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CASE REPORT
Heart failure

Type 1 cluster of differentiation 36 deficiency-related cardiomyopathy accelerates heart failure with co-existing mitral valve prolapse: a case report

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Background Free fatty acid is a major energy source in the healthy heart and cluster of differentiation 36 (CD36) partially regulates the rate of myocardial fatty acid uptake. Here, we report a case of CD36 deficiency-related cardiomyopathy with a unique pathophysiology. Heart failure was accelerated by co-existing mitral valve prolapse (MVP) without a distinct phenotype of hypertrophic or dilated cardiomyopathy.

Case summary A middle-aged man was aware of dyspnoea and hospitalized for heart failure with MVP. Cluster of differentiation 36 deficiency was found based on the absence of myocardial ^{123}I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) uptake by myocardial scintigraphy. Type I CD36 deficiency was further diagnosed by the lack of CD36 in both platelets and monocytes by flow cytometry. Left ventricular muscle was obtained intraoperatively, and a histological examination reflected compensative hypertrophy of cardiomyocytes with myofibrillar loss and reactive fibrosis. The microvascular structure around the cardiomyocytes was highlighted by immunohistochemical staining for CD31, while CD36 expression was absent. He had an operation of mitral valve replacement and improved heart failure.

Discussion Cluster of differentiation 36 deficiency potentially mediates various pathological conditions in the heart. Incidental CD36 deficiency-related cardiomyopathy may accelerate heart failure in the presence of co-existing heart diseases. BMIPP scintigraphy might be helpful for predicting CD36 deficiency.

Keywords CD36 deficiency • Myocardial scintigraphy • Cardiomyopathy • Mitral valve prolapse • Case report

Learning points

- Incidental cluster of differentiation 36 (CD36) deficiency-related cardiomyopathy may accelerate heart failure in the presence of co-existing heart diseases.
- ^{123}I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) scintigraphy might be helpful for predicting CD36 deficiency.

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Introduction

Cluster of differentiation 36 (CD36) is abundantly expressed in cardiac muscle[1] and partially regulates the rate of myocardial fatty acid uptake in humans.[2] It has been reported that CD36 deficiency is associated with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM),[3–5] but the influence of CD36 deficiency in the heart has not been investigated in detail and pathological reports are scarce. We incidentally diagnosed CD36 deficiency in a heart failure patient with mitral valve prolapse (MVP), based on the absence of myocardial ^{123}I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) uptake by myocardial scintigraphy. Advanced myocardial damage was found histologically in heart muscle obtained surgically. In the present case, CD36 deficiency may have accelerated heart failure with co-existing MVP before it resulted in a distinct phenotype of primary cardiomyopathies.

Timeline

Time	Events
10 years previously	Started treatment for hypertension
Month 0	Started treatment for heart failure with left ventricular systolic dysfunction and mitral valve prolapse
Month 1	^{123}I-15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP) scintigraphy and flow cytometry detected the absence of cluster of differentiation 36 in platelets and monocytes
Month 2	^{18}F-Fluorodeoxyglucose positron emission tomography
Month 3	Collected autologous blood
Month 4	Surgical procedure, sampling of left ventricular heart muscle

