Clinical Medicine Insights: Case Reports

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Manuscript Type: Case Report	Manuscript Title: Possibly Late-Onset Arrhythmogenic Right Ventricular Cardiomyopathy:Unique Triglyceride Deposition by Analysis of Lipid Contents
Author Names: Kentaro Yamamoto, Xin Guo, Kenichi Mizutani, Nozomu Kurose, Motona Kumagai, Akihiro Shioya, Satoko Nakada, Rie Terauchi, Yoshihiko Ikeda, Hirofumi Aoki, Kouji Kajinami, Sohsuke Yamada	
Keywords:	
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Clinical Medicine Insights: Case Reports *October 25th, 2018*

Dr. and Prof. Hussein Foda, Editor-in-Chief

Dear, Dr. and Prof. Hussein Foda, Editor-in-Chief:

At first, we would like to express our many thanks to the editors and reviewers for their hard works and valuable, constructive suggestions. All suggestions are quite critical and made up for the deficiency of our original case report.

We had just submitted our manuscript of 'Case Report', entitled "Late-Onset Arrhythmogenic Right Ventricular Cardiomyopathy: Unique Triglyceride Deposition by Analysis of Lipid Contents (Ms ID: ICR-2018-0046)" approximately 3 months ago.

We received favorable comments from the Editors and Reviewers, and thus, its paper could be acceptable but necessary for substantial revise. Since we do believe that these new and extensively additional works in this revised manuscript can include much more beneficial information to understand the rare case of **Arrhythmogenic Right Ventricular Cardiomyopathy**, we have written the revised version as soon as possible, newly entitled "**R1**: **Possibly Late-Onset Arrhythmogenic Right Ventricular Cardiomyopathy: Unique Triglyceride Deposition by Analysis of Lipid Contents**".

On the way to revision, Drs. Hirofumi Aoki (M.D.) & Kouji Kajinami (M.D. and Ph.D. and Prof.) (Department of Cardiology, Kanazawa Medical University, Ishikawa, Japan) helped us to extensively revise the present paper through many valuable and constructive comments, and thus, have been new co-authors of the current

manuscript.

This manuscript has not been published elsewhere and is not under consideration by another journal. Moreover, a native English-speaking scientific doctor (Mr. Brian Quinn from Japan Medical Communication) had carefully checked this manuscript in its entirety, making it more precise and readable. We have followed his advice and revised our manuscript accordingly. All authors have approved the manuscript. We do hope that you will consider the present revised manuscript for publication in the ***Clinical Medicine Insights: Case Reports***.

We are looking forward to hearing from you at your earliest convenience. Thank you so much.

Yours faithfully,

Sohsuke Yamada, M.D., Ph.D.,

Department of Pathology and Laboratory Medicine, Kanazawa Medical University, 1-1 Uchinada, Ishikawa, 920-0293, Japan. Tel: 81-76-218-8264; Fax: 81-76-286-1207; and E-mail: sohsuke@kanazawa-med.ac.jp

Reviewer comments 2:

Thanks for letting me revise this interesting clinical case by Yamamoto, et al.

Although the topic is intruiguing, I ask to review the paper acoording to the follow comments:

-please clarify how the novelty of this case can make an impact on the clinical practice. If the lipid content is predomintatly of triglicerides, why is this clinically relevant? is it confirmed, how will improve the disease management?

Response:

At first, we would like to express our many thanks to the reviewer for his or her significant comments. Based on the various helpful suggestions, we have extensively revised our manuscript. Thank you so much for your help in improving our manuscript.

Those suggestions are one of the critical points in our case report. We have agreed the reviewer's comments completely, and thus, revised extensively the 'Discussion' section, as follows:

"…… The findings overlap with those of TG-deposit cardiomyovasculopathy (TGCV), a distinct entity, whose primary is genetic mutations in *adipose TG lipase*, an essential molecule for hydrolysis of intracellular TG [4]. We propose that this unique TG deposition in our **possibly** late-onset ARVC case might be one of new clues to understand its enigmatic etiology. **However, the etiology of TGCV could be very different from that of ARVC [1,4]. In fact, unlike TGCV, approximately 40% of patients with ARVC have shown mutations in genes encoding desmosomal proteins, such as plakoglobin, desmoplakin, plakophilin 2, desmocollin 2 or desmoglein 2 [1]. Furthermore, in marked contrast to ARVC, TGCV with *adipose TG lipase*-mutations/deficiency is**

characterized by profound intracellular, but not extracellular, TG deposition in multiple tissues, including cardiomyocytes or smooth muscle cells [4]. Despite that, Hirano *et al.* have more recently reported that the medium-chain TG (i.e., tricaptan) diet may be beneficial on the treatments for the TGCV patients, based on a growing body of data from *adipose TG lipase*-knockout mice models [5]. Nevertheless, it would be intriguing to assess the significance of lipid analysis for **the** ARVC **management** on future studies**,** after collecting and investigating a larger number of early- and late-onset ARVC cases examined. This short case report could interest the scientific community, taken together with potentially specific, new findings of ARVC." (pages 7 to 8)

- Was the genetic test performed in this patient? The initial diagnosis was made only because of the ECG abnormalities?

