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Type Ⅰ CD36 Deficiency Associated With Metabolic Syndrome and Vasospastic Angina: A Case Report

Masataka KAMIYA, MD
Akihiro NAKAGOMI, MD, FJCC
Yukichi TOKITA, MD
Masahiro YASUTAKE, MD
Yoshiki KUSAMA, MD, FJCC
Morimasa TAKAYAMA, MD, FJCC
Teruo TAKANO, MD, FJCC

Abstract

A 54-year-old man was admitted to our hospital for evaluation of chest pain occurring at rest in the morning. ST segment depression was observed during a treadmill exercise test. Coronary angiography identified spontaneous spasm of the proximal right coronary artery, and right coronary obstruction was improved from 90% to about 50% stenosis after intracoronary administration of nitroglycerin. Myocardial iodine-123 beta-methyl-*p*-iodophenyl-pentadecanoic acid uptake was absent, but thallium-201 uptake during single photon emission computed tomography was normal, and neither platelet nor monocyte expression of the CD36 molecule was observed, indicating type Ⅰ CD36 deficiency. High blood pressure, elevated plasma triglyceride and fasting plasma glucose levels, and low high-density lipoprotein values suggested metabolic syndrome. The final diagnosis was type Ⅰ CD 36 deficiency associated with metabolic syndrome and vasospastic angina.

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Key Words

■**Cells** (**CD36 deficiency**) ■**Angina pectoris** (**vasospastic**)
■**Metabolism** (**metabolic syndrome**)

INTRODUCTION

CD36 deficency may be related to the "metabolic syndrome," which is strongly associated with atherosclerotic cardiovascular disease. CD36 deficiency may also be linked with hypertrophic cardiomyopathy. We describe a case of CD36 deficiency complicated with vasospastic angina and metabolic syndrome.

CASE REPORT

A 54-year-old Japanese man was admitted to our hospital for evaluation of chest pain that occurred at rest in the early morning. A treadmill exercise test revealed asymptomatic ST segment depression in leads Ⅱ, Ⅲ, aV_F, and V_4 to V_6 (**Fig. 1**), and Holter monitoring showed ST segment depression at rest in the morning. Transthoracic echocardiography showed no asynergy and no evidence of left ventricular hypertrophy, suggesting vasospastic angina. The patient's blood pressure was 148/82 mmHg, and glycosylated hemoglobin, fasting plasma glucose, and triglyceride levels were 8.1%, 137 mg/d*l*, and 183 mg/d*l*, respectively, indicating that he had some features of metabolic syndrome.

日本医科大学附属病院 第一内科学講座：〒113−8603 東京都文京区千駄木1−1−5
The First Department of Internal Medicine, Nippon Medical School, Tokyo
Address for correspondence: NAKAGOMI A, MD, FJCC, The First Department of Internal Medicine, Nippon Medical School, Sendagi 1−1−5, Bunkyo-ku, Tokyo 113−8603; E-mail: nakagomi@nms.ac.jp
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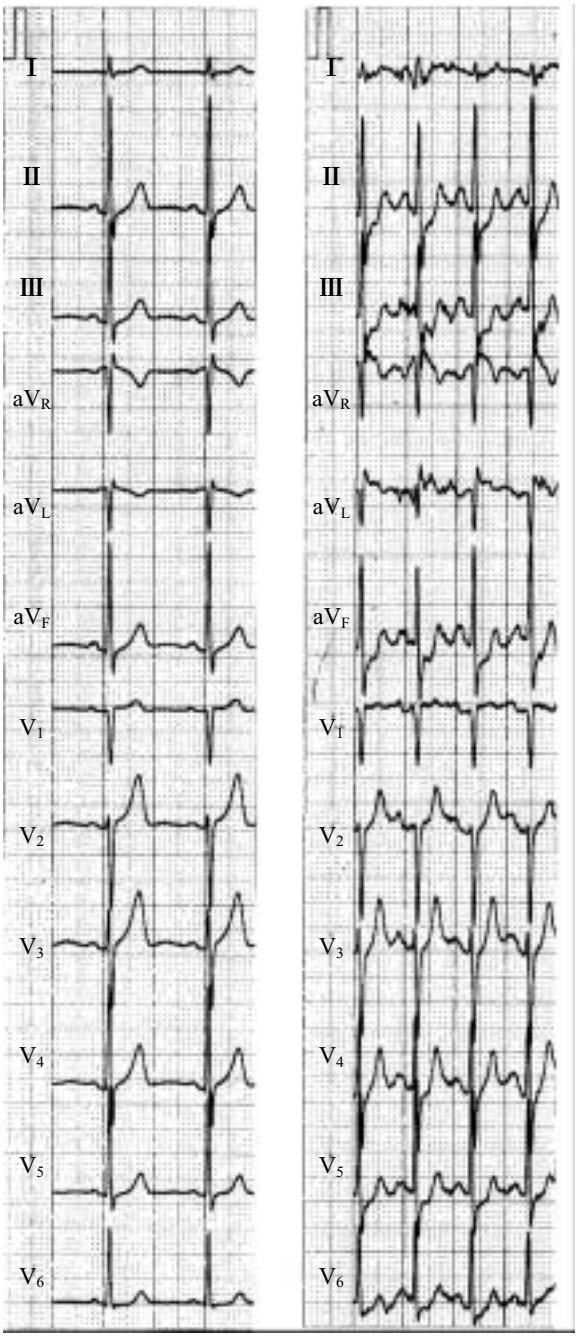

