Imaging inflammatory lesions by radiolabelled peptides and antibodies

L.K. Anzola Fuentes, MD, PhD
September 21, 2020
University of Groningen (virtual event)

Promotors:
Prof. A. Signore
Prof. A.W.J.M Glaudemans
Prof. R.A.J.O Dierckx

Nuclear medicine techniques for imaging inflammation have had huge progress and have enormously expanded over the past twenty years in parallel with the understanding of the pathogenesis of chronic inflammatory diseases and the role of different immune cells and cytokines.

Several new radiopharmaceuticals have been developed, able to detect early and late pathologic events at a molecular level. The name "molecular nuclear medicine", therefore refers to all those radiopharmaceuticals and techniques used in nuclear medicine to visualise, and often quantify, the molecular events involved in a disease. We cannot stress enough the importance of this branch of medicine, not only in the diagnostic setting but also in prognosis and treatment management. The key clinical feature of molecular nuclear medicine relies on the ability to *in vivo* detect the components and phases of diverse disorders, besides the solely morphological changes detected by most other imaging procedures. This characteristic provides the rationale for the use of molecular imaging techniques for early diagnosis and treatment decision making.

In this monography, we have focused mainly on the contribution and the role of molecular nuclear medicine to detect early phases of chronic inflammation by the use of radiolabelled peptides and monoclonal antibodies (mAbs).

Several radiopharmaceuticals have been used for imaging different chronic inflammatory conditions. Their mechanisms of accumulation in chronic lymphocytic inflammatory sites vary; for non-specific radiopharmaceuticals such as ^{67}Ga-citrate and ^{99m}Tc-HIG, the accumulation in tissues depends upon enhanced capillary transudation, secondary to increased vascular permeability and increased blood supply. Tissue accumulation of more specific radiopharmaceuticals such as ^{99m}TcmAbs and ^{99m}Tc-cytokines depends upon the antigen-antibody interaction or a specific receptor-binding process, thus allowing the histopathological characterisation of the inflammatory process and the definition of its severity and type. Even though there is not one single ideal radiopharmaceutical for imaging all chronic inflammatory diseases, some combination of them could be used for the complete understanding of the histopathology involved and, therefore, to identify a specific and tailored therapy. Moreover, these novel tools can detect cell binding and the presence of cytokines in patients suspected of an inflammatory condition based on laboratory tests. These agents can also demonstrate active inflammation in patients without systemic inflammatory response and can predict response to treatment. Today, clinicians have the possibility to choose between different options according to the purpose and clinical requirements.

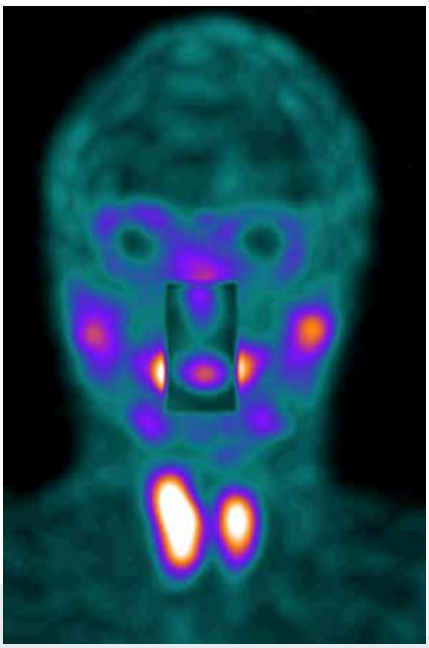

Figure 1. Somatostatin receptor scintigraphy (SRS) in a patient with active Graves' disease and Sjögren's disease. Note the abnormal uptake of the radiotracer in thyroid gland, salivary glands and periorbitary region secondary dysthyroid orbitopathy.

