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Case Report

Imaging of $\alpha_v\beta_3$ integrin expression in rheumatoid arthritis with [^{68}Ga]Ga-NODAGA-RGDyk PET/CT in comparison to [^{18}F]FDG PET/CT

Imagerie de l'expression de l'intégrine $\alpha_v\beta_3$ dans la polyarthrite rhumatoïde en TEP/TDM au [^{68}Ga]Ga-NODAGA-RGDyk en comparaison à la TEP/TDM au [^{18}F]FDG

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ABSTRACT

[^{68}Ga]Ga-NODAGA-RGDyk PET/CT and [^{18}F]FDG PET/CT were performed in a 65-year-old woman during the work-up of a squamous cell carcinoma of the tongue within a clinical study protocol. Images revealed both tracers' uptake in the primary tumor and cervical lymph nodes, but also bilaterally in the shoulders, elbows, wrists, metacarpophalangeal, interphalangeal, and hip joints. The patient had been diagnosed with rheumatoid arthritis 8 years prior to the examination. Images showed a significantly higher [^{18}F]FDG than [^{68}Ga]Ga-NODAGA-RGDyk uptake in primary tumor and cervical lymph nodes. However, the patient with moderately active rheumatoid arthritis had similar levels of [^{68}Ga]Ga-NODAGA-RGDyk and [^{18}F]FDG uptake in the involved joints, but with no [^{68}Ga]Ga-NODAGA-RGDyk uptake in the surrounding muscles, unlike with [^{18}F]FDG. Our case suggests that [^{68}Ga]Ga-NODAGA-RGDyk PET/CT allows imaging of integrins expression in rheumatoid arthritis, including integrins expressed in synovial angiogenesis, with potentially a better signal-to-noise ratio than on [^{18}F]FDG PET/CT.

Mots clés :
Polyarthrite rhumatoïde
Angiogenèse
RGD
FDG
Imagerie par TEP

RÉSUMÉ

Une TEP/TDM au [^{68}Ga]Ga-NODAGA-RGDyk ainsi qu'une TEP/TDM au [^{18}F]FDG ont été réalisées dans le cadre d'un protocole de recherche clinique chez une femme de 65 ans suivie pour un carcinome épidermoïde de la langue. Les images ont révélé des hyperfixations de la tumeur primitive ainsi que des adénopathies cervicales, mais aussi bilatérales des épaules, des coudes, des poignets, des articulations métacarpophalangiennes, interphalangiennes et de la hanche. La patiente avait été diagnostiquée d'une polyarthrite rhumatoïde 8 ans avant l'examen. Les images ont montré une captation du [^{18}F]FDG beaucoup plus intense que celle du [^{68}Ga]Ga-NODAGA-RGDyk dans la tumeur primitive ainsi que dans les adénopathies cervicales. En revanche, chez cette patiente qui présentait des signes cliniques d'activité modérée de polyarthrite rhumatoïde au moment des examens, les articulations hyperfixantes ont montré des taux similaires de captation du [^{68}Ga]Ga-NODAGA-RGDyk et du [^{18}F]FDG, mais sans aucune fixation du [^{68}Ga]Ga-NODAGA-RGDyk dans les muscles environnants contrairement au [^{18}F]FDG. Notre cas suggère que l'imagerie de l'expression des intégrines dans la polyarthrite rhumatoïde, incluant les intégrines exprimées dans l'angiogenèse synoviale, est explorable en TEP/TDM au [^{68}Ga]Ga-NODAGA-RGDyk, avec potentiellement un meilleur rapport signal/bruit qu'en TEP/TDM au [^{18}F]FDG.

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1. Case report

We report the case of a 65-year-old woman who underwent [^{68}Ga]Ga-NODAGA-RGDyk PET/CT and [^{18}F]FDG PET/CT for imaging angiogenesis of a known squamous cell carcinoma of the tongue within a clinical study protocol. The patient was referred for baseline PET/CT scans for staging before receiving chemotherapy and radiotherapy. The protocol was approved by the Ethics Commission Vaud (CER-VD #120/12). A written informed consent was obtained. Images revealed both tracers' uptake in primary tumor and cervical lymph nodes, but also bilaterally in the shoulders, elbows, wrists, metacarpophalangeal, interphalangeal, and hip joints. The patient had been diagnosed with seronegative rheumatoid arthritis (RA) 8 years ago based on the presence of persistent symmetrical polyarthritis with an inflammatory reaction (C-reactive protein 12 mg/L), negativity for anti-cyclic citrullinated peptide antibody and rheumatoid factor, and excellent response after starting corticosteroid therapy. A combination therapy with corticosteroids, methotrexate, and salazopyrine had been initiated, followed later by adalimumab and tocilizumab. At the time of the study, the anti-rheumatic therapy had been suspended during chemotherapy. She presented moderately active rheumatoid arthritis with arthralgia and mild joint swelling of her metacarpophalangeal joints.

