ESC European Society of Cardiology

European Heart Journal - Case Reports (2020) **4**, 1–7
doi:10.1093/ehjcr/ytaa048

CASE REPORT
Cardiac imaging

Soluble tumour necrosis factor-alpha receptor improved the function, hypertrophy, and granular sparkling appearance of the left ventricular myocardium in systemic amyloid A amyloidosis: a case report

Sawa Miyagawa *, Tadashi Miyamoto, and Yukihito Sato

Division of Cardiology, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan

Received 15 April 2019; first decision 22 May 2019; accepted 12 February 2020; online publish-ahead-of-print 16 March 2020

Background About 7% of amyloid A (AA) amyloidosis cases are accompanied by heart disease. Although several studies have recently reported that specific biologicals improved renal function in AA amyloidosis, little evidence is available regarding heart disease in AA amyloidosis.

Case summary A 57-year-old woman with rheumatoid arthritis presented with sudden worsening of renal function. Echocardiography revealed granular sparkling appearance in the ventricular septum and posterior wall (PW). Echocardiography indicated left ventricular (LV) diastolic dysfunction. Global longitudinal strain (GLS) exhibited an apical sparing pattern. Cardiac biopsy demonstrated amyloid A deposition on immunostaining. Soluble tumour necrosis factor-alpha receptor etanercept therapy was initiated. Four years later, echocardiography showed improved diastolic function, including *E*/*A* and *E*/e', and decreased wall thickness in both the interventricular septum and PW of the left ventricle. Granular sparkling appearance had diminished. Moreover, the LV dysfunction improved on GLS. Five years later, the medication was gradually losing effect and the patient had worsening pain in the joints; moreover, articular destruction was observed on radiography. The patient was switched to abatacept therapy. Echocardiography showed recurrence of LV hypertrophy and electrocardiogram showed down-sloped ST depression in V4–6 leads.

Discussion This case indicates that etanercept can be effective for heart disease in AA amyloidosis. Of particular, interest is the improvement of granular sparkling appearance in addition to cardiac function improvement noted in this case.

Keywords Cardiac amyloidosis • Soluble TNF-alpha receptor • Diastolic function • Granular sparkling appearance • Case report

* Corresponding author. Tel: +81 6 6480 7000, Fax: +81 6 6480 7001, Email: saku.vt721@gmail.com

Handling Editor: Tor Biereing-Sørensen

Peer-reviewers: Rami Riziq Yousef Abumuaileq, Rafael Vidal-Perez, and Hajnalka Vágó

Compliance Editor: Max Sayers

Supplementary Material Editor: Vishal Shahil Mehta

© The Author(s) 2020. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Learning points

- Amyloid A (AA) amyloidosis accompanied by cardiac lesions is rare and, to our knowledge, no effective therapy has been discovered so far.
- In this case, the granular sparkling appearance in the left ventricular myocardium and other echocardiographic parameter, such as interventricular septum and posterior wall thickness, improved after biological therapy using etanercept.
- Cardiac AA amyloidosis could be a potentially reversible condition if the underlying disease is controllable.

Introduction

Amyloidosis comprises a group of diseases in which abnormal protein aggregates, amyloid fibrils, accumulate in the tissues. There are about 30 different types of amyloidosis. The two most common types of systemic amyloidosis are light-chain amyloidosis (AL) and inflammatory amyloidosis [amyloid A (AA) amyloidosis].[1] In AA amyloidosis, serum AA protein is deposited throughout the body.[2] Chronic inflammatory diseases underlie AA amyloidosis. About 7% of AA amyloidosis cases are accompanied by heart disease.[1] Although studies have indicated that specific biologic therapies improve renal function in AA amyloidosis, little evidence is available regarding heart disease in AA amyloidosis.[3] Etanercept, a tumour necrosis factor (TNF) inhibitor, is a biological that is used to treat autoimmune diseases, such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, and psoriatic arthritis.[4] However, etanercept treatment-related improvements in heart disease remain unreported. We report a rare case in which etanercept ameliorated the clinical and echocardiographic cardiac AA amyloidosis findings.

