Current imaging techniques in rheumatology: MRI, scintigraphy and PET

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Summary

The first-line imaging technique for diagnosis inflammation in musculo-skeletal organs in rheumatoid arthritis (RA) is planar X-ray examination, which was for many years the first and the only single tool for RA diagnostics and response evaluation. Today, in the era of more aggressive RA treatment, ultrasound examination (US) and magnetic resonance imaging (MRI) are also frequently used. US is used to detect early signs of inflammation within the soft tissue. MRI allows to assess the soft tissue and bone marrow involvement in case of inflammation and/or infection. MRI is capable of detecting more inflammatory lesions and erosions than US, X-ray, or CT. Standard scintigraphy plays a crucial role, and data from positron emission tomography (PET) are also promising. These functional imaging techniques are used in detection of inflammation and/or infection in case of ambiguous results being obtained by other techniques or at other clinics. In patients with RA, scintigraphy plays a key role in the differential diagnosis of hip, knee, etc. endoprosthesis disorders, including mechanical or septic loosening.

Key words: rheumatoid arthritis • imaging: X-ray • CT • MRI • scintigraphy • PET

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Magnetic Resonance Imaging

In contrast to X-ray, CT and US, MRI allows to assess both the soft tissue and the bone marrow affected by inflammation that precedes the development of destructive lesions observed by X-Ray of CT (Figure 1A, 1B). Basic indications for MRI examinations in rheumatoid patients include [1–3]:
- assessment of inflammatory lesions of joint cavities, sheaths and bursae (synovial thickening, synovial congestion, effusion);
- assessment of bone lesions (bone marrow edema, geodes, erosions, damaged articular cartilage);
- assessment of inflammatory lesions and injuries within tendons;
- assessment of inflammatory lesions within muscles;
- diagnostics of rheumatoid complications, e.g. cervical spine complications in RA.

The advantages of MRI include:
- assessment of bone marrow inflammatory lesions (the bone marrow edema is not detectable by any other method while it may precede the development of destructive bone lesions in the course of inflammation); (Figure 2A–C);
- assessment of all articular surfaces (exact determination of the number of erosions and geodes, cartilage defects, etc.);
- assessment of spinal lesions (i.e. stenosis of the spinal canal or any conflicts with neural structures; destructive lesions and complications in the atlanto-occipital region, spinal cord and brain lesions);
- higher specificity due to the ability to use multiple sequences and i.v. contrast-enhanced scans;
- capability to carry out semi-quantitative assessments of inflammatory lesions by assessing the intensity of enhancement.

MRI scans of individual anatomical regions are performed using dedicated surface coils (e.g. knee coil, pelvic coil, hand coil, foot coil, etc.). Whole body MRI scans are also performed to search for inflammatory foci.

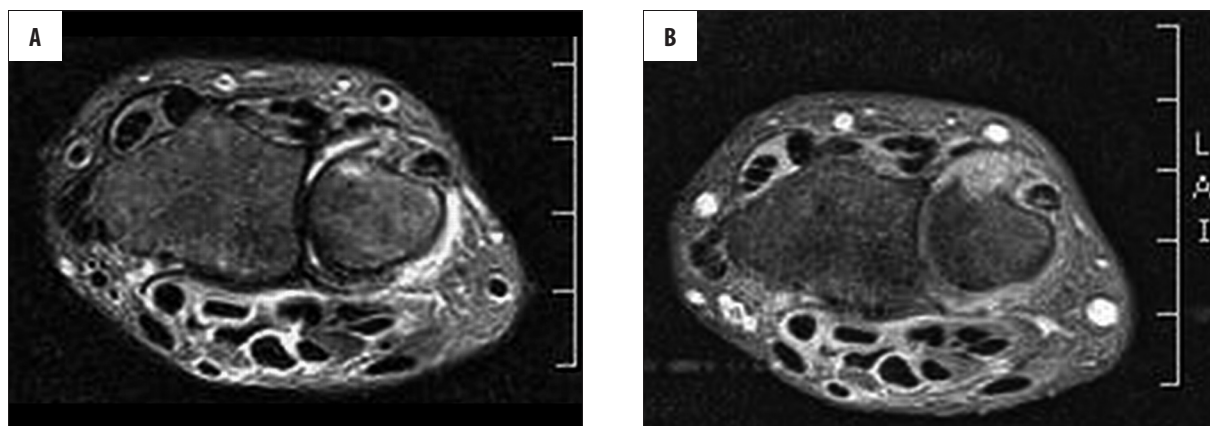Primary assessments include T1-, T2-, and PD-weighed images and fat-saturated sequences (STIR/TIRM or fat sat).