[^{68}Ga]Ga-NODAGA-RGDyk PET/CT images were acquired 86 min after intravenous administration of 197 MBq [^{68}Ga]Ga-NODAGA-RGDyk. [^{18}F]FDG PET/CT images were acquired 71 min after intravenous administration of 236 MBq [^{18}F]FDG. [^{68}Ga]Ga-NODAGA-RGDyk in comparison to [^{18}F]FDG PET/CT image demonstrated different distributions in the pathological regions. Compared to [^{68}Ga]Ga-NODAGA-RGDyk images, [^{18}F]FDG images demonstrated a very significantly higher uptake in primary tumor and cervical lymph nodes (Fig. 1). While the patient with moderately active RA had similar levels of [^{68}Ga]Ga-NODAGA-RGDyk and [^{18}F]FDG uptake in the involved joints (mean $\pm$ SD SUV_{max}: 2.00 $\pm$ 0.73 and 2.19 $\pm$ 0.66, respectively). However, [^{68}Ga]-Ga-NODAGA-RGDyk uptake in surrounding muscles was lower than [^{18}F]FDG (SUV_{max} measured in a spherical 3 cm^3 volume of interest drawn in the gluteal muscle: 0.57 and 0.78, respectively); therefore, the mean [^{68}Ga]Ga-NODAGA-RGDyk joint-to-muscle background ratio was higher than [^{18}F]FDG (3.51 $\pm$ 0.73 and 2.80 $\pm$ 0.66, respectively). Movement disorder induced by pain in patients suffering from RA could potentially impair the evaluation of joint inflammation with [^{18}F]FDG PET/CT [1].

RA is an autoimmune disorder of unknown etiology. The disease is characterized by systematic, symmetric, and erosive synovitis. RA synovitis exhibits massive proliferative synovial membranes, leukocyte infiltration, and neovascularization. The formation of synovial proliferative fibrovascular tissue known as pannus is directly responsible for cartilage and bone destruction, integrins playing a central role in triggering this proliferation [2,3].

Various radiolabeled derivatives of arginine-glycine-aspartic acid (RGD)-peptides have been developed for imaging of $\alpha_v\beta_3$ integrin expression [4–7]. Increased $\alpha_v\beta_3$ expression has been