Response:

The answers are 'No, the genetic test was not performed.' & 'Yes, the initial diagnosis was made only because of the ECG abnormalities', and thus, we have revised them as follows:

"…. The clinicians diagnosed as late-onset ARVC**, based on the ECG abnormalities. But, the cardiomyocytic biopsy findings from the right-sided interventricular septum showed no extracellular lipid accumulations 6 and 1 and half years before his death, respectively. According to the echocardiography, left ventricular function gradually worsened over the 6**

years. Neither the genetic test nor the evaluation for possible causes of infection was performed. ….." (page 5)

- How was the LV function over the 6 years (from diagnosis to death)? any echo data?

Response:

Thanks so much for your constructive suggestions, again. We have revised it as follows:

"…. **According to the echocardiography, left ventricular function gradually worsened over the 6 years.** ….." (page 5)

Reviewer comments 3 :

The authors present here a case report of an elderly subject with a diagnosis of ARVC who died for pericardial effusion /ascites. His heart was analyzed, and tissue analysis found higher content of triglycerides respect to a control heart.

- I personally do not see anything special in the etiology of this disease:

Late onset: ARVC onset is usually in young adults, but this manuscript reports a late-phase, very compromised ARVC. Therefore, one cannot conclude anything about its onset unless documented in late adulthood. It could just be asymptomatic.

Response:

At first, we would like to express our many thanks to the reviewer for his or her significant and valuable comments. Based on the various helpful suggestions, we have extensively revised our manuscript. Thank you so much for your help in improving our manuscript.

We do respect the reviewer's comments as possible, and thus, we have written the revised version, newly entitled "**R1: Possibly** Late-Onset Arrhythmogenic Right Ventricular Cardiomyopathy: Unique Triglyceride Deposition by Analysis of Lipid Contents". Accordingly, we have thoroughly replaced it with '**possibly** late-onset ARVC' from 'Abstract' to 'Figure Legends'.

Ascites and pericardium effusion: it is known that inflammation and infection may be concomitant or even worsening ARVC. Proofs are missing for the cause of death (could have been due to arrhythmic events).

Response:

Thanks so much for your constructive suggestions, again. We have extensively revised it from 'Abstract' to 'Case Report', as follows:

"We presented an unusual arrhythmogenic right ventricular cardiomyopathy (ARVC) case of a late sixties elderly male's death, due to severe pericardial/pleural effusion and ascites**, and arrhythmic events**, with unique pathological features. ….." (pages 3,4,5)

TG content: I contest that the results of this tissue lipid contents are unexpected: ARVC hearts are described as substituted by adipose tissue, and this is the case also in this report. Adipose tissue lipid composition is 95% triglycerides and only 1% cholesterol; therefore we expect triglycerides being more present in an ARVC heart respect to a control.

Response:

We have partly agreed to the reviewer's comments. As described in this manuscript, we have examined the cardiac muscle lipid profiles, by using the commercial assay kits (Wako Pure Chemical Co., Osaka, Japan) for 'total' cholesterol, including not only cholesterol-ester but also free cholesterol. This is one cause of the unexpected data for lipid contents analysis (Figure 3).

-We can recognize that this is the first report of a lipidomic analysis in an ARVC hearts. However, the authors should correct the sentence "To our knowledge, we for the first time have analyzed the lipid contents on the ARVC cardiomyocytes, and subsequently, reported unexpected results regarding an increased volume of TG, but not cholesterol." Changing "To our knowledge, we for the first time have analyzed the lipid contents on the ARVC tissue samples, and subsequently, reported confirming results regarding an increased volume of TG, but not cholesterol.

