LETTER

Cardiac AA amyloidosis in a patient with rheumatoid arthritis and systemic sclerosis: the therapeutic potential of biological reagents

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Reactive amyloid A (AA) amyloidosis is a serious and life-threatening systemic complication of rheumatoid arthritis (RA) (1), and the AA amyloid deposition usually affects the kidneys and gastrointestinal tract (2–4). Unlike AL amyloidosis, the prevalence of cardiac involvement in reactive AA amyloidosis is low, affecting only about 10% of patients, and clinically overt heart failure is usually present in the terminal phase of the disease course in addition to end-stage renal disease (ESRD) (5). In general, the prognosis of patients with cardiac amyloidosis is known to be poor, with an average survival time of 1 to 2 years after diagnosis, and can even be as short as 6 months once clinically overt heart failure has appeared (6).

Here we report a rare case of congestive heart failure as the presenting sign of reactive AA amyloidosis associated with RA and systemic sclerosis (SSc), which was managed with anti-tumour necrosis factor (TNF) therapy. The patient, a 67-year-old woman, was hospitalized as an emergency admission because of chest oppression and exertional dyspnoea in December 2009. Initially, she had visited our hospital because of Raynaud's phenomenon, sclerodactyly, persistent dry cough, and multiple joint pain in 1993. She was positive for serum rheumatoid factor (78.1 IU/mL), anti-nuclear antibody (×640), and anti Scl-70 antibody. Radiographs of the hands showed bone erosions in her metacarpophalangeal joints, and chest computed tomography revealed interstitial pneumonia. Taking all these findings together, she was diagnosed as having RA associated with SSc and interstitial pneumonia. Treatment with low-dose glucocorticoid and bucillamine (BCL) was then started. In 1996, urinary protein was positive in routine laboratory examinations, and a percutaneous kidney biopsy specimen showed diffuse membranous changes in the glomeruli without amyloid deposition. BCL was stopped, and the proteinuria disappeared within a few months. The patient was then treated with a combination of salazosulfapyridine, mizoribine, and low-dose glucocorticoid, and retained persistent positivity for serum C-reactive protein (CRP) at around 1–3 mg/dL. Two months prior to admission to our hospital, the patient had developed cardiac decompensation and was treated with diuretics, but exertional dyspnoea had gradually returned about 1 week before admission. On admission, chest radiography showed significant cardiomegaly and pulmonary congestion. Laboratory examination showed hypoxaemia and marked elevation of the B-type natriuretic peptide (BNP) level at 1221.5 pg/mL. Although a 24-h creatinine clearance test indicated mild kidney dysfunction (50.0 mL/min), no urinary abnormality was observed. Transthoracic echocardiography showed diffusely hypokinetic left ventricular motion, and the ejection fraction was 40%, reflecting deterioration in comparison with 2 years previously (Table 1). Adenosine-induced stress-redistribution thallium-201 myocardial scintigraphy revealed low accumulation and reperfusion in the anterior, lateral, and inferior areas of the left ventricle, indicating triple vessel disease. However, a cardiac catheterization study was unable to demonstrate any significant stenotic lesion. Transcatheter endomyocardial biopsy was performed from the right ventricle, and the biopsy specimen showed significant deposits of a haematoxylin-positive substance in the extracellular spaces between the myocardiocytes (Figure 1A). These deposits were positive for Congo red staining with green birefringence under polarizing microscopy, and the staining disappeared after incubation with potassium permanganate (Figure 1B–D). Immunohistochemical analysis confirmed that these deposits were AA amyloid. Gastroduodenal mucosal biopsy was also performed and the specimens obtained were also positive for AA amyloid. On the basis of these findings, the patient was diagnosed as having systemic reactive AA amyloidosis associated with RA and systemic sclerosis. (SSc) After introduction of a combination of furosemide, candesartan, spironolactone, and carbedilol, her cardiac symptoms were improved from New York Heart

DOI: 10.3109/03009742.2011.569754

Table 1. Clinical course.

