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CASE REPORT
Heart failure

Cardiac light-chain deposition disease and hints at diagnosing: a case report

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Background Light-chain deposition disease (LCDD) is a systemic disorder characterized by non-amyloidotic light-chain deposition in various organs with Bence-Jones type monoclonal gammopathy. Although known as monoclonal gammopathy of renal significance, it may involve interstitial tissue of various organs, and in rare cases, proceeds to organ failure. We present a case of cardiac LCDD in a patient initially suspected of dialysis-associated cardiomyopathy.

Case summary A 65-year-old man with end-stage renal disease requiring haemodialysis presented with fatigue, anorexia, and shortness of breath. He had a history of recurrent congestive heart failure and Bence-Jones type monoclonal gammopathy. A cardiac biopsy performed for suspected light-chain cardiac amyloidosis was negative for diagnostic Congo-red stain, however, paraffin immunofluorescence examination for light-chain suggested diagnosis of cardiac LCDD.

Discussion Cardiac LCDD may go undetected leading to heart failure due to lack of clinical awareness and insufficient pathological investigation. In heart failure cases with Bence-Jones type monoclonal gammopathy, clinicians should consider not only amyloidosis but also interstitial light-chain deposition. In addition, in patients with chronic kidney disease of unknown cause, investigation is recommended to rule out cardiac light-chain deposition disease concomitant with renal LCDD. Although LCDD is relatively rare it occasionally affects multiple organs; therefore, it would be better to describe it as a monoclonal gammopathy of clinical significance rather than one of renal significance.

Keywords Cardiac light-chain deposition disease • Monoclonal gammopathy of clinical significance • Cardiac magnetic resonance T1 mapping • Paraffin-immunofluorescence • Case report

ESC Curriculum 2.3 Cardiac magnetic resonance • 6.5 Cardiomyopathy • 6.9 Cardiac dysfunction in oncology patients • 2.1 Imaging modalities

Learning points

- Light-chain deposition disease (LCDD) is a systemic disease that affects not only kidney but various organs including heart.
- Cardiac magnetic resonance T1 mapping may be useful to screen for cardiac LCDD.
- Immunofluorescence on protease-digested, formalin-fixed, paraffin-embedded tissue may be useful for pathological evaluation of cardiac LCDD.

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Introduction

Light-chain deposition disease (LCDD) is a systemic disease induced by non-amyloidotic monoclonal light-chain deposition based on plasma cell dyscrasia.[1] Although LCDD is well known among clinicians as monoclonal gammopathy of renal significance (MGRS), cardiac manifestation of LCDD may be overlooked resulting in its under diagnosis. Since early clinical intervention is essential to achieve positive outcomes in cases with cardiac LCDD, dissemination of knowledge about the disease and its diagnosis is needed. This report presents the case of a patient with cardiac LCDD and describes its diagnosis using[1] cardiac magnetic resonance (CMR) T1 mapping and[2] immunofluorescence on protease-digested, formalin-fixed, paraffin-embedded section, hereafter referred to as paraffin-immunofluorescence (IF-P).

Timeline

Case presentation

A 65-year-old Japanese man with end-stage renal disease (ESRD) under haemodialysis was admitted with the complaint of chronic heart failure (CHF). He had no family history of renal or cardiac disease.

Some 15 years prior to presentation for the current complaint, he was diagnosed with hypertension, dyslipidaemia, and chronic kidney disease (CKD). Urinalysis at that time showed non-nephrotic proteinuria without haematuria, but his serum creatinine gradually elevated to 3.4 mg/dL (reference interval 0.60–1.00 mg/dL) over 7 years. About 8 years prior, his CKD was examined and 1.1 g/day of kappa type Bence-Jones protein (BJP-κ) was detected by urinary immune-electrophoresis. In addition, serum immune-electrophoresis detected BJP-κ and serum FLC assay showed elevated κ type free light chain (FLC). However, serum immunoglobulin levels were close to normal. Although those findings suggested a possibility of MGRS, no renal biopsy was performed due to atrophied renal cortex. Screening for myeloma at that time showed

