

Case Report

Premature Acute Myocardial Infarction in a Young Patient With Sitosterolemia

Yoshihiro Yamada, MD, PhD,^a Keiki Sugi, MD, PhD,^a Yodo Gatate, MD,^a

Takaaki Senbonmatsu, MD, PhD,^a Ikuo Inoue, MD, PhD,^b Kenji Fukushima, MD, PhD,^c

Atsushi Iguchi, MD, PhD,^d Hiroyuki Nakajima, MD, PhD,^d Toshihiro Muramatsu, MD, PhD,^a

Shintaro Nakano, MD, PhD,^a and Hayato Tada, MD, PhD^e

^a Department of Cardiology, Saitama Medical University International Medical Center, Saitama, Japan

^b Department of Endocrinology and Diabetes, Saitama Medical University, Saitama, Japan

^c Department of Nuclear Medicine, Saitama Medical University International Medical Center, Saitama, Japan

^d Department of Cardiovascular Surgery, Saitama Medical University International Medical Center, Saitama, Japan

^e Department of Cardiovascular and Internal Medicine, Kanazawa University School of Medicine, Ishikawa, Japan

ABSTRACT

Sitosterolemia is a rare, inherited, autosomal recessive disorder of lipid metabolism characterized by increased levels of plant sterols, such as sitosterol and campesterol, xanthomas, and accelerated atherosclerosis. In a 15-year-old boy exhibiting ST-elevation acute myocardial infarction, lipid panels, including plant sterol, and genetic testing for the *ATP-binding cassette sub-family G member 5 (ABCG5)* gene mutation, confirmed the diagnosis of sitosterolemia. A comprehensive lipid panel and genetic testing should be considered in patients with premature coronary artery disease to prevent disease progression through dietary and pharmacologic interventions specific to sitosterolemia.

RÉSUMÉ

La sitostérolémie est une maladie génétique rare à transmission autosomique récessive touchant le métabolisme des lipides, qui est caractérisée par une augmentation des taux de stérols végétaux comme le sitostérol et le campesterol, la présence de xanthomes et une athérosclérose accélérée. Chez un garçon âgé de 15 ans ayant subi un infarctus aigu du myocarde avec élévation du segment ST, le diagnostic de sitostérolémie a été confirmé par un bilan lipidique comprenant un dosage des stérols d'origine végétale et un test génétique de dépistage de la mutation du gène *ABCG5 (ATP-binding cassette sub-family G member 5)*. Un bilan lipidique exhaustif et un test génétique doivent être envisagés chez les patients présentant une coronaropathie prématurée afin de prévenir la progression de la maladie grâce à des interventions d'ordre tant diététique que pharmacologique propres à la sitostérolémie.

Case

A previously healthy 15-year-old boy was transported to the hospital due to ventricular fibrillation. On arrival, he demonstrated recurrent ventricular fibrillation (Supplemental Fig. S1, A and B) for which he required cardiopulmonary resuscitation. On day 10, he suffered from ST-elevation myocardial infarction (Supplemental Fig. S1B). Emergency coronary angiography revealed intimal irregularity at multiple sites, with severe stenosis in the left main trunk (Fig. 1, A-C). He underwent emergent on-pump coronary artery bypass grafting.

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Ethics Statement: The research reported has adhered to the relevant ethical guideline.

Corresponding author: Dr Yoshihiro Yamada, Department of Cardiology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka City, Saitama 350-1298, Japan. Tel.: +81-42-984-4302; fax: +81-42-984-4591.

E-mail: yyama@saitama-med.ac.jp

See page 1087 for disclosure information.

Novel Teaching Points

- In patients with premature coronary artery disease, sitosterolemia should be considered as a potential etiology.
- In patients with sitosterolemia, specific dietary and medical treatments should be prescribed in order to prevent the progression of atherosclerosis.

Three months post-surgery, he presented with fatigue due to low-output syndrome. Radiography showed cardiomegaly (Supplemental Fig. S1C), and echocardiography showed severely decreased left ventricular ejection fraction (18%) with an enlarged left ventricle (Supplemental Fig. S1D).

