CJC Open 6 (2024) 1116–1120

Case Report

Acute Coronary Syndrome in a 40-Year-Old Man with Triglyceride Deposit Cardiomyovasculopathy: A Case Report

Hiroyuki Yamamoto, MD, PhD,[a,b] Yoshihiko Ikeda, MD, PhD,[c] Kazuhiro Satomi, MD, PhD,[a] and Ken-ichi Hirano, MD, PhD[d]

[a] *Department of Cardiology, Tokyo Medical University Hospital, Tokyo, Japan*

[b] *Department of Cardiovascular Medicine, Narita-Tomisato Tokushukai Hospital, Chiba, Japan*

[c] *Department of Pathology, National Cerebral and Cardiovascular Centre, Osaka, Japan*

[d] *Department of Triglyceride Science, Graduate School of Medicine, Osaka University, Osaka, Japan*

Triglyceride deposit cardiomyovasculopathy (TGCV) is an emerging disease in which defective intracellular triglyceride lipolysis results in cellular steatosis and energy failure, mainly involving vascular smooth muscle cells and cardiomyocytes. TGCV can lead to potentially life-threatening coronary artery disease (CAD), heart failure, and arrhythmia.[1,2] The characteristics of CAD in TGCV are pathologically, angiographically, and functionally unique compared to those of classic cholesterol-induced atherosclerosis.[1,2] Early diagnosis remains challenging because plasma triglyceride level and body mass index are irrelevant. Here, we describe the diagnosis and management of a young adult patient with TGCV with severe diffuse triple-vessel CAD who presented with acute coronary syndrome (ACS).

Case Report

A 40-year-old, previously healthy, nonobese man was admitted to our hospital with an unknown onset of chest pain and dyspnea, which gradually worsened. He had no past or family medical history of premature CAD, including familial hypercholesterolemia. The patient had no history of cigarette smoking or illicit drug use. On admission, his vital signs were as follows: blood pressure, 91/51 mm Hg; heart rate, 61 beats per minute. His body weight and height were 65 kg and 170 cm, respectively (body mass index, 22.5 kg/m^2). Cardiac examination revealed normal heart sounds and an S3 gallop without murmur. No jugular venous distention, hepatomegaly, or leg edema were observed. Laboratory workup revealed a slightly elevated troponin I level of 117.5 pg/mL (reference value: < 10). His hepatorenal function was unremarkable. Metabolic profile tests revealed the following: a total cholesterol level of 156 mg/dL (reference value: 142-248); a triglyceride (TG) level of 181 mg/dL (reference value: 50-150); a low-density lipoprotein cholesterol level of 80 mg/dL (reference value: 70-140); a uric acid level of 5.0 mg/dL (reference value: < 7.8); a fasting blood-glucose level of 98 mg/dL (reference value: < 110); and a glycated-hemoglobin level of 5.6% (reference value: < 6.0%). Coagulation test results were unremarkable. Electrocardiogram revealed normal sinus rhythm with global ST-segment depression in multiple leads, with isolated ST-segment elevation in lead aVR, suggesting severe myocardial ischemia (Supplemental Fig. S1). Chest radiograph revealed cardiomegaly without pulmonary congestion. Echocardiography revealed severely reduced left ventricular systolic function with a left ventricular ejection fraction of 36%, and an enlarged left ventricular end-diastolic diameter of 58 mm. Therefore, ACS was suspected. As coronary angiography revealed severe diffuse triple-vessel CAD (Fig. 1, A and B), the patient underwent urgent coronary artery bypass grafting (CABG) followed by a conventional medical regimen (Fig. 1, C and D). Cardiac magnetic resonance imaging with late gadolinium enhancement revealed a diffuse subendocardial scar (Fig. 1E). A thorough investigation of risk factors for atherosclerosis was negative, except for mild hypertriglyceridemia. However, this young-adult patient presented with a severe diffuse triple-vessel CAD phenotype of unknown etiology. This mismatching finding prompted us to perform diagnostic tests for TGCV, which is an emerging cardiovascular disorder with a high mortality rate, characterized by unique atherosclerosis with TG accumulation caused by defective intracellular TG lipolysis.[1,2] A single-photon emission computed

Received for publication May 13, 2024. Accepted June 11, 2024.

