

LETTER TO THE EDITOR

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Triglyceride deposit cardiomyovasculopathy: a rare cardiovascular disorder

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Abstract

Triglyceride deposit cardiomyovasculopathy (TGCV) is a phenotype primarily reported in patients carrying genetic mutations in *PNPLA2* encoding adipose triglyceride lipase (ATGL) which releases long chain fatty acid (LCFA) as a major energy source by the intracellular TG hydrolysis. These patients suffered from intractable heart failure requiring cardiac transplantation. Moreover, we identified TGCV patients without *PNPLA2* mutations based on pathological and clinical studies. We provided the diagnostic criteria, in which TGCV with and without *PNPLA2* mutations were designated as primary TGCV (P-TGCV) and idiopathic TGCV (I-TGCV), respectively. We hereby report clinical profiles of TGCV patients. Between 2014 and 2018, 7 P-TGCV and 18 I-TGCV Japanese patients have been registered in the International Registry. Patients with I-TGCV, of which etiologies and causes are not known yet, suffered from adult-onset severe heart disease, including heart failure and coronary artery disease, associated with a marked reduction in ATGL activity and myocardial washout rate of LCFA tracer, as similar to those with P-TGCV. The present first registry-based study showed that TGCV is an intractable, at least at the moment, and heterogeneous cardiovascular disorder.

Keywords: Adipose triglyceride lipase, Atherosclerosis, Rare disease, Triglyceride-deposit cardiomyovasculopathy, Triglyceride metabolism

Triglyceride (TG) and orphan diseases

TG is a major energy source for mammals. In normal condition, TG is either received via the diet, or synthesized endogenously and stored in adipose tissues. When required, TG is hydrolyzed by various enzymes called lipases and releases long-chain fatty acid (LCFA), which is delivered to

non-adipose tissues for the production of ATP. It has been known that the ectopic TG deposition in non-adipose tissues causes some orphan diseases. In 1953, Jordans reported two brothers with phenotype of skeletal myopathy and vacuolar formation of peripheral leukocytes, called Jordans' anomaly [1]. Fifty years later, Fischer et al. found that this phenotype is associated with mutations in *PNPLA2* [2] encoding adipose TG lipase (ATGL) [3, 4], an essential molecule located in cytoplasmic lipid droplets for the intracellular TG hydrolysis [5, 6], and designated this phenotype as neutral lipid storage disease with myopathy (NLSM). Clinical manifestations of NLSM appeared variable from mild to severe symptoms [7–13], which could be at least partially explained by function of mutated ATGL proteins

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Ken-ichi Hirano: The principal investigator for the Japan TGCV study group supported by the grants from the Ministry of Health, Labour and Welfare and the Japan Agency for Medical Research and Development (A-MED)

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[14]. Another phenotype of NLSLD involving the skin was reported as NLSLD with ichthyosis (NLSLD-I) by Chanarin and Dorfman in the 1970s [15–17]. The genetic cause of NLSLD-I was found to be mutations in *ABHD5* encoding CGI-58, a co-enzyme of ATGL [18]. Using skin fibroblasts and iPS cells from patients with NLSLDs, unique intracellular metabolism of TG has been extensively analyzed. These cell-biological experiments showed that cytoplasmic lipid droplets are dynamic cellular organelles interacting with ATGL, CGI-58, and other proteins, and could be a therapeutic target [19–23].

Discovery of TG-deposit cardiomyovascuopathy (TGCV) with *PNPLA2* (ATGL) mutation

Since the early 1980s, patients with Jordans' anomaly and severe heart failure (HF), though very rare, had been reported in Japan [24]. In the early 2000s, our institution started to take care of two patients with severe HF and vacuolar formation in peripheral leukocytes. HF was progressive and intractable, and a couple of years later, they became candidates for

cardiac transplantation (CTx). Preoperative examination of their hearts exhibited dilated cardiomyopathy-like morphology in chest X-ray and ultrasonography; however, endomyocardial biopsy specimens showed neutral lipid deposition in cardiomyocytes [25]. When they underwent CTxs, pathological and biochemical analyses of their explanted hearts were performed, demonstrating that their coronary arteries showed unusual coronary atherosclerosis with TG deposition in endothelial and smooth muscle cells (SMCs). We named this novel phenotype as TGCV [26–28]. These patients were identified as homozygous for genetic mutations in *PNPLA2* encoding ATGL, which is also known to be responsible for NLSLD-M as described above [2].