Response:

We have completely agreed to the reviewer's suggestions. Thanks so much for his or her valuable comments. We have thoroughly deleted the word of 'surprisingly' from 'Abstract' to 'Discussion', and revised that sentence as

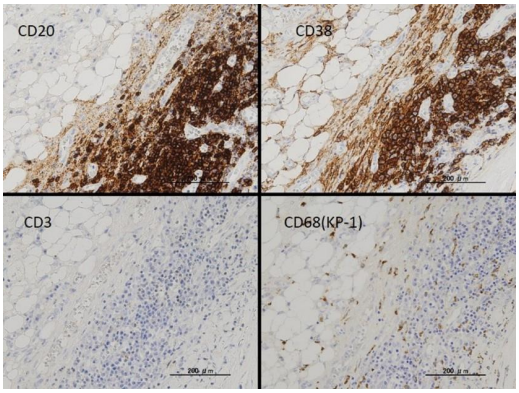
follow:

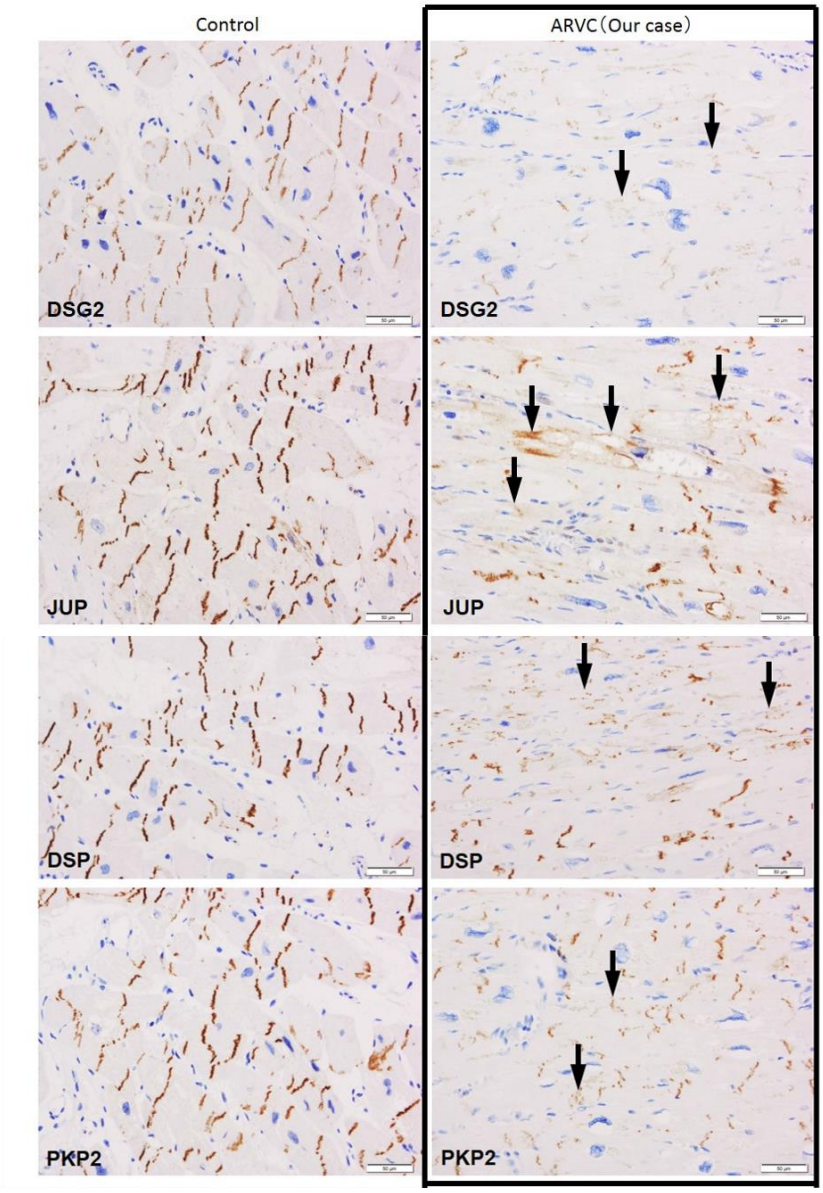
"It is most likely that our ARVC autopsy case is clinicopathologically remarkable for one reason at least: To our knowledge, we for the first time have analyzed the lipid contents on the ARVC **tissue samples**, and subsequently, reported **confirming** results regarding an increased volume of TG, but not cholesterol. ….." (page 7)

-Why the authors do not show CD20/CD38 characterization and desmosomal proteins at intercalated disks?

Response:

We do respect the reviewer's suggestions, as possible. In this case report, we have considered that these immunohistochemical data are not so critical, because we would like to focus on 'Analysis of Lipid Contents'. Furthermore, the immunohistochemical analyses for desmosomal proteins at intercalated disks are especially ongoing research for the group of Yoshihiko Ikeda (one of co-authors) *et al*. Despite that, we have shown them below, only within this 'Response to Reviewers'.