Time	Events and interpretation of findings	Echocardiogram (findings recorded by different sonographers after resolution of congestive heart failure)	ECG (chest V5 induction)	Dry-weight and cardiothoracic ratio	Serum FLC level
8 years prior	CKD was examined as serum creatinine level elevated to 3.4 mg/dL. Monoclonal gammopathy was first revealed at first with 1.1 g/day of BJP-κ in urinary electrophoresis.	LAD 34, IVSTd/PWTd 8/9, LVDd/Ds 51/31, LVEF (Simpson) 71%, E/A 0.80, DcT 254 ms, E/e′ 7.2, AR-, AS-, MR -, MS-, TRPG no data		CTR 43.4%	FLC-κ>3800 mg/L FLCκ/λ ratio >100
5 years prior	Induction of haemodialysis.			DW 80.0 kg CTR 43.3%	
4 years prior	First episode of congestive heart failure. After that, DW was reduced further to reduce cardiac workload.			DW 77.2 kg↓ CTR 51.8%↑	
3 years prior	Second episode of congestive heart failure. CAG showed no significant stenosis. Echocardiogram showed sustained diastolic dysfunction despite of DW reduction. Add: 2.5m/day bisoprolol	LAD 46, IVSTd/PWTd 12/12, LVDd/Ds 56/38, LVEF (Simpson) 60.3%, E/A 1.62, DcT 160 ms, E/e′ 9.3, AR-, AS-, MR 1/4, MS-, TRPG 16.8 mmHg		DW 72.3 kg↓ CTR 52.1%↑	
1 year prior	Left ventricular systolic dysfunction worsened and furthermore, thickening ventricular wall and left high voltage in ECG suggested worsened cardiac hypertrophy. Diagnosis at that time was 'Dialysis-associated cardiomyopathy'	LAD 41, IVSTd/PWTd 13/14, LVDd/Ds 45/34, LVEF(Simpson) 50.9%, E/A 0.74, DcT 180 ms, E/e′ 8.2, AR-, AS-, MR 1/4, MS-, TRPG 9.0 mmHg		DW 71.5 kg↓ CTR 51.8%↓	
6 months prior	Fatigue, anorexic and shortness of breath (NYHA-III) developed.				
From admission to DRd induction (6 months after)	First suspected 'AL-Amyloidosis', but no evidence. According to interstitial κ-light-chain deposition in myocardial specimen, final diagnosis was 'Cardiac LCDD'. Add: 4 mg/day perindopril	LAD 41, IVSTd/PWTd 14/13, LVDd/Ds 47/37, LVEF(Simpson) 44.0%, E/A 0.97, DcT 284 ms, E/e′ 35.7, AR-, AS-, MR 1/4, MS-, TRPG 13.2 mmHg		DW 70.6 kg↓ CTR 51.0%↓	FLC-κ 9617.9 mg/L FLCκ/λ ratio 142.28

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Time	Events and interpretation of findings	Echocardiogram (findings recorded by different sonographers after resolution of congestive heart failure)	ECG (chest V5 induction)	Dry-weight and cardiothoracic ratio	Serum FLC level
1 month after DRd	Resolution of heart failure symptoms (NYHA-III⇒NYHA-I) Withdraw: perindopril, Add: 5 mg/day enalapril every non-HD day enalapril			DW 61.5 kg↓ CTR 49.2%↓	FLC-κ 1904.4 mg/L FLCκ/λ ratio 28.21
6 months after DRd	Improvement prolonged native T1 time (1400~1450 ms⇒1300~1350 m)			DW 64.8 kg↑ CTR 49.0%↓	FLC-κ 719.0 mg/L FLCκ/λ ratio 9.54
9 months after DRd		LAD 39, IVS/PW 14/11, LVDd/Ds 49/41, LVEF(Simpson) 49.0%, E/A 0.77, DcT 177 ms, E/e′ 25.1, AR-, AS-, MR 1/4, MS-, TRPG 13.3 mmHg		DW 67.0kg↑ CTR 47.0%↓	FLC-κ 380.0 mg/L FLCκ/λ ratio 13.57

A, atrial filling velocity; AL, amyloid light-chain; AR, aortic regurgitation; AS, aortic valvular stenosis; BJP, Bence-Jones protein; CAG, coronary angiography; CKD, chronic kidney disease; CTR, cardiothoracic ratio; DcT, deceleration time; DRd, daratumumab, lenalidomide, and dexamethasone; DW, dry-weight; IVSTd, intraventricular septum thickness in diastole; E, early diastolic filling velocity; e′, early diastolic mitral annular velocity; ECG, electrocardiogram; FLC, free light chain; LAD, left atrial dimension; LCDD, light-chain deposition disease; LVDd/Ds, left ventricular end-diastolic dimension in diastole/systole; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral valve stenosis; PWTd, posterior left ventricular thickness in diastole; TRPG, tricuspid regurgitation pressure gradient.

