTLV-I antibody was determined by ELISA (Etest-ATL kit; Eisai, Tokyo, Japan) or particle agglutination assay (Serodia-ATL Kit; Fujirebio, Tokyo, Japan). Informed consent for the usage of samples obtained by the biopsy was obtained from all the participating patients as of the commencement of the study, and the study was conducted with the approval of the Human Ethical Committee of our institution. Immunohistochemistry was performed by the labelled streptavidin–biotin method (Histofine Staining Kit; Nichirei, Tokyo, Japan) using mouse anti-CXCL12 monoclonal antibody or goat anti-CXCL13 polyclonal antibody (R&D Systems, Minneapolis, MN, USA) [2] with microwave epitope retrieval for the detection of CXCL13. Negative control sections were treated with normal mouse IgG or normal goat serum. Mann–Whitney U-test, the chi-square test or Fisher’s exact probability test was used for the statistical analysis. P-value < 0.05 was statistically significant.

The gender and age were similar in 32 HTLV-I-seronegative (male/female 3:29; age 56.9 ± 14.9 years) and 32 HTLV-I-seropositive (male/female 4:28; age 58.5 ± 12.6 years) pSS patients, as well as in 9 HTLV-I-associated myelopathy (HAM)-pSS patients (male/female 1:8; age 61.6 ± 8.9 years). Sicca symptoms were observed in 83.3–100% of patients among the groups. Differences in anti-SS-A/SS-B antibodies (Mesacup SS-A/Ro test and SS-B/La Test; Medical & Biological Laboratories, Nagoya, Japan) and IgG concentrations at the time of biopsy were not statistically significant irrespective of HTLV-I infection. Strikingly, ectopic GC was low in HTLV-I-seropositive pSS (1/32, 3.1%) as compared with HTLV-I-seronegative pSS (6/32, 18.8%) (P = 0.045), and 0% in HAM-pSS.

Expression of CXCL13 was observed in 0–10% of monocellular nuclei (MNCs) of HTLV-I-seronegative pSS without ectopic GC patients or HTLV-I-seropositive pSS patients (Fig. 1). In HTLV-I-seronegative pSS (n = 6) with ectopic GC patients, the expression of CXCL13 was found dominantly in the light zone of ectopic GC. All of the cases showed >50% of MNCs