	October 2007	October 2009	December 2009	February 2010	July 2010
Symptoms	–	Dyspnoea	Dyspnoea, chest oppression NYHA III	Exertional dyspnoea NYHA II	Exertional dyspnoea NYHA II
Events	–	–	Emergency hospitalization	Endomyocardial biopsy	anti-TNF therapy
Treatment	PSL 7.5 mg MZR, SSZ	PSL 7.5 mg MZR, SSZ	PSL 7.5 mg, MZR, SSZ Furosemide 40 mg	PSL 7.5 mg, MZR, SSZ Furosemide 40 mg Candesartan 1 mg Spironolactone 50 mg Carvedilol 2.5 mg Etanercept 25 mg/week	PSL 7.5 mg, MZR, SSZ Furosemide 40 mg Candesartan 1 mg Carvedilol 2.5 mg Etanercept 25 mg/week
CRP (mg/dL)	3.07	2.66	4.73	1.05	0.08
SAA (mg/dL)	–	–	404.8	163.9	18.2
BNP (pg/mL)	21.3	465	1221.5	200.3	111.6
Echocardiography					
LVd/s (mm)	42/10	–	48/38	–	40/29
LVEF (%)	63	–	42	–	54
IVST/PWT (mm)	11/10	–	11/11	–	11/11
TR/PG (mmHg)	Trace/–	–	II/19	–	Trace/11

NYHA, New York Heart Association class grade; PSL, prednisolone; MZR, mizoribine; SSZ, salazosulfapyridine; CRP, C-reactive protein; SAA, serum amyloid A; BNP, B-type natriuretic peptide; LVd/s, left ventricular diastolic/systolic dimension; LVEF, left ventricular ejection fraction; IVST, interventricular septum thickness; PWT, posterior left ventricular wall thickness; TR, tricuspid regurgitation; PG, pressure gradient.

Association (NYHA) class grade III to grade II. Since her RA disease activity had not been fully controlled, we decided to use an anti-TNF agent, etanercept, at 25 mg per week. At the latest follow-up (6 months), the patient was in a stable condition without any adverse events, and the serum levels of both CRP and serum AA (SAA) were within normal limits. In addition, thallium-201 myocardial scintigraphy and echocardiography have shown a slight improvement in coronary blood flow and cardiac function.

Recently, many rheumatologists have focused on therapy with biologics, not only for control of RA disease activity but also as potential agents for the treatment of reactive AA amyloidosis through their strong suppression of acute-phase reactants such as SAA (7, 8). In addition, some very large-scale prospective studies have examined the therapeutic efficacy of anti-TNF therapy for chronic heart failure, focusing on the levels of serum TNF. However, the results of the RENEWAL study and the ATTACH study demonstrated no significant beneficial effect of infliximab or etanercept for patients with chronic heart failure (9, 10). As the present patient had interstitial pneumonia and renal dysfunction that could have been interpreted as severe adverse effects of the strong immunosuppressive therapy, etanercept was considered to be safer than other biological reagents

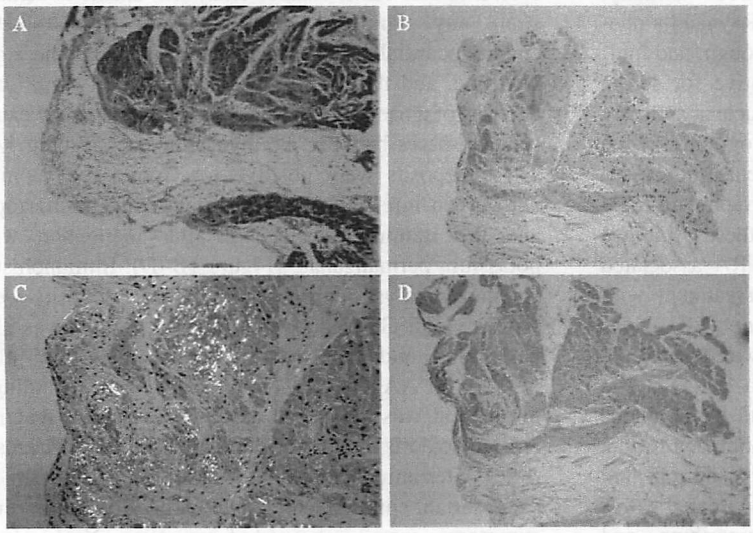

Figure 1. Histopathological findings of endomyocardial biopsy specimens. (A) Hematoxylin and eosin stain, x200, (B) Congo red stain, x200 (C) Congo red stain, x400 and examined under polarization microscopy. (D) Congo red staining with prior potassium permanganate incubation. x200

because of its short half-life. Therefore, we decided to use etanercept at a low dose of 25 mg once a week, as the RECOVER study had shown that this dose at least did not worsen the composite clinical status score at 24 weeks of treatment (10).

Our patient has shown good tolerance to anti-TNF therapy and her cardiac function has remained stable, or improved slightly, with a combination of diuretics, angiotensin II receptor-blocker, and beta-blocker. We will continue our careful follow-up for a longer period and intend to accumulate similar cases so as to obtain more data on the longer-term effect of this therapy for cardiac AA amyloidosis, with regard to not only therapeutic tolerability but also overall patient survival.

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Accepted 4 March 2011