Postmortem analyses revealed undiagnosed individuals with TGCV

Retrospective postmortem analyses of autopsied cases identified individuals with TGCV phenotype who had TG deposit in both myocardium and coronary arteries, as presented in Fig. 1. A 38-year-old man suddenly died

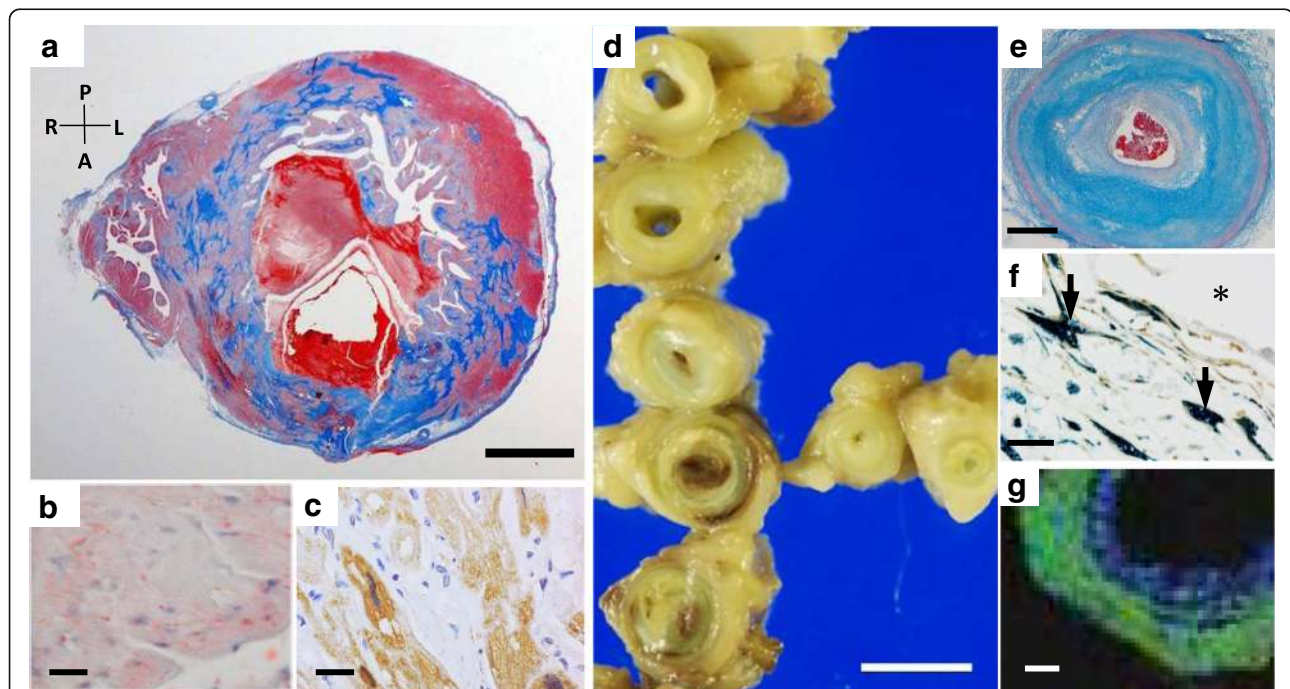


Fig. 1 Pathological analysis of the autopsied heart of a 38-year-old man with TGCV phenotype without *PNPLA2* mutation. Panel **a** The transverse section of the autopsied heart stained with Masson's trichrome showed circumferential patchy fibrosis of the left ventricular wall. The letters A, L, R, and P denotes anterior, left, right, and posterior, respectively. Panel **b** Lipid droplets (LDs) stained with oil red O in the cytoplasm of cardiomyocytes. Panel **c** Immunostaining for ATGL (Cell Signaling, Danvers, MA). Cardiomyocytes showed positive reactivity for ATGL. Panel **d** Coronary arteries with diffuse concentric-type stenosis. Panel **e** The transverse section of coronary artery was stained with Masson's trichrome. Coronary artery revealed intimal thickening and fibroatheromatous lesions. Panel **f** Double-staining of Sudan black B and α -smooth muscle actin (Dako, Tokyo, Japan). Smooth muscle cells (brown color) with lipid droplet (blue color) distributed diffusely in the media and intima (arrows in Panel **f**). Asterisk represents the vascular lumen. Panel **g** TG (m/z 879.7) was identified as green and blue colors depending on the intensity. TG signals were diffusely detected in the arterial wall by imaging mass spectrometry. Green color denotes relatively higher intensity of TG than blue color. Myocardial and coronary TG contents (3.64 and 19.44 mg/g of tissue, respectively) were higher in this patient, compared with each of control group (1.4 ± 1.0 , and 6.2 ± 4.8 mg/g of tissue, respectively). The detailed clinical profile of this patient is reported as Case 10 in the reference [29]. Scale bars: 1 cm in Panel **a**, 20 μ m in Panel **b** and **c**, 5 mm in Panel **d**, 1 mm in Panel **e**, 20 μ m in Panel **f**, 200 μ m in Panel **g**