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Figure 1. Early form of rheumatoid arthritis (RA). Thickening and congestion (active inflammation) of the synovial membrane within the distal radioulnar joint (synovitis) and of the synovial membranes of tendon sheaths within all finger flexor and extensor compartments (tenosynovitis) in the MRI scans acquired using T2FS (**A**) and T1FS CE (**B**) sequences.

Figure 2. Non-differentiated arthritis. X-Ray of hands: a discrete thickening of the shade originating from the soft tissues of the 2nd digit of the right hand (**A**); MRI scan of right hand: bone marrow edema within the proximal phalanx of the 2nd digit (osteitis, osteomyelitis); synovitis within the MCP 2 joint and somewhat smaller synovitis within the MCP3 joint in transverse (**B**) and frontal (**C**) plane T1FSCE images.

Intravenous contrast-enhanced MRI scans are performed mainly in differential diagnosis of synovitis with effusion. MRI signal intensities allow differentiating between individual elements of the musculo-skeletal system, i.e. muscles, tendons and ligaments, hyaline cartilage, fibrous

Figure 3. Rheumatoid arthritis (RA). Case 1: Two foci of bone marrow edema within the right hand capitate and hooked bones in T2TIRM (**A**) and T1FSCE (**B**) scans; Case 2: numerous carpal bone erosions in T1SE (**C**) and T1FSCE (**D**) scans.

cartilage, cortical layer, cancellous bone, vessel, nerves and adipose tissue. Each of these tissues and structures is characterized by specific signal intensities and morphologies in normal and pathological conditions in the imaging sequences listed above. Images are assessed in at least two perpendicular planes [1–3].

The ultrasound (US) has a similar capability to differentiate between individual soft tissue types (muscles, tendons, ligaments, subdermal tissue, synovial membrane, etc.). Thanks to dynamic technological advances, ultrasound scans became one of the leading methods for diagnosing motor organs [4–7]. The advantage of MRI as compared to other techniques is the ability to assess bone marrow. In rheumatoid patients, bone marrow edema (BME) is suggestive of inflammation (osteitis, osteomyelitis). It is the
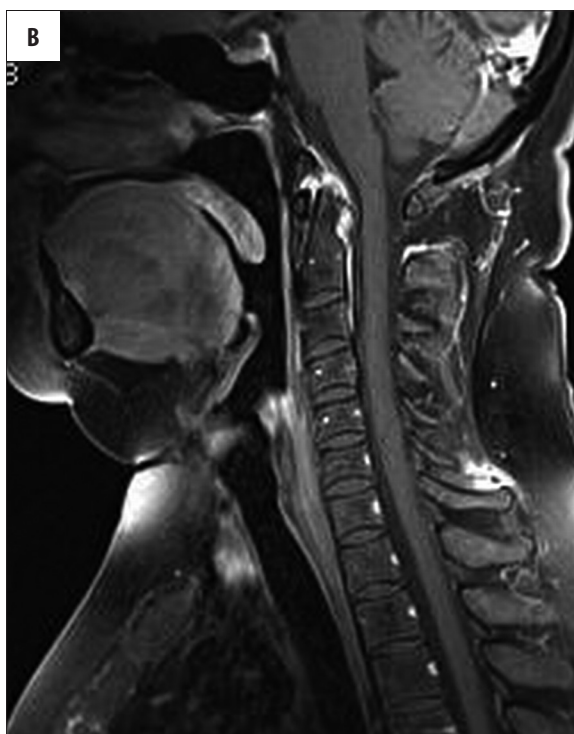
Figure 4. Dislocation of the atlanto-axial joint, axis tooth erosions and synovitis within the C1/2 joint as observed in radiographic imaging (**A**) and MRI T1FSCE scan (**B**).

main diagnostic criterion in active inflammatory lesions, particularly in the course of axial spondylopathy [1–3]. Bone marrow edema is responsible for signal enhancement in T2-weighed images (particularly with attenuation of the fat tissue signals). In T1-weighed images, bone marrow edema is hypointense against the lighter normal marrow. Following intravenous administration of contrast, regions of bone marrow edema are enhanced, particularly in T1-weighed sequences with fat signal saturation. Bone marrow edema is a symptom that commonly precedes erosions (Figure 3A–D).

