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A patient with type I CD36 deficiency whose myocardium accumulated ^{123}I-BMIPP after 4 years

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A 73-year-old man with aortic regurgitation was examined by ^{123}I-α-methyl-*p*-iodophenyl-pentadecanoic acid (BMIPP) myocardial single photon emission computed tomography (SPECT) in 1995. Myocardial accumulation was not evident on either the early or the delayed image obtained 15 minutes and 3 hours, respectively, after injecting ^{123}I-BMIPP. Flow cytometric analysis of CD36 expression in monocytes and platelets identified a type I CD36 deficiency. The patient was hospitalized for severe heart failure in 1999. Upon admission, the cardiothoracic ratio on chest X-rays was 73%, and the left ventricular end-diastolic diameter on echocardiograms was enlarged to 77 mm. On the second day, we performed ^{123}I-BMIPP myocardial SPECT. Myocardial accumulation was evident in the delayed, but not in the early image. We repeated ^{123}I-BMIPP myocardial SPECT on the 10th day after admission. Myocardial accumulation was evident on both early and delayed images. ^{99m}Tc-tetrofosmin myocardial SPECT was immediately performed after ^{123}I-BMIPP myocardial SPECT to distinguish myocardial from pooling images in the left ventricle, but, because the images from both ^{99m}Tc-tetrofosmin and ^{123}I-BMIPP myocardial SPECT were idential, we considered that the ^{123}I-BMIPP myocardial SPECT images reflected the actual myocardial condition.

The CD36 molecule transports long-chain fatty acid (LCFA) on the myocardial membrane, but ^{123}I-BMIPP scintigraphy does not show any myocardial accumulation in patients with type I CD36 deficiency, indicating that myocardial LCFA uptake occurs through CD36 on the human myocardial membrane. Even though our patient had type I CD36 deficiency, BMIPP was uptaken by the myocardium during heart failure, suggesting a variant pathway on the human myocardial membrane for LCFA uptake.

Key words: BMIPP, type I CD36 deficiency, myocardial uptake

INTRODUCTION

CD36 is a multifunctional membrane glycoprotein that acts as a receptor for thrombospondin, collagen and oxidized low density lipoprotein.[1–4] A recent report indicates that the myocardium does not accumulate ^{123}I-15-(*p*-iodophenyl)-3-*R,S*-methylpentadecanoic acid (^{123}I-BMIPP), which is a branched long chain fatty acid found in patients with type I CD36 deficiency. This suggested that CD36 is a myocardial receptor for long chain fatty acids (LCFA).[5–7] The present study examines a patient with type I CD36 deficiency whose myocardium accumulated ^{123}I-BMIPP in 1999, but not in 1995.

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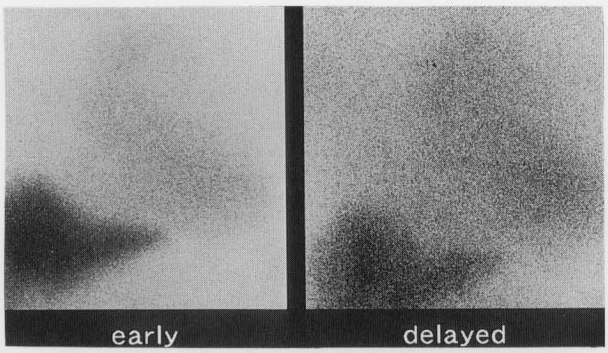
CASE REPORT

A 73-year-old male was admitted to our hospital because of difficulty breathing at rest. He had been diagnosed with hypertension and mild diabetes mellitus (HbA_{1C},

5.6–6.0%) in 1985. He was originally admitted to our hospital in 1993 because of congestive heart failure based on aortic regurgitation. Coronary angiography at that time showed no stenosis. He was hospitalized several times after this episode, so valve replacement was recommended, but he refused surgery; so medical treatment was continued. He was given verapamil 80 mg, isosorbide dinitrate 40 mg, furosemide 40 mg, pironolactone 10 mg, enalapril 2.5 mg, digoxin 0.25 mg, warfarin 3.0 mg, and aspirin 80 mg.

