

Rheumatic diseases: knowledge update on scintigraphic assessment

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Scintigraphy has a role in the diagnosis and follow up of rheumatic diseases, in that it can provide important complementary information along with the clinical and radiographic evaluations of different disease conditions of the joints and periarticular structures. The scintigraphic pattern of different arthropathies varies depending on the type and phase of the condition. Some conditions affect mainly small or large joints while others affect both, in either a symmetric or asymmetric fashion. Radionuclides used in the diagnosis and follow up of these conditions include Tc99m MDP (Methylene diphosphonate), In-111 labeled leucocytes, labeled poly and monoclonal antibodies such as Tc99m-labeled

human polyclonal immunoglobulin G and Tc99m-anti-E-selectin-Fab, Tc99m-HMPAO labeled leukocytes, Tc99m SC (Sulfur Colloid), Tc99m nanocolloid and F-18 FDG (Fluorodeoxyglucose). SPECT (Single Photon Emission Computed Tomography) and pinhole techniques add a diagnostic value to the scintigraphic methods. F-18 FDG positron emission tomography has a potential to quantitatively assess the degree of arthritis activity.

Key words: arthritis, scintigraphy, imaging

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Introduction

The study of arthritis can be difficult because of the wide variety of disease patterns, the significant overlap of its various types and the lack of clear and unified classification of this group of disorders. This review provides an overview of the evaluation of the common arthropathies and related joint disorders in a simplified version that will help the reader identify their major scintigraphic and correlative imaging patterns.

Generally, several modalities are used to diagnose and follow up joint diseases. Standard radiographs remain the initial modality of choice among the morphologic modalities after clinical evaluation. Scintigraphy is

needed in certain situations to help in the differential diagnosis and to evaluate the activity of the diseases. Among the scintigraphic methods, bone scan is the technique most helpful and cost effective.

The value of bone scan was illustrated in Australia by Duncan¹ who studied 136 bone scans, which is the most common diagnostic imaging modality requested by Australian rheumatologists. The primary indications for scanning were to confirm a clinical diagnosis (38%), to exclude a diagnosis (34%), and to accurately localize the site of pain (17%). The common diseases that rheumatologists were attempting to confirm or exclude with bone scanning were inflammatory arthritis such as rheumatoid arthritis and differentiate it from malignancy and fracture. Bone scans were successful in excluding a diagnosis in 87% and confirming a diagnosis in 80%. In 32%, bone scans altered the clinical diagnosis, and in 43% changed the course of disease management. Bone scan results prevented further investigations in 60% of cases.¹ Single head and dual head pinhole images were reported to enhance further the role of bone scintigraphy in joint diseases.² The added value of dual head pinhole bone scintigraphy using the two opposing pinhole-collimated detectors is to obtain one pair of magnified images of bone and joint at one time with a reduction in the scan time.³

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Classification

No unified classification for the many types of joint diseases is available. Arthropathies however can be grouped into two main categories: inflammatory and non-inflammatory joint diseases⁴ (Table 1). The group of inflammatory joint disease includes immunoinflammatory, infectious and crystal deposit. While the non-inflammatory joint disease is exemplified by the common osteoarthritis or degenerative joint disease, which can be idiopathic (primary) or secondary, the other group is the soft tissue or periarticular syndromes or soft tissue diseases. This review discusses the scintigraphic changes in some common rheumatic diseases (joint diseases), mainly rheumatoid arthritis, septic arthritis, degenerative joint disease, crystal arthropathy and periarticular soft tissue diseases.