Fig. 1 Treadmill exercise test revealed asymptomatic ST segment depression in leads Ⅱ, Ⅲ, aVF, and V_4 to V_6
Left: Before exercise. *Right*: After exercise.

We did not perform an acetylcholine provocation test, a sensitive method for detecting vasospastic angina. However, coronary angiography identified spontaneous spasm of the proximal right coronary artery, and right coronary obstruction was improved from 90% to about 50% stenosis after intracoronary administration of nitroglycerin (**Fig. 2**). Interestingly, there was no myocardial iodine-123 beta-methyl-*p*-iodophenyl-pentadecanoic acid (^{123}I-BMIPP) uptake, but uptake of thallium-201 on single photon emission computed tomography images was normal, and flow cytometric analysis showed neither platelet nor monocyte CD36 molecule expression (**Fig. 3**). Therefore, the final diagnosis was type Ⅰ CD36 deficiency.

DISCUSSION

Absence of myocardial uptake of ^{123}I-BMIPP, a radio-iodinated long-chain fatty acid analogue, probably due to impairment in long-chain fatty acid metabolism in the myocardium, has been observed in patients with type Ⅰ CD36 deficiency. Total absence of myocardial long-chain fatty acid uptake was found in about 0.5% of Japanese patients who underwent ^{123}I-BMIPP scintigraphy.[1)]

CD36, a multifunctional membrane-type glycoprotein, is expressed on various human cells, such as monocytes, platelets, adipocytes, cardiomyocytes, and endothelial cells. CD36 is considered a platelet receptor for thrombospondin, and a class B scavenger receptor for oxidized low-density lipoprotein on macrophages. It is a major transporter of long-chain fatty acid in adipose tissue, heart, and skeletal muscle. Thus, CD36 may be important in atherosclerosis, inflammation, and myocardial fatty acid metabolism.[2)]

Genetic CD36 deficiency has been reported in less than 3% of the Japanese population and less than 0.3% of the European population. The incidence of type Ⅰ CD36 deficiency, in which neither platelets nor monocytes express CD36, is only about one-seventh that of type Ⅱ CD36 deficiency, in which monocytes but not platelets express CD36.[3)] The present case showed that patients with CD36 deficiency may have some features of the "metabolic syndrome", because our patient had high blood pressure and high triglyceride and glucose levels, and low high-density lipoprotein cholesterol levels.

CD36 is a receptor for oxidized low-density lipoprotein on macrophages, so CD36 deficiency may induce an antiatherogenic state because macrophages had reduced binding for oxidized low-density lipoprotein *in vitro*. However, *in vivo*, CD36 deficiency is related to atherogenic disease. One of the possible mechanisms of the "metabolic syndrome" in patients with CD36 deficiency is