He was admitted to our hospital again because of congestive heart failure in 1995. A blood analysis examination showed blood glucose 124 mg/dl (–119); Free fatty acid, 1.28 mEq/l (0.10–0.80); total cholesterol, 193 mg/dl (–220); triglyceride, 111 mg/dl (–170); high density lipoprotein, 66 mg/dl (29–70). The cardiothoracic ratio on chest X-ray was 64%. Echocardiography revealed an end-diastolic dimension of the left ventricle of 69 mm; an end-systolic dimension of 53 mm; a fractional shortening of 22%; an ejection fraction of 43%; a left atrium diameter of 24 mm and an aortic diameter of 40 mm with severe aortic and mild mitral regurgitation. ^{123}I-BMIPP myocardial scintigraphy was performed to estimate myocardial fatty acid metabolism. While fasting at rest, 111 MBq of BMIPP (Nihon Medi-Physics Co., Nishinomiya, Japan) was intravenously injected, then anterior planar and single photon emission computed tomography (SPECT) images were obtained 15 minutes and 3 hours later with a digital gamma camera (901A; Toshiba Co., Tokyo, Japan) to which a collimator exclusively for ^{123}I was attached. In the planar study, data were obtained for 5 minutes and collected on a 128 × 128 matrix. SPECT data were collected from a 64 × 64 matrix in 32 directions, namely every 6° between a left posterior oblique angle of 45° and a right anterior oblique angle of 45° for 30 seconds per direction. Data were entered into an on-line nuclear medicine data processor (GMS550U; Toshiba Co., Tokyo, Japan). The original image was reconstituted by smoothing at 5 points. Tomographic images along the vertical long, horizontal long and short axes were created with a Shepp & Logan filter. The threshold level was 20% and absorption was not corrected. The heart-to-mediastinum uptake ratio (H/M) was calculated as the average count per pixel in the left ventricular myocardium divided by the average count per pixel in the upper mediastinum and used as an index of myocardial ^{123}I-BMIPP uptake from the planar image. The normal vales for H/M on early and delayed ^{123}I-BMIPP images in our hospital were 2.6 ± 0.2, 2.2 ± 0.2, respectively. In this patient, myocardial scintigraphy with ^{123}I-BMIPP revealed no myocardial accumulation (Fig. 1a, b) and the heart-to-mediastinum uptake ratios (H/M) on early and delayed images were 1.1 and



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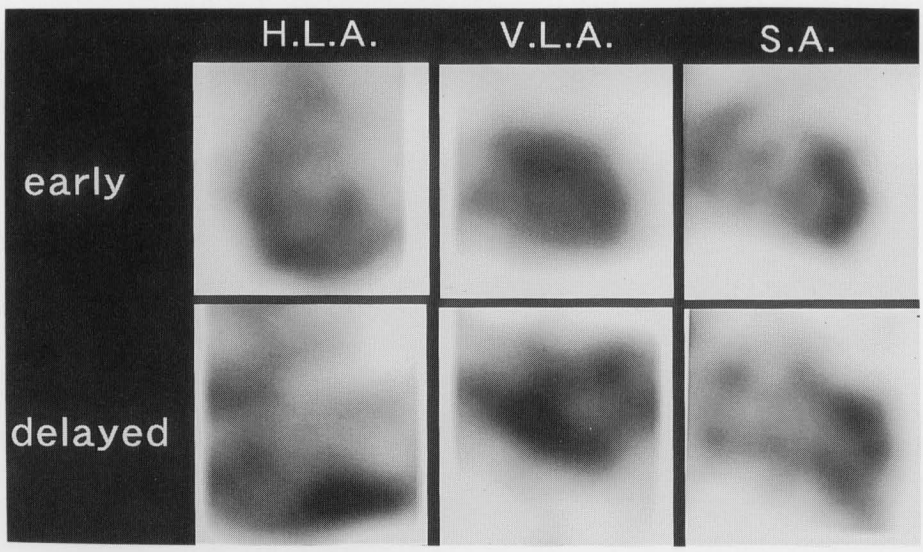


b

Fig. 1 ^{123}I-BMIPP myocardial planar and SPECT myocardial images in 1995. Planar images (a) reveal no myocardial ^{123}I-BMIPP uptake and SPECT images (b) show neither myocardial ^{123}I-BMIPP uptake nor pooling in the left ventricle.