When assessing peripheral joints, the advantage of MRI over ultrasound imaging consists in its capabilities of multiplanar imaging (allowing for a higher number of erosions and geodes being detected by MRI), contrast-enhanced assessments (synovial fluid, erosions) and bone marrow lesion assessment. When assessing the spine, MRI scans in rheumatoid patients are usually acquired in sagittal and transverse planes, most commonly with the purpose to assess the atlanto-occipital region (synovial pathologies, axis tooth erosions, dislocations, intussusception) if X-ray images are unambiguous (Figure 4A, 4B). In case of secondary degenerative lesions, MRI facilitates the assessment of spinal canal stenosis (precise assessment of intervertebral joints, yellow ligaments, lesions within discs and vertebrae).

MRI assessments are usually qualitative. Quantitative systems for the assessment of inflammation of hands include the

RAMRIS scale or the single-hand SAMIS scale. Both scales are attempts at standardizing the assessment of inflammatory lesions in RA [3]. Faster and simpler systems of computer-based analyses also become available. The RAMRIS scale was developed in 2002 by the EULAR-OMERACT group. It allows the assessment of synovitis (0 – unremarkable image; 1 – slight synovial congestion; 2 – moderate synovial congestion; 3 – significant synovial congestion); bone marrow edema (0 – unremarkable, 1 – edema affecting 1-33% of bone volume; 2 – edema affecting 34–66% of bone volume; 3 – edema affecting 67–100% of bone volume); and erosions (a scale of 0 to 10, based on the percentage volume of erosion compared to the volume of the bone being examined, in increments of 10%). Other quantitative methods consist in the measurement of synovial thickness, volume over a specific layer, overall volume of inflamed synovial membrane within the joint (inflammatory load), or the signal intensity (SI) (following intravenous contrast administration.

Other MRI techniques include diffusion-weighted imaging (DWI) and diffusion tensor imaging DTI) used in the search for inflammatory foci in rheumatology. Reports are available on the use of DTI in the assessment of muscles (e.g. in dermatomyositis) and cartilage structure.

MRI spectroscopy facilitates the assessment of tissue metabolism; for example, attempts have been made to use ^{31}P-MRS imaging in juvenile dermatomyositis.

Standard Bone Scintigraphy

Scintigraphy is a functional examination that visualizes bone metabolic lesions developing in the course of benign

and malignant diseases that usually by far precede the structural lesions visualized by conventional radiographic methods [8]. In benign lesions, scintigraphy is helpful in differentiation of bone metabolic diseases, systemic diseases involving bones and joints, traumatic lesions, degenerative overload lesions, and other bone and joint disorders of unknown etiology [9]. In the diagnostics of malignancies, scintigraphy plays the principal role in the assessment of bone metastases along with determination of the stage and metabolic characteristics of the tumor [10,11]. Areas of increased accumulation of radioisotopes, known as hot spots are indicative of increased bone turnover, while areas of lower or no accumulation of radionuclide, known as cold spots, are indicative of bones being destroyed by expansive bone loss processes [10]. In addition, scintigraphy is used in assessing the response to anticancer treatment and in qualifying patients for palliative treatment of pain due to bone metastases [12]. Scintigraphy is used for differentiation of primary bone tumors. The ability to use different radionuclide markers facilitates differential diagnostics of malignant tumors from inflammation- or infection-related tumors, while the ability to use different scanning sequences facilitates differentiation of benign and malignant tumors [8,12].

Bone scintigraphy is performed in adult and pediatric patients, symptomatic or asymptomatic, and is particularly useful for diagnosing:
- inflammations of joints and other arthropathies (RA, spondyloarthropathy, hemophilic arthropathy, etc.);
- primary bone tumors and bone metastases;
- occult fractures and acute or chronic overload syndromes;
- causes of endoprosthesis loosening (mechanical *vs.* septic)
- pathological fractures;
- infection of bones and adjacent tissues (joints and adjacent soft tissues);
- ischemic necrosis;
- algodystrophy;
- bone infartcion;
- vitality of bone grafts;
- bone pains of unknown origin;
- Pagets' disease;
- other metabolic diseases of bones, including renal osteodystrophy, pulmonary osteodystrophy, etc.;
- osteoblastic activity prior to radiation therapy of tumors with strontium (^{89}Sr), samarium (^{153}Sm), rhenium (^{188}Re), and lutethium (^{177}Lu) radioisotopes.