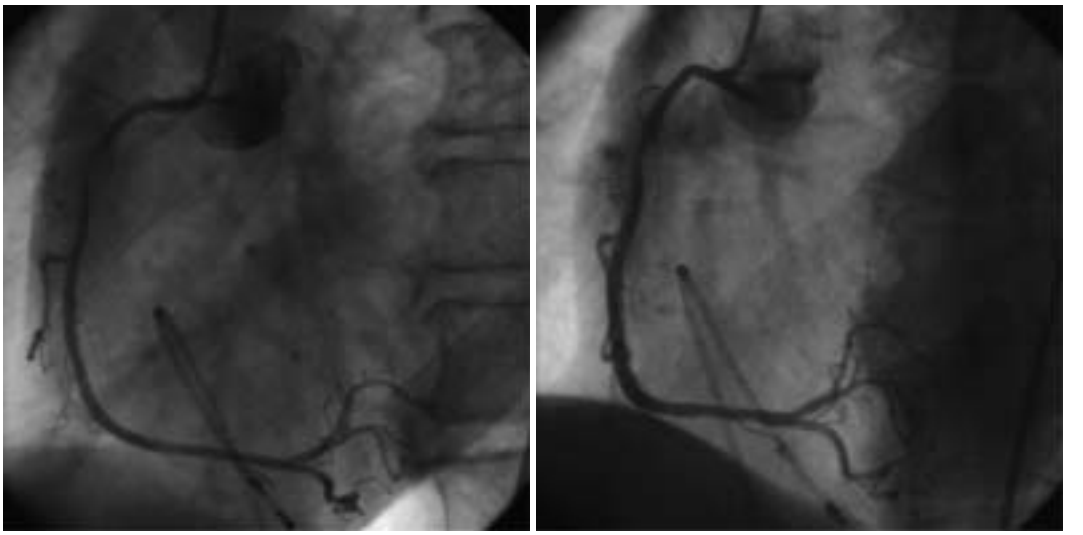

Fig. 2 Coronary angiograms showing that right coronary obstruction was improved from 90%(*left*) to about 50%(*right*)stenosis after intracoronary administration of nitroglycerin

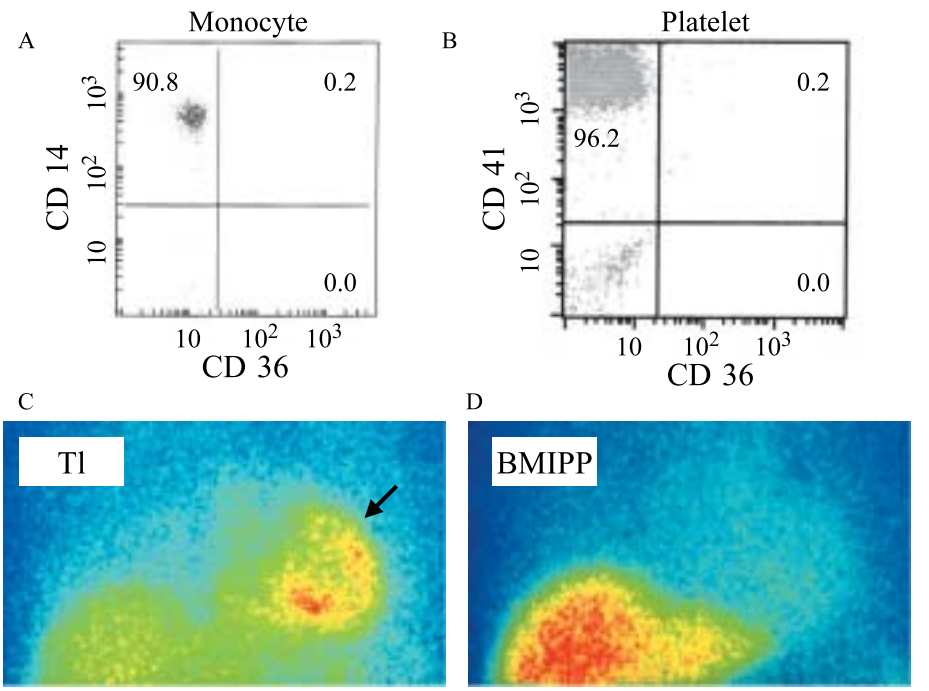

Fig. 3 Two-color flow cytometric analysis for surface expression of CD36 showing that CD36 was not expressed on monocytes(*A*)or platelets(*B*)
Accumulation of myocardial thallium-201(*arrow*)was seen(*C*)with no myocardial iodine-123 BMIPP uptake(*D*), but increased accumulation of BMIPP in the liver was observed. BMIPP = beta-methyl-*p*-iodophenyl-pentadecanoic acid.

