

Mitochondrial Cardiomyopathy with a Unique $^{99m}\text{Tc-MIBI}/^{123}\text{I-BMIPP}$ Mismatch Pattern

Ryosuke Tashiro¹, Noriko Onoue¹, Hiroya Rikimaru², Kenichi Tsukita³, Hiroshi Fujita¹,
Nobuhiro Yamaguchi¹, Takeshi Ishizuka¹, Yasushi Suzuki³,
Hiroyoshi Suzuki⁴ and Tsuyoshi Shinozaki¹

Abstract

A 42-year-old man was referred to our hospital due to chest pain, diabetes mellitus, and sensorineural hearing loss. Transthoracic echocardiography revealed diffuse left ventricular hypokinesis. He was diagnosed with mitochondrial disease and a c.A3243G mutation was identified in his mitochondrial DNA. This case of mitochondrial cardiomyopathy demonstrated a low uptake of $^{123}\text{I-BMIPP}$, while the uptake of $^{99m}\text{Tc-MIBI}$ was preserved. In contrast, previous reports have noted the increased uptake of $^{123}\text{I-BMIPP}$ and the decreased uptake of $^{99m}\text{Tc-MIBI}$. This is the first study to show this unique $^{99m}\text{Tc-MIBI}/^{123}\text{I-BMIPP}$ mismatch pattern. We also discuss the relationships among the cardiac scintigraphy, cardiac magnetic resonance imaging, and histopathology findings.

Key words: mitochondrial cardiomyopathy, $^{99m}\text{Tc-MIBI}$, $^{123}\text{I-BMIPP}$, cardiac magnetic resonance, late gadolinium enhancement

(Intern Med 56: 321-325, 2017)

(DOI: 10.2169/internalmedicine.56.7525)

Introduction

Mitochondrial cardiomyopathy can manifest with various cardiac phenotypes, such as left ventricle (LV) hypertrophy, dilatation, wall motion abnormality, and lethal ventricular arrhythmia; these symptoms range from subclinical to critical conditions (1). The severity of myocardial dysfunction also predicts the prognosis of patients with mitochondrial disease, which highlights the importance of noninvasive assessment for myocardial dysfunction. Myocardial perfusion/metabolism mismatch (the decreased uptake of technetium-99m methoxyisobutylisonitrile [$^{99m}\text{Tc-MIBI}$]/the increased uptake of 123-labeled 15-4-iodophenyl-3-(R, S)-methyl-pentadecanoic acid [$^{123}\text{I-BMIPP}$]) has been reported in patients with mitochondrial cardiomyopathy (2, 3). However, the previous studies did not compare the morphological images of patients with this condition.

In the present case, we compared images of myocardial perfusion ($^{99m}\text{Tc-MIBI}$ scintigraphy), fatty acid metabolism ($^{123}\text{I-BMIPP}$ scintigraphy), and morphology (cardiac magnetic resonance [CMR] and histology), and found that the images of our patient, who had a mismatch between perfusion and metabolism, were unique from those in the previous reports.

Case Report

A 42-year-old man (157 cm, 48.4 kg) was referred to our hospital with left chest pain, diabetes mellitus, and sensorineural hearing loss. His mother had diabetes mellitus; however, she did not have hearing loss or cardiovascular disease. At admission, his blood pressure was 121/79 mmHg, his heart rate was 82 beats/min with a regular pulse, and his percutaneous oxygen saturation was 98% in room air. Although systolic heart murmurs were audible at the base

¹Division of Cardiology, Sendai Medical Center, National Hospital Organization, Japan, ²Division of Radiology, Sendai Medical Center, National Hospital Organization, Japan, ³Division of Neurology, Sendai Medical Center, National Hospital Organization, Japan and ⁴Division of Pathology and Laboratory Medicine, Sendai Medical Center, National Hospital Organization, Japan