Table 1. Major types of joint disease with main examples

A. Inflammatory joint disease
• Infectious
– Infectious arthritis
• Non infectious
– Rheumatoid arthritis
– Crystal deposition arthropathies (Gouty arthritis, CPPD)
– Sacroiliitis
– Neuropathic joint disease
– Spondyloarthropathies
– Ankylosing spondylitis
– Psoriatic arthritis
– Reactive arthritis (formerly Reiter's disease)
– Inflammatory bowel disease associated arthritis
B. Non-inflammatory joint disease
• Primary osteoarthritis
• Secondary osteoarthritis

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory disease characterized by symmetrically erosive synovitis that causes pain, swelling, stiffness and loss of function in the joints affected. It is thought that microvascular injury and mild synovial cell proliferation occur first along with obliteration of small blood vessels. Synovial inflammatory response is triggered by immune complexes in the blood and synovial tissue through activation of plasma protein complement. This complement activation stimulates release of kinin and prostaglandin, which causes increased vascular permeability in the synovial membranes, and attracts leukocytes out of the circulation to the synovial membrane. Inflammation eventually spreads

from the synovial membrane to the articular cartilage, joint capsule and the surrounding tendons and ligaments, with resultant pain, loss of function and joint deformity. The small joints of the hands and joints in the feet, wrists, elbows, ankles and knees are the most commonly affected.

Clinical, laboratory, radiological and functional criteria are used to assess and follow up patients with RA. A gold standard for the assessment of synovitis activity is not available.⁵ X-rays are used to determine osteopenia and joint destruction, while on bone scintigraphy the disease presents symmetrically with increased perfusion and delayed uptake periarticularly in the areas of the joints affected, commonly the small joints of the hands and joints of the feet, wrists, elbows, ankles and knees. In-111 and Tc99m-labeled poly- and monoclonal antibodies are also used to image rheumatoid arthritis. Tc-99m polyclonal human immunoglobulin-G (HIG) has been shown to be a successful agent in the depiction of active inflammation in rheumatoid arthritis.⁶

Sahin compared the uptake behaviors of Tc-99m HIG and Tc-99m MDP in rheumatoid arthritis. Twenty five patients with rheumatoid arthritis and its variants presenting with active inflammation were included in this study. Target-to-background (T/B) ratios were obtained exclusively over the joint regions. Tc-99m HIG T/B ratios of the active joints in rheumatoid arthritis were significantly higher than those of the non-active joints and the control group of patients with well diagnosed osteoarthritis. Tc-99m HIG T/B ratios in active joints showed a progressive increase between 2 and 24 hour images. The T/B ratios in Tc-99m MDP bone scans were higher in all active joints than in joints of non-active rheumatoid arthritis and those of controls, but significant differences were only detected in wrist and elbow joints, and the detection rate of active joint inflammation with Tc99m HIG was higher than with Tc99m MDP.⁷

Monoclonal antibody, which reacts with porcine E-selectin was evaluated in imaging rheumatoid arthritis. Tc99m labeled Fab fragment of 1.2B6 and Tc99m HDP were used by Jamar, et al⁸ in 10 patients. Images were obtained 4 and 20-24 hours after injection. Two normal volunteers were also imaged. Diagnostic accuracy, using joint tenderness or swelling

as the clinical standard, was 88%, higher than that of Tc99m-HDP (57%) as a result of the low specificity of the latter in rheumatoid arthritis. No uptake of Tc99m-Fab was observed by inactive or normal joints, whereas Tc99m-HDP was taken up by all joints to a variable degree, making the decision as to whether a particular joint is actively involved or chronically damaged very difficult. The authors concluded that Tc99m-anti-E-selectin-Fab scintigraphy can be used successfully to image synovitis with better specificity than Tc99m-HDP bone scanning.⁸

Labeled leukocytes have been used to evaluate the disease activity and are a promising method for this purpose. In a recent study by Gaal and associates,⁹ the applicability of 99mTc-hexamethylpropylene amine oxime (99mTc-HMPAO)-labeled leukocyte joint scintigraphy in the assessment of disease activity was tested in 21 patients with rheumatoid arthritis. The degree of accumulation of 99mTc-HMPAO leukocytes showed no correlation with a patient's age and gender, duration of disease, use of disease modifying anti-rheumatic drugs or any laboratory parameters. However, a significant correlation was found between the global regional accumulation of the labeled leukocytes of the hands and feet and the clinical assessment of joint activity.⁹