Scintigraphic bone scans are divided into static scans with static bone metabolic images being recorded usually several hours after administration of radionuclide marker, and dynamic scans, in which continuous acquisition by gamma cameras allows tracing the radioisotope flow from the initial moment of administration over the arterial, mesenchymal and delayed, i.e. skeletal phases [8].

The first phase allows for visualization of perfusion in the projection of the examined structure. After several minutes, in the phase referred to as mesenchymal phase, passive congestion of tissues characterized by pathological metabolism of bones and adjacent tissues is visualized. In the third,

delayed phase of examination, incorporation of radioisotope into the bone provides bone metabolic images characteristic for particular nosological enitities [8,10]. In terms of acquisition techniques, scintigraphy scans are divided into scans with radionuclide distribution being presented across a single plane (2D), within a particular region of interest (spot) or whole body (WB) scans. Scintigraphic scans may be supplemented by single photon emission computed tomography (SPECT) scans, facilitating spatial 3D acquisition capabilities typical of all tomographic techniques. In addition, SPECT scans may be integrated within structural CT scans. Modern SPECT/CT instruments facilitate virtually simultaneous acquisition of the structure and metabolism of the particular organ, allowing for precise determination of locations in which the radioisotope is or is not accumulated [13].

Bone scintigraphy is a highly sensitive, but not a very specific method. Improvement of method specificity requires precise information in clinical referrals and descriptions of imaging studies, both structural and functional (scintigraphic) conducted to date [10]. Following administration of a particular radiopharmaceutical agent, the examination visualizes the metabolic activity of the lesion, usually visible as a "hot" spot (of enhanced metabolism as compared to the surrounding normal tissue) or a "cold" spot (of reduced metabolism) [14–16]. Enhanced radioisotope uptake is observed in inflammatory, tumor and post-traumatic lesions, as well as in other metabolic conditions characterized by enhanced osteoblastic-osteoplastic activity (Figure 5). Physiological uptake of the radioisotope occurs also in normal structures, such as sacroiliac joints and growth cartilages. However, there are certain elements that allow for differentiation of particular nosological entities [10]. In case of inflammatory and/or inflammatory-infective lesions, enhanced accumulation of radiomarker is observed in the mesenchymal phase of the examination (phase II), corresponding to synovitis [17]. Tumor lesions, particular primary malignant bone tumors are characterized by clearly enhanced accumulation of radionuclides in the first and the second phase of the examination as well as in the third phase of the examination due to high bone turnover associated with bone remodeling (destruction); in case of poorly differentiated tumors (G3), central deficiencies of radionuclides may be observed within the hot foci of the tumor masses due to the necrosis of highly expansive tumors.