Received for publication April 4, 2016; Accepted for publication June 14, 2016

Correspondence to Dr. Ryosuke Tashiro, tashiro0329@gmail.com

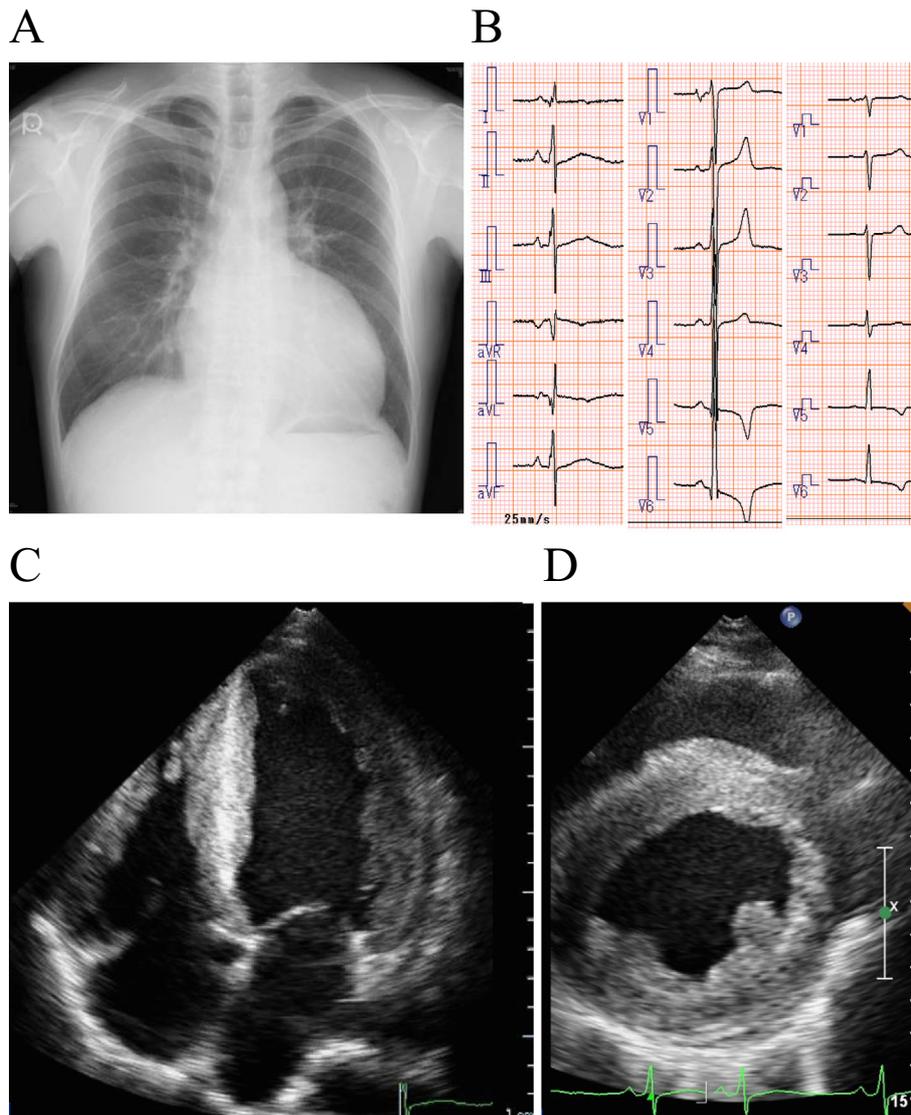


Figure 1. The results of the physiological examinations. (A) Chest radiography reveals cardiomegaly (cardiothoracic ratio, 59%) and mild pulmonary congestion. (B) An electrocardiogram reveals a prominent R wave progression in V3-6 and a negative T wave in V5-6. (C, D) Transthoracic echocardiograms reveal the thickening of the left and right ventricle walls. The left ventricle ejection fraction is 40%.

(4LSB), there was no jugular venous distention, and his breathing sounds were normal. Hepatomegaly and splenomegaly were not present, and there was no edema in his extremities. Mild exophoria and intellectual deterioration were observed.

