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Molecular Imaging of Inflammatory Arthritis and Related Disorders

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Rheumatic disorders comprise a number of diseases that range from benign, mildly symptomatic degenerative disease to severe systemic disorders such as giant-cell vasculitis with dramatic consequences such as acute blindness. The former is relatively common, whereas the latter is rare. In between, commonly encountered disorders such as rheumatoid arthritis and the various spondyloarthritides, with or without peripheral enthesitis, are daily challenges for the caring physician. Clinical evaluation is of utmost importance and is constantly described under the form of specialist guidelines in all parts of the world. Objective assessment of inflammatory arthritis and related disorders is of interest both for the care of the individual patient and for the assessment of the effects of the many novel experimental therapies proposed in this field, most of them being very expensive. High-resolution ultrasound, CT and spectral CT, MRI using various sequences, and molecular imaging using either gamma camera imaging (including SPECT-CT) or PET-CT are all proposed for a better assessment of these diseases. This review focuses on the several nuclear medicine techniques that are or may become useful to helping provide better patient care in this field and is mainly oriented to inflammatory rheumatic disorders, excluding mechanical degenerative diseases.

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Introduction

Rheumatic diseases are common disorders with most often a chronic course and disability features. Their economic burden may be as high as 1%-2.5% of the gross national product of Western nations: this burden includes direct medical costs, the costs of short- and long-term disability, and premature mortality. Impact on the quality of life is of particular importance and that has fostered major decisions in terms of budgetary choices in favor of those patients.[1,2] These disorders can be grouped into four categories: degenerative joint disease that may affect up to 15% of the population and is better called osteoarthritis (OA) in its inflammatory forms; chronic inflammatory rheumatism, with rheumatoid arthritis (RA) being the prototype; rheumatic disorders with predominant involvement of the axial skeleton, exemplified by spondyloarthropathies; and systemic disorders, including many entities, of which only vasculitides will be dealt with in this review.

OA results in various degrees of pain and disability and is usually imaged by x-ray techniques, ultrasonography, and MRI, with a lesser role for functional imaging techniques, which will not be discussed here.

RA and the other inflammatory diseases are sometimes more challenging as far as the therapeutic options are concerned. The prevalence of RA is about 0.6%-1% in the US population with a predominance in women. RA is the most prevalent autoimmune disease. Its cost was estimated to reach 19.3 billion US dollars in 2010.[1,3] Recent market surveys showed worldwide that biologicals used in inflammatory disorders (arthritis and inflammatory bowel disease) represent thousands of US dollars per patient per month and tens of billion of US dollars in sales. A cost-effectiveness analysis recently demonstrated that many biologicals result in major cost savings in RA,[4] although a large meta-analysis was more inconclusive.[5] Although recent therapies are efficient,[6] only two of three

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patients with RA gain real benefit from these expensive medicines because of treatment failure, intolerance or unacceptable side effects (eg, infections), and perhaps the development of antidrug antibodies.[7]

Choosing the right treatment for the right patient at the right time is essential.[8] Therefore, the differentiation between pure—chronic and stabilized—anatomical changes and active disease is essential to improve patients' outcome and quality of life. The diagnosis of the inflammatory disorders relies mainly on their clinical features, and many clinical scores have been developed to establish diagnosis and prognostic features.[9] Clinicians though are very interested in obtaining objective, independent evaluation of the patients' status using medical imaging. Many techniques can be used, including those using x-rays (plain films, CT scan with or without intravenous or intra-articular iodinated contrast medium), ultrasonography using high-frequency probes, various sequences of MRI, and nuclear medicine imaging using either gamma emitters with planar imaging or SPECT-CT and PET-CT. Various approaches are used and there are no universal guidelines to answer specific questions in the field of rheumatology. In particular, the role of ultrasonography, nuclear medicine, and MRI remains either debated or at an experimental level in many clinical situations. Several scientific societies, however, are working hard to find the best approach to these patients, with or without imaging.

This review covers the use of various nuclear medicine imaging modalities in the three main fields of interest for the rheumatologist as described previously.

