Imaging myocardial inflammation of various etiologies with ^{99m}Tc-depreotide SPET/CT

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Abstract

Previous reports suggested the accumulation of technetium-99m-depreotide trifluoroacetate (^{99m}Tc-D) at the sites of active infection or inflammation. Binding of depreotide to over-expressed somatostatin receptors in activated lymphocytes and macrophages probably accounts for the depiction of inflammation. We speculated that myocardial inflammation could also be illustrated by ^{99m}Tc-D scintigraphy. *We report on 3 patients* with the clinical diagnosis of myocarditis of various etiologies, in which ^{99m}Tc-D SPET/CT demonstrated obvious tracer uptake in the myocardium of the left ventricle. *In conclusion*, we suggest that depreotide imaging can depict myocardial inflammation, thus supporting clinical diagnosis.

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Introduction

A wide spectrum of tissue injury can affect myocardium. Non-invasive differentiation of these injuries is clinically important. Myocarditis is included among these injuries, and is defined as inflammation of myocardial tissue [1]. It is an uncommon, potentially life-threatening disease that presents with a wide range of symptoms. Myocarditis has been reported in up to 12% of young adults presenting with sudden death and is an important underlying etiology of other myocardial diseases [2]. Most often, myocarditis is due to common viral infections, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated. In patients with a clinical history, symptoms, and clinical findings that suggest acute myocardial disease, a combination of electrocardiogram (ECG) and seromarkers such as troponin are usually used to determine acuity, extent, and location of the myocardial injury [3]. However, current diagnostic approaches have limitations. The accuracy of ECG to detect myocardial inflammation is often low, and this may result in inappropriate treatment [4]. Serum biomarkers of myocardial injury such as creatine kinase, CK-MB and troponin may be increased, but the prevalence of an increased troponin T in biopsy-proven myocarditis, however, is only 35%-45% [5]. Although endomyocardial biopsy has been considered the gold standard for many years, in recent years cardiac magnetic resonance imaging (CMR) seems to have a significant role in non-invasive diagnosis of myocarditis. We report on 3 patients with various types of myocarditis imaged with ^{99m}Tc-D.

Method

In all patients the diagnosis of myocardial inflammation was based on history, clinical signs, ECG, laboratory and echocardiographic data and negative coronary angiography. A CMR study was undertaken in two of the cases and provided evidence of myocarditis. No myocardial biopsy samples were obtained.

Patients were imaged within 7-15 days from clinical presentation, 3h after the intravenous administration of 740MBq ^{99m}Tc-D, (NeoSPECT^{TM}, CIS bio International, France). Planar views in anterior and left anterior oblique projections were obtained, followed by single photon emission tomography/ computerized tomography (SPET/CT) performed by a hybrid system (Millenium VG gamma camera with the "Hawkeye" facility, GE Medical Systems, USA). A written informed consent was received by the patients. In one patient there was a follow-up study a few months later. Quantification of ^{99m}Tc-D uptake was undertaken on attenuation-corrected coronal slices and was achieved by means of regions of interest (ROI) drawn over the myocardium of the left ventricle (LV) and over adjacent ribs. The ratio of the myocardial counts to the average counts of 3 consecutive ribs was calculated. Based

on our experience from SPET/CT imaging in patients evaluated for solitary pulmonary nodules, as well as for the initial staging of malignant lymphoma [6], slight uptake of ^{99m}Tc-D in the myocardium is a common finding and should be considered as normal. The normal range was determined from a cohort of 85 such patients. The average ±SD of myocardium/rib ratio was found to be 0.68±13, resulting in a upper normal value (average+2SD) of 0.94.

Case 1

The first case was a 23 years old male, admitted to the Emergency Department with chest pain, ST-segment elevation in V2-V5 leads, and increased cardiac troponin I (cTnI). Echocardiography revealed moderate lateral wall hypokinesis, and a very small quantity of pericardial effusion. LV ejection fraction (EF) was 45%. A week prior to admission the patient was diagnosed with orchitis-epididymitis of unknown etiology. The clinical diagnosis was viral myo-pericarditis. Imaging with ^{99m}Tc-D demonstrated diffusely increased tracer uptake in the myocardium (Fig. 1), in line with the clinical diagnosis. The myocardium/rib uptake ratio was 1.2. Results of a CMR study performed a few days later were concordant with the scintigraphic findings. The patient after hospitalization and proper medical treatment had an uncomplicated course with gradual improvement of symptoms and cardiac function.