Case presentation

A 57-year-old woman with RA was referred to the Department of Nephrology for abrupt worsening of renal function. The initial physical examination revealed the following: height, 161.7 cm; weight, 53.6 kg; blood pressure, 120/85 mmHg; and heart rate, 75 b.p.m. There was no cardiac murmur. She had pitting pedal oedema. The electrocardiogram (ECG) did not reveal low voltage or evidence of left ventricular hypertrophy (LVH) (*Figure 1D*). Echocardiography revealed ventricular septal wall (13 mm, normal value; 8–12 mm) and posterior wall (PW; 14 mm, normal value; 8–12 mm) thickening (*Figure 1A* and *Table 1*). Although the LV ejection fraction (EF) was decreased to 46%, the LV end-diastolic diameter was 48 mm (normal value; 39–55 mm). The parasternal long-axis view revealed increased luminance, also called 'granular sparkling appearance', in the ventricular septum and PW (*Figure 1A*). The *E*/*A* ratio of the LV transmitral flow (TMF) was elevated to 2.0 (normal value; $E/A \leqq 0.8$ and $E \leqq 50$ cm/s), and deceleration time shortened to 127 ms (normal value: 160–240) (*Figure 1B* and *Table 1*). In addition, a dominant D wave was noted in the pulmonary venous flow, and the *E*/*E*' was 18.8 (normal value: <10) (*Table 1*), indicating impaired LV diastolic function. Global longitudinal strain (GLS) exhibited an apical sparing pattern (*Figure 1C*). Cardiac amyloidosis was suspected. All the subsequent echocardiographic examinations were performed with the same echo gain and depth settings using the Philips iE33 ultrasound system.

Blood test results revealed mild normocytic anaemia and severe renal dysfunction. With respect to the course of renal impairment, the patient's serum creatinine level was 2.6 mg/dL (female normal range: 0.46–0.79 mg/dL) at the initial presentation, and she was treated by a family doctor. Nine months later, her renal function deteriorated suddenly with a serum creatinine level of 9.5 mg/dL; the nephrologist established an arteriovenous fistula for dialysis. Ten months after initial presentation, dialysis was initiated and maintained thereafter. No increase in monoclonal γ-globulin was observed in a serum proteinogram. Urine samples tested negative for the Bence Jones protein.

Timeline

Initial presentation	• Renal dysfunction detected during regular consultations with the doctor for rheumatoid arthritis of the knee. • Serum creatinine level: 2.6 mg/dL (female normal range: 0.46–0.79 mg/dL).
9 months	• Sudden renal function deterioration was noted. • Serum creatinine level, 9.5 mg/dL; blood urea nitrogen level, 115 mg/dL (normal range: 8–20 mg/dL). • Gastric and duodenal biopsies were performed. We found the deposition of amyloid A (AA) amyloid in stroma. • AA • amyloidosis was diagnosed.
10 months	• Dialysis was initiated. • Atrial flutter was observed. Echocardiography revealed diastolic dysfunction and a granular sparkling appearance in the ventricular septum and posterior wall.
11 months	• Catheter ablation and cardiac biopsy were performed. • Cardiac AA amyloidosis was diagnosed. • Etanercept therapy (25 mg/day) was initiated.
4.5 years	• Echocardiography revealed improvements in diastolic function and amelioration of granular sparkling appearance.
6 years	• Joint pain exacerbated and the treatment was switched from etanercept therapy to abatacept therapy.