DSG2 : Desmoglein 2 (PROGEN Biotechnik)
JUP : Plakoglobin (PROGEN Biotechnik)
DSP : Desmoplakins 1&2 (PROGEN Biotechnik)
PKP2 : Plakophilin 2 (PROGEN Biotechnik)

-Have the Authors evaluated possible causes of infection? (viruses? Bacteria?)

Response:

The answer is 'No', and thus we have revised it as follow:

"**Neither the genetic test nor the evaluation for possible causes of infection was performed**. ….." (page 5)

- The discussed comparison with TGCV is potentially interesting, but need a different approach: direct comparison with this kind of diseased hearts, and isolation of CMs or SMCs to see triglyceride accumulation in these cells. Moreover, a genetic characterization (main ARVC genes and adipose TG lipase) would be needed.

Response:

Those suggestions are one of the critical aspects in our case report. Thanks so much for your constructive suggestions, again. We have agreed the reviewer's comments completely, and thus, revised extensively the 'Discussion' section, as follows:

"…… The findings overlap with those of TG-deposit cardiomyovasculopathy (TGCV), a distinct entity, whose primary is genetic mutations in *adipose TG lipase*, an essential molecule for hydrolysis of intracellular TG [4]. We propose that this unique TG deposition in our **possibly** late-onset ARVC case might be one of new clues to understand its enigmatic etiology. **However, the etiology of TGCV could be very different from that of ARVC [1,4]. In fact, unlike TGCV, approximately 40% of patients with ARVC have shown mutations in genes encoding desmosomal proteins, such as plakoglobin, desmoplakin, plakophilin 2, desmocollin 2 or desmoglein 2 [1]. Furthermore, in marked**

contrast to ARVC, TGCV with *adipose TG lipase*-mutations/deficiency is characterized by profound intracellular, but not extracellular, TG deposition in multiple tissues, including cardiomyocytes or smooth muscle cells [4]. Despite that, Hirano *et al.* have more recently reported that the medium-chain TG (i.e., tricaptan) diet may be beneficial on the treatments for the TGCV patients, based on a growing body of data from *adipose TG lipase*-knockout mice models [5]. Nevertheless, it would be intriguing to assess the significance of lipid analysis for **the** ARVC **management** on future studies**,** after collecting and investigating a larger number of early- and late-onset ARVC cases examined. This short case report could interest the scientific community, taken together with potentially specific, new findings of ARVC." (pages 7 to 8)

- From line 29 pag 7 to line 14 pag 8 the sentences are an exact repetition of previous sentences. Please rephrase.

Response:

We have completely agreed the reviewer's suggestions, and thus, deleted those sentences and revised extensively the 'Discussion' section, as follows:

"…… Nevertheless, it would be intriguing to assess the significance of lipid analysis for **the** ARVC **management** on future studies**,** after collecting and investigating a larger number of early- and late-onset ARVC cases examined. This short case report could interest the scientific community, taken together with potentially specific, new findings of ARVC." (page 8)

- At least a age-sex and healthy state of the control sample should be given.

Response:

Thanks so much for your kind and helpful comments. We have revised it, as follow:

"…… **A**ccording to the lipid contents analysis [3], the TG content (Figure 3A), but not the total cholesterol content (Figure 3B), in our patient's right and left ventricular cardiac muscle was much higher than that in the control subject **from the recent autopsy case of a late sixties elderly male without any evidence of cardiac diseases.**……" (pages 6 to 7)

Case Report

R1: Possibly Late-Onset Arrhythmogenic Right Ventricular Cardiomyopathy: Unique Triglyceride Deposition by Analysis of Lipid Contents

Kentaro Yamamoto [1], Xin Guo [1], Ken-ichi Mizutani [1], Nozomu Kurose [1], Motona Kumagai [1], Akihiro Shioya [1], Satoko Nakada [1], Rie Terauchi [2], Yoshihiko Ikeda [3], Hirofumi Aoki [4], Kouji Kajinami [4], Sohsuke Yamada [1, 2]*

Departments of [1]Pathology and Laboratory Medicine; & [4]Cardiology, Kanazawa Medical University, Ishikawa, Japan; [2]Department of Pathology, Kanazawa Medical University Hospital, Ishikawa; and [3]Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan.

Short running title: TG deposit in ARVC.

Word count: **1,304** words (Abstract **159** words); References: **5**; and 3 Figures.

