Pericardial effusion in the course of Fabry disease cardiomyopathy: a case report

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Background
Fabry disease (FD) is an X-chromosome-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal α-galactosidase A activity.

Case summary
A 51-year-old Japanese woman with a previous diagnosis of FD presented with pericardial effusion. The exudative pericardial fluid contained globotriaosylsphingosine. Left ventricular hypertrophy progressed despite regular administration of agalsidase alfa every 2 weeks over a 7-year period, with increases in plasma levels of globotriaosylsphingosine and interleukin (IL)-18. In addition, the IL-6 level in the pericardial fluid was markedly higher than that in plasma.

Discussion
This case suggests that elevated IL-6 and IL-18 levels in pericardial fluid and plasma indicate the severity of FD cardiomyopathy.

Keywords
Inflammation • Hypertrophy • Cytokine • Fabry disease • Case report

Introduction
Fabry disease (FD) is an X-chromosome-linked inherited glycosphingolipid metabolism disorder caused by deficient or absent lysosomal α-galactosidase A activity.1 In patients with FD, the progressive accumulation of globotriaosylceramide and globotriaosylsphingosine (lyso-Gb3), a deacylated derivative of globotriaosylceramide, in all organs, as well as inflammation, leads to left ventricular (LV) hypertrophy.3,4 It is unknown whether the levels of proinflammatory cytokines are elevated in proportion to the lyso-Gb3 level and LV hypertrophy.

Learning points
• Globotriaosylsphingosine is a useful biomarker of the severity of Fabry disease (FD) and the effectiveness of enzyme replacement therapy (ERT).
• Evaluation of pro-inflammatory cytokines (e.g. interleukin-18) might provide information regarding the response to ERT.
• Early ERT should be initiated to ameliorate the progression of FD cardiomyopathy.
hypertrophy in patients undergoing long-term enzyme replacement therapy (ERT). Herein, we present the case of a patient who developed pericardial effusion, a rarely observed presentation in FD, and exhibited elevated proinflammatory cytokine levels in the pericardial fluid and plasma. We also discuss the implications of these findings in association with FD cardiomyopathy.

**Timeline**

| Age | Year (AD) | Symptom |
|-----|-----------|---------|
| 8   | 1975      | Pain in the extremities induced by fever and exercise |
| 15  | 1982      | Diagnosed with Fabry disease
• α-Galactosidase A activity (15.4 nmol/mg protein/h; reference range, 31–47)
| 42  | 2009      | Palpitation and chest discomfort
• Hypertrophic cardiomyopathy (12/15 mm)
| 44  | 2012      | Initiation of 0.2 mg/kg agalsidase alfa every 2 weeks |
| 51  | 2018      | Shortness of breath at rest and during sleep
• Progressed left ventricular hypertrophy (22/20 mm) with pericardial effusion |
| 51  | 2019      | Pericardiocentesis |

**Case presentation**

A 51-year-old unemployed, married Japanese woman was admitted to our hospital to determine the aetiology of pericardial effusion. At 8 years of age, she had complained of pain in the extremities induced by fever and exercise. At 15 years of age, she had been diagnosed with FD on the basis of reduced α-galactosidase A activity (15.4 nmol/mg protein/h; reference range, 31–47 nmol/mg protein/h) and the presence of inclusion bodies in the peroneal nerve. Subsequently, a 3 bp deletion (GAG) at position c.1072 of the α-galactosidase A gene was identified as the mutation site. Her father died with FD on the basis of reduced α-galactosidase A activity (15.4 nmol/mg protein/h; reference range, 31–47 nmol/mg protein/h) and the presence of inclusion bodies in the peroneal nerve. Her mother’s α-galactosidase A activity was 37.3 nmol/mg protein/h at diagnosis. No relatives had the same diagnosis or any medical history that could be suspected as FD (Table 1, pedigree chart). She was not followed up between the ages of 15 and 42 years. At 42 years of age, she complained of palpitations and chest discomfort. Transthoracic echocardiography revealed cardiac involvement with hypertrophic cardiomyopathy. At 44 years of age, she was started on 0.2 mg/kg agalsidase alfa therapy administered every 2 weeks without additional drugs. However, LV concentric hypertrophy progressed (Figure 1A) and plasma brain natriuretic peptide (BNP) levels continued to increase (Figure 1B) over a period of 7 years.