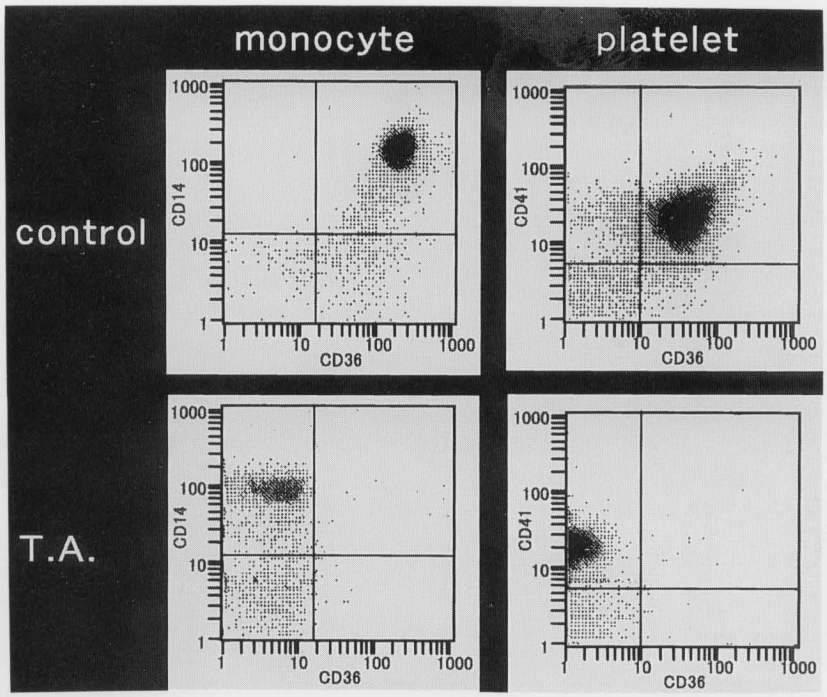


Fig. 2 Flow cytometric analysis of CD36 expression on the surfaces of monocytes and platelets. CD36 is expressed on surfaces of control monocytes and platelets, but not on those from the patient.

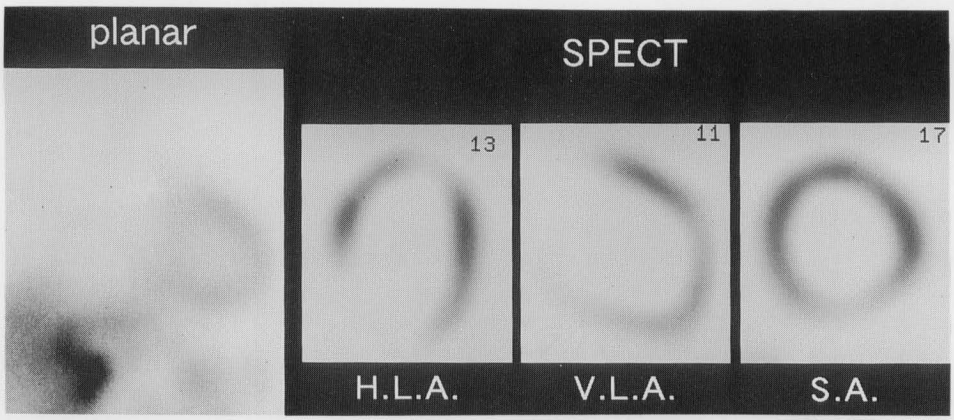
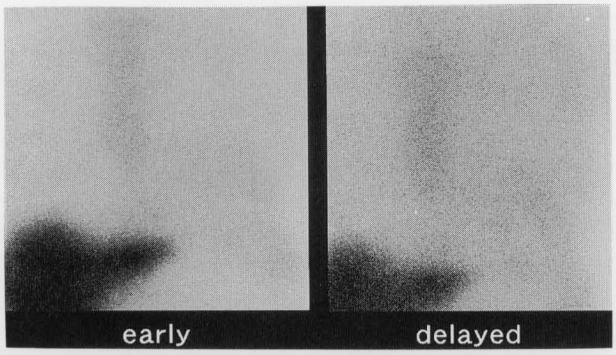