Case presentation

A 52-year-old man began to be treated for hypertension in 2006 and blood pressure had been controlled since then and did not have the other any comorbidities. He was aware of dyspnoea in the summer of 2016 and cardiomegaly was noted in a chest X-ray as part of a medical checkup in August 2017. On admission to our hospital, his blood pressure and heart rate were 118/78 mmHg and 66/min, respectively. Heart sounds showed mid-systolic click with systolic murmur. Abnormal lung sound was not noted. Leg oedema was shown and New York Heart Association (NYHA) classification was Class III. Left ventricular systolic dysfunction with severe hypokinesis in inferior area and MVP with severe mitral regurgitation (MR) were noted by echocardiography (Supplementary material online, *Figure S1*). Left ventricular internal diameter in diastole, left ventricular internal diameter in systole, and left ventricular ejection fraction were 67.6 mm, 56.0 mm, 34.9%, respectively. We started the usual medical treatment for heart failure and performed further examinations. Treatment with beta blocker, angiotensin II receptor blocker, calcium channel blocker, and diuretics was started and brain natriuretic peptide improved from 401 pg/mL to 167 pg/mL. Neither the characteristics of systemic disorders such as Marfan syndrome and Ehlers–Danlos syndrome nor a family history of cardiac diseases including cardiomyopathy, sudden cardiac death, or MVP were noted. In addition, there were no indications of previous infection, hormonal diseases, diabetes, intake of cardiotoxic material, or cardiac hypertrophy due to hypertension. Mild hypokinesis in the inferior wall was detected by echocardiography (Supplementary material online, *Figure S1*) and perfusion defect was detected by thallium scintigraphy, but angiography did not reveal coronary artery disease. Intramural delayed enhancement with a linear pattern was detected in the interventricular septum by contrast-enhanced magnetic resonance imaging. This patient showed heart failure with reduced ejection fraction (HFrEF). However, the morphological and functional phenotype could not be associated with major prototypical cardiomyopathies such as HCM or DCM.

Notably, the heart lacked BMIPP uptake by BMIPP scintigraphy and showed increased ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake by ^{18}F-FDG positron emission tomography (*Figure 1*). These results suggested that cardiomyocytes exhibited reduced free fatty acid metabolism and enhanced glucose metabolism. We diagnosed type 1 CD36 deficiency, where both platelets and monocytes lack CD36 by flow cytometry (Supplementary material online, *Figure S2*). The surgical procedures considered were mitral valve replacement, tricuspid annuloplasty, and left atrial appendage closure, but not mitral annuloplasty. In the latest European Society of Cardiology guideline,[6] MVP constitutes a Class I recommendation for patients with MVP and severe MR. But in the secondary or functional MR which results from an imbalance between closing and tethering forces on the valve secondary to alterations in left ventricular geometry, mitral valve replacement should be considered in patients with unfavourable morphological characteristics. Because of the presence of CD36 deficiency, we were worried about a dysfunctional mitral valve base which could lead to a future exacerbation of mitral valve regurgitation. There was no ruptured mitral chordae tendineae or mitral leaflet perforation. The histological observations of mitral valve showed mild myxoid change and hyalinosis without any specific changes (Supplementary material online, *Figure S3*). Cardiac muscle was biopsied from the posterior wall of the left ventriculum during surgical procedures. Conventional histological observation revealed hypertrophic cardiomyocytes with enlarged nuclei and myofibrillar loss. Perivascular and interstitial fibrosis (i.e. reactive fibrosis but not replacement fibrosis) were moderately associated (*Figure 2*). The microvascular structure around the cardiomyocytes was highlighted by immunohistochemical staining for CD31 (platelet endothelial cell adhesion molecule-1 (PECAM-1)) (*Figure 3A*), but CD36 expression was absent in the myocardial tissue (*Figure 3B*). No specific condition was suggested by transmission electron microscopy (data not shown). After 6 months from surgical procedure, the heart failure was improved and NYHA classification was changed from Class III to Class I. In echocardiography, paravalvular MR was not observed and left ventricular ejection fraction was 44.4%.