Case 2

The second patient was a 35 years old female presenting with exertional dyspnea 3 months after a normal birth delivery. The patient had reduced LV performance (EF 40%) and moderate enlargement of right and left ventricles. The echocardiographic findings met the criteria of peripartum cardiomyopathy (PCM). Clinical and laboratory markers (C-reactive protein, cTnI) were indicative of myocardial inflammation. There was no history of cardiologic disease before pregnancy. Clinical diagnosis was PCM. Depreotide imaging depicted increased myocardium uptake, with an uptake ratio of 1.9, indicating myocardial inflammation (Fig. 2). The patient, during and after hospitalization, was given medical treatment for heart failure, but was lost from follow up thereafter.

Case 3

The third patient was a 28 years old female with multiple sclerosis on interferon-beta-1a therapy, presenting with exertional dyspnea. Cardiac troponins were marginally elevated and ECG revealed T-wave inversion in all leads. Echocardiography demonstrated moderate left ventricular enlargement with diffuse hypokinesis. The EF was 35%. Serologic test for common viral infections was negative. Clinical diagnosis was myocarditis of unknown etiology (possibly of autoimmune origin or interferon-induced). Depreotide imaging demonstrated increased myocardium uptake, with myocardium/rib ratio 1.83 (Fig. 3). Findings from CMR were consistent with myocardial inflammation. The patient received medical treatment for heart failure plus corticosteroids, while interferon was discontinued. Two months later the patient was symptom-free with echocardiography demonstrating a significant improvement in LV performance. A second nuclear study revealed a decrease of the ratio of myocardium/rib uptake to 1.27, in concordance with objective improvement (Fig. 3).

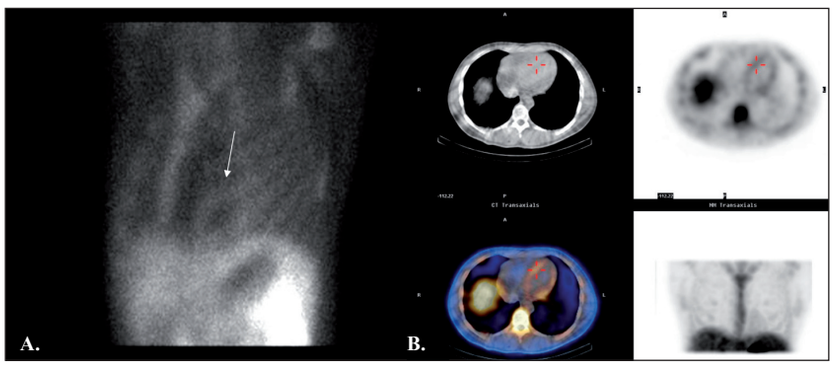

Figure 1. Images of case 1. **A**. Left anterior oblique planar view demonstrates increased depreotide myocardium uptake (white arrow). **B**. Transverse CT, SPET, fused and MIP images of the SPET/CT study confirm diffusely increased uptake in the left ventricle. Myocardium/rib uptake ratio =1.2 (upper normal limit = 0.94).

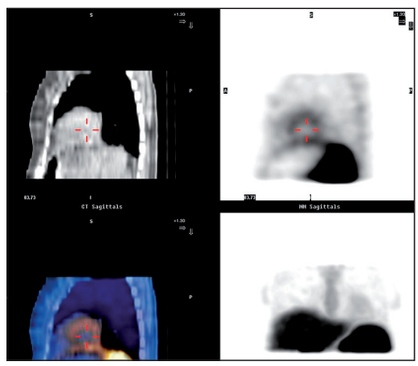

Figure 2. Images of case 2. Sagittal CT, SPET, fused and MIP images demonstrating myocardium with increased depreotide uptake (myocardium/rib ratio =1.9).