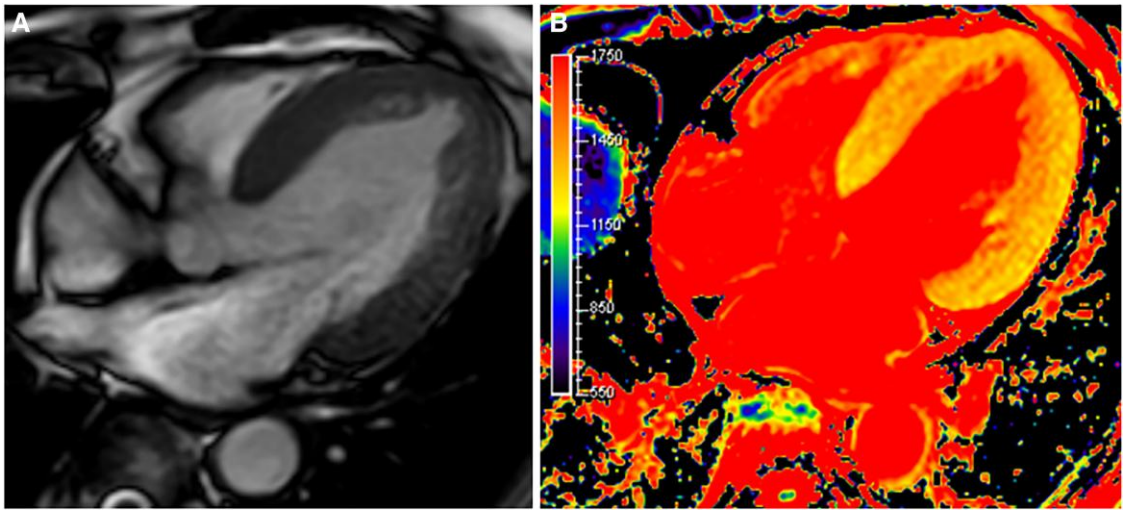

Figure 1 Cardiac magnetic resonance four-chamber view showing diffuse mild thickness of the left ventricular wall (*A*). Native T1 mapping showed significantly prolonged native T1 time comparable with cardiac amyloidosis. The control T1 value in our hospital is 1245.3 ± 37.5 ms (*B*).

no evidence of bone lesion and informed consent to undergo a bone marrow biopsy was withheld. Although there was no diagnostic evidence of myeloma, plasma cell dyscrasia was suspected. Five years prior, he was diagnosed with ESRD and was started on haemodialysis (videos of echocardiogram at that time are shown in Supplementary material online, *Figure S1*).

Four years prior, he developed his first congestive heart failure and 1 year later his second despite dry-weight (DW) reduction (baseline, 5 years prior: 80.0 kg→4 years prior: 77.2 kg→3 years prior: 72.3 kg). After that, DW was reduced further (3 years prior: 72.3 kg→1 year prior: 71.5 kg) and medication 2.5 mg/day bisoprolol was started to reduce cardiac workload, however, echocardiogram findings suggested