Corresponding author: Hiroyuki Yamamoto, MD, PhD, Department of Cardiology, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. Tel.: +81 3 3342 6111; fax: +81 3 5381 6652.

E-mail: hyamamoto19700908@gmail.com

See page 1120 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.06.004

Novel Teaching Points

- TGCV is an emerging cardiovascular disorder characterized by defective intracellular triglyceride lipolysis mainly in the vascular smooth muscle cells and cardiomyocytes.
- The etiology of ACS with diffuse atherosclerotic lesions in young adults includes TGCV.
- A combination of myocardial scintigraphy and histology is useful for diagnosing TGCV, whereas plasma TG level and body mass index are not relevant.
- CABG and supplemental tricaprin might be promising treatment alternatives for severe diffuse triple-vessel CAD in patients with TGCV.

tomography image with ^{123}I-β-methyl iodophenylpentadecanoic acid (^{123}I-BMIPP) revealed a low myocardial washout rate (WR) of 3.1% (the cutoff value for TGCV diagnosis < 10%; Supplemental Table S1), reflecting defective myocardial TG lipolysis (Fig. 1F). Endomyocardial biopsy (EMB) revealed moderate myocardial hypertrophy with vacuolar degeneration (Fig. 1G), and many tiny myocardial lipid droplets positive for perilipin-2 (PLIN2) encoding a gene responsible for constitutive lipid droplet—associated protein, which can detect intracellular lipid deposition in nonadipocytes (Fig. 1H, arrows), and adipose triglyceride lipase (ATGL), an essential molecule for intracellular TG hydrolysis (Fig. 1I, arrows). Transmission electron microscopy confirmed myofibrillar degeneration (arrows), myocardial lipid accumulation (arrowheads), and mitochondrial proliferation (Fig. 1J). Consequently, the patient fulfilled the diagnostic criteria for TGCV (Supplemental Table S1). As his exertional chest pain persisted 1 year after CABG, the patient started taking a tricaprin supplement, which reportedly can facilitate myocardial TG lipolysis in patients with TGCV.[3] Follow-up coronary computed tomography angiography at 1.5 years after tricaprin treatment demonstrated considerable regression of diffuse atherosclerotic lesions, with a concurrent reduction in extracellular volume (Fig. 2A-F), along with an improved ^{123}I-BMIPP-WR of 21.5% (Fig. 2G) and echocardiographic findings (left ventricular ejection fraction, 50%; left ventricular end-diastolic diameter, 50 mm). The patient remained clinically stable over the 3-year follow-up period.

Discussion

We report a unique case of a young-adult patient who had TGCV with severe diffuse triple-vessel CAD, and ACS. As described, this patient had normal body mass index and blood pressure, suggesting that his severe cardiovascular phenotype is unlikely to be related to metabolic syndrome or hypertriglyceridemia.

TGCV is an emerging cardiovascular disorder, first reported in Japanese patients with heart failure requiring cardiac transplantation. In TGCV, defective intracellular TG lipolysis causes cellular steatosis and energy failure, mainly involved in vascular smooth muscle cells and cardiomyocytes. A major characteristic of TGCV is unique atherosclerosis with TG accumulation caused by defective intracellular TG lipolysis, leading to potentially life-threatening CAD, which is resistant to standard cholesterol-lowering therapies and percutaneous coronary intervention.[1,2,4] Recently, the incidence of ACS in young adults has increased steadily, posing a serious public health burden. Most ACS etiologies in young adults account for plaque rupture or erosion due to premature atherosclerosis. In contrast, nonatherosclerotic etiologies have now received attention. Generally, the typical angiographic features of ACS in young adults include single-vessel CAD with focal dissection and/or stenosis or an isolated thrombus. Nevertheless, the condition in our case manifested as severe diffuse triple-vessel CAD. Because intrinsic coronary artery dysfunction caused by abnormal intracellular TG accumulation may result in concentric circular diffuse coronary artery stenosis,[1,2] the diffuse CAD phenotype may be an important red flag for TGCV.