In everyday clinical practice, the most common isotopic markers are technetium ^{99m}Tc-labeled bisphosphonates, most commonly sodium medronate (MDP). Besides few exceptions, normal bone scintigram (lack of pathological uptake of the radionuclide marker) excludes active osteoarthropathies presenting with increased perfusion, congestion or, at a later stage and upon postponed examination, active metabolic remodeling of the bone [10]. In case of suspected bone infections, scintigraphic images may not be specific and the conditions may not always be differentiated by standard bone scintigraphy. In such cases, other scintigraphic methods are applied, including these employing ^{99m}Tc-labeled antibodies or antibody fragments, and leukocytes labeled *in vitro* with ^{99m}Tc-HMPAO (hexamethyl-propylene amino oxime) or ^{111}In Oxine (8-hydroxyquinoline). In addition, examinations with gallium citrate (^{67}Ga) are also performed.
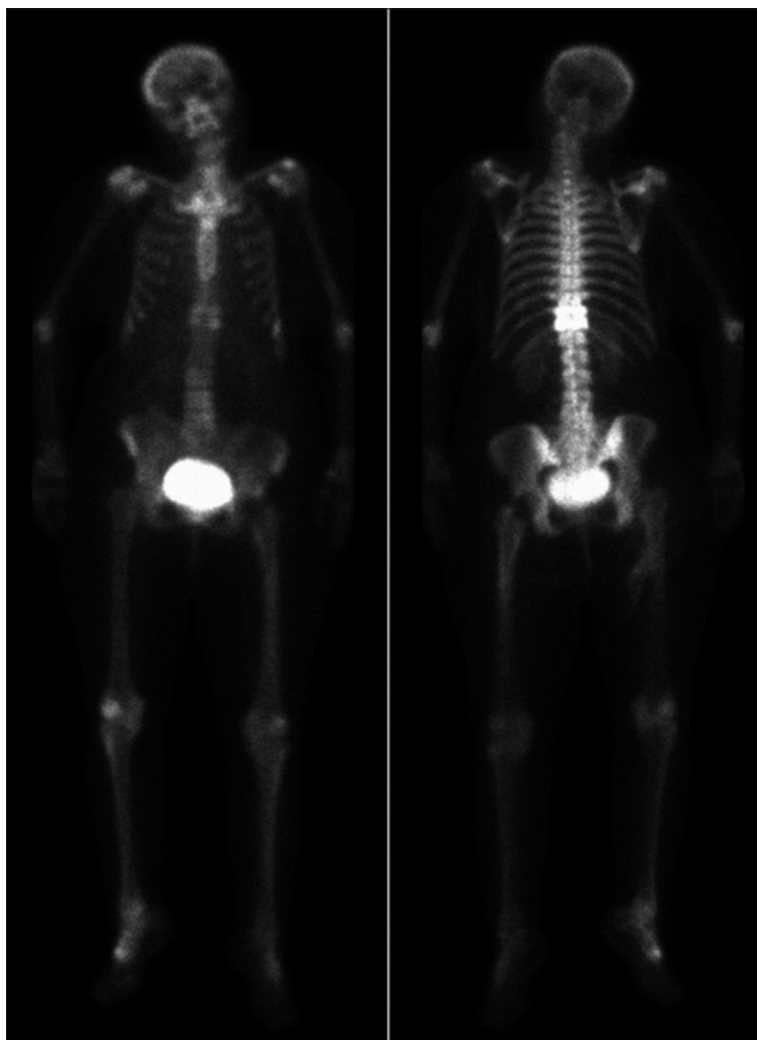
Figure 5. Osteoporotic compression fracture at the Th11 and Th12 level in a 61-year-old female patient after left hip replacement; no features of endoprosthesis loosening in bone scintigraphy. Visible degenerative overload lesions within the right patellar joint and right metatarsus (AP and PA projections; whole body scan (WB) following administration of 740MBq ^{99m}Tc MDP); the image was taken 3 h after intravenous administration of the radiomarker.

However, it should be noted that scintigraphic examinations performed to differentiate inflammatory processes from inflammatory/infectious processes must always include a standard bone scan with ^{99m}Tc MDP and a subsequent examination to detect infection according to one of the methods listed above (Figure 6A, 6B). Differential diagnostics is possible only when a combination of these examinations is performed [18]. In case of suspected acute or subacute infection, ^{99m}Tc-labeled antibodies or antibody fragments and ^{99m}Tc-HMPAO- or ^{111}In Oxine-labeled leukocytes are used [19,20]. In case of persistent, chronic inflammation accompanied by infection, combination of ^{67}Ga and the standard triphasic bone scan, ^{99m}Tc MDP, seems to be preferable [21,22]. When diagnosing recurring infections in patients with chronic inflammation-infection of bones and marrow, the optimum solution involves combination of ^{111}In Oxine and ^{99m}Tc-labeled sulfur colloid scintigraphy. At some sites, leukocytes are still being labeled with ^{99m}Tc-HMPAO due to the lower radiation doses which might potentially be of importance, particularly in children. In case of spondyloarthritis, the method of choice is scintigraphy with gallium (^{67}Ga) citrate [23].

When diagnosing complex infections following surgical procedures, such as arthroplasty, the first-line scintigraphic method involves the use of ^{111}In Oxine-labeled leukocytes and ^{99m}Tc-labeled sulfur colloid to examine the bone marrow reticuloendothelial system in order to identify the source of the infection and to differentiate the infection from marrow proliferation secondary to periprosthetic surgical procedure. Combination of both examinations allows determination of the infection based on the accumulation of labeled leukocytes and the lack of accumulation of sulfur colloids, which are accumulated in the bone marrow in a manner similar to labeled leukocytes. Enhanced specificity of this examination can be obtained when the scans are acquired 1 h, 4 h, and 20 h after administration. An alternative solution might be scintigraphic examination with ^{67}Ga and ^{99m}Tc MDP, particularly using the SPECT, and particularly the SPECT/CT tomographic technique. This type of examination is preferred in suspected chronic infections [24,25].