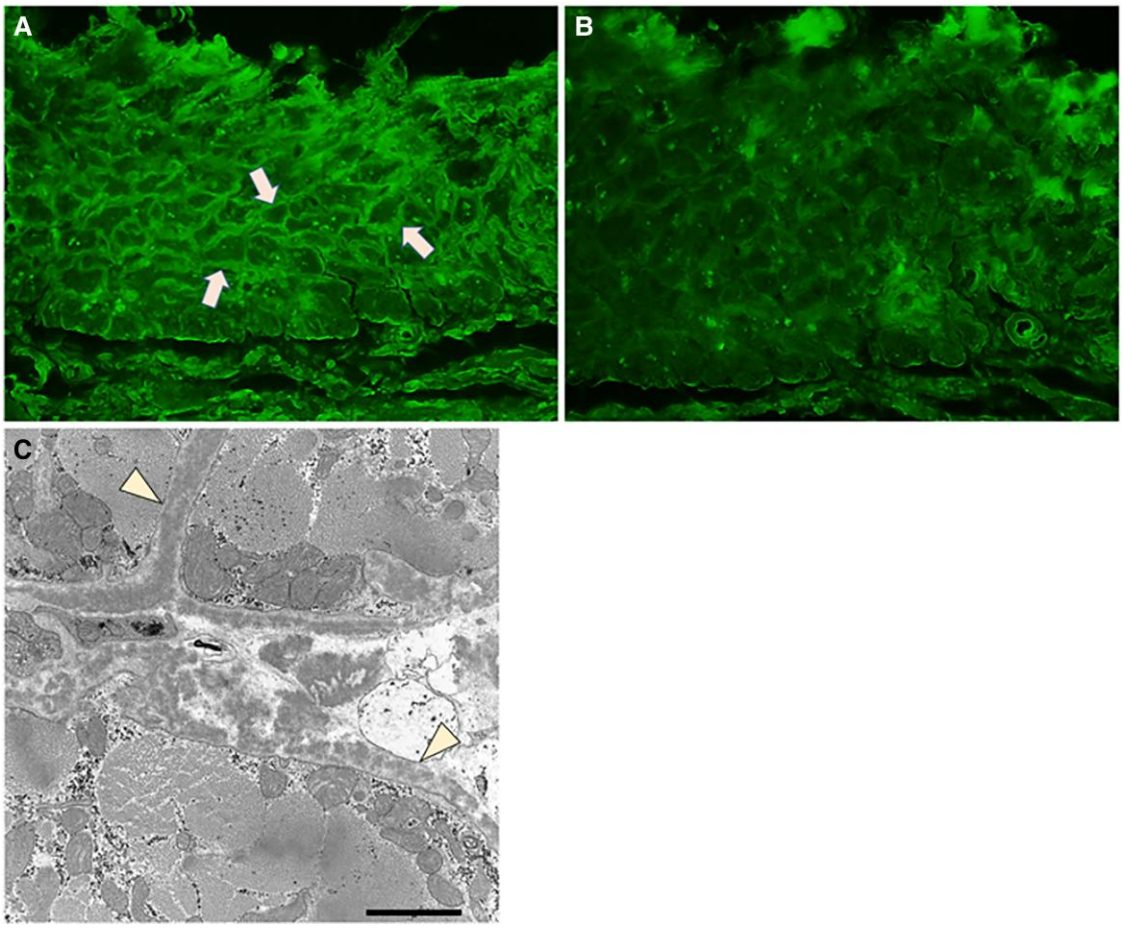

Figure 2 Cardiac biopsy histopathology. Immunofluorescence for kappa light-chain on formalin-fixed paraffin-embedded section showed positive staining around each myocardium (*A*, arrow) in contrast to lambda light chain (*B*). Electron microscopy revealed powdery deposition in the perimyocardium and interstitial areas (*C*, arrowhead) indicating kappa light-chain deposition.

sustained diastolic dysfunction both with increased early diastolic filling velocity (E)/early diastolic mitral annular velocity (e′) (3 years prior: 9.3→1 year prior: 8.2) and reduced deceleration time (3 years prior: 160 ms→1 year prior: 180 ms). In addition, thickening intraventricular septum and posterior left ventricular and left ventricular high-voltage revealed by electrocardiogram suggested worsened cardiac hypertrophy.

One year prior, echocardiogram showed reduced left ventricular ejection fraction suggesting worsened systolic function (baseline, 5 years prior: 71%→1 year prior: 50.9%), and 6 months prior he developed fatigue, anorexia, and shortness of breath: New York Heart Association (NYHA) Functional Classification Class III (Moderate).

Although the cause of heart failure was initially suspected to be congestion, which is not unusual in patients receiving haemodialysis, ineffectiveness of DW reduction suggested an underlying aetiology should be investigated, and he was referred to our hospital for further investigation of CHF.