Defective TG lipolysis can be assessed using myocardial scintigraphy by calculating the myocardial WR of ^{123}I-BMIPP, which is an established radioactive analog of long-chain fatty acids. After intravenous administration, ^{123}I-BMIPP is taken up into cardiomyocytes via CD36, a fatty-acid transporter. Most of it are incorporated into the TG pool, hydrolyzed by intracellular lipases, including ATGL, and eventually washed out from cardiomyocytes. Thus, the low ^{123}I-BMIPP-WR reflects defective intracellular lipolysis of TG and the metabolic defect in TGCV, and it is a key factor for the diagnosis of TGCV, even at an earlier stage of the disease.[2,5] Furthermore, our recent study demonstrated that the histologic analysis of lipid deposition using antibodies against ATGL and PLIN2 in EMB specimens could characterize TGCV, along with the ^{123}I-BMIPP-WR, in myocardial scintigraphy.[6] Therefore, cardiac nuclear imaging in combination with EMB was useful for diagnosing TGCV in the present case.

The appropriate management of CAD in patients with TGCV remains unclear. A cohort study suggested that patients with TGCV and CAD had a substantially higher incidence of in-stent restenosis after percutaneous coronary intervention and standard medical treatment.[4] Whereas tricaprin (glyceryl tridecanoate), a class of medium-chain TG, has the potent ability to promote myocardial TG lipolysis and is a potential therapeutic alternative. A multicentre randomized controlled trial conducted in Japan (phase IIa) showed that tricaprin promotes myocardial lipolysis in patients with TGCV.[7] Tricaprin treatment has been reported to regress coronary atherosclerosis in patients with TGCV.[3] In the present case, the combination of CABG and tricaprin improved the patient's clinical symptoms of severe diffuse triple-vessel CAD. In Japan, a phase IIb/III clinical trial of a first-in-class orphan drug with the active ingredient tricaprin or trisdecanoin is underway (jRCT2051210177). Future prospective studies on CAD management are warranted.