irrespective of intensive treatment for coronary artery disease (CAD) and HF. His heart was heavy in weight and hypertrophied with multiple myocardial fibrous scars. Coronary arteries showed diffuse and concentric stenosis in multi-vessels. Biochemical analyses and imaging mass spectrometry showed TG deposition in both myocardium and coronary arteries [29, 30]. TG-deposit SMCs were observed in his renal and mesenteric arteries as well (data not shown). These data mimic genetic ATGL deficiency; however, the immunoreactive mass of ATGL was detected, and the genetic test using genomic DNA extracted from stored specimens showed no mutation in all exons and exon/intron boundaries of *PNPLA2* gene (data not shown). In addition, pathological records showed that he did not have skeletal myopathy.

Development of diagnostic methods for TGCV

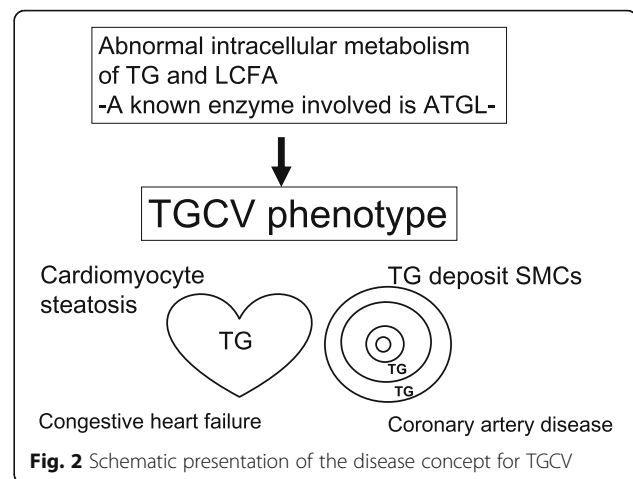
The above postmortem studies suggested that it is difficult to diagnose TGCV, and many undiagnosed patients should have died, which motivated us to develop diagnostic tools and methods for TGCV. We reported that myocardial scintigraphy with iodine-123- β -methyl iodophenyl-pentadecanoic acid (BMIPP) [31, 32], a radioactive analogue of LCFA, was useful in detecting abnormal LCFA metabolism in patients with TGCV [33, 34]. In addition, we reported the use of automated hematology analyzers to detect Jordans' anomaly in patients with *PNPLA2* mutation [35–37]. Recently, we developed CT-based TG imaging to detect myocardial and coronary TG deposition [34, 38] and selective immunoinactivation assay to measure functional ATGL activities using peripheral leukocytes [39].