Fig. 3 ^{99m}Tc-tetrofosmin myocardial planar and SPECT images in 1995. Planar and SPECT images show myocardial accumulation.

1.2, respectively. Flow cytometry revealed the absence of CD36 expression on both platelets and monocytes (Fig. 2), so the patient was diagnosed with a type I CD36 deficiency. Myocardial perfusion images were also obtained with a low energy, high-resolution, parallel-hole collimator 30 minutes after 740 MBq of ^{99m}Tc-tetrofosmin (Nihon Medi-Physics Co., Nishinomiya, Japan) was intravenously injected. The image processing and data analyses were similar to those for ^{123}I-BMIPP, except that the duration of imaging in one direction was 20 seconds. ^{99m}Tc-tetrofosmin myocardial SPECT showed myocardial accumulation (Fig. 3).

After contracting a cold in 1999, with severe appetite loss and breathing difficulty, the patient again attended our hospital. Upon admission, his blood pressure was 126 over 82 mmHg, and his pulse was 118 beats per minute with a regular rhythm. A diastolic regurgitant murmur and moist rale were audible. Pitting edema was evident in the lower extremities. A blood chemistry analysis showed blood glucose 132 mg/d*l*; free fatty acid 1.08 mEq/*l*; total cholesterol 191 mg/d*l*; triglyceride 137 mg/d*l*; high density lipoprotein 42 mg/d*l* and brain natriuretic peptide 950 pg/m*l* (–18.4). A specimen of arterial blood under oxygen inhalation (3 *l*/min) revealed an oxygen partial pressure of 115.8 mmHg, a carbon dioxide partial pressure of 51.9 mmHg and pH 7.337. The cardiothoracic rate on chest



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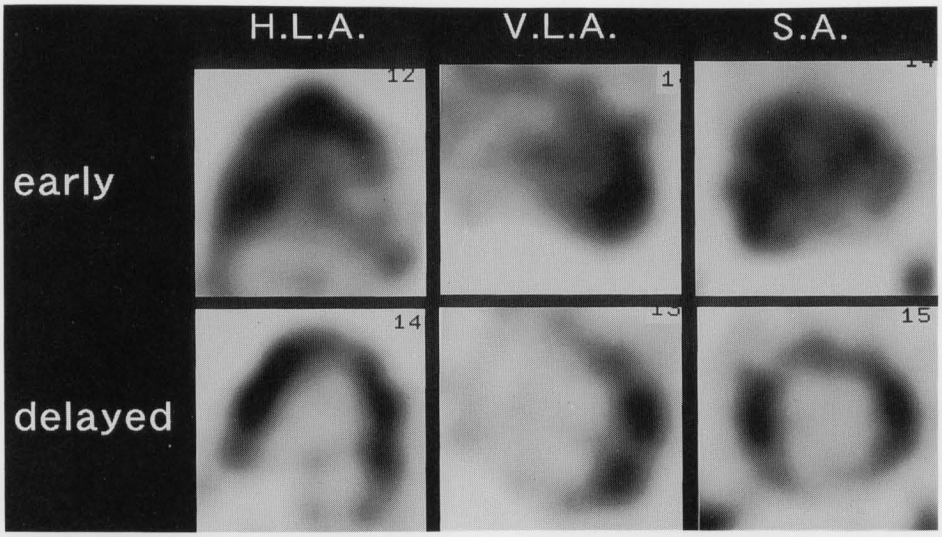

b

Fig. 4 ^{123}I-BMIPP myocardial planar and SPECT images on day 2 of hospitalization in 1999. (a) Planar images reveal myocardial BMIPP uptake, degree of BMIPP pooling in left ventricle and great blood vessels is reduced compared with 1995. (b) Early SPECT images show pooling, delayed images revealed myocardial uptake.