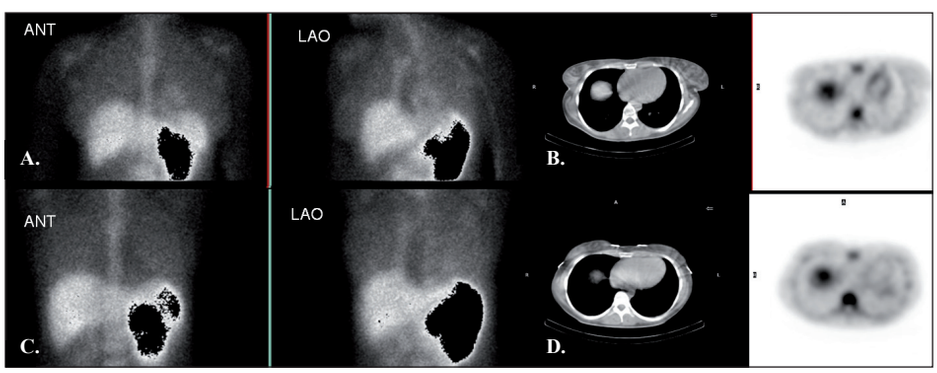

Figure 3. Images of case 3. **A** . Anterior and left anterior oblique planar views during acute phase demonstrate increased depreotide myocardial uptake. **B**. Two months later with the patient in remission, obviously reduced uptake is evident in the same views. **C**. Transverse CT and SPET images during acute phase, and **D**. Two months later. Myocardium/rib ratio decreased from 1.82 to 1.27.

Discussion

It is assumed that the true incidence of non-fatal myocarditis is higher than actually diagnosed, mostly due to the challenges of establishing the diagnosis in standard clinical settings [1]. Typically, in older patients myocarditis is diagnosed only after excluding ischemic heart disease. Although diagnosis is usually based on clinical, laboratory, ECG, and echocardiographic findings, endomyocardial biopsy may be indicated in selected cases. The Dallas criteria were proposed in 1986 to provide a histopathologic classification for the diagnosis of myocarditis [7]. Although these criteria have been used for more than 20 years, they are limited by variability in expert interpretation, lack of prognostic value, discrepancy with other markers of viral infection and immune activation in the myocardium, and low sensitivity that is at least partly due to sampling error [8]. Newer techniques, based on immunohistochemistry, seem to have greater sensitivity than the Dallas criteria and may have better prognostic value [9]. A recent consensus statement recommends that endomyocardial biopsy should be reserved for patients with heart failure who are likely to have specific myocardial disorders with unique prognoses and specific treatment recommendations [10].

Non-ivasive imaging of myocarditis seems to have an increasingly important role in diagnosis. Historically, indium-111 antimyosin antibody and gallium-67 citrate nuclear imaging have been used to diagnose myocarditis [11]. In current clinical practice, nuclear medicine is only rarely used to diagnose myocarditis. The CMR is used with increasing frequency for non-invasive assessment of patients with suspected myocarditis. With a unique potential for tissue characterization, particularly with the use of T1- and T2-weighted images, CMR can evaluate three markers of tissue injury, that is, intracellular and interstitial edema, hyperemia and capillary leakage, and necrosis and fibrosis [7]. So, CMR has become the primary tool for non-invasive assessment of myocardial inflammation in patients with suspected myocarditis. A recent white paper, written by the International Consensus Group on Cardiovascular Magnetic Resonance in Myocarditis, states that "a cardiac MRI study should be performed in symptomatic patients with clinical suspicion of myocarditis in whom the MRI results will affect clinical management" [1].

Technetium-99m-depreotide has been used for the investigation of solitary pulmonary nodules and lung cancer imaging [12, 13]. There have been previous reports regarding the accumulation of ^{99m}Tc-D at the site of active infection or inflammation [14]. Our group has published a case with myocardial ^{99m}Tc-D uptake in a patient with thrombotic thrombocytopenic purpura, indicating inflammatory reaction to thrombotic/hemorrhagic myocardial damage [15]. Based on the aforementioned data, and due to the fact that our hospital has no CMR available, we speculated that we could depict myocarditis with ^{99m}Tc-D imaging. To the best of our knowledge there is no other report in the literature regarding imaging of myocardial inflammation with ^{99m}Tc-D.