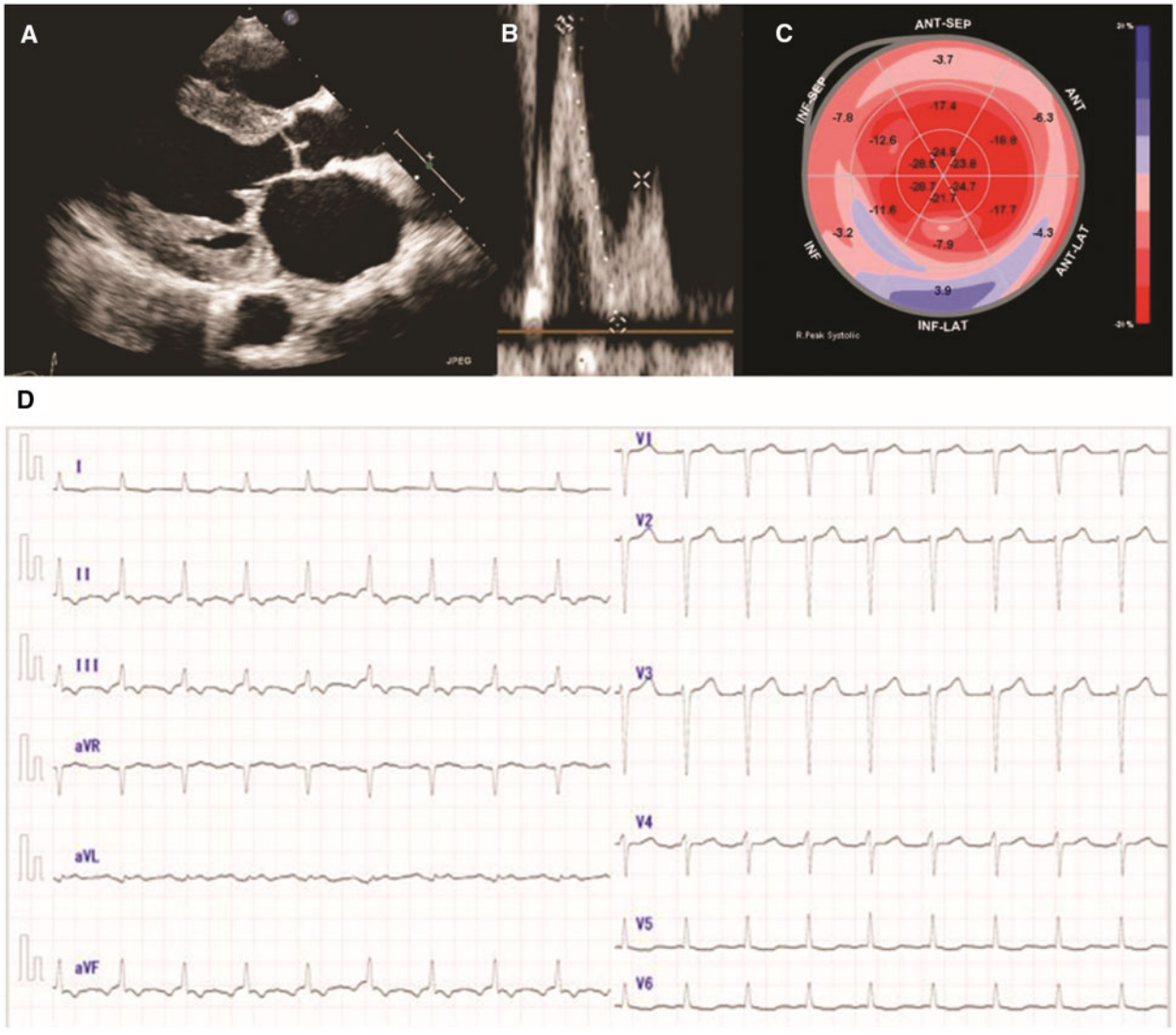


Figure 1 Pre-treatment images (10 months after the initial presentation). (*A*) B-mode echocardiogram reveals left ventricular hypertrophy with granular sparkling. (*B*) Doppler echocardiographic findings of transmitral flow show a restrictive pattern before treatment. (*C*) Global longitudinal strain map shows an apical sparing pattern before treatment. (*D*) Electrocardiogram.

Table 1 Time courses of echocardiographic parameters before and after etanercept therapy and after switching to abatacept therapy

	At diagnosis	4.5 years after the initial presentation	5.5 years after the initial presentation
LAESVI (mL/m^2)	78.5	55	51
LVEF (%)	46	65	60
IVS thickness (mm)	13	11	14
PW thickness (mm)	14	11	13
E/*A* ratio	1.08/0.54	0.79/0.74	0.71/0.92
E/*E*' ratio	18.8	15.7	16.3
Deceleration time (ms)	127	209	155
LVGLS (%)	-13.8	-17.3	-14.3
EFSR	3.3333	3.7572	4.1958
RELAPS	1.321	0.998	0.767

A, filling velocity after atrial contraction; *E*, early diastolic filling velocity; *E*', early diastolic mitral annulus velocity; EFSR, ejection fraction to global longitudinal strain ratio; IVS, interventricular septum; LAESVI, left atrial volume measure in ventricular systole in mL indexed to body surface area; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global endo peak longitudinal strain; PW, posterior wall; RELAPS, relative apical sparing (ratio of apical longitudinal/sum of base and mid longitudinal strain).