Chest radiography revealed an increase in the cardiothoracic ratio (59%) and mild pulmonary congestion (Fig. 1A). Twelve-lead electrocardiography detected a normal sinus rhythm and a high amplitude R wave with an inverted T wave in the left lateral precordial leads (Fig. 1B). Transthoracic echocardiography detected thickening of the LV walls (septum, 16 mm; posterior wall, 16 mm), as well as thickening of the right ventricle (RV) free wall, the slight dilatation of the LV (LV end-diastolic diameter, 54 mm) and diffuse LV systolic dysfunction (ejection fraction, 40%; using Simpson's method) (Fig. 1C and D). The pressure gradient of the

tricuspid regurgitation was 47 mmHg.

His levels of troponin T and N-terminal pro-brain natriuretic peptide were elevated to 0.107 ng/mL and 1,616 pg/mL, respectively. His fasting glucose level was 172 mg/dL and his glycated hemoglobin was 7.0%. The resting serum and cerebrospinal fluid lactate concentrations had increased to 27.0 mg/dL (normal range, 3-17 mg/dL) and 31.8 mg/dL (normal range, 14-21 mg/dL), respectively. Brain computed tomography and magnetic resonance imaging revealed prominent calcification in the bilateral basal ganglia and cerebellar atrophy. Mitochondrial cDNA sequencing detected a c.A3243G mutation, and the patient was diagnosed with mitochondrial disease.

To investigate the cause of his cardiac dysfunction, cardiac catheterization was performed after medical treatment. His pulmonary artery pressure was normal (31/11 mmHg,

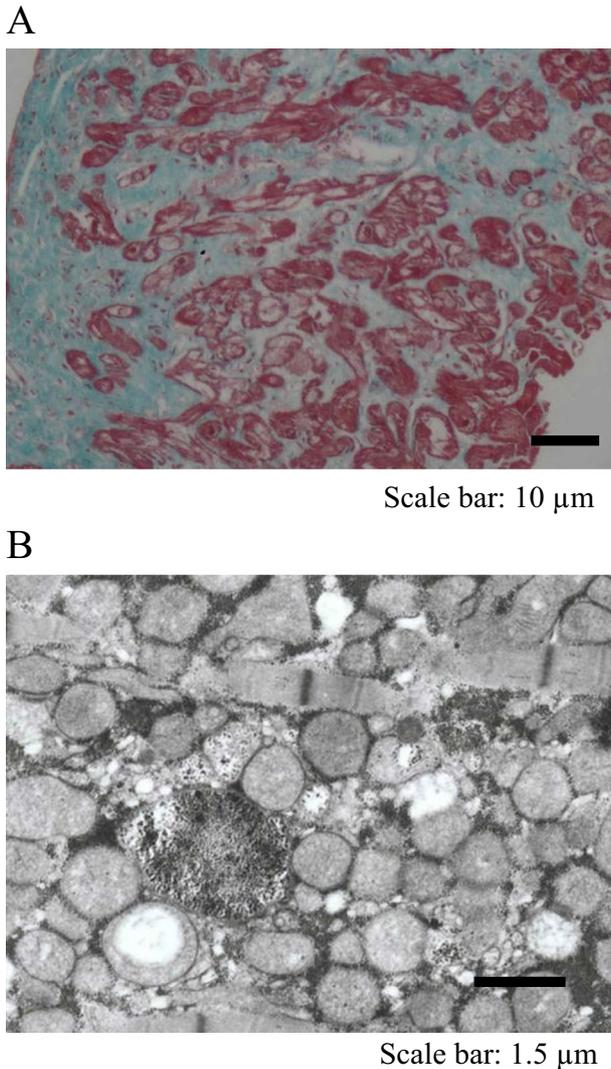


Figure 2. The histopathological findings. (A) A light microscopy image reveals interstitial fibrosis and hypertrophic myocytes with vacuoles (Elastica-Masson staining, 100 \times). (B) An electron microscopy image reveals an increased number of mitochondria with variable sizes and shapes.

mean 18 mmHg) with an increase in the LV end-diastolic pressure (20 mmHg). His cardiac index was preserved (3.08 L/min/m²), and the coronary angiography findings were normal. Left ventriculography revealed diffuse LV hypokinesis (ejection fraction, 27%). Endocardial biopsy was performed to obtain a sample of the interventricular RV wall. The microscopic findings revealed the rupture and degeneration of the myocardial fibers, which were surrounded by fibrosis (Fig. 2A). Electron microscopy detected an increase in the number of mitochondria, which varied in size and morphology (Fig. 2B).