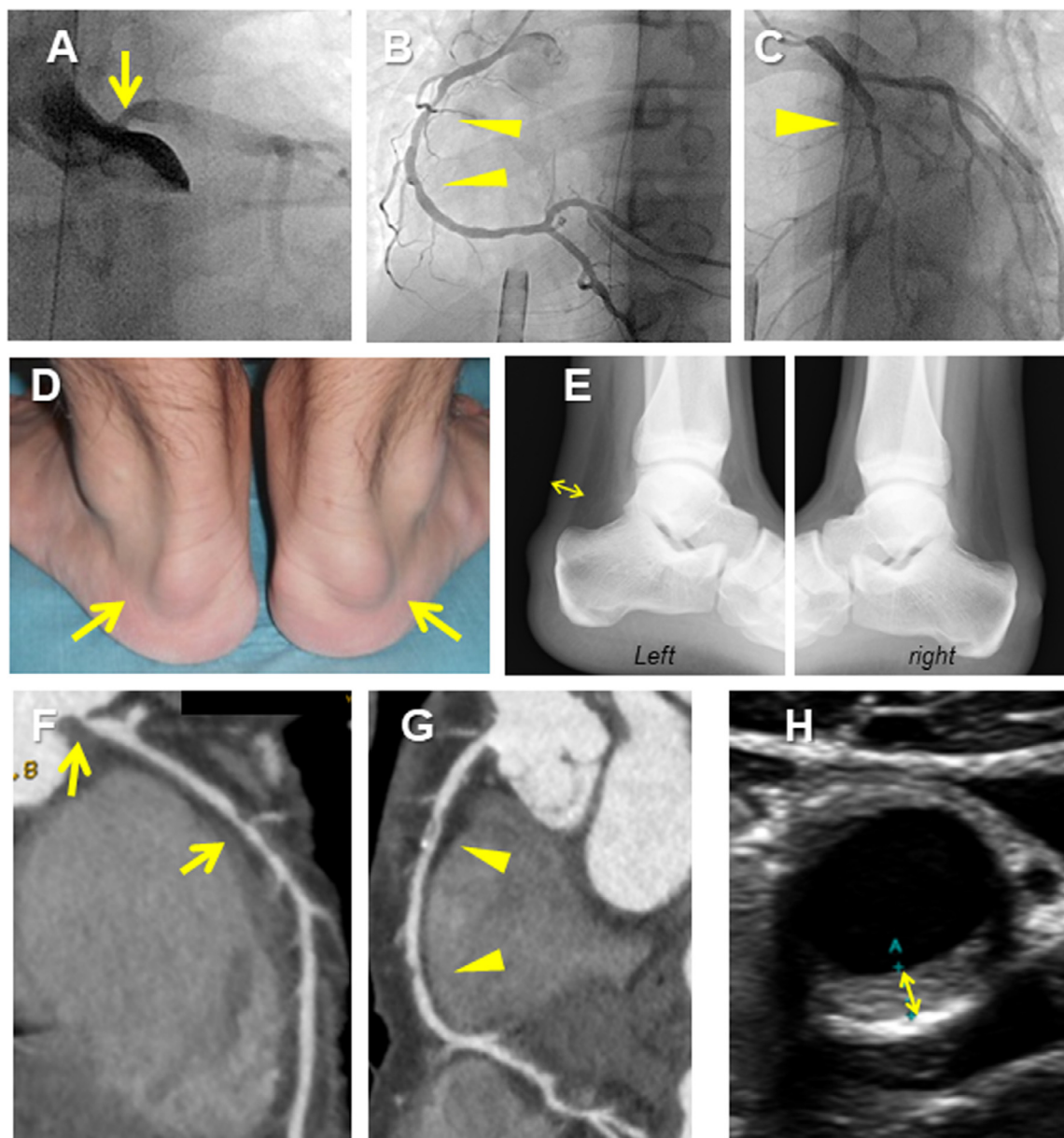


Figure 1. Evidence of atherosclerosis. (A-C) Coronary angiography shows severe stenosis in the ostial left main trunk (arrow) and intimal irregularity in the right coronary artery and left anterior artery (arrowheads). (D) Tendinous xanthomas on the Achilles tendon (arrows). (E) Radiographs show a thickened Achilles tendon (11 mm; arrows). (F, G) Cardiac computed tomography angiography shows low-density plaques in the left main trunk and left anterior descending artery (arrows) and the right coronary artery (arrowheads). (H) Left common carotid artery ultrasonography shows thickening of the intima-media complex (1.5 mm; arrowheads).