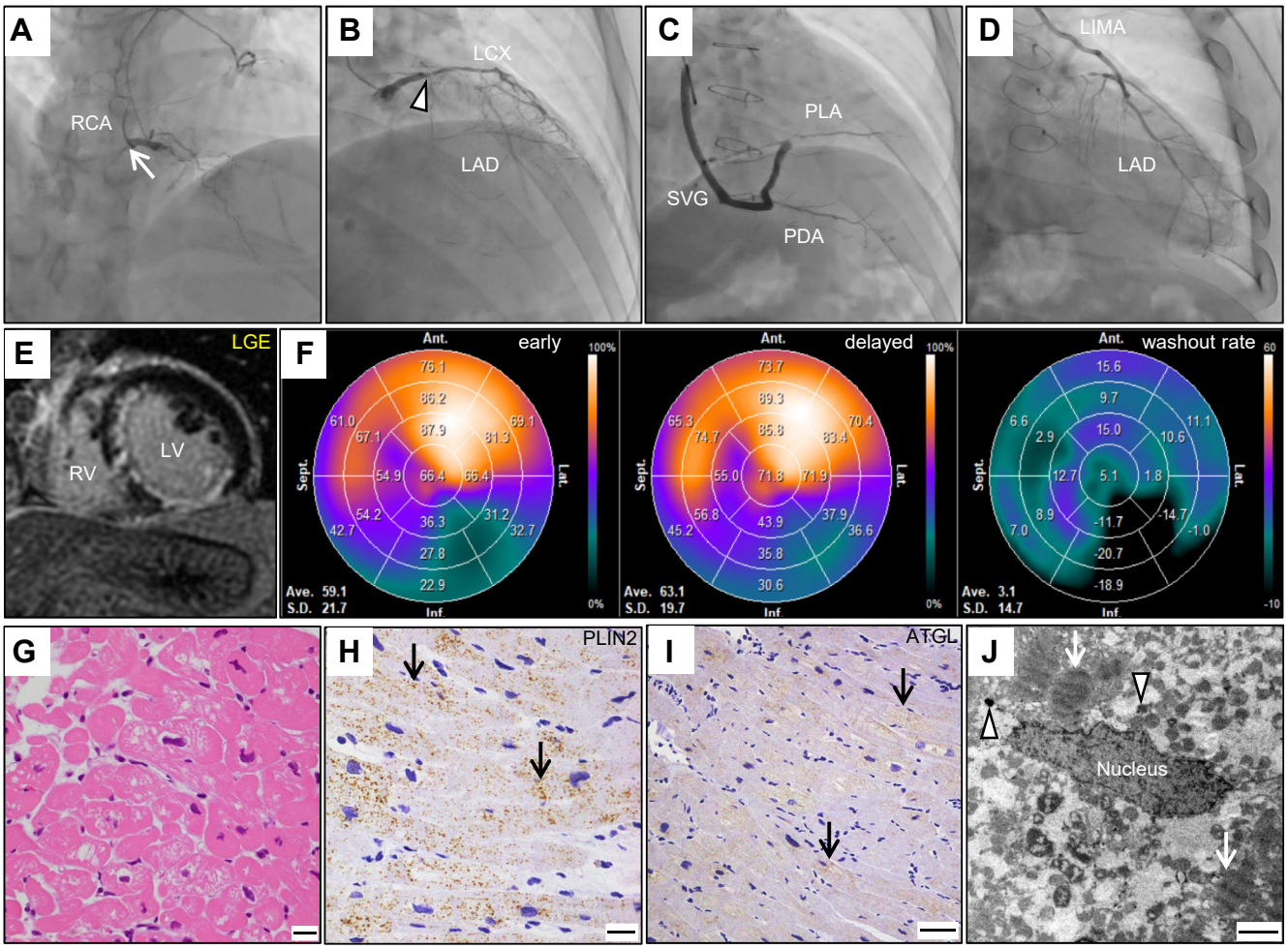

Figure 1. Diagnostic approach to triglyceride deposit cardiomyovasculopathy (**A, B**) Initial coronary angiography (CAG) reveals severe diffuse triple-vessel coronary artery disease. The proximal part of the right coronary artery (RCA) reveals chronic total occlusion (**arrow**); the proximal left ascending artery (LAD) reveals subtotal occlusion (**arrowhead**); and the distal part of the left circumflex artery (LCX) reveals 99% diffuse stenosis. (**C, D**) Postoperative CAG revealed that the left internal mammary artery (LIMA) was anastomosed to the LAD, and a saphenous vein graft (SVG) was anastomosed to both the posterior descending artery (PDA) and the posterolateral artery (PLA). Note the diffuse narrowing of the native coronary arteries. (**E**) A late gadolinium enhancement (LGE) image reveals the subendocardial enhancement localized to the antero-septum, septum, inferior wall and infero-lateral wall, with sparing of the majority of the anterior wall. (**F**) A bullseye map of single-photon emission computed tomography image employing ^{123}I-β-methyl iodophenyl-pentadecanoic acid reveals a considerable decreased myocardial washout rate of 3.1%. (**G-I**) Microscopic features of endomyocardial biopsy. (**G**) Photomicrographs after hematoxylin and eosin staining reveals moderate myocardial hypertrophy with vacuolar degeneration. (**H, arrows**) Numerous small lipid droplets are highlighted within the cardiomyocytes with an antibody against perilipin-2 (PLIN2). (**I, arrows**) Adipose triglyceride lipase (ATGL)-positive cardiomyocytes are observed. (**J**) Transmission electron microscopy reveals myofibrillar degeneration (**arrows**), myocardial lipid accumulation (**arrowheads**), and mitochondrial proliferation. Scale bars: (**G, H, J,** 20 μm; **I**, 50 μm). Ant., anterior wall; Ave., average; Inf., inferior wall; Lat., lateral wall; LV, left ventricle; RV, right ventricle; S.D., standard deviation; Sept., septal wall.

This study has several limitations. First, the genetic cause or background of TGCV in this patient remains undetermined. A known genetic cause of TGCV is mutations in *PNPLA2* encoding ATGL; however, this possibility was unlikely in this patient because the immunoreactive mass of ATGL was positive in his EMB specimens, as shown in Figure 1. Approximately 95% of the patients diagnosed with TGCV in Japan do not have ATGL deficiency. The cause of the metabolic adaptation remains unclear: Genes and molecules other than ATGL might be considered.[6] Second, the prevalence of TGCV in ethnicities other than Japanese is an important area for future research and clinical focus. Because myocardial scintigraphy using ^{123}I-BMIPP is performed in Japan only, those outside of Japan may not understand the importance of the ^{123}I-BMIPP-WR. Hopefully, ^{123}I-BMIPP myocardial scintigraphy will be used worldwide in the near future.