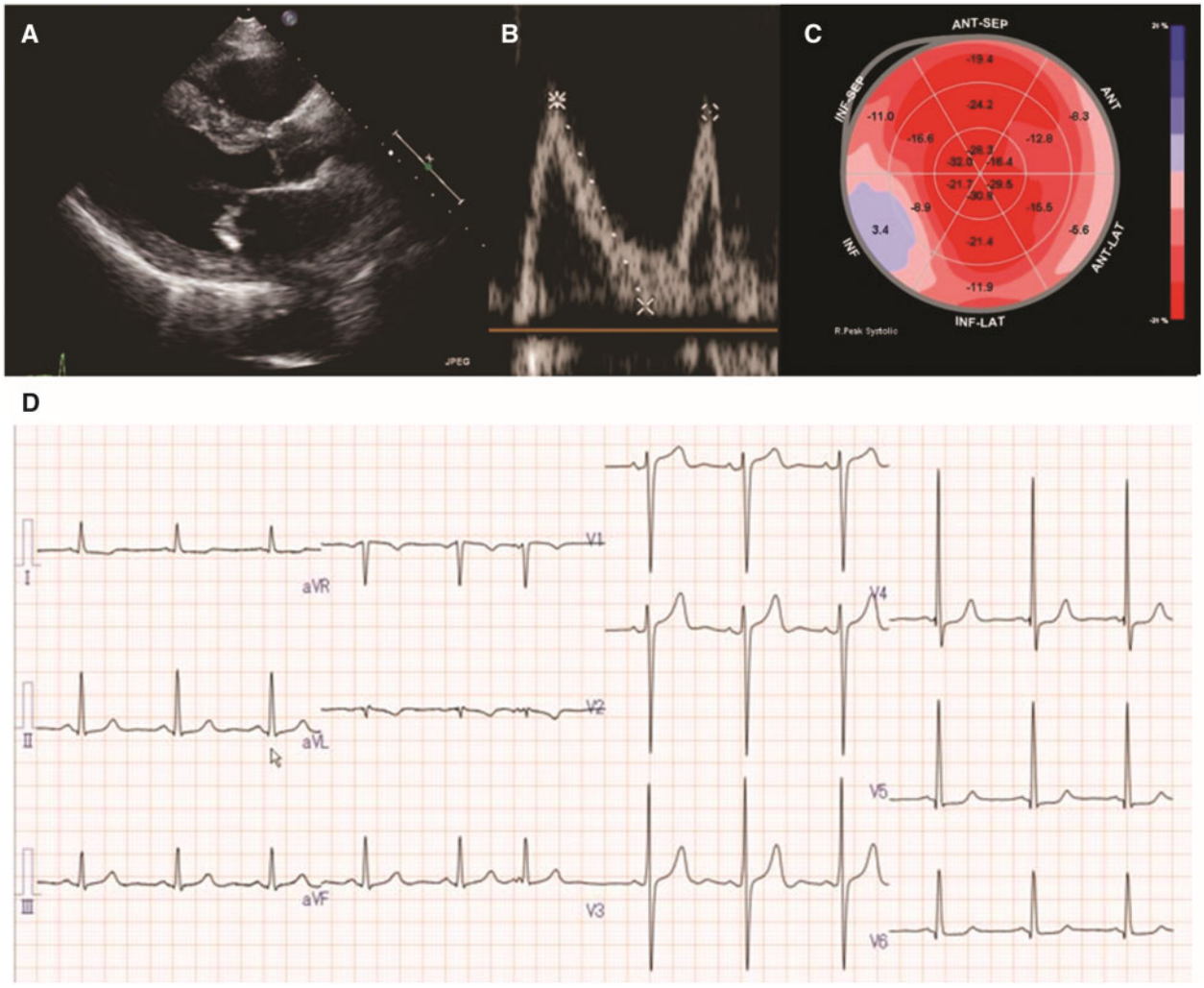


Figure 2 Post-treatment images (4.5 years after the initial presentation). (*A*) The granular sparkling appearance improved. (*B*) Doppler echocardiographic findings of transmitral flow. The restrictive pattern has improved after treatment. (*C*) The apical sparing pattern has improved after treatment, as shown in the global longitudinal strain map. (*D*) Electrocardiogram.

To confirm a diagnosis of amyloidosis, gastric mucosal biopsy was performed. Haematoxylin and eosin staining showed amorphous eosinophilic materials confirmed by Congo red staining. Subsequent cardiac biopsy revealed AA deposition confirmed by immunostaining. The patient was diagnosed as having systemic AA amyloidosis with cardiac involvement.