At 51 years of age, she experienced shortness of breath at rest and during sleep, accompanied by a weight gain of 3 kg in 2 months. She received 20 mg/day of furosemide orally once a day for a month at an outpatient clinic. However, we discontinued its administration before the admission day because it did not affect the severity of pericardial effusion despite the 3-kg reduction in body weight as shown below. She had been receiving ERT regularly until the time of admission. Her blood pressure, heart rate, and respiratory rate were 128/70 mmHg, 60 beats/min, and 14 breaths/min, respectively. Her heart sounds were normal and systolic murmurs were audible at the 5th left sternal border. Chest X-ray revealed an increased cardiothoracic ratio compared with that 1 year prior (Figure 2A and B). Twelve-lead electrocardiogram showed T-wave inversions in leads I, II, aVL, aVF, and V3–6 and a high voltage in the precordial leads (Figure 2C). Protein (1+) was detected in urine, and blood test results showed increased levels of cardiac troponin-T (0.24 ng/mL; cut-off, 0.1 ng/mL) and BNP (66.1 pg/mL; cut-off, 18.4 pg/mL). Her C-reactive protein (CRP) level was 0.06 mg/dL (cut-off, 0.14 mg/dL).

Transthoracic echocardiography revealed 65% LV ejection fraction without abnormal regional wall motion. Additionally, previously unrecognized pericardial effusion was noted (Figure 3A–C). Cardiac cine magnetic resonance imaging revealed diffuse LV hypertrophy with circumferential pericardial effusion (Figure 3D) and increased signal intensity on non-enhanced T2-weighted imaging (Figure 3E) and late gadolinium enhancement (Figure 3F). These findings suggested potential myocardial damage with oedema/inflammation and fibrosis in the anterior and lateral walls. A cardiac catheterization study revealed the presence of a 27 mmHg pressure gradient at the mid-LV cavity; however, other intracardiac pressures, i.e., pulmonary artery wedge pressure, pulmonary artery pressure, right ventricular pressure, and right atrial pressure and cardiac output values were within normal ranges. Endomyocardial biopsy specimens demonstrated vacuolated myocytes mixed with normal myocytes (Figure 4A), cytoplasmic granular inclusions (Figure 4B), laminated inclusion bodies (Figure 4C), infiltration of macrophages (Figure 4D), T lymphocytes (Figure 4E), and interstitial fibrosis (Figure 4F). Figure 5A–E summarizes the changes in the plasma levels of lyso-Gb3, tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-18, and high-sensitivity (hs)-CRP proportional to the changes in LV mass over the 7-year period of agalsidase alfa therapy. The lyso-Gb3 level, which initially decreased from 19 to 13 nmol/L [reference range, 0.37 ± 0.11 nmol/L (mean ± standard deviation, SD)] over the first 2 years, increased thereafter in proportion with increasing LV mass [reference range, 93 ± 16 g/m2 (mean ± SD)] (Figure 5A). The levels of TNF-α (reference range, 0.75–1.66 pg/mL), IL-6 (cut-off, 4 pg/mL), and hs-CRP (cut-off, 1500 pg/mL) remained within the normal range (Figure 5B, C, and E). The IL-18 levels [reference range, 126 ± 44.5 pg/mL (mean ± SD)] increased despite ERT (Figure 5D). Echocardiography-guided pericardiocentesis was performed to drain 700 mL of pericardial fluid to relieve her symptoms and obtain the sample. Pericardial fluid analysis conducted at 7 years and 3 months since ERT revealed the presence of exudate. Cytological examination was negative for malignant cells, and bacterial cultures were negative for infection.
However, lyso-Gb3 (14 nmol/L), IL-18 (135 pg/mL), TNF-α (1.19 pg/mL), and hs-CRP (343 ng/mL) were detected in the pericardial fluid. The level of IL-6 was higher (885 pg/mL) in the pericardial fluid than in plasma (2.3 pg/mL; Figure 5F).

She started receiving 1.25 mg of bisoprolol once-a-day from the day of discharge. The pericardial fluid persists to date, as observed at every 6-month examination; however, anti-inflammatory drugs were not administered because the patient was asymptomatic and her hs-CRP level was within the normal range. The pericardial effusion disappeared spontaneously 1.5 years after pericardiocentesis. She continues to receive ERT to date.

**Discussion**

Cardiac manifestation of FD indicates LV hypertrophy and fibrosis. These symptoms can develop due to the accumulation of lysosomal globotriaosylceramide and lyso-Gb3. Moreover, secondary myocardial damage includes inflammation and immune activation. The circulating levels of IL-6, IL-18, IL-1β, TNF-α, monocyte chemoattractant protein-1, intercellular adhesion molecule-1, and soluble vascular adhesion molecule are higher in patients with FD than in control individuals.

The most common causes of pericardial effusions include infections, cancer, and connective tissue disease, and 12–20% of patients...
Figure 2  Chest X-rays 1 year previously (A) and on the day (B) of admission; 12-lead electrocardiogram on the day of admission (C).