Crystal Deposition Arthropathies

GOUTY ARTHRITIS

Gout is a metabolic disorder that results from the deposition of monosodium urate monohydrate crystals in various sites in the body, especially joint cartilage. The disease is rare in children and premenopausal females and uncommon in males under 30 years of age. The prevalence is influenced by genetic factors, alcohol consumption, obesity, and hypertension. It is closely linked to purine metabolism and kidney function. Most cases of gout are characterized by sudden onset of severe acute monoarticular arthritis. Gout passes through four stages; asymptomatic hyperuricemia, acute gout (mono or polyarticular), intercritical (interval gout), and chronic tophaceous gout. The ankle, the knee and the first metatarsophalangeal joint were the joints most often affected.¹⁰⁻¹¹ The most typical however is that of the metatarsophalangeal joint of the big toe, called podagra. Evaluation includes clinical,

laboratory and X-ray findings characteristic to gout. Recently, a case of gouty tophus of the patella was evaluated by positron emission tomography (PET) using a combination of an amino acid analog emitter, L-[3-F-18]-alpha-methyl tyrosine (FMT), which does not accumulate in malignancies and showed increased metabolic activity and the glucose analog emitter F-18-fluoro-2-deoxy-D-glucose (FDG), which essentially accumulates in malignancies and did not show appreciable activity. This report suggests that PET may be useful for the preoperative evaluation of gouty tophus including detection and differentiation from malignant tumors.¹²

INFECTIOUS ARTHRITIS

Bone infections are complex processes that can manifest in various ways and mimic many other diseases. It is common in adults and children, and in immunologically compromised patients. The onset could be seen in individuals with no comorbidities, in those with a history of trauma and post-operative joint replacements, or among patients with diseases such as diabetes, hemaglobinopathies, and arthritis.

The dilemma that faces the medical practitioner is reaching an early and accurate diagnosis of these infections. Although physical examination, laboratory tests such as white blood cell count and blood cultures, and standard radiographs are often positive in later stages of osteomyelitis, these parameters are not adequate for diagnosis in the early stages. Modern imaging plays a crucial role in aiding clinicians in the early diagnosis. For this reason, physicians should be aware of the many imaging techniques appropriate in skeletal infections. When this is combined with the patient's clinical background and an understanding of the pathophysiologic basis behind skeletal infections, effective decision making can be made in choosing an optimal imaging examination.

In children, infectious (septic) arthritis is usually secondary to hematogenous seeding but can also be produced by direct extension of osteomyelitis. More than half of the patients are less than 2 years old. A recent history of trauma is found in a third of patients and nearly 50% are with recent otitis media or upper respiratory tract infection. Infectious arthritis secondary to adjacent osteomyelitis

can occur in joints where the metaphysis is within the capsule (hip or shoulder). It can be found in infants, because of the epiphyseal location of osteomyelitis. *Staph. aureus* is the major causative agent, followed by the Streptococcus species. In children less than 2 years old, *Hemophilus influenzae* is the main causative agent although its incidence is decreasing since the introduction of vaccination.¹³

Patients may present with fever, pain, limitation of movement and limp, and infants may demonstrate joint dislocation. The hip and knee are the joints most often affected in children and the shoulder in the neonate. Rapid cartilage destruction and bone ischemia caused by raised intracapsular pressure lead to sequelae such as growth discrepancies, limitation of movement and dislocation. Accordingly, the condition is an orthopedic emergency, and any delay in diagnosis often leads to catastrophic sequelae. Permanent loss of joint function occurs in up to 25-50% of patients.¹⁴⁻¹⁶

The diagnosis is clinical and by joint aspiration. Combination of joint and blood cultures allows identification of the germ in two thirds of cases.^{13,16} Ultrasound allows rapid identification of joint effusion and serves as a guide for aspiration. It should be noted that ultrasound cannot differentiate whether the joint effusion is the result of infection or just inflammation since the severity of effusion of the septic condition may not be greater than the non-infectious synovitis.¹⁷ Sonography could also detect the extent of the infection since it may reveal the periosteal elevation, subperiosteal abscess and cortical erosion much earlier than X-ray if metaphyseal osteomyelitis occurred.¹⁸ In cases of equivocal ultrasonography and to evaluate whether osteomyelitis is present, bone scan is the modality to be used.