Atrial flutter occurred at 10 months after the initial presentation. One month later, catheter ablation was performed.

Because the patient was undergoing haemodialysis, biologic therapy using a soluble TNF-alpha receptor (etanercept) was initiated at an initial dose of 25 mg every 7 days. Forty-four months later, the dose was decreased to 25 mg every 10 days because of improvements in RA symptoms. Forty-nine months later, the etanercept dose was further decreased to 25 mg every 14 days. Although β-blocker treatment was attempted for heart failure, drug-induced hepatopathy contraindicated its continuous use.

Four and a half years after the initial presentation, echocardiography showed that the E/A ratio of the TMF and the D-wave height of the pulmonary venous flow had both decreased (*Figure 2B* and *Table 1*), indicating improvements in diastolic function. Both the interventricular septum (IVS) and PW thicknesses in the left ventricle had decreased (*Table 1*). Each mean gain during the entire phase was measured offline with custom software (QLAB, Philips Healthcare, Andover, MA, USA) in the myocardium at the IVS and LV PW, compared to that of left atrial cavity as a reference (*Figure 4*). We confirmed the decrease in the myocardial gain quantitatively after etanercept treatment, particularly in the PW (*Table 2*). Taken together, these results suggested that the granular sparkling appearance diminished remarkably (*Figure 2A*). Moreover, LV systolic dysfunction improved in terms of GLS (*Figure 2C*).

Although the patient's serum C-reactive protein (CRP) had been maintained under 1.0 mg/dL (normal range: ≦0.14 mg/dL) up

until that time, it gradually increased to >1.0 mg/dL thereafter. Five and a half years after the initial presentation, echocardiography showed recurrence of LVH (*Figure 3A*), and ECG showed deteriorating down-sloped ST depression in several leads, especially in leads V4–6 (*Figure 3D*). Six years after the initial presentation, joint pain was exacerbated, and articular destruction was observed through radiography. The patient's serum CRP level was elevated to 10 mg/dL. Increasing the etanercept dosage did not ameliorate the arthritis. The biologic was changed from etanercept to abatacept—a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin fusion protein. No dialysis-associated complications have been reported during these 6 years.

Table 2 Myocardial gain: the difference of gain between myocardium and cavity

	IVS	PW
At diagnosis	19.91	23.43
4.5 years after the initial presentation	17.76	11.26
5.5 years after the initial presentation	20.79	22.89

Granular sparkling pattern improved after the etanercept treatment. In the posterior wall, in particular, the difference between pre- and post-treatment was substantial. After clinical exacerbation, this parameter also exhibited deterioration.

Discussion

To the best of our knowledge, this is the first case wherein the soluble TNF-alpha receptor, etanercept, improved the granular sparkling appearance of the LV myocardium in systemic AA amyloidosis. Amyloid deposits in AA amyloidosis comprise the serum amyloid A protein, a high-density apolipoprotein serving as a dynamic acute phase reactant. It is a precursor produced in response to