Figure 3  Transthoracic echocardiographic images (A, parasternal long-axis view; B, parasternal short-axis view; C, apical four-chamber view); cardiac magnetic resonance images (D, cine image; E, dark-blood sequence for non-enhanced T2-weighted image; F, delayed gadolinium-enhanced image). The yellow arrows (E, F) suggest oedema/inflammation and fibrosis, respectively.
Figure 4 Histology (A, haematoxylin–eosin staining; B, toluidine blue staining with glutaraldehyde fixation; C, electron microscopy; D, PG-M1⁺ macrophages; E, CD3⁺ T lymphocytes; F, Azan staining). (A, B, D, E, and F, Bar = 50 μm; C, Bar = 2 μm). Arrowheads (D, E) indicate macrophages and T lymphocytes in each panel, respectively.

Figure 5 Changes in the plasma levels of globotriaosylsphingosine (A), tumour necrosis factor-α (B), interleukin-6 (C), interleukin-18 (D), and high-sensitivity C-reactive protein (E) in proportion to the changes in the left ventricular mass (g/m²). The ratio of pericardial to plasma globotriaosylsphingosine, interleukin-6, interleukin-18, tumour necrosis factor-α, and high-sensitivity C-reactive protein concentrations (F). Globotriaosylsphingosine concentrations were measured using liquid chromatography–tandem mass spectrometry. Left ventricular mass was measured using the equation given by Devereux et al. and was indexed to body surface area. Arrows indicate the day of pericardiocentesis. ERT, enzyme replacement therapy; Lyso-Gb3, globotriaosylsphingosine.
with chronic heart failure demonstrate haemodynamically irrelevant pericardial effusion.\textsuperscript{13} However, pericardial effusion is rarely observed in FD.\textsuperscript{2} Although polymerase chain reaction was not performed and, as such, viral pericarditis could not be excluded; however, other major causes of pericarditis were excluded (e.g. infection, cancer, connective tissue disease, or myocarditis). We demonstrated the presence of lyso-Gb3 in the pericardial fluid for the first time. The pericardial fluid reflects the interstitial composition of the heart and contains molecules released from cardiomyocytes and diffused from the plasma.\textsuperscript{14,15} Management of pericardial effusion depends on whether it is haemodynamically stable or not (cardiac tamponade), neoplastic aetiology, or elevated inflammatory markers to suspect pericarditis.\textsuperscript{13} An echocardiographic follow-up is suggested every 6 months for idiopathic moderate effusions. Our patient was haemodynamically stable, and elevation of hs-CRP was not apparent during the clinical course of the disease. The prohypertrophic action of IL-6\textsuperscript{16} and the role of lyso-Gb3 in the induction of inflammation\textsuperscript{2} might reflect the severity of FD cardiomyopathy. Our patient also had an elevated plasma IL-18 level before ERT initiation, which remained high over the course of the therapy. IL-18 is a prohypertrophic inflammatory cytokine that has been shown to be associated with poor response to ERT.\textsuperscript{4}

Our patient was diagnosed with FD in 1982, whereas ERT (agalsidase alfa) has been available in Japan since 2007. Her medical records did not indicate LV hypertrophy at the time of diagnosis; this hypertrophy might have progressed over the 30-year period before ERT initiation. The considerable myocardial damage observed on cardiac magnetic resonance imaging and biopsy specimen results suggest the resistance of the present case to ERT. This also suggests that early ERT initiation is considered to improve the outcomes of patients with FD and cardiomyopathy.\textsuperscript{11}

\section*{Conclusion}

This is the first reported case of pericardial effusion as a possible manifestation of FD that suggests that elevated levels of IL-6 and IL-18 are clinical markers of cardiac involvement.

\section*{Lead author biography}

Toshihiro Tsuruda has received the MD degree and the PhD degree from Miyazaki Medical College, Miyazaki, Japan in 1992 and 2000, respectively. He was a research fellow at Mayo Clinic, Rochester, MN, USA between 2000 and 2003. He has appointed at Department of Internal Medicine, Circulatory and Body Fluid Regulation, Faculty of Medicine, University of Miyazaki (Assistant Professor) in 2007, and Associate Professor since 2018. His main interested research area was (i) vasoactive peptides and cytokines in cardiovascular homeostasis, and (ii) stromal cells in cardiovascular remodelling.

\section*{Supplementary material}

Supplementary material is available at \textit{European Heart Journal - Case Reports} online.

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

\section*{Consent:} This study was approved by the Human Investigation Review Committee and conforms to the principles outlined in the Declaration of Helsinki, as revised in 2013. The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

\section*{Conflict of interest:} None declared.

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