Nomenclature, definition, and classification of TGCV

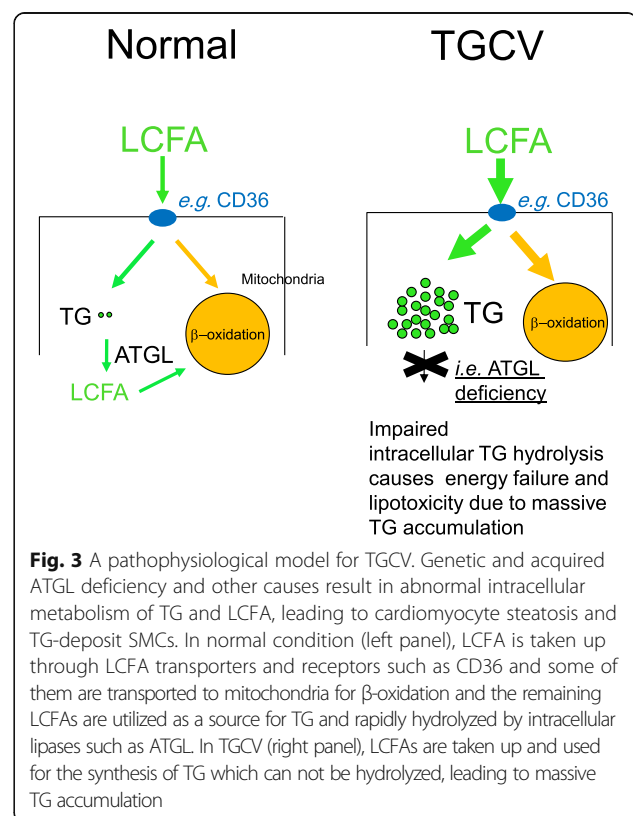
It is well known that disease nomenclature is made not only by their genotypes, but also by their phenotypes in many diseases and by discoverer's names in some diseases. The nomenclature of TGCV was made by its phenotype that TG accumulated in both myocardium and coronary arteries, resulting from abnormal intracellular metabolism of TG and LCFA (Fig. 2) [26–28]. ATGL is a known enzyme involved in the phenotypic expression of TGCV. The Japan TGCV study group provided the diagnostic criteria for TGCV, in which TGCV with and without *PNPLA2* mutations was designated as primary TGCV (P-TGCV) and idiopathic TGCV (I-TGCV), respectively [40–42].

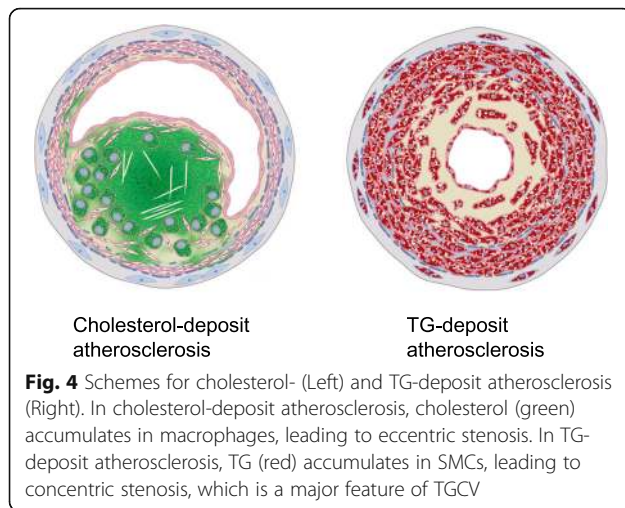
Pathophysiology of TGCV

The pathophysiological schema of TGCV is shown in Fig. 3. In normal condition (left panel, Fig. 3), LCFAs are taken up through transporters and receptors such as CD36. Some are transported to the mitochondria for β -oxidation, and the remaining LCFAs are utilized as a source of TG and rapidly hydrolyzed by intracellular



lipases such as ATGL. In TGCV (right panel, Fig. 3), LCFAs are taken up and used to synthesize TG that cannot be hydrolyzed due to ATGL insufficiency, leading to energy failure and lipotoxicity with massive TG accumulation [28, 43]. It is emphasized that TG-deposit atherosclerosis is an important characteristic of TGCV [44] and distinct from usual cholesterol-deposit atherosclerosis, because the former showed diffuse and concentric narrowing formed by TG-deposit SMCs, whereas the latter showed discrete and eccentric stenosis initiated by the response to injury in the endothelium and





accumulation of cholesterol-laden macrophages [45] (Fig. 4). We reported that TG-deposit SMCs and endothelial cells had pro-inflammatory and vulnerable phenotype in vitro [46, 47].