The patient subsequently underwent resting ^{99m}Tc-MIBI cardiac scintigraphy (600 MBq), and single-photon emission computed tomography (SPECT) images were obtained at 60 minutes (the early phase) and 240 minutes (the delayed phase) after the injection (4). In the early phase, the uptake of ^{99m}Tc-MIBI did not decrease (Fig. 3A). The heart-to-

mediastinum ratio was 2.89 in the early phase and 2.79 in the delayed phase, respectively. The global washout rate in the delayed phase increased by 25% (normal range: 11 \pm 5%). The uptake of ^{99m}Tc-MIBI in the RV free wall appeared to be enhanced in the early phase (Fig. 3A). ¹²³I-BMIPP (111 MBq) was administered intravenously, and SPECT images were obtained at 35 minutes after the injection (5). The uptake of ¹²³I-BMIPP was decreased in the anterior, septal, and inferior walls (Fig. 3B). CMR was performed to estimate late gadolinium enhancement (LGE), which was observed from the midmyocardium to the epicardium of the anterior wall, as well as in the midmyocardium of the septal and inferior walls (Fig. 3C). The LGE margin was obscure and its intensity was inhomogeneous. The ^{99m}Tc-MIBI/¹²³I-BMIPP mismatch pattern (non-decreased ^{99m}Tc-MIBI uptake/decreased ¹²³I-BMIPP uptake) was confirmed via bull's eye mapping (Fig. 3D).

During the patient's hospitalization, we treated his congestive heart failure with furosemide. We prescribed enalapril (2.5 mg/day) and carvedilol (1.25 mg/day) to expect preventive effect for the progression of cardiomyopathy (6, 7).

Discussion

Mitochondrial cardiomyopathies elicit a complicated myocardial dysfunction, which is not fully understood. This is the first report to describe the relationship between myocardial perfusion, metabolism, and morphology, and to reveal a unique ^{99m}Tc-MIBI/¹²³I-BMIPP mismatch pattern in a patient with mitochondrial cardiomyopathy. Our imaging findings revealed a decrease in the uptake of ¹²³I-BMIPP, using LGE in CMR as an anatomical reference. In contrast, previous studies have reported an increase in the uptake of ¹²³I-BMIPP in mitochondrial cardiomyopathy (without providing anatomical reference images). The mechanism underlying this observation may be related mitochondrial respiratory chain failure, which leads to the excessive production of nicotinamide adenine dinucleotide (NADH), which then causes an increase in the concentration of glycerol-3-phosphate (to oxidize the excess NADH) and ultimately leads to increased levels of triglycerides. According to this mechanism, ¹²³I-BMIPP (a fatty acid analogue) is incorporated into the cardiomyocytes' pool of triglycerides (3, 8). In our patient, the distribution of the areas that showed a low uptake of ¹²³I-BMIPP was consistent with the distribution of LGE, which suggests that the low uptake of ¹²³I-BMIPP might be correlated with the low number of viable myocytes or fibrosis, rather than an energy production from fatty acid metabolism to the glycolytic pathway (as in other cardiomyopathies). Thus, the extent of the ¹²³I-BMIPP uptake may depend on the balance between the mitochondrial respiratory chain failure and the viable myocyte mass, whereby the loss of a certain number of myocytes might outweigh the increased uptake of ¹²³I-BMIPP.