*Corresponding author: Sohsuke Yamada, M.D., Ph.D., Department of Pathology and Laboratory Medicine, Kanazawa Medical University, 1-1 Uchinada, Ishikawa, 920-0293, Japan. Tel: 81-76-218-8264; Fax: 81-76-286-1207; and E-mail: sohsuke@kanazawa-med.ac.jp

Abstract

We presented an unusual arrhythmogenic right ventricular cardiomyopathy (ARVC) case of a late sixties elderly male's death, due to severe pericardial/pleural effusion and ascites**, and arrhythmic events**, with unique pathological features. The hypertrophic heart grossly displayed yellowish to yellow-whitish predominantly in the variably thinned wall of the dilated right ventricle. Microscopic findings showed diffuse fatty/fibrofatty replacement in not only the right but left ventricular myocardium, together with an outer lymphoplasmacytic infiltrate. **A**ccording to the lipid contents analysis, the triglyceride content, but not the cholesterol content, in our patient's right and left ventricular cardiac muscle was much higher than that in the control subject. We propose that this unique triglyceride deposition in our **possibly** late-onset ARVC case might be one of new clues to understand its enigmatic etiology. Further prospective studies are needed to validate the presence and significance of a greater volume of triglyceride deposit, after collecting and investigating a larger number of early- and late-onset ARVC cases examined.

Key Words: Arrhythmogenic right ventricular cardiomyopathy (ARVC), triglyceride (TG), lipid analysis.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a well-known genetic cardiomyopathy that most commonly affects young adults [1,2]. ARVC is characterized by progressive replacement of ventricular cardiomyocytes with variable amounts of fatty and fibrofatty tissue, and thus, usually results in sudden cardiac death [1,2]. We herein presented an unusual ARVC case of a late sixties elderly male's death, due to severe pericardial/pleural effusion and ascites**, and arrhythmic events**, with unique pathological features. Especially, according to the lipid contents analysis, the triglyceride (TG) content, but not the cholesterol content, in our patient's right and left ventricular cardiac muscle was surprisingly much higher than that in the control subject. We would like to propose that this unique TG deposition in our **possibly** late-onset ARVC case might be one of new clues to understand its enigmatic etiology.

Case Report

The patient presented here, a late sixties elderly male, showing right ventricular cardiac hypertrophy and dilation with occasional atrial tachycardia in a background of T wave inversion and mean QRS duration ≥105 ms in V1 through V3, by twelve-lead

electrocardiogram **(ECG)** recording, 6 years before his death. The clinicians diagnosed as late-onset ARVC**, based on the ECG abnormalities. But, the cardiomyocytic biopsy findings from the right-sided interventricular septum showed no extracellular lipid accumulations 6 and 1 and half years before his death, respectively. According to the echocardiography, left ventricular function gradually worsened over the 6 years. Neither the genetic test nor the evaluation for possible causes of infection was performed**. He died due to severe pericardial effusion (1,600 mL), pleural effusion (500 mL; 900 mL)**,** huge ascites (7,600 mL) **and arrhythmic events**, approximately 2 months after the onset of general fatigue, cardiac failure and/or dyspnea. There was no history of essential hypertension, diabetes mellitus, dyslipidemia, malignancy, immunosuppressive disorders, or unusual infections. At autopsy, the hypertrophic and balloon-like appearing heart, weighing 477 g, grossly displayed yellowish to yellow-whitish predominantly in the dilated right ventricle (Figure 1A). On the myocardial cut surface (Figure 1B) and its scanning magnification (Figure 1C), the cross-section characteristically demonstrated a diffuse fatty/fibrofatty replacement in not only the overtly yellow-whitish and thinned right ventricular wall, but the variably thickened left ventricular myocardium. The coronary arteries displayed

mild atherosclerosis with wide patency, and foci of myocardial infarction were absent (Figure 1B & C). The schema of fatty/fibrofatty replacement in the right and left ventricles was shown, partly revealing the disappearance/absence of the right ventricular myocardium (Figure 1D).