Dynamic bone scintigraphy (triphasic) is used as the first line diagnostic method in differentiating the causes of hip endoprosthesis (EP) loosening. Normal examination result excludes EP loosening. Persistent accumulation of radionuclide is observed for 12 months after the surgical procedure; in some cases, this period may be longer, depending on the location and type of the EP. In case of characteristic
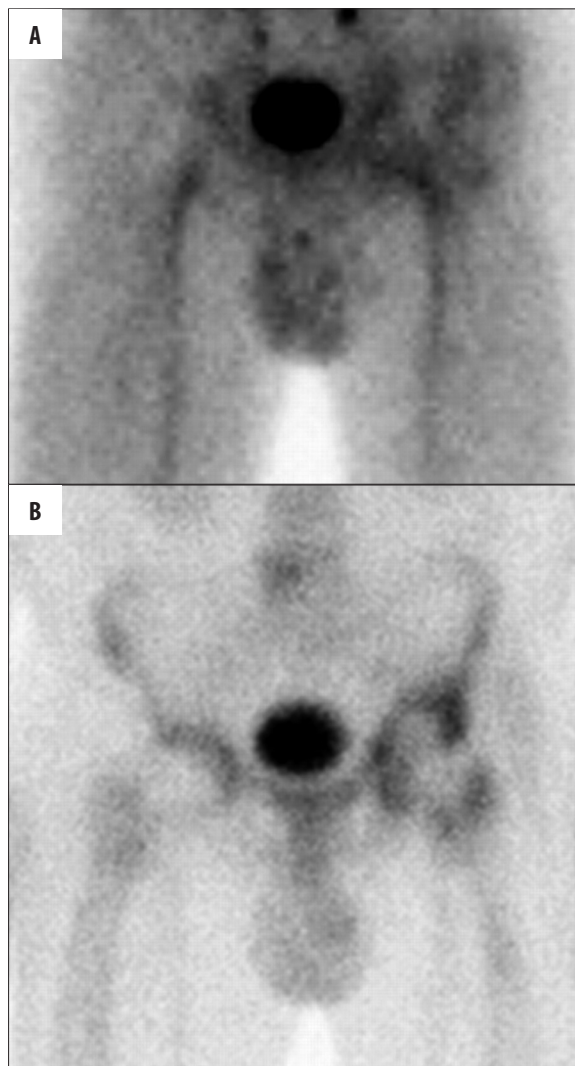
Figure 6. Differentiation of mechanical/septic loosening of hip endoprosthesis in a 58-year-old male patient. The dynamic scan carried out in the second phase of examination reveals intensive accumulation of radiomarker in the endoprosthesis projection on the left. Delayed scans taken in AP (**A**) and PA (**B**) projections reveal intense accumulation of radiomarker within the projection of both trochanters, particularly in PA projection, and within the acetabulum of the endoprosthesis; overall image very likely corresponding to septic loosening; the result was confirmed intraoperatively.
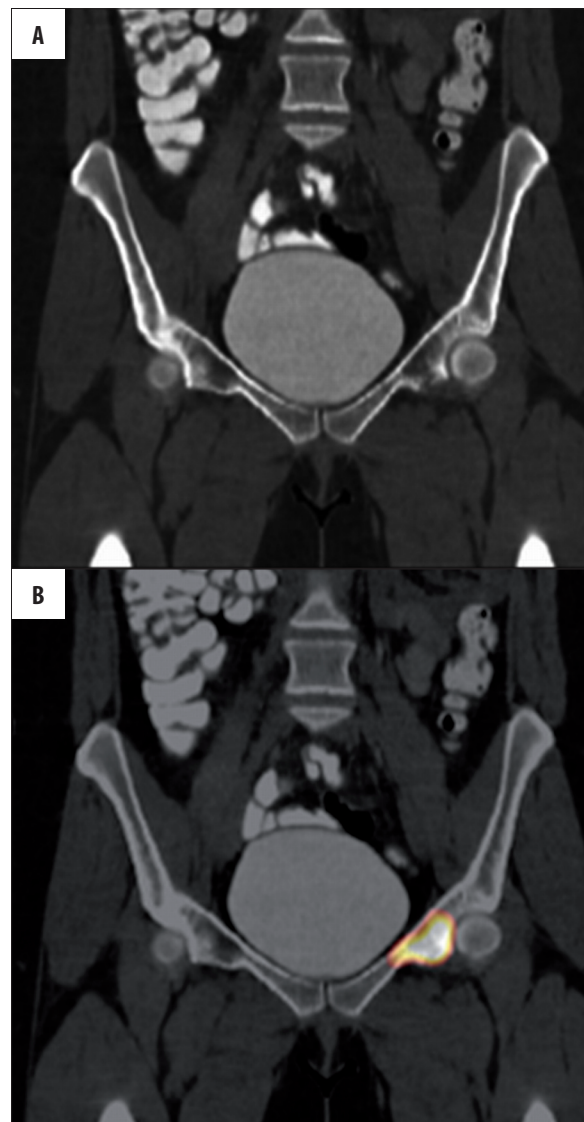

