Upregulated myocardial CXCR4-expression after myocardial infarction assessed by simultaneous GA-68 pentixafor PET/MRI

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INTRODUCTION

Just recently, inflammatory processes after myocardial infarction (MI) as an important additional factor for cardiac remodeling have come to the fore. As a consequence, there is an urgent unmet clinical need for tracers targeting specifically non-pathogen-driven, inflammatory processes in the heart. Here, we present the potential of a novel PET tracer targeting the expression of the chemokine receptor 4 (CXCR4) on inflammatory cells after acute MI. CXCR4 belongs to the family of G-protein-coupled receptors and is involved in biological processes such as the entry of HIV-1, the development of metastasis and several inflammatory conditions. The CXCR4 receptor is expressed only at low levels on the surface of circulating lymphocytes, macrophages, and neutrophils, but is highly upregulated when these cells infiltrate inflamed tissues. In addition, CXCR4 expression is strongly increased on the cell surface under hypoxic conditions via the stimulation of HIF (hypoxia-inducible factor). Therefore, the CXCR4 receptor represents an attractive molecular target to identify the presence of activated inflammatory cells located in the post-ischemic myocardium.

Recently, Ga-68 pentixafor, a ligand with high affinity and selectivity to hCXCR4-receptors[2,3] (IC_{50} = 5 nM) that exhibits excellent pharmacokinetics and dosimetry in humans[4,5] has been introduced and successfully tested in first human studies.[4,6] Due to its rapid blood and renal clearance,[5] pentixafor might also be useful for the detection of inflammatory cells both in atherosclerotic plaques and in the myocardium (Figure 1).

To the best of our knowledge, we describe here for the first time the successful use of Ga-68 pentixafor for the assessment of inflammatory processes in the myocardium in a human by simultaneous PET/MRI.

CASE PRESENTATION

A 53-year-old patient was referred to our hospital with sudden onset of retrosternal pain and excessive sweating. The electrocardiogram showed ST elevations in V1 to V6 and the patient was subsequently sent to the cath lab. The cardiac catheterization revealed an occlusion of the proximal LAD which was recanalized and stented with a drug-eluting stent. After intervention, the CK rose to 5748 U/L and the Troponin T peaked at 12870 ng/mL. On day 3 after MI, the patient underwent a simultaneous Ga-68 pentixafor PET/MRI (Biograph mMR, Siemens Healthcare, Erlangen) as well as a Tc-99m sestamibi SPECT scan (Symbia, Siemens Healthcare, Erlangen). The perfusion scan revealed an absent perfusion in the LAD territory including the apex. Late gadolinium enhancement images demonstrated transmural scar tissue and microvascular obstruction in the same location as well as a left ventricular thrombus in the apex. Ga-68 pentixafor PET images showed markedly increased CXCR4 expression in the infarct area, indicating active inflammatory processes at the site of infarction (Figure 1).