Microscopic findings uniquely showed a transmural fatty (Figure 2A) and fibrofatty (Figure 2B) replacement in the markedly thinned right ventricular wall, accompanied by an outer lymphoplasmacytic infiltrate (Figure 2A & C), as shown in Figure 1D. In immunohistochemistry, these infiltrating inflammatory cells were predominantly positive for CD20/CD38 **(not shown)**. By contrast, the remnant right ventricular cardiomyocytes were overtly hypertrophic, occasionally containing bizarre nuclei (Figure 2D). Specifically, those intercalated disks immunohistochemically showed a significantly reduced expression of several desmosomal proteins, including plakoglobin (not shown) [1]. Overall, these cardiac features confirmed as a final diagnosis of unusual **possibly** late-onset ARVC. **A**ccording to the lipid contents analysis [3], the TG content (Figure 3A), but not the total cholesterol content (Figure 3B), in our patient's right and left ventricular cardiac muscle was much higher than that in the control subject **from the recent autopsy case of a late sixties elderly male without**

any evidence of cardiac diseases. To examine the above cardiac muscle lipid profiles, each snap tissue of the cardiac muscle (100 mg) was homogenized and extracted with chloroform-methanol (2/1 v/v) solution, as described previously [3]. The organic phase was dried and resolubilized in 2-propanol. Then, the TG and cholesterol contents were determined using commercial assay kits (Wako Pure Chemical Co., Osaka, Japan).

Discussion

It is most likely that our ARVC autopsy case is clinicopathologically remarkable for one reason at least: To our knowledge, we for the first time have analyzed the lipid contents on the ARVC **tissue samples**, and subsequently, reported **confirming** results regarding an increased volume of TG, but not cholesterol. The findings overlap with those of TG-deposit cardiomyovasculopathy (TGCV), a distinct entity, whose primary is genetic mutations in *adipose TG lipase*, an essential molecule for hydrolysis of intracellular TG [4]. We propose that this unique TG deposition in our **possibly** late-onset ARVC case might be one of new clues to understand its enigmatic etiology. **However, the etiology of TGCV could be very different from that of ARVC [1,4]. In fact, unlike TGCV, approximately 40% of patients with ARVC have shown**

mutations in genes encoding desmosomal proteins, such as plakoglobin, desmoplakin, plakophilin 2, desmocollin 2 or desmoglein 2 [1]. Furthermore, in marked contrast to ARVC, TGCV with *adipose TG lipase*-mutations/deficiency is characterized by profound intracellular, but not extracellular, TG deposition in multiple tissues, including cardiomyocytes or smooth muscle cells [4]. Despite that, Hirano *et al.* have more recently reported that the medium-chain TG (i.e., tricaptan) diet may be beneficial on the treatments for the TGCV patients, based on a growing body of data from *adipose TG lipase*-knockout mice models [5]. Nevertheless, it would be intriguing to assess the significance of lipid analysis for **the** ARVC **management** on future studies**,** after collecting and investigating a larger number of early- and late-onset ARVC cases examined. This short case report could interest the scientific community, taken together with potentially specific, new findings of ARVC.

List of Abbreviations Used

ARVC, Arrhythmogenic right ventricular cardiomyopathy; TG, triglyceride.

Declarations

Ethics approval and consent to participate.

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient and his family on admission for the publication of this case report and any accompanying images

Availability of Data and Materials

The dataset supporting the findings and conclusions of this case report is included within the article.

Funding

This work was partly supported by a grant from the Kanazawa Medical University Fund, Ishikawa, Japan (to S.Y.).

Conflicts of Interests

The authors declare that they have no conflicts of interests.

Authors' contributions

SY and KY participated in conception of the idea and writing of the manuscript. SY, KY, XG, KM, NK, MK, AS, SN, RT, YI, **HA and KK** performed the clinical investigation and pathological/immunohistochemical interpretation of this unusual ARVC. All authors have read and approved the final manuscript.

Acknowledgments

This paper is based upon the Presentation at the 107th annual meeting of The Japanese Society of Pathology, in 2018, and its presenter of Kentaro Yamamoto, first author of this paper, has received the Young Medical Student's Award, The Japanese Society of Pathology, for his presentation. We would like to thank Dr. Hiroyoshi Akao, PhD, Department of Cardiology, Kanazawa Medical University, Ishikawa, Japan, for his helpful comments, and thank Mrs. Yuka Hiramatsu & Mrs. Chikako Yonenaga for their

expert technical assistance.

References

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5. **Suzuki A, Yamaguchi S, Li M, Hara Y, Miyauchi H, Ikeda Y, Zhang B, Higashi M, Ikeda Y, Takagi A, Nagasaka H, Kobayashi K, Magata Y, Aoyama T, Hirano KI. Tricaprin Rescues Myocardial Abnormality in a Mouse Model of**

Triglyceride Deposit Cardiomyovasculopathy. *J Oleo Sci* 2018, 67: 983–989.