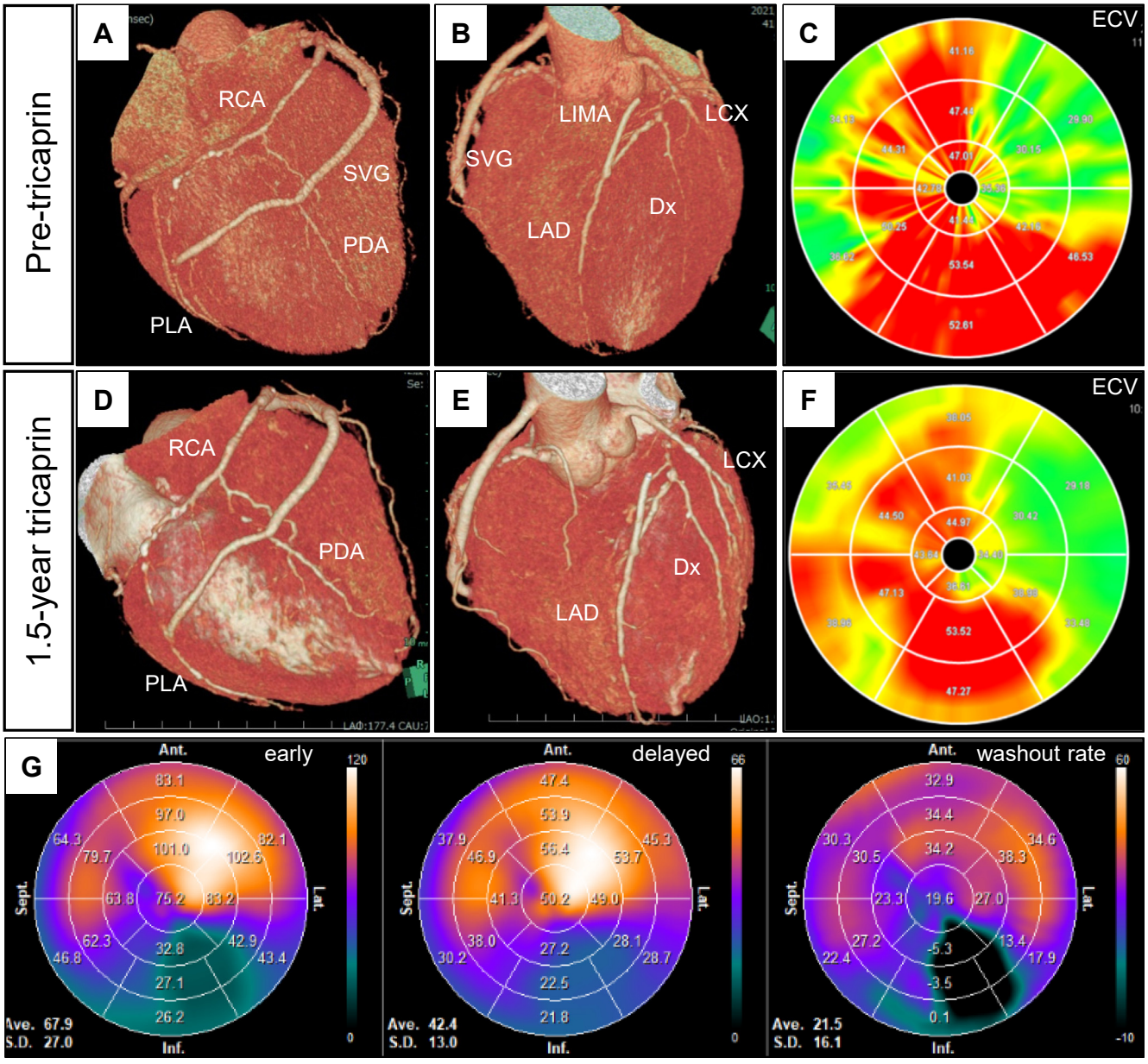

Figure 2. The effects of tricaprin treatment on coronary artery disease and the associated myocardial fibrosis. (**A, B, D, E**) Volume-rendering reconstructions and (**C, F**) myocardial extracellular volume (ECV) polar maps. (**A, B**) Coronary computed tomography angiography (CCTA) confirms the patency of the left internal mammary artery (LIMA) to the left ascending artery (LAD) and the saphenous vein graft (SVG) to the posterior descending artery (PDA) and the posterolateral artery (PLA). Note that the native coronary arteries are diffusely stenosed or partially occluded. (**D, E**) Post-treatment CCTA reveals the improvement in the atherosclerotic lesions in the native coronary arteries with concurrent luminal dilatation. (**C**) ECV analysis calculated using late iodine-enhanced cardiac imaging shows that an increase in ECV area, an index of myocardial fibrosis, is observed at baseline and (**F**) improves considerably at 1.5-years post-treatment (mean ECV: baseline, 41%; post-treatment, 36%). (**G**) Post-treatment bullseye map of single-photon emission computed tomography image with ^{123}I-β-methyl iodophenyl-pentadecanoic acid reveals a marked improvement in the myocardial washout rate, of 21.5%. Ant., anterior wall; Dx, diagonal; Inf, inferior wall; Lat., lateral wall; LCX, left circumflex artery; RCA, right coronary artery; Sept., septal wall.

Conclusion

We reported a case of a young-adult patient with TGCV with severe diffuse triple-vessel CAD, who presented with ACS and was treated successfully with CABG, followed by tricaprin therapy. With increased awareness of the disease concept and the utilization of myocardial scintigraphy, the identified number of patients with TGCV in the late-middle and elderly populations has been increasing in Japan.[2] Therefore, in examinations of even young-adult patients with unexplained diffuse CAD, the differential diagnosis should include TGCV, an emerging rare cardiovascular disorder, to evaluate risk stratification and consider therapeutic opportunities using supplemental tricaprin.

Ethics Statement