On admission, he was anorexic and complained of fatigue and shortness of breath. He had no fever and his vital signs were unremarkable but for hypertension (166/96 mmHg). His height was 178 cm, and weight was 70.6 kg, which had reduced by 3 kg over 1 year. A physical examination revealed no significant findings but pitting oedema in his lower extremities. Blood tests before haemodialysis showed no cytopenia, a normal range of values for liver enzymes, no electrolyte imbalances, elevated serum creatinine (8.80 mg/dL), elevated brain natriuretic peptide (BNP) (1599.2 pg/mL, reference interval <18.4 pg/mL), and elevated troponin-T (0.205 ng/mL, reference interval <0.0014 ng/mL). Chest radiography after haemodialysis showed mild cardiomegaly (cardiothoracic ratio 52.4%) without pleural effusion. Electrocardiogram showed normal voltage and ST-T segment depression in Leads I and II and V4 through V6. Coronary arteriography showed no significant stenosis. Echocardiogram showed reduced ejection fraction (51.0%) without asynergy or valvular abnormality, but diffuse thickening of the left ventricular wall without a granular sparkling appearance and a typical apical sparing. Furthermore, CMR without gadolinium enhancement, which was performed on suspicion of amyloid light-chain (AL) amyloidosis, showed diffuse mild thickness of left ventricular wall with significantly prolonged native T1 time (1400–1450 ms, longer than control range in our hospital: 1245.3 ± 37.5 ms; *Figure 1A and B*), however, myocardial biopsy showed no evidence of amyloid; light microscopy revealed only moderate endocardial and perivascular fibrosis and was Congo-red stain negative. In addition, α-galactosidase A enzyme activity and α-galactosidase A gene analysis showed no evidence of Fabry disease. Although negative findings for AL-amyloidosis and Fabry disease suggested dialysis-associated cardiomyopathy again, further investigation with IF-P revealed interstitial kappa light-chain deposition (*Figure 2A and B*).

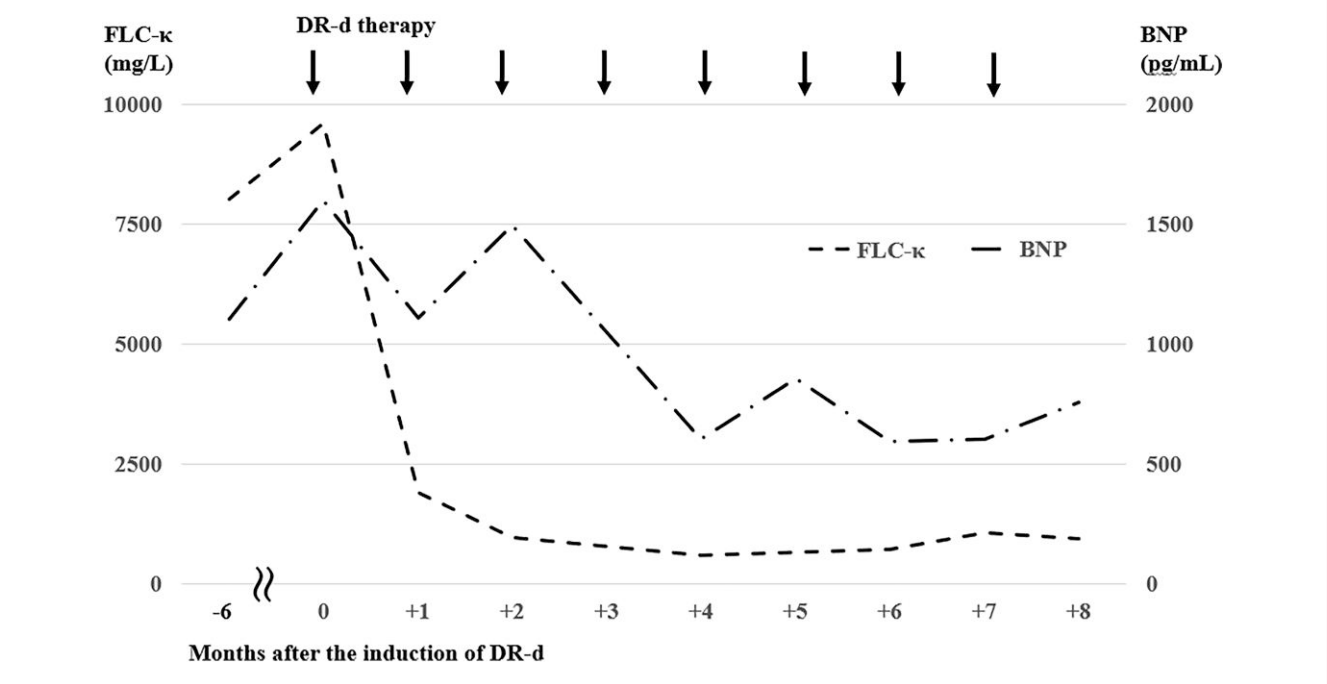

Figure 3 Clinical course. Levels of both serum-free light chain-κ and plasma brain natriuretic peptides dramatically decreased after starting daratumumab, lenalidomide, and dexamethasone. *Daratumumab, lenalidomide, and dexamethasone regimen: lenalidomide 5 mg/day (21days); daratumumab and dexamethasone 1800 and 20 mg/week, respectively delivered on Days 1, 8, 15, and 22 of treatment.