The uptake of ^{99m}Tc-MIBI in the early phase was not de-

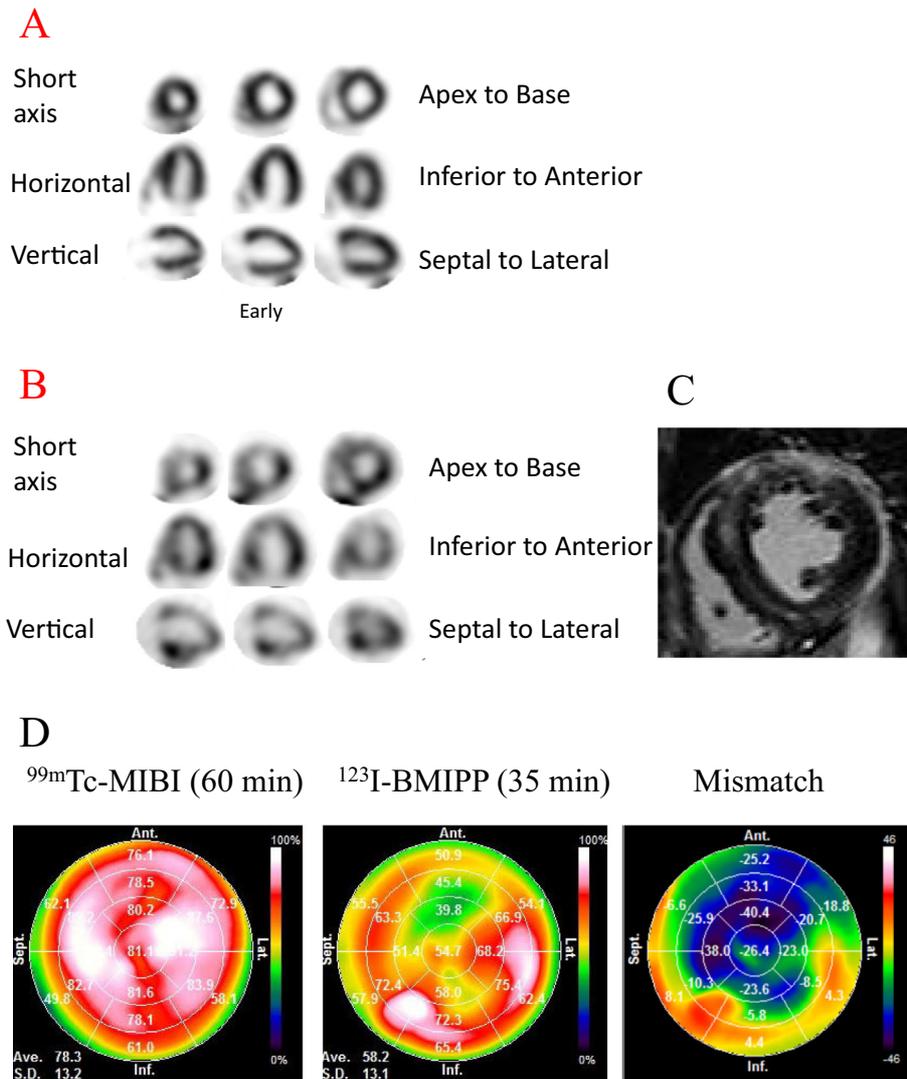


Figure 3. Cardiac scintigraphy and cardiac magnetic resonance imaging. (A) The uptake of ^{99m}Tc -MIBI is not decreased in the early phase. (B) The uptake of ^{123}I -BMIPP is decreased in the anterior, septal, and inferior walls. (C) Late gadolinium enhancement (LGE) is observed from the midmyocardium to the epicardium of the anterior wall, as well as in the midmyocardium of the septal and inferior walls. (D) Bull's eye mapping shows the ^{99m}Tc -MIBI/ ^{123}I -BMIPP mismatch pattern (non-decreased ^{99m}Tc -MIBI uptake/decreased ^{123}I -BMIPP uptake). ^{99m}Tc -MIBI: technetium-99m methoxyisobutylisonitrile. ^{123}I -BMIPP: 123-labeled 15-4-iodophenyl-3-(R, S)-methyl-pentadecanoic acid.