A clinical case presentation of I-TGCV

A 58-year-old woman was referred to our hospital due to sudden chest tightness with ST-segment elevation in the electrocardiogram, followed by cardiopulmonary arrest. Under the diagnosis of acute myocardial infarction, she underwent coronary artery bypass grafting (CABG). Past history included type 2 diabetes mellitus requiring insulin treatment and hemodialysis. Cytoplasmic vacuoles in her peripheral polymorphonuclear leukocytes were observed less frequently (<10% of neutrophils), compared with that in genetic ATGL deficiency (panel A in Fig. 5). ATGL activity in peripheral leukocytes was very low, comparable to that of genetic ATGL deficiency, as shown in Table 1. Myocardial washout rate (WOR) of BMIPP was defective in scintigraphy (panel B in Fig. 5). Pathological analyses of endomyocardial biopsy specimens demonstrated numerous vacuoles filled with stained lipid but positive reactivity for ATGL in cardiomyocytes and adipocytes (right, panel C in Fig. 5). Coronary CT angiogram showed diffuse narrowing coronary arteries, and in TG imaging [25], outside-in involvement of diffuse and abundant lipid components expressed as low CT numbers was seen within the wall in a peninsular pattern (arrows in panel D in Fig. 5). Her laboratory data and imaging tests were similar to those observed in TGCV with genetic ATGL deficiency, except for the conserved expression of ATGL protein in the myocardium. However, it is noted that the case was clinically distinct from genetic ATGL deficiency because there was no skeletal myopathy and no elevation of MM type creatine kinase. Genetic tests showed no mutations or substitutions in any of the

exons or intron/exon boundaries of genes encoding ATGL, 1-acylglycerol-3-phosphate O-acyltransferase, hormone-sensitive lipase, or GOS2 (data not shown).

Clinical characteristics of P- and I-TGCV

Table 1 shows the clinical characteristics of 7 and 18 patients with P- and I-TGCV, respectively, registered to the international registry for NLSD and TGCV between February 2014 and March 2018 in Japan. Both TGCV types were adult onset with chest pain at rest or dyspnea and palpitation. Most patients with either types of TGCV developed severe HF or CAD with diffuse narrowing multivessel lesions or both. Myocardial metabolism of LCFA, detected by WOR of BMIPP and ATGL activities in peripheral leukocytes, was reduced in both TGCV types. Most patients with P-TGCV developed intractable and critical HF, as reported recently [26, 48, 49]. Two of them underwent CTx [26, 48]. Many patients with I-TGCV required percutaneous coronary intervention and CABG. As comorbidity, neither type of TGCV had skin lesions, which suggests that TGCV is not associated with NLSD-I. All patients with P-TGCV had skeletal myopathy, whereas none of those with I-TGCV did. Five of 7 and 3 of 18 registered patients with P- and I-TGCV, respectively, died.