Authorization for the use of case information and materials was obtained from the Institutional Review Board of Narita-Tomisato Tokushukai Hospital, Chiba, Japan.

Patient Consent

The authors confirm that written consent for submission and publication of this case report, including the images, was obtained from the patient.

Funding Sources

This study was partially supported by a rare disease research grant from the Ministry of Health, Labour, and Welfare of Japan (grant No. 24FC1007) to K.H.

Disclosures

K.H. has held the position of Joint Research Chair in collaboration with Toa Eiyo Ltd. (Tokyo, Japan) since February 2021 and has served as a medical advisor for Toa Eiyo Ltd. since December 2021. K.H. has a related patent pending (JP2021008689). The other authors have no conflicts of interest to disclose.

References

1. Hirano K, Ikeda Y, Zaima N, Sakata Y, Matsumiya G. Triglyceride deposit cardiomyovasculopathy. N Engl J Med 2008;359:2396-8.
2. Hirano K, Miyauchi H, Nakano Y, et al. Overall survival rate of patients with triglyceride deposit cardiomyovasculopathy. JACC Advances 2023;2:100347.
3. Hirano K, Higashi M, Nakajima K. Remarkable regression of diffuse coronary atherosclerosis in patients with triglyceride deposit cardiomyovasculopathy. Eur Heart J 2023;44:1191.
4. Nakano Y, Suzuki M, Hirano KI, et al. Association of triglyceride deposit cardiomyovasculopathy with drug-eluting stent restenosis among patients with diabetes. JAMA Netw Open 2020;3:e2012583.
5. Nakajima K. Triglyceride deposit cardiomyovasculopathy: how to recognise a new disease entity. Heart 2021;107:93-5.
6. Ikeda Y, Shiba M, Yamamoto H, et al. Distinct myocardial triglyceride lipolysis pathways in primary and idiopathic triglyceride deposit cardiomyovasculopathy. ESC Heart Fail 2024;11:1275-8.
7. Miyauchi H, Hirano KI, Nakano Y, et al. 123I-BMIPP scintigraphy shows that CNT-01 (tricaprin) improves myocardial lipolysis in patients with idiopathic triglyceride deposit cardiomyovasculopathy: first randomized controlled, exploratory trial for TGCV. Ann Nucl Cardiol 2022;8:67-75.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.06.004.