OSTEOARTHRITIS

Osteoarthritis (OA) is a joint disease that mostly affects the cartilage. OA can be primary with no known predisposing factors, or secondary due to several etiologies. Both idiopathic and secondary forms of osteoarthritis have the same pathologic characteristics. Primary or idiopathic osteoarthritis is the most common type of non-inflammatory joint disease. Although it affects any joint, the joints most commonly involved are in the hands, wrists, lower cervical spine, lumbar spine, sacroiliac,

hips, knees, ankles and feet. Symptoms include mainly joint pain, swelling, reduced mobility of the joint and joint stiffness which lasts less than thirty minutes. Clinically, crepitations in the joint, bony enlargement, nodules like Heberden's or Bouchard's nodes can be seen in the joints affected. X-ray may show peripheral osteophytes, reduced joint space, subchondral sclerosis and bony cyst formation. Aging is an important risk factor although the cause of osteoarthritis is unknown. Premature cartilage degeneration due to an inherited genetic defects encoding for the structural components of articular cartilage has been suggested as the etiology of this condition.

Primary osteoarthritis progresses with age. A diagnosis of secondary osteoarthritis is made when the predisposing cause is known, e.g. following intra-articular fracture or other traumas (post-traumatic osteoarthritis), rheumatoid diseases, neurogenic and metabolic disorders, drugs and recurrent hemarthrosis, as may occur among hemophiliac patients, and following certain forms of osteochondrosis and osteonecrosis. The pain of osteoarthritis is caused by intracapsular tension, muscle spasm, abnormal stress on the bone and increased intra-osseous venous pressure.

The changes of osteoarthritis are usually seen on standard radiographs as well as other morphologic modalities. On bone scintigraphy, increased periarticular uptake is commonly seen as an incidental finding in the commonly involved joints mentioned earlier. The degree of uptake is proportional to the severity of the disease.¹⁹

ANKYLOSING SPONDYLITIS

Stiffening and fusion (ankylosis) of the spine and sacroiliac joints causing most frequently low back pain and stiffness characterize this chronic inflammatory disease, which is the most common type of the seronegative spondyloarthropathies. Ankylosing spondylitis (AS) affects predominantly the axial joints particularly the sacroiliac joints and spine, with a strong genetic predisposition associated with HLA B27. Other joints such as hips, knees and shoulders are involved in approximately 30% of patients. The condition usually affects boys, and begins in adolescence with inflammation of fibrocartilage in cartilaginous joints (primarily in the vertebrae) along with infiltration of inflammatory cells (mainly macrophages and

lymphocytes) in the fibrous tissue of the joint capsule, cartilage and periosteum. This process is followed by repair of cartilaginous structures by proliferation of fibroblasts that secrete collagen, which later becomes organized into fibrous scar. The scar eventually becomes calcified and ossified causing loss of flexibility and fusion of joints.²⁰ The principal musculoskeletal lesions associated with AS are enthesitis and synovitis with sacroiliitis. Extra-articular features include eye lesions, most commonly uveitis and iritis, aortic regurgitation, enteritis, colitis, prostatitis and salpingitis. X-ray and MRI may show sacroiliitis, squaring of lumbar vertebrae, vertical syndesmophytes and loss of definition of apophyseal joints.

Scintigraphically, patterns vary according to the disease stage. In the early stage, scintigraphy reveals typically but not always symmetrical intense tracer uptake in both sacroiliac joints. Associated spinal lesions may or may not be present at this stage. Later, as the spine becomes involved pinhole scintigraphy reveals patchy uptake in the apophyseal joints, horizontal band like uptake in the disco-vertebral junctions, and midline segmental uptake in spinous processes and the interspinous ligaments.² Table 2 summarizes the classic scintigraphic findings of main rheumatic disorders.