Imaging of RA

Since the early times of nuclear medicine, many efforts were dedicated to finding an objective way to make the diagnosis and assess the extent and severity of disease. The use of bone-seeking agents, such as ^{99m}Tc-labeled diphosphonates, was very sensitive but actually identified those affected joints with bone remodeling, which may not be those that are currently actively involved by inflammation.[10] Specificity was low,[11] and the technique, although still in use, is only requested to assess specific situations such as complications of the disease, including osteoporotic fractures, postoperative changes, and the assessment of orthopedic hardware complications. The major drawback of bone scintigraphy is its inability to differentiate RA from degenerative changes, that is, OA.

Therefore, a number of tracers were developed to better assess the inflamed joints rather than the affected joints. Facing the Celsus' and Galien's clinical hallmarks, tumor, rubor, calor, dolor, and functio laesa, such tracers should prove more objective measures of disease than clinical examination. Every component of the inflammatory process was targeted with variable success. Tracers in general use such as radiolabeled leukocytes,[12] ^{99m}Tc-(nano)colloids, and ^{67}Ga-citrate[13] met with limited success. Probably, the most widely used commercially available tracer was ^{99m}Tc-human immunoglobulin G (HIG).[14,15]

Other agents were pursued with success in experimental clinical settings: they include lymphocytes with anti-CD4,[16] anti-CD3,[17] and anti-CD20 (rituximab)-labeled antibodies,[18] macrophages with the folate receptor, cytokines and cytokine receptors, such as interleukin 2 (IL2), IL2R, and IL6, and tumor necrosis factor-alpha (TNF-α), and monoclonal antibodies (moAbs) against E-selectin labeled with either ^{111}In or ^{99m}Tc.[19,20] The latter was superior to nonspecific ^{99m}Tc-HIG and bone scanning (Fig. 1) and was extensively studied in both preclinical and clinical settings.[19,21] E-selectin, an inducible endothelial adhesion molecule, was a particularly attractive target because its expression is almost null in the steady state and the molecule is highly and rapidly induced by potent cytokines such as ILs. Therefore, uptake in normal joints is negligible, whereas inflamed joints show intense uptake that overcomes accumulation of less specific tracers, in terms of contrast, and hence sensitivity. All tracers showed promise compared with clinical assessment in early clinical use because of the objective assessment of affected joints and the superior reproducibility compared with clinical assessment. None of these tracers, however, reached the clinical stage probably because their commercial development was deemed not feasible for regulatory or financial reasons. In the 1990s, ^{18}F-FDG-PET emerged as a potent tool for the assessment of patients with cancer but its use in inflammation will be detailed further.

^{99m}Tc-HIG

In the late 1980s, radiolabeled nonspecific immunoglobulin G (IgG) was developed as a tracer for imaging infection. Rubin et al were testing a monoclonal antibody against *Pseudomonas aeruginosa* type I; in experiments using an irrelevant control IgG, they were able to show its accumulation at the site of infection and that this accumulation could be imaged.[22] Further experiments using ^{125}I- and ^{111}In-radiolabeled human polyclonal IgG (HIG) confirmed the ability of this agent to image infectious and inflammatory lesions with better image quality than ^{67}Ga-citrate.[23] These findings led to clinical applications of radiolabeled HIG, first in infection (orthopedic hardware, diabetic foot, pyrexia of unknown origin, opportunistic infections in neutropenic, and immunocompromised patients) and later in sterile inflammation, such as RA.[24]

Shortly after, a cold kit for labeling HIG with ^{99m}Tc (Mallinckrodt Medical, Petten, The Netherlands) was developed, aiming at replacing ^{67}Ga-citrate and radiolabeled white blood cells. The kit containing 1 mg of modified human polyclonal IgG from a pool of healthy donors allowed easy, efficient, and stable coordination of the ^{99m}Tc label. Pioneer work by Breedveld et al demonstrated that this tracer was suitable for imaging aseptic arthritis.[14]

Many investigations were devoted to the identification of the uptake mechanisms of ^{99m}Tc-HIG in the inflamed synovium. After intravenous injection, the tracer distributes in the vascular compartment with about two-thirds remaining in plasma after 4-6 hours.[25] Excretion, in the form of free ^{99m}Tc-pertechnetate, occurs mainly through the urinary tract, probably after intrarenal metabolism and binding of sulfhydryl groups to metallothionein.[26] In normal volunteers, the

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