change in the dynamic of long-chain fatty acid as demonstrated by BMIPP scintigraphy. In the CD36 deficiency state, the uptake of BMIPP is increased markedly in the liver, but decreased in the heart. The increased flux of long-chain fatty acid into the liver is believed to be related to the increased secretion of very-low-density lipoprotein and the expression of hyperlipidemia and insulin resistance. The other possibility is that CD36 deficient patients have changes in PPAR γ-mediated signaling and fatty-acid metabolism associated with insulin resistance.[4)]

Our patient had vasospastic angina. A reduction of endothelium-derived relaxing factor production, probably due to early intramural atherosclerotic plaque formation and insulin resistance associated with hyperinsulinemia, may have been important in the coronary atherosclerotic obstructions and vasospasm.[5,6)] Our patient had some features of the "metabolic syndrome" and we thought that this was related to the vasospastic angina.

CD36 deficiency is associated with atherosclerotic disease, but is often reported in patients with hypertrophic cardiomyopathy in heart disease.[7)] In our CD36 deficiency patient, left ventricular hypertrophy was not observed, but vasospastic angina was considered to be related to metabolic syndrome.

要　約

Ⅰ型CD36欠損症にメタボリックシンドロームと冠攣縮性狭心症がみられた1例

神谷　仁孝　　中込　明裕　　時田　祐吉　　安武　正弘

草間　芳樹　　高山　守正　　高野　照夫

症例は54歳，男性．早朝，安静時胸痛の精査目的で入院し，トレッドミル運動負荷検査により無症候性ST低下が認められたため，冠動脈造影を施行した．右冠動脈起始部の90%狭窄は，ニトログリセリン冠動脈注入後に50%狭窄へと改善したため，冠攣縮性狭心症と診断した．Tl-BMIPP心筋シンチグラムにより，Tlは心臓に集積するが，BMIPPは無集積であり，かつフローサイトメトリーにより血小板および単球上にCD36の発現が認められなかったことから，Ⅰ型CD36欠損症と診断した．本症例は，高血圧症・高トリグリセリド血症・耐糖能障害・低HDLコレステロール血症を併せ持つことから，Ⅰ型CD36欠損症にメタボリックシンドロームと冠攣縮性狭心症がみられたまれな症例と思われたので報告した．

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References

1) Tanaka T, Nakata T, Oka T, Ogawa T, Okamoto F, Kusaka Y, Sohmiya K, Shimamoto K, Itakura K: Defect in human myocardial long-chain fatty acid uptake is caused by FAT/CD36 mutations. J Lipid Res 2001; **42**: 751−759
2) Febbraio M, Hajjar DP, Silverstein RL: CD36: A class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. J Clin Invest 2001; **108**: 785−791
3) Watanabe K, Toba K, Ogawa Y, Kodama M, Hirono S, Ohkura Y, Hanawa H, Nakamura Y, Aoki Y, Fuse I, Aizawa Y, Miyajima S, Kusano Y, Nagatomo T, Hasegawa G, Naito M: Hypertrophic cardiomyopathy with type Ⅰ CD36 deficiency. Jpn Circ J 1998; **62**: 541−542
4) Hirano K, Kuwasako T, Nakagawa-Toyama Y, Janabi M, Yamashita S, Matsuzawa Y: Pathophysiology of human genetic CD36 deficiency. Trends Cardiovasc Med 2003; **13**: 136−141
5) Oyama N, Urasawa K, Sakai H, Fujii S, Kitabatake A: Insulin resistance relates to acetylcholine-induced microvascular vasoconstriction in a patient with vasospastic angina: Potential implication of causalities between hyperinsulinemia and coronary microcirculation failure. Heart Vessels 2005; **20**: 72−76
6) Shinozaki K, Hattori Y, Suzuki M, Hara Y, Kanazawa A, Takaki H, Tsushima M, Harano Y: Insulin resistance as an independent risk factor for carotid artery wall intima media thickening in vasospastic angina. Arterioscler Thromb Vasc Biol 1997; **17**: 3302−3310
7) Nakata T, Nakahara N, Sohmiya K, Okamoto F, Tanaka T, Kawamura K, Shimamoto K: Scintigraphic evidence for a specific long-chain fatty acid transporting system deficit and the genetic background in a patient with hypertrophic cardiomyopathy. Jpn Circ J 1999; **63**: 319−322