Figure 7. Metabolically active lesion within the left hip acetabular region (medial compartment – an image of a bone metastasis in a patient with a neuroendocrine tumor). Frontal plane pelvic CT scan with slight thinning of the bone structure at the left hip acetabulum; the image is not unambiguous (**A**). SPECT/CT image (**B**), [99mTc] HYNICTOC marker (radiolabeled synthetic analogue of somatostatin (SST) receptor), specific binding of radionuclide-labeled SST analog characteristic of neuroendocrine tumors.

high accumulation at the EP stem apex (within the femoral shaft), particularly at the third phase of the examination, with simultaneous lack of other pathological radionuclide accumulation foci and negligible clinical suspicion of septic loosening, the image is indicative of mechanical loosening of the EP stem. Septic background of EP loosening is confirmed by leukocytes labeled *in vitro* with [99mTc]-HMPAO or [111In] Oxine and [99mTc]-labeled sulfur colloid. In case of chronic processes (lasting more than 1 month), the preferred radionuclide marker is gallium ([67Ga]) citrate.

Currently, modern scintigraphic imaging in rheumatology may be based on labeling molecular targets, including IL-1,

TNF or apoptotic processes (Anexin V). Labeling an interleukin 1 receptor antagonist and development of a labeled monoclonal anti-YNF antibody may be helpful in the search for inflamed synovial membrane [26–28].

Positron Emission Tomography

Positron Emission Tomography (PET) is a type of scintigraphic molecular imaging based mostly on the metabolism of glucose within the bone and joint system as well as in the remaining body structures. In practice, PET scans in rheumatoid patients are based on [18FDG]. Other markers are not used due to availability reasons. FDG-PET scans are

characterized by limited usefulness due to the high cost of examinations and limitations similar as those encountered in standard scintigraphic examinations, mostly associated with the use of radioactive substances. The level of radioactivity to which the patient is exposed is higher for PET scans as compared to SPECT scans. The method is widely used in oncology; it is of lower importance in the diagnostics of connective tissue disorders. PET is characterized by a slightly better linear resolution compared to standard scintigraphy; also the higher signal-to-noise ratio (the number of counts at the PET detector) leads to better clarity of functional images of this type [29,30].

The hybrid technology of PET/CT facilitates obtaining structural computed tomography (CT) images during PET acquisition ([18]FDG metabolism). The result of the study may be evaluated in a quantitative manner based on the standard uptake value (SUV), i.e. the average accumulation of radionuclide in the particular lesion. Despite these advantages, there are also some limitations to the applicability of PET. For example, the diagnosis of loosening or the search for septic loosening assessed from a PET scan is characterized by the lack of unified diagnostic criteria for examination (in is unclear whether the qualitative, or quantitative SUV assessment should be used). Another disadvantage is the diversity of accumulation of FDG within the EP.

In addition, there is a possibility of enhanced accumulation of the radionuclide within the remodeled bone without any signs of infection as compared to the infectious-inflammatory infiltration of activated leukocytes. In addition, radionuclide accumulation can be observed in FDG-PET scans for many months after the surgical procedure, as in the case of standard bone scintigraphy. The slight improvement in functional examination sensitivity achieved by PET technology is probably incommensurate to the cost of examination as compared to standard bone scintigraphy. Linear resolution of is ca. 4.4 mm for PET instruments and ca. 7.8 mm for SPECT instruments. PET is incapable of identifying anatomical lesions with the accuracy of standard structural examinations; therefore, the images are obtained using hybrid PET/CT instruments, similar to SPECT/CT instruments. In addition, the method has a limited specificity due to the use of non-specific, oncophilic [18]FDG marker. A solution might consist in performing several scintigraphic scans characterized by similar sensitivity, but better specificity due to the use of different markers. From the scientific standpoint, scintigraphic examinations, particularly PET/CT may be used in molecular studies of inflamed synovial cells or molecular surface markers of ongoing active inflammation. Methyl-^{11}C-choline, known as a proliferation marker in oncological examination, may be used as phospholipid biosynthesis precursor (phosphatidylcholine) to assess synovial hypertrophy within joint cavities even when other inflammatory markers are not observed [29,30].