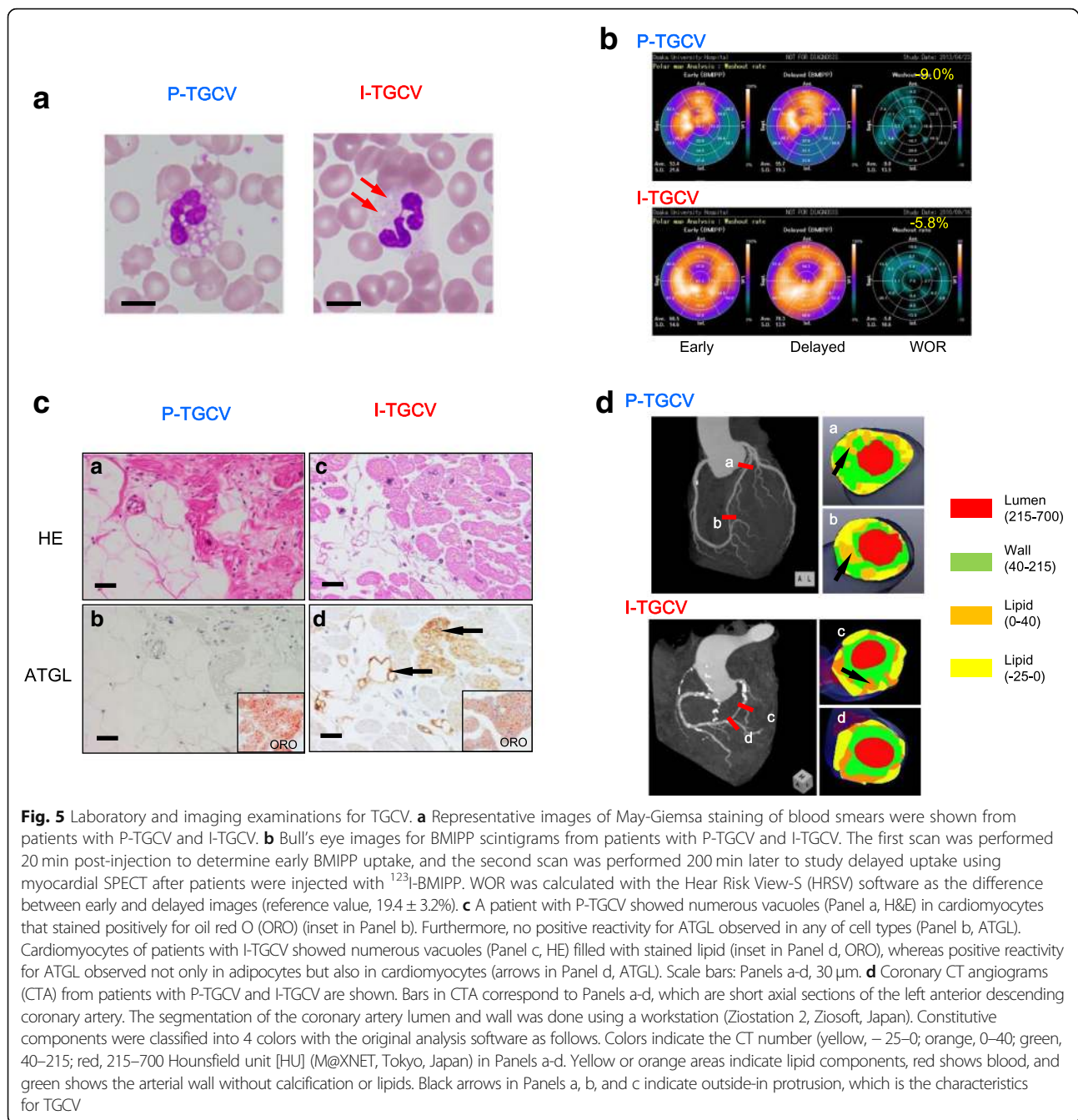
Differential diagnosis of TGCV

Myocardial disorders such as dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, mitochondrial cardiomyopathy, alcoholic heart disease, and metabolic myocardial disorders (e.g., Fabry disease, Pompe disease, cholesteryl ester storage disease) need to be differentiated from TGCV [41, 42].

Furthermore, known diabetic and metabolic heart diseases need to be differentiated from TGCV. One is diabetic cardiomyopathy, which was originally defined as cardiomyopathy without significant stenosis in epicardial coronary arteries [50]. Another concept is epicardial fat accumulation, which is the overdeposition of TG in physiological tissues. TGCV is distinct from these two entities because TGCV is characterized by the ectopic deposition of TG in the cardiomyocytes and SMCs with apparent involvement of epicardial coronary arteries, as shown in Figs. 1 and 5.