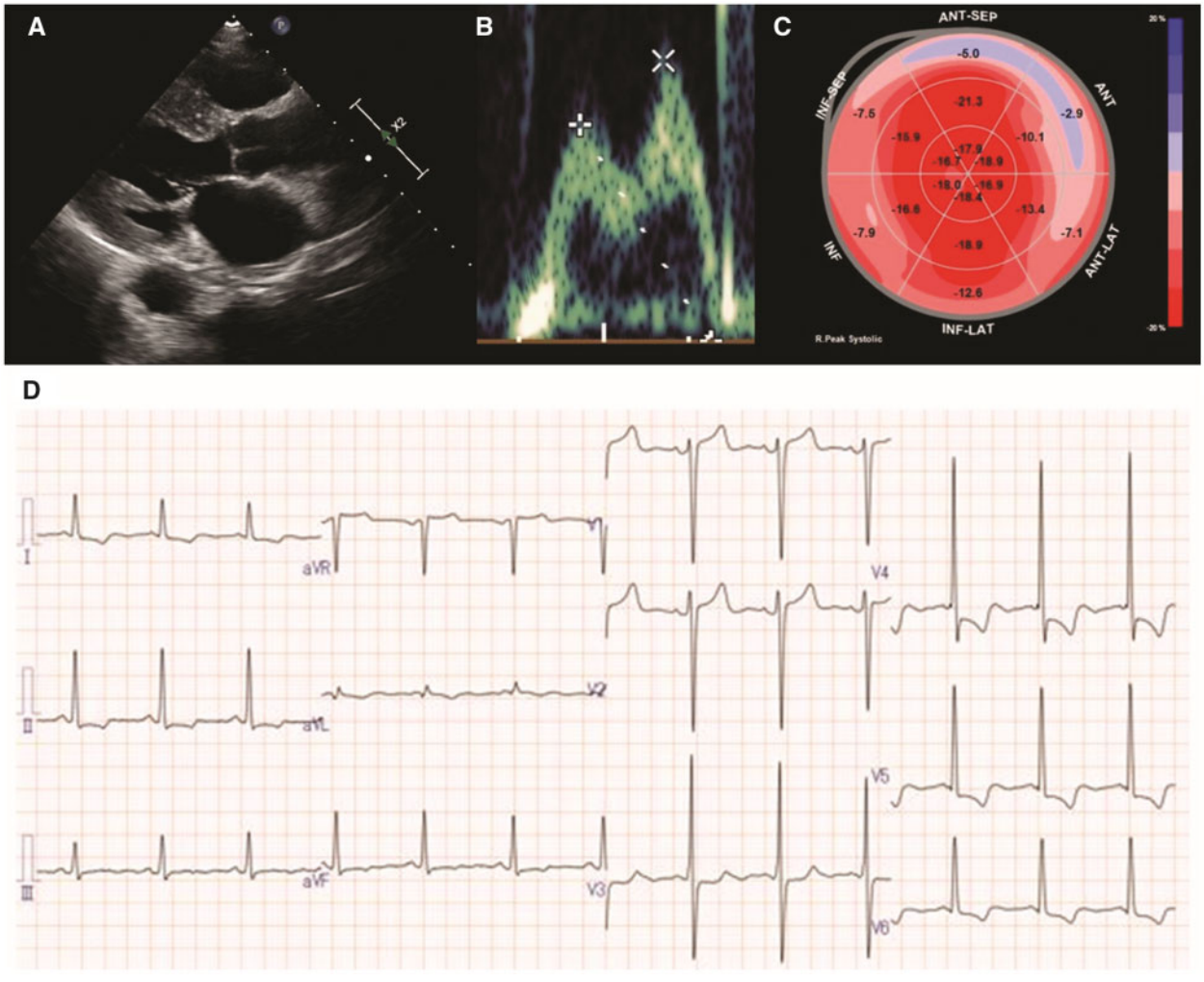


Figure 3 Post-treatment images (5.5 years after the initial presentation). (*A*) Left ventricular wall thickening again. (*B*) Doppler echocardiographic findings of transmitral flow. Transmitral flow still shows an abnormal relaxation pattern. The A wave exhibits compensated elevation. (*C*) The global longitudinal strain map almost shows an apical sparing pattern. (*D*) Electrocardiogram with ST depression in several leads.

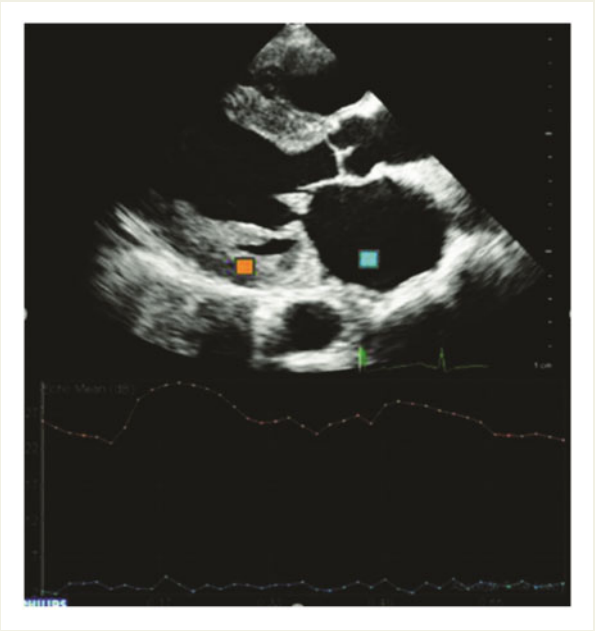


Figure 4 Instantaneous echo gain is measured offline in the myocardium at the left ventricular posterior wall (orange square), compared to that of the left atrial cavity as a reference (blue square).