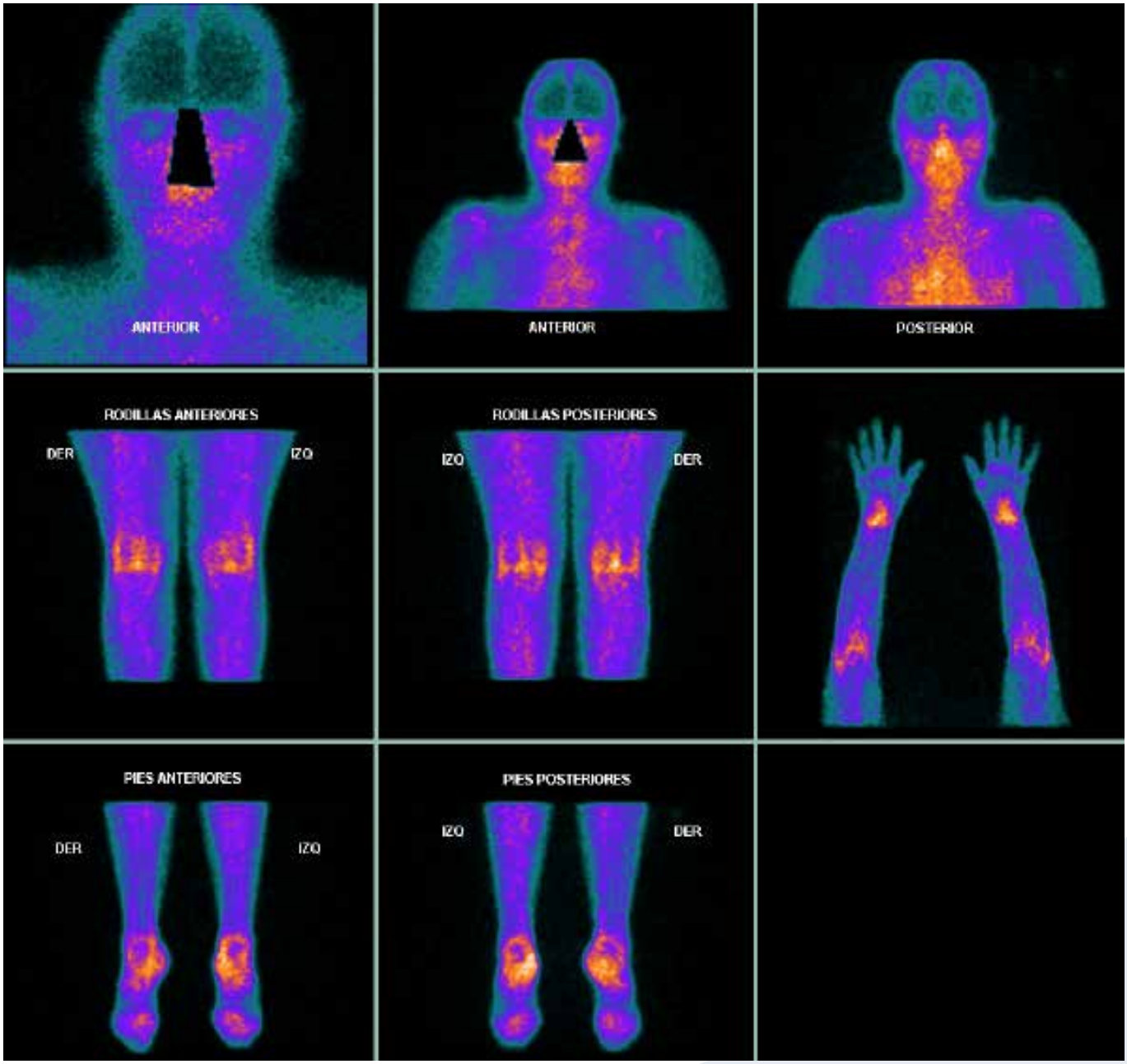

Figure 2. SRS in a patient with active rheumatoid arthritis showing abnormal uptake of the tracer in knees, ankles, carpal joints, and shoulders.

Radiolabelled cytokines and mAbs are an emerging class of molecules for imaging inflammation. These radiopharmaceuticals bind to their targets with high affinity and specificity, and therefore have excellent diagnostic potential for imaging patients with chronic inflammatory diseases.

One of the key type of cytokines involved in the process of inflammation is tumour necrosis factor alpha (TNFα). With the introduction of anti-TNFα monoclonal antibodies over the past decade, treatment of inflammatory diseases has evolved, with remarkable contributions in controlling signs and symptoms of inflammation and slowing tissue destruction. However, some of these drugs may lose efficacy over time or induce adverse events in many patients. Prompt application to the right medication tailored to the patient's molecular status avoids unnecessary costs; labelled agents may help to find out whether

TNFα is present in the inflammatory process and could, as a result, help in prediction of therapeutic efficacy and stratification in each specific patient. Currently available evidence shows different possibilities of labelled anti-TNFα antibodies like ^{99m}Tc-Infliximab and ^{99m}Tc-Adalimumab for diagnosis and therapy, with great potential in clinical practice. Published reports have demonstrated that molecular imaging with anti-TNFα mAbs can be used for cost-effective treatment decisions such as selection of patients who are best candidates for anti-TNFα therapy.

Somatostatin is a cyclic hormone that regulates several cell processes via specific receptors expressed throughout the body. This hormone was initially known only as a regulating factor but today is well recognised as a potent drug and imaging tool. The discovery of its different receptors and molecular subtypes gave raise to interdisciplinary research, leading to the use of somatostatin analogues in routine clinical practice. The high density expression of these receptors in different inflammatory cells and tissues, has allowed chronic inflammatory diseases such as rheumatoid arthritis (RA), Sjögren's disease and idiopathic pulmonary fibrosis, to be evaluated with different radiolabelled somatostatin analogues to be used with SPECT and PET with encouraging results, showing interesting clinical potential. Reported evidence is mainly supported by observational studies designed to investigate different groups of chronic inflammatory conditions:
For endothelial inflammation and vulnerable plaques, the most frequently evaluated pathologic entity with PET somatostatin analogue molecules (^{68}-GaDOTA NOC-TATE-TOC), promising correlations were described between quantitative uptake and histopathology, emphasising the role of somatostatin receptor scintigraphy (SRS) for this condition. In idiopathic pulmonary fibrosis, the reported experience shows attractive results, emphasising the utility of ^{68}Ga and ^{111}In tracers in high concordance with other imaging and functional techniques, demonstrating the activity degree of an inflammatory processes and subsequent implications in prognosis and therapeutic decision making.

RA and Sjögren's disease were also positively impacted by radiolabelled somatostatin analogues. Current evidence shows the capacity of this tool to identify sites of active inflammation and to predict which joints could be successfully treated with biologic drugs. In Sjögren's disease, these novel molecular imaging tools for the first time permit the evaluation of the whole body and allows the detection of secondary sites of non-suspected active inflammation, that traditionally were not possible to evaluate with conventional techniques. Furthermore, these radiolabelled agents showed significant superiority to identify salivary gland compromise compared to sialoscintigraphy, currently included in the ACR/EULAR criteria.

The overall evidence shows that SRS is able to play a crucial role for diagnosis, prognosis and therapy response in different chronic inflammatory diseases. This monography is intended to enrich the vast field of nuclear medicine by gathering in a comprehensive manner the current experience of theranostics in inflammatory diseases.

lkanzola@gmail.com ♦