Academia-initiated development of specific treatment for TGCV

We found that the chow with tricaprins, TG form of capric acid, improved LCFA metabolism, lipid deposition, cardiac function, and life span in ATGL-targeted mice [4], raising a therapeutic hypothesis that capric acid may be an alternative energy source and reduce TG deposition and lipotoxicity in TGCV [51]. Based upon



these data, the Osaka University Hospital manufactured GMP-graded capsules containing the active gradients called CNT-01. We developed the assay to measure plasma capric acid levels [52, 53]. After finishing toxicity tests using rats and dogs required, we are finally conducting investigator-initiated clinical trials.

Comparison between NLS-D-I, NLS-D-M, and TGCV

As mentioned above, the nomenclature of TGCV was made by its phenotype that TG accumulated in both

myocardium and coronary arteries, resulting from abnormal intracellular metabolism of TG and LCFA (Figs. 2 and 3). As described in the first paragraph in this letter, there have been known related disorders; NLS-D-M and NLS-D-I. Figure 6 shows the comparison of phenotype and genotype between TGCV and NLS-Ds. NLS-D-M and NLS-D-I are caused by mutations in *PNPLA2* and *ABHD5*, mainly involved in the skeletal muscle and skin, respectively. Genotype of P-TGCV is known to be *PNPLA2* mutation which is responsible for NLS-D-M as well.

Table 1 Patients' characteristics of Primary and Idiopathic TGCV

	Primary <i>n</i> = 7	Idiopathic <i>n</i> = 18
General Status		
Age (years)	55.7 ± 12.7	64.6 ± 14.7
Sex (female, male) (n)	(2, 5)	(9, 9)
BMI (kg/m ²)	19.4 ± 3.4	25.4 ± 5.0
Family history for CVD	7	13
ATGL expression		
PNPLA2 mutation	Yes	No**
ATGL activities in leukocytes (nmol/h/mg)* (reference value 52 ± 13 nmol/h/mg)	5.3 ± 8.3	12 ± 9
Vacuole formation in polymorphonuclear leukocytes (%)	~ 100%	< 10%
Heart disease		
Mean age of symptom onset (years)	37.7 ± 9.2	55.9 ± 12.5
Angina at rest (n)	3	10
Dyspnea or palpitation (n)	4	8
Clinical diagnosis at registration		
Angina pectoris (rest, effort) (n)	1 (1,0)	13 (11, 2)
Heart failure (n)	5	8
Critical arrhythmia (n)	4	1
History of myocardial infarction (n)	0	4
NYHA classification (I, II, III, IV) (n)	(1, 1, 2, 3)	(2, 5, 11, 0)
Coronary angiography or CT angiogram		
Affected branch (single vessel, multivessels) (n)	(0, 5)	(4,14)
Diffuse narrowing (n)	5	18
Washout rate in BMIPP scintigram (%) (reference value 19.4 ± 3.2%)	—3.2 ± 4.8	1.4 ± 8
Treatment history		
Percutaneous coronary intervention (n)	0	7
Coronary artery bypass grafting (n)	0	5
Cardiac transplantation (n)	2	0
Comorbidity		
Skin lesions (n)	0	0
Skeletal myopathy (n)	7	0
Diabetes mellitus (n)	2	15
Outcome		
Death (n) (before, after registration)	5 (3, 2)	3 (2, 1)

*Three patients with P-TGCV and fourteen with I-TGCV were enrolled

We did not have opportunity for the measurement in the remaining four patients with P-TGCV and four with I-TGCV

**Two patients were dismissed before the genetic analysis

The Japan TGCV study group certified I-TGCV according to the diagnostic guideline

Abbreviations: CT Computed tomography, CVD Cardiovascular disease, TGCV Triglyceride deposit cardiomyovasculopathy

Phenotype	NLSD-I	NLSD-M	TGCV	
			Primary	Idiopathic
Genotype	ABHD5 mutation	PNPLA2 mutation	PNPLA2 mutation	No PNPLA2 mutation
Major tissue involved	Skin	Skeletal muscle	Heart Vessel	