X-rays was enlarged to 73%. Echocardiography revealed an end-diastolic dimension of the left ventricle of 77 mm; an end-systolic dimension of 68 mm; a fractional shortening of 10%; an ejection fraction of 22%; a left atrium diameter of 34 mm and an aortic diameter of 42 mm with severe aortic and mitral regurgitation accompanied by moderate pulmonary and tricuspid regurgitation.

We performed ^{123}I-BMIPP myocardial scintigraphy on the day after admission with the same apparatus, image processing and data analysis procedures that we used in 1995. Although the early images revealed cardiovascular pooling as they did in 1995, the delayed images showed mild myocardial accumulation (Fig. 4a, b). The H/M values on the early and delayed planar images were 1.3 and 1.6, respectively. A few days later, because the patient fell into respiratory failure due to complicating pneumonia, so he was placed on a respirator. Although he recovered from respiratory failure, congestive heart failure did not significantly improve. Premature ventricular contractions were frequently observed on monitor electrocardiograms, so we performed ^{123}I-BMIPP myocardial scintigraphy again on the tenth day after admission. Myocardial ^{123}I-BMIPP accumulated according to the early and delayed SPECT images (Fig. 5). The H/M values on the early and delayed planar images were 1.6 and 1.7, respectively. ^{99m}Tc-tetrofosmin myocardial SPECT performed immediately after ^{123}I-BMIPP myocardial SPECT showed the same myocardial images as ^{123}I-BMIPP myocardial SPECT (Fig. 5). Therefore, the ^{123}I-BMIPP myocardial SPECT images were considered as the true myocardial images. Another flow cytometric analysis revealed the absence of CD36 expression on both platelets and monocytes. Two days later, the patient developed sudden ventricular tachycardia and fibrillation. Despite cardiopulmonary resuscitation, he died.

DISCUSSION

The heart requires large amounts of energy to maintain the pumping function that supplies blood to all systemic organs. Between 60% and 90% of the energy requirement is supplied by fatty acid metabolism, which is the most efficient means of energy production, but the mechanism of myocardial uptake of fatty acid from the blood has not been fully elucidated.