The first patient had a viral induced myocarditis after orchitis-epididymitis. Myocardial inflammation could be depicted satisfactorily with depreotide. Myocarditis was also indicated by cardiac MRI findings.

The second patient had a clinical diagnosis of peripartum cardiomyopathy, a relatively rare disease with an incidence of approximately 1/2000-3000 live-births. In some cases PCM can have devastating consequences and should be promptly identified and correctly treated [16]. Overall prognosis of PCM is good in the majority of cases, although some patients may progress to irreversible heart failure. Early diagnosis is important and effective treatment reduces mortality rates and increases the chance of complete recovery of ventricular systolic function. The criteria for diagnosis are: the development of heart failure in the last month of pregnancy or within 5 months of delivery; the absence of a determinable etiology for heart failure; and the absence of demonstrable heart disease before the last month of pregnancy [17]. Echographic parameters of LVEF < 45% and end-diastolic dimension index of greater than 2.7cm/m2 have been proposed to better classify the dysfunction [18]. The etiology of PCM is still unknown, and many potential causes have been proposed but not proven. The etiology is not fully understood and several physiopathological mechanisms have been proposed, including viral myocarditis, abnormal immune response to pregnancy, abnormal response to the haemodynamic stress of pregnancy, increased myocyte apoptosis, cytokine-mediated inflammation, excessive prolactin production etc. Recent research has suggested an increased role of prolactin metabolism in PCM in susceptible patients [19, 20]. Molecular markers of an inflammatory process are found in most of the patients, with 90% of the patients showing high levels of plasma C-reactive protein. This could indicate a chronic inflammatory state, which is higher in more unstable patients [21]. Small series of patients with PCM imaged with MRI have been published and demonstrated signs of myocardial inflammation [22]. The presence of inflammation in PCM, regardless of the etiologic factor, could explain the increased depreotide myocardial uptake in our patient.

The clinical diagnosis of the third patient was myocarditis of undefined etiology. Although there are a few reports of interferon induced myocarditis, these concern mainly interferon-α [23] and interferon-γ [24], although there are conflicting results. There are few reports connecting interferon-beta with myocarditis induction as side effect. In contrast, interferon-beta has been used for treatment of some viral origin myocarditis [25]. Autoimmune myocarditis is another possible cause, since the patient suffered from multiple sclerosis. There is also evidence for an increased occurrence of other autoimmune diseases in patients with multiple sclerosis and their first-degree relatives [26]. There is a case report of a patient with multiple sclerosis and idiopathic dilated myocardiopathy [27], which is considered by some investigators of autoimmune origin [28]. The development of autoimmunity to cardiac muscle in response to infectious or other stimuli has been proposed as a mechanism by which myocarditis leads to dilated cardiomyopathy. Irrespective of the etiology, myocardial inflammation demonstrated by CMR was also depicted by depreotide imaging.

In conclusion, in the three cases presented here with suspected myocarditis, unequivocally increased myocardial uptake of ^{99m}Tc-D was evident on SPET/CT scintigraphy, which supported the clinical diagnosis. The current work indicates that this agent depicts myocardial inflammation of various aetiologies and could be useful in clinical practice. Obviously, a firm conclusion can not been drawn from a few cases. Experimental data and larger clinical studies are needed to confirm these findings.

The authors declare that they have no conflicts of interest.