Figure Legends

Figure 1. Gross examination of the heart on the present possibly late-onset ARVC. **(A)** On gross examination, the hypertrophic and balloon-like appearing heart shows markedly yellowish to yellow-whitish predominantly in the dilated and thinned right ventricle. Bar = 5 cm. **(B)** The myocardial cut surface characteristically reveals a diffuse fatty/fibrofatty replacement in not only the overtly yellow-whitish and thinned right ventricular wall, but the variably thickened left ventricular myocardium. The coronary arteries show mild atherosclerosis with wide patency, and foci of myocardial infarction are absent. Bar = 1 cm. **(C)** On the scanning magnification of myocardial cut surface, the cross-section makes foci of the fatty/fibrofatty replacement very clear (H&E stains). **(D)** Correspondingly, the schema of fatty/fibrofatty replacement (*yellow*) with an outer lymphoplasmacytic infiltrate (*purple*) in the right and left ventricles is shown, partly revealing the disappearance/absence of the right ventricular myocardium.

Figure 2. Microscopic examination of the heart on the present possibly late-onset ARVC. (A) Low-power view uniquely shows a transmural fatty and fibrofatty

replacement in the markedly thinned right ventricular wall, accompanied by an outer chronic inflammatory cells infiltrate. Bar = 1 mm. **(B)** These fibrous foci are overtly blue-stained with Masson's trichrome staining. Bar = 500 μm. **(C)** On high-power view, those infiltrating inflammatory cells predominantly consists of B-lymphocytes and plasma cells. Bar = 200 μm. **(D)** The remnant, hypertrophic right ventricular cardiomyocytes occasionally have bizarre nuclei. Bar = 50 μm.

Figure 3. Analysis of the lipid contents for the cardiac muscle from our possibly late-onset ARVC and the control subject. (A) Intriguingly, the triglyceride (TG) content in our patient's right (RV) and left ventricular (LV) cardiac muscle is 3-folds higher than that in the control subject. But, the TG contents in the cardiac muscle from the interventricular septum (IVS) show no remarkable change between our ARVC case and the control. **(B)** Surprisingly, the total cholesterol (Cho) contents in the cardiac muscle from RV/IVS/LV are not relatively large in volume, and have no remarkable change between the current **possibly** late-onset ARVC case and the control subject.