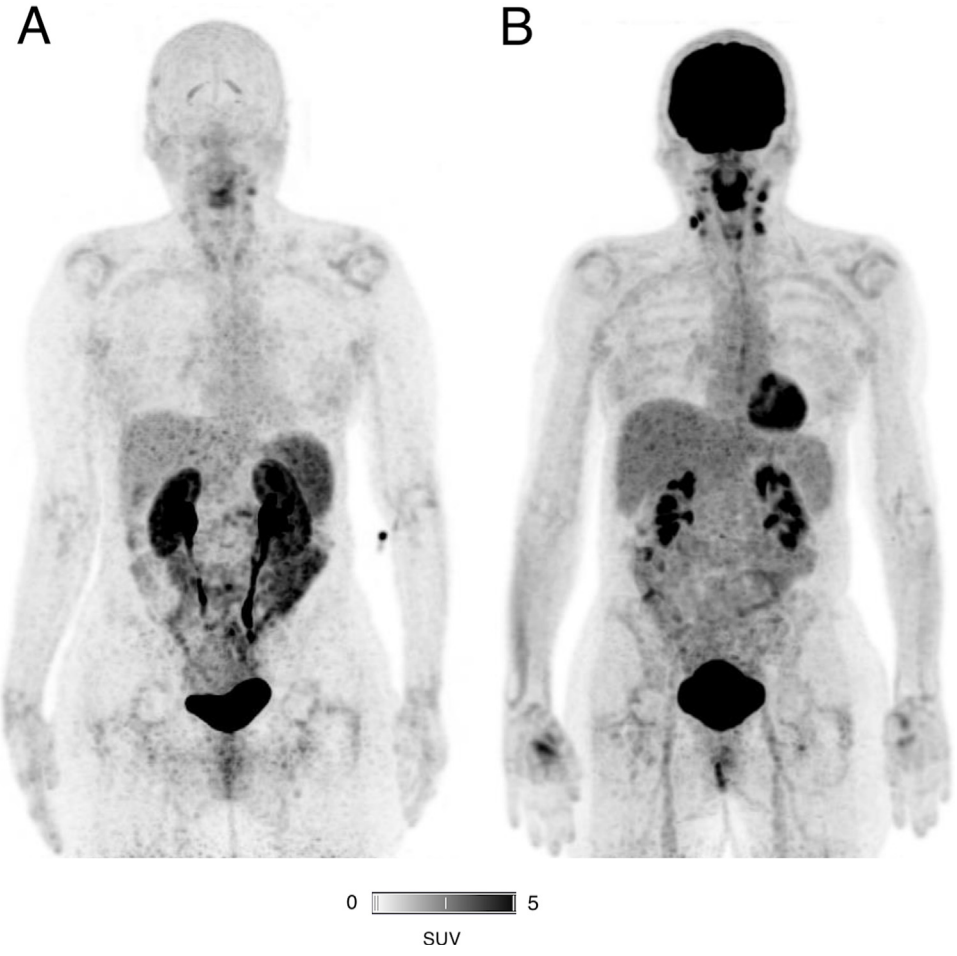

Fig. 1. A. [^{68}Ga]Ga-NODAGA- RGDyk PET/CT maximum intensity projection (MIP) view. B. [^{18}F]FDG PET/CT MIP view.
A. TEP/TDM au [^{68}Ga]Ga-NODAGA-RGDyk, vue maximum intensity projection (MIP). B. TEP/TDM au [^{18}F]FDG, vue MIP.

observed in tumor angiogenesis, new blood vessels formed after myocardial infarction, or blood vessels in chronic inflammatory processes. Integrin $\alpha_v\beta_3$ is also expressed by some cancer cells, such as glioblastoma and melanoma, and in cells involved in extracellular matrix remodeling as well as fibroblasts and activated macrophages [6,7]. NODAGA-RGDyK, (cyclo[L-arginyl-glycyl-L-alpha-aspartyl-D-tyrosyl-N6-([4,7-bis(carboxymethyl)octahydro1H-1,4,7- triazonin- 1-yl]acetyl])-L-lysyl]), is a new RGD peptide designed for PET imaging of $\alpha_v\beta_3$ integrin expression. The compound c(RGDyK) showed high affinity for the integrin $\alpha_v\beta_3$ in vivo binding assays [8]. The component NODAGA is a derivate of the NOTA system which has no influence on receptor-specific binding and possesses high binding properties for radiometals with an ion radius like ^{68}Ga [9]. [^{68}Ga]Ga-NODAGA-RGDyk has favorable biokinetics and safety profile [10,11].

The development of an extensive network of new blood vessels in the synovial membrane is typically found in the evolution of rheumatoid synovitis and evaluation of synovial angiogenesis using PET/CT could be of interest to improve the understanding of this disease [1,12]. Recently, Adipoe et al. showed, in a proof-of-concept study, a strong correlation between power Doppler ultrasound (US) in the joints of patients with RA and the uptake of [^{99m}Tc]Tc-maraciclatide, a radiolabelled tracer containing the RGD tripeptide motif with high affinity for integrin $\alpha_v\beta_3$ dedicated to scintigraphic imaging [13]. Their data are consistent with the previous study from Zhu et al., which preliminarily indicates the potential effectiveness of integrin imaging for evaluating RA joints [1]. Although patients with RA are typically monitored with US which detects synovitis, in a cheaper and non-invasive way, nuclear medicine techniques can provide whole body quantitative information in a single acquisition, with an easier interpretation of scans compared with US or MRI. Such new integrin imaging would mostly be interesting in a research setting, or to easily assess the global burden of the disease, which could potentially guide treatment decisions. Our case suggests that synovial angiogenesis in RA could be depicted using [^{68}Ga]Ga-NODAGA-RGDyk PET/CT, with potentially a higher signal-to-noise background ratio compared with [^{18}F]FDG PET/CT.

Disclosure of interest

The authors declare that they have no competing interest.

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