Bibliography

1. Friedrich MG., Sechtem U, Schulz-Menger J et al. Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. *J Am Coll Cardiol* 2009; 53: 1475-87.
2. Doolan A, Langois N, Semsarian C et al. Causes of sudden cardiac death in young Australians. *Med J Aust* 2004; 180: 110-2.
3. Stensaeth KH, Hoffmann P, Fossum E et al. Cardiac magnetic resonance visualizes acute and chronic myocardial injuries in myocarditis. *Int J Cardiovasc Imaging* 2011.DOI 10.1007/s10554-011-9812-7.
4. Masoudi FA, Magid DJ, Vinson DR et al. Implications of the failure to identify high-risk electrocardiogram findings for the quality of care of patients with acute myocardial infarction: results of the Emergency Department Quality in Myocardial Infarction (EDQMI) study. *Circulation* 2006; 114: 1565-71.
5. Morgera T, Di Lenarda A, Dreas L et al. Electrocardiography of myocarditis revisited: clinical and prognostic significance of electrocardiographic changes. *Am Heart J* 1992; 124: 455-67.
6. Apostolopoulos DJ, Papandrianos NI, Symeonidis et al. Technetium-99m depreotide imaging by single photon emission tomography/low resolution computed tomography in malignant lymphomas: comparison with gallium-67 citrate. *Ann Nucl Med* 2010; 9: 639-47.
7. .Blauwet LA, Cooper LT. Myocarditis. *Progress in Cardiovascular Diseases* 2010; 52: 274-28.
8. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation* 2006; 11: 593-5.
9. Kindermann I, Kindermann M, Kandolf R et al. Predictors of outcome in patients with suspected myocarditis, *Circulation* 2008; 118: 639-48.
10. Cooper LT, Baughman KL, Feldman AM et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Circulation* 2007; 116: 2216-33.
11. Sarda L, Colin P, Boccara F et al. Myocarditis in patients with clinical presentation of myocardial infarction and normal coronary angiograms. *J Am Coll Cardiol* 2001; 37: 786-92.
12. Boundas D, Arsos G, Karatzas N et al. The contribution of conventional nuclear molecular imaging in characterising the nature of a growing solitary pulmonary nodule. Report of a case. *Hell J Nucl Med* 2007; 10: 29-32.
13. Boundas D, Karatzas N. Nuclear medicine procedures in lung cancer imaging. *Hell J Nucl Med* 2004; 7: 149-57.
14. Papathanasiou ND, Rondogianni PE, Pianou NK et al. ^{99m}Tc-depreotide in the evaluation of bone infection and inflammation. *Nucl Med Commun* 2008; 29: 239-46.
15. Spyridonidis T, Patsouras N, Papandrianos N et al. ^{99m}Tc-Depreotide SPECT/CT depicts myocardial involvement in a case of thrombotic thrombocytopenic purpura. *Clin Nucl Med* 2008; 33: 874-5.
16. Cemin R, Janardhanan R, Daves M. Peripartum Cardiomyopathy: An Intriguing Challenge. Case Report with Literature Review. *Current Cardiology Reviews* 2009; 5: 268-72.
17. Elkayam U. Clinical Characteristics of Peripartum Cardiomyopathy in the United States: Diagnosis, Prognosis, and Management. *JACC* 2011; 54: 659-70.
18. Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. *Obstet Gynecol* 1999; 94: 311-6.
19. Hilfiker-Kleiner D, Kaminski K, Podewski E et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007; 128: 589-600.
20. Sliwa K, Blauwet L, Tibazarwa K et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof of concept pilot study. *Circulation* 2010; 121: 1465-73.
21. Sliwa K, Forster O, Libhaber E et al. Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. *Eur Heart J* 2006; 27: 441-6.
22. Renz DM, Röttgen R, Habedank R. Neue Erkenntnisse der peripartalen Kardiomyopathie durch die Magnetresonanztomografie des Herzens. *Herz* 2011; 183: 834-41.
23. Khakoo A, Halushka M, Rame E et al. Reversible cardiomyopathy caused by administration of interferon α. *Nature Reviews Cardiology* 2005; 2: 53-7.
24. Reifenberg K, Lehr HA, Torzewski M et al. Interferon-gamma induces chronic active myocarditis and cardiomyopathy in transgenic mice. *Am J Pathol* 2007; 171: 463-72.
25. Kuehl U, Pauschinger M, Schwimmbeck PL et al. Interferon-β treatment eliminates cardiotropic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. *Circulation* 2003; 107: 2793-8.
26. Henderson RD, Bain CJ, Pender MP. The occurrence of autoimmune diseases in patients with multiple sclerosis and their families. *J Clin Neurosci* 2000; 7: 434-7.
27. Sellbach A, Pender M. Multiple Sclerosis with Idiopathic Dilated Cardiomyopathy: A Case Report. *European Neurology* 2005; 53: 214-5.
28. Mobini R, Maschke H, Waagstein F. New insights into the pathogenesis of dilated cardiomyopathy: Possible underlying autoimmune mechanisms and therapy. *Autoimmun Rev* 2004; 3: 277-84.