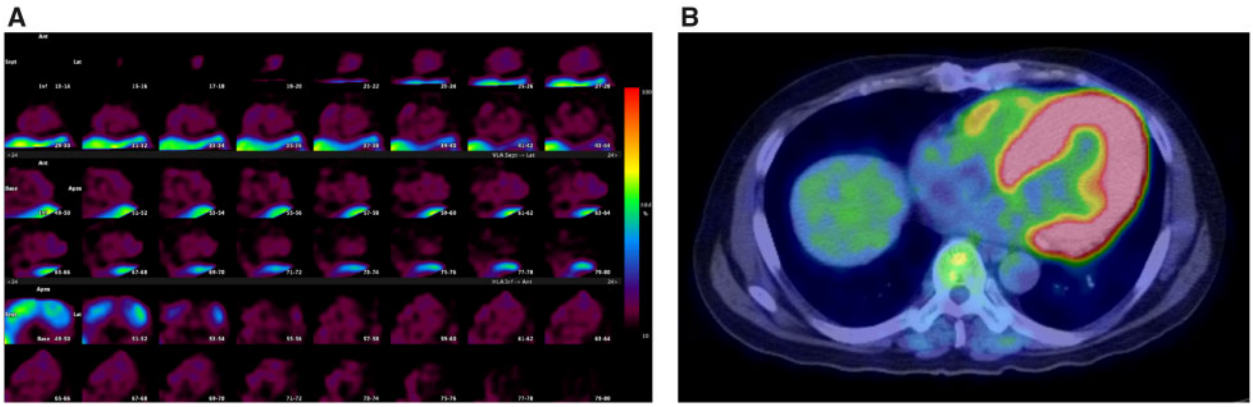


Figure 1 BMIPP scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography. (*A*) Image obtained at rest, 30 min after BMIPP administration. The heart showed reduced BMIPP uptake. (*B*) An axial ^{18}F-fluorodeoxyglucose positron emission tomography image is shown. The heart showed increased ^{18}F-fluorodeoxyglucose uptake.