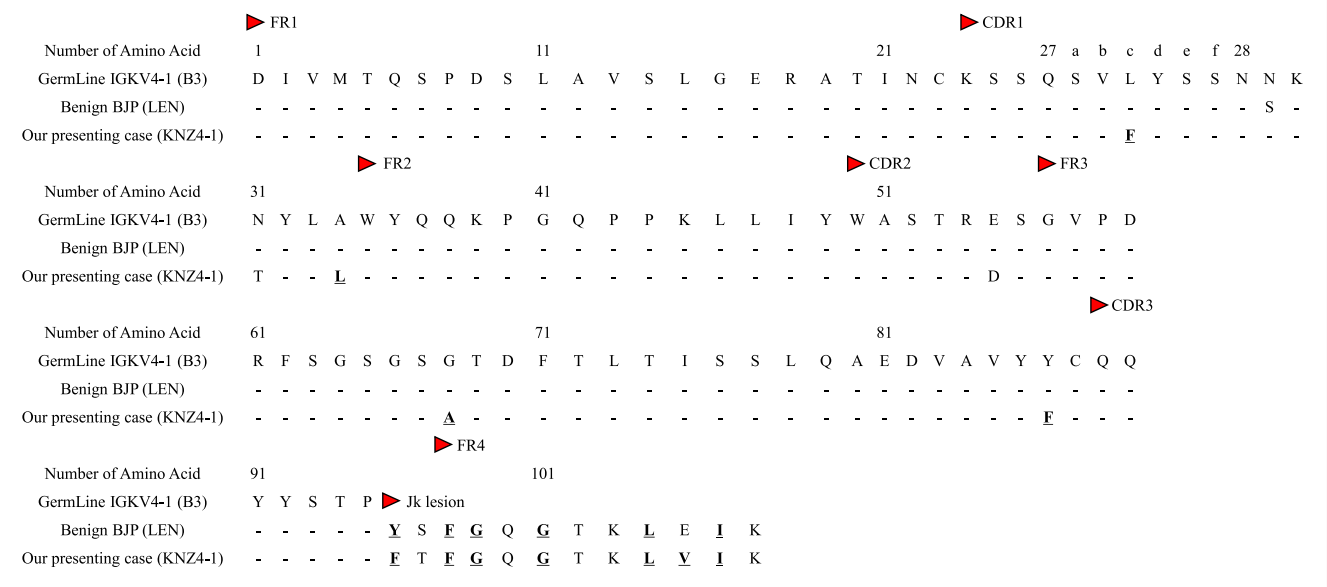

Figure 4 Amino acid sequence of the pathogenetic clone. Comparison of amino acid sequences among germline, benign Bence-Jones protein (LEN) and the present case (KNZ4-1). LEN had one mutation in contrast to KNZ4-1, which had five including four hydrophobic residues. In addition, KNZ4-1 had one additional glycosylation with mutation of 31st amino acid (N > T). *LEN is a known benign Bence-Jones protein.

Concurrently, electron microscopy revealed interstitial deposition of amorphous dense particles (*Figure 2C*), which supported the diagnosis of cardiac LCDD and the cause of CKD was assumed to be renal LCDD.

Upon reassessment of plasma cell dyscrasia, he was definitively diagnosed with multiple myeloma with biopsy-proven 21% (>10%) clonal bone marrow plasmacytes and myeloma-defining biomarkers. Except for undeterminable renal manifestation, there was no evidence of

myeloma-defining events under modification by haemodialysis and erythropoietin-stimulating agents.