Figure 1

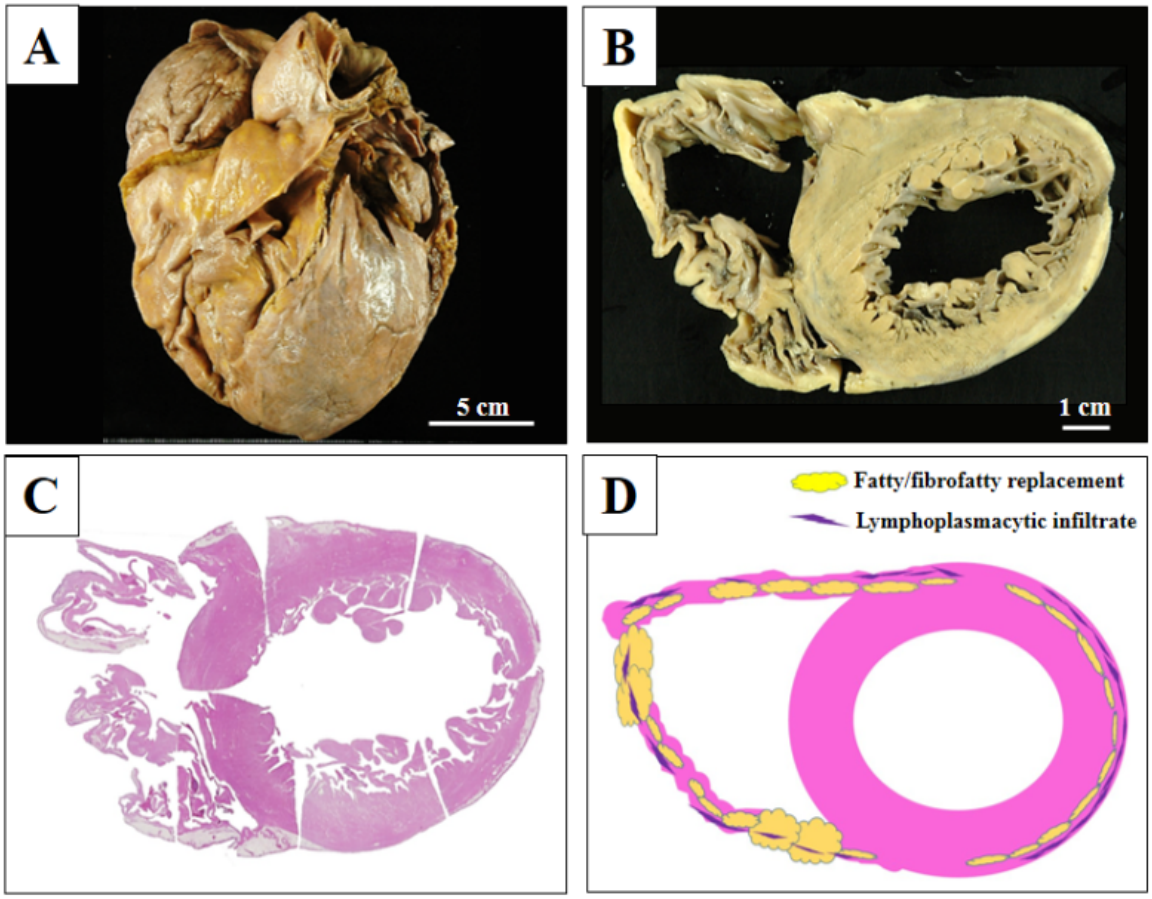

Figure 2

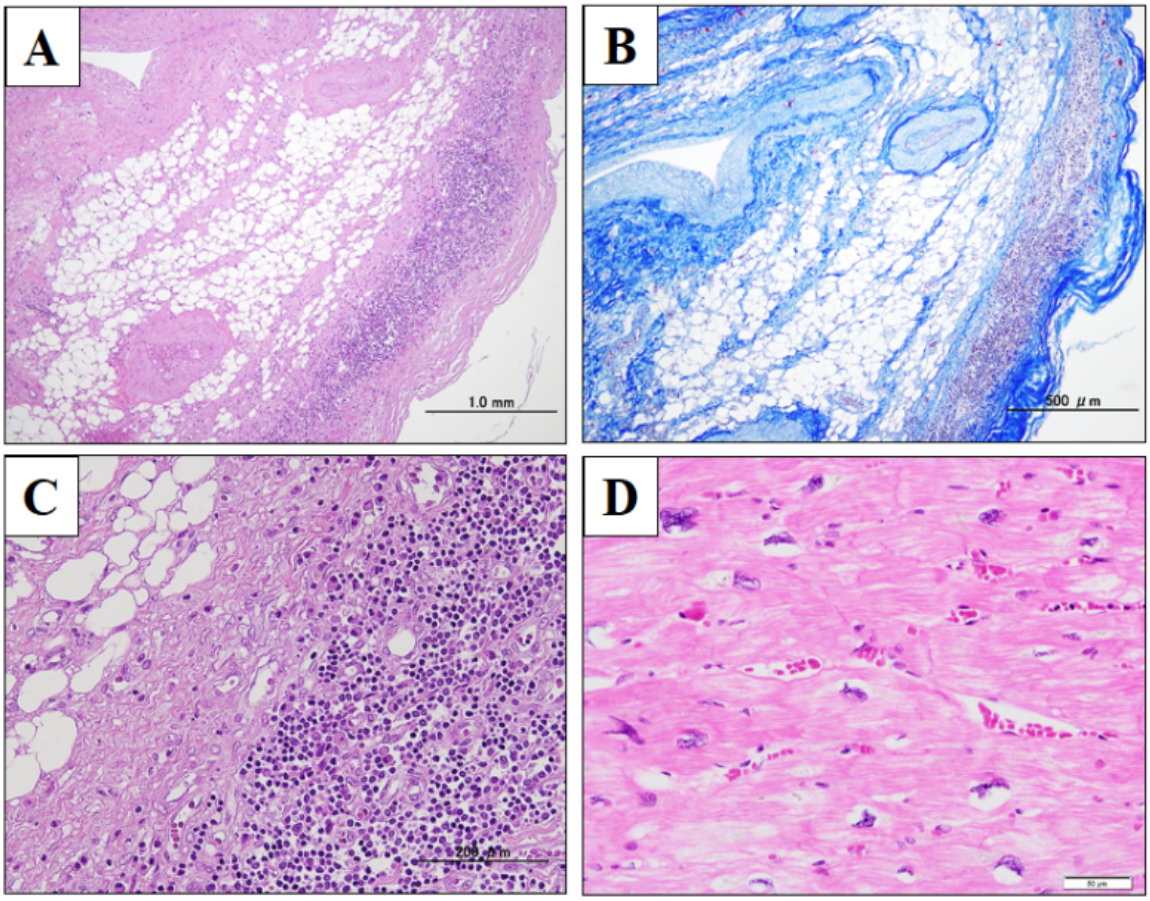

Figure 3