The branched chain fatty acid, ^{123}I-BMIPP, was devel-

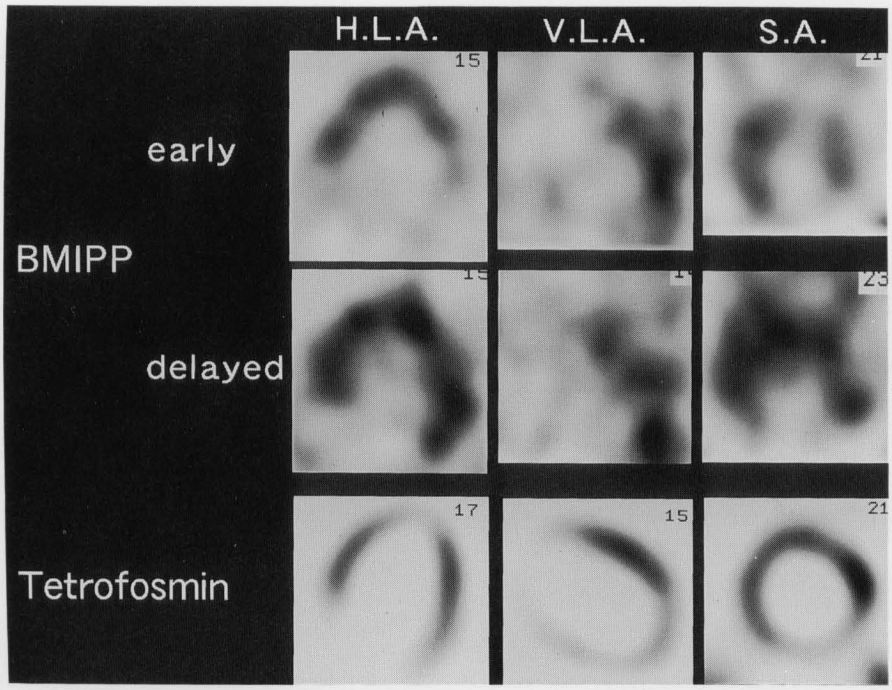

Fig. 5 ^{123}I-BMIPP and ^{99m}Tc-tetrofosmin myocardial SPECT images on the tenth hospital day in 1999. Both early and delayed ^{123}I-BMIPP images show myocardial uptake. ^{99m}Tc-tetrofosmin images obtained immediately after ^{123}I-BMIPP imaging show myocardial uptake similar to that of ^{123}I-BMIPP images.

oped to investigate myocardial fatty acid metabolism for SPECT imaging. This procedure is widely applied for diagnosing heart diseases and evaluating pathological conditions.[8,9] Several recent reports indicated that myocardial ^{123}I-BMIPP does not accumulate in patients with a type I CD36 deficiency, suggesting that LCFA such as ^{123}I-BMIPP are taken into the myocardium from the blood via CD36.[2,5–7,10,11]

^{123}I-BMIPP did not accumulate in the myocardium of the patient described here in 1995, and flow cytometry showed an absence of CD36 expression on both platelets and monocytes in 1995 and 1999. Therefore, the patient was diagnosed as being type I CD36 deficient. He developed congestive heart failure based on aortic regurgitation. Despite medical treatment, his condition progressively deteriorated over the next four years. He was again admitted to our hospital because of congestive heart failure in 1999.

On the second day after admission in 1999, mild myocardial accumulation was evident on delayed images of ^{123}I-BMIPP myocardial SPECT. Furthermore, on the tenth day, mild myocardial ^{123}I-BMIPP accumulated according to both the early and delayed images, and the H/M value on planar images had increased. These findings suggested that a different pathway and/or mechanism was responsible for fatty acid uptake into the myocardium from the blood. The lipid concentrations in 1995 and in 1999 did not significantly differ and a re-examination by flow cytometry showed a type I CD36 deficiency, so that we ruled out the notion that changes in the metabolic products in the blood had caused myocardial ^{123}I-BMIPP accumulation in this patient. ^{123}I-BMIPP was uptaken by the myocardium during heart failure, suggesting that a neuro-hormonal imbalance such as an increase in catecholamine levels had changed in the pathway and/or altered the mechanism of fatty acid uptake into the myocardium from the blood, but we did not analyze the catecholamine concentration, so the role of this factor remains unknown. Several reports indicated that myocardial ^{123}I-BMIPP uptake is decreased in patients with congestive heart failure,[12,13] but myocardial ^{123}I-BMIPP was uptaken during severe heart failure in this patient. The long-term fate of ^{123}I-BMIPP in patients with a CD36 deficiency has never been investigated, so whether or not pathways and/or mechanisms of myocardial LCFA uptake change in such patients remains unknown.

A study with palmitate positron emission tomography has found mild myocardial palmitate accumulation even in patients with a CD36 deficiency.[14] In addition, several basic studies have shown that long chain fatty acids are taken into the myocardium from the blood through a 40 kDa plasma membrane long-chain fatty acid-binding protein (FABPpm), and that an 88 kDa long-chain fatty acid translocase (FAT/CD36), and a 60-kDa long-chain fatty acid trans protein (FATP) are involved.[15,16] Therefore, another pathway might exist in the human myocardium.

Furthermore, under conditions such as severe congestive heart failure and/or type I CD36 deficiency, LCFA might be absorbed by passive diffusion. The mechanisms and pathways of LCFA uptake in the human myocardium have not been fully elucidated. Further basic and clinical investigations are required.

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