Upon admission, 4 mg/day perindopril was added and his DW fell (70.6 kg at admission→61.5 kg 6 months later) reducing cardiac workload. From 6 months after admission, he was treated with daratumumab, lenalidomide, and dexamethasone (DRd), which was standard therapy for transplant-ineligible multiple myeloma (*Figure 3*). After starting DRd his serum FLC-κ level decreased dramatically; he improved to NYHA Class I in 1 month and BNP decreased monthly. In contrast, elevated troponin-T persisted, possibly due to complications from ESRD. At 6 months after starting DRd, CMR showed shortening prolonged native T1 time, but echocardiogram showed stable ejection fraction (videos of echocardiogram at the induction of DRd therapy and 9 months after that are shown in Supplementary material online, *Figures S2 and S3*).

Transcriptome analysis with cDNA extracted from frozen bone marrow before DRd revealed that the pathogenetic clone was a somatic mutation of IGKV4-1, which was reported to overrepresent in LCDD (*Figure 4*).[2]

Discussion

The presence of cardiac LCDD may be overlooked in cases of CHF when, as in the present case, receiving haemodialysis and assumed to have dialysis-associated cardiomyopathy if renal LCDD is not diagnosed. Because cardiac LCDD might exist concomitant with renal LCDD, close attention to the history of patients with ESRD is essential.[3]

Pozzi *et al.*[4] reported 21 cases of latent cardiac light-chain deposition among 63 autopsy cases with histologically proven renal LCDD. Since this report suggests higher frequency of cardiac light-chain deposition among cases with extra renal deposition, which itself is an independent factor of reduced survival rate in LCDD, clinicians should be aware that LCDD may affect not only kidney, but other organs such as heart and liver. Furthermore, cardiac LCDD may develop without apparent renal dysfunction, which implies that cardiac LCDD is always an unmissable differential diagnosis of CHF in cases with BJP.[5] Although AL amyloidosis is usually suspected in such cases, non-amyloidotic light-chain deposition should be additionally evaluated if Congo-red staining shows negative.

The present case report suggests two procedures to assess a patient for possible cardiac LCDD. First, CMR T1 mapping to screen for it. Second, IF-P for pathological evaluation. Cardiac magnetic resonance T1 mapping is known to be an advanced diagnostic tool for cardiac amyloidosis, which has characteristics similar to cardiac LCDD in terms of extracellular deposition.[6] Cardiac magnetic resonance T1 mapping does not require gadolinium enhancement, so it can be used in ESRD patients who are at greater risk of nephrogenic systemic sclerosis, which is a serious adverse effect of gadolinium enhancement.

Histological evaluation is essential for the diagnosis of cardiac LCDD but an agreed protocol has not yet been established. In the present case, initial evaluation with polymer-based immunohistochemistry revealed no significant difference in staining between κ and λ. Similarly, a case of pulmonary LCDD was diagnosed by IF-P although immunohistochemistry revealed no difference in staining between κ and λ.[7] While it is hypothesized that the antibodies used in immunofluorescence recognize FLC more readily than complete ones in intact immunoglobulin, the reason why only IF-P could detect a significant difference in staining in those cases remains unclear.

Consensus on a treatment protocol for cardiac LCDD has not yet been established. While three cases were reported to regain cardiac function following chemotherapy for plasma cell dyscrasia, thus demonstrating that cardiomyopathy from light-chain deposition may be reversible, another case was reported to have died from cardiac failure following conservative treatment.[5,8–10] Based on histological findings, light-chain deposits distributed throughout the myocardium in perimuscular sites and arterial walls seem to cause diastolic dysfunction and conduction abnormalities. Given this hypothesis, reduction of monoclonal light-chain might improve the prognosis via decreasing interstitial deposition.

Conclusions

Our case report demonstrated that cardiac LCDD is likely to be underdiagnosed but may be reversible with appropriate and timely treatment. There is the need for a greater awareness of extra-renal deposition and the potential for cardiac involvement. It is suggested that CMR T1 mapping and IF-P might contribute to diagnosis.

Lead author biography

Ryo Nishioka, MD, graduated from Jichi Medical University in 2010 and is currently working as a Clinical and Research Fellow of Department of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan. He has an interest in the association between immune abnormality and organ dysfunction, especially, investigate into the pathogenetic mechanism of monoclonal gammopathy-associated diseases.

Supplementary material

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

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

Consent: The authors confirm that written consent, in line with COPE guidelines, for submission and publication of this case report including images and associated text has been obtained from the patient.

Conflict of interest: None declared.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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