In addition, close correlation was demonstrated between the volume of inflamed synovial membrane (pannus) and its enhancement following intravenous contrast administration in MR examination as well as accumulation of FDG-PET as determined by SUV measurements [31]. Thus, FDG-PET may be potentially used in the monitoring of the

efficacy of treatment of RA and other systemic diseases on the basis of SUVs. As mentioned before, the use of other radionuclides facilitates obtaining PET images at the cellular or even subcellular level, as in the case of scintigraphic scans [29–31].

Conclusions

Modern diagnostics of rheumatic diseases is based on X-ray, ultrasound and MRI examinations. Due to the introduction of ultrasound and MRI images into several clinical classifications, clinicians have the knowledge on the capabilities and limitations of both techniques. Scintigraphic scans and PET scans are relatively less common.

It appears that the standard bone scan remains a very underestimated technique. Below is a list of potential applications of standard scintigraphic scans in everyday clinical practice.

1. To detect active metabolic remodeling processes (e.g. joint pains or bone pains), whole body (WB) scans are acquired, preferably using the WB-SPECT/CT technique (Figure 7A, 7B), affording an overview of all pathological foci of bone metabolism and often verifying the potential activity of pathological lesions identified in structural studies (e.g. X-ray, US, CT, or MRI);

2. When active inflammation is suspected, scintigraphic scan must involve the triphasic technique with a standard ^{99m}Tc MDP for optimum characterization in all three phases; In acute rheumatoid arthritis, the uptake is observed in all three phases with predominant accumulation in the second phase and usually also in the third phase upon active bone remodeling. In case of an inflammatory process within a particular joint and lesions within the synovial membrane and joint structures, accumulation is predominant in the second phase with possible moderate accumulation in the third (skeletal) phase of the scan. In subacute and chronic inflammation, elevated accumulation of radionuclide is observed in delayed phase images (phase III) around the affected joints;

3. When searching for infectious foci, standard bone scintigraphy (^{99m}Tc MDP) in a triphasic technique is supplemented with other scintigraphic techniques making use of radiopharmaceuticals that facilitate detection of infectious lesions depending on location and phase of the pathological process and the capabilities and experience of the center where scintigraphic scans are performed;

4. When diagnosing focal lesions located within bones, joints and adjacent soft tissue structures and characterized by generally unclear pathological nature (inflammation, tumor), standard three-phasic bone scintigraphy may be of help when interpreted along with the results of structural examinations such as CT, US and MRI. In addition, in case of indecisive images, the diagnostic methods may be supplemented by more specific radiopharmaceuticals, particularly upon clinical suspicion of infectious-inflammatory foci;

5. In case of degenerative and degenerative overload lesions, standard bone scintigraphy with SPECT tomographic images allows precisely location and assessment of the metabolic activity of numerous lesions visible in structural examinations, for example when precisely assessing facet joint osteoarthritis, perfectly visible in

SPECT/CT scans with potential difficulties in the analysis of multilevel discopathy accompanying pathological involvement of many facet joints;

6. Precise assessment of the activity of other lesions in the course of pain syndromes associated with degenerative, overload, osteoporotic lesions, etc. Scintigraphic scans with visible pathological accumulation of radionuclide at delayed phase of the examination encompass metabolically active marginal osteophytosis, bone resorption manifested by active erosions or bone remodeling, "fresh" end plate fractures, osteophyte fractures/infractions, etc;

7. In sacroiliac arthritis, scintigraphic examination, particularly when conducted using the SPECT technique, precisely identifies the extent of joint involvement; in addition, planar(WB), spot or SPECT/CT scans allow to precisely identify inflammation with the possibility of semiquantitative assessment and treatment efficacy evaluation;

8. When diagnosing endoprosthesis (EP) loosening, the scintigraphic image depends on the type elapsing from endoprosthesis placement and the type of the endoprosthesis. In case of cemented hip endoprostheses, enhanced uptake is maintained for the first 6 months or longer, up to 9–12 months. Focal uptake at the apex of the femoral bone after this period might be indicative of loosening of EP's acetabulum; more characteristic is the enhanced accumulation within the EP stem apex, usually suggesting stem loosening. In non-cemented prostheses, enhanced accumulation may persist even for more than 2 years, with accumulation at head apex being suggestive rather of remodeling than loosening. After total knee replacement, enhanced accumulation of radionuclide is observed usually for up to one year, while EP pathologies within the knee may pertain to both the tibial and the femoral component. In cases of septic loosening, additional scintigraphy options should be considered for improving the specificity of diagnosis (see above).

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