Table 2. Scintigraphic patterns of major joint diseases

Disease	Scintigraphic Patterns
Rheumatoid arthritis	Symmetrical uptake involving small and large joints
Gouty arthritis	Uptake of metatarsophalangeal joint of the great toe and large joints, commonly symmetric
Ankylosing spondylitis	Symmetrical intense tracer uptake in both sacroiliac joints and spine
Osteoarthritis	Uptake of large joints, symmetrical in primary type
Reactive arthritis	Asymmetric uptake of large and small joints and spine
Psoriatic arthritis	Asymmetrical uptake of large and small joints typically of upper extremity including fingers and spine
Infectious arthritis	Uptake involving a large joint
Enteropathic arthritis	Uptake of large joints (asymmetric), sacroiliac joints (symmetric) and spine

PERIARTICULAR SOFT TISSUE SYNDROMES

Periarticular soft tissue syndromes such as tenosynovitis, bursitis, and plantar fasciitis are characterized by local pain, tenderness, and swelling in the bursa, tendon sheath, or enthesitis (the insertion of tendon, ligament, or capsule into the periarticular bones). Individ-

ual lesions may present as bursitis, tenosynovitis, capsulitis, fibrosis, or calcification. Trauma and repeated physical irritation are the common causes of this painful inflammation in the periarticular soft tissue structures. Idiopathic lesions are not rare.

Generally, standard radiograph often plays a decisive role in the diagnosis of bursitis, tenosynovitis, and plantar fasciitis. Ultrasonography can play a crucial role in confirming the diagnosis of bursitis and in guiding needle aspiration. Bursitis shows abnormal amount of fluid in the bursae and the associated synovial hypertrophy on ultrasound.²¹⁻²² In these conditions planar bone scan may reveal increased tracer uptake in the regions of the involved bursa, tendon, or enthesitis. However, the anatomical site of a lesion is extremely difficult to assess by planar imaging. In contrast, pinhole scintigraphy can reveal the anatomy of a lesion so that it points to the diagnosis of bursitis or tenosynovitis. It should be noted that in bursitis and tenosynovitis, bone scintigraphy may reveal intense tracer uptake when secondary erosion, reactive osteitis, and sclerosis in the neighboring bone are present. These secondary bone alterations are seen in association with trochanteric bursitis, subdeltoid bursitis, supra-acromial bursitis, sub-acromial bursitis, sub-Achilles tenosynovitis and plantar fasciitis.²

References

- Duncan I, Dorai-Raj A, Khoo K, Tymms K, Brook A. The utility of bone scans in rheumatology. *Clin Nucl Med* 1999;24:9-14.
- Bahk Y. *Combined scintigraphic and radiographic diagnosis of bone and joint diseases*. 2nd ed. Berlin: Springer; 2000.
- Bahk YW, Kim SH, Chung SK, Kim JH. Dual-head pinhole bone scintigraphy. *J Nucl Med* 1998;39:1444-8.
- McCarthy D, editor. *Arthritis and allied conditions*. Philadelphia: Lea and Fabiger;1984.
- Vos K, Van der Linden E, Pauwels EK. The clinical role of nuclear medicine in rheumatoid arthritis patients. A comparison with other diagnostic imaging modalities. *Q J Nucl Med* 1999;43:38-45.
- Cindas A, Gokce-Kustal Y, Kirth PO, Caner B. Scintigraphic evaluation of synovial inflammation in rheumatoid arthritis with (99m) technetium-labelled human polyclonal immunoglobulin G. *Rheumatol Int* 2001;20:71-7.