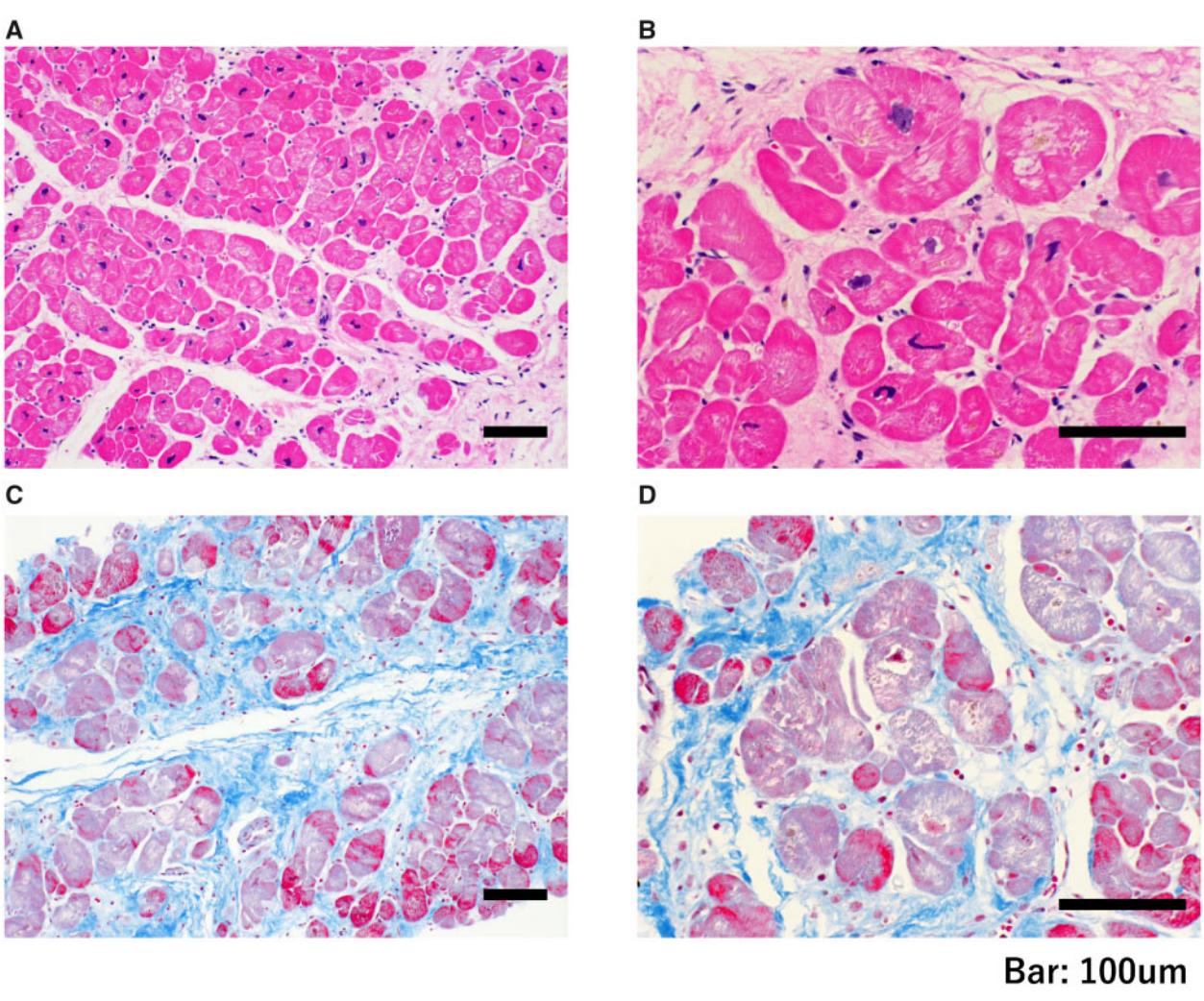


Figure 2 Conventional histopathology of the left ventricular tissue. (*A*) Low-power and (*B*) high-power views of haematoxylin and eosin stain (bar: 100 μm). Cardiomyocytes reflect compensative hypertrophy with nuclear deformity and myofibrillar loss. (*C*) Low-power and (*D*) high-power views of Masson's trichrome (MT) stain (bar: 100 μm). Progression of perivascular and interstitial fibrosis is seen.

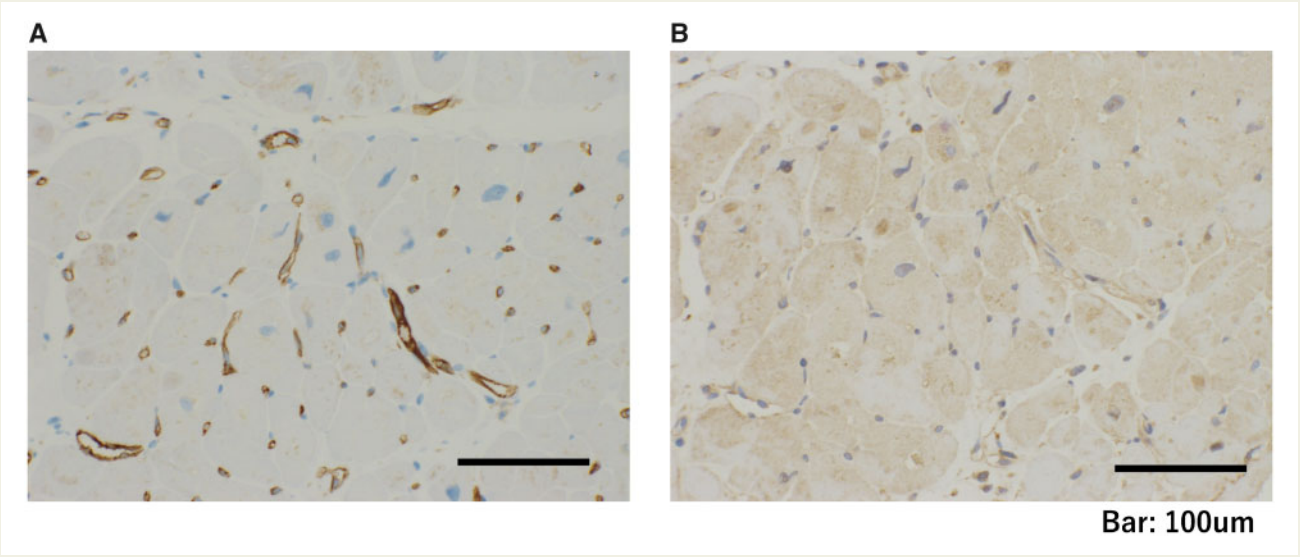


Figure 3 Immunostaining for CD31 and CD36. (*A*) CD31 immunostaining, which is a positive control marker for vascular endothelial cells. (*B*) Immunostaining for CD36 in the present case. A loss of CD36 immunoreactivity was noted.