transcriptional stimuli from various proinflammatory cytokines, including interleukin (IL)-1, IL-6, and TNF-alpha under persistent inflammation.[5] Only 7% of AA amyloidosis cases are accompanied by heart disease, compared to 57% of the AL type.[1]

In previous studies, the incidence of AA amyloidosis in RA patients ranged from 7% to 26% and may be attributable to differences in RA treatments and genetic backgrounds.[6] The actual incidence of AA amyloidosis in RA is, however, unclear and may be underestimated. For AA amyloidosis in patients with RA, RA treatment, such as therapy with cytotoxic agents and biologics represses inflammation and might ameliorate amyloidosis symptoms.[2,7] Although methotrexate is usually used as an anchor drug for AA amyloidosis in patients with RA, we could not use it because of the risk of end-stage renal failure.

Etanercept is a fusion of the TNF soluble receptor and Fc region of a Type 1 human immunoglobulin G that inhibits the proinflammatory cytokine TNF-alpha. [8] Etanercept has been approved for the treatment of RA in Japan since 2005, and its indication was revised to include the prevention of joint destruction in 2012.[8]

In a previous study, etanercept therapy for AA amyloidosis was found to have a reduced adverse effect on renal function and higher survival ratio compared to cyclophosphamide.[3] With respect to other biologics, a humanized antihuman IL-6 receptor antibody (tocilizumab) improved cardiac hypertrophy in patients with AA amyloidosis.[9] However, cardiac functions, including EF, TMF, and GLS, have not (to our knowledge) been reported to improve in response to any treatment, including etanercept therapy.

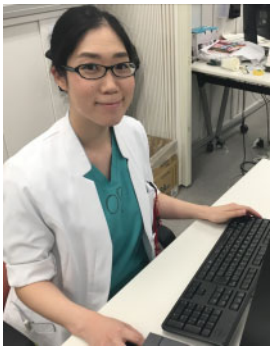
In AL amyloidosis, a proteasome inhibitor, bortezomib, improved EF, TMF, and *E/E'* but had no effect on amyloid deposition.[10] A ^{99}mTc-PYP scintigram showed that autologous peripheral blood stem cell transplantation (PBSCT) in AL cardiac amyloidosis ameliorates amyloid deposition.[8] Moreover, PBSCT improves TMF.[11]

In our case, etanercept treatment improved the patient's heart structurally and functionally over time, as confirmed by visual assessment and quantitative improvement. These findings, to our knowledge, have not been reported previously. Moreover, we found no study that reported that biological drugs, such as etanercept, alleviate the granular sparkling appearance in AA amyloidosis. For diagnosis and follow-up, cardiovascular magnetic resonance (CMR) is a better option than echocardiography. However, our patient had renal dysfunction, and CMR using gadolinium was not performed because of her renal dysfunction. To overcome the problem of operator variability in echocardiographic findings, the same operator examined this patient during the 6-year period.

In general, the mechanisms of effective amyloidosis treatments are thought to involve amyloid absorption from diseased organs by medication-induced suppression of amyloid fibril synthesis.[6] Therefore, we believe that the same mechanism was involved in our case, which would explain the improvement in cardiac hypertrophy and systolic and diastolic functions, as well as alleviation of the myocardial granular sparkling appearance, resulting in clinical amelioration. We also hypothesize that the effectiveness of etanercept gradually decreased, resulting in the patient's condition worsening. We can detect worsening hypertrophy not only by worsening of the granular sparkling appearance but also by the increase in IVS and PW thickness. Therefore, we can estimate that amyloid deposits are accumulating in the myocardium. We fully understand how useful parameters using cardiac strains, such as ejection fraction to GLS ratio or relative apical sparing are, however, in our case, such parameters are not reflective of the disease (*Table 1*).[12] Aggravation of LVH on echocardiography (with ST depression but without change of R wave voltage in chest leads, which suggests something accumulating in but not loading on the left ventricle) reappeared after the effectiveness of etanercept for RA decreased, indicating the association between the effectiveness of etanercept and cardiac manifestation.

Altogether, treatment with the soluble TNF-alpha receptor, etanercept, might be an effective therapeutic option for AA amyloidosis with cardiac involvement. Early intervention with etanercept for cardiac AA amyloidosis might result in a good prognosis.