creased in this case. One of the interpretations of the preserved uptake of ^{99m}Tc -MIBI may be the presence of preserved blood flow and viable myocytes. In this case, the unique LGE pattern (obscure margins and inhomogeneous intensity) may reflect the scattered viable myocytes that were surrounded by fibrosis, which were also detected in our histological examination. This pattern is distinct from the homogeneous LGE pattern that is observed in cases of myocardial infarction. It is possible that the preserved myocytes in the LGE-positive area affect the uptake of ^{99m}Tc -MIBI. The volume effect of the thickening LV wall might also explain the non-decreased uptake of ^{99m}Tc -MIBI (similar to the effect in patients with hypertrophic cardiomyopathy) and the enhanced uptake of ^{99m}Tc -MIBI in the RV free wall.

Furthermore, the washout rate for ^{99m}Tc -MIBI increased in this case, which is consistent with the findings of previous studies (2, 3, 8). In this context, mitochondrial dysfunction impairs the retention of the ^{99m}Tc -MIBI tracer in myocytes, which leads to an increased washout rate for ^{99m}Tc -MIBI. Nevertheless, our unique ^{99m}Tc -MIBI/ ^{123}I -BMIPP mismatch pattern (non-decreased ^{99m}Tc -MIBI uptake/decreased ^{123}I -BMIPP uptake) is distinct from the patterns in previous reports (decreased ^{99m}Tc -MIBI uptake/increased ^{123}I -BMIPP uptake) (2, 3). The ^{99m}Tc -MIBI/ ^{123}I -BMIPP mismatch pattern in the present case can be considered to be a nonspecific phenomenon in patients with dilated cardiomyopathy (9). This discrepancy may be related to the stages or diverse phenotypes of mitochondrial cardiomyopathy.

In conclusion, multimodality imaging allows us to evaluate the relationship between myocardial perfusion, metabolism, and morphology. Further studies are needed to elucidate the complex processes of myocardial damage in patients with mitochondrial cardiomyopathy.

The authors state that they have no Conflict of Interest (COI).

References

1. Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. *Tex Heart Inst J* **40**: 385-394, 2013.
2. Matsuo S, Nakajima K, Kinuya S, et al. Cardiac scintigraphic findings of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: A case report. *Exp Clin Cardiol* **13**: 93-95, 2008.
3. Ikawa M, Kawai Y, Arakawa K, et al. Evaluation of respiratory chain failure in mitochondrial cardiomyopathy by assessments of ^{99m}Tc -MIBI washout and ^{123}I -BMIPP/ ^{99m}Tc -MIBI mismatch. *Mitochondrion* **7**: 164-170, 2007.
4. Hayashi D, Ohshima S, Isobe S, et al. Increased ^{99m}Tc -Sestamibi washout reflects impaired myocardial contractile and relaxation reserve during dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. *J Am Coll Cardiol* **61**: 2007-2017, 2013.
5. Matsuo S, Nakamura Y, Takahashi M, et al. Myocardial metabolic abnormalities in hypertrophic cardiomyopathy assessed by iodine-123-labeled beta-methyl-branched fatty acid myocardial scintigraphy and its relation to exercise-induced ischemia. *Jpn Circ J* **62**: 167-172, 1998.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* **334**: 1349-1355, 1996.
7. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* **325**: 293-302, 1991.
8. Takagi Y, Suzuki K, Kou S, et al. A case of mitochondrial encephalopathy detected dysfunction of cardiac muscle of mitochondria by cardiac nuclear medicine. *Shinzo* **46**: 629-638, 2014 (in Japanese, Abstract in English).
9. Yoshida A, Takano H, Asai K, et al. Comparison of perfusion-metabolism mismatch in ^{99m}Tc -MIBI and ^{123}I -BMIPP scintigraphy with cardiac magnetic resonance in patients with dilated cardiomyopathy. *J Card Fail* **19**: 445-453, 2013.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).