7. Sahin M, Bernay I, Basoglu T, Canturk F. Comparison of Tc-99m MDP, Tc-99m HSA and Tc-99m HIG uptake in rheumatoid arthritis and its variants. *Ann Nucl Med* 1999;13:389-95.
8. Jamar F, Houssiau FA, Devogelaer JP, Chapman PT, Haskard DO, Beaujean V, et al. Scintigraphy using a technetium 99m-labelled anti-E-selectin Fab fragment in rheumatoid arthritis. *Rheumatology* 2002;41:53-61.
9. Gaal J, Mezes A, Siro B, Varga J, Galuska L, Janoky G, et al. 99m Tc-HMPAO labelled leukocyte scintigraphy in patients with rheumatoid arthritis: a comparison with disease activity. *Nucl Med Commun* 2002;23:39-46.
10. Mijiyawa M. Gout in patients attending the rheumatology unit of Lome Hospital. *Br J Rheumatol* 1995;34:843-6.
11. Koh WH, Seah A, Chai P. Clinical presentation and disease associations of gout: a hospital-based study of 100 patients in Singapore. *Ann Acad Med Singapore* 1998;27:7-10.
12. Sato J, Watanabe H, Shinozaki T, Fukuda T, Shirakura K, Takagishi K. Gouty tophus of the patella evaluated by PET imaging. *J Orthop Sci* 2001;6:604-7.
13. Fink CW, Nelson JD. Septic arthritis and osteomyelitis in children. *Clin Rheum Dis* 1986;12:423-35.
14. Goldenberg D. Septic arthritis. *Lancet* 1998;351:197-202.
15. Piro MH, Mandel BF. Septic arthritis. *Rheum Dis Clin North Am* 1997;23:239-58.
16. Welkon CJ, Long SS, Fisher MC, Alburger PD. Pyogenic arthritis in infants and children: A review of 95 cases. *Pediatr Infect Dis* 1986;5:669-76.
17. Tien Y, Chih H, Lin G, Hsien S, Lin S. Clinical application of ultrasonography for detection of septic arthritis in children. *Kaohsiung J Med Sci* 1999;15:542-9.
18. Mah ET, LeQuesne GW, Gent RJ, Paterson DC. Ultrasonic features of acute osteomyelitis in children. *J Bone Joint Surg Br* 1994;76:969-74.
19. McCrae F, Shouls J, Dieppe P, Watt I. Scintigraphic assessment of osteoarthritis of the knee joint. *Ann Rheum Dis* 1992;51:939-42.
20. Rupani HD, Holder LE, Espinola DA, Engin I. Three phase radionuclide bone imaging in sports medicine. *Radiology* 1985;156:187-96.
21. Craig JG. Infection: Ultrasound-guided procedures. *Radiol Clin North Am* 1999;37:669-78.
22. Cardinol E, Bureau NJ, Aubin B, Chhem RK. Role of ultrasound in musculoskeletal infections. *Radiol Clin North Am* 2001;39:191-200.

CME/CPD Questions

After you have completed reading the article *Rheumatic diseases: knowledge update on scintigraphic assessment*, take the test given below. Circle T (True) or F (False) in the answer sheet (page 96) to show the correct answer to each question. Questions 1 to 10 are related to the content in this article.

1. Tc99m polyclonal human immunoglobulin-G can be used to depict active inflammation in rheumatoid arthritis.
2. Tc99m-anti-E-selectin-Fab scintigraphy can be used successfully to image synovitis in rheumatoid arthritis patients.
3. Gouty arthritis is rare in children and premenopausal females and uncommon in males under 30 years of age.
4. In children, infectious (septic) arthritis is usually secondary to hematogenous seeding but can also be produced by direct extension of adjacent osteomyelitis.
5. The hip and knee joints are rarely affected in infectious arthritis in children.
6. Permanent loss of joint function occurs in up to 5% of patients with infectious arthritis.
7. There is no gold standard for the assessment of sinovitis activity.
8. Primary osteoarthritis is the most common type of non-inflammatory joint diseases.
9. There is no association between ankylosing spondylitis and HLA -B 27.
10. Trauma and repetitive physical rotation are common predisposing factors for soft-tissue inflammation.