Discussion

We encountered a case of Type 1 CD36 deficiency with MVP. Cluster of differentiation 36 deficiency was incidentally found in a heart failure patient. However, loss of myocardial CD36 expression and an advanced cardiomyopathic histology, including compensative hypertrophy, myofibrillar loss, and reactive fibrosis, were confirmed at the post-operative examination. Latent CD36 deficiency-related cardiomyopathy may have accelerated heart failure with co-existing MVP.

Cluster of differentiation 36 is expressed in vascular endothelial cells and cardiomyocytes, where it regulates the rate of myocardial fatty acid uptake in humans.[2] While free fatty acid is a major energy source in the healthy heart, in CD36 deficiency, the heart needs to metabolize other energy sources. It has been reported that, while myocardial concentrations of adenosine triphosphate and phosphocreatine are maintained, genes related to fatty acid metabolism are reduced and those related to ketone body metabolism and glucose metabolism are increased in CD36 knockout mouse.[7] Changes in metabolism may be associated with myocardial damage related to heart failure and cardiomyopathies, but the detailed mechanism remains to be elucidated.[1,8]

It has been reported that CD36 deficiency is associated with HCM.[5,9] Kusaka *et al.*[4] reported that treatment with Sulfo-N-succinimidyl palmitate, an inhibitor of fatty acid transporter, increased heart weight in rat. It has also been reported that CD36 deficiency is associated with DCM.[3] Hirooka *et al.*[3] reported that improvement of cardiac function by medical treatment was associated with an increase in fatty acid metabolism in a patient with both DCM and CD36 deficiency. Tanaka *et al.*[5] reviewed 14 cases of CD36 deficiency including HCM, DCM, and pressure-overload cardiac hypertrophy. In the present case, heart failure was not based on such typical phenotypes of primary cardiomyopathies. However, left ventricular histology showed non-specific but advanced myocardial degeneration. Thus, we found CD36-related cardiomyopathy along with exacerbated heart failure with MVP.

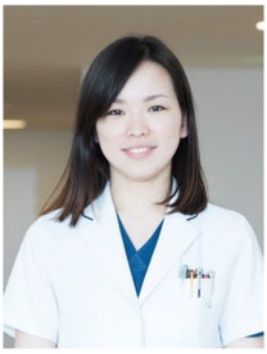
Mitral valve prolapse, which is defined as abnormal slack of the mitral valve leaflets into the left atrium, afflicts 2–3% of the general population.[10] Mitral valve prolapse may be hereditary, especially regarding connective tissue disorders such as Marfan syndrome and obstructive HCM. In the present case, no specific hereditary background or mechanical complication of ischaemic heart disease was noted. Although the influence of CD36 deficiency on the development of MVP cannot be fully excluded, the mitral valve morphology was not much different than those in usual MVP cases. The incidence of MVP is much greater than that of CD36 deficiency, and there has been no previous report of a case of CD36 deficiency with MVP. Taken together, our findings suggest that CD36 deficiency and MVP may have occurred together by chance. Not all cases of MVP without progression of MR and heart failure require surgical treatment. Various causes of the progression of MVP have been suggested: for example, genetic modifiers, environmental factors (smoking, diet, body mass index, and hypertension), and non-modifiable characteristics such as race and sex.[11] In the present case, co-existing CD36 deficiency-related cardiomyopathy and MVP may have promoted the progression of heart failure. Cardiac function improved after surgery, but we continue to carefully watch this case for the progression of cardiomyopathy.

Conclusion

We presented a case of Type 1 CD36 deficiency-related cardiomyopathy with MVP. In Japan and other Asian countries, a relatively larger percent of the population is expected to carry CD36 deficiency than elsewhere.[12] BMIPP scintigraphy might be helpful for predicting CD36 deficiency for patients with unexplained left ventricular dysfunction. It should be noted that latent CD36 deficiency-related

cardiomyopathy may accelerate heart failure with co-existing heart diseases. Further studies will be needed to clarify the cardiac involvement of CD36 deficiency.

Lead author biography



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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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