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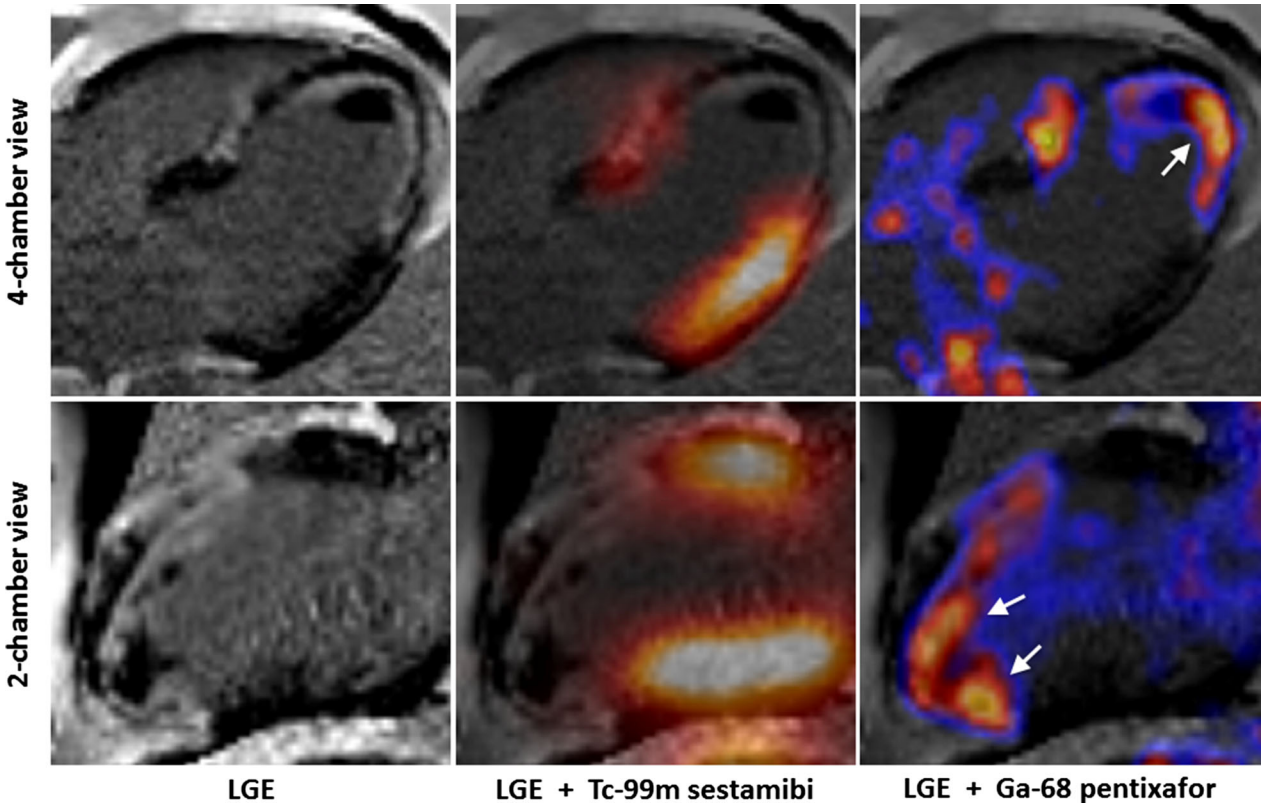

Figure 1. 2- and 4-chamber views of the late gadolinium enhancement (LGE) MR images show transmural scar in the LAD territory. Furthermore, large areas of microvascular obstruction and a left ventricular thrombus can be observed (*left column*). Tc-99m sestamibi SPECT images demonstrate absent perfusion corresponding to the scar area on MR images (*middle column*). Ga-68 pentixafor PET images reveal markedly increased CXCR4 expression in the infarct area, indicating active inflammatory processes (*right column*).

DISCUSSION

Despite advances in medical and interventional therapy after MI, many surviving patients still develop heart failure. Optimal outcome after MI depends on a coordinated healing process that balances debris removal with repair of the myocardial extracellular matrix. An excessive inflammatory response after acute MI might both promote adverse remodeling and heart failure. Development of imaging techniques, which allows for precise evaluation of the immune response taking place in the heart after acute MI, might help select those patients who could benefit from specific treatments aimed at reducing the anti-inflammatory reaction in the myocardium.[1] However, no specific imaging biomarker is available to monitor post-infarct inflammation.

In most studies investigating inflammation after MI, F-18 fluorodeoxyglucose (FDG) was the employed tracer. The most important limitation of FDG is, however, its non-specific uptake in cells with glycolytic metabolism. In particular, myocardial and skeletal muscle frequently exhibit increased FDG uptake, which often hampers a precise and accurate analysis. In addition, imaging with FDG requires patients to fast at least 6 to 12 hours before radiotracer injection to reduce unspecific uptake by myocardial cells and is often associated with poor image contrast in diabetic patients. Consequently, there is an urgent clinical need for new molecular imaging biomarkers targeting specifically activated inflammatory cells in the post-ischemic myocardium. The data obtained in this case demonstrate that Ga-68 pentixafor is a promising new tracer to address that medical need.

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