Lead author biography



Sawa Miyagawa worked as a 5th-year cardiologist at Amagasaki General Medical Center in Japan at the period of writing. She graduated from Kyoto University, Faculty of medicine in 2014. She is interested not only in clinical cardiology but also in fundamental medical research. Therefore, she is now especially engaged in revealing the mechanism of atherosclerosis as a postgraduate student of Kyoto University while working as a cardiologist.

Supplementary material

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

Acknowledgements

The authors are grateful to S. Ikeda (MD) and T. Kuragaichi (MD) for clinical advice, T. Horie (MD-PhD) for finishing our figure, and T. Obata (Sonographer) for reporting of the transthoracic echocardiography findings.

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.

References

1. Saba M, Tohme A, Abadjian G, Haddad F, Ghayad E. Multisystemic amyloidosis. Clinical study of 39 patients in Lebanon. *Presse Med* 2005;**34**:640–646.
2. Ishii W, Kishida D, Suzuki A, Shimojima Y, Matsuda M, Hoshii Y, Ikeda S. A case with rheumatoid arthritis and systemic reactive AA amyloidosis showing rapid regression of amyloid deposition on gastroduodenal mucosa after a combined therapy of corticosteroid and etanercept. *Rheumatol Int* 2011;**31**:247–250.
3. Nakamura T, Higashi S, Tomoda K, Tsukano M, Shono M. Effectiveness of etanercept vs cyclophosphamide as treatment for patients with amyloid A amyloidosis secondary to rheumatoid arthritis. *Rheumatology* 2012;**51**:2064–2069.
4. Gottenberg J-E, Merle-Vincent F, Bentaberry F, Allanore Y, Berenbaum F, Fautrel B, Combe B, Durbach A, Sibilia J, Dougados M, Mariette X; Club Rhumatismes et Inflammation. Anti-tumor-necrosis factor alpha therapy in fifteen patients with AA amyloidosis secondary to inflammatory arthritides: a follow-up report of tolerability and efficacy. *Arthritis Rheum* 2003;**48**:2019–2024.
5. Real de Asua D, Costa R, Galvan JM, Filiqheddu MT, Trujillo D, Cadinanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. *Clin Epidemiol* 2014;**6**:369–377.
6. Nakamura T. Amyloid A amyloidosis secondary to rheumatoid arthritis: pathophysiology and treatment. *Clin Exp Rheumatol* 2011;**5**:850–857.
7. Obici L, Merlini G. Amyloidosis in autoinflammatory syndromes. *Autoimmun Rev* 2012;**12**:14–17.
8. Takeuchi T, Miyasaka N, Kawai S, Sugiyama N, Yuasa H, Yamashita N, Sugiyama N, Wagerle LC, Vlahos B, Wajdula J. Pharmacokinetics, efficacy and safety profiles of etanercept monotherapy in Japanese patients with rheumatoid arthritis: review of seven clinical trials. *Mod Rheumatol* 2015;**2**:173–186.
9. Hattori Y, Ubara Y, Sumida K, Hiramatsu R, Hasegawa E, Yamanouchi M, Hayami N, Suwabe T, Hoshino J, Sawa N, Oohashi K, Takaichi K. Tocilizumab improves cardiac disease in a hemodialysis patient with AA amyloidosis secondary to rheumatoid arthritis. *Amyloid* 2012;**19**:37–40.
10. Tamaki H, Naito Y, Lee-Kawabata M, Taniguchi Y, Hao H, Hirota S, Hasegawa S, Masuyama T, Ogawa H. Sustained improvement in cardiac function with persistent amyloid deposition in a patient with multiple myeloma-associated cardiac amyloidosis treated with bortezomib. *Int J Hematol* 2010;**92**:655–658.
11. Yagi S, Akaike M, Ozaki S, Moriya C, Takeuchi K, Hara T, Fujimura M, Sumitomo Y, Iwase T, Ikeda Y, Aihara K-I, Kimura T, Nishiuchi T, Abe M, Matsumoto T. Improvement of cardiac diastolic function and prognosis after autologous peripheral blood stem cell transplantation in AL cardiac amyloidosis. *Intern Med* 2007;**46**:1705–1710.
12. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, Kuznetsova T, Voigt J-U. Echo parameters for differential diagnosis in cardiac amyloidosis. *Circ Cardiovasc Imaging* 2017;**10**:e005588.