This patient had tendinous xanthomas on the Achilles tendon bilaterally (Fig. 1D) and thickening of the Achilles tendon (Fig. 1E). Coronary computed tomography angiography (CCTA) and carotid ultrasonography revealed evidence of atherosclerosis (Fig. 1F-H).

A lipid panel revealed elevated low-density lipoprotein-cholesterol (LDL-C 180 mg/dL or 4.7 mmol/L) and plant sterols (sitosterol 53 $\mu\text{g}/\text{mL}$ [reference interval: 0.99-3.88 $\mu\text{g}/\text{mL}$]¹ or 127.8 $\mu\text{mol}/\text{L}$ [reference interval: 2.4-9.4 $\mu\text{mol}/\text{L}$]¹ and campesterol 38 $\mu\text{g}/\text{mL}$ [reference interval: 2.14-7.43 $\mu\text{g}/\text{mL}$]¹ or 94.8 $\mu\text{mol}/\text{L}$ [reference interval: 5.3-18.5 $\mu\text{mol}/\text{L}$]¹) with atorvastatin 10 mg/day. Genetic testing confirmed a homozygous missense mutation in the *ATP-binding cassette sub-family G*

member 5 (ABCG5) gene (ENST00000260645. 1:c. 1166G > A, ENSP00000260645. 1:p. Arg389His). Both parents had a heterozygous missense mutation in the same *ABCG5* gene, but his older sister lacked this pathogenic variant. He was diagnosed as having sitosterolemia; hematologic disorder was not present.

Conventional anti-heart failure medications were titrated. Specific dietary (plant sterol restriction) and medical treatments (ezetimibe 10 mg daily, colestimide 3000 mg daily, and atorvastatin 20 mg daily) were started, which decreased the serum levels of LDL-C to 35 mg/dL, sitosterol to 33 $\mu\text{g}/\text{mL}$, and campesterol to 20 $\mu\text{g}/\text{mL}$ 5 months later.

The patient has been clinically stable with his lipid panel well controlled for 2 years. He is currently listed as a candidate