Fig. 6 Relationship between TGCV and NLSDs. Comparison of phenotype and genotype between NLSD-I, NLSD-M and TGCV

Issues to be resolved

The following points are important focus for future researches:

1. Possible clinical continuum between P-TGCV and NLSD-M
As mentioned above, both P-TGCV and NLSD-M is caused by genetic ATGL deficiency. It would be of interest to know whether patients with NLSD-M have TG-deposit atherosclerosis, which is the important feature for P-TGCV.
2. Etiologies of I-TGCV and its prevalence in countries other than Japan
As shown in Table 1, 13 out of 18 patients with I-TGCV had family history of cardiovascular disease, suggesting that any genetic factors might be involved in the pathogenesis of I-TGCV. The mechanism underlying downregulation of ATGL activities of I-TGCV and possible involvement of other lipases and related enzymes is of significance to elucidate. In order to elucidate these issues, the development of screening methods for the diagnosis of I-TGCV is under way in our laboratory.

Conclusions

TGCV is a severe cardiovascular disorder named by its phenotype of cardiomyovascular TG deposition, of which etiologies seem heterogeneous.

Methods

1. Pathological, laboratory, and clinical imaging
Standard procedures were performed as described (please see legends of Figs. 1 and 5).
2. International registry for NLSD/TGCV
On the World Rare Disease Day 2014, we launched the international registry for neutral lipid storage diseases, TG-deposit cardiomyovascular, and related disorders (Clinical Trial gov. NCT02830763). The present patients with TGCV were registered according to the study protocol after obtaining written consent. The protocol was approved by the Osaka University Hospital Ethical Committee (approval no. 13204).

Abbreviations

ATGL: Adipose triglyceride lipase; BMIPP: Iodine-123- β -methyl iodophenyl-pentadecanoic acid; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CTA: CT angiograms; CTx: Cardiac transplantation; HF: Heart failure; Hu: Hounsfield unit; LCFA: Long-chain fatty acid; NLSD: Neutral lipid storage disease; NLSD-I: NLSD with ichthyosis; NLSD-M: NLSD with myopathy; SMCs: Smooth muscle cells; TG: Triglyceride; TGCV: Triglyceride-deposit cardiomyovascularopathy; WOR: Washout rate

Acknowledgments

The authors thank Dr. Kosuke Tsukamoto for playing a part in constructing the international registry. The authors would like to thank Ms. Mao Ishikawa and Yoshie Yabe for their excellent secretarial work.

Funding

This study was partially supported by research grants from the Ministry of Health, Labour and Welfare and the Japan Agency of Medical Research and Development (A-MED; grant no. 17ek0109092h0003), Nihon Medi-Physics Co., Ltd., and the Tochino Foundation to KH.

Availability of data and materials

The datasets generated and/or analyzed in the current study are available from the corresponding author on reasonable request.

Authors' contributions

ML wrote the manuscript and contributed to data analyses and discussion. KH designated the research concept and contributed to the discussion and writing of the manuscript. YoI performed autopsy for the undiagnosed case (Fig. 1), collected data, and contributed to the discussion and writing of the manuscript. KH and JK took care of the clinically identified I-TGCV case (Fig. 5). CH, BZ, JK, KSu, HM, ASu, YH, AT, Yal, KKo, MH, YF, NZ, SYamag, RS, and SYamad collected data and contributed to the discussion. HNaK, KaK, E S, S-PH, YNaK, Tln, YS, Y Yasui, YNaG, ASa, SK, KSh, HH, DN, Tld, TA, HNai, and HNag interpreted and discussed the data. KuK designated the registry, collected data, and contributed to the discussion. All the authors have read and revised the manuscript and approved the final manuscript.

Ethics approval and consent to participate

The protocol of the international registry was approved by the Osaka University Hospital Ethical Committee (Approved No. 13204).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 2 January 2019 Accepted: 1 May 2019

Published online: 11 June 2019

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