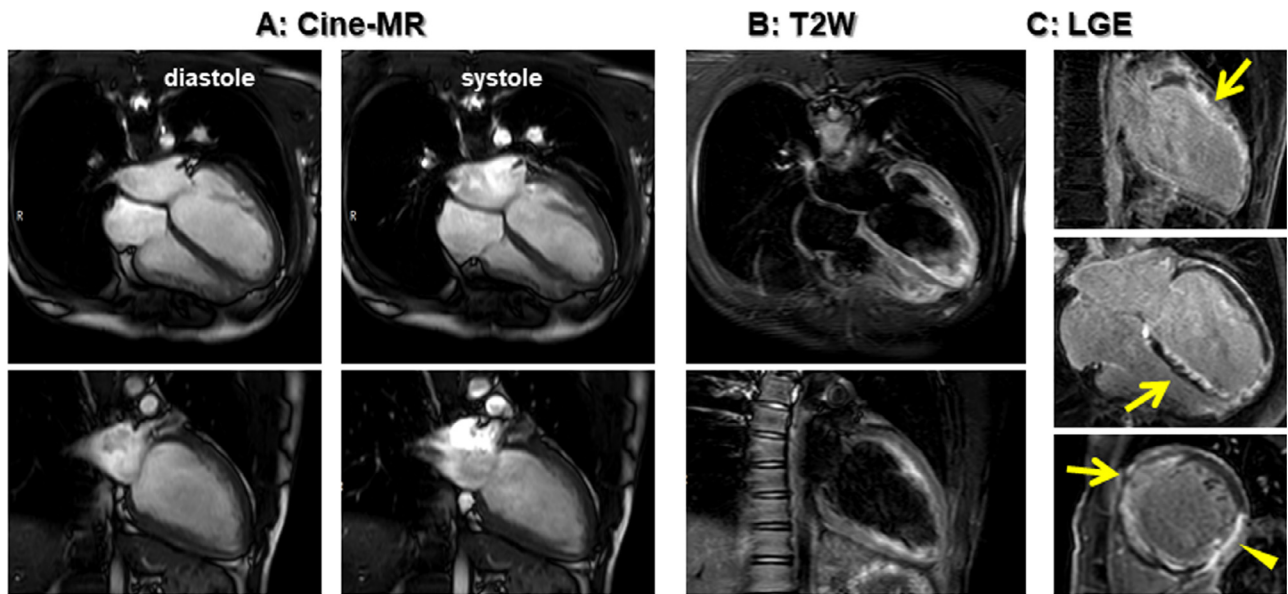


Figure 2. Cardiac magnetic resonance imaging: (A) Cine-magnetic resonance (MR) imaging shows a diffuse hypokinetic left ventricle. (B) Fat-suppression T2-weighted (T2W) imaging shows no high-intensity signals in myocardium. (C) Late-gadolinium enhancement (LGE) observed transmurally in the anterior and anteroseptal areas (arrows) and endo-myocardially in the inferior and posterior areas (arrowhead), suggesting extensive irreversible myocardial damage.

recipient for heart transplantation. Multiple imaging tests demonstrated extensive irreversible myocardial damage (Fig. 2 and Supplemental Fig. S2).

Discussion

Sitosterolemia is caused by mutations in either the *ABCG5* or *ABCG member 8 (ABCG8)* gene.² The Exome Aggregation Consortium estimated that 1 in ~220 individuals have loss-of-function mutations in either the *ABCG5* or *ABCG8* gene.³ Thus, the prevalence of sitosterolemia can be estimated to be much greater than currently thought. In fact, we have shown that at least a subset of patients with sitosterolemia are misdiagnosed as having familial hypercholesterolemia, suggesting that the correct diagnosis of sitosterolemia has been overlooked in many patients.⁴ Moreover, it has been shown that the clinical phenotype of sitosterolemia varies greatly, probably due to individual patients' dietary habits, making it difficult to identify accurately.³ In our case, we confirmed the presence of systemic atherosclerosis from imaging modalities along with the presence of xanthomas. Subsequently, lipid panels, including plant-sterol, and genetic testing for the *ABCG5* gene mutation confirmed the diagnosis of sitosterolemia. In terms of age at development of coronary atherosclerosis, we have found previously that myocardial infarction is typically observed from age 30 years and up in men, and from age 50 years and up in women among patients with heterozygous familial hypercholesterolemia.⁵ Accordingly, we need to be aware of rare conditions, including sitosterolemia, in cases exhibiting premature atherosclerosis before those ages.

ABCG5 plays an important role in selective excretion of sterols from the liver and intestine. Homozygous *ABCG5/ABCG8* loss-of function mutations result in increased intestinal absorption and decreased biliary plant sterol levels.⁶

Elevated levels of both serum cholesterol and plant sterol can contribute to premature atherosclerosis. Patients theoretically should avoid foods rich in plant sterol.¹ Pharmacotherapy aimed at suppressing the absorption of plant sterol with ezetimibe and enhancing its excretion with biliary sequestrants such as colestimide is recommended. Statins can reduce LDL-C levels in sitosterolemic patients, although their effects may be limited.²

Conclusion

Our patient with sitosterolemia caused by a homozygous *ABCG5* mutation manifested fatal ST-elevation myocardial infarction, leading to severe ischemic cardiomyopathy. A comprehensive lipid panel and genetic testing should be considered in patients with premature coronary artery disease to prevent disease progression through dietary and pharmacologic interventions specific to sitosterolemia.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at doi